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ORIGINAL INVESTIGATION

5-HT modulation by acute tryptophan depletion of human instrumental contingency judgements

Henry W. Chase · Molly J. Crockett · Rachel M. Msetfi · Robin A. Murphy · Luke Clark · Barbara J. Sahakian · Trevor W. Robbins

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Abstract
Introduction The concept of 'depressive realism', that depression leads to more accurate perception of causal control, has been influential in the field of depression research, but remains controversial. Recent work testing contingency learning has suggested that contextual processing might determine realism-like effects. Serotonin (5-hydroxytryptamine, (5-HT)), which is implicated in the pathophysiology of depression, might also influence contextual processing. Using acute tryptophan depletion (ATD), we tested the hypothesis that dysfunctional serotoninergic neurotransmission influences contingency judgements in dysphoric subjects via an effect on contextual processing.

Materials and methods We employed a novel contingency learning task to obtain separate measures (ratings) of the causal effect of partcipants' responses and efficacy of the background context over an outcome. Participants, without a history of depression, completed this task on and off ATD in a double-blind, placebo-controlled, within-subjects design.

Results As with other work on contingency learning, the effects of ATD were related to baseline mood levels. Although no overall effects of ATD were observed, the subgroup of participants with low Beck depression inventory (BDI) scores showed reduced ratings of contextual control and improved accuracy of contingency judgements under positive contingencies following ATD, compared to placebo. High BDI

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H. W. Chase · M. J. Crockett · L. Clark · B. J. Sahakian · T. W. Robbins
Behavioural and Clinical Neuroscience Institute,
Department of Experimental Psychology,
University of Cambridge,
Downing Street,
Cambridge CB2 3EB, UK

H. W. Chase (✉)
Room B60 Psychology, School of Psychology,
University Park, University of Nottingham,
Nottingham NG7 2RD, UK
e-mail: henry.chase@nottingham.ac.uk

M. J. Crockett · L. Clark · T. W. Robbins
Department of Experimental Psychology, University of Cambridge,
Downing Street,
Cambridge CB2 3EB, UK

R. M. Msetfi
Division of Health Research, School of Health and Medicine,
Lancaster University,
Lancaster, UK

R. A. Murphy
Department of Experimental Psychology, University of Oxford,
South Parks Road,
Oxford OX1 3UD, UK

B. J. Sahakian
Department of Psychiatry,
University of Cambridge School of Clinical Medicine,
Addenbrooke's Hospital,
Cambridge, UK

participants demonstrated low accuracy in contingency judgements, regardless of serotoninergic status.
Conclusions No effect of ATD on contingency judgements was observed in the group as a whole, but effects were observed in a subgroup of participants with low BDI scores. We discuss these data in light of the context processing hypothesis, and prior research on 5-HT and depressive realism.

Keywords Serotonin · Control · Learning · Depression

Introduction

Depression is a debilitating disorder with wide-ranging motivational, cognitive and behavioural consequences that has been linked to reduced levels of serotonin (5-hydroxytryptamine, (5-HT)). In this study, we explore whether manipulation of 5-HT levels is related to changes in learning that have been observed in depression. A common symptom reported by patients is the perception that their control over events is diminished, which is thought to be related to feelings of hopelessness (Abramson et al. 1989). This loss of efficacy pervades many aspects of life and has been linked to the ability to learn the actual causal relation between events and their outcomes. For example, Alloy and Abramson (1979) carried out several experiments that involved varying the degree of control that pressing a button had over the illumination of a light. They found that mildly depressed or dysphoric participants differed from nondysphoric participants in their ratings of causal control. In the critical conditions when there was no objective contingency between action and outcome, and participants should have felt that they had no control over the light turning on, those who were dysphoric believed they had less control over the light than the nondysphoric participants, who tended to perceive a positive relationship between their behaviour and the light. This result, subsequently replicated (Benassi and Mahler 1985; Martin et al. 1984), has had an impact on theories of depression, as well as the methodology and understanding of human contingency learning (Shanks 2007). The effect is called 'depressive realism', because it was thought that depression leads to a more accurate or balanced evaluation of how little control people actually have over events.

