The selective serotonin reuptake inhibitor sertraline alters learning from aversive reinforcements in patients with depression: evidence from a randomized controlled trial

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The selective serotonin reuptake inhibitor sertraline alters learning from aversive reinforcements in patients with depression: evidence from a randomized controlled trial

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ABSTRACT

Selective serotonin reuptake inhibitors (SSRIs) are first-line pharmacological treatments for depression and anxiety. However, little is known about how pharmacological action is related to cognitive and affective processes. Here, we examine whether reinforcement learning processes mediate the treatment effects of SSRIs. Reinforcement learning provides a promising framework as both serotonin and depression have been linked to specific reinforcement learning processes such as automatic Pavlovian inhibition. The PANDA trial was a multicentre, double-blind, randomized clinical trial in UK primary care comparing the SSRI sertraline with placebo for depression and anxiety. 655 patients were recruited and randomly assigned to sertraline (326, 50%) and placebo (329, 50%). Patients received 50 mg sertraline or placebo daily for one week, then 100 mg sertraline daily for up to 11 weeks. Patients were followed up after 2, 6, and 12 weeks. Patients performed an affective Go/NoGo reinforcement-learning task three times during the trial and computational models were used to infer reinforcement learning processes. There was poor task performance: only 54% of the task runs were informative, with more informative task runs in the placebo than the active group. There was no evidence for the preregistered hypothesis that Pavlovian inhibition was affected by sertraline. Exploratory analyses revealed that sertraline increased how fast participants learned from losses and faster learning from losses was associated with more severe generalised anxiety symptoms. Furthermore, in the sertraline group, early increases in Pavlovian inhibition were associated with improvements in depression after 12 weeks. In conclusion, sertraline was effective in treating anxiety, yet it increased learning from losses, and the rate of learning from losses was positively related to anxiety. Poor task performance limits the interpretability and likely generalizability of the findings and highlights the critical importance of developing acceptable and reliable tasks for use in clinical studies.
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1 INTRODUCTION

Anxiety and depression are the most common mental health problems, often occurring together and constituting a significant fraction of the global disease burden[1,2,3]. Selective serotonin reuptake inhibitors (SSRIs) are first-line pharmacological treatments for depression[4,5] and anxiety disorders[6]. However, how SSRIs work after the initial pharmacological action on the serotonin transporter remains poorly understood[7]. Neuropsychological models propose that antidepressants alter cognitive processing which might lead to improvement in depressive and anxiety symptoms[8]. Reinforcement learning provides a framework for investigating links between cognitive and biological processes and hence the effect of SSRIs on cognition[9]. Preclinical and experimental research has established that several cognitive functions relevant to the aetiology of anxiety and depression are sensitive to SSRIs (e.g. Roiser et al. [10,11], Harmer [12], Guitart-Masip et al. [13], Geurts et al. [14], Michely et al. [15,16], Lan and Browning [9]). However, there is little evidence tying these experimental effects of SSRIs on cognition to improvement in symptoms in clinical settings as only a few randomized clinical trials (RCTs) have evaluated candidate mechanisms to explain treatment effects[17,18,19]. Evaluations in the context of RCTs comparing SSRIs and placebo provide a strong test of whether specific cognitive or learning processes are the mechanisms through which SSRIs alleviate symptoms of anxiety and depression.

Here, we examined whether SSRIs improve anxiety symptoms by altering reinforcement learning processes, specifically aversive Pavlovian control. Aversive Pavlovian control refers to the automatic, stereotyped inhibition of actions in the face of negative expectations[20,21], an effect that can be robustly observed in humans using neurocognitive probes[22,23,24]. Aversive Pavlovian control is a promising candidate mechanism as it has been shown to be sensitive to serotonergic functioning in animals[25,26,27,28] and humans[29,30,31,32,14], and is related to symptoms of both anxiety and depression[33,31,34,35,36]. Indeed, inhibiting behaviour in response to negative expectations is increased in depression[11], while avoidance driven by negative expectations is a core component of anxiety disorders[37]. Finally, modification of aversive Pavlovian control is an important target of psychotherapeutic interventions such as behavioural activation[38]. In terms of mechanisms, computational models have suggested formal relationships between rumination, acute reduction in central serotonin levels, and reduction of aversive Pavlovian control[33,39]. Furthermore, at a neural level the subgenual anterior cortex has been suggested to be involved in aversive Pavlovian control[40,41] and is known to be involved in anxiety[42,43,44] and depression[45,46,47]. In addition, depression has been reported to affect appetitive Pavlovian control (with blunting[48,49,50,51,52] and possibly reduced specificity[34,35]), and serotonin has been suggested to affect appetitive Pavlovian processes[53,15].

As such, the existing literature suggests that aversive—and possibly appetitive—Pavlovian control may mediate the effect of SSRIs on anxiety and depression. Here, we report a test of this hypothesis in the context of the PANDA randomized controlled trial (RCT; Lewis et al. [54]). This trial compared sertraline to placebo for the treatment of depression in primary care in the UK [55,54]. PANDA found no evidence that sertraline reduced depressive symptoms to a clinically meaningful extent at 6 weeks, with only a weak effect at 12 weeks. However, they found evidence that sertraline reduced *anxiety* at 6 and 12 weeks. We measured Pavlovian inhibition and a number of other reinforcement learning processes during this trial using computational modelling of the affective Go/NoGo task[24]. This is a well-established learning paradigm in which computational analyses allow appetitive and aversive Pavlovian processes to be measured[24].

We pre-registered an analysis plan investigating five main hypotheses (osf.io/7q8v2). The pri-

mary analyses aimed to test whether treatment with the SSRI sertraline alters aversive Pavlovian control and whether aversive Pavlovian control is related to anxiety, i.e. whether Pavlovian inhibition might mediate the effect of sertraline on anxiety. We also examined the relationship between appetitive Pavlovian biases and depressive symptomatology. Overall, task compliance was poor, and the primary hypotheses were not supported. However, exploratory analyses did reveal that higher changes in aversive Pavlovian bias early on were linked to more severe depression after 12 weeks. Additionally, there was an effect of SSRI treatment on the aversive learning rate at week 2 and an association between learning from losses and anxiety.

