Meta-analytic evidence for altered mesolimbic responses to reward in schizophrenia

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Abstract:

Dysfunction of reward-related neural circuitry in schizophrenia (SCZ) has been widely reported, and may provide insight into the motivational and cognitive disturbances that characterize the disorder. Although previous meta-analyses of reward paradigms in SCZ have been performed, a meta-analysis of whole-brain coordinate maps in SCZ alone has not been conducted. In the present study, we performed an activation likelihood estimate (ALE) meta-analysis, and performed follow-up analysis of functional connectivity and functional decoding of identified regions. We report several salient findings that extend prior work in this area. First, an alteration in reward-related activation was observed in the right ventral striatum, but this was not solely driven by hypoactivation in the SCZ group compared to healthy controls. Second, the region was characterized by functional connectivity primarily with the lateral prefrontal cortex and supplementary motor area (SMA), as well as subcortical regions such as the thalamus which show structural deficits in SCZ. Finally, although the meta-analysis showed no regions outside of the ventral striatum to be significantly altered, regions with higher functional connectivity showed a greater number of sub-threshold foci. Together, these findings confirm the alteration of ventral striatal function in SCZ, but suggest that a network-based approach may assist future analysis of the functional underpinnings of the disorder.

1. Introduction:

Whilst patients with schizophrenia (SCZ) exhibit deficits across a variety of cognitive domains (Dickinson, et al., 2004), a focus on reward and motivational systems has also had considerable importance as a means of characterizing the behavioral and neural dysfunction that accompanies this disorder. Paradigms designed to assess the function of these systems offer a number of valuable avenues for investigation: first, they can be simplified to reduce the impact of cognitive deficits (Waltz, et al., 2007); second, they offer a variety of opportunities for translation, given that the majority of research employing experimental animals uses reinforcement for behavioral control; third, the neural basis of reward is now quite well characterized, which facilitates the generation of precise hypotheses for schizophrenia.

There has been considerable focus on abnormalities of dopaminergic signaling in SCZ – including the function of the VTA/SN and projection regions including the striatum (e.g. Chuhma, et al., 2017), and these abnormalities are often thought to underlie two sets of SCZ symptoms related to learning and motivation. First, there are widely replicated deficits of reinforcement learning, motivation and positive affective responses, particularly associated with negative symptoms. Although there have been demonstrations of intact affective responses in SCZ (Kring and Caponigro, 2010), patients with schizophrenia often show deficits of choice that would require an approximately normative representation of expected value – for example, in effort based paradigms (Barch, et al., 2014) or those that require choices to be made on the bases of outcome value rather than learned habits (Gold, et al., 2012). In these examples, abnormalities across individuals also correlates with variation in self-reported 'negative' symptoms, supporting the proposed relationship between motivated behavior as assessed in the laboratory and anhedonic symptomatology. Second, there is parallel interest in alterations of associative learning that also accompany SCZ. Given that similar psychological learning mechanisms have been proposed to describe both causal learning and reward-based (reinforcement) learning (Dickinson, et al., 1984; Gershman, 2015), it may be that abnormalities in reward-based paradigms can reflect deficits in the former. In such a scenario, altered

causal learning could readily account for ‘positive’ symptoms of SCZ such as delusions (Feeney, et al., 2017).

In humans, functional neuroimaging methods have proved a central source of evidence to explore the neural basis of these relationships *in vivo* (Maia and Frank, 2017), even though the capability of fMRI to examine dopaminergic signaling itself is at best indirect. There already exists a quantity of neuroimaging evidence of dysfunction in reward processing in schizophrenia, which has been integrated within two prior meta-analyses. The first (Zhang, et al., 2016) combined studies of SCZ with major depression – another psychiatric illness characterized by high levels of anhedonia (Treadway and Zald, 2011). The study identified deficits in the response of the ventral striatum to rewards anticipation and outcome. A second by Radua and colleagues (Radua, et al., 2015) focused on the ventral striatum using a region of interest (ROI)-based approach, and was restricted to studies of patients with SCZ or those at high risk for psychosis. As with the study of Zhang and colleagues, the authors confirmed striatal dysfunction accompanying the disorder; they estimated the underlying effect as medium sized (Cohen’s d~=0.5-0.7), both for reward anticipation and outcome.

