Psychopharmacology (2011) 217:271–278
DOI 10.1007/s00213-011-2278-4

ORIGINAL INVESTIGATION

The D2 antagonist sulpiride modulates the neural processing of both rewarding and aversive stimuli in healthy volunteers

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Received: 10 September 2010 / Accepted: 22 March 2011 / Published online: 15 April 2011
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Abstract
Rationale Animal studies indicate that dopamine pathways in the ventral striatum code for the motivational salience of both rewarding and aversive stimuli, but evidence for this mechanism in humans is less established. We have developed a functional magnetic resonance imaging (fMRI) model which permits examination of the neural processing of both rewarding and aversive stimuli.
Objectives The aim of the study was to determine the effect of the dopamine receptor antagonist, sulpiride, on the neural processing of rewarding and aversive stimuli in healthy volunteers.
Methods We studied 30 healthy participants who were randomly allocated to receive a single dose of sulpiride (400 mg) or placebo, in a double-blind, parallel-group design. We used fMRI to measure the neural response to rewarding (taste or sight of chocolate) and aversive stimuli (sight of mouldy strawberries or unpleasant strawberry taste) 4 h after drug treatment.
Results Relative to placebo, sulpiride reduced blood oxygenation level-dependent responses to chocolate stimuli in the striatum (ventral striatum) and anterior cingulate cortex. Sulpiride also reduced lateral orbitofrontal cortex and insula activations to the taste and sight of the aversive condition.
Conclusions These results suggest that acute dopamine receptor blockade modulates mesolimbic and mesocortical neural activations in response to both rewarding and aversive stimuli in healthy volunteers. This effect may be relevant to the effects of dopamine receptor antagonists in the treatment of psychosis and may also have implications for the possible antidepressant properties of sulpiride.

Keywords Dopamine · Reward · D2 antagonist · Sulpiride · fMRI · Ventral striatum

Introduction

Recent advances in neuroimaging have allowed the identification of the neural systems activated during reward processing and motivational behaviour in humans (Knutson and Cooper 2005). Studies using functional magnetic resonance imaging (fMRI) have revealed increased activity in the ventral striatum during the presentation of primary or secondary rewarding stimuli such as pleasant pictures, music, food, or monetary reward (Blood and Zatorre 2001; Lane et al. 1997; O'Doherty et al. 2001a, b). The medial prefrontal cortex and the anterior/pregenual cingulate are also reported to be important in the neural response to pleasant stimuli and reward-motivated behaviour (Bechara et al. 1996; Kahnt et al. 2010; Kringelbach et al. 2003; Rolls et al. 2003b, 2010; Rolls and McCabe 2007). Conversely, aversive stimuli have been found to activate the lateral orbitofrontal cortices, the amygdala and caudate nuclei (Fitzgerald et al. 2004; Rolls et al. 2003a; Zald et al. 2002).

Dopamine pathways are known to play a key role in reward-based mechanisms through dopamine release from ventral tegmental area neurons at their terminals in the nucleus accumbens, ventral striatum (Bjorklund and Dunnett 2007). Moreover, the role of dopamine extends to the processing of aversive stimuli, giving rise to the notion that dopamine pathways determine the motivational salience of environ-

Electronic supplementary material The online version of this article (doi:10.1007/s00213-011-2278-4) contains supplementary material, which is available to authorized users.

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mental stimuli whether positively or negatively valenced (Matsumoto and Hikosaka 2009). Previous studies which have examined the influence of dopamine manipulation on the neural processes of reward and punishment in humans are consistent with this proposal. For example, (Knutson et al. 2004) found that amphetamine administration modulated prefrontal and striatal activations produced by monetary reward and loss, whilst Menon et al. (2007) reported that the dopamine receptor antagonist, haloperidol, abolished the striatal response to the prediction error involved in learning an aversive conditioned response.

