Psychological Medicine

cambridge.org/psm

Original Article

Cite this article: Wolke SA *et al* (2019). Modulation of anterior cingulate cortex reward and penalty signalling in medication-naive young-adult subjects with depressive symptoms following acute dose lurasidone. *Psychological Medicine* **49**, 1365–1377. https://doi.org/10.1017/S0033291718003306

Received: 1 April 2018
Revised: 8 October 2018
Accepted: 12 October 2018
First published online: 4 January 2019

Key words:
Anterior cingulate cortex; depression; fMRI; lurasidone; penalty; reward

Author for correspondence:
Selina A. Wolke,
E-mail: selina.wolke@kcl.ac.uk

CAMBRIDGE UNIVERSITY PRESS

Modulation of anterior cingulate cortex reward and penalty signalling in medication-naive young-adult subjects with depressive symptoms following acute dose lurasidone

Selina A. Wolke[1,2], Mitul A. Mehta[3], Owen O'Daly[3], Fernando Zelaya[3], Nada Zahreddine[4], Hanna Keren[2], Georgia O'Callaghan[2], Allan H. Young[5], Ellen Leibenluft[6], Daniel S. Pine[7] and Argyris Stringaris[2]

[1]Department of Child and Adolescent Psychiatry, Institute of Psychiatry, Psychology, and Neuroscience, King's College London, London, UK; [2]Mood Brain and Development Unit, Emotion and Development Branch, National Institute of Mental Health, National Institutes of Health, MD, USA; [3]Department of Neuroimaging, Institute of Psychiatry, Psychology, and Neuroscience, King's College London, London, UK; [4]Department of Psychiatry, Saint-Joseph University, Beirut, Lebanon; [5]Department of Psychological Medicine, Institute of Psychiatry, Psychology, and Neuroscience, King's College London, London, UK; [6]Section on Mood Dysregulation and Neuroscience, Emotion and Development Branch, National Institute of Mental Health, National Institutes of Health, MD, USA and [7]Section on Development and Affective Neuroscience, Emotion and Development Branch, National Institute of Mental Health, MD, USA

Abstract

Background. Aberrations in reward and penalty processing are implicated in depression and putatively reflect altered dopamine signalling. This study exploits the advantages of a placebo-controlled design to examine how a novel D_2 antagonist with adjunctive antidepressant properties modifies activity in the brain's reward network in depression.

Methods. We recruited 43 medication-naïve subjects across the range of depression severity (Beck's Depression Inventory-II score range: 0–43), including healthy volunteers, as well as people meeting full-criteria for major depressive disorder. In a double-blind placebo-controlled cross-over design, all subjects received either placebo or lurasidone (20 mg) across two visits separated by 1 week. Functional magnetic resonance imaging with the Monetary Incentive Delay (MID) task assessed reward functions via neural responses during anticipation and receipt of gains and losses. Arterial spin labelling measured cerebral blood flow (CBF) at rest.

Results. Lurasidone altered fronto-striatal activity during anticipation and outcome phases of the MID task. A significant three-way Medication-by-Depression severity-by-Outcome interaction emerged in the anterior cingulate cortex (ACC) after correction for multiple comparisons. Follow-up analyses revealed significantly higher ACC activation to losses in high- *v.* low depression participants in the placebo condition, with a normalisation by lurasidone. This effect could not be accounted for by shifts in resting CBF.

Conclusions. Lurasidone acutely normalises reward processing signals in individuals with depressive symptoms. Lurasidone's antidepressant effects may arise from reducing responses to penalty outcomes in individuals with depressive symptoms.

Introduction

Multiple studies implicate reward and dopaminergic system dysfunction in the pathogenesis of major depressive disorder (MDD). Yet, only few studies use experimentally controlled designs to probe the role of these systems in MDD. Here, we examine the acute effects of lurasidone, a novel D_2 antagonist with adjunctive antidepressant properties, on neural responding to reward in depression using two functional imaging modalities.

Depressed patients display alterations across several key phases of reward processing. Blunting of neural responses when anticipating or obtaining rewards (Knutson *et al.*, 2008; Pizzagalli *et al.*, 2009; Keren *et al.*, 2018) is associated with anhedonia, while increased reactivity to losses may underlie the behavioural avoidance that is characteristic of depression (Stringaris *et al.*, 2015; Luking *et al.*, 2016; Engelmann *et al.*, 2017; Hevey *et al.*, 2017). Recently, a direct link has been found between reduced mid-brain dopamine transporter density and neural activity during reward processing within the mesolimbic pathway in healthy and depressed human participants (Dubol *et al.*, 2018).

These findings make reward processing an attractive treatment target. Dopaminergic compounds provide a promising way to manipulate fronto-striatal reward pathways (Pessiglione

et al., 2006; Jocham *et al.*, 2011, 2014; Chowdhury *et al.*, 2013; Dean *et al.*, 2016; Harmer *et al.*, 2017). Surprisingly, however, very few studies have used dopaminergic drugs to probe the association between neural reward signalling and depression. Recently, Admon *et al.* (2017) showed that a single-dose of the dopamine receptor antagonist amisulpride normalised reward processing by increasing reward-related striatal activation and corticostriatal connectivity in depressed individuals. This effect is thought to result from transient increases in dopamine signalling at low amisulpride doses (Schoemaker *et al.*, 1997; Admon *et al.*, 2017). Strengthening of striatal functioning through dopamine antagonists has been shown before in healthy volunteers (Mehta *et al.*, 2003; Handley *et al.*, 2013) and is presumed to occur through presynaptic D_2/D_3 autoreceptor blockade (Fernandez-Seara *et al.*, 2011, Goozee *et al.*, 2014).

It may seem counterintuitive that some antipsychotics are antidepressant in augmentation treatment for bipolar and MDD, given that D_2 antagonism (a central feature of all antipsychotics) is known to suppress reward-related striatal activation, for example, with haloperidol (Pessiglione *et al.*, 2006; Pleger *et al.*, 2009; Oei *et al.*, 2012). However, olanzapine, quetiapine and lurasidone, which are efficacious adjunctive antidepressants [olanzapine (Tohen *et al.*, 2003, 2014), quetiapine (Suppes *et al.*, 2014; Suttajit *et al.*, 2014), lurasidone (Loebel *et al.*, 2014*a*, 2014*b*; Nelson *et al.*, 2015; Suppes *et al.*, 2016*a*, 2016*b*)] differ from haloperidol in their broader profile, including greater serotonergic action. Indeed, blockade of serotonergic 5-HT receptors (5-HT_{1A}, 5-HT_{2A}, 5-HT_{7}) stimulates striatal dopamine release and in addition to this, serotonergic neurons directly impact upon reward (and predominantly aversive) processing (Boureau and Dayan, 2011; Huang *et al.*, 2012; Inaba *et al.*, 2013; Liu *et al.*, 2014; Cohen *et al.*, 2015; Hayashi *et al.*, 2015; Li *et al.*, 2016). However, there are few studies that have assessed modulation of loss anticipation and feedback with antidepressant drugs. The evidence thus far points to a pattern of blunting of aversive events with acute administration of selective serotonin reuptake inhibitors (SSRIs) (McCabe *et al.*, 2010; Macoveanu *et al.*, 2013, 2014; Macoveanu, 2014), but crucially also with D_2 antagonists that have anti-depressant properties [amisulpride (Admon *et al.*, 2017) and aripiprazole (Bolstad *et al.*, 2015)]. These findings raise the intriguing possibility that dopamine antagonists with adjunctive antidepressant properties may exert their effects via *reward* and/or *penalty* signal normalisation.

In this paper, we test whether an acute dose of 20 mg lurasidone, a D_2 receptor antagonist (Loebel and Citrome, 2015) with demonstrated antidepressant properties in monotherapy and in combination treatment (Loebel *et al.*, 2014*a*, 2014*b*; Suppes *et al.*, 2016*a*; Goldberg *et al.*, 2017), influences reward and penalty signal in depression. Lurasidone was selected because it is the most recently licensed dopamine antagonist with antidepressant properties and there is no information with regards to its effects on brain reward and penalty signalling (Loebel *et al.*, 2014*a*, 2014*b*; Nelson *et al.*, 2015; Nierenberg *et al.*, 2015; Suppes *et al.*, 2016*a*, 2016*b*; Goldberg *et al.*, 2017). We employ a randomised, placebo-controlled cross-over design with functional magnetic resonance imaging (fMRI) and arterial spin labelling (ASL) imaging acquired on two separate occasions per individual. This design overcomes the limitations of correlational studies through randomisation and experimental manipulation. Since symptoms of MDD fall on a continuous dimension (Angst *et al.*, 2000; Ayuso-Mateos *et al.*, 2010), we recruited medication-naïve subjects across the range of depression severity, including healthy volunteers, as well as people meeting full-criteria for MDD. This research approach is in line with the Research Domain Criteria framework (Morris and Cuthbert, 2012) [e.g. as in Stringaris *et al.* (2015) where symptom levels are related to the brain measurements]. It also does justice to findings concerning the genetic underpinnings of common mental illness (Plomin *et al.*, 2009) as well as current approaches to understanding neural system perturbation in a dimensional way (Matthews and Hampshire, 2016).

Depression is characterised by hyporeactivity to reward (Knutson *et al.*, 2008; Forbes *et al.*, 2009; Pizzagalli *et al.*, 2009; Gotlib *et al.*, 2010; Admon *et al.*, 2015; Luking *et al.*, 2016; Keren *et al.*, 2018) and hyperactivity to aversive stimuli (Gotlib *et al.*, 2010; Admon *et al.*, 2015; Luking *et al.*, 2016; Engelmann *et al.*, 2017), and thus an antidepressant effect could be brought about by increasing reward, decreasing salience to negative events, or, both simultaneously. Given the relative paucity of literature on processing of losses (Keren *et al.*, 2018), our study is designed to interrogate both anticipation and feedback of rewards and penalties. We hypothesise a normalisation of fronto-striatal reward and/or penalty function following acute-dose administration in depression. More specifically, we anticipate that subjects scoring high on depression will show a baseline difference in fronto-striatal activity which will be reverted by acute-dose lurasidone. We first explore the expectation that the dopamine antagonist lurasidone will show striatal blunting during the anticipation phase, in line with numerous findings with D_2 antagonist drugs (Pessiglione *et al.*, 2006; Pleger *et al.*, 2009). Although, we note that a structurally similar drug, amisulpride has shown opposite effects (Admon *et al.*, 2017). An intriguing question is whether any blunting in reward processing that occurs with these drugs could have beneficial effects when dealing with loss. This is important given findings from serotonergic drugs that show on the one hand blunting of reward processing and on the other, amelioration of negative feedback (McCabe *et al.*, 2010; Macoveanu *et al.*, 2013, 2014; Macoveanu, 2014), which could underlie its antidepressant effects. In addition, we seek to address a key concern in pharmacoimaging studies, namely that shifts in global or regional cerebral blood flow (CBF) could underlie changes observed in a blood oxygenated level dependent (BOLD) fMRI signal. We therefore also use ASL, an imaging modality that allows the quantification of CBF at rest, to disentangle global and regional CBF changes from a BOLD fMRI signal.