One hypothesis attributes this effect to processing of context cues rather than any ability to perceive action–outcome relations more accurately. Normally, people are likely to perceive their actions as having control over outcomes to the extent that the outcome does not occur when they do not act. In this way, judgements of control are influenced by sensitivity to the presence of possible alternative causes of the outcome. The more negative evidence they receive about other possible causes of the outcome, the stronger becomes the association between action and outcome. On the other hand, the association between action and outcome diminishes if the outcome is strongly predicted by context alone. Thus, differences in judgements of action–outcome relationships may result from differences in context processing. More experience with the context and the absence of any outcomes will strengthen the association between the action and the outcome, this effect being modelled by a standard computational account of associative learning (e.g., Rescorla and Wagner 1972). To test the context exposure hypothesis, Msetfi et al. (2005, 2007) manipulated the duration of the intertrial interval (ITI) and found that, unlike dysphoric participants, the judgements of control in nondysphoric participants increased as a result of increased context exposure during the ITI. This result suggests that depression is accompanied by a reduced sensitivity to learning about cues that are outside personal control.

The aim of the present study was to explore the neurochemical basis of these biases using a 5-HT manipulation. Given the hypothesis that depression is accompanied by serotoninergic dysfunction, we tested the effects of acute tryptophan depletion (ATD) on contingency learning. ATD is a dietary manipulation, usually administered as a drink which reduces brain 5-HT levels (Carpenter et al. 1998). It has been proposed to model aspects of the serotoninergic dysfunction which accompanies depression (Cowen 2008)—although without affecting mood in participants without a history of depression (Ruhe et al. 2007)—and is also a means of evaluating the contribution of 5-HT to cognition in general (Fusar-Poli et al. 2006; Mendelsohn et al. 2009). Our expectations regarding serotoninergic contributions to contingency learning were also shaped by learning studies carried out with experimental animals. Exploiting the fact that the trace conditioning procedure results in increased contextual conditioning compared to the delay conditioning procedure, Wilkinson and colleagues (1995) showed that forebrain 5-HT depletion reduced avoidance of contexts in which rats experienced trace conditioning compared to delay conditioning, via a place preference test. In a second study, the authors observed that 5-HT release in the hippocampus was increased by contexts in which rats had experienced aversive trace conditioning, but less so in contexts in which rats had experienced aversive delay conditioning (Wilkinson et al. 1996). Together, these studies support the notion that depression-linked alterations in context learning might be related to reduced levels of 5-HT. This study was designed to test this hypothesis.

Participants completed an action–outcome contingency learning task both on and off ATD. The task required learning both a positive and an uncorrelated relationship

between an action and an outcome signalled by the context in which the task was presented. Hence, the paradigm bore similarities to that of Wilkinson and colleagues, in that, participants were exposed to different conditioning procedures in two contexts (the cover story described two different rooms in a house). The task was designed to obtain estimates of participants' ratings of their perceived instrumental control (action–outcome) and perceived contextual control (context–outcome) over an outcome in order to attempt to measure both action–outcome and context–outcome associations. When the participants were exposed to a positive contingency between action and outcome, we expected instrumental control ratings to increase and contextual control ratings to decrease, consistent with greater learning of the action's effectiveness compared to the context. Presented with an uncorrelated or zero contingency, we expected the action–outcome rating to be relatively low. However, the context–outcome rating might be expected to increase as the contingency between context and outcome is greater under zero contingencies than positive contingencies: retrieval of the positive contingency context might influence learning about the zero contingency context and hence, cause a strengthening of context–outcome associations in the latter context. Consequently, we predicted a contingency by rating type interaction as evidence of learning performance on the task.

We also recorded Beck depression inventory (BDI) scores (Beck et al. 1961), a measure of depressive symptomatology, as participants recruited from a normal population can show substantial variance in this measure. Due to the literature on the effect of differences in BDI on contingency learning (Alloy and Abramson 1979; Msetfi et al. 2005, 2007), we also considered the possibility that BDI might moderate the effects observed. In the supplementary information, we include an analysis of our pilot data with the task, demonstrating that participants split on a relatively low BDI criterion show a different pattern of rating. We use the same BDI criterion to analyse our ATD/placebo data (presented in "Effect of BDI").

Methods

Participants

The experimental protocol was approved by the Norfolk Research Ethics Committee. Seventeen healthy participants were screened for neurological and psychiatric disorders, and gave written informed consent before participating in the study. Exclusion criteria included history of cardiac, hepatic, renal, pulmonary, neurological, psychiatric or gastrointestinal disorders, medication/drug use, and personal or family history of major depression or bipolar affective disorder. Participants were financially compensated for participating. After the screening interview, participants were assigned to receive either the tryptophan-depleting drink (ATD) or the placebo mixture on the first session in a double-blind, approximately counterbalanced order. The causal learning task was administered as part of a larger cognitive assessment. Two subjects were excluded from the analysis of behavioural data, as they did not follow instructions. One of these participants did not respond at all in one condition and the other responded on 93% of trials resulting in limited exposure to no action/context only experience.