We have developed an experimental paradigm which allows the study of the neural responses to primary and secondary rewarding and aversive stimuli in the human brain using fMRI. Using this approach, we have been able to show that the chocolate stimuli activate parts of the reward system such as the striatum, the medial orbitofrontal cortex and pregenual cingulate gyrus, whereas the unpleasant strawberry conditions activate the lateral orbitofrontal cortex and insula cortex (McCabe et al. 2010; Rolls and McCabe 2007). We have also shown that unmedicated patients recovered from depression have reduced ventral striatal responses to primary reward, suggesting trait abnormalities in reward mechanisms in those at risk of mood disorder (McCabe et al. 2009). The aim of the present study was to use the dopamine receptor antagonist, sulpiride, to examine the effects of dopamine D2/D3 receptor blockade on the neural responses to rewarding and aversive stimuli in our model. We hypothesised that sulpiride would lower the response in ventral striatum to chocolate reward and also diminish the neural processing of an aversive taste in lateral orbitofrontal cortex.

Materials and methods

Participants

Thirty healthy volunteers were randomised to receive a single oral dose with sulpiride (400 mg, $n=15$), or placebo ($n=15$), in a double-blind between-groups design. We used a between-groups design to minimise the effects of practice or habituation to the stimuli used in this study. Volunteers were also matched for age and gender (see Table 1). Ethical approval was provided by the Oxford Research Ethics Committee B and written informed consent was obtained from all participants before screening and after a complete description of the study was given. Exclusion criteria for all subjects were current or past Axis-1 disorder on the Structured Clinical Interview for DSM-IV (Spitzer et al. 2004) and any contraindications to MRI, e.g. pacemaker, mechanical heart valve, hip replacement, metal implants.

Table 1 Group demographic and psychosocial measures

Measure	Sulpiride ($n=15$), mean (SD)	Placebo ($n=15$), mean (SD)
Age (years)	22 (3.3)	22 (2.2)
Gender, M/F	7/8	8/7
BDI	1.8 (2.3)	2 (3.8)
TRAIT	34 (7.4)	36 (8.1)
FCPS	130 (14.4)	127 (16.5)
SHAPS	21 (3)	21 (4)
BMI	22 (2)	22.7 (3)
Choc craving	6.5 (1.6)	6.7 (1.7)
Choc liking	7.6 (1.7)	8.1 (1.3)
Choc freq eat	2.8 (2)	2.8 (1.8)

One-way ANOVAs, all $p>0.077$

BDI Beck Depression Inventory, *FCPS* Fawcett–Clarke Pleasure Scale, *SHAPS* Snaith–Hamilton Pleasure Scale, *BMI* body mass index

None of the participants took current medication apart from the contraceptive pill. Before drug administration and to ensure group matching, baseline information was collected using the Beck Depression Inventory (BDI; Beck et al. 1961), State-Trait Anxiety Inventory (Spielberger 1983), the Fawcett–Clarke Pleasure Scale (FCPS; Fawcett et al. 1983), and the Snaith–Hamilton Pleasure Scale (SHAPS; Snaith et al. 1995). The participants also completed a "chocolate questionnaire" to measure liking, craving and frequency of eating chocolate (Rolls and McCabe 2007). Body mass index (BMI) was also calculated for each volunteer. To assess the effects of the treatment, the following questionnaires were taken before and after the treatment: visual analogue scales (VAS) of happiness, sadness, anger, disgust, alertness and anxiety, and the State Anxiety Inventory (Spielberger 1983). Volunteers also completed the Positive Affect Negative Affect Schedule (PANAS; Watson et al. 1988) before and after the treatment.

Overall design

We compared brain responses to rewarding and aversive stimuli across the two drug groups. Each of the following conditions were applied nine times in a randomised order (see Electronic supplementary material (ESM) Table S1): chocolate in the mouth, chocolate picture, chocolate in the mouth with chocolate picture, strawberry in the mouth, strawberry picture, strawberry in the mouth with strawberry picture. Subjective effects of the stimuli were measured by psychophysical ratings of "pleasantness", "intensity" and "wanting" made on every trial by the subjects during the fMRI acquisition. The participants were instructed not to eat chocolate for 24 h before the scan and to eat only a small lunch on the day of scanning. Mood state was recorded on the study day with the BDI (Beck et al. 1961).

