Impaired Subjective Wellbeing in schizophrenia is associated with reduced anterior cingulate activity during reward processing

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Abstract

Background

Patients with schizophrenia have substantially reduced 'Subjective Wellbeing' (SW) compared to healthy individuals. It has been suggested that diminished SW may be related to deficits in the neural processing of reward but this has not directly been shown. It was hypothesized that in schizophrenia lower SW will be associated with attenuated reward-related activation in the 'reward network'.

Methods

Twenty patients with schizophrenia with a range of SW underwent an fMRI reward task. The brain activity underlying reward 'anticipation' and 'outcome' in schizophrenia was examined and compared to those of 12 healthy participants using a full factorial analysis. Region of interest of areas within the reward network and whole-brain analyses were conducted to reveal neural correlates of SW.

Results

Reward-related neural activity in schizophrenia was not significantly different to healthy participants, however, the patients with schizophrenia showed significantly diminished SW. Both ROI and whole-brain analyses confirmed that SW scores in the patients correlated significantly with activity specifically in the dorsal anterior cingulate cortex (dACC) during both reward anticipation and reward outcome. This association was not seen in the healthy participants.

Conclusions

In patients with schizophrenia reduced activation of the dACC during multiple aspects of reward processing is associated with lower Subjective Wellbeing. As the dACC has been widely linked to coupling of reward and action, and the link to SW is apparent over anticipation and outcome, these findings suggest that SW deficits in schizophrenia may be attributable to reduced integration of environmental rewarding cues, motivated behaviour and reward outcome.

Introduction

While treatment of schizophrenia has focussed on reduction of the clinical presence of positive symptoms, there has been increasing recognition of the importance of patients' subjective experiences of illness as an important therapeutic target and key predictor of outcome (Karow *et al.*, 2007). Approximately one third of patients with schizophrenia treated with antipsychotic medication experience dysphoria (Voruganti *et al.*, 2001) which can influence clinical and functional outcome and compliance (Naber *et al.*, 2005). Patient Subjective Wellbeing (SW) can be measured with the Subjective Wellbeing under Neuroleptics scale (SWN (Naber, 1995)) which assesses patients' psychological and emotional state and can be differentiated from other related constructs such as depression and anhedonia. SW is a multidimensional construct and measures patients' perceptions of social integration, self-control, emotional-regulation, mental functioning, and physical functioning. It is also a distinct outcome measure in schizophrenia (Lambert & Naber, 2004) and is a central predictor of medication compliance (Karow *et al.*, 2007); however, the neural basis of poor SW remains unclear.

Subjective experience is intricately linked with dopaminergic functioning and reward processing. Alterations in dopaminergic tone manifest negative changes to subjective experience, such as increased dysphoria, and lower subjective well-being following consumption of antipsychotic administration (Voruganti & Awad, 2004), the administration of which depletes dopaminergic transmission (de Haan *et al.*, 2000). Accordingly SW is generally higher in patients treated with atypical rather than typical antipsychotics despite similar efficacy in reducing positive symptoms (Naber *et al.*, 2001; Karow & Naber, 2002) most likely due to these compounds producing lower striatal D2 receptor blockade. The level of ventral striatal (VS) dopamine receptor binding is associated with SW in medicated patients with schizophrenia (Mizrahi *et al.*, 2007). The ventral striatum is central to reward

processing, and it has been widely shown that activation in the VS is elevated during reward anticipation (e.g. Schott *et al.*, 2008). The VS signal reflects DA activity (Knuston & Gibbs, 2007), and this signal has been shown to be absent in healthy participants following dopamine-depletion with AMPT (da Silva Alves *et al.*, 2010).

Together this evidence then suggests that the relationship between SW and altered dopaminergic function may be underpinned by a central role of dopamine in reward-based learning. In this way, the antipsychotic olanzapine (a dopamine antagonist) which reduces reward-related brain activation in the reward network (Abler *et al.*, 2007), interferes with neural activation in reward areas during reward processing and reduces subjective experience in healthy participants after only a single dose (Schlagenhauf *et al.*, 2007). Reduced anticipation of reward in schizophrenia is also associated with anhedonia (Gard *et al.*, 2007). Dysfunction of the reward network in patients with schizophrenia will, therefore, negatively impact processing of, and motivation towards, environmental reward cues, which we propose forms the mechanism for low SW in schizophrenia.

