

SSRI enhances sensitivity to background outcomes and modulates response rates: A randomized double blind study of instrumental action and depression



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ABSTRACT

Serotonin reuptake inhibitors (SSRIs) have immediate effects on synaptic levels of serotonin but their therapeutic effects are often delayed. This delay has been suggested to reflect time required for new learning and therefore that SSRIs might be having effects on the learning process. We examined the effects of elevating serotonin levels, through short-term SSRI administration (escitalopram), on learning about perceptions of instrumental control. A randomised double blind procedure was used to allocate healthy people, categorised as mildly depressed (high BDI ≥ 10 ; $n = 76$) or not depressed (low BDI ≤ 5 ; $n = 78$) to either a drug (escitalopram, 10 mg/7 days) or placebo control group. Following treatment, participants were trained with a simple task that involved learning the effectiveness of an instrumental action (key press) and the background context at eliciting an outcome (auditory cue) where there was no programmed contingency. The effects of the drug were (i) to moderate response rates and (ii) to enhance sensitivity to the background or context rate of occurrence of the outcome. These findings suggest that serotonin modulates learning about the long-term rate of outcomes, which supports perception of instrumental control, and that this may provide a clue to the mechanism for supporting the development of the therapeutic effects of the drug.

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1. Introduction

Discovering the mechanism by which antidepressant drug treatments that target serotonin (e.g., selective serotonin reuptake inhibitors: SSRI; see Duman, Heninger, & Nestler, 1997) exert their therapeutic effects has been elusive (Sharp & Cowen, 2011). SSRIs maintain levels of serotonin in the synaptic cleft by inhibiting the serotonin transporter from attracting serotonin back to the pre synaptic neuron. The inhibition of the transporter is measurable soon after drug treatment but clinically significant effects are days if not weeks away (Harmer, Goodwin, & Cowen, 2009). One hypothesis has been that it is the longer-term psychological effects of serotonin levels on perceptions and learning that are part of the mechanism. Indeed, there is evidence that relearning the relations between positive and negative valenced emotional or

self-referential content is involved (Bruhl, Kaffenberger, & Herwig, 2010; Harmer, Shelley, Cowen, & Goodwin, 2004; Merens, Booij, Haffmans, & van der Does, 2008).

Serotonin has also been implicated in other aspects of learning (for a review, see Harvey, 2003). For example, serotonin is involved in responsiveness to punishment (for a review, see Cools, Roberts, & Robbins, 2008), contextual learning (Cassaday, Shilliam, & Marsden, 2001; Wilkinson, Humby, Robbins, & Everitt, 1996) and behavioural inhibition (Crockett, Clark, & Robbins, 2009; Robbins & Arnsten, 2009). There is also evidence for serotonin's involvement in learning tasks that generate emotional responses due to their ambiguity, for example because task requirement change across the course of the training regime (e.g., reversal learning; Clark, Cools, & Robbins, 2004). In the latter case, ambiguous cue learning also activates stress responses for which serotonin has been shown to play a role (Brigman et al., 2009; Clarke et al., 2005). Moreover, depression, one of the primary treatment targets for SSRIs, is associated with perceived changes in instrumental learning (Alloy & Abramson, 1979; Msetfi, Murphy, Simpson, &

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Kornbrot, 2005). Theories of learned helplessness (Seligman, 1975) and depressive realism (Alloy & Abramson, 1979) suggest that depression is associated with altered sensitivity to instrumental contingencies either as a cause or consequence of the disorder.

In a discrete trial instrumental contingency procedure, participants are provided a discriminative signal S_d for when an instrumental response (R) may result in an outcome (O). The probabilistic schedule involves varying the contingency between the response and the outcome, such that the difference in the likelihood of the outcome on trials in which the instrumental response is performed [$p(O|R)$] and the likelihood of the outcome on trials without a response [$p(O|noR)$] is the overall contingency. A positive contingency is one in which the likelihood of the outcome is greater when the response has been performed [$p(O|R) > p(O|noR)$]. The case of extreme ambiguity though, the zero contingency, is one in which the likelihood of the outcome is the same whether or not a response is emitted [$p(O|R) = p(O|noR)$]; Hammond, 1980].