Accepting the findings of the previous meta-analyses, it nevertheless remains unknown whether there are reward-related abnormalities outside of the striatum which can be consistently observed in SCZ. In particular, although the hypotheses informing the focus on the striatum are strong, a whole brain approach can reduce the impact of biases associated with ROIs. To address this gap, we performed an Activation Likelihood Estimation (ALE) meta-analysis of SCZ versus control whole brain contrasts of reward related activation, coupled to reward anticipation and/or outcome. We also provided two sets of analyses to characterize the findings further. In the first, we performed two kinds of functional connectivity analysis – Meta-Analytic Connectivity Modeling (MACM) and resting state fMRI (rsfMRI). Given that we hypothesized that we would observe alterations in the striatum, this analysis would provide further detail about the nature of the abnormality. We also examined whether previously observed structural abnormalities in SCZ (Nickl-Jockschat, et al., 2011) would overlap with identified functional abnormalities,

or regions connected with them. Finally, we performed functional decoding, employing the domain/paradigm information within the BrainMap database, to characterize regions of functional abnormalities, and functionally connected regions. This provided a measure of how selective activation in the regions was to reward, as opposed to other psychological domains or paradigms.

2. Methods

2.1. Study identification/selection

We conducted a PubMed database (http://www.ncbi.nlm.nih.gov/pubmed) search using the search strings "schizophrenia reward learning fMRI" and "schizophrenia prediction error fMRI". Details of the study inclusion and exclusion criteria are described within a PRISMA flowchart (Table 1). Studies were included if they (1) were published in a peer-reviewed journal, (2) assessed neural correlates of reward learning in schizophrenia patients and compared them to healthy controls, (3) performed whole-brain analysis of functional MRI or PET neuroimaging data, and (4) reported results in standard stereotactic space (Montreal Neurological Institute [MNI] (Holmes, et al., 1998); Talairach & Tournoux [TAL] (Talairach and Tournoux, 1988). Studies were excluded if they (1) did not report all peak coordinates of the clusters obtained by a contrast, (2) reported only coordinates for contrasts studying samples with mixed diagnoses (e.g., combining patients with schizophrenia and those with major depressive disorder to one patient sample or (3) did not compare schizophrenia patients to healthy controls, but to another patient group (or a mixed sample consisting of a patient group and healthy controls). A total of 20 studies met our inclusion criteria (see Table 2). From these studies, peak coordinates were extracted and used for further analyses.

2.2. Activation Likelihood Estimation (ALE)

The meta-analysis was conducted using a revised version (Eickhoff, et al., 2012; Eickhoff, et al., 2009) of the activation likelihood estimation (ALE) approach for coordinate-based meta-analysis of neuroimaging results (Laird, et al., 2005; Turkeltaub, et al., 2002; Turkeltaub, et al., 2012). ALE is based upon the notion that reported foci can be treated as centers of 3D Gaussian probability distributions, which reflect the spatial uncertainty associated with each reported set of coordinates (Eickhoff, et al., 2012; Eickhoff, et al., 2009; Turkeltaub, et al., 2002). Brain regions which show a convergence of foci across studies which is higher than expected by chance, i.e. a random distribution of studies across the brain, can then be identified. All reported foci for a given experiment were combined for each voxel to produce a modeled activation map

(MA map; Turkeltaub, et al., 2012). ALE scores describing the convergence of coordinates for each location were then calculated via the union of individual MA maps. To distinguish areas where the convergence between studies was greater than it would be expected by chance (i.e. to separate true convergence from noise), ALE scores were compared to a nonlinear histogram integration based on the frequency of distinct MA values (see Eickhoff, et al., 2012). For statistical inference, the ensuing statistical parametric maps were then thresholded at $p<0.05$ (cluster-level FWE, corrected for multiple comparisons, cluster-forming threshold at voxel level $p<0.001$ (Eickhoff, et al., 2012). We pooled our main analysis across hyper- and hypoactivation, since we were mainly interested in general aberrant activation changes associated with dysfunctional reward processing in schizophrenia. In addition, some studies showed complex interactions between anticipation and outcome which could not be neatly categorized as one or the other (Morris, et al., 2012). However, we also conducted a separate sub-analysis of hypo-activation studies to confirm the robustness of the findings. There were not enough hyper-activation studies (SCZ>HC) for a valid analysis.