2 METHODS

2.1 ETHICS

The National Research Ethics Service Committee, East of England - Cambridge South approved the study (ref: 13/EE/0418). The MHRA gave clinical trial authorization. Written informed consent was obtained from each participant before the study.

2.2 PARTICIPANTS

We present secondary analyses of data acquired in the context of the PANDA trial. PANDA was a randomized, double-blind, placebo-controlled pragmatic study investigating the clinical effectiveness of sertraline on depressive symptoms as the primary outcome. The trial was registered with EudraCT (2013-003440-22; protocol number 13/0413; version 6.1) and ISRCTN (reference ISRCTN84544741) with the primary aim of testing the clinical effectiveness of sertraline in primary care, as well as investigating the role of depression severity and duration[54].

Patients (aged 18-74 years) were recruited from 179 primary care surgeries in four UK sites (Bristol, Liverpool, London, York). The critical entry criterion was that general practitioners (GPs) and/or patients were uncertain about the potential benefits of an antidepressant. No lower or higher thresholds were set on depression severity or duration. The exclusion criteria were: unable to understand or complete study questionnaires in English; antidepressant treatment in past 8 weeks; comorbid psychosis, schizophrenia, mania, hypomania, bipolar disorder, dementia, eating disorder, or major alcohol or substance abuse; and medical contraindications for sertraline. Patients were randomised to sertraline or placebo, stratified by severity, duration, and site, and followed up after 2, 6, and 12 weeks (for baseline characteristics see Table 1). Patients received 50 mg sertraline or placebo daily for one week, then 100 mg sertraline daily for up to 11 weeks. Medication could be increased to 150 mg in consultation with the local principal investigator in cases of non-response after six weeks. The study was double-blind: study patients, care providers, and all members of the research team were blinded to the study treatment allocation (for the full trial protocol cf. Salaminios et al. [55]). The trial began recruiting participants in January 2015 and was completed in November 2017.

2.3 MEASUREMENTS

The Go/NoGo task (Fig. 1A) was designed to study Pavlovian appetitive and aversive influence on choice by crossing action (go vs nogo) and valence (rewards vs losses; cf. Guitart-Masip et al. [24]). Participants were verbally instructed that each fractal would lead to a more favourable outcome with either go or nogo, but that outcomes were probabilistic (cf. Fig. 1 for detailed task description).

	placebo (N = 221)	sertraline (N = 214)	p-value
Age (years)	36.03 (12.97)	36.84 (14.29)	0.535
GAD-7	9.6 (5.11)	9.27 (5.19)	0.496
PHQ-9	12.47 (5.66)	11.71 (5.77)	0.171
BDI	24.19 (9.9)	24.06 (10.17)	0.889
Site			
Bristol	98 (44%)	92 (43%)	0.681
Liverpool	39 (18%)	37 (17%)	0.681
York	48 (22%)	47 (22%)	0.681
London	36 (16%)	38 (18%)	0.681
CIS-R total score			
0-11	37 (17%)	45 (21%)	0.389
12-19	58 (26%)	51 (24%)	0.389
≥ 20-49	126 (57%)	117 (55%)	0.389
CIS-R depression duration (years)			
< 2	146 (66%)	147 (69%)	0.559
≥ 2	75 (34%)	67 (31%)	0.559
Highest educational qualification			
A Level or higher	165 (75%)	160 (75%)	0.929
GCSE, standard grade, or other	53 (24%)	50 (23%)	0.929
No formal qualification	3 (1%)	3 (1%)	0.929
Antidepressants in the past			
Yes	97 (44%)	100 (47%)	0.523
No	124 (56%)	113 (53%)	0.523
Gender			
Male	101 (46%)	84 (39%)	0.174
Female	120 (54%)	130 (61%)	0.174
Ethnicity			
White	205 (93%)	198 (93%)	0.936
Ethnic minority	16 (7%)	15 (7%)	0.936
Financial difficulty			
Living comfortably or doing alright	130 (59%)	121 (57%)	0.663
Just about getting by	66 (30%)	66 (31%)	0.663
Finding it difficult or very difficult	25 (11%)	26 (12%)	0.663
Employment status			
In paid employment	159 (72%)	146 (69%)	0.439
Not employed	62 (28%)	67 (31%)	0.439
Marital status			
Married or living as married	86 (39%)	74 (35%)	0.218
Single	110 (50%)	107 (50%)	0.218
Separated, divorced, or widowed	25 (11%)	32 (15%)	0.218

Table 1: This table shows baseline characteristics for participants providing informative Go/NoGo task data (N=435). Data are reported in N (%) or mean (SD). There was no evidence for differences in baseline characteristics between the treatment groups shown by the p-values (≤ 0.05). PHQ-9=Patient Health Questionnaire, 9-item version total score (possible range 0–27). GAD-7=Generalised Anxiety Disorder Assessment, 7-item version total score (possible range 0–21). BDI=Beck Depression Inventory, 21-item version total score (possible range 0–63). CIS-R=Clinical Interview Schedule-Revised measuring depression severity score (possible range 0–21).

Each task administration employed a different fractal set. Fractal sets were randomized across participants and assessment timepoints. The Go/NoGo task was assessed at baseline, at 2 weeks (follow-up 1), and at 6 weeks (follow-up 2), but it was not part of the 12 weeks assessment (follow-up 3). The Generalised Anxiety Disorder Assessment (GAD-7; Spitzer et al. [56]), the Patient Health Questionnaire-9 (PHQ-9; Kroenke et al. [57]), and the Beck Depression Inventory (BDI; Beck et al. [58]) were completed at baseline and every follow-up. Several baseline variables were acquired (cf. Table 1). A flowchart of the trial and the primary measurements for this study are included in the Supplementary Materials Fig. A.1.

2.4 Computational Models

Previously published computational models for this task[24,59,36,60] provide formal, quantitative descriptions of the evolution of decisions over the course of learning during the task. The core parameters of interest in the models are the Pavlovian parameters. These capture appetitive Pavlovian influences through the extent to which participants automatically emit 'go' responses when faced with reward stimuli, and aversive Pavlovian inhibition through the extent to which they automatically emit 'nogo' responses when faced with loss stimuli. The Pavlovian processes are separate from instrumental learning processes, which emit 'go' and 'nogo' according to which of the two actions is more likely to lead to the better outcome. Other parameters include reward and loss sensitivity, learning rates, irreducible noise, and an overall 'go' bias.

