Neurobiology of Learning and Memory 131 (2016) 76–82

Contents lists available at ScienceDirect

Neurobiology of Learning and Memory

journal homepage: www.elsevier.com/locate/ynlme

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

Rachel M. Msetfi [a,b,*], Poornima Kumar [c], Catherine J. Harmer [d], Robin A. Murphy [e]

[a] Centre for Social Issues Research, Department of Psychology, University of Limerick, Limerick, Ireland
[b] Health Research Institute, University of Limerick, Limerick, Ireland
[c] Center for Depression, Anxiety and Stress Research, McLean Hospital/Harvard Medical School, Belmont, MA, United States
[d] Department of Psychiatry, University of Oxford, Oxford, United Kingdom
[e] Department of Experimental Psychology, University of Oxford, Oxford, United Kingdom

ARTICLE INFO

Article history:
Received 17 August 2015
Revised 14 January 2016
Accepted 4 March 2016
Available online 11 March 2016

Keywords:
Escitalopram
SSRI
Serotonin
Learning
Perceived control
Context
Response rate
Depression

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 $\geqslant$ 10: $n = 76$) or not depressed (low BDI $\leqslant$ 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.

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, &

* Corresponding author at: Department of Psychology, University of Limerick, Castletroy, Limerick, Ireland. Fax: +353 (0)61 233211.
E-mail address: rachel.msetfi@ul.ie (R.M. Msetfi).

http://dx.doi.org/10.1016/j.nlm.2016.03.004
1074-7427/

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 $\geqslant$24 at screening and/or randomisation visit were excluded from participation. Only participants with BDI $\leqslant$5 or $\geqslant$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 ($BDI_{rand} \leqslant 5$: n = 78) or high BDI ($BDI_{rand} \geqslant 10$: 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