Stimuli

Stimuli were delivered to the subject's mouth through three Teflon tubes (one for the tasteless rinse control described below, one for chocolate taste and one for strawberry taste); the tubes were held between the lips. Each tube was connected to a separate reservoir via a syringe and a one-way syringe activated check valve (model 14044-5, World Precision Instruments, Inc.), which allowed 0.5 ml of any stimulus to be delivered manually at the time indicated by the computer. The chocolate was formulated to be liquid at room temperature, with a list of the six stimulus conditions described in Table 1. A control tasteless solution, 0.5 mL of a saliva-like rinse solution (25×10^{-3} mol/L KCl and 2.5×10^{-3} mol/L $NaHCO_3$ in distilled H_20), was used between trials (tl in ESM Table S1); when subtracted from the effects of the other stimuli, this allowed somatosensory and any mouth movement effects to be subtracted from the effects produced by the other oral stimuli (de Araujo et al. 2003a; O'Doherty et al. 2001c). This allows the taste, texture and olfactory areas to be shown independently of any somatosensory effects produced by introducing a fluid into the mouth (de Araujo et al. 2003a, b; de Araujo and Rolls 2004; O'Doherty et al. 2001c). The aversive stimulus was a strawberry drink (Rosemount Pharmaceuticals Ltd.) which was rated as intense as the chocolate, but unpleasant in valence (McCabe et al. 2009). Both the liquid chocolate and the strawberry had approximately the same sweetness and texture, which enabled them to pass freely through the Teflon delivery tubes.

Experimental procedure

At the beginning of each trial, one of the six stimuli chosen by random permutation was presented. If the trial involved an oral stimulus, this was delivered in a 0.5-mL aliquot to the subject's mouth. At the same time, at the start of the trial, a visual stimulus was presented, which was either the picture of chocolate, of mouldy strawberries or a grey control image of approximately the same intensity. The image was turned off after 7 s, at which time a small green cross appeared on a visual display to indicate to the subject to swallow what was in the mouth. After a delay of 2 s, the subject was asked to rate each of the stimuli for "pleasantness" on that trial (with +2 being very pleasant and −2 very unpleasant), for "intensity" on that trial (0 to +4) and for "wanting" (+2 for wanting very much, 0 for neutral, and −2 for very much not wanting). The ratings were made with a VAS in which the subject moved the bar to the appropriate point on the scale using a button box. After the last rating, the grey visual stimulus indicated the delivery of the tasteless control solution, which was also used as a rinse between stimuli; this was administered in exactly the same way as a test stimulus, and the subject was cued to swallow after 7 s by the green cross. The tasteless control was always accompanied by the grey visual stimulus. On trials on which only the picture of chocolate was shown, there was no rinse, but the grey visual stimulus was shown in order to allow an appropriate contrast, as described below. There was then a 2-s delay period that allowed for swallowing followed by a 1-s gap until the start of the next trial. A trial was repeated for each of the six stimulus conditions shown in ESM Table S1, and the whole cycle was repeated nine times. The instruction given to the subject was (on oral delivery trials) to move the tongue once as soon as a stimulus or tasteless solution was delivered in order to distribute the solution round the mouth to activate the receptors for taste and smell, and then to keep still for the remainder of the 7-s period until the green cross was shown, when the subject could swallow. This procedure has been shown to allow taste effects to be demonstrated clearly with fMRI using the procedure of subtracting any activations produced by the tasteless control from those produced by a taste or other stimulus (de Araujo et al. 2003a, b; de Araujo and Rolls 2004; O'Doherty et al. 2001c).

fMRI scan

The experimental protocol consisted of an event-related interleaved design using in random permuted sequence the six stimuli described above and shown in ESM Table S1. Images were acquired with a 3.0-T Varian/Siemens whole-body scanner at the Oxford Centre for Clinical Magnetic Resonance Imaging where T2*-weighted EPI slices were acquired every 2 s (TR=2). Imaging parameters were selected to minimise susceptibility and distortion artefact in the orbitofrontal cortex (Wilson et al. 2002). Coronal slices (33) with in-plane resolution of 3×3 mm and between plane spacing of 4 mm were obtained. The matrix size was 64×64 and the field of view was 192×192 mm. Acquisition was carried out during the task performance, yielding 972 volumes in total. A whole brain T2*-weighted EPI volume of the above dimensions and an anatomical T1 volume with coronal plane slice thickness 3 mm and in-plane resolution of 1.0×1.0 mm were also acquired.