2.4.1 Data validation

To evaluate whether the existing data was in principle sufficient to assess the key hypotheses, and to provide an informative a-priori estimate of power, two authors (J.M. and Q.J.M.H) were provided with blinded access to the behavioural task data only, but without access to group allocation, demographics, or measures of symptoms. These authors fitted different reinforcement learning (RL) models (for a list of the models, see Supplementary Materials B RL models) as de- scribed previously in the literature (cf. Huys et al.[61] and Supplementary Materials B Model Fitting Procedure & Model Comparison). All datasets of the study were combined, disregarding within-subject information (i.e. treating repeated sessions as independent task assessments). In the supplements, we report the recoverability and reliability of the parameters (cf. Supplementary Materials Fig. B.2&B.3 and Table B.1).

Models were fitted separately to the data and compared using the integrated Bayesian Information Criterion (iBIC; Fig. 2A) at the group level, where the individual likelihoods were first integrated over the individual parameters using a sampling procedure and then summed over all individuals. The most parsimonious model included learning rates, outcome sensitivities, and Pavlovian biases, all separated in rewarding and punishing contexts. Figure 2C shows that simulated data captured the empirical data qualitatively. Hence, standard models of the task are able to parametrically capture the variability of behavioural performance in the task across individuals and sessions on a trial-by-trial level.

In the Go/NoGo task, non-informative responses (e.g. always emitting the same response) cannot provide information about Pavlovian or other cognitive processes and therefore do not inform parameter estimates. Whether the data of a particular task run are meaningful can be evaluated formally by examining whether a model encompassing the core processes provides a more parsimonious account of the behavioural data than a random baseline model. In other words, to examine whether the observed behavioural data meaningfully constrained the model parameter estimates, we compared the integrated likelihood of the most parsimonious model to the integrated likelihood of a random baseline model for each dataset from each individual at each session.

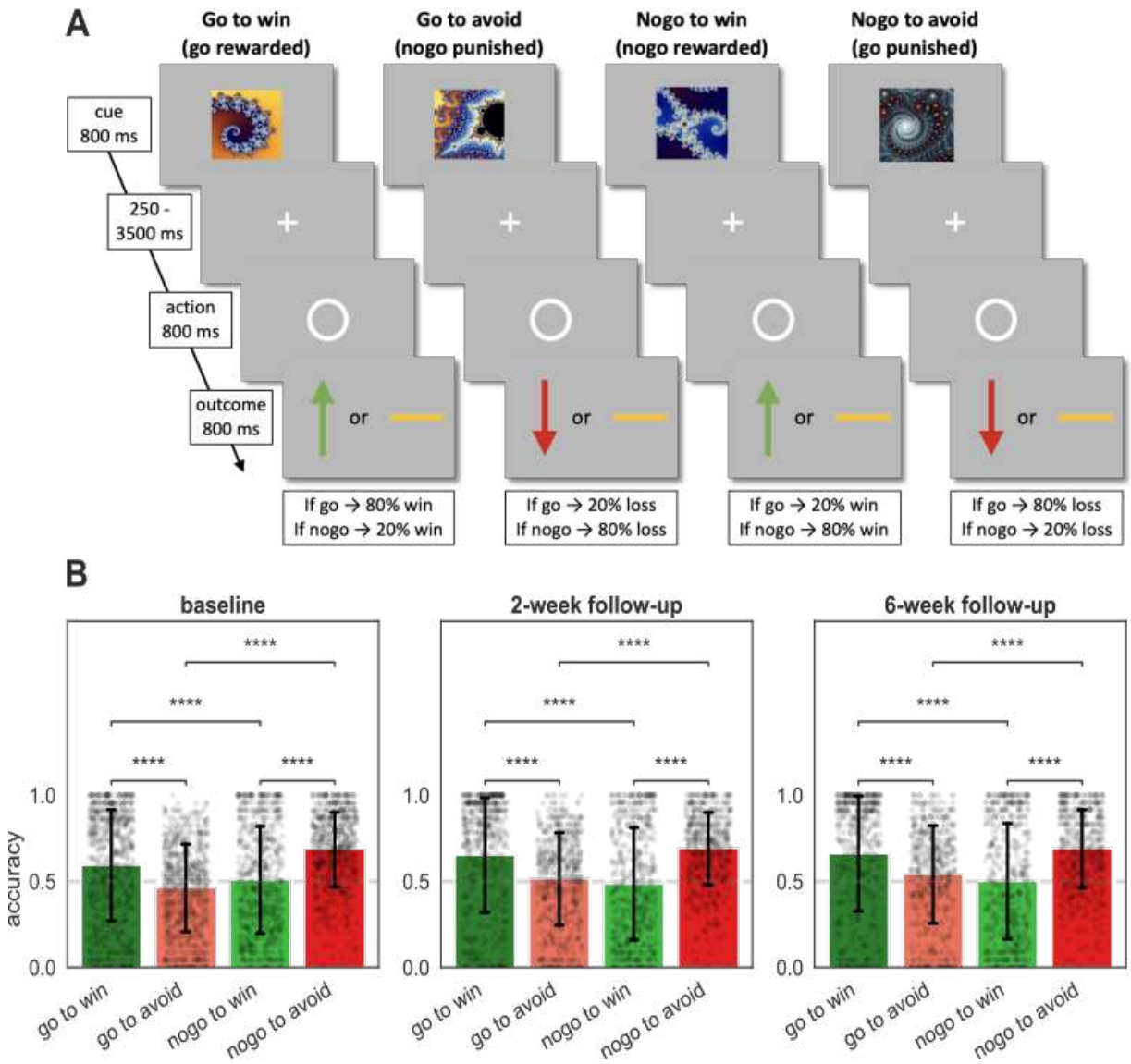

Figure 1: **Task and Performance**. **A)** The Go/NoGo task consisted of four different conditions. On each trial one of four possible fractal images was shown. Actions were required in response to a circle that followed the fractal image after a variable delay. After a brief delay, the outcome was presented: a green upward arrow for a win, a red downward arrow for a loss, or a horizontal bar for a neutral outcome. In the go-to-win condition, pressing the key ('go') led to a reward with 80% and a neutral outcome with 20% probability, vice versa if they did not press the key ('nogo'). In the go-to-avoid condition, pressing the key ('go') led to a neutral outcome with 80% and a loss with 20% probability. In the nogo-to-win, not pressing the key ('nogo') led to a reward with 80% and a neutral outcome with 20% probability. In the nogo-to-avoid condition, not pressing the key ('nogo' response) led to a neutral outcome with 80% and a loss with 20% probability. Each task administration consisted of 96 trials, with 24 trials per condition. **B)** Mean percentage of correct responses in each of the four conditions. Black dots depict participants and black error bars depict standard deviation of the mean (SD). Dashed lines depict chance level. Post hoc comparisons were implemented by means of repeated measures t-tests showing a significant difference in accuracy between Pavlovian congruent (got to win and nogo to avoid) and incongruent conditions (go to avoid and nogo to win). Significance $* \leq 0.05$, $** \leq 0.01$, $*** \leq 0.001$, $**** \leq 0.0001$