General procedure

Participants completed the contingency learning task on two separate sessions, each separated by at least 1 week. Participants were asked to abstain from food, alcohol and caffeine from midnight before each session. Testing sessions commenced in the morning (between 0830 and 1030 hours). Upon arrival, participants completed self-report questionnaires (trait measures and baseline mood rating), gave a blood sample, and ingested either the placebo or the tryptophan-depleting amino acid drink. After a resting period of approximately 5.5 h (to ensure stable and low tryptophan levels), participants completed a second mood rating questionnaire, gave a second blood sample, and completed the test battery. Self-report mood was assessed at three other time points during the battery.

Behavioural task

A computerised causal learning task, programmed in a version of Visual Basic software (Realbasic, version 2006) was administered on a Macintosh computer. The cover story required that participants imagine that they are in a house that has a hidden stereo system in each of the rooms. They have access to a remote control, on which there are buttons that can be pressed (action) to turn on music (outcome) in each of the rooms. Participants are informed that the residents of the house have reported that the remote control works intermittently in some rooms, and sometimes, the music switches on when no one is touching the remote control, so the remote control must be tested.

Therefore, during each experimental trial, participants entered one of two rooms, context X or Y, represented by pictures on the computer screen. The order in which these appeared was determined by a fixed, pseudorandom sequence. There was a period of 3-s during which they could choose whether or not to respond by pressing the relevant button on the remote control. If the music

switched on, it would do so at the end of the 3-s period (for 2 s), or else the room would remain quiet for 2 s. Each trial was 5 s long and was separated by a 15-s ITI which took place in another room (context Z). The entire procedure comprised 64 trials, of which half took place in context X and half in context Y. Contexts X and Y were represented as the yellow and green rooms for half the participants and the peach and blue rooms for the other half with appropriate counterbalancing of colours between X and Y. Context Z was represented by either a red or purple room. Participants were instructed to press the button on approximately half of trials in order to get an evenly distributed sampling of actions and outcomes upon which to base their contingency judgments. At the end of the procedure, participants were required to make ratings of the effectiveness of their actions (henceforth 'action ratings'), as well as the context's effectiveness (henceforth 'context ratings'), in producing the outcome. This rating was made by moving a slider on a standard 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.' Response rates were also recorded.

In this task, the causal relationships between the actions and outcome were calculated using the ΔP statistic. ΔP is measure of the one-way contingency between binary events and is the difference between the conditional probabilities of the outcome, given the occurrence and the non-occurrence of the action (Allan 1980). It yields a value that varies from +1 (perfect causal relationship) through 0 (no relationship) to −1 (perfect preventative relationship). We programmed that there be no relationship between action and outcome in context X and a moderately causal relationship in context Y. Programmed trial frequencies are shown in Table 1.

Table 1 Programmed frequency of each trial type in context X and context Y

	Zero context X	Positive context Y
Action (+)	12	12
Action (−)	4	4
No Action (+)	12	4
No Action (−)	4	12
p (outcome|action)	0.75	0.75
p (outcome|no action)	0.75	0.25
p (outcome)	0.75	0.5
ΔP	0	0.5

The + and − symbols refer to the presence and absence, respectively, of an outcome on a given trial. The exact trial type frequencies are dependent on response rates and are recorded by the computer software

Acute tryptophan depletion method

In the ATD procedure, tryptophan (TRP) was depleted by ingestion of a liquid amino acid load that did not contain TRP, but did include other large neutral amino acids (LNAAs). Amino acid mixtures (prepared by SHS International, Liverpool, UK) were in identical proportions to those used in previous studies (Young et al. 1985) and were as follows:

ATD: L-alanine, 4.1 g; L-arginine, 3.7 g; L-cystine, 2.0 g; glycine, 2.4 g; L-histidine, 2.4 g; L-isoleucine, 6 g; L-leucine, 10.1 g; L-lysine, 6.7 g; L-methionine, 2.3 g; L-proline, 9.2 g; L-phenylalanine, 4.3 g; L-serine, 5.2 g; L-threonine, 4.9 g; L-tyrosine, 5.2 g; and L-valine, 6.7 g. Total: 75.2 g.