Materials and methods

Participants

Forty-three participants (28 female, 15 male) were recruited using the research volunteer recruitment webpage at King's College London, social media and posters at university counselling services across London.

We recruited young people across a range of depression and anhedonia scores in the community as symptoms of MDD are known to fall on a continuum (Angst *et al.*, 2000; Ayuso-Mateos *et al.*, 2010), allowing us to assess the role of symptom level in reward processing on and off lurasidone (see text and online Figs S2–S4 in the Supplementary Methods). Inclusion criteria restricted recruitment to right-handed individuals 18–25 years of age with no contraindications to MRI, no serious medical conditions and no lifetime substance dependence. Please refer to the online Supplementary Methods for full details of inclusion

and exclusion criteria. Table 1 provides demographic and clinical information for the entire sample ($n = 43$). Online Table S1 in the Supplementary Methods provides demographic and clinical characteristics of recruited participants according to depression severity cut-off scores from the Beck's Depression Inventory-II (BDI-II). Participants received £230 in compensation for attending the assessment appointment and both scanning visits, in addition to their winnings from the fMRI task. All participants provided written informed consent, as approved by the Ethics Subcommittee of Psychiatry, Nursing & Midwifery Research (RESC reference number: PNM/13/14-122).

Design and procedure

Depression and anhedonia scores were assessed using the BDI-II (Beck *et al.*, 1996) and the Snaith–Hamilton Pleasure Scale (SHAPS) (Snaith *et al.*, 1995). On the basis of BDI-II scores, participants who were eligible following this screening procedure were invited to the assessment appointment.

Figure 1 illustrates the procedure and timeline of the study. At the assessment appointment, participants first completed a pre-MRI safety screening. Participants then completed questionnaires to assess handedness (Edinburgh Handedness Inventory) and IQ (National Adult Reading Test) (Nelson and Willison, 1991). This was followed by the Mini International Neuropsychiatric Interview version 6.0.0 (M.I.N.I.) (Sheehan *et al.*, 1998) which assessed past and present mental health disorders. Participants' height, weight, heart rate, blood pressure and electrocardiogram (ECG) were measured by the experimenter and blood samples (for Full Blood Count and Liver Function Tests) were taken by a study physician. Participants provided a urine sample for drug testing and for pregnancy testing in female participants. Participants were guided through the scanning procedure in a mock scanner and completed training for the Monetary Incentive Delay (MID) task.

If participants fulfilled the inclusion criteria after the assessment appointment, they were invited to take part in two scan days. There was a 97% retention rate in the study and this is illustrated in online Fig. S1 in the Supplementary Methods. Participants were randomised into one of two drug administration orders: placebo-lurasidone (placebo at visit one and lurasidone at visit two), or lurasidone-placebo. Both scan days followed the same schedule. On arrival at the imaging centre, participants had their heart rate and blood pressure measured and filled in two brief questionnaires to measure sedation [Visual Analogue Scale (VAS) (Herbert *et al.*, 1976) and state-anxiety (State Trait Anxiety Inventory; STAI) (Spielberger *et al.*, 1970)]. Next, the experimenter administered a capsule of either lurasidone (20 mg) or placebo. This dose was selected to minimise post-synaptic D_2 blockade (la Fougere *et al.*, 2005), as in similar studies of related medications (Admon *et al.*, 2017). Given the pharmacokinetic profile of lurasidone, the pill was consumed, followed by a 350 calorie meal (Greenberg and Citrome, 2017). Peak plasma levels of lurasidone are reached at approximately 3 h after tablet ingestion and the plasma half-life is 18 h (Greenberg and Citrome, 2017). In order to align the study assessments with peak plasma levels the MRI scan took place 3 h after tablet consumption (Fig. 1). Prior to the MRI scan, 2 h 45 min after drug administration, the experimenter measured participants' heart rate and blood pressure again, and participants completed the VAS and STAI questionnaires. The scan lasted approximately 1.5 h and included structural scans, ASL and a functional scan acquisition while completing the MID task. After the scan, and approximately 4.5 h after drug administration, the experimenter assessed the participants' heart rate and blood pressure, the VAS/STAI questionnaires were completed and ECG was collected. Participants were paid in cash for their winnings from the MID task and were discharged.

Table 1. Demographic and clinical characteristics of participants in a study investigating the effect of lurasidone on reward and penalty processing

	Participants ($N = 43$)	
Characteristic	Mean	S.D. (range)
Age (years)	21.83	2.05 (18–25)
Beck Depression Inventory-II	13.89	12.83 (0–43)
Snaith–Hamilton Pleasure Scale	12.18	8.49 (0–29)
	N	%
Female	28	65.12
Caucasian	36	83.72
Current subthreshold depression	7	16.28
Current MDD	11	25.58
Lifetime MDD	15	34.88
Lifetime MDD and current subthreshold depression	5	16.28
Lifetime MDD and current MDD	10	23.26
Current comorbid anxiety disorders	10	23.26

fMRI task

The MID task used in the current study was an adaptation of the task from, for example Knutson and colleagues (Knutson *et al.*, 2001). The task involves anticipation and receipt of monetary rewards and penalties. The task elicits robust fronto-striatal responses in healthy individuals and has high scan-rescan reliability (Plichta *et al.*, 2012; Wu *et al.*, 2014). During the anticipation and receipt of monetary reward and penalties, several studies using this task have demonstrated altered fronto-striatal activation in depressed individuals compared with healthy controls (Knutson *et al.*, 2008; Pizzagalli *et al.*, 2009; Carl *et al.*, 2016). This makes the MID task well-suited for the current study and further details are provided in the online Supplementary Methods.

MRI acquisition parameters

The MRI acquisition parameters are described in the online Supplementary Methods.

fMRI data analysis

ASL pre-processing

Spatial normalisation of the CBF maps was achieved using Automated Software for ASL Processing (ASAP; Mato Abad *et al.*, 2016). This pipeline employs the Statistical Parametric Mapping suite (SPM, Functional Imaging Laboratory, University College London, London, UK, version 12 – https://www.fil.ion.ucl.ac.uk/spm). Full details are provided in the online Supplementary Methods.

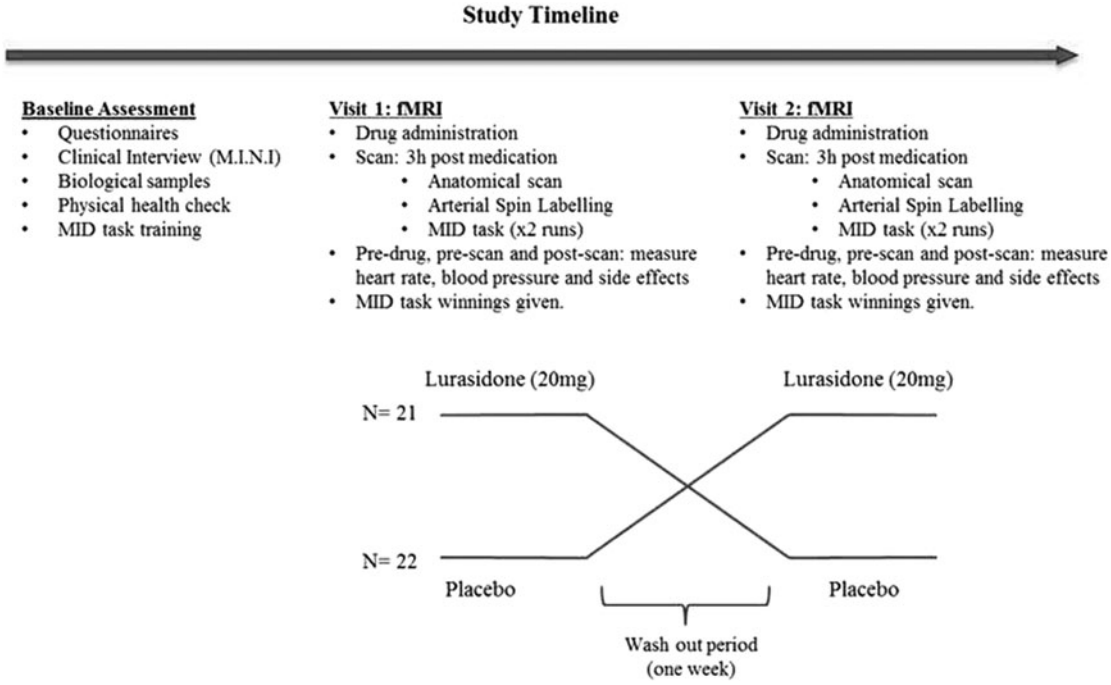

Fig. 1. Procedure and timeline for a study investigating the effect of lurasidone on reward and penalty processing.

fMRI pre-processing

fMRI data were preprocessed and quality assured using SPM12 in Matlab version (R2016b). This consisted of reorientation to the AC-PC line, slice timing correction, motion correction (Friston *et al.*, 1996), multi-channel segmentation and co-registration to each participant's structural image. The normalise estimate & write function within SPM12 was used, with the Montreal Neurological Institute template (MNI152). Smoothing was completed using a Gaussian kernel of 4 mm full-width half-maximum.