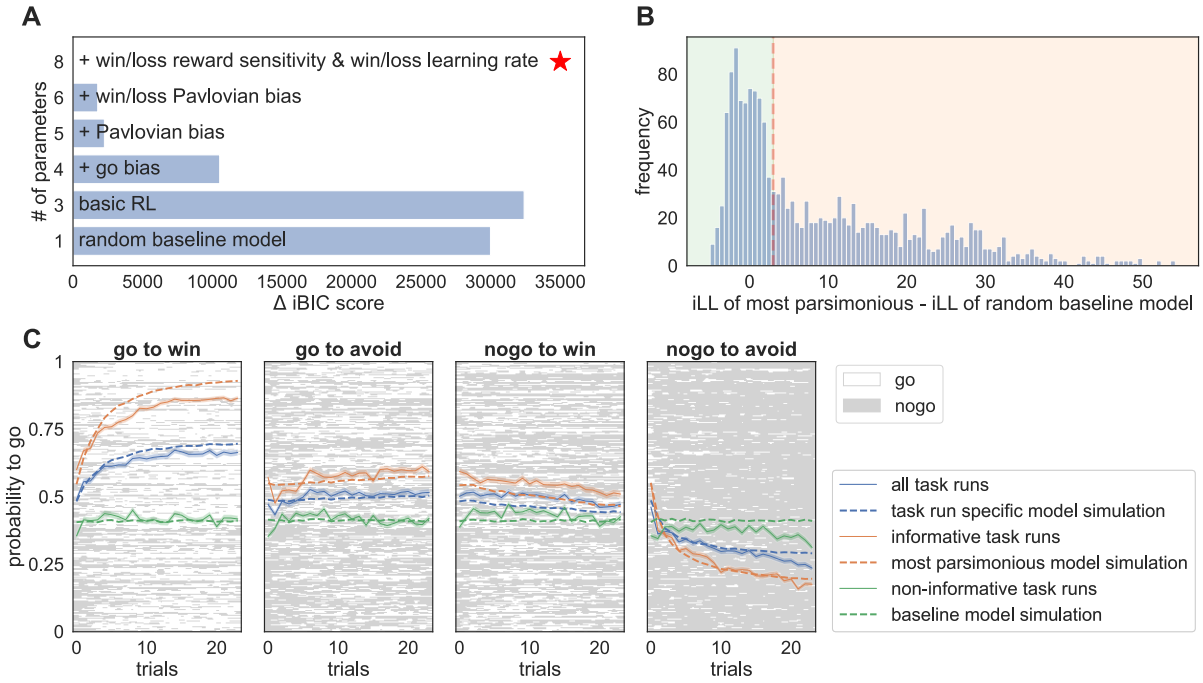

Figure 2: **Computational modeling of the Go/NoGo task**. **A)** shows the differences in integrated Bayesian Information Criterion (iBIC) scores for all models tested compared to the most parsimonious model (red star), where a smaller iBIC score indicates a more parsimonious model. All models are modified Q-learning models (Rescorla Wagner - RW) with two pairs of action-values ('go' and 'nogo') for each stimulus. The y-axis shows the number of free parameters for each model. The most parsimonious model includes separate learning rates for rewards and punishments, win and loss sensitivities, appetitive and aversive Pavlovian biases, irreducible noise, and a constant bias factor added to the action-value for 'go'. **B)** shows the histogram of the difference between the integrated loglikelihood (iLL) of the most parsimonious model and the iLL of the random baseline model. Datasets were declared as informative if the data was more than three times more likely to have occurred under the most parsimonious model (vertical red dashed line). **C)** The four subplots show the average learning curves in blue (averaged over participants; solid line) for each condition separately. Each row of the raster images shows the choices of each participant. 'Go' responses are depicted in white, and 'nogo' responses are depicted in grey. Additionally, the average 'go' probability was separated into included datasets (orange) and excluded datasets (green). The solid line refers to empirical data and the dashed line to simulated data from the most parsimonious model. Informative datasets (orange) show that participants, on average, seem to learn over trials, which can be captured qualitatively well by the most parsimonious model. In contrast, the average 'go' probability of non-informative/excluded datasets (green) appears to have no temporal relation, hence showing no learning over trials. Further, it is well captured by the random baseline model.

The integrated likelihood integrated over an individual's parameters refers to the likelihood of the data given the group-level hyperparameters. A task run was deemed as missing if the integrated likelihood of the random baseline model was higher than that of the most parsimonious model (Fig. 2B).

The parameters for each informative task run were extracted from the most parsimonious model to test the hypotheses.

2.5 Preregistration

The key hypotheses and analyses were pre-registered on OSF (osf.io/7q8v2; cf. Supplementary Materials Table D.3).

2.6 Statistical Analyses

Predictors of missing and non-informative data at baseline were identified using a univariate logistic regression. Significantly related baseline variables were used as covariates in all further analyses.

To investigate drug effects, we employed a mixed-effects linear regression (analysis type 1) using group allocation as the independent variable and the parameter estimate (e.g. aversive Pavlovian bias) as the dependent variable controlling for stratification variables (baseline CIS-R total score in three categories, duration of depressive episode in two categories, and site) and including random intercepts. We reported mean differences (*MD*), 95% confidence intervals (*CI*), and the corresponding p-values (*p*).