SW has, however, been shown to improve with the antipsychotic aripiprazole despite high striatal D2 receptor blockade (Mizrahi *et al*, 2009) and Mizrahi *et al.* (2007) report strong correlations between SW and D2 receptor binding in cortical brain regions. These findings suggest SW is not just a function of striatal D2 receptor binding and may be related to functioning of extra-striatal brain regions. In following, this study aimed to investigate the neural correlates of SW in schizophrenia using fMRI, specifically the relationship between SW and activation of the 'reward network' in response to rewarding stimuli but also across the whole-brain to investigate extra-striatal neural correlates. We primarily hypothesized that in schizophrenia patients lower SW will be associated with attenuated reward-related activation in regions of the ‘reward network’ and this would be confirmed by ROI analyses of these regions. Also, SW-related changes in activation in these regions will be greater in the

anticipatory phase than the outcome phase. It has recently been suggested that the SWN scale, despite being designed for use in schizophrenia, may be valid in healthy volunteers (Vothknecht *et al.*, 2012) hence we carried out a subsequent exploratory analysis investigating whether there was a similar relationship between SW and brain activity in healthy participants.

Method

Design

Patients with schizophrenia and healthy control participants underwent fMRI during a modified Monetary Incentive Delay reward task (see Knutson *et al.*, 2001). Behavioural data were analysed to establish the degree to which performance and ratings of outcome were related to SW. The fMRI data were analysed to examine (a) brain activation during the anticipatory and consummatory phases of the reward task per se in patients and healthy participants; and (b) brain activity within areas of the reward network which correlated with SW scores using region of interest analyses. Whole-brain analyses were also conducted to reveal areas of the brain other than reward-regions which correlated with SW.

Participants

Twenty male dextral patients with DSM-IV diagnosis of schizophrenia and twelve healthy participants took part. Patients were on average 36.5 years old (sd=6.9) and had an average National Adult Reading Test-2 (Nelson & Willison, 1991) IQ score of 101.6 (sd=11.6). Healthy participants had a mean age of 30.7 years (sd=7.3) and an IQ of 106.4 (sd=9.2), thus patients were on average 5 years older, but neither IQ scores nor ages were significantly different.

Patients were moderately symptomatic (Positive And Negative Syndrome Scale (Kay *et al.*, 1987) mean total = 57.5 (sd=15.2) (subscale means (sd): positive scale = 15.8 (7.3), negative scale = 13.7 (5.6) and general scale = 28.1 (6.3)) and had low extrapyramidal side effects (Simpson-Angus Scale (Simpson & Angus, 1970) mean=4.54 (sd=3.2), Extrapyramidal Symptom Rating Scale (Chouinard *et al.*, 1980) mean = 2.14 (sd=2.6) and Barnes Akathisia scale (Barnes, 1989) mean=1.33 (sd=3.2; median = 0.0)). None of the 20 patients had Parkinsonism.

Six patients received olanzapine (7.5-25mg), 4 risperidone (2-6mg; one patient: 37.5mg/14days of risperidone consta), 2 zuclopenthixol (400mg), 2 clozapine (50-300mg), 1 flupentixol (30mg/14days), two quetiapine (100/300mg), one received aripiprazole (20mg). , one received combination chlorpromazine (100mg) and sulpride (600mg) and one was unmedicated (Chlorpromazine equivalent dose mean = 229.5, sd=145.72, range 75-600). After complete description of the study to the subjects, written informed consent was obtained. Ethical approval was provided by Camden and Islington Community Local Research Ethics Committee (ref: 08/H0722/22).

Measures

All participants completed the following scales: Subjective Well-being under Neuroleptics scale short version (20 items, 7-pt Likert scale; (Naber, 1995)) which provides a SW score out of 120 points and quantifies judgements on five factors: emotional regulation, mental functioning, physical functioning, self-control, and social integration; and the Beck Depression Inventory-2 (Beck *et al.*, 1996). The SWN is best interpreted as a total score (Vothknecht *et al.*, 2012) as used here. The patients also completed the Simpson-Angus Scale, Extrapyramidal Symptom Rating Scale, and the Barnes Akathisia scale measures of medication side-effects.

fMRI procedure

Subjects completed a version of the Monetary Incentive Delay (MID) task (Knutson *et al.*, 2001) in which visual cues predict potential outcome, and where performance – the reaction time of a button press to a target - determines reward outcome. The two phases examined in the study are the anticipatory phase (after the cue presentation); and an outcome phase (trial outcome). All participants were trained before the scanning session to preclude measuring learning mechanisms. Each 18.5s trial consisted of cue presentation (duration 2-8 seconds), followed by presentation of a brief 'target' square (initially 250ms, then adjusted by the algorithm) then, after a delay of 2-8 seconds the outcome of the trial is displayed for 2-8 seconds.