ASL statistical analysis

To test for statistical significant changes in resting CBF we carried out a paired-sample *t* test, which compared the CBF maps collected after administration of lurasidone against those acquired after placebo. Quantitative measures of global CBF and striatal CBF were extracted for each participant after placebo and lurasidone. The striatal region-of-interest (ROI) was formed by combining anatomically defined binary masks of the caudate, putamen and nucleus accumbens (NAcc) (see online Fig. S7 in the Supplement) (O'Doherty *et al.*, 2004). A repeated-measures analysis of covariance (ANCOVA) was performed for global and striatal CBF with the following factors: *Medication* (placebo, lurasidone) as the within-subject variable, *Medication Order* (placebo-lurasidone, lurasidone-placebo) as the between-subject factor and *Depression Severity* (total BDI-II score) as the covariate of interest. To test if changes in baseline CBF were related to the BOLD findings, the change in CBF between the two sessions was entered as covariates in all subsequent analyses. Specifically, the change in CBF values for a given region was used as covariates for the same region in the fMRI analyses.

fMRI first-level model

The BOLD signal was modelled with a canonical haemodynamic response function that was convolved with the onset times of task regressors to compute parameter estimates using the general linear model (GLM) at the single-subject level. The GLM included nine task-related regressors: passive condition, three cues (neutral, win, loss) and five outcomes [with (win outcome following win cue), missed win (no-change outcome following a win cue), loss (penalty outcome following a loss cue), avoided loss (no-change outcome following a loss cue) and neutral outcome (no-change outcome following a neutral/no-incentive cue)]. High-pass temporal filtering (128 s cut-off) was used to remove low-frequency artefacts. Estimated movement parameters were added to the design matrix. These included six rigid-body movement parameters, a regressor accounting for frame-wise displacement (i.e. the 3D movement from volume 1–2, 2–3 etc.), and additional binary regressors to indicate image volumes with spikes greater than 1 mm, and images either side of the spike (i.e. motion scrubbing and padding). Movement analyses are described in the online Supplementary Methods.

fMRI statistical analysis

Anticipation and outcome

Following previous findings that depression is associated with differential fronto-striatal abnormalities in response to anticipation *v.* receipt of monetary outcomes (Pizzagalli *et al.*, 2009) statistical analyses were separately conducted for the cue and outcome phases of the task.

To test *a priori* hypotheses regarding fronto-striatal responses to the anticipation and outcome of reward and penalty, we conducted a ROI analysis. Mean activations were extracted from seven bilateral anatomical masks of the caudate, putamen, NAcc, orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), insula and amygdala for each participant for the following contrasts of interest: (i) anticipation neutral > baseline, (ii) anticipation win > baseline, (iii) anticipation loss > baseline, (iv) *Reward Outcome*: feedback win > missed win and (v) *Penalty Outcome*:

feedback loss > avoided loss. This analytic approach has been used previously (Admon *et al.*, 2017) and mitigates possible spillover effects of cue type on the neural responses to outcomes. Masks were collapsed across hemispheres because hemispheric effects on task activation were non-significant and because of the high correlation between hemispheric ROIs. To avoid circular analysis (Kriegeskorte *et al.*, 2009), whole regions from atlas toolboxes in SPM12 were used (see online Fig. S7 in the supplementary data). These ROIs were chosen in accordance with meta-analytical findings of the neural correlates of reward and penalty processing (Diekhof *et al.*, 2012; Bartra *et al.*, 2013; Zhang *et al.*, 2013).

For the anticipation phase of the task, a repeated-measures ANCOVA was performed for each ROI with the following factors: *Medication* (placebo, lurasidone) and *Anticipation Cue* (neutral, win, loss) as within-subject variables, *Medication Order* as the between-subject factor, and *Depression Severity* (total BDI-II score) as the covariate of interest.

To test our hypothesis regarding normalisation of reward and/or penalty responses, we conducted a repeated measures ANCOVA for each ROI. This included the factors: *Medication* (placebo, lurasidone) and *Outcome Type* (reward, penalty) as within-subject variables, *Medication Order* as the between-subject factor, and *Depression Severity* (total BDI-II score) as the covariate of interest. We predicted that normalisation responses in depressed individuals on lurasidone would be captured by a *Medication*-by-*Depression Severity*-by-*Outcome Type* interaction. We expected to find no effect of *Medication Order*.

In order to examine further the drug effects on the neural signal, we examined how the difference in neural activity ($\Delta_{\text{neural activity}}$) between placebo and lurasidone in each ROI varied across depression scores. For this, Pearson correlation coefficients were estimated.

To complement our primary dimensional analyses (using a continuous measure of depression), we also examined our hypothesis regarding normalisation of responses using categorical groups in a repeated measures ANOVA model (Fig. 4). We used severity cut-off scores for the BDI-II (Beck *et al.*, 1996, Krefetz *et al.*, 2002, Kumar *et al.*, 2002) to compare individuals with *low depressive symptoms* [total BDI-II score: 0–16 (normal-mild mood disturbance), $n = 24$] to individuals with *high depressive symptoms* [total BDI-II score: 17–43 (borderline-severe depression), $n = 18$] on placebo and lurasidone (Strober *et al.*, 1981; Barrera and Garrisonjones, 1988; Whitaker *et al.*, 1990; Ambrosini *et al.*, 1991; Marton *et al.*, 1991; Canals *et al.*, 2001).

For all of the above ROI analyses, the threshold for statistical significance was set at ($p < 0.007$) following Bonferroni adjustment for seven multiple ROI comparisons. We also tested the association between dimensional anxiety scores and brain activation in an ANCOVA, with *Anxiety Severity* (total score on the anxiety subscale of the Hospital Anxiety and Depression Scale) as the covariate of interest.

In order to model the effects of lurasidone and depression status beyond the fronto-striatal network targeted in the ROI analyses, exploratory whole brain analyses were also conducted (see the online Supplementary Methods and Results).

Results

Behavioural results

A repeated measures ANCOVA with *Medication* (placebo or lurasidone) and *Cue Type* (reward, penalty, neutral) as the within-subject variables, *Medication Order* (placebo-lurasidone, lurasidone-placebo) as the between-subject variable and *Depression Severity* (total BDI-II score) as the covariate of interest was completed for (i) *Total Winnings*, (ii) *Mean Reaction Time* (RT) and (iii) *Accuracy*. Performance data are presented in online Table S2 in the Supplementary Results. In all analyses, there were no effects of *Medication Order* or interactions with *Medication Order* (all p values > 0.050). In all analyses there were no significant three-way interactions between either (i) *Total Winnings*, (ii) *Mean RT* or (iii) *Accuracy* and *Medication* and *Depression Severity*. Significant two way interactions between *Cue Type* and *Mean RT*, and *Cue Type* and *Accuracy* are presented in the online Supplementary Results. We also examined the effect of *Medication*, *Medication Order* and *Depression Severity* on the change in *Sedation* ratings (total VAS scores) and *State-anxiety* ratings (total STAI score) from pre-drug administration (Measure 1) to peak-of-drug (Measure 2). There were no significant main effects or interactions (all p values > 0.050) (please refer to the online Supplementary Results).

Reward processing (blood-oxygen-level dependent signal) results

Response to outcomes

Primary analyses

These primary analyses are conducted with depression measured as a continuous variable. In order to test the hypothesis that lurasidone would increase activation to reward outcomes and decrease responses to penalties in depressed individuals, we conducted a repeated-measures ANCOVA. *Medication* (placebo, lurasidone) and *Outcome Type* (*Reward Outcome v. Penalty Outcome*) were the within-subject variables, *Medication Order* was the between-subject factor and *Depression Severity* (total BDI-II score) was the covariate of interest ($n = 40$). Three participants were excluded from the analyses (please refer to the online Supplementary Results). The repeated measures ANCOVA revealed a significant *Medication*-by-*Depression Severity*-by-*Outcome Type* interaction in the ACC ($F = 8.10$, df = 1, 37, $p = 0.007$), after passing Bonferroni adjustment for seven multiple ROI comparisons. The interaction fell short of Bonferroni-adjusted significance in the OFC ($F = 4.47$, df = 1, 37, $p = 0.041$) and insula ($F = 4.90$, df = 1, 37, $p = 0.033$). There were no significant interactions with *Medication Order* (all p values >0.050).

To understand the significant three-way interaction, we conducted two repeated-measures ANCOVAs for *Reward Outcome* ($n = 41$) and *Penalty Outcome* separately ($n = 41$ after excluding outliers, please refer to online Supplementary Results).

This revealed a significant *Medication*-by-*Depression Severity*-by-*Penalty Outcome* interaction in the ACC ($F = 11.98$, df = 1, 38, $p = 0.001$). Figure 2 demonstrates that under placebo, individuals with higher depressive symptoms had greater ACC activity during penalty outcomes. However, this trend was not found under lurasidone. Put simply, brain activity to penalties in the ACC in individuals with elevated depression scores under lurasidone, but not placebo, resembles brain activity of individuals with low depressive symptoms. In keeping with this result, we found that ΔACC (the difference between neural activity under lurasidone and placebo) was negatively correlated with depression severity. Figure 3 illustrates the finding that the absolute difference in neural activity between lurasidone and placebo increased as a function of depression scores.

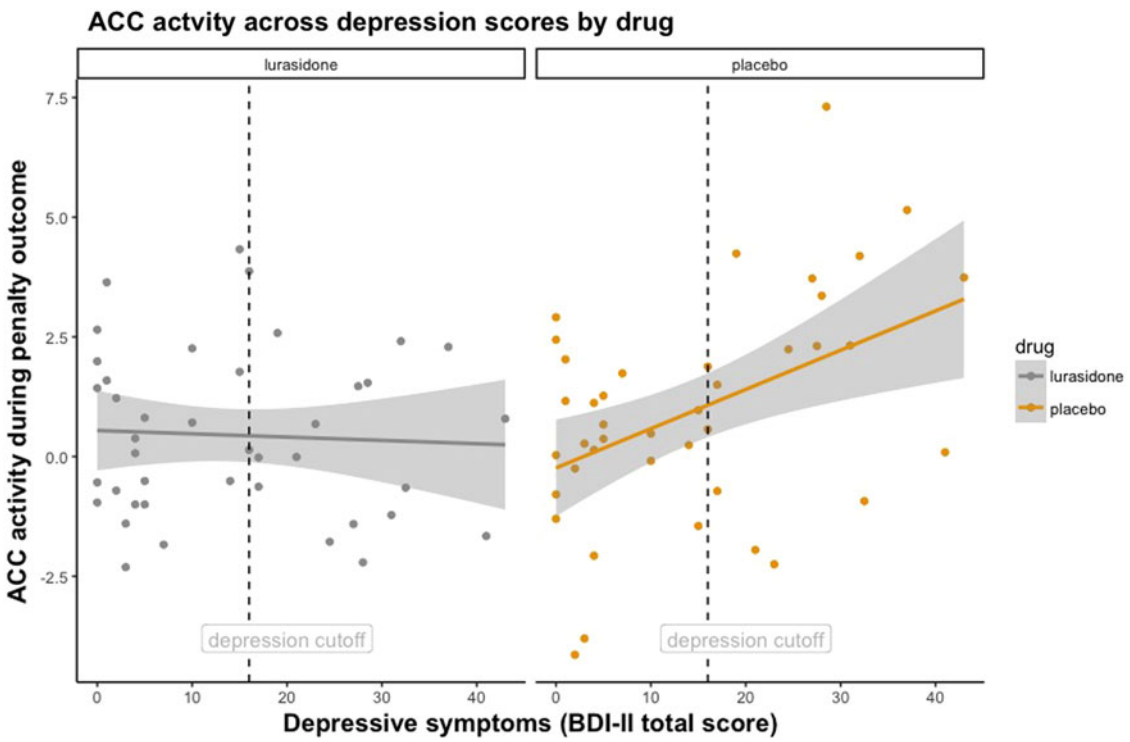

Fig. 2. Facet plot illustrating ACC response during Penalty Outcome across continuous depression scores under lurasidone and placebo. Dashed vertical line denotes depression severity cut-off score on the BDI-II.