2.3. Task-based functional connectivity: meta-analytic connectivity modeling (MACM)

Meta-analytic connectivity modeling (MACM: Eickhoff, et al., 2011) is a complementary means of estimating functional connectivity from contrast maps rather than correlations between regional time series. As such, it provides further insight into interactions between different regions under a task-based context, as opposed to the task-independent estimates of functional connectivity derived from resting state acquisitions. In the present study, we used the brain region derived from the ALE-meta analysis was considered as a seed, and evaluated its connectivity with other brain regions. We first identified all experiments in the BrainMap database (http://www.brainmap.org; Laird, et al., 2011; Laird, et al., 2009) featuring at least one focus of activation within the seed. Only studies reporting group analyses of functional mapping experiments of healthy subjects were included, while experiments dealing with disease or drug effects were excluded. We performed MACM in healthy subjects only, since we aimed to identify general

neurobiological networks entailing our regions of interest, irrespective of a particular diagnosis or intervention at hand. Subsequently, we performed a coordinate-based meta-analysis to identify consistent co-activations across experiments using ALE. Results were thresholded at $p < .05$ corrected for multiple comparisons applying FWE correction on the cluster-level (cluster-forming threshold at voxel-level of $p < .001$).

2.4. Task-independent connectivity: "resting state"

In addition, we also delineated the task independent resting-state functional connectivity pattern of the ALE-derived cluster. Resting state fMRI images of 124 healthy subjects between 20 and 75 years of age (mean: 46.56 ± 17.56; 84 females, 40 males) from the NKI/Rockland sample were obtained through the 1000 Functional Connectomes Project (www.nitrc.org/projects/fcon_1000/). During the resting state scans subjects were instructed to keep their eyes closed and to think about nothing in particular but not to fall asleep (which was confirmed by post-scan debriefing). For each subject 260 resting state EPI images were acquired on a Siemens TimTrio 3T scanner using blood-oxygen-level-dependent (BOLD) contrast (gradient-echo EPI pulse sequence, TR = 2.5s, TE = 30ms, flip angle = 80°, in plane resolution = 3.0 x 3.0mm^2, 38 axial slices (3.0 mm thickness) covering the entire brain). The first four scans were excluded from further processing analysis using SPM8 to allow for magnet saturation. The remaining EPI images were first corrected for movement artifacts by affine registration using a two pass procedure in which the images were first aligned to the initial volumes and subsequently to the mean after the first pass. The obtained mean EPI of each subject was then spatially normalized to the MNI single subject template using the 'unified segmentation' approach (Ashburner and Friston, 2005). The ensuing deformation was applied to the individual EPI volumes. To improve signal-to-noise ratio and compensate for residual anatomical variations images were smoothed with a 5-mm Full Width Half Maximum (FWHM) Gaussian kernel.

In line with conventional methods of rsfMRI analysis, the time-series data of each voxel were corrected for the following nuisance variables (cf. Jakobs, et al., 2012; Satterthwaite, et al., 2013): the six

motion parameters derived from the realignment step, and their first derivative; timeseries reflecting mean gray matter, white matter and cerebrospinal fluid were obtained via a weighted average across voxels, using a weight determined by the assigned probability of membership to a given tissue class by the SPM8 segmentation step. After regressing out these variables, the resulting residual timeseries were band pass filtered between 0.01 and 0.08Hz. As with the other analyses, data were thresholded with a cluster-forming threshold of $p<0.001$ uncorrected, and a cluster threshold of $p<0.05$ FWE-corrected.

2.5. Functional characterization: decoding

To further characterize the cluster obtained by the ALE meta-analysis, we examined significant functional associations with behavioral domains and paradigm classes across experiments indexed in the BrainMap database (http://www.brainmap.org; Laird, et al., 2011; Laird, et al., 2009) both within the cluster itself, and also the CCN. Within this framework, behavioral domains describe mental processes and are defined by contrasts (divided in the broad subcategories of action, cognition, emotion, interoception, and perception), whereas paradigm classes represent specific tasks (e.g., n-back, Go/No-Go, Stroop; for a detailed BrainMap taxonomy, see http://www.brainmap.org/taxonomy). We performed both forward and reverse inference: forward inference denotes the probability of a particular task activating a brain region; reverse inference refers to the probability of a psychological process being engaged given activation in a specific brain region. In other words, in the forward inference approach we assessed whether the probability of activation of the cluster/CCN given a particular mental process [P(Activation|Task)] was higher than activation [P(Activation)] at baseline, that is, finding a (random) activation from BrainMap in the respective regions. Significance was assessed using a binominal test ($p < .05$), corrected for multiple comparisons using false discovery rate (FDR). In the reverse inference approach, the cluster/CCN's functional profile was determined by identifying the most likely behavioral domains and paradigm classes following its activation. Here, significance was assessed by means of a chi-square test ($p < .05$; FDR corrected).