fMRI analysis

The imaging data were analysed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/). Pre-processing of the data used realignment, reslicing with sinc interpolation, normalisation to the Montreal Neurological Institute (MNI) coordinate system and spatial smoothing with a 6-mm full width at half-maximum isotropic Gaussian kernel. Time series non-sphericity at each voxel was estimated and corrected for (Friston et al. 2002), and a high-pass filter with a cutoff period of 128 s was applied. In the single event

design, a general linear model was then applied to the time course of activation where stimulus onsets were modelled as single impulse response functions and then convolved with the canonical haemodynamic response function (Friston et al. 1994). Linear contrasts were defined to test specific effects. Time derivatives were included in the basis functions set. Following smoothness estimation, linear contrasts of parameter estimates were defined to test the specific effects of each condition with each individual dataset. Voxel values for each contrast resulted in a statistical parametric map of the corresponding t statistic, which was then transformed into the unit normal distribution (SPM Z). The statistical parametric maps from each individual dataset were then entered into second-level, random effects analyses accounting for both scan-to-scan and subject-to-subject variability. SPM converts the *t* statistics to *Z* scores (Table 2). We examined simple main effects of group with one-sample *t* tests, for all chocolate stimuli together or all strawberry stimuli, thresholded at $p=0.001$ and whole brain cluster-corrected ($p<0.05$ family-wise errors (FWE) for multiple comparisons). To assess between-group differences for each condition, two-sample *t* tests were used, thresholded at $p=0.05$ and whole brain cluster-corrected ($p<0.05$ FWE for multiple comparisons). We examined between-group differences for all the positive chocolate together, all the aversive strawberry together and for each contrast separately. Plots of contrast estimates are extracted using the plots tool in SPM8. Coordinates of the activations are listed in the stereotactic space of The Montreal Neurological Institute's ICBM152 brain (Table 2 and ESM Table S3).

Results

Demographic details and mood ratings

There were no significant differences between the two groups as determined by one-way ANOVAs for age, gender, BMI, chocolate liking and attitudes to food (EAT), all ($p>0.07$, Table 1). There were no significant differences between the two groups as determined by one-way ANOVAs for measures of anhedonia (SHAPS, FCPS) or mood (BDI) (all $p>0.07$, Table 1). There were no significant effects of group [$F(1,27)=1.6$, $p=0.2$], between the sulpiride- and placebo-treated groups on VAS (alertness, disgust, drowsiness, anxiety, happiness, nausea and sadness) or PANAS [$F(1,27)=0.36$, $p=0.55$], as determined by repeated measures ANOVAs (ESM Table S2).

Ratings of stimuli

Ratings of pleasantness, intensity and wanting for the stimuli were obtained during the scanning on each trial for every condition. All subjects rated the strawberry picture and taste as unpleasant and the chocolate stimuli as pleasant. Using repeated measures ANOVA with "ratings" as a first factor with three levels—pleasantness, intensity and wanting—and "condition" as a second factor with six levels (see ESM Table S1 for six condition levels), there was no significant effect of group [$F(1,28)=1.6$, $p=0.2$] or group × condition interaction [$F(1,28)=1.72$, $p=0.2$] (see ESM Fig. S1).

fMRI responses

ESM Table S3 provides a summary of the main effects of one-sample *t* tests for the positive chocolate stimuli and the aversive strawberry stimuli. Table 2 provides a summary of the results of the interaction with group.

Main effect of task

As expected, the positive chocolate stimuli activated reward-relevant circuitry including the ventral striatum, the putamen, the anterior insula and parts of the anterior cingulate cortex. The unpleasant strawberry stimuli activated areas involved in aversive processing including the posterior insula cortex and the lateral orbitofrontal cortex, but not the ventral striatum (ESM Table S3).

Effect of sulpiride on chocolate reward

The sulpiride group, compared to placebo, showed less blood oxygenation level-dependent (BOLD) activation to the chocolate stimuli in the areas known to play a key role in reward, including the ventral striatum and the anterior cingulate cortex (Figs. 1a, b and 2a, b.).