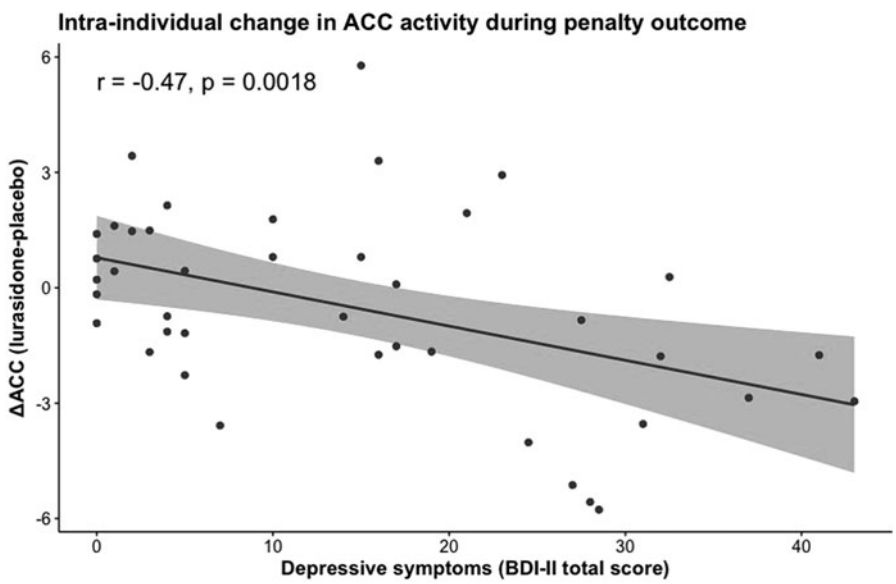

Fig. 3. Intra-individual change in penalty related ACC activity (the difference between neural activity under lurasidone and placebo) as a function of continuous depression scores.

A similar pattern of results, namely a signal normalisation, was found in the OFC ($F = 4.94$, df = 1, 37, $p = 0.032$), but the interaction fell short of significance after Bonferroni adjustment (see the online Supplementary Results).

We then examined the *Medication*-by-*Depression Severity*-by-*Reward Outcome* interaction across the seven ROIs. This also displayed a pattern of signal normalisation, although in an opposite direction to *Penalty Outcome*, as lurasidone had its strongest effect of *increasing* responses to reward outcomes in individuals with high depression severity. This trend fell short of significance in the NAcc ($F = 4.87$, df = 1, 38, $p = 0.033$) and ACC ($F = 5.92$, df = 1, 37, $p = 0.020$) following Bonferroni correction.

Secondary analyses

Complementing the primary (continuous variable) analyses, we sought to replicate our results using categorical analyses. A repeated-measures ANOVA with *Medication* (placebo, lurasidone) and *Outcome Type* (*Reward Outcome v. Penalty Outcome*) as the within-subject variables and *Depression Group* (low *v.* high depressive symptoms) and *Medication Order* as

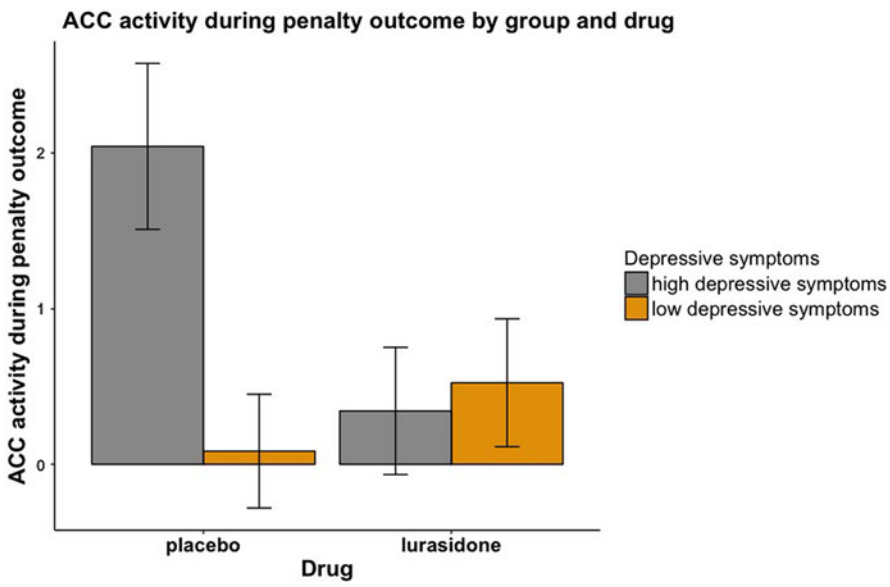

Fig. 4. Box plot illustrating ACC Response to Penalty Outcomes (loss > avoided loss). Depression severity cut-off scores from the BDI-II, with individuals with low depressive symptoms (total BDI-II score: 0–16, $n = 24$) *v.* high depressive symptoms (total BDI-II score: 17–43, $n = 18$).

the between-subject factors ($n = 40$), revealed a significant *Medication*-by-*Depression Group*-by-*Outcome Type* interaction in the ACC ($F = 8.68$, df = 1, 38, $p = 0.005$).

Figure 4 illustrates these findings using BDI-II cut-off scores, with individuals with low depressive symptoms (total BDI-II score: 0–16, $n = 24$) *v.* high depressive symptoms (total BDI-II score: 17–43, $n = 18$). Post-hoc *t* tests showed that participants with high depressive symptoms receiving placebo had significantly greater ACC activation to *Penalty Outcomes* than participants with high depressive symptoms receiving lurasidone ($T = 2.17$, df = 19, $p = 0.043$), and participants with low depressive symptoms receiving placebo ($T = 2.32$, df = 37, $p = 0.026$). There was no significant difference between individuals with high BDI-II scores on lurasidone and individuals with low BDI-II scores on placebo ($T = 0.48$, df = 37, $p = 0.634$). Together, these findings indicate that brain activity to penalties in the ACC in individuals with elevated depression scores under lurasidone, but not placebo, resembles brain activity of healthy volunteers.

To summarise, across reward and penalty outcomes, lurasidone had its strongest effect of increasing responses to reward outcomes and decreasing responses to penalty outcomes in individuals with high depression severity (Figs 2–4). The pattern and significance of the results remained when the outliers were included in the analysis (see the online Supplementary Results).

Response to cues

In contrast to the outcome results, there were no significant interactions with depression in the anticipation phase of the task. Instead, the repeated measures ANCOVA revealed a significant *Medication*-by-*Anticipation Cue* interaction in the ACC ($F = 8.16$, df = 2, 72, $p = 0.001$) and caudate ($F = 7.78$, df = 2, 72, $p = 0.001$). Post-hoc tests show that lurasidone reduced responses to win and loss cues *v.* placebo, and increased responses for neutral cues in the ACC and caudate. This fell short of significance in the OFC ($F = 3.94$, df = 2, 72, $p = 0.024$) and amygdala ($F = 3.85$, df = 2, 72, $p = 0.026$).

Anxiety severity analyses and exploratory whole-brain findings for the anticipatory and outcome phases of the task are presented in the online Results Section of the Supplementary data.

Cerebral blood flow (CBF)

In order to ensure that the BOLD results in the ACC were independent of changes in underlying CBF, we tested the effects of acute lurasidone administration on global and regional blood flow. As shown in Fig. 5, a paired-samples *t* test across the whole-brain showed that lurasidone increased CBF in bilateral putamen relative to placebo during rest in the whole sample ($n = 43$). Significant increases in blood flow were not observed in the ACC. The repeated measures ANCOVA revealed that the extracted global and striatal CBF values were not related to *Depression Severity* ($F = 0.02$, df = 1, 40, $p = 0.903$), *Medication Order* ($F = 0.44$, df = 1, 40, $p = 0.903$), or any three-way interactions with these respective factors ($F = 0.01$, df = 1, 40, $p = 0.952$); ($F = 1.10$, df = 1, 40, $p = 0.300$). The change in CBF values for each of the seven ROIs were extracted and used as covariates for the same region in the fMRI BOLD analyses. This did not lead to any changes in the results: non-significant results remained non-significant and significant results remained significant. In particular, the *Medication*-by-*Depression Severity*-by-*Outcome Type* interaction in the ACC ($F = 8.13$, df = 1, 36, $p = 0.007$).

Discussion

In this study, we compared the effects of lurasidone and placebo on neural responding to reward and penalties in medication-naïve young-adult subjects across the range of depression severity. During the anticipation phase of the task, we found that lurasidone reduced responses to win and loss cues *v.* placebo, and increased responses for neutral cues in the ACC and caudate across the entire sample (i.e. regardless of depression severity). We found that brain activity in the ACC to *Penalty Outcomes* in individuals with high symptoms of depression under lurasidone, but not placebo, resembled brain activity of individuals with low symptoms of depression. Specifically, lurasidone *reduced* ACC signalling to negative feedback in young people with elevated depressive symptoms. Increased regional and global blood flow under lurasidone did not drive the BOLD findings. These results provide evidence for abnormalities in neural reward-penalty systems in depression and highlight the potential of

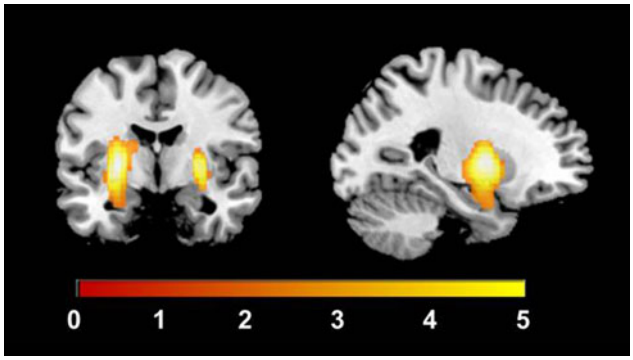

Fig. 5. Increased CBF in bilateral putamen for lurasidone relative to placebo during rest in the whole sample ($n = 43$). Significant at the peak level whole-brain analyses, family-wise error-corrected (left putamen $x = -26$, $y = -4$, $z = 2$, $t = 6.15$: $p = 0.002$, right putamen $x = 28$, $y = -2$, $z = 2$, $t = 5.50$: $p = 0.015$). Bar represents T-value.

targeted pharmacological treatments (dopaminergic agents) to normalise penalty related processing in depression.