Nonhuman and human animals are able to discriminate a wide range of these contingencies (e.g., Hammond, 1980; Wasserman, Elek, Chatlosh, & Baker, 1993). Accounts of this learning suggest that animals encode the two rates of outcome occurrences either in terms of competitive associations (e.g., Murphy & Baker, 2004; Rescorla & Wagner, 1972) or rates that can be compared as part of a decision process (e.g., Gibbon & Balsam, 1981). Regardless of the type of encoded representation, the strength of instrumental responding and judgements of instrumental action are closely tied to the corresponding strength of the background context as a signal for the outcome. Therefore, learning about the relative effectiveness of a response and the context in which the response occurs is a mechanism for contingency learning.

Of particular relevancy here is that serotonin has been linked to learning about context. For example, research with rats has shown that serotonin depletion, induced through lesions, impaired learning about contextual stimuli (e.g., Wilkinson et al., 1996; although see Cassaday et al., 2001). Initial research with human instrumental contingency learning, using acute tryptophan depletion (ATD) to deplete serotonin, was also suggestive of an effect on context learning (Chase et al., 2011). Chase et al. found that, for those with very low depression scores, ratings of the context's relation with the outcome, O, were low on ATD in comparison to the placebo.

However, these effects attributed to context learning could themselves be due to different aspects of learning. The first and most obvious factor is that serotonin might be involved directly in the memory of learning of the association between the context and the outcome, or in updating that learning once it has been established (Chase et al., 2011). Secondly, serotonin might be involved in peripheral changes in response sensitivity, which also affects exposure to context (e.g., Byrom, Msetfi, & Murphy, 2015). There is evidence, for instance, that people with depression learn about instrumental contingencies differently due to an overall reduction in responding (Blanco, Matute, & Vadillo, 2012). Therefore, studies of the effects of serotonin manipulations on instrumental learning need to investigate the relation between measures of context association and rates of responding.

In this study, we test the direct effect of serotonin on instrumental contingency learning and the interaction with existing levels of depressed mood. We used a behavioural task that asked participants to discover whether there was a contingency between their response and the outcome in specific contexts. In each of two conditions, the experimenter programmed contingency between the response and the outcome was zero and the rate at which the outcomes occurred varied (labelled as low and high outcome density conditions: Alloy & Abramson, 1979; Msetfi et al., 2005). On the basis of previous experiments, depressed mood was predicted to suppress the perception of instrumental contingency or

control (e.g., Msetfi et al., 2005). Participants were categorised on the basis of their mood state and then given either short-term exposure to an SSRI or placebo. We monitored rates of responding following explicit instruction to generate moderate rates of responding. We also monitored judgments of the control that the participants perceived between responding and the outcome, and that between the context and the outcome. We investigated whether SSRI administration altered responding and perceptions of control.

2. Methods

2.1. Participants

Participants were recruited through advertisements in local newspapers and college mailing lists. All gave written informed consent to take part in the study. This task was completed as a part of a multicentre study conducted in Kings College, London, Universities of Manchester and Oxford with full ethical approval from the respective local research ethics committees. Participants were screened with the Structured Clinical Interview for DSM-IV and excluded from participation if they demonstrated any current or previous history of AXIS-I psychiatric disorders (except depression in dysphoric volunteers), currently pregnant, or left-handed. All participants attended screening, randomisation and test visits. During screening, participants completed a number of measures including the National Adult Rating Test (NART: Nelson, 1982). Mood state was assessed using the Beck Depression Inventory and Hamilton Depression Scale (BDI: Beck, Ward, Mendelson, Mock, & Erbaugh, 1961; HAM-D: Hamilton, 1960) at all visits. Participants with a HAM-D score ≥ 24 at screening and/or randomisation visit were excluded from participation. Only participants with BDI ≤ 5 or ≥ 10 during the randomisation visit were included ($N = 164$). This is a standard procedure that reduces the frequency of false positives in identifying people as non-depressed or depressed (Bumberry, Oliver, & McClure, 1978). In addition, 10 participants did not follow the behavioural task instructions and responded at extremely high ($>75\%$ of trials) or very low rates ($<25\%$ of trials). These exclusions are important and ensure the contingency experienced by the participant is similar to that programmed by the experimenter. For instance, a participant that responds on every trial or no trials will not experience the outcome during both type of event but as long as there is some of both type of behaviour (withholding and acting) the contingencies programmed will be experienced by the participant. The final sample included 154 participants who ranged in age from 18 to 45 ($M = 24.34$, $SE = .44$), of whom 73 were men and 81 were women. Participant characteristics for each experimental group are given in Table 1 (BDI, HAMD, NART) and did not vary with drug treatment or the experimental manipulation, outcome density. All participants assigned to the high BDI groups scored significantly higher on BDI, HAMD and NART than low BDI groups (all $F > 4.47$, all $p < .04$).