Effect of sulpiride on aversive strawberry

The sulpiride group relative to placebo showed less BOLD activation to the strawberry stimuli in areas known to play a key role in processing aversive stimuli including the lateral orbitofrontal cortex and insula, as illustrated in Fig. 3. Relative to placebo, the sulpiride group also had less BOLD activation to the unpleasant strawberry taste in the precentral gyrus (Table 2).

Discussion

Our results indicate that a single dose of the D2/3 receptor antagonist, sulpiride, can decrease the neural processing of reward in the ventral striatum and anterior cingulate despite no change in subjective mood. Furthermore, we found that sulpiride decreased activation to the aversive sight and taste

Table 2 Regions showing significant effect of treatment on each condition relative to placebo

Brain region	MNI coordinates			*Z* score (cluster size)	Significance (*p* value)
	X	*Y*	*Z*		
All choc stimuli					
Placebo > Sulpiride					
Ventral Striatum	14	16	−2	3.40 (2445)	0.05[a]
Chocolate in the mouth plus the sight of chocolate					
Placebo > Sulpiride					
Anterior cingulate	10	16	30	3.33 (2205)	0.05
	0	4	34	3.04 (2205)	0.05
Temporal gyrus	34	−26	8	3.44 (5860)	<0.001
All straw stimuli					
Placebo > Sulpiride					
LOFC	34	32	−8	4.16 (2265)	<0.001
Strawberry in the mouth:					
Placebo > Sulpiride					
Precentral gyrus	54	6	38	3.65 (745)	<0.001[a]
Insula	34	16	10	3.33 (745)	<0.001[a]

p values: thresholded at $p=0.05$ uncorrected

LOFC lateral orbitofrontal cortex

[a] Thresholded at $p=0.01$ uncorrected; whole brain fully corrected cluster level ($p<0.05$ FWE for multiple comparisons)

of mouldy strawberries in the insula and lateral orbitofrontal cortex.

The decreased striatal activation to reward seen with sulpiride is in keeping with our hypothesis that inhibition of dopamine transmission would negatively impact on the neural processing of pleasant stimuli. A recent study which examined the effects of a single dose of the antipsychotic olanzapine on neural processing of delayed incentive salience of monetary reward in healthy volunteers also reported reduced ventral striatal activation (Abler et al. 2007), whilst Knutson et al. (2004) found that the dopamine agonist amphetamine increased the duration (but decreased the peak) of ventral striatal response to win anticipation. Interestingly, a hyperactive striatal response to reward was also found in patients with schizophrenia, supporting the notion that psychosis may represent a state of abnormal salience (Kapur 2003). From this viewpoint, dopamine receptor antagonists may produce therapeutic benefit in psychosis by decreasing the tendency of patients to ascribe novelty and motivational importance to irrelevant stimuli. Unfortunately, this effect of antipsychotic drugs may also be directed towards normal motivational drives, perhaps accounting for the association of antipsychotic treatment with emotional blunting and indifference to normal social reinforcers.

We also found decreased activation to the aversive stimuli in brain regions such as the lateral orbitofrontal cortex and the insula which have been previously shown to encode the processing of unpleasant stimuli (Fitzgerald et al. 2004; Small et al. 2001) and specifically also in the current model of aversion processing (Horder et al. 2010; McCabe et al. 2009, 2010). Interestingly, therefore, it