There were five cue types: large win, small win, small loss, large loss and neutral (no financial reward or punishment). Each of three fMRI runs (see Figure 1) consisted of 24 trials each of high reward (HR; £5) low reward (LR; £0.5), small loss (SL -£0.5) and large loss (LL; -£5) trials and 48 control trials (where there was no potential for gain or loss), giving a total of 144 trials. Hitting the target that appears after the cue (button press RT within the target window) results in a positive outcome: financial gain in the 'win' trials, and prevention of loss in the 'lose' trials. Missing the target (reacting too slowly) results in negative outcome: no gain in the 'win' trials, and a loss in the 'lose' trials. An algorithm shifts the target reaction time window such that the participant 'hits' in 66% of trials, and 'misses' in 34% of trials ensuring sufficient data for 'hit' and 'miss' trials irrespective of relative absolute performance. Each of three runs lasted 14m 48s producing a total scan time of 44m24s.

Participants then rate their satisfaction at the outcome on a 9-point Likert visual analogue scale (VAS) from "not satisfied" to "very satisfied" (duration 3 seconds). This was included so as to be sure that patients exhibited a range of subjective valences that reflected reward outcome differences to demonstrate that the task elicited subjectively rewarding

responses. There was a final 0.5 second 'fixation cross'. All money won and lost by the participant was representational, however, to ensure motivation, and anticipation and outcome effects, payment to participants was proportional to their game profits (between £15 and £25).

Scanning parameters

448 gradient-echo echo-planar BOLD images (TR/TE: 2000/25 ms, flip angle: 75°, matrix: 64 x 64, FOV=220) were acquired on a 3 Tesla GE Excite II MR scanner (GE Healthcare, USA) during each of run of the task. Each whole-brain image contained 38 non-contiguous slices of 2.4-mm thickness separated by a distance of 1 mm and an in-plane isotropic voxel resolution of 3.4 mm.

Analysis

Behavioural data analysis

Mean consummatory VAS scores of post-outcome satisfaction for each cue type and target response (hit and miss) were calculated. A repeated-measures ANOVA was conducted to reveal effects of valence (positive or negative outcome), magnitude of outcome, target response, and group on VAS scores. Between-groups ANOVA of total money accrued by participants were conducted. Further correlation analyses were conducted to determine the relationship between VAS scores and SW and to examine the relationship between CPZ-equivalent dose and outcomes scores in the patients.

fMRI data processing and analysis

fMRI data were preprocessed and analysed using SPM5 (Statistical Parametric Mapping, Wellcome Department of Imaging Neuroscience, University of London, UK). Data

were realigned across sessions to the first image of the first image of the first series, normalised to a standard-brain template and smoothed using an 8-mm FWHM Gaussian kernel. Analyses were conducted in the context of the general linear model (Friston *et al.*, 1998) to determine:

(i) brain regions associated with reward processing (anticipation and outcome) to reveal any abnormalities in reward-processing in the patient group in the first instance; and;

(ii) whether ROI analyses of the reward network would reveal that SW in the patient group was associated with reward-related BOLD response in the reward network and whether whole-brain analyses would reveal whether activity in other, non-reward network areas correlated with SW; and,

(iii) whether the healthy participants showed a similar pattern.