2.2. Study design

2.2.1. Drug treatment and depression groups

Participants were categorised on the basis of their scores on the BDI, low BDI ($BDI_{rand} \leq 5$; $n = 78$) or high BDI ($BDI_{rand} \geq 10$; $n = 76$), with men and women being equally distributed across groups, $\chi^2(1) = .92$, $p = .34$. A double blind randomised design was used and participants either received 7 days of either placebo or escitalopram at 10 mg per day (recommended initial dosage for depression treatment). Test day was on the 7th day from their first administration. This time frame and dosage were chosen as it is

Table 1
Participant characteristics (BDI, HAMD, NART) and frequencies (n) for each experimental group. Values in parentheses refer to the standard error of the mean.

BDI group ^a	Drug group	Outcome density	
		Low	High
Low BDI	Placebo	n = 19 BDI = .68(1.05) HAMD = .05(.76) NART = 116.22(1.16)	n = 19 BDI = .68(1.05) HAMD = .16(.76) NART = 116.52(1.16)
		n = 18 BDI = .47(1.11) HAMD = .05(.76) NART = 116.38(1.23)	n = 22 BDI = .36(.97) HAMD = .16(.76) NART = 118.04(1.08)
	Escitalopram 10 mg	n = 22 BDI = 17.09(.97) HAMD = 9.05(.71) NART = 113.94(1.08)	n = 15 17.87(1.18) HAMD = 9.40(.86) NART = 114.56(1.31)
		n = 14 BDI = 18.86(1.22) HAMD = 7.40(.66) NART = 115.01(1.35)	n = 25 BDI = 16.52(.91) HAMD = 10.29(.89) NART = 116.60(1.01)
High BDI	Placebo	n = 22 BDI = 17.09(.97) HAMD = 9.05(.71) NART = 113.94(1.08)	n = 15 17.87(1.18) HAMD = 9.40(.86) NART = 114.56(1.31)
		n = 14 BDI = 18.86(1.22) HAMD = 7.40(.66) NART = 115.01(1.35)	n = 25 BDI = 16.52(.91) HAMD = 10.29(.89) NART = 116.60(1.01)
	Escitalopram 10 mg	n = 22 BDI = 17.09(.97) HAMD = 9.05(.71) NART = 113.94(1.08)	n = 15 17.87(1.18) HAMD = 9.40(.86) NART = 114.56(1.31)
		n = 14 BDI = 18.86(1.22) HAMD = 7.40(.66) NART = 115.01(1.35)	n = 25 BDI = 16.52(.91) HAMD = 10.29(.89) NART = 116.60(1.01)

^a Note that Low BDI participants received a BDI score of ≤5 whereas High BDI participants received a BDI score of ≥10.

consistent with the duration of SSRI treatment after which depressed patients' depression ratings begin to reduce (see Harmer & Cowen, 2013).