Next, we examined whether parameter estimates relate to depressive or anxiety symptoms using a mixed-effects multiple linear regression (2) with the parameter estimate as independent variable and log-transformed symptom scores (e.g. GAD-7 total score) as dependent variable. Random slopes and intercepts per individual were included. We controlled for group allocation and stratification variables. We reported regression coefficients (β), 95% confidence intervals (*CI*), and the corresponding p-values (*p*).

For both analyses we performed separate mixed-effects models for baseline and week 2, baseline and week 6 and over all three time-points. To investigate a potential drug time interaction, we additionally performed a regression including a group-time interaction. The group variable in the mixed-effects models was coded [0,1,1] for a patients allocated to sertraline and [0,0,0] for a patients allocated to placebo. Both groups have a 0 at baseline because they were unmedicated at that time.

To investigate whether a baseline parameter estimate predict treatment outcome, we performed a simple linear regression predicting symptom score at week 12 controlling for symptoms at baseline, group allocation, and stratification variables.

As an exploratory analysis we examined whether early change in aversive Pavlovian bias (week 2 - baseline) relates to log-transformed BDI total score at week 12 using a simple linear regression including an interaction effect between group-allocation and Pavlovian bias.

Exploratory analyses repeated the analysis type 1 above for each individual parameter and used Bonferroni-correction to correct for testing multiple parameters ($p \leq \frac{0.05}{8} \leq 0.00625$). Additionally, we conducted simple linear regression examining group differences in parame-

ter slopes (early change = week 2 - baseline; late change = week 6 - week 2). We also repeated analysis type 2 for each of the parameter estimates and the three psychological measures (GAD-7, PHQ-9, BDI) and used Bonferroni-correction to correct for testing multiple parameters ($p \leq \frac{0.05}{8*3} \leq 0.002$).

3 RESULTS

655 patients were recruited and randomly assigned to sertraline (326, 50%) and placebo (329, 50%). Two patients in the sertraline group did not complete a substantial proportion of the baseline assessment and were excluded. Additionally, 25 patients (9 from the sertraline group and 16 from placebo) did not complete the Go/NoGo task at any time-point. This left 628 participants (315 sertraline and 313 placebo) for analyses (cf. Fig. A.1 in Supplementary Materials). Task data for 7 patients at baseline, 99 patients at 2 weeks, and 145 patients at 6 weeks were missing. Missing follow-up data were more common in participants who had higher baseline depressive and anxiety symptoms, financial difficulties, were from ethnic minorities and recruited from London (cf. Supplementary Materials Table E.4). Missing data did not differ statistically by treatment allocation.

3.1 BASIC TASK CHARACTERISTICS

Examination of the average percent correct response per condition showed the typical interaction pattern characteristic for Pavlovian inference found in previous studies[24,59,36,60] at all measurement points (Fig. 1B). Performance was better in Pavlovian congruent (go to win and nogo to avoid) than incongruent (go to avoid and nogo to win) conditions ($|t| \in [4.61, 16.68]$, $p < 0.001$). There were no differences in average performance between patients allocated to sertraline and patients allocated to placebo ($|MD| \in [0.00, 0.03]$, $p > 0.05$).

3.2 COMPUTATIONAL MODELLING RESULTS

Overall, 747 (46%)[1] task runs did not contain interpretable and informative behavioural data. Variables associated with non-informative behaviour were higher age, lower education, and past antidepressant use. At week 2 non-informative task runs (N=230, 43%) were more likely in patients who were allocated to the sertraline group (57%, $X^2 = 7.06$, $p = 0.008$). In addition, baseline anxiety score, depression severity, and employment status were predictive of non-informative behaviour at week 6 (cf. Supplementary Materials Table E.5). For all further analyses we focused on the 886 informative task runs from 435 patients (66% of those originally randomised) and adjusted for significant predictors of non-informative data as covariates. Characteristics of the remaining sample according to study arm are shown in Table 1. Baseline characteristics of the sample were not statistically distinguishable between treatment groups.

The effect of sertraline on anxiety remained significant in the smaller included sample (week 2: $MD = -0.05$, $CI = [-0.09, -0.01]$, $p = 0.013$; week 6: $MD = -0.11$, $CI = [-0.16, -0.06]$,

[1]This number deviates from the preregistration because 8 task runs (4 informative and 4 non-informative) were excluded due to the following reasons: i) six participants were not randomized despite completing baseline assessments; ii) one participant did not complete a substantial proportion of the baseline assessment despite conducting the GoNogo task at baseline and 2-week follow-up.

$p \leq 0.001$; over time: $MD = -0.06$, $CI = [-0.1, -0.03]$, $p \leq 0.001$).

3.2.1 Preregistered Hypotheses

The preregistered hypotheses were not supported (Table 2): there was no evidence that the aversive Pavlovian inhibition was affected by sertraline (Fig. 3A,B); that aversive Pavlovian inhibition was related to anxiety symptoms; that the baseline aversive Pavlovian bias was predictive of treatment response; that the appetitive Pavlovian bias was associated with depression or that the reward sensitivity was related to anhedonia.

H1) effect of sertraline on aversive Pavlovian bias

	placebo mean (SD)	sertraline mean (SD)	mean difference [95% CI]	p-value
Follow-up assessments (weeks)				
baseline	-0.5 (0.82)	-0.55 (0.79)		
2	-0.55 (0.79)	-0.71 (0.79)	-0.12 [-0.28,0.05]	0.17
6	-0.70 (0.83)	-0.77 (0.85)	0.12 [-0.06,0.30]	0.21
over time	..	..	-0.01 [-0.14,0.12]	0.90
group by time interaction	..	..	..	0.16

H2) association between aversive Pavlovian bias and log-transformed GAD-7 total score

	regression coefficient [95% CI]	p-value
Follow-up assessments (weeks)		
2	-0.01 [-0.04,0.01]	0.40
6	-0.02 [-0.05,0.01]	0.13
over time	-0.02 [-0.05,0.00]	0.10

H4) association between *baseline* aversive Pavlovian bias and log-transformed GAD-7 total score at week 12

	regression coefficient [95% CI]	p-value
	-0.02 [-0.04,0.02]	0.38

H5) association between appetitive Pavlovian bias and log-transformed PHQ-9 total score

	regression coefficient [95% CI]	p-value
Follow-up assessments (weeks)		
2	-0.02 [-0.05,0.01]	0.27
6	-0.03 [-0.07,0.00]	0.07
over time	-0.03 [-0.06,0.00]	0.10