Reward related activations

First-level event-related general linear models (GLMs) were constructed for each participant. GLMs included a regressor predicting the BOLD response to each of 2 phases (anticipation/outcome), 5 cue types (high reward/ low reward/control trials/low loss/high loss) by outcomes (win/lose) convolving a vector of delta functions for the onset of the stimuli for that condition with the canonical haemodynamic response function. Effects of head motion were minimised by the inclusion of six realignment parameter vectors as regressors of no interest. These first level contrast images were entered into a second-level, random-effects 2 x 5 x 2 full-factorial analysis. The main effects of anticipation and outcome were then established ($p<.05$, FWE-corrected) for the two groups to confirm that the task elicits reward-related activity; and group x reward interaction effects were investigated at $p<.05$ FWE-corrected to reveal any group differences. MNI co-ordinates were converted to

Talairach space using mni2tal (Brett; http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach).

SW analysis

For the patient group the principal covariate of interest, total SW score, was included in a full-factorial model to identify brain regions where activity correlated with SW scores. Regions of interest (ROI) were chosen of 4 key a priori regions based on previous publications: anterior cingulate cortex (ACC), cingulate gyrus (CG), ventral striatum (VS), and caudate nuclei (CN) regions (see Haber & Knuston, 2010). The ventral striatum mask was taken from Mawlawi *et al.* (2001), the remainder from Pickatlas software (Maldjian *et al.*, 2003). As multiple ROIs were being investigated the significance level (α) for assessing effects from the ROI analysis was Bonferroni corrected to $p<.0125$ (FWE-corrected). Separate and combined analyses were conducted for the anticipation and outcome phases. A final whole brain analysis was also performed to examine areas outside the reward network which correlated with SW. The significance threshold for whole-brain analyses was set at $p<.05$ (FWE-corrected). These analyses were also conducted in an exploratory fashion in the healthy participants.

Results

Subjective Well-being

Patients (mean = 87.1 *(sd = 14.1)* showed significantly lower SW than healthy volunteers (mean = 100.5 *(sd = 13.6)*, $p<0.01$). Figure 1 below shows the distribution of SW scores for the two groups. The patients showed mild levels of depression (mean BDI score = 11.8 *(sd=9.2)* which was significantly greater than the healthy controls (mean = 4.4 *(sd=4.3)* ($p <0.01$). SW and BDI scores significantly correlated ($r=-0.7$, $p<.005$)

---- *Figure 1 here* ----

Behavioural data

As expected, hit outcomes rated on the VAS scale, were judged more satisfying than miss outcomes ($F(1,31)=109.4$, $p<.001$); rewarding trials more satisfying that loss trials ($F(1,31)=39.30$, $p<.001$) and larger rewards more satisfying than smaller rewards ($F(1,31)=8.55$, $p<.01$). There were no group effects of hit rates or reaction times (see table 1). There was also no main effect of group on VAS scores, nor with respect to outcome or magnitude of reward. There was a modest difference on VAS scores between the groups with respect to trial valence ($F(1,31)=5.51$, $p<.05$). Patients were less dissatisfied at missing an opportunity to avoid a loss than were controls (see figure 2): this was evident as a trend for small losses and as a statistically significant effect for large losses ($t(1,31)=2.65$, $p<.05$). Healthy participants (mean = 57.29 *(sd=18.83)* gained significantly more money than the patients (mean = 28.87 *(sd=38.70)* ($t(1,31)=2.37$, $p=.024$). CPZ-equivalent dose did not correlate with VAS or hit rate performance measures but did correlate with mean reaction reaction time ($r=0.48$, $p=.032$).

---- *Figure 2 here* ----

SW and VAS scores in the patient group

There were no significant correlations between average absolute hit or miss VAS scores, nor VAS scores subtracting control trial VAS scores, with subjective well-being scores in any condition. Neither the mean nor condition-specific reaction times correlated with SW (all $p>0.05$).

fMRI

Reward anticipation

Reward anticipation for all participants was associated with activity in several clusters covering bilateral inferior frontal and superior temporal gyri, insula and ventral striatum, as well as medial frontal and cingulate gyri, left pre- and post-central gyri, thalamic medial dorsal nuclei, right parahippocampal gyrus, and left and right brainstem (Figure 3A, $p<.05$ FWE-corrected; Figure 3B shows separate overlaid groups maps). There were no voxels showing a significant group x reward interaction, even with a liberal threshold ($p<.001$ uncorrected) indicating no significant between-groups differences in brain region activation involved in reward anticipation.