Our findings are consistent with the notion that acute dose of drugs with antidepressant properties, either as used in monotherapy or combination treatment, can have an effect on brain processes implicated in depression (Harmer *et al.*, 2017). For example, SSRIs reduce negative bias and amygdala response to negative emotional stimuli (Harmer *et al.*, 2009; Murphy *et al.*, 2009). In our study, the effects of normalisation where localised to the ACC, a region that integrates diverse striatal and prefrontal functions (Haber and Knutson, 2010). For example, the ACC and ventral striatum (VS) show functional connectivity at rest (Pan *et al.*, 2017) and input from the ACC to the VS allows for flexible deployment and adaptation of behaviour to changing circumstances (Holroyd and Coles, 2002; Walton *et al.*, 2007; Alexander and Brown, 2011; Holroyd and Yeung, 2012; Walsh and Anderson, 2012; Holroyd and Umemoto, 2016; Umemoto and Holroyd, 2016; Shahnazian and Holroyd, 2017). Electrophysiological (electroencephalogram) studies have shown that the feedback negativity (FRN), an event-related potential which indicates the early appraisal of feedback and appears larger following the presentation of negative feedback, has its origins in the ACC (Gehring and Willoughby, 2002; Holroyd and Coles, 2002; Holroyd *et al.*, 2004; Hajcak *et al.*, 2005; Yeung *et al.*, 2005). Specifically, an FRN signal may be generated as ACC neurons shift from encoding expected to actual outcomes (i.e. a prediction error signal) (Hyman *et al.*, 2017). In our study, participants with higher depression severity on placebo showed greater ACC response to negative feedback. This is congruent with evidence of heightened sensitivity to negative outcomes in depression and its association with elevated loss-related signals in the ACC, and connected regions such as the anterior insula and striatum.

It has been postulated that increased ACC activity in depressed individuals to loss outcomes reflects biased stimuli representations that mediate choice behaviour, including preferential attention, planning and self-referential processing towards losses (Sylvester *et al.*, 2003; Grimm *et al.*, 2009; Gotlib *et al.*, 2010). A normalisation of ACC response in depressed individuals on lurasidone therefore suggests that lurasidone may act to decrease salience and processing of loss events.

Inter-individual differences between low and high depression severity subjects could account for the findings that lurasidone attenuated response to penalty outcomes in individuals with high depression severity only. Indeed, depression is associated with baseline differences in availability and function of 5-HT and/or D_2 receptors and reductions in binding relative to healthy volunteers (Suhara *et al.*, 1992; Yatham *et al.*, 1999; Sheline *et al.*, 2004; Yatham *et al.*, 2005). Thus, in accordance with previous findings that more divergent patterns of reward/penalty processing at baseline are associated with greater post-intervention change (Vrieze *et al.*, 2013; Rice *et al.*, 2015; Burkhouse *et al.*, 2016; Walsh *et al.*, 2016), it could be that subjects with more severe depressive symptoms have more 'room for improvement' following acute lurasidone administration.

In addition to attenuating penalty outcome responses, lurasidone reduced neural responses in the ACC and caudate during the anticipation of loss and reward cues across the entire sample (i.e. regardless of depression severity). This is in line with studies showing attenuated reward-related striatal activation during reward anticipation and decision making with D_2 antagonist haloperidol (Pessiglione *et al.*, 2006; Pleger *et al.*, 2009). However, no effect has been reported for prediction of losses (Pessiglione *et al.*, 2006). There are various mechanisms which could account for the finding in this study, all of which are speculative at the moment. First, lurasidone may modulate tonic and phasic dopamine firing either directly by D_2 antagonism or indirectly via antagonism at serotonergic 5-HT receptors (5-HT_{2A}, 5-HT_7). Antagonism at D_2 receptors could act to block and reduce dopamine release, thereby also attenuating the BOLD signal. Alternatively, lurasidone may, at low doses, like amisulpride increase striatal dopamine release by preferentially blocking presynaptic dopamine auto-receptors. Increased dopamine availability may act to increase tonic levels of dopamine, in turn decreasing the phasic firing of dopamine neurons and the sensitivity of the dopamine reward system (Grace, 1991), thereby potentially reducing BOLD signal to anticipation cues. Although it must be noted that ascribing the changes seen to one or more receptor systems is highly speculative as the precise mechanism by which BOLD signal is modulated cannot be determined with fMRI alone.

It is notable, that in line with previous studies utilising dopamine antagonists (Lahti *et al.*, 2003; Lahti *et al.*, 2005; Handley *et al.*, 2013; Goozee *et al.*, 2014), we show here that lurasidone increased striatal CBF at rest. Increases in blood flow following antipsychotic lurasidone administration may be related to increased neuronal metabolism in striatal areas due to the large density of D_2 receptors (Goozee *et al.*, 2014), with blockade of D_2 receptors in the striatum potentially resulting in disinhibition of D_2 receptor-containing medium spiny neurons (Fernandez-Seara *et al.*, 2011). Our results showed that the penalty and reward-related findings were unchanged after controlling for baseline shifts in global and striatal CBF, and highlight the utility of multi-modal fMRI in identifying if the effects of the drug administered are indeed neuronal.

Our study also showed a pattern in which lurasidone potentiated striatal (NAcc) activity to reward outcomes in young adults with elevated depressive symptoms. These findings did not survive stringent correction for multiple comparisons and should therefore be interpreted with appropriate caution. We note, that these results are in keeping with recent findings by Admon *et al.* (2017) who showed that a single-dose of the dopamine receptor antagonist amisulpride normalises reward processing by increasing reward-related striatal activation and connectivity between the striatum and mid-cingulate cortex in depressed individuals.

This study has several strengths. First, we tested the association between reward processing and depression using randomisation and experimental manipulation, thereby overcoming several of the limitations of correlational studies in drawing causal inferences. Second, the cross-over, within-subject design affords higher statistical power than a parallel design by minimising subject variance as each individual acts as their own control, and increasing the drug variance. Third, we recruited medication-naïve subjects across the range of depression severity, thus avoiding the confound of medication (Pessiglione *et al.*, 2006; Abler *et al.*, 2007).

This study also has limitations. Caution should be exercised with the interpretation of our results as 'normalising'. In the absence of any behavioural effect there is no evidence for better performance of the task on lurasidone, there is no clear main effect of depressive symptoms on the task (i.e. no deficit to improve) and no other triangulating measure of response to negative outcomes which can be linked to function. Nevertheless, it could be argued that lurasidone changes an activity in the ACC that might be beneficial. Further studies need to address both the behavioural deficit and the neural changes in parallel. This has proven challenging as it requires alignment between different levels of explanation including task, neural, clinical and behavioural (Keren *et al.*, 2018).

Our study was not designed to capture changes in depressive symptoms following lurasidone and therefore it is unclear how these would correlate with brain responses. However, our strategy of searching for the signal of an intervention in the first place is consistent with current recommendations to boost drug discovery (Krystal and State, 2014). The next piece of information which would be needed to infer causality, is whether lurasidone-induced neural changes (reduced penalty related ACC signalling and increased reward-related NAcc signalling) predict a decline in depressive and anhedonic symptoms (Shiroma *et al.*, 2014; Godlewska *et al.*, 2016). This would require longer-term lurasidone treatment in longitudinal studies with assessment of pre-post changes in behavioural and neural responses. Antidepressants seem to exacerbate reward deficits early in treatment (Kumar *et al.*, 2008; McCabe *et al.*, 2010; Marutani *et al.*, 2011) prior to normalisation following longer-term (2–6 week) treatment (Stoy *et al.*, 2012; Scholl *et al.*, 2017; Walsh *et al.*, 2017). Thus, in line with longer-term dosing studies, repeated dosing with lurasidone could lead to increasing anticipation of rewards with more chronic exposure to the drug. Although speculative, one could predict a behavioural activation model of the antidepressant mechanism of action of lurasidone, with normalisation of responses to outcomes (consummation), prior to a normalisation of neural anticipatory signals with longer-term treatment (Dimidjian *et al.*, 2011).

We note that we used two contrasts for the outcome type: reward and penalty outcome. Whilst this is standard in the literature in similarly designed studies (Admon *et al.*, 2017), an alternative modelling could be four levels: reward, missed reward, penalty and avoided penalty outcomes relative to no incentive outcomes. In addition, the recruitment was designed for analysis of depressive symptoms as a continuum, and as such any analysis of those with higher scores contrasted with lower scores may be underpowered. Interestingly we were able to replicate the results of Admon *et al.* (2017), as lurasidone potentiated striatal (NAcc) activity to reward outcomes using such categories but this did not survive correction for multiple comparisons.

In conclusion, our study shows that an acute dose of dopaminergic agent, lurasidone, transiently decreased penalty related ACC activity in individuals with high symptoms of depression. These findings suggest that modulation of dopamine transmission may help to normalise processing of negative outcomes in depressed individuals through the alteration of ACC signalling. Thus, ACC signalling may provide a new target for engagement in future drug development studies. Using an experimental medicine design such as the one used in this study, could help identify relevant compounds which could then be tested further in using longer-term follow-up.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291718003306.

Acknowledgements. We thank all participants who have generously given their time to taking part in this study. We thank the Wellcome Trust (093909/Z/10/A) and National Institute for Health Research (NIHR) Biomedical Research Centre (BRC) at South London and Maudsley NHS Foundation Trust and King's College London for funding this independent research project. We also thank the NIHR-BRC for funding Selina Wolke's Ph.D. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health. We thank Miss Hazel Deacon for her assistance in administration and data entry. We also thank Brian Knutson for providing the images used in the MID task. Preliminary results from this study were presented (via poster) at the American Academy of Child and Adolescent Psychiatry (AACAP) 63rd Annual Meeting, New York, NY, USA, 24–29 October 2016 and the International Society for Bipolar Disorders Annual Conference, Washington DC, USA, 4–7 May 2017.

Funding. This study was funded by the Wellcome Trust (093909/Z/10/A) and National Institute for Health Research (NIHR) Biomedical Research Centre (BRC) at South London and Maudsley NHS Foundation Trust and King's College London.