H6) association between reward sensitivity and log-transformed PHQ-9 anhedonia item score

	regression coefficient [95% CI]	p-value
Follow-up assessments (weeks)		
2	-0.02 [-0.09,0.04]	0.51
6	0.03 [-0.03,0.10]	0.64
over time	-0.00 [-0.06,0.05]	0.88

Table 2: Mixed-effect linear models were used to investigate our pre-registered hypotheses (only informative data N_{task_runs}=886; $N_{patients}$=435, 66% of those randomised). We tested whether sertraline alters aversive Pavlovian control (Hypothesis 1; H1) and whether aversive Pavlovian control is related to anxiety (Hypothesis 2; H2). Hypothesis 3 regarding the aversive Pavlovian bias as a mediator for the effect of sertraline on anxiety was not investigated as there was no evidence for H1 and H2. Hypothesis 4 (H4) tested whether aversive Pavlovian bias at baseline before starting SSRI treatment predicted treatment outcome. Hypothesis 5 (H5) examined the relationship between the appetitive Pavlovian bias and depressive symptoms. Hypothesis 6 (H6), tested for a relationship between reward sensitivity and anhedonia.

3.2.2 Exploratory Analyses

Two sets of results in the exploratory analyses are noteworthy. The first relates to early change in the aversive Pavlovian bias. The slope of the aversive Pavlovian bias between baseline and week 2 was positively related to depressive symptoms at week 12 (log-transformed PHQ9 total score: $\beta = 0.06$, $CI = [0.0, 0.11]$, $p = 0.044$; log-transformed BDI total score: $\beta = 0.07$, $CI = [0.01, 0.13]$, $p = 0.016$). A larger increase in aversive Pavlovian bias was associated with more severe subsequent depressive symptoms. Furthermore, the BDI model revealed an interaction between group allocation and early change in the aversive Pavlovian bias ($\beta = 0.14$, $CI = [0.02, 0.26]$, $p = 0.024$; Fig. 3C). That is, early change in aversive Pavlovian bias was more strongly related to BDI scores at week 12 in the sertraline group ($\beta = 0.14$, $CI = [0.05, 0.23]$), than in the placebo group ($\beta = 0.02$, $CI = [-0.03, 0.07]$). However, note that sertraline had no effect on the early change in aversive Pavlovian bias ($MD = -0.08$, $CI = [-0.32, 0.15]$, $p = 0.49$).

The second set of findings relates to the speed at which participants adapted behaviour following losses (the loss learning rate). There was an effect of sertraline on the loss learning rate at week 2 ($MD = 0.6$, $CI = [0.22, 0.97]$, $p = 0.002$; Fig. 3D). The sertraline group learned faster from losses at week 2 than the placebo group. Early change in loss learning rate (week 2 - baseline) was higher in the sertraline group (MD=0.75, CI=[0.18,1.3], p=0.009; Fig. 3E), whereas later change (week 6 minus week 2) was lower in the sertraline group ($MD = -0.72$, $CI = [-1.27, -0.17]$, $p = 0.011$; Fig. 3E). In the sertraline group, the early change was different from zero ($t = 2.74$, $p = 0.007$), whereas the later change was not ($t = -0.32$, $p = 0.75$). In contrast, in the placebo group, the early change did not differ from zero ($t = -0.70$, $p = 0.483$), but the late change did ($t = 3.44$, $p < 0.001$). Hence, the group difference in the late change was due to an increase in loss learning rate from baseline to week 6 in the placebo group. Finally, the loss learning rate was also positively associated with the anxiety scores (at week 2: $\beta = 0.01$, $CI = [0.0, 0.02]$, $p = 0.047$; at week 6: $\beta = 0.02$, $CI = [0.0, 0.03]$, $p = 0.016$; across all sessions: $\beta = 0.02$, $CI = [0.01, 0.03]$, $p = 0.001$). However, there was no evidence for an association between anxiety symptoms and either the loss learning rate at baseline ($\beta = 0.01$, $CI = [-0.0, 0.02]$, $p = 0.24$) or the early change in loss learning rate (week 2 - baseline; $\beta = -0.02$, $CI = [-0.04, 0.01]$, $p = 0.164$).

Repeating these analyses on the complete sample including all task runs resulted in a broadly consistent pattern of effects (c.f. Supplementary Materials C Findings of the Whole Sample).