---- *Figure 3 here* ----

Reward outcome

There was a significant main effect ($p<.05$ FWE-corrected) of reward at outcome in the right inferior parietal lobule, right middle and inferior frontal gyri, bilateral thalamus and cerebellum/declive; and a small region within the right superior temporal gyrus. There was no group x condition interaction, even with a liberal threshold ($p<.001$), indicating that the patients and healthy participants were not significantly different in terms of the brain regions involved in processing reward outcome.

Subjective Well-being in schizophrenia

Within the patient group a single model incorporating both anticipation and outcome phases of the task revealed that SW was related to activation within the anterior cingulate cortex (ACC) in both ROI ($p<.0125$ FWE-corrected) and whole-brain analyses ($p<.05$, FWE-corrected; see conjunction image in figure 3C, below). The relationship between brain activation and SW across phases was unique to the ACC and not seen in any other brain region. This relationship was robust across phases of reward anticipation as shown by separate analyses of these phases, below.

Anticipation and Subjective Wellbeing

Several cortical areas were significantly associated with SW (FWE, $p<.05$), including anterior cingulate cortex (ROI-level, $p<.01$ FWE-corrected; whole-brain analysis, all peak voxels $p<.05$ FWE-corrected; see table 2;). In the whole-brain analyses significant associations were also apparent within the occipital lobe and bilateral middle frontal gyri.

---- Table 1 here ----

Outcome and Subjective Wellbeing

Region of interest analyses revealed a significant associated with ACC activation ($p<.01$, FWE-corrected) but not in cingulate gyrus, caudate or ventral striatum masks**.** In the whole-brain analysis, several regions were significantly associated with SW in the outcome phase ($p<.05$, FWE) including in the ACC and within the posterior cingulate (negatively, peak voxel $p<.01$, FWE-corrected). Since these additional regions activated were not hypothesized we list them as a table (see table 2 below) but do not venture a further interpretation at this time. Subsequent *posthoc* analysis showed that the beta coefficients for the association of SW with miss outcomes were significantly greater than for hit trials

($F(1,9)=5.99$, $p<.05$). In order to discount the possibility that reaction times to stimuli may impact on BOLD response in this study, a final analysis was conducted which showed that reactions times did not correlate with activity in the ACC region associated with SW scores. Also, to show that the reward and SW effects are not confounded by medication a further post-hoc analysis demonstrated that neither reward-related activity nor activity in regions which showed an association with SW were associated with chlorpromazine-equivalent (CPZ) dose ($p<.001$ uncorrected). There was ample variation in CPZ dose for a relationship to be detected had one been present.

---- Table 2 here ----

Mood and reward processing

A final post-hoc analysis was conducted to investigate the relationship between mood (as measured by the BDI) and reward-related activation in the patient group to investigate the specificity of SW to dACC activation. The SW vector was replaced by the BDI vector and the analyses were re-run. No regions within the regions of interest correlated significantly with BDI during the anticipation phase however during the outcome phase the dACC was significantly correlated with neural activation as shown by both R.O.I. and whole-brain analyses ($p<.05$ FWE-corrected; locus at 2,12,26).

Healthy Participants and Subjective Wellbeing

In healthy participants there were no significant associations with SW seen at the whole-brain analysis in, or near the region dACC region, nor in the R.O.I. analyses. Between-groups analysis confirmed that the relationship between SW and activity in the dACC was significantly greater in patients compared to healthy participants ($p<.0001$).

Discussion

This study examined the neural correlates of Subjective Wellbeing (SW) in schizophrenia using a monetary incentive delay (MID) reward paradigm in order to test the hypothesis that reward network activity is associated with SW. As anticipated, the level of SW was significantly lower overall in the patients compared to healthy controls. Reward-related neural activity in both groups during anticipation of reward was consistent with that seen in previous studies and involved the insula, ventral striatal and supplementary motor/motor area activity. Both healthy participants and patients demonstrated good discrimination of reward outcome as shown by visual analogue scale ratings supporting the fact that cues and outcomes were rewarding in nature.

As expected, ventral striatal (VS) activity represented anticipation to rewarding stimuli, consistent with other studies (e.g. Knutson *et al.*, 2001), yet there were no significant differences in VS activity (whole-brain or region-of-interest) between the patients and healthy volunteers. It has previously been shown that patients treated with the newer atypical antipsychotics at appropriate doses show 'normalised' VS reward-related activity relative to healthy participants (Schlagenhauf *et al.*, 2007; Abler *et al.*, 2008; Juckel *et al.*, 2006) potentially reflecting a putative normalising effect of these medications on dopaminergic transmission.