2.6. Functional connectivity: conjunction analyses

We aimed to identify patterns of FC independent of modality, that is, irrespective of the subjects' mental state (i.e., task or rest). We thus performed a conjunction analysis between MACM and resting-state connectivity networks identified for the seed region using the minimum statistics (Nichols, et al., 2005), resulting in a "consensus connectivity network" (CCN) of the seed region(s).

Thus far, the described analyses were planned *a priori*: that is, although functional connectivity and decoding analyses were contingent on the findings of the ALE, we planned to perform them regardless of the ALE findings. However, we also performed two post-hoc analyses to test secondary hypotheses which emerged from the resulting findings. First, we performed a further conjunction analysis, examining the overlap between the CCN with a prior meta-analysis of structural deficits in SCZ (Nickl-Jockschat, et al., 2011).

2.7. Further analysis of the distribution of MA values around the brain.

The second post-hoc analysis involved the rsfMRI maps described in section 2.4: here, we examined the distribution of non-significant MA values from the main effect of group ALE analysis. We hypothesized that regions with high rsfMRI connectivity with the significant ALE cluster would show higher MA values. As described in the results, the whole brain distribution of rsfMRI connectivity was positively skewed, so separate comparisons of MA scores were performed between regions which were associated with different sections of the distribution. Note that the MACM analysis was not used for this analysis, as MACM values tend not to follow a smooth, continuous distribution.

3. Results:

3.1. ALE

A significant main effect was seen in the right ventral striatum, but no other region (Table 3; Figure 1). Seven studies contributed to this cluster, of which six contributed to in roughly similar proportion to the

significant activation and one contributed very little. A post-hoc analysis of studies which were categorized as hypoactivations in the SCZ group (e.g. HC>SCZ) yielded a similar, significant cluster in the same region (k=130).

3.2. *MACM and RS fMRI: seed region connectivity*

We evaluated the functional connectivity of the striatal seed identified by the ALE analysis using MACM and rsfMRI together (Table 4). Three clusters were identified by the conjunction of these two techniques (the CCN): primarily, in a large subcortical cluster including the bilateral striatum, thalamus and anterior insula. In addition, clusters were observed in the SMA and the left DLPFC (Figure 2). The MACM map alone revealed a similar pattern, although with larger (and bilateral) cortical activations including the DLPFC, parietal and SMA regions. By contrast, the rsfMRI analysis revealed a more medial rather than lateral emphasis in the PFC, including ventromedial and frontal polar PFC regions, and both rostral and dorsal aspects of the anterior cingulate cortex. Other significant findings were seen in the midbrain, amygdala and cerebellum. Interestingly, *negative* or anticorrelated connectivity was seen in similar parietal regions to the MACM analysis.

3.3. *Functional Decoding*

Two decoding analyses were performed, one of the right ventral striatal region identified by the ALE analysis, and one of the CCN which was derived from this seed (Table 5). Both the seed region and the network were both characterized by reward, emotion and cognition paradigms, as well as several other tasks with affective or cognitive components. Examples of affective tasks included pain, happiness, and sadness, as well as discrimination based paradigms such as gustation, olfaction and taste which may include affective components. Examples of cognitive tasks included delay match to sample and mental rotation.

3.4. *Overlap of CCN and structural differences in SCZ*

We computed another conjunction with this map, this time examining the overlap between this multi-modal connectivity map and previous meta-analysis of structural abnormalities in SCZ (Nickl-Jockschat, et al.,

2011). Notably, there was overlap between the connectivity map and regions identified with both greater and less grey matter concentration in SCZ compared to HC (see Table 4). The former region included the left putamen, while the latter included the thalamus and left ventral striatum. This analysis demonstrates that although the overlap between reward-related and structural abnormalities was not confirmed in this analysis (no overlap in the right ventral striatum was observed), there were nevertheless areas of structural abnormality which are functionally connected to the identified locus.