2.2.2. Behavioural task

The computerized learning task was programmed using visual basic (REALbasic, 2009, release 2.1) software as reported elsewhere (e.g., Msetfi, Wade, & Murphy, 2013). Participants were required to learn the relation between pressing a key on the keyboard (the spacebar) and the occurrence of an auditory cue presented through the computer speakers. During each trial, a simulated button appeared on the screen for 3 s during which time participants chose whether or not to press the button using the keyboard. The auditory outcome was programmed to occur on the basis of probability and it did so at the end of a 3 s limited hold period (for a total of 2 s), or else no sound was presented for 2 s before the start of the next trial. Each of 40 trials was separated from the next by a 15 s inter-trial-interval (ITI). Two dependent measures were recorded. First, the probability of responding was measured as the number of trials on which the button was pressed versus the total number of experienced trials. As in other similar studies (Alloy & Abramson, 1979; Msetfi et al., 2013), participants were instructed to press the button on approximately half of trials in order that they might have sufficient experience on which to base judgements. Secondly, participants were required to make explicit ratings of the effectiveness of their own actions ('action ratings') in controlling the outcome, as well as how causal the background context was ('context ratings'), in signalling the outcome. Ratings were made by moving a on screen slider on a numeric scale where the range of possible values varied from +100, labelled 'totally control', through 0, labelled 'no influence', to −100, labelled as 'totally prevent.'

The contingency between actions and outcome was determined by the difference between the probability of the outcome on trials in which the participant performed the response [$p(O|R)$] and the probability of the outcome on trials with no response [$p(O|NoR)$]. The difference between these two probabilities, ΔP is a measure of the overall contingency (Allan, 1980). For all participants in this study, the two probabilities were always equal and therefore the contingency $\Delta P = 0$. Participants had no control over the outcome. However, for one group of participants the probability of outcome on any given trial was low, $p = .25$, while for the other group, the probability was high, $p = .75$. The cover story (described in Msetfi et al., 2013) presented to participants was to imagine that they were learning about a faulty button that could be pressed (action) to turn on auditory music (outcome). Participants were told that the button may only work intermittently and that sometimes the outcome might come on without pressing the button.

3. Results

3.1. Probability of response

The probability of a response was calculated for each participant [$p(R) = n \text{ action trials} / \text{total trials } 40$], see Table 2, and analysed using a between subjects analysis of variance. The analysis showed that there was a higher probability of responding in the low outcome density ($M = .53, SE = .089$) than in the high outcome density condition ($M = .48, SE = .084$), $F(1, 138) = 13.68, p < .001, \mu^2 = .09$. There was also a significant BDI by drug treatment interaction, $F(1, 138) = 5.94, p = .016, \mu^2 = .041$. The data relevant to this interaction are displayed in Table 2 and show that there was a significant effect of BDI group on $p(R)$ in the placebo condition, $F(1, 146) = 7.09, p = .009, \mu^2 = .046$, such that low BDI participants responded

Table 2
Probability of making a response as a function of outcome density (OD), drug and BDI group. Values for standard errors of the mean are shown in parentheses.

Outcome density	Drug group			
	Placebo		Escitalopram 10 mg	
	Low BDI	High BDI	Low BDI	High BDI
Low OD	.56 (.020)	.51 (.018)	.52 (.020)	.54 (.023)
High OD	.50 (.020)	.45 (.022)	.46 (.018)	.49 (.017)

NB: Low BDI participants received a BDI score of ≤5 whereas High BDI participants received a BDI score of ≥10.

at a higher level than high BDI participants. However, this was not the case in the drug condition, $p = .18$, as the drug affected $p(R)$ for both high and low BDI participants $F(1,146) = 3.94$, $p = .049$, $\mu^2 = .026$; $F(1,146) = 4.18$, $p = .043$, $\mu^2 = .028$. This means that when participants were taking the drug there was no difference in response probability, suggesting that the drug acted to stabilize responding. For low BDI participants, responding was less on the drug than on the placebo, whereas for high BDI participants their response levels were higher on the drug than the placebo.

3.2. Control ratings

In addition to responding, participants provided ratings of perceived control of the action and the context at producing the outcome. We analysed the ratings data using a mixed factorial analysis of variance. Judgement (response or context) was the repeated measures factor, and between subjects factors were drug treatment (escitalopram 10 mg, Placebo), BDI (low, high), gender (male, female) and outcome density (low, high). In this analysis, in order to control for any variations in experienced contingency across participants, the individual experienced contingency for each participant was included in the model as a covariate ($M = -.002$, $SE = .014$). Initial analyses showed there were no significant effects or interactions involving any of the experimental manipulations on this particular variable, all $ps > .2$, so inclusion of the covariate is justified (Miller & Chapman, 2001).