We anticipated that activation of the reward network would underpin subjective wellbeing scores. In line with this, a dorsal region of the anterior cingulate cortex (dACC) was significantly associated with SW scores, however, contrary to expectation this was observed in both the anticipation and outcome phases rather than the anticipation period alone. The dorsal ACC has been linked to a range of cognitive processes, such as attention, cognitive control, conflict-monitoring, response inhibition, self-reflection, and set-switching capacity, and is also involved in the modulation of reward processing through its widespread

projections to affective, cognitive, and motor cortical areas (see Haber & Knutson, 2010). Critchley *et al.* (2001) reported that a distinct region of anterior cingulate (slightly more anterior than the locus reported here) was commonly activated by both uncertainty and arousal in a reward task suggesting the dACC represents *both* expected reward and motivation. Considerable evidence shows that the ACC is active during reward anticipation (e.g. Kirsch et al., 2003; Knutson et al., 2008) and single-cell neurons in the dACC in humans have been shown to 'code' reward properties while dACC ablation disrupts reward-related behavioural adjustment (Williams *et al.*, 2004). The dACC thus plays a key role in forming associations between reward and appropriate action (Haber & Knutston, 2010). As activity in this region is associated with SW in both anticipatory and outcome phases it suggests that dACC may represent the motivational significance of current actions or cognitions (Ochsner *et al.*, 2001) and integrate rewarding environmental cues, behaviour and outcome.

Absent dACC activation has been reported in patients with schizophrenia during anticipation of reward (Quintana *et al.*, 2004; Abler *et al.*, 2008), and the effects of olanzapine in healthy participants reported by Abler *et al.* (2007) extend to include dorsal anterior cingulate activity (proximally located to the peak voxel that correlated with SW in this study) which was one of three regions, including the VS, reduced by olanzapine compared to placebo during reward-related processing. Healthy volunteers also show reduced anterior cingulate activity after AMPT-related dopamine depletion (de Silva Alves *et al.*, 2010). Hence, these compounds that act to reduce dopaminergic transmission also reduce reward-related dorsal anterior cingulate activity.

ACC activity has also been linked with depression (Bench *et al.*, 1992) and more rostrally and ventrally with anhedonia in healthy participants (Keedwell *et al.*, 2005; Harvey *et al.*, 2007). Patients with Major Depression have been shown to differ from healthy subjects

in the relationship between valence of reward anticipation and ACC, but not nucleus accumbens activity (Knutson *et al.*, 2008); and those who respond clinically to antidepressant medication show increases in ACC D2 receptor binding that is greater than increases in VS binding (Larisch *et al.*, 1997). Hence, together there may be a strong link between ACC functioning and a broader sense of well-being.

The strong relationship between SW and dACC activation was not seen in the exploratory analysis in the healthy participants. In healthy individuals, while acute AMPT reduces reward-network activation, it had no significant effect on SWN scores (Da Silva Alves *et al.*, 2010) despite effects on dACC and striatal activation. Specificity of this association to patients may be attributable to the gross differences in dopaminergic reward system functioning in schizophrenia relative to healthy people per se, or alternatively or additionally via the further impact that antipsychotic medication has on these systems. It may also be the case that the scale is more ecologically-valid in patient groups, following neuroleptic administration - the sequelae of which the scale has been designed to measure, or, with respect to the lack of association between DA changes and SW reported by Da Silva Alves *et al.* (2010), that the scale is not sensitive to drug effects over a short period of time. The sample size in the healthy group was also small which may account for lack of positive association and the SWN item questions are of a more general nature rather than would relate to acute and short-term 'state' effects. Further resolution of this discrepancy is beyond the scope of this paper, but future research should extend examination of the neural correlates of SW in the healthy population and in a larger group.

It was proposed that SW must have a dopaminergic foundation to account for the relationship between reduced SW and antipsychotic medication. Whilst there is no direct evidence linking the two in the present study, there is support for an effect of antipsychotic action on ACC function. Antipsychotic medication is associated with reduced ACC rCBF in

patients with schizophrenia (Miller *et al.*, 1997), whilst impaired activation in a similar dorsal ACC location in schizophrenia patients can be restored with apomorphine administration (Dolan *et al.*, 1995) – a D1/2 agonist - demonstrating that there is a significant neuromodulatory effect of dopamine on ACC functioning. While it is not possible in the context of this study, without data on receptor occupancy, to conclusively report that low SW leads to attenuated engagement of the ACC in reward processing, the data suggests an association which warrants further investigation.