3.5. Relationship between ALE (MA values) and rs-functional connectivity

We pursued a second analysis relating the functional connectivity of the main effect striatal cluster identified in the ALE analysis. We hypothesized that foci from the studies included in the ALE analysis, excluding those which produced the significant cluster, would nevertheless be distributed in a non-random fashion around the brain. Specifically, we hypothesized that regions which are functionally connected to the identified striatal cluster would show a greater concentration of foci, despite the fact that these foci did not reach significance. We investigated this first by examining the distribution of rsfMRI connectivity magnitudes across the whole brain (outside of the seed region itself): a strongly skewed distribution was observed. We split this distribution into three categories (Figure 3): first, negative connectivity which varied from the minimum value (z=-0.1146: blue voxels in Figure 3) to zero; second, low positive connectivity, which varied from 0 to 0.1146 (red voxels in Figure 3); third, high positive connectivity, which was z>0.1146 and hence outside a symmetrical distribution from -0.1146 to 0.1146 (green voxels in Figure 3). High positive connectivity was restricted to the striatum. Low positive connectivity was spread more widely in other reward-related and default mode network regions. Negative connectivity was seen in regions such as the parietal and visual cortex. As expected, MA values were higher in the high positive connectivity regions compared to the other two regions ($T=35.068$, $p<0.001$). In addition, MA values were higher in low positive connectivity regions compared to the negative connectivity region ($T=17.74$, $p<0.001$): although the absolute magnitude of the difference was small, the analysis benefited from a large number of voxels.

These significant differences refute the null hypothesis that sub-threshold MA values are randomly distributed throughout the brain, and are instead preferentially connected to regions that are functionally connected to the right ventral striatum.

4. Discussion

In the present study, we report, to our knowledge, the first whole brain meta-analysis of reward related brain activations in schizophrenia. Our findings complement two previous studies, one using an ROI approach (Radua, et al., 2015) and one using trans-diagnostic inclusion criteria (Zhang, et al., 2016), by confirming an alteration in ventral striatal BOLD signal in SCZ compared to controls. However, our findings also extend these previous reports. In particular, the finding was not driven purely by studies reporting hypoactivation in the SCZ group compared to controls, but also contained three studies reporting hyperactivations (SCZ > HC) – either directly or via an interaction term (Morris, et al., 2012). Notably, these three studies were all outcome-locked, consistent with the notion that the deficit in SCZ may reflect reduced learning rather than an overall blunting of reward (see also Luijten, et al., 2017 applying a similar reasoning to other disorders). Specifically, a reduced anticipatory response might result from a reduction in the learning rate, and reflect a slower transfer from outcome to reward related responses. This account would predict intact or enhanced outcome-locked activation, with reduced anticipatory activation. This account is also consistent with behavioral evidence of reinforcement learning deficits in SCZ (Waltz, et al., 2007), as well as outcome-locked null results (Culbreth, et al., 2016b). It cannot explain all findings however, including reports of outcome-locked deficits – several of which contributed to our significant findings (see Table 3). In addition, more recent behavioral evidence has emphasized the role of working memory in impaired learning performance in SCZ, as opposed to the reinforcement learning system (Collins, et al., 2017). It seems likely therefore that the reported alteration in the VS may reflect a

combination of factors, which may include the influence of altered learning rate, but also participant heterogeneity (including illness duration) or antidopaminergic medication.

Notably, evidence of reward related deficits in SCZ was not obtained for other brain regions outside of the ventral striatum. However, a subsequent analysis suggested that this may be due to a lack of power to detect such differences. We tested the null hypothesis that reported foci, and hence Modelled Activation (MA) values, that were not within the identified region would be distributed randomly across the brain. In fact, higher MA values were found in regions which were more strongly functional connected to the significant striatal cluster. This finding operated at two levels. First, there were a set of voxels outside of the significant region that nevertheless showed very high functional connectivity values – primarily within the striatum. These voxels also showed very high MA values, outside of the significant cluster. This would not be unexpected – the cluster itself is only the peak of an underlying accumulation of foci, and thus this finding could simply reflect proximity to the cluster, as well as non-significant findings in homologous left hemispheric structures. However, a separate distribution of voxels was identified which showed smaller positive functional connectivity. Importantly, these regions showed higher MA values, and hence a higher presence of reported foci, than regions which were anticorrelated with the striatum. There are a number of implications of these findings. First, they suggest that at least a proportion of the non-significant foci outside of the striatum may be 'false negatives', and might be identified in better powered analyses. Interestingly, a recent study by Cremers et al. (2017) explores two potential generic representations of a given psychological process in the brain: either a distributed representation with numerous small peaks, perhaps within a large scale-network; or one localized representation with a single strong peak. Clearly, the main ALE findings are more consistent with the latter representation, but our findings suggest that network-led analysis methods may help to parse distributed 'false-negative' activations within meta-analytic approaches (see also Crossley, et al., 2016). Second, we would expect regions of the brain that show connectivity with the striatum to show similar functional properties in independent measures, and this expectation appears to be borne out by the data. The key question arising from this is whether foci in distal regions reflect a