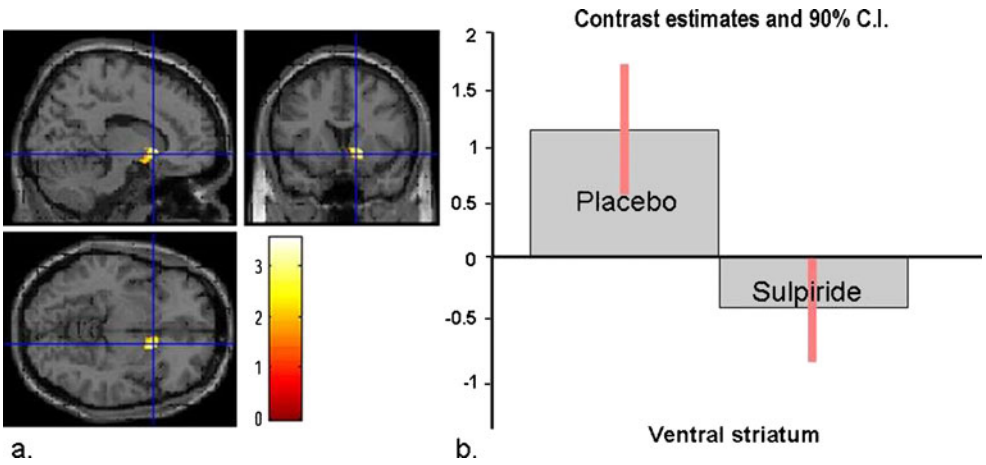

Fig. 1 **a** All chocolate stimuli (placebo vs. sulpiride): Axial, sagittal and coronal image of decreased ventral striatum in the sulpiride group compared to the placebo group, activations thresholded at $p=0.01$ uncorrected and whole brain cluster-corrected ($p<0.05$ FWE for multiple comparisons). **b** Contrast estimates for ventral striatum at 14 16 −2 for sulpiride and placebo

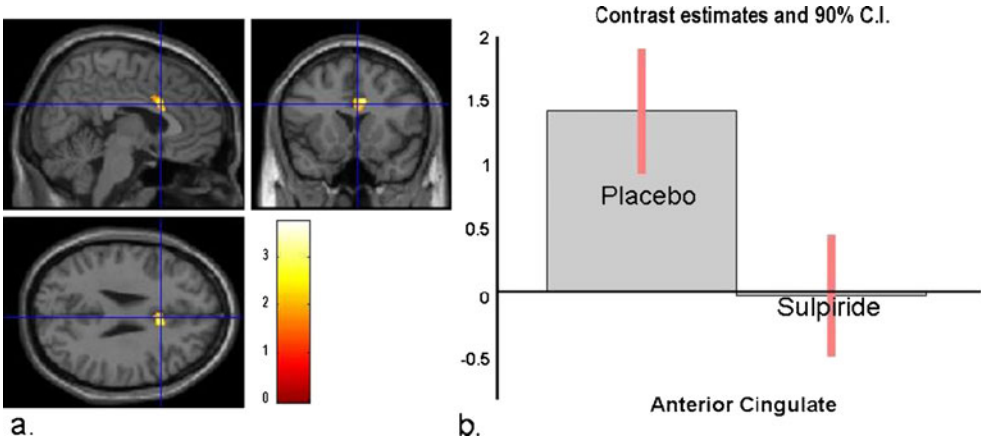

Fig. 2 **a** Chocolate in the mouth plus the sight of chocolate (sulpiride vs. placebo): Axial, sagittal and coronal image of decreased anterior cingulate cortex activation in the sulpiride group compared to the placebo group, activations thresholded at $p=0.05$ uncorrected and whole brain cluster-corrected ($p<0.05$ FWE for multiple comparisons). **b** Contrast estimates for anterior cingulate at 10 16 30 for sulpiride and placebo

seems that antipsychotics not only have the ability to reduce the attribution of salience to rewarding stimuli but also are able to dampen the response to negatively valenced stimuli. These results therefore support the idea that dopamine is involved in the salience of both positive and negative events (Knutson et al. 2004; Schultz 2010a, b). Furthermore, recent studies examining the effects of pharmacological manipulation of dopamine in both Parkinson's disease (PD) and Tourette's syndrome found that dopamine enhancement in PD enhanced reward learning and dopamine blockade in Tourettes enhanced punishment avoidance (Palminteri et al. 2009). These data suggest that modulating dysfunctional dopamine systems enhances decision making by redressing the reward–punishment imbalance. Preclinical studies on the effects of antipsychotics also indicate that dopamine blockade in the striatum disrupts avoidance performance and that this may be due to the reduced activation of instrumental behaviour (Maia and Frank 2011). Moreover, studies examining behavioural strategies in response to uncertainty in schizophrenic patients implicate decreased dopamine in the prefrontal complex as underpinning such dysfunction (Strauss et al. 2011).