Disclosure. Selina Wolke's Ph.D. is funded through a 3-year National Institutes of Health Research (NIHR) Maudsley Biomedical Research Centre (BRC) Ph.D. Studentship based at the Institute of Psychiatry, Psychology and Neuroscience, King's College London. Dr Argyris Stringaris has received funding from the Wellcome Trust and the UK National Institutes of Health Research, funds from University College London for a joint project with Johnson & Johnson, and royalties from Cambridge University Press and Oxford University Press. Prof. Mitul Mehta has received research funding from Eli Lilly, Roche and Takeda and has acted as a consultant for Cambridge Cognition and Lundbeck. Prof. Allan Young is employed by King's College London and is an Honorary Consultant SLaM (NHS UK) and has received grant funding from the Medical Research Council and Wellcome Trust (UK). Prof. Young is part of advisory boards for all major pharmaceutical companies with drugs used in affective and related disorders and has no shareholdings in pharmaceutical companies. Prof. Young has initiated studies for Embolden Study (AZ), BCI Neuroplasticity study, Aripiprazole Mania Study, Eli Lilly, Lundbeck and Wyeth. Dr Owen O'Daly and Dr Fernando Zelaya are with the Institute of Psychiatry, Psychology and Neuroscience, King's College London and report no potential conflicts of interest. Dr Nada Zahreddine is based at the Department of Psychiatry, Saint-Joseph University, Beirut, Lebanon and has nothing to declare. Drs Stringaris, Leibenluft, Pine, Keren and O'Callaghan are with the National Institute of Mental Health and have nothing to declare.

Author ORCIDs. Selina A. Wolke, 0000-0001-6762-0456; Allan H. Young, 0000-0003-2291-6952.

References

Abler B, Erk S and Walter H (2007) Human reward system activation is modulated by a single dose of olanzapine in healthy subjects in an event-related, double-blind, placebo-controlled fMRI study. *Psychopharmacology* **191**, 823–833.

Admon R, Nickerson LD, Dillon DG, Holmes AJ, Bogdan R, Kumar P, Dougherty DD, Iosifescu DV, Mischoulon D, Fava M and

Pizzagalli DA (2015) Dissociable cortico-striatal connectivity abnormalities in major depression in response to monetary gains and penalties. *Psychological Medicine* **45**, 121–131.

Admon R, Kaiser RH, Dillon DG, Beltzer M, Goer F, Olson DP, Vitaliano G and Pizzagalli DA (2017) Dopaminergic enhancement of striatal response to reward in major depression. *American Journal of Psychiatry* **174**, 378–386.

Alexander WH and Brown JW (2011) Medial prefrontal cortex as an action-outcome predictor. *Nature Neuroscience* **14**, 1338–1344.

Ambrosini PJ, Metz C, Bianchi MD, Rabinovich H and Undie A (1991) Concurrent validity and psychometric properties of the Beck Depression Inventory in outpatient adolescents. *Journal of the American Academy of Child and Adolescent Psychiatry* **30**, 51–57.

Angst J, Sellar R and Merikangas KR (2000) Depressive spectrum diagnoses. *Comprehensive Psychiatry* **41**, 39–47.

Ayuso-Mateos JL, Nuevo R, Verdes E, Naidoo N and Chatterji S (2010) From depressive symptoms to depressive disorders: the relevance of thresholds. *The British Journal of Psychiatry* **196**, 365–371.

Barrera M and Garrisonjones CV (1988) Properties of the Beck depression inventory as a screening instrument for adolescent depression. *Journal of Abnormal Child Psychology* **16**, 263–273.

Bartra O, McGuire JT and Kable JW (2013) The valuation system: a coordinate-based meta-analysis of BOLD fMRI experiments examining neural correlates of subjective value. *Neuroimage* **76**, 412–427.

Beck AT, Steer RA, Ball R and Ranieri WF (1996) Comparison of Beck Depression Inventories-IA and -II in psychiatric outpatients. *Journal of Personality Assessment* **67**, 588–597.

Bolstad I, Andreassen OA, Groote I, Server A, Sjaastad I, Kapur S and Jensen J (2015) Effects of haloperidol and aripiprazole on the human mesolimbic motivational system: a pharmacological fMRI study. *European Neuropsychopharmacology* **25**, 2252–2261.

Boureau YL and Dayan P (2011) Opponency revisited: competition and cooperation between dopamine and serotonin. *Neuropsychopharmacology* **36**, 74–97.

Burkhouse KL, Kujawa A, Kennedy AE, Shankman SA, Langenecker SA, Phan KL and Klumpp H (2016) Neural reactivity to reward as a predictor of cognitive behavioral therapy response in anxiety and depression. *Depression and Anxiety* **33**, 281–288.

Canals J, Blade J, Carbajo G and Domenech-Llaberia ED (2001) The Beck Depression Inventory: psychometric characteristics and usefulness in nonclinical adolescents. *European Journal of Psychological Assessment* **17**, 63–68.

Carl H, Walsh E, Eisenlohr-Moul T, Minkel J, Crowther A, Moore T, Gibbs D, Petty C, Bizzell J, Dichter GS and Smoski MJ (2016) Sustained anterior cingulate cortex activation during reward processing predicts response to psychotherapy in major depressive disorder. *Journal of Affective Disorders* **203**, 204–212.

Chowdhury R, Guitart-Masip M, Lambert C, Dayan P, Huys Q, Düzel E and Dolan RJ (2013) Dopamine restores reward prediction errors in old age. *Nature Neuroscience* **16**, 648–653.

Cohen JY, Amoroso MW and Uchida N (2015) Serotonergic neurons signal reward and punishment on multiple timescales. *Elife* **4**, 1–25.

Dean Z, Horndasch S, Giannopoulos P and McCabe C (2016) Enhanced neural response to anticipation, effort and consummation of reward and aversion during bupropion treatment. *Psychological Medicine* **46**, 2263–2274.

Diekhof EK, Kaps L, Falkai P and Gruber O (2012) The role of the human ventral striatum and the medial orbitofrontal cortex in the representation of reward magnitude – an activation likelihood estimation meta-analysis of neuroimaging studies of passive reward expectancy and outcome processing. *Neuropsychologia* **50**, 1252–1266.

Dimidjian S, Barrera M, Martell C, Munoz RF and Lewinsohn PM (2011) The origins and current status of behavioral activation treatments for depression. *Annual Review of Clinical Psychology* **7**, 1–38.

Dubol M, Trichard C, Leroy C, Sandu AL, Rahim M, Granger B, Tzavara ET, Karila L, Martinot JL and Artiges E (2018) Dopamine transporter and reward anticipation in a dimensional perspective: a multimodal brain imaging study. *Neuropsychopharmacology* **43**, 820–827.

Engelmann JB, Berns GS and Dunlop BW (2017) Hyper-responsivity to losses in the anterior insula during economic choice scales with depression severity. *Psychological Medicine* **47**, 1–13.

Fernandez-Seara MA, Aznarez-Sanado M, Mengual E, Irigoyen J, Heukamp F and Pastor MA (2011) Effects on resting cerebral blood flow and functional connectivity induced by metoclopramide: a perfusion MRI study in healthy volunteers. *British Journal of Pharmacology* **163**, 1639–1652.

Forbes EE, Hariri AR, Martin SL, Silk JS, Moyles DL, Fisher PM, Brown SM, Ryan ND, Birmaher B, Axelson DA and Dahl RE (2009) Altered striatal activation predicting real-world positive affect in adolescent major depressive disorder. *American Journal of Psychiatry* **166**, 64–73.

Friston KJ, Williams S, Howard R, Frackowiak RSJ and Turner R (1996) Movement-related effects in fMRI time-series. *Magnetic Resonance in Medicine* **35**, 346–355.

Gehring WJ and Willoughby AR (2002) The medial frontal cortex and the rapid processing of monetary gains and losses. *Science* **295**, 2279–2282.

Godlewska BR, Browning M, Norbury R, Cowen PJ and Harmer CJ (2016) Early changes in emotional processing as a marker of clinical response to SSRI treatment in depression. *Translational Psychiatry* **6**, 1–7.

Goldberg JF, Ng-Mak D, Siu C, Chuang CC, Rajagopalan K and Loebel A (2017) Remission and recovery associated with lurasidone in the treatment of major depressive disorder with subthreshold hypomanic symptoms (mixed features): post-hoc analysis of a randomized, placebo-controlled study with longer-term extension. *CNS Spectrums* **22**, 373–373.

Goozee R, Handley R, Kempton MJ and Dazzan P (2014) A systematic review and meta-analysis of the effects of antipsychotic medications on regional cerebral blood flow (rCBF) in schizophrenia: association with response to treatment. *Neuroscience and Biobehavioral Reviews* **43**, 118–136.

Gotlib IH, Hamilton JP, Cooney RE, Singh MK, Henry ML and Joormann J (2010) Neural processing of reward and loss in girls at risk for major depression. *Archives of General Psychiatry* **67**, 380–387.

Grace AA (1991) Phasic versus tonic dopamine release and the modulation of dopamine system responsivity – a hypothesis for the etiology of schizophrenia. *Neuroscience* **41**, 1–24.

Greenberg WM and Citrome L (2017) Pharmacokinetics and pharmacodynamics of lurasidone hydrochloride, a second-generation antipsychotic: a systematic review of the published literature. *Clinical Pharmacokinetics* **56**, 493–503.

Grimm S, Ernst J, Boesiger P, Schuepbach D, Hell D, Boeker H and Northoff G (2009) Increased self-focus in major depressive disorder is related to neural abnormalities in subcortical-cortical midline structures. *Human Brain Mapping* **30**, 2617–2627.

Haber SN and Knutson B (2010) The reward circuit: linking primate anatomy and human imaging. *Neuropsychopharmacology* **35**, 4–26.

Hajcak G, Holroyd CB, Moser JS and Simons RF (2005) Brain potentials associated with expected and unexpected good and bad outcomes. *Psychophysiology* **42**, 161–170.

Handley R, Zelaya FO, Reinders AATS, Marques TR, Mehta MA, O'Gorman R, Alsop DC, Taylor H, Johnston A, Williams S, McGuire P, Pariante CM, Kapur S and Dazzan P (2013) Acute effects of single-dose aripiprazole and haloperidol on resting cerebral blood flow (rCBF) in the human brain. *Human Brain Mapping* **34**, 272–282.

Harmer CJ, O'Sullivan U, Favaron E, Massey-Chase R, Ayres R, Reinecke A, Goodwin GM and Cowen PJ (2009) Effect of acute antidepressant administration on negative affective bias in depressed patients. *American Journal of Psychiatry* **166**, 1178–1184.