Placebo: Same as ATD, plus 3.0 g of L-tryptophan. Total: 78.2 g.

For females, 20% reductions in the above quantities were used to account for lower body weight (Cools et al. 2008). The drinks were prepared by stirring the mixture and lemon-lime flavouring into 200 ml tap water.

Self-report measures

The positive and negative affect scale (PANAS; Watson et al. 1988) was administered on five separate occasions throughout the session. We analyzed the difference in PANAS positive and negative affect scores from two time points: immediately before drink ingestion, and immediately before the causal learning task. The BDI (Beck et al. 1961) was used to assess individual differences in depressive symptomatology.

Analysis of plasma samples

Blood samples (10 ml) were analysed to determine the total plasma TRP level and the TRP:ΣLNAA ratio. This ratio was calculated from the serum concentrations of total tryptophan divided by the sum of the large neutral amino acids (tyrosine, phenylalanine, valine, isoleucine, leucine) and is important because the uptake of TRP in the brain is strongly associated with the amounts of other competing LNAAs due to nonspecific transport across the blood–brain barrier. Venous samples were taken in lithium heparin tubes and stored at −20°C. Plasma TRP concentrations were determined by an isocratic high-performance liquid chromatography (HPLC) method of analysis. Plasma proteins were removed by precipitation with 3% trichlororacetic acid and centrifugation at 3,000 rpm, 4°C degrees for 10 min, then pipetted into heparin aliquots. An aliquot was diluted in mobile phase before injection onto the HPLC analytical column. Fluorescence end-point detec-

Table 2 Effects of drink and time on mood and tryptophan depletion, as measured by TRP:ΣLNAA ratio

	Positive mood ATD	Negative mood ATD	Positive mood placebo	Negative mood placebo	TRP:ΣLNAA ATD	TRP:ΣLNAA placebo
Time 1	3.91 (0.22)	1.25 (0.11)	3.70 (0.19)	1.15 (0.050)	0.14 (0.011)	0.12 (0.0010)
Time 2	3.74 (0.17)	1.10 (0.05)	3.83 (0.21)	1.06 (0.025)	0.024 (0.0072)	0.16 (0.028)

tion was used to identify TRP. Depletion data from one participant was missing.

Data analysis

Raw ratings of control were inputted into a repeated measures ANOVA, including the within-subject factors of contingency (zero, positive), rating type (action, context) and drink (ATD, placebo). Greenhouse–Geisser corrections were used where assumptions regarding homogeneity of variance were violated. Mood and the degree of TRP depletion were also analysed using ANOVA, including the factors time (before, after the session) and drink (ATD, placebo). Finally, an analysis was conducted in light of a possible effect of individual differences in depression: this is introduced and discussed further in the "Results" section.

Results

Demographic, mood and depletion data

Fifteen participants were included in the final analysis. Mean age was 26.6 years (SE 1.78) and the mean years of education were 17.4 (SE 0.5). A repeated measures ANOVA with treatment (ATD, placebo), time point (baseline, +5.5 h) and affect type (positive, negative) found no main effect of or interaction involving ATD on PANAS ratings of affect at time of testing (ATD by time: $F(1,14)=1.937$, $p=0.186$; $F(1,14)<1$ in all other cases). An effect of affect type was observed ($F(1,14)=305.509$, $p<0.001$), where positive mood was rated higher than negative mood. No other significant effects or interactions were observed. Mood rating data are presented in Table 2.

Biochemical results

The ATD procedure resulted in significant reductions in both plasma TRP levels and the TRP:ΣLNAA ratio. Change scores revealed an interaction between TRP:ΣLNAA reduction and drink ($F(1,12)=22.71$, $p<0.001$): the TRP:ΣLNAA ratio was reduced following the ATD drink ($t(13)=-10.88$, $p<0.001$), but not following the placebo ($t(13)=1.29$, $p=0.22$). Biochemical data are presented in Table 2.