Overall, there was a significant 4-way interaction between drug treatment, gender, outcome density and cue, $F(1,137) = 4.28$, $p = .04$, $\mu^2 = .03$. This particular interaction was not affected by mood level because the highest level 5-way interaction was not reliable, $F < 1$. These analyses, as we will go on to explain, revealed two distinct patterns of drug and mood effects. Firstly, the analysis for the placebo group showed strong discrimination between action and context ratings, $F(1,71) = 19.74$, $p < .001$, $\mu^2 = .22$, and this cue effect did not depend on outcome density, $F(1,71) = 1.45$, $p = .2$, $\mu^2 = .02$ (see Fig. 1). In the drug treatment group, both the cue effect, $F(1,75) = 25.26$, $p < .001$, $\mu^2 = .25$, and density by cue interaction were significant, $F(1,75) = 14.93$, $p < .001$, $\mu^2 = .17$. This was because the cue effect was large and significant in high outcome density groups, $F(1,46) = 56.14$, $p < .001$, $\mu^2 = .55$, but not reliable in low outcome density groups, $F < 1$. In addition, the data split by drug group showed a gender effect was only present in the placebo condition, where females tended to make higher ratings

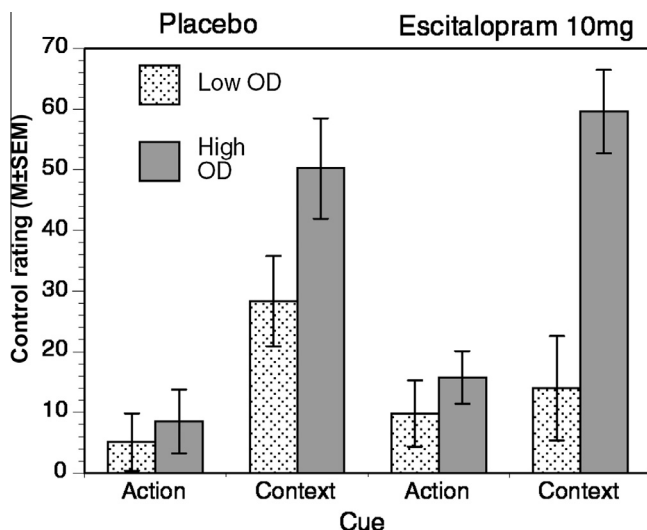


Fig. 1. Mean ratings of control as a function of drug group and outcome density (OD). Error bars correspond to the standard error of the mean.

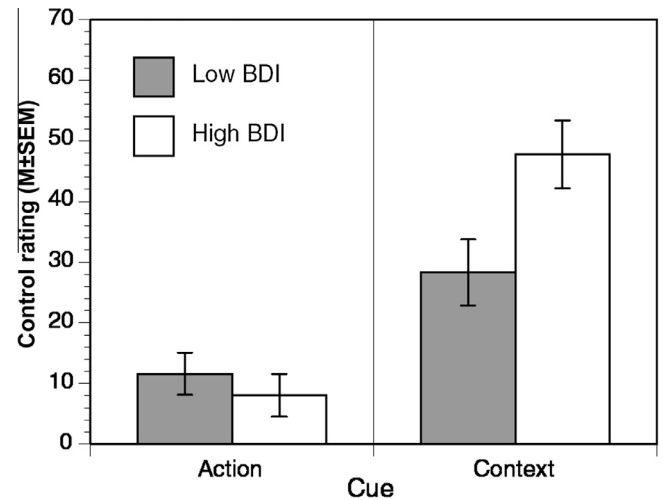


Fig. 2. Mean control rating for action and context as a function of BDI group. Error bars correspond to the standard error of the mean.

than males, $F(1,71) = 5.97$, $p = .02$, $\mu^2 = .08$. In general, both placebo and drug groups considered that the context was more related to the occurrence of the outcome than their response, this was expected since in both contingency conditions participants behaviour could not increase the likelihood of the outcome. However, the drug group in comparison to the placebo group demonstrated greater discrimination between their action as the cause of the outcome and the context, at the higher levels of outcome density. Overall, the drug seems to have contributed to a learning effect that caused greater sensitivity to the different background rates for the outcomes.