Harmer CJ, Duman RS and Cowen PJ (2017) How do antidepressants work? New perspectives for refining future treatment approaches. *The Lancet Psychiatry* **4**, 409–418.

Hayashi K, Nakao K and Nakamura K (2015) Appetitive and aversive information coding in the primate dorsal raphe nucleus. *Journal of Neuroscience* **35**, 6195–6208.

Herbert M, Johns MW and Doré C (1976) Factor analysis of analogue scales measuring subjective feelings before and after sleep. *Psychology and Psychotherapy: Theory, Research and Practice* **49**, 373–379.

Hevey D, Thomas K, Laureano-Schelten S, Looney K and Booth R (2017) Clinical depression and punishment sensitivity on the BART. *Frontiers in Psychology* **8**, 1–7.

Holroyd CB and Coles MGH (2002) The neural basis of human error processing: reinforcement learning, dopamine, and the error-related negativity. *Psychological Review* **109**, 679–709.

Holroyd CB and Umemoto A (2016) The research domain criteria framework: the case for anterior cingulate cortex. *Neuroscience and Biobehavioral Reviews* **71**, 418–443.

Holroyd CB and Yeung N (2012) Motivation of extended behaviors by anterior cingulate cortex. *Trends in Cognitive Sciences* **16**, 122–128.

Holroyd CB, Larsen JT and Cohen JD (2004) Context dependence of the event-related brain potential associated with reward and punishment. *Psychophysiology* **41**, 245–253.

Huang M, Horiguchi M, Felix AR and Meltzer HY (2012) 5-HT1A and 5-HT7 receptors contribute to lurasidone-induced dopamine efflux. *Neuroreport* **23**, 436–440.

Hyman JM, Holroyd CB and Seamans JK (2017) A novel neural prediction error found in anterior cingulate cortex ensembles. *Neuron* **95**, 447–456.

Inaba K, Mizuhiki T, Setogawa T, Toda K, Richmond BJ and Shidara M (2013) Neurons in monkey dorsal raphe nucleus code beginning and progress of step-by-step schedule, reward expectation, and amount of reward outcome in the reward schedule task. *Journal of Neuroscience* **33**, 3477–3491.

Jocham G, Klein TA and Ullsperger M (2011) Dopamine-mediated reinforcement learning signals in the striatum and ventromedial prefrontal cortex underlie value-based choices. *Journal of Neuroscience* **31**, 1606–1613.

Jocham G, Klein TA and Ullsperger M (2014) Differential modulation of reinforcement learning by d2 dopamine and NMDA glutamate receptor antagonism. *Journal of Neuroscience* **34**, 13151–13162.

Keren H, O'Callaghan G, Vidal-Ribas P, Buzzell G, Brotman MEL, Pan P, Meffert L, Kaisera A, Wolke S, Pine D and Stringaris A (2018) Reward processing in depression: a conceptual and meta-analytic review across electrophysiological and fMRI studies. *American Journal of Psychiatry* **175**, 1111–1120.

Knutson B, Adams CM, Fong GW and Hommer D (2001) Anticipation of increasing monetary reward selectively recruits nucleus accumbens. *Journal of Neuroscience* **21**, 1–5.

Knutson B, Bhanji JP, Cooney RE, Atlas LY and Gotlib IH (2008) Neural responses to monetary incentives in major depression. *Biological Psychiatry* **63**, 686–692.

Krefetz DG, Steer RA, Gulab NA and Beck AT (2002) Convergent validity of the Beck Depression Inventory-II with the Reynolds Adolescent Depression Scale in psychiatric inpatients. *Journal of Personality Assessment* **78**, 451–460.

Kriegeskorte N, Simmons WK, Bellgowan PS and Baker CI (2009) Circular analysis in systems neuroscience: the dangers of double dipping. *Nature Neuroscience* **12**, 535–540.

Krystal JH and State MW (2014) Psychiatric disorders: diagnosis to therapy. *Cell* **157**, 201–214.

Kumar G, Steer RA, Teitelman KB and Villacis L (2002) Effectiveness of Beck Depression Inventory-II subscales in screening for major depressive disorders in adolescent psychiatric inpatients. *Assessment* **9**, 164–170.

Kumar P, Waiter G, Ahearn T, Milders M, Reid I and Steele JD (2008) Abnormal temporal difference reward-learning signals in major depression. *Brain* **131**, 2084–2093.

la Fougere C, Meisenzahl E, Schmitt G, Stauss J, Frodl T, Tatsch K, Hahn K, Moller HJ and Dresel S (2005) D-2 receptor occupancy during high- and low-dose therapy with the atypical antipsychotic amisulpride: a I-123-iodobenzamide SPECT study. *Journal of Nuclear Medicine* **46**, 1028–1033.

Lahti AC, Holcomb HH, Weiler MA, Medoff DR and Tamminga CA (2003) Functional effects of antipsychotic drugs: comparing clozapine with haloperidol. *Biological Psychiatry* **53**, 601–608.

Lahti AC, Weiler MA, Medoff DR, Tamminga CA and Holcomb HH (2005) Functional effects of single dose first- and second-generation antipsychotic administration in subjects with schizophrenia. *Psychiatry Research: Neuroimaging* **139**, 19–30.

Li Y, Zhong W, Wang D, Feng Q, Liu Z, Zhou J, Jia C, Hu F, Zeng J, Guo Q, Fu L and Luo M (2016) Serotonin neurons in the dorsal raphe nucleus encode reward signals. *Nature Communications* **7**, 1–15.

Liu Z, Zhou J, Li Y, Hu F, Lu Y, Ma M, Feng Q, Zhang JE, Wang D, Zeng J, Bao J, Kim JY, Chen ZF, El Mestikawy S and Luo M (2014) Dorsal raphe neurons signal reward through 5-HT and glutamate. *Neuron* **81**, 1360–1374.

Loebel A and Citrome L (2015) Lurasidone: a novel antipsychotic agent for the treatment of schizophrenia and bipolar depression. *BJPsych Bulletin* **39**, 237–241.

Loebel A, Cucchiaro J, Silva R, Kroger H, Hsu J, Sarma K and Sachs G (2014*a*) Lurasidone monotherapy in the treatment of bipolar I depression: a randomized, double-blind, placebo-controlled study. *American Journal of Psychiatry* **171**, 160–168.

Loebel A, Cucchiaro J, Silva R, Kroger H, Sarma K, Xu J and Calabrese JR (2014*b*) Lurasidone as adjunctive therapy with lithium or valproate for the treatment of bipolar i depression: a randomized, double-blind, placebo-controlled study. *American Journal of Psychiatry* **171**, 169–177.

Luking KR, Pagliaccio D, Luby JL and Barch DM (2016) Depression risk predicts blunted neural responses to gains and enhanced responses to losses in healthy children. *Journal of the American Academy of Child and Adolescent Psychiatry* **55**, 328–337.

Macoveanu J (2014) Serotonergic modulation of reward and punishment: evidence from pharmacological fMRI studies. *Brain Research* **1556**, 19–27.

Macoveanu J, Rowe JB, Hornboll B, Elliott R, Paulson OB, Knudsen GM and Siebner HR (2013) Playing it safe but losing anyway-serotonergic signaling of negative outcomes in dorsomedial prefrontal cortex in the context of risk-aversion. *European Neuropsychopharmacology* **23**, 919–930.

Macoveanu J, Fisher PM, Haahr ME, Frokjaer VG, Knudsen GM and Siebner HR (2014) Effects of selective serotonin reuptake inhibition on neural activity related to risky decisions and monetary rewards in healthy males. *Neuroimage* **99**, 434–442.

Marton P, Churchard M, Kutcher S and Korenblum M (1991) Diagnostic utility of the Beck depression inventory with adolescent psychiatric outpatients and inpatients. *Canadian Journal of Psychiatry-Revue Canadienne De Psychiatrie* **36**, 428–431.

Marutani T, Yahata N, Ikeda Y, Ito T, Yamamoto M, Matsuura M, Matsushima E, Okubo Y, Suzuki H and Matsuda T (2011) Functional magnetic resonance imaging study on the effects of acute single administration of paroxetine on motivation-related brain activity. *Psychiatry and Clinical Neurosciences* **65**, 191–198.

Mato Abad V, Garcia-Polo P, O'Daly O, Antonio Hernandez-Tamames J and Zelaya F (2016) ASAP (automatic Software for ASL processing): a toolbox for processing Arterial Spin Labeling images. *Magnetic Resonance Imaging* **34**, 334–344.

Matthews PM and Hampshire A (2016) Clinical concepts emerging from fMRI functional connectomics. *Neuron* **91**, 511–528.

McCabe C, Mishor Z, Cowen PJ and Harmer CJ (2010) Diminished neural processing of aversive and rewarding stimuli during selective serotonin reuptake inhibitor treatment. *Biological Psychiatry* **67**, 439–445.

Mehta MA, McGowan SW, Lawrence AD, Aitken MRF, Montgomery AJ and Grasby PM (2003) Systemic sulpiride modulates striatal blood flow: relationships to spatial working memory and planning. *Neuroimage* **20**, 1982–1994.

Morris SE and Cuthbert BN (2012) Research Domain Criteria: cognitive systems, neural circuits, and dimensions of behavior. *Dialogues in Clinical Neuroscience* **14**, 29–37.

Murphy SE, Norbury R, O'Sullivan U, Cowen PJ and Harmer CJ (2009) Effect of a single dose of citalopram on amygdala response to emotional faces. *British Journal of Psychiatry* **194**, 535–540.

Nelson C and Willison J (1991) *The Revised National Adult Reading Test–Test Manual*. Windsor, UK: NFER-Nelson 991, pp. 1–6.

Nelson C, Suppes T, Tsai J, Mao Y, Pikalov A and Loebel A (2015) Lurasidone for major depressive disorder with mixed features: effect of baseline depression severity on clinical outcome. *Neuropsychopharmacology* **40**, 330–331.

Nierenberg A, Tsai J, Mao Y, Pikalov A, Suppes T and Loebel A (2015) Efficacy of lurasidone in major depression with mixed features: pattern of improvement in depressive and manic symptoms. *Neuropsychopharmacology* **40**, 141–142.

O'Doherty J, Dayan P, Schultz J, Deichmann R, Friston KJ and Dolan RJ (2004) Dissociable roles of ventral and dorsal striatum in instrumental conditioning. *Science* **304**, 452–454.