Behavioural results

As predicted, a significant interaction between contingency and measure was observed ($F(1,14)=8.16$, $p=0.013$). Contrary to our predictions, however, we did not see an effect of tryptophan depletion on context ratings (ATD by measure interaction; ATD by measure by contingency interaction: $F(1,14)<1$ in both cases). Similarly, no main effect of ATD or contingency by ATD interaction was observed ($F(1,14)<1$ in both cases). Planned analysis of the separate contingencies, collapsed across drink, revealed that participants ascribed significantly greater causal control to action than context under positive contingency ($t(14)=3.939$, $p=0.001$), and numerically greater control to the context over action under zero contingency, but this effect was not statistically significant ($t(14)=-1.592$, $p=0.134$). Action ratings were larger under positive than zero contingencies ($t(14)=2.834$, $p=0.013$); context ratings were numerically, but not statistically greater under zero than positive contingencies ($t(14)=1.459$, $p=0.167$). Data are presented in Fig. 1.

Effect of BDI

It should be noted that the discrimination performance of the group as a whole, reflected in the contingency by

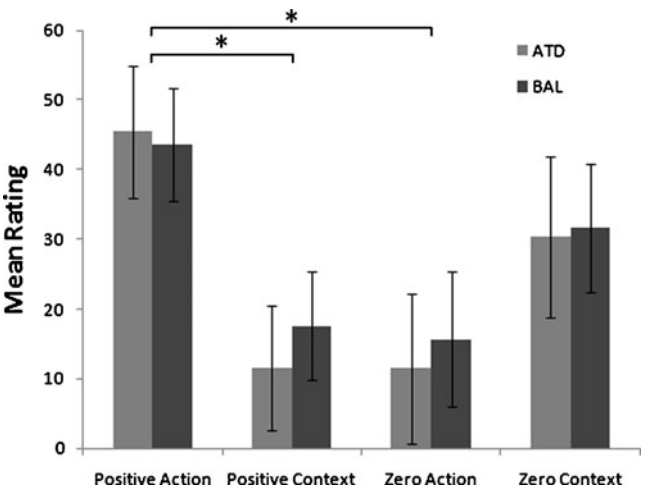

Fig. 1 Action and context ratings as a function of contingency, rating, and drink. *Dark grey bars* indicate ratings given after taking the placebo drink (BAL), *light coloured bars* represent ratings made after taking the ATD drink. Significant differences ($p<0.05$) between conditions (collapsed across drink) are marked with *asterisks*

measure interaction, was slightly less reliable than we had anticipated. In addition to the variability in discrimination performance, the participants' BDI scores were also quite variable. Reanalysis of our previous studies with the task had suggested that it might be sensitive to relatively small differences in BDI, with accurate discrimination performance only observed in participants with low (<6) BDI scores. This data is included with a detailed analysis in the supplementary information. A stronger test of our hypotheses could therefore be performed in a group which would show robust conditioning.

We consequently performed an analysis to investigate the potential moderating effect of BDI on the ATD effect. We performed a median split, categorising participants as either low BDI (BDI≤5, $n=7$) or high BDI (BDI=6–21, $n=8$) on this measure. The high and low BDI groups were matched for age ($t(13)<1$) and education ($t(13)=-1.4$, $p=0.2$). Each group had similar number of males and females (low BDI: three males; high BDI: two males).

To begin with, we performed a Friedman test on each group separately, testing the null hypothesis that the ratings from all of the conditions (drink, contingency, rating type) would be similar regardless of the experimental treatment. A significant difference between the conditions was observed in the low BDI group ($\chi^2=24.673$, d$F=7$, asymptotic $p=0.001$) but not the high ($\chi^2=2.527$, d$F=7$, asymptotic $p=0.925$); in other words, there was no evidence of differential performance between any of the conditions in the high BDI group and hence, little evidence of learning, consistent with the data presented in the supplementary information. The result of the test in the high BDI group also suggested that there was not a behavioural effect of ATD in this group: discrimination scores were numerically smaller on ATD than placebo.

We therefore focussed on the low BDI group (see Fig. 2) performing planned contrasts to assess the degree of learning, and to contrast the context and action ratings following the ATD or placebo treatment. As with the analysis from the full group of 15, no evidence of differential performance between action, context, or as a result of the ATD was observed on the zero contingency condition ($\chi^2=5.318$, d$F=3$, exact $p=0.153$), but differential performance between the conditions was observed at positive contingencies ($\chi^2=15.174$, d$F=3$, exact $p<0.001$). Separate investigation of the effect of ATD on the context and action ratings revealed that ATD reduced context ratings ($\chi^2=6.000$, d$F=1$, exact $p=0.031$), but had no effect on action ratings ($\chi^2=1.286$, d$F=1$, exact $p=0.453$). A significant difference between action and context ratings for the positive contingency room was observed only under ATD ($\chi^2=7.000$, d$F=1$, exact $p=0.016$), but not placebo ($\chi^2=3.571$, d$F=1$, exact $p=0.125$). ATD significantly increased discrimination scores (action–context) under positive contingencies, compared to placebo ($\chi^2=7.000$, d$F=1$, exact $p=0.016$).