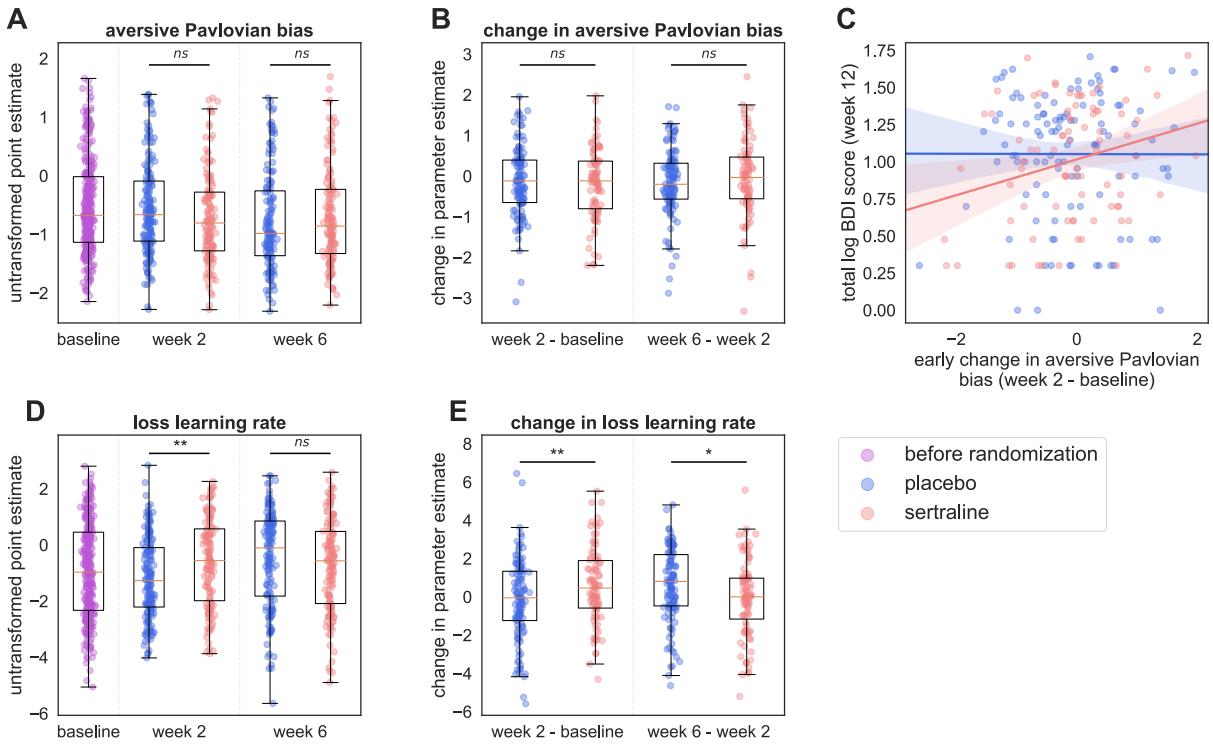

Figure 3: **Effects of Sertraline on RL Parameters**. **A)** shows the aversive Pavlovian bias at baseline and at the follow-ups separated into drug groups (blue,left=placebo; red,right=sertraline). **B)** shows the change in aversive Pavlovian bias between sessions separately for the drug groups. **C)** Early changes in the aversive Pavlovian bias predict treatment outcome. This figure shows the relation between the change from baseline to week two in the aversive Pavlovian bias and log-transformed BDI total score (only of participants which had an informative task run at baseline and week 2). In blue the placebo group and in red the sertraline group. An interaction effect was observed between group and early change in the aversive Pavlovian predicting depression at 12 weeks driven by a significant association between the early change and log-transformed BDI total score at 12 weeks (blue,left=placebo; red,right=sertraline). **D)** shows the loss learning rate at baseline and at the follow-ups separated into drug groups (blue,left=placebo; red,right=sertraline). **E)** shows the change in loss learning rate between sessions separately for the drug groups. Significance $* \leq 0.05$, $** \leq 0.01$, $*** \leq 0.001$, $**** \leq 0.0001$

3.2.3 Task Reliability

Parameters varied in reliability (*ICC* ranging from 0 to 0.72; cf. Supplementary Materials Table B.1). The Pavlovian biases and the go bias were the most reliable parameters ($ICC > 0.55$). Those parameters also significantly changed over time. The Pavlovian parameters decreased (aversive: $\beta = -0.1$, $CI = [-0.16, -0.04]$, $p = 0.001$; appetitive: $\beta = -0.08$, $CI = [-0.13, -0.04]$, $p < 0.001$) and the go bias increased ($\beta = 0.13$, CI = [0.05,0.21], p<0.001) over sessions which likely led to an increase in task accuracy ($\beta = 0.02$, $CI = [0.01, 0.03]$, $p < 0.001$). We note that age reduced accuracy ($\beta = -0.03$, $CI = [-0.04, -0.02]$, $p < 0.001$), most likely due to increasing Pavlovian biases (aversive: $\beta = 0.19$, $CI = [0.11, 0.26]$, $p < 0.001$; appetitive: $\beta = 0.16$, $CI = [0.11, 0.21]$, $p < 0.001$) and reducing go bias with age ($\beta = -0.4$, $CI = [-0.49, -0.32]$, $p < 0.001$).

4 DISCUSSION

We investigated the effects of the SSRI sertraline on reinforcement learning mechanisms in the PANDA trial, a pragmatic multicentre, double-blind, placebo-controlled, randomised clinical trial. SSRIs are first-line pharmacological treatments for depression and anxiety, but the mechanism of SSRI action is still unknown. A better understanding of how SSRIs work could lead to improved response predictions and new, refined treatments. Our goal was to identify clinically relevant mechanisms to link receptor action to cognition and affective processing. Reinforcement learning enables such links and hence is a promising framework for investigating the mechanisms of SSRI action. To our knowledge, this is the first study analysing a reinforcement learning task performed multiple times throughout a clinical trial. The PANDA trial was the largest individual placebo-controlled trial not funded by the pharmaceutical industry. The sample was recruited in primary care based on clinical equipoise, and depressive symptoms ranged from mild to severe. Findings might therefore be of relevance to the broader primary care population. As sertraline acts through similar mechanisms as other SSRIs [62], the findings may also be relevant for other SSRIs. However, the study has important limitations. The task was developed and previously validated in a lab setting; not optimized for repeated testing; and had known poor test-retest reliability[59,63]. Most importantly, the task appeared to be unacceptable to patients. This is suggested by the strikingly poor average performance. These limitations speak to more general issues in psychometric task design, which are being addressed in recent research[64,65,66,67,68,69].

Due to the poor task performance, almost half of the performed task runs were excluded. Early on (at week 2) non-informative data was more prevalent in the sertraline group, suggesting that patients in the active group may have responded more randomly. Such randomness can be a signature of low overall motivation to perform the task. One possibility is that such a broad motivational reduction could be a signature of SSRI-induced affective blunting[70,71,72,73]. However, there were no discernible differences in symptoms between patients who provided informative and non-informative data at week 2, and sertraline had a positive impact on learning at week 2 in the included sample. These findings speak against a broad blunting effect.

The primary goal of this study was to test whether aversive Pavlovian bias mediates the effect of sertraline on anxiety. We found no evidence supporting an influence of sertraline on aversive Pavlovian bias. This result contrasts with previous research suggesting that Pavlovian inhibition is sensitive to serotonin[30,29,14,74]. There are several possible reasons for this discrepancy. First, it may be that serotonin manipulations have different effects on Pavlovian inhibition in samples with and without depression and/or anxiety. While the current study was performed in a clinical population, previous studies primarily examined healthy volunteers. Second, previous research focused on acute changes via tryptophan depletion[30,29,14,74] or a single administration of an SSRI citalopram[13] rather than the chronic administration examined here. It has long been posited that acute and chronic SSRI administration have opposite effects (e.g. Harmer et al. [75,76]). Third, we cannot rule out that some of the Pavlovian inhibition signal is conflated with the loss learning signal as there are non-negligible correlations between parameters (cf. Supplementary Materials Fig. B.3). This is likely compounded by broader issues with data quality, which in turn reduce the ability of models to distinguish aversive Pavlovian inhibition and learning from losses.