In addition to the effects of drug group, we also found evidence that depressed mood was related to increased perception of context control over the outcome (see Fig. 2). BDI group affected the difference between action and context ratings, $F(1,137) = 5.38$, $p = .02$, $\mu^2 = .04$; this interaction was independent of both outcome density, treatment, and the combination of the two variables, all $Fs < 1$. These data are shown in Fig. 2. For the Low BDI group, ratings reliably discriminated between action and context, $F(1,137) = 9.50$, $p = .002$, $\mu^2 = .065$, but discrimination was smaller than in the high BDI group, in which the cue effect was large, $F(1,137) = 40.38$, $p < .001$, $\mu^2 = .23$. Moreover, context ratings were significantly higher in the high BDI than low BDI groups, $F(1,137) = 5.22$, $p = .02$, $\mu^2 = .04$. This was not the case for action ratings, $F < 1$. Therefore, depressed mood corresponded to higher context ratings irrespective of outcome density or drug administration.

3.3. Mediation analysis

Given previous research linking response rates to context sensitivity (Byrom et al., 2015) and depression (Blanco et al., 2012), and the preceding results that suggest a drug effect on levels of responding and sensitivity to the context, we explored the links between drug treatment, BDI, $p(R)$ and perceived context sensitivity using a moderated mediation analysis. Mediation analysis uses regression to work out the causal or directional relation between factors. In order to do this, we calculated a raw difference score, which is a measure of control that contrasts sensitivity to the context with the response, such that positive values represent less perceived control (context minus response rating). These data were then entered into a conditional mediation model (Preacher, Rucker, & Hayes, 2007) using PROCESS in SPSS (version 20). This analysis tested the conditional effect of drug treatment on the indi-

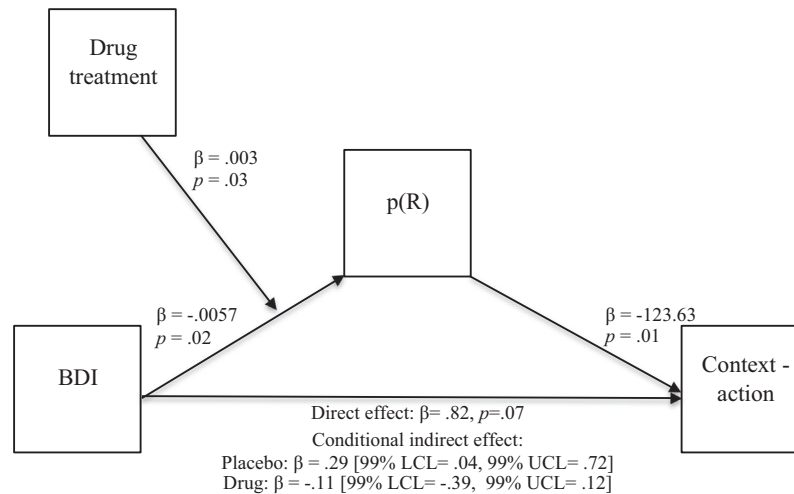


Fig. 3. Indirect effect of BDI score, through probability of response [$p(R)$], on the difference between context and action ratings, conditional upon drug treatment group.

rect effect of BDI score (as a continuous variable rather than group) on ratings through $p(\text{response})$ (see Fig. 3).

The results show that in general, higher BDI scores are consistent with a lower probability of response ($\beta = -.006$, $p = .02$), and that a lower probability of response predicts higher context rating ($\beta = -123.63$, $p = .01$). However, drug treatment also moderated these effects. For people on the placebo, higher BDI scores predicted greater positive discrimination between context and action ratings, but this effect was completely mediated through the lower response probability ($\beta = .29$, 99% CL [.04, .72]). However, when on the drug, probability of response did not mediate the BDI and judgement relationship ($\beta = -.11$, 99% CL [-.39, .12]). This finding is also consistent with the mood dependent drug effect on behaviour levels reported above.

4. Discussion

The findings of this study show that the effects of the SSRI escitalopram and depressed mood on instrumental control primarily involve changes in sensitivity to the background rate of occurrence of outcomes. Seven-day escitalopram administration increased discrimination between action and context ratings, particularly when outcomes occurred frequently, and enhanced sensitivity to the density of outcomes occurring in the experimental context. These findings are consistent with the idea that increased levels of serotonin improve environmental outcome sensitivity and are inconsistent with any notion that the drug had a nonspecific effect on perceptions of control.