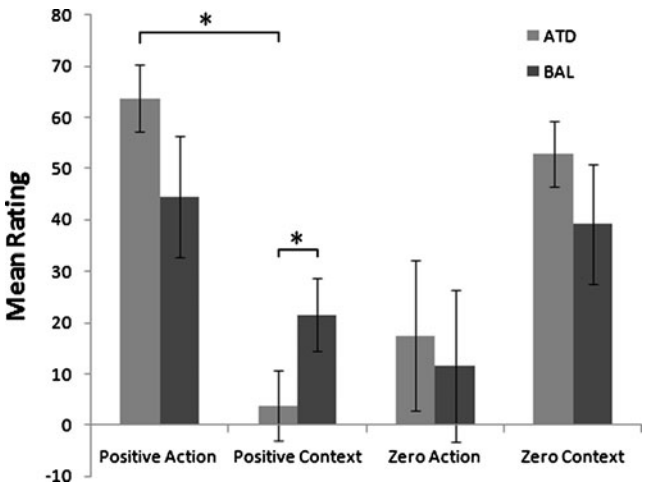

Fig. 2 Action and context ratings as a function of contingency, rating, and drink in the low BDI group alone. *Dark grey bars* indicate ratings given after taking the placebo drink (BAL), *light coloured bars* represent ratings made after taking the ATD drink. Significant differences ($p<0.05$) between conditions, describing an effect of the drink, are marked with *asterisks*

Summary

In the present study, we employed a novel contingency learning task to assess the effect of ATD on contextual judgments. The pattern of results produced by the task was broadly in line with our expectations, in that ratings of control over the outcome by action were greater than by context under positive contingencies. The reverse pattern was observed under zero contingencies, although the difference between the ratings was not significant. There was no effect of ATD on context or action ratings when the participants were considered as a whole, under either of the two contingencies employed. In light of our previous studies (see supplementary information), we performed an analysis in which we split the group by BDI score. ATD altered context ratings and enhanced discrimination, but only for the low BDI group, and only under positive contingencies. High BDI participants showed no evidence of discrimination between action and context as causes of the outcome, and showed no differential conditioning under either contingency, either following the ATD or placebo drink.

Discussion

In this study, we evaluated participants' judgements of their instrumental control versus perceived contextual control

over an outcome in a contingency learning paradigm while serotonin (5-HT) levels were manipulated using ATD on a within-subjects basis. As expected, a positive contingency between action and control was associated with higher ratings of control by the participant and weaker ratings of control by the context. As anticipated, the reverse pattern was seen under zero contingencies, although the effect was not significant.

We had set out to test the hypothesis that the ATD manipulation, as a model of depression, would selectively influence context learning with a related effect on the perception of action contingency. Across the entire sample, this hypothesised effect was not observed: all participants gave similar ratings of control of the outcome by action or context whether on ATD or placebo. However, a subgroup of participants with very low (<6) BDI scores did show a significant reduction in context ratings under positive contingencies. ATD also resulted in a nonsignificant increase in ratings of control under this contingency, and consequently an enhanced discrimination of the causal basis of the outcome (action > context) under positive contingencies was observed following ATD. In contrast, participants who scored equal to or above the median on the same depression measure displayed little ability to discriminate between their own control over outcomes, in contrast to that of the context. Their performance was not affected by ATD administration. These findings, although restricted to a subgroup of the sample, do nevertheless suggest that 5-HT might play a role in context learning, and that these effects may be moderated by depression score.