downstream epiphenomenon of the striatal alteration, and are implicated only by the functional connections with the striatum. Alternatively, there may be an alteration in the whole network, which is only manifest in the striatum due to, for example, arbitrary reasons to do with experimental design, or the masking influence of other networks in less selective regions. It may be worth considering partial least squares (PLS: (McIntosh and Lobaugh, 2004)) or equivalent analyses to address the network in its entirety.

We also describe two further lines of evidence further to characterize the regional group differences. First, the regions identified in the main effects analysis were used as seeds for connectivity analyses using MACM and resting state fMRI. The connectivity of the striatal seeds generally conformed to the 'associative/cognitive' and 'motor' cortico-striatal loops within Alexander and colleagues' scheme (Alexander, et al., 1986), incorporating thalamus, dorsal ACC/SMA and left DLPFC. Evidence for an involvement of the 'affective' loop was less evident, however, although significant functional connectivity with the medial OFC and ACC was observed using rsfMRI alone. Although the affective functions of the ventral striatum are often emphasized in neuroimaging studies tends, there is nevertheless evidence of a role in other domains including cognitive flexibility (van Schouwenburg, et al., 2010). In the present study, further evidence for a more general role was obtained from a functional decoding of the regions using the BrainMap database. This resource describes the paradigms and psychological domains in the literature which have been shown to activate this region, and thus provide a sense of the selectivity of the region's activation properties. With respect to the striatal cluster we identified, there was no evidence of a selectivity for the regions engaged for reward over and above cognition and emotion in general – although reward was an important route by which the region could be activated. Together, these findings from the decoding and the connectivity analysis raise the possibility (although do not provide decisive evidence) that cognitive rather than affective aspects of the paradigms may be contributing to the neural abnormalities. A relevant example is a study by Culbreth, et al., (2016a), which employed a reversal learning paradigm. We included the win-related maps in the present study, but interestingly, the effect of response switching elicited somewhat stronger group differences in the striatum than reward *per se*. This type of paradigm offers crucial

avenues for unpicking reward-related responses from other cognitive demands. More generally, an emphasis on the 'associative' fronto-striatal loop is consistent with work using Positron Emission Tomography (PET) with which abnormalities in this circuit have been demonstrated in SCZ (Kegeles, et al., 2010).

In addition, several distal regions which exhibited functional connectivity with the regions of striatal alteration also showed evidence of structural abnormalities in SCZ in a prior meta-analysis (Nickl-Jockschat, et al., 2011), including the thalamus and other regions of the striatum. It remains unclear the extent to which structural deficits contribute to the functional abnormalities that we observe, and it may be that both increases and decreases in the volume of different basal ganglia structures can influence its functional properties. Thalamic abnormalities are well established in SCZ (Murray and Anticevic, 2017), and in the present context, thalamic structural abnormalities in SCZ may lead to altered modulatory influences on reward related function via its connectivity with this striatum.

Our findings are also relevant for the implication of reward circuitry across psychiatric disorders (Zhang, et al., 2016). At first pass, our findings are quite concordant with reward-related hypoactivation observed in mood disorders, although one meta-analysis reported a slightly more anterior and medial focus within the striatum as hypoactive in major depressive disorder (MDD: Zhang, et al., 2013), compared to the region we have identified here. The extent to which this is significant, and also not a function of minor methodological differences, might be established in future work. An intriguing possibility, if there are true differences in the location of ventral striatum abnormalities across SCZ and MDD, is whether such differences are these are related to differential (as opposed to overlapping) symptom profiles between the disorders – including cognitive or affective deficits respectively.

Limitations

One important limitation of the present study was that we did not pre-register the meta-analysis before conducting it. We are not aware of any neuroimaging meta-analysis studies that have used the PROSPERO

repository (www.crd.york.ac.uk/prospero/), but we anticipate that this will be used routinely for pre-registration of clinical neuroimaging meta-analysis in the future.