Oei NYL, Rombouts S, Soeter RP, van Gerven JM and Both S (2012) Dopamine modulates reward system activity during subconscious processing of sexual stimuli. *Neuropsychopharmacology* **37**, 1729–1737.

Pan PM, Sato JR, Salum GA, Rohde LA, Gadelha A, Zugman A, Mari J, Jackowski A, Picon F, Miguel EC, Pine DS, Leibenluft E, Bressan RA and Stringaris A (2017) Ventral striatum functional connectivity as a predictor of adolescent depressive disorder in a longitudinal community-based sample. *American Journal of Psychiatry* **174**, 1112–1119.

Pessiglione M., Seymour B., Flandin G., Dolan R. J. and Frith C. D. (2006) Dopamine-dependent prediction errors underpin reward-seeking behaviour in humans. *Nature* **442**, 1042–1045.

Pizzagalli DA, Holmes AJ, Dillon DG, Goetz EL, Birk JL, Bogdan R, Dougherty DD, Iosifescu DV, Rauch SL and Fava M (2009) Reduced caudate and nucleus accumbens response to rewards in unmedicated individuals with major depressive disorder. *American Journal of Psychiatry* **166**, 702–710.

Pleger B, Ruff CC, Blankenburg F, Kloppel S, Driver J and Dolan RJ (2009) Influence of dopaminergically mediated reward on somatosensory decision-making. *PLoS Biology* **7**, 1–10.

Plichta MM, Schwarz AJ, Grimm O, Morgen K, Mier D, Haddad L, Gerdes ABM, Sauer C, Tost H, Esslinger C, Colman P, Wilson F, Kirsch P and Meyer-Lindenberg A (2012) Test-retest reliability of evoked BOLD signals from a cognitive-emotive fMRI test battery. *Neuroimage* **60**, 1746–1758.

Plomin R, Haworth CMA and Davis OSP (2009) Common disorders are quantitative traits. *Nature Reviews Genetics* **10**, 872–878.

Rice F, Rawal A, Riglin L, Lewis G and Dunsmuir S (2015) Examining reward-seeking, negative self-beliefs and over-general autobiographical memory as mechanisms of change in classroom prevention programs for adolescent depression. *Journal of Affective Disorders* **186**, 320–327.

Schoemaker H, Claustre Y, Fage D, Rouquier L, Chergui K, Curet O, Oblin A, Gonon F, Carter C, Benavides J and Scatton B (1997) Neurochemical characteristics of amisulpride, an atypical dopamine D-2/D-3 receptor antagonist with both presynaptic and limbic selectivity. *Journal of Pharmacology and Experimental Therapeutics* **280**, 83–97.

Scholl J, Kolling N, Nelissen N, Browning M, Rushworth MFS and Harmer CJ (2017) Beyond negative valence: 2-week administration of a serotonergic antidepressant enhances both reward and effort learning signals. *PLoS Biology* **15**, 1–30.

Shahnazian D and Holroyd CB (2017) Distributed representations of action sequences in anterior cingulate cortex: a recurrent neural network approach. *Psychonomic Bulletin, Review* **25**, 302–321.

Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R and Dunbar GC (1998) The Mini-International Neuropsychiatric Interview (MINI): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *Journal of Clinical Psychiatry* **59**, 22–33.

Sheline YI, Mintun MA, Barch DM, Wilkins C, Snyder AZ and Moerlein SM (2004) Decreased hippocampal 5-HT2A receptor binding in older depressed patients using F-18 altanserin positron emission tomography. *Neuropsychopharmacology* **29**, 2235–2241.

Shiroma PR, Thuras P, Johns B and Lim KO (2014) Emotion recognition processing as early predictor of response to 8-week citalopram treatment in late-life depression. *International Journal of Geriatric Psychiatry* **29**, 1132–1139.

Snaith RP, Hamilton M, Morley S, Humayan A, Hargreaves D and Trigwell P (1995) A scale for the assessment of hedonic tone – the Snaith–Hamilton Pleasure Scale. *British Journal of Psychiatry* **167**, 99–103.

Spielberger CD, Gorsuch RL and Lushene RE (1970) Manual for the state-trait anxiety inventory. *Self-Evaluation Questionnaire* 1–24.

Stoy M, Schlagenhauf F, Sterzer P, Bermpohl F, Haegele C, Suchotzki K, Schmack K, Wrase J, Ricken R, Knutson B, Adli M, Bauer M, Heinz A and Stroehle A (2012) Hyporeactivity of ventral striatum towards incentive stimuli in unmedicated depressed patients normalizes after treatment with escitalopram. *Journal of Psychopharmacology* **26**, 677–688.

Stringaris A, Vidal-Ribas Belil P, Artiges E, Lemaitre H, Gollier-Briant F, Wolke S, Vulser H, Miranda R, Penttila J, Struve M, Fadai T, Kappel V, Grimmer Y, Goodman R, Poustka L, Conrod P, Cattrell A, Banaschewski T, Bokde AL, Bromberg U, Buchel C, Flor H, Frouin V, Gallinat J, Garavan H, Gowland P, Heinz A, Ittermann B, Nees F, Papadopoulos D, Paus T, Smolka MN, Walter H, Whelan R, Martinot JL, Schumann G and Paillere-Martinot ML (2015) The brain's response to reward anticipation and depression in adolescence: dimensionality, specificity, and longitudinal predictions in a community-based sample. *American Journal of Psychiatry* **172**, 1215–1223.

Strober M, Green J and Carlson G (1981) Utility of the Beck depression inventory with psychiatrically hospitalized adolescents. *Journal of Consulting and Clinical Psychology* **49**, 482–483.

Suhara T, Nakayama K, Inoue O, Fukuda H, Shimizu M, Mori A and Tateno Y (1992) D1 dopamine receptor-binding in mood disorders measured by positron emission tomography. *Psychopharmacology* **106**, 14–18.

Suppes T, Datto C, Minkwitz M, Nordenhem A, Walker C and Darko D (2014) Effectiveness of the extended release formulation of quetiapine as monotherapy for the treatment of acute bipolar depression. *Journal of Affective Disorders* **168**, 485–493.

Suppes T, Kroger H, Pikalov A and Loebel A (2016*a*). Lurasidone adjunctive with lithium or valproate for bipolar depression: a placebo-controlled trial utilizing prospective and retrospective enrolment cohorts. *Journal of Psychiatric Research* **78**, 86–93.

Suppes T, Silva R, Cucchiaro J, Mao Y, Targum S, Streicher C, Pikalov A and Loebel A (2016*b*). Lurasidone for the treatment of major depressive disorder with mixed features: a randomized, double-blind, placebo-controlled study. *American Journal of Psychiatry* **173**, 400–407.

Suttajit S, Srisurapanont M, Maneeton N and Maneeton B (2014) Quetiapine for acute bipolar depression: a systematic review and meta-analysis. *Drug Design Development and Therapy* **8**, 827–838.

Sylvester CYC, Wager TD, Lacey SC, Hernandez L, Nichols TE, Smith EE and Jonides J (2003) Switching attention and resolving interference: fMRI measures of executive functions. *Neuropsychologia* **41**, 357–370.

Tohen M, Vieta E, Calabrese J, Ketter TA, Sachs G, Bowden C, Mitchell PB, Centorrino F, Risser R, Baker RW, Evans AR, Beymer K, Dube S, Tollefson GD and Breier A (2003) Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. *Archives of General Psychiatry* **60**, 1079–1088.

Tohen M, Kanba S, McIntyre RS, Fujikoshi S and Katagiri H (2014) Efficacy of olanzapine monotherapy in the treatment of bipolar depression with mixed features. *Journal of Affective Disorders* **164**, 57–62.

Umemoto A and Holroyd CB (2016) Exploring individual differences in task switching: persistence and other personality traits related to anterior cingulate cortex function. *Progress in Brain Research* **229**, 189–212.

Vrieze E, Pizzagalli DA, Demyttenaere K, Hompes T, Sienaert P, de Boer P, Schmidt M and Claes S (2013) Reduced reward learning predicts outcome in major depressive disorder. *Biological Psychiatry* **73**, 639–645.

Walsh MM and Anderson JR (2012) Learning from experience: event-related potential correlates of reward processing, neural adaptation, and behavioral choice. *Neuroscience and Biobehavioral Reviews* **36**, 1870–1884.

Walsh E, Carl H, Eisenlohr-Moul T, Minkel J, Crowther A, Moore T, Gibbs D, Petty C, Bizzell J, Smoski MJ and Dichter GS (2016) Attenuation of frontostriatal connectivity during reward processing predicts response to psychotherapy in major depressive disorder. *Neuropsychopharmacology* **42**, 831–843.

Walsh A, Browning M, Drevets W, Furey M and Harmer C (2017) Dissociable temporal effects of bupropion on behavioural measures of emotional and reward processing in major depressive disorder. *Biological Psychiatry* **81**, 353–354.

Walton ME, Croxson PL, Behrens TEJ, Kennerley SW and Rushworth MFS (2007) Adaptive decision making and value in the anterior cingulate cortex. *Neuroimage* **36**, 142–154.

Whitaker A, Johnson J, Shaffer D, Rapoport JL, Kalikow K, Walsh BT, Davies M, Braiman S and Dolinsky A (1990) Uncommon troubles in

young-people – prevalence estimates of selected psychiatric-disorders in a nonreferred adolescent population. *Archives of General Psychiatry* **47**, 487–496.

Wu CC, Samanez-Larkin GR, Katovich K and Knutson B (2014) Affective traits link to reliable neural markers of incentive anticipation. *Neuroimage* **84**, 279–289.

Yatham LN, Liddle PF, Dennie J, Shiah IS, Adam MJ, Lane CJ, Lam RW and Ruth TJ (1999) Decrease in brain serotonin 2 receptor binding in patients with major depression following desipramine treatment – a positron emission tomography study with fluorine-18-labeled setoperone. *Archives of General Psychiatry* **56**, 705–711.

Yatham LN, Goldstein JM, Vieta E, Bowden CL, Grunze H, Post RM, Suppes T and Calabrese JR (2005) Atypical antipsychotics in bipolar depression: potential mechanisms of action. *Journal of Clinical Psychiatry* **66**, 40–48.

Yeung N, Holroyd CB and Cohen JD (2005) ERP correlates of feedback and reward processing in the presence and absence of response choice. *Cerebral Cortex* **15**, 535–544.

Zhang WN, Chang SH, Guo LY, Zhang KL and Wang J (2013) The neural correlates of reward-related processing in major depressive disorder: a meta-analysis of functional magnetic resonance imaging studies. *Journal of Affective Disorders* **151**, 531–539.