An association between estimated dopamine D2R occupancy ('fitting' medication dose to dopamine receptor occupancy data) and positive and negative affect in schizophrenia has recently been shown using a daily experiential sampling method (Lataster *et al.*, 2010). Greater estimates of receptor occupancy were associated with a worsening of feelings of positive and negative affect supporting the link between dopamine and subjective experience and adds ecological validity to the present and other studies which investigate subjective experience using more general, 'offline' questionnaires.

We did not find the anticipated correlation between SW and VS activation based on earlier data linking antipsychotic medication with impairments in VS functioning. This may be due to the VS response to reward in the patient group being unimpaired. As patients had lower SW scores, but unimpaired VS activity, this implicitly suggests that VS functioning does not underpin SW. Elsewhere Mizrahi and colleagues (Mizrahi *et al.*, 2009) report an association between VS dopamine D2 receptor blockade and SW but only in patients receiving conventional antipsychotics not those receiving aripiprazole. In patients taking aripiprazole, there was a wide range of SW scores (including low scores), at the same time as homogenously high VS D2 receptor blockade across the group, again suggesting that SW is not simply reducible to VS D2 receptor blockade. Using PET, Mizrahi *et al.* (Mizrahi *et al.*, 2007) showed that temporal cortex D2 receptor blockade was more strongly associated with

SW than striatal blockade again indicating that the link between striatal function and SW is not encapsulated. Lastly, studies which find associations between SW and VS activity, for example (Mizrahi *et al.*, 2009), generally only investigated striatal (and cerebellar) regions in the first instance. Investigations of other extra-striatal regions, such as the ACC, may reveal the activity in these regions provide a fuller account of SW. Despite previous links between SW and VS and other reward-network regional DA binding, and medication effects, this study demonstrates a functional mechanism between SW reward processing per se.

Limitations

Whilst the SWN scale shows good inter-rater reliability and face validity, non-specific biases in completing self-relevant questionnaires may impact on SW ratings. Monetary reward was only representational - participants received a (lower) amount than trials indicated which may have impacted on the rewarding saliency of the cues. However, there is little to suggest this was the case given that VS activity was linked to reward in the primary analysis and varied by magnitude and valence of reward. Although mean ages were not significantly different an improvement would have been to better age-match the groups. CPZ-equivalent dose was associated with mean reaction time but this is most likely attributable to sedative effects of antipsychotic medication on speed of reactions. CPZ-equivalent doses were not associated with SWN, subjective VAS ratings nor hit rates.

There was a moderate correlation between SWN and BDI. Subsequent analysis of the neural correlates of BDI scores revealed some of the pattern of findings that SW held with reward-related neural activity although this was limited to the outcome not anticipation phase. Together this suggests that SW and depression may be overlapping constructs and that dACC activity may be related to a broader sense of well-being. However, SWN is not just reducible to BDI – a substantial proportion (46%) of the variance of SWN remained

unexplained by BDI scores, supporting the utility of conducting independent analyses. Indeed SW is the central predictor of medication compliance (Karow *et al.*, 2007) and constitutes a distinct outcome measure in schizophrenia (Lambert & Naber, 2004) hence investigating SW as a specific target of research is warranted. Examination of the items on these scales also reveals that they are founded on different constructs. The SWN focusses on social integration, self-control, emotional-regulation, mental functioning, and physical functioning which differ from the cognitive and affective components measured by the BDI. Additionally, there may be a causal relationship between mood and SW and this could be in either direction, hence future research should further examine the precise relationship between these measures and the potential dissociation between mood and subjective well-being with respect to anticipation and consumption of reward.