Reducing reactivity to and salience attribution of aversive stimuli is a common goal in treatments of disorders characterised by negative affectivity and may help explain why antipsychotic drugs are sometimes found to be beneficial in the treatment of anxiety and depression. In particular, substituted benzamides such as sulpiride and amisulpiride are commonly used clinically in some countries for the treatment of chronic mood disorders such as dysthymia (Lecrubier et al. 1997). Furthermore, a similar effect on aversive processing was also seen with 7-day administration of the SSRI citalopram in our model in healthy volunteers (McCabe et al. 2010).

Previous studies have shown that schizophrenia involves hyperactivity of dopamine neurons in the basal ganglia, but decreased activity in the prefrontal cortex (Epstein et al. 1999; Lewis 1995; Meyer-Lindenberg et al. 2002). It is therefore of great interest that we found decreased activation to the pleasant chocolate reward in the ventral striatum yet did not find any increased prefrontal cortex activity at the statistical threshold used here. It is important to assess whether such effects may be seen with a larger sample of volunteers and increased statistical power. The current study used a between-subjects, placebo-controlled

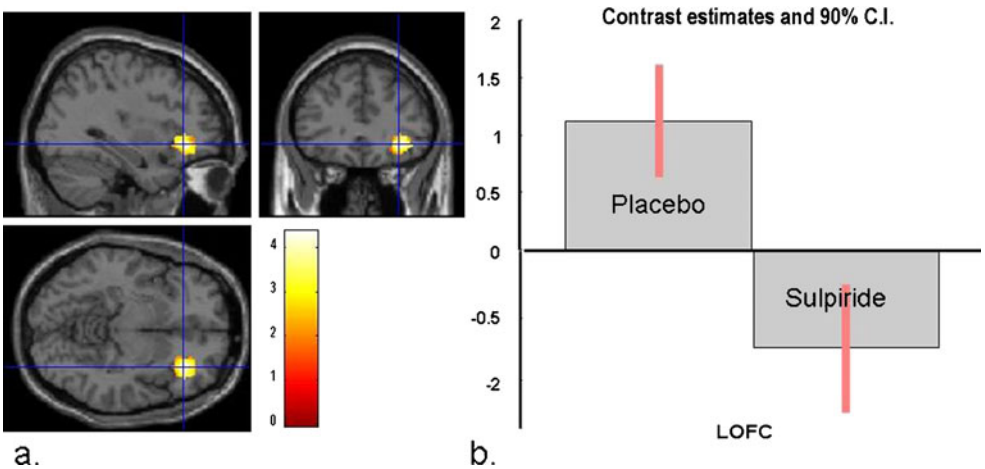

Fig. 3 **a** All strawberry stimuli (placebo vs. sulpiride): Axial, sagittal and coronal image of decreased LOFC activation in the sulpiride group compared to the placebo group, activations thresholded at $p=0.05$ uncorrected and whole brain cluster-corrected ($p<0.05$ FWE for multiple comparisons). **b** Contrast estimates for LOFC at 34 32 −8 for sulpiride and placebo

design to minimise the effects of practice or habituation to the stimuli used here. In future studies, we plan to explore the effects of drug manipulations in this model using a within-subjects design to minimise inter-subject variability. Such an approach may ultimately improve statistical power and be useful in the future application of this model.

Taken together, the results from this study show that a single dose of the antipsychotic drug sulpiride can differentially modulate neural activity in response to rewarding and aversive stimuli in healthy volunteers. These findings may have implications for the mode of action of drugs such as sulpiride in the treatment of psychosis and mood disorders. Studies in patients will be required to see whether the effects we have seen are related to the therapeutic actions of sulpiride in clinical populations.

Acknowledgments This work was supported by the Medical Research Council Grant no (HQRORVO). We would like to acknowledge Mr Leo McCabe for the photography.

Financial disclosures Dr. McCabe has received consultancy from P1vital Ltd. Dr. Harmer is on the advisory board of P1vital Ltd. and holds shares in the same company. She is also the company director of Oxford Psychologists. Dr. Harmer has received fees for consultancy from Servier, GlaxoSmithKline, Astra Zeneca, Johnson&Johnson, P1vital, Roche and EiSai. Professor Cowen has been a paid member of the advisory boards of Eli Lilly, Servier and Lundbeck and has been a paid lecturer for Eli Lilly, Servier, GlaxoSmithKline. Miss Huber reports no biomedical financial interests or potential conflicts of interest.

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