Exploratory analyses identified relationships between sertraline, aversive processing, and symptoms. First, sertraline affected learning from losses but not from rewards. This finding is in keep-

ing with well-supported empirical evidence demonstrating that serotonin modulation impacts learning[77,78,79,15], and specifically punishment learning[80,81,82,83]. Prolonged serotonin alterations have downstream effects including augmented learning and plasticity[84,85]. In the current dataset, the learning rate from losses increased over the first two weeks of sertraline treatment relative to placebo. The placebo group then 'caught up', removing the group differences in loss learning rate at six weeks. Changes in the performance of learning tasks are frequently observed and thought to represent a type of meta-learning, i.e. learning more broadly about the strategy of performing a task rather than learning within the task itself[86,87,88,89,90]. As such, the late change in performance in the placebo group compared to the early change in the sertraline group suggests that sertraline may have increased the speed at which this meta-learning may have occurred and may have done so by specifically altering behavioural adaptation after losses within the task. One complication is that, at 2 weeks, there was already some evidence for changes in anxiety symptoms, and an inverse causal path (with anxiety mediating the effect of sertraline) cannot be excluded.

The loss learning rate was correlated with anxiety symptoms at both follow-up time points and over all measurement points. This is, in principle, in line with previous research outlined in a recent meta-analysis reporting higher punishment learning rates and slightly lower reward learning rates in patients[91]. Yet, this is difficult to reconcile with, first, the SSRI-induced increase in learning from punishment, and second the fact that both anxiety and depression are treated by SSRIs, and are linked to heightened punishment learning themselves. Interestingly, a similar conundrum was present in the literature on learned helplessness, which was associated with increased levels of serotonin[92], but could also be reversed as a response to SSRIs [93,94,95,96]. Hence, coupling increases in serotonin levels with a simple account of serotonin levels on behaviour is unlikely to be able to explain SSRI effects. Indeed, the serotonin system is known to be exquisitely complex, with many different serotonin receptors distinctively distributed[97]. A possible explanation could be that SSRIs facilitate learning faster in a punishing environment, thus leading to less negative and more positive (or neutral) feedback. It is interesting to consider how this bias towards learning from losses might be linked to mood. Self-reports of happiness are linked to positive prediction errors[98], suggesting that negative prediction errors might similarly influence negative affective states. In other words, SSRIs might gradually improve mood by enhancing negative expectations through faster loss learning, thereby giving rise to less disappointing and more rewarding experiences.

Finally, improvements in depressive symptoms in the sertraline group were preceded by an early decrease in the aversive Pavlovian bias. In other words, patients on sertraline showed a higher increase in their tendency to withhold an action when facing a loss between baseline and the 2-week follow-up, the higher their depressive symptoms were after 12 weeks.

Overall, the findings draw a complex picture involving aversive processing, sertraline and symptoms, possibly reflecting the known complexity of the serotonin system. Despite the methodological limitations and the failure to support the preregistered hypotheses, the exploratory data suggest alterations in the processing of losses. A tentative possibility is that SSRIs alter the speed of learning from losses early on, inducing a shift from Pavlovian to instrumental learning when confronted with losses. The alteration in aversive Pavlovian bias was not directly linked to sertraline. However, sertraline appeared to modulate the association between Pavlovian inhibition and future treatment outcome. Reducing aversive Pavlovian control might hence promote approach responses in a punishing environment, facilitating unexpected rewarding experiences and thus helping to alleviate depressive symptoms.

4.1 Limitations

Inclusion in the trial was based on clinical equipoise, i.e. inclusion was based on an uncertainty whether medication could clinically be help for a particular person. This may have decreased the power to detect difference from placebo. For mechanistic studies such as the current one, it could be better to study a cohort of typical responders, i.e., patients who are prescribed medication with clinical confidence.

Extensive validation analyses showed that task performance was frequently objectively poor resulting in a large fraction of the task runs being non-informative. Non-informative task runs had to be excluded from analyses because formally they cannot provide information about cognitive mechanisms. We attempted to address this by correcting for baseline variables that were significantly associated with non-informative task runs. The sertraline and the placebo group in the final informative sample continued to be matched on baseline characteristics. Nevertheless, the exclusion of data has severely curtailed the power in the study. Furthermore, because non-informative data was more common in the drug than the non-drug arm, a causal interpretation is no longer warranted.

The poor task performance has important implications for future mechanistic research in this domain. Although the task has been extensively used in laboratory studies[24], combined with neuroimaging[99], pharmacological[13] and other interventions and adapted[100,101,59], it did not prove effective in a longitudinal clinical trial. This reinforces the paramount importance of acceptability and effectiveness testing of cognitive measurements for translational research and calls for an involvement of stakeholders in the design of research tasks.

The relationships between cognitive mechanisms and symptoms were weak. This probably reflects more general findings in the field[65], but also the specific limitations around data quality mentioned above which limit the strength of possible associations[102]. We also note that our computational modelling approach was very conservative in that all parameters were allowed to change freely between participants and sessions, with no constraints for within-participant data.

4.2 Conclusion

In conclusion, this was the first large-scale examination of specific reinforcement learning processes in a pragmatic RCT for depression. Specific reinforcement learning mechanisms did show a relationship to aspects of depression and anxiety and its treatment with SSRIs, but this was weak and not as hypothesized a priori. Sertraline influenced aversive processing in the first two treatment weeks by altering how participants learn to execute a passive or active action to avoid loss. Moreover, symptoms were associated with aversive processing but how this relationship relates to SSRI appears complex. The fact that almost half of the data was non-informative emphasizes the importance of developing patient-acceptable task probes.

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6 Author Contributions

GlL secured the funding of the clinical trial. GlL and LD were responsible for writing the detailed protocol, trial management and data collection. MM provided the software for Go/NoGo experiment and helped with data management. MM and LD contributed to the training of the researchers. JM and QJMH performed the computational modelling of the Go/NoGo task and planned the analyses with input from all authors. JM and QJMH wrote the initial draft of the manuscript. All authors contributed to and approved the final manuscript.

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8 Competing Interests

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