Importantly, however, escitalopram administration counteracted one of the key effects of depressed mood. This was that those with higher levels of depressed mood tended to rate context as a stronger controller of outcomes than their own actions, and this effect was entirely mediated through low rates of responding. In other words, higher levels of depression resulted in low levels of behaviour and a strong perception of the background context as a cause of the outcome rather than instrumental action. Escitalopram administration influenced levels of behaviour. In those with high depression scores, low response rates seen in the placebo condition, and in other research (Blanco et al., 2012) were higher on the drug and similar to low BDI response rates. Interestingly, the opposite pattern was evident in those with low depression scores. Thus, increased levels of serotonin whilst on the drug eliminated the indirect relation between higher levels of depression and low

contrast between the background context and the instrumental action as causes of the outcome.

These findings add to previous research on serotonin and learning and the implication of this is that one of the effects of SSRIs is to moderate learning about instrumental contingencies. For example, the findings of a previous study involving serotonin reduction using tryptophan depletion and contingency learning with neutral stimuli are consistent with an effect on perceived control mediated by context learning (Chase et al., 2011). In that study, reducing serotonin levels in low BDIs reduced context ratings in contrast to action ratings, but only when participants did have control over the outcome. Consistent with that, in the present experiment, increasing serotonin levels produced enhanced response-context discrimination, and outcome density sensitivity in context ratings. However, this was an effect that was evident in conditions of no control.

The findings of this study are also consistent with the idea that learning includes a requirement to code the baseline or long term outcome rate. Previous research has explicitly suggested that the tonic component of the serotonin signal codes long-run average reward or, as described here, outcome density (Daw, Kakade, & Dayan, 2002; see also Dayan & Balleine, 2002). Furthermore, rodent research shows that escitalopram has an excitatory effect on firing patterns of dopamine in the ventral tegmental area (Schilström et al., 2011), which also codes reward predictor error in learning (Hollerman & Schultz, 1998). This is relevant, because prediction error is the incremental output of associative models that explain contingency learning (Baker, Murphy, & Vallee-Tourangeau, 1996). In the present experiment, escitalopram effects were revealed in context ratings suggesting that some effects of serotonin may be more about processing or learning about the density of rewards or outcomes occurring over time in that context rather than simply representing the context.

The present findings also suggest an additional mechanism through which depression, and changes in serotonin levels specifically, affect perceived control. In this study and elsewhere (e.g., Blanco et al., 2009, 2012), higher levels of depression reduced levels of responding, here producing stronger context-action discrimination (i.e. context ratings > action ratings). It could be argued that reduced levels of behaviour would allow a person more experience of the background context on its own and the opportunity to sample outcomes occurring in the absence of the action, thus, in associative terms, strengthening the context-outcome relationship. In the present study, increasing levels of

serotonin through escitalopram administration produced higher response rates in mildly depressed participants than those recorded on the placebo. Conversely, non-depressed participants response probability was lower on the drug than the placebo. Thus on the drug there were no response rate differences between the mildly depressed and non-depressed groups and behaviour did not mediate the depression and judgement relationship. This finding is also consistent with other evidence for reduced activity levels in depression (Camacho, Roberts, Lazarus, Kaplan, & Cohen, 1991) which also mediate depression effects on contingency learning (Blanco et al., 2012). However, our findings show that this pattern can be alleviated with the administration of SSRIs, further suggesting that serotonin plays a modulating or stabilizing role on behavioural activity in a manner dependent on pre-existing depression levels.

A key difference between this work and most previous studies is that effects of depressed mood have been shown on action ratings specifically (e.g., Alloy & Abramson, 1979; Blanco et al., 2012; Msetfi et al., 2005; although see Chase et al., 2011). In this study depression, and indeed SSRI effects, were focussed on context ratings. We note, however, that while previous studies involved action and outcome scenarios in which the context was implicitly present, it was not explicitly described or rated as part of the experimental task. It is possible then that when context is implicit in the experimental scenario and thus the rating that is made, as in real life, participants' ratings of their own control over outcomes also implicitly incorporate the context–outcome connection (i.e. control rating = context–action rating).