Patients acquired significantly less financial gain than healthy participants. There were no significant group differences in hit-rate or reaction time to account for this, however as a large cue results in a '£5' gain or loss then attaining winning outcomes on only a few additional trials could mean a large difference in the final amount won. Between-groups VAS ratings were not significantly different although patients were less sensitive than the healthy group to suffering large losses. Lower sensitivity to negative feedback requires further investigation, however, Schlagenhauf *et al.* (2009), recently reported that patients but not healthy volunteers show significantly attenuated ventral striatal signal in response to suffering loss outcomes compared to avoiding loss outcomes whereas there were no group differences after gaining or losing positive reward. Patients with schizophrenia may be behaviourally and/or neurally less sensitive to negative outcomes and this may reflect disturbed error-signal processing (ibid), or speak to impairments in learning from feedback in schizophrenia (Averbeck *et al.*, 2011).

Conclusions

Patients with schizophrenia showed reduced SW. Activation within a dorsal region of the ACC held a significant relationship with SW over both anticipation and outcome phases of a reward task which was not seen in the healthy. This could be due to greater disturbance of the broader dopaminergic reward system in schizophrenia or via medication effects. The ACC is involved in the integration of action and reward and one interpretation is that poor SW may result from a reduced coupling and integration of reward, action and outcome. Intuitively, a state in which there is decreased functional association or learning between reward, action and outcome could manifest an attenuation of one's sense of well-being if actions within a personal repertoire are not linked in a routine way to reward. Future research should examine the interaction between reward processes, D2 receptor blockade and SW to further identify the anatomical and neurochemical pathways underlying subjective wellbeing and identify suitable interventional targets.

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Conflicts of interest

None.

Ethical Standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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Figures and tables

Figure 1 showing the distribution of SW scores for the healthy control (N=12) and patient (N=20) groups.

Figure 2 showing patient (N=20) and healthy control (N=12) subjective VAS scores for each condition outcome, as rated after reward outcome. Blue lines represents miss trials, and the green lines represent hit trials.

Figure 3 showing (A) activity related to anticipation of reward in all participants (p<.05 FWE-corrected); (B) the activation maps of common regions of activation for the two groups overlaid (threshold of p<.001 for illustration; yellow=healthy; red=schizophrenia); and (C) the unique overlap of the SW-related ACC activation during anticipation (blue) and outcome (red) in the schizophrenia group. As can be seen there is a clearly defined overlap at talairach co-ordinates: 2,11, 27.

Table 1 showing mean (sd) group hit rate and reaction times for each salient cue type and total amount gained.

Measure	Cue	Group	
		Schizophrenia	Healthy
Hit Rate (%)	Large Win	60.59 (12.01)	66.05 (7.82)
	Small Win	60.88 (12.59)	67.42 (7.70)
	Large Loss	62.67 (14.07)	68.10 (9.21)
	Small Loss	66.08 (10.28)	66.84 (7.85)
	Control	37.00 (16.33)	44.44 (12.88)
Reaction Time (ms)	Large Win	243.75 (21.19)	232.52 (22.74)
	Small Win	248.32 (28.45)	245.11 (26.32)
	Large Loss	252.31 (19.71)	233.61 (22.03)
	Small Loss	248.53 (30.24)	236.91 (21.69)
	Control	273.24 (39.22)	256.68 (39.94)
Amount Gained (‘£’)		28.87 (38.70)	57.29 (18.83)

Table 2 showing the peak voxels and p values (p<0.05, FWE-corrected) that held a significant association with the SW covariate during anticipation and outcome.

Phase	Hemisphere	Region	Talairach coordinates	F	peak p (FWE-corr)
Anticipation	R	Inferior Occipital Gyrus	36 -88 -4	6.25	0.001
	L	Lingual Gyrus	-20 -97 -2	6.05	0.001
	R	Anterior Cingulate	6 9 24	5.8	0.003
	R	Precentral Gyrus	42 -5 59	5.79	0.003
	R	Middle Frontal Gyrus	57 8 38	5.52	0.006
	L	Middle Occipital Gyrus	-30 -95 0	5.49	0.007
	L	Middle Frontal Gyrus	-32 -3 59	5.06	0.024
Outcome	L	Cuneus/Occipital lobe	-10 -82 36	7.197	<0.001
	R	Lingual gyrus	18 -76 -6	7.185	<0.001
	R	Cuneus/Occipital lobe	10 -94 20	6.954	<0.001
	L/R	Posterior Cingulate	4 -56 2	5.618	<0.005
	L/R	Anterior Cingulate	2 12 28	4.97	<0.05