Although we did not see any evidence of a general ATD effect on ratings of contextual control, a parsimonious account of the effect of ATD we observed on contingency judgements in the low BDI group relates to the idea that 5-HT plays a role in the extinction of contextual associations. A key question arising from the data is why the effect of ATD should only be evident for positive contingencies. One important difference between the zero and positive contingency conditions is the availability of experience that weakens context associations in the form of non-reinforced, action-absent trials (see Baker et al. (in press) for a discussion). The positive contingency condition includes three times as many (12) of these trial types as the zero contingency condition, which includes relatively few (4; see Table 1). The reverse is true of trials that might be predicted to strengthen the context association, because the zero contingency has three times as many reinforced, action-absent trials. Given that positive contingency ratings were selectively affected by ATD, whereas zero contingency ratings were not significantly affected, one might conclude that the acquisition of the context association is intact, but that ATD enhances the extinction of context associations. In addition, the notion that 5-HT depletion leads to an enhancement of contextual extinction can also account for the data of Wilkinson et al. (1995) who found that global forebrain 5-HT depletion in rats reduced contextual conditioning during a trace conditioning procedure, without affecting conditioning to discrete cues.

However, it is important to note that, in the low BDI group, context ratings (and the action ratings) for the positive contingency on ATD are numerically more positive than the low BDI group data presented in the supplementary information. In some sense, this is problematic for the extinction account, as it is not obvious how a new group of participants similar to those reported in the supplementary information could show an additional reduction in their context ratings following an ATD procedure. To address this possible criticism, it is important to remember that a feature of the within-subject design meant that arbitrary variance associated with different usage of the rating scale between participants could be mitigated. In addition, it seems likely, both theoretically and in light of the data presented in this study, that the associations can compete and interact with one another: for example, a weaker context association would be expected to have a smaller moderating effect on the acquisition of an action–outcome association. For these reasons therefore, we argue that it is the relative positions of the ratings—under the different conditions—that is of key theoretical importance, as opposed to their absolute positions. More direct tests of the context extinction hypothesis might employ repeated ratings across a given session in order to assess the degree to which context extinction predicts the acquisition of action–outcome association.

The ATD effect was only measurable in the low BDI group. The BDI scores in this study (median = 6) were in general too low to be of any clinical significance, although two participants showed high BDI scores (19, 21), and none of them had a declared history of depression. So any potential implications of these findings based on depression are clearly tentative. That being said, ATD effects are known to differ amongst individuals and depend, to some extent, on individual vulnerability to 5-HT dysregulation (e.g., Jans et al. 2007). It is possible that a preexisting dysregulation conceals the ATD effect in this group, for which we have some evidence, given the differential degree of depletion in the two groups. The findings we report here are only partially consistent with previous work, suggesting that depression is associated with a selective alteration in the associability of contextual stimuli (Msetfi et al. 2005). Here, ATD, which has been used to model aspects of depression, did produce the change in context ratings as described above. However, the high BDI group demon-

strated little evidence of learning, being unable to discriminate between situations in which their actions did and did not control outcomes. In fact, their control ratings did not distinguish between action and context, a tendency that was not influenced by ATD. These findings sit somewhat awkwardly with the concept of depressive realism. If realism is defined as being able to distinguish between situations of no control and some control, then the high BDI participants in this study were certainly not realistic. A similar pattern was observed in the larger data set presented in the supplementary information. Together, these data suggest that high BDI participants are unable to discriminate action and context as putative causes of the outcome. The reason for this failure is likely to be related to the use of multiple contexts, in light of the fact that high BDI participants typically show accurate performance on contingency learning tasks employing a positive contingency between action and outcome (Alloy and Abramson 1979).

The most notable limitation of the study is the small number of participants. Future studies with a more substantial power might confirm the extent to which the effect observed in the present study is replicable and whether other less powerful effects have been missed as a result of type II errors. In addition, the nonparametric statistical test we used (Friedman test) is conservative, and a larger group of participants would have afforded the use of parametric statistics. A purpose of including the subgroup analysis is to raise the possibility that future studies of contingency judgements in healthy participants undergoing ATD might pre-select participants based on clinically insignificant levels of depression, as our results suggest that even low levels of heterogeneity in depressive symptomatology might have substantial effects on the behavioural response to ATD. A second limitation is the ambiguity regarding ATD as a method of serotoninergic modulation: the manner and degree to which central nervous system 5-HT is modulated is not well understood (for example, see Fusar-Poli et al. 2006; van der Plasse et al. 2007 for discussion).

Summary

This is the first demonstration that ATD improves instrumental contingency judgements in a group of participants with below average levels of depressed mood. The results provide partial support for depressive realism and an account based on the modification of context learning. It is clear that a more complex picture of mood effects at the neurobiological level is emerging. However, the results more broadly support the role of 5-HT in instrumental contingency judgement, for which there is some prior neurobiological support.

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