The focus on context ratings was not entirely unexpected as this was the case in our previous work. For example, Chase et al., 2011 found that serotonin depletion via ATD enhanced the discrimination between action and context specifically in positive (but not zero) contingency conditions. In the current study, positive contingencies were not included but we found that increased serotonin levels enhanced action–context discrimination and outcome rate sensitivity in a zero contingency condition. At first glance, these findings may appear incompatible. However, consider that in positive contingency conditions, in order to produce the enhanced discrimination effect, ATD could either improve the extinction of the context outcome relation or weaken the initial acquisition of the context outcome relation. In contrast, in zero contingency conditions, in order to improve both discrimination AND outcome sensitivity as in the current study, escitalopram would have to improve acquisition of the context–outcome relation. Thus serotonin depletion via ATD and serotonin increase due to drug administration can both improve action–context discrimination but these effects will be dependent on the contingencies involved. Taken together, the current findings are consistent with previous research in rats showing that serotonin depletion interferes with the acquisition of context associations (Wilkinson et al., 1996) and that SSRI administration increases contextual conditioning (Cassaday & Thur, 2015).

This analysis of depression and drug effects on context ratings is based on the assumption that the context rating represents the strength of the context outcome relation or association. Some learning theories (e.g., Rescorla & Wagner, 1972), but not all (e.g., Miller & Matzel, 1988), would postulate that an experimental effect on the context association should be mirrored in the strength of the action association due to a process of cue competition. Whilst overall we can see evidence in these data for cue competition (ie context > action in zero contingency conditions), the experimental manipulations here affected one but not both variables suggesting the independence of action and context ratings. Although a considerable body of research evidences cue competition in contingency learning (e.g., Baker, Mercier, Vallee-Tourangeau, Frank, & Pan, 1993; Chapman & Robbins, 1990;

Dickinson, Shanks, & Evenden, 1984; Vallée-Tourangeau, Murphy, Drew, & Baker, 1998), other studies do not, and describe a non-competitive learning process (e.g., Haselgrove & Evans, 2010; Matute, Arcediano, & Miller, 1996).

Earlier we hypothesised that the cognitive and neurochemical intersection in depression is evident at the level of processing context information. The data we describe here do support this hypothesis. The results of this study have shown that the effects of depression and short-term administration of escitalopram are not simply obverse as might have been a reasonable prediction. On the contrary, the effects of depression and serotonin are distinct though revealed by the same medium, the relation between context and outcome. Depression may be consistent with a characteristic reduction in behaviour and motivation (e.g., Seligman, 1967) but this results in a corresponding increased sensitivity to the general predictiveness of context. In this experiment, depressed mood reduced levels of behaviour and stronger context ratings, possibly allowing the associative link between context and outcome to develop strongly (e.g., Rescorla & Wagner, 1972). Escitalopram administration not only diminished the link between depression, activity levels and judgements but also resulted in a greater sensitivity to levels of outcome occurrence over time as defined by their occurrence in a context. It is tempting to speculate at this point that herein may lie some of the variability in the psychological effects of antidepressant drugs. If the psychological effect of the drug is exerted, at least partially, through learning about rates of outcomes occurring in the environment, then any subsequent impact of this on perceived control would therefore be dependent on the outcome contingencies to which the patient was exposed.

One of the major treatments of depression, specifically the SSRI escitalopram, does not act to enhance the sense of control directly, at least as measured here. The effect of the drug was to modulate behaviour and to enhance sensitivity to how well the context signalled the occurrence of outcomes. Given that the availability of outcomes will vary between situations and individuals, there is likely to be variability in the effect that this drug has on people's feelings of personal control or agency. Although the focus of much research on serotonergic function in depression has focussed on emotional stimuli (e.g., Bruhl et al., 2010; Harmer et al., 2004; Merens et al., 2008), here we show that learning about neutral, everyday events, is also affected by the experience of depression and impacted by the administration of antidepressants. These findings give further insight into the several subtle ways in which the cognitive effects of serotonin intervention have their therapeutic effect on depression over time.

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