The meta-analysis included seven studies which contributed to findings, confirming a reasonable underlying effect size (Radua, et al., 2015). Our capacity to provide confirmatory evidence using different methods mitigates potential concerns about potential bias of different approaches. For example, ALE requires that ROI analyses are excluded, whereas the method employed by Radua and colleagues does not. Nevertheless, both studies are dependent on overlapping data sources, and only larger data sets will allow potential biases associated with different methods and inclusion/exclusion criteria to become clearer. One important limitation of our statistical approach was that we treated nested designs as independent. Thus, non-independence may have slightly affected the estimation of the true effect size: however, it seems unlikely that this bias had a major impact, as multiple contrasts from the same experiment did not contribute to the identified cluster. The non-random distribution of ALE values around the brain suggests that there may nevertheless be clusters which we are not yet powered to identify. Modest power could also be compounded by participant heterogeneity.

Medication is a crucial confound between the patient and control groups, as most patient cohorts in the present analysis were medicated. There are two primary routes by which medication status may influence the results. First, antipsychotic medications may influence reward-evoked BOLD response: this proposal has been tested several times, with mixed results (Insel, et al., 2014; Jocham, et al., 2014; McCabe, et al., 2011). The second route is that medicated patients are likely to show different clinical characteristics from un-medicated, both directly as a result of the medication, but also potentially due to differences in disease progression and other selection biases. In future studies, a focus on symptom dimensions may provide a step towards resolving the contribution of participant heterogeneity (Insel, et al., 2010). In addition, a consideration of disease progression in its entirety, including high risk cohorts as well as first episode and chronic patients may help identify abnormalities that are consistent across phases of the illness (Radua, et al., 2015).

Returning to the question of patient heterogeneity, its influence in the present context remains unknown. In particular, the relative impact of individual differences in cognitive impairment, positive or negative symptoms versus comorbid symptoms such as depression (see e.g. (Arrondo, et al., 2015), or even 'trait-like' heterogeneity (i.e. variability which can characterize a cohort: (Brugger and Howes, 2017)) is beyond the scope of the present work. In principle, it would be possible to conduct meta-analyses of whole brain correlations of symptom dimensions against reward related activity to address this, but these maps are not always reported. Nevertheless, aside from the concerns about medication described above, our findings imply that investigating striatal activity with respect to symptoms of schizophrenia may be a productive approach due to the presence of a substantial effect of group. Furthermore, substance abuse disorders (SUDs) occur frequently in SCZ (Dervaux, et al., 2001), and individuals with SUDs appear to have superficially similar patterns of reward-related abnormality to some individuals with SCZ (Luijten, et al., 2017). Whether or not our findings can be confirmed when controlling for SUDs remains to be confirmed.

A further, crucial impediment to inferences about heterogeneity is the fact that a variety of different paradigms were employed by different studies. Indeed, examining the studies that contribute to the significant cluster reveals a mix of different paradigm designs and contrasts. While we might expect different research groups to examine patient cohorts with different clinical characteristics, differences in the paradigms employed may also be as important. An underlying assumption of our approach is that reward-related activations operate as a stable, trait-like phenomenon, insofar as an individual's neural reward reactivity can be ascertained from a given paradigm. While the present results suggest that this approach has been at least partially fruitful, it is worth noting that there is also considerable evidence suggesting that the reward system can adapt to local reward rate (adaptive coding: Tobler, et al., 2005). A recent study identified several regions in the caudate and the insula in which patients with SCZ showed a different pattern of contextual adaptation to reward rate than healthy controls (Kirschner, et al., 2016). An implication of this study is that alterations in activation coupled to a particular class of reward-related event need to be considered in light of the event's value within the overall reward context. This may be seen as

part of a much wider challenge for future work: namely, to determine the extent to which trait-like properties of neural reward coding which reflect symptoms of schizophrenia can be identified independent of the stimulus and reward contingencies employed.

Summary

In the present study, we performed a whole brain ALE meta-analysis of reward paradigms comparing SCZ and healthy controls. Our findings confirm the presence of ventral striatal abnormalities, but also qualify the view that there is a simple hypoactivation of reward circuitry in SCZ. Our analyses suggest that a network-based approach, such as partial least squares, may be a productive future direction, in addition to conventional analyses of different paradigm and the clinical characteristics of patient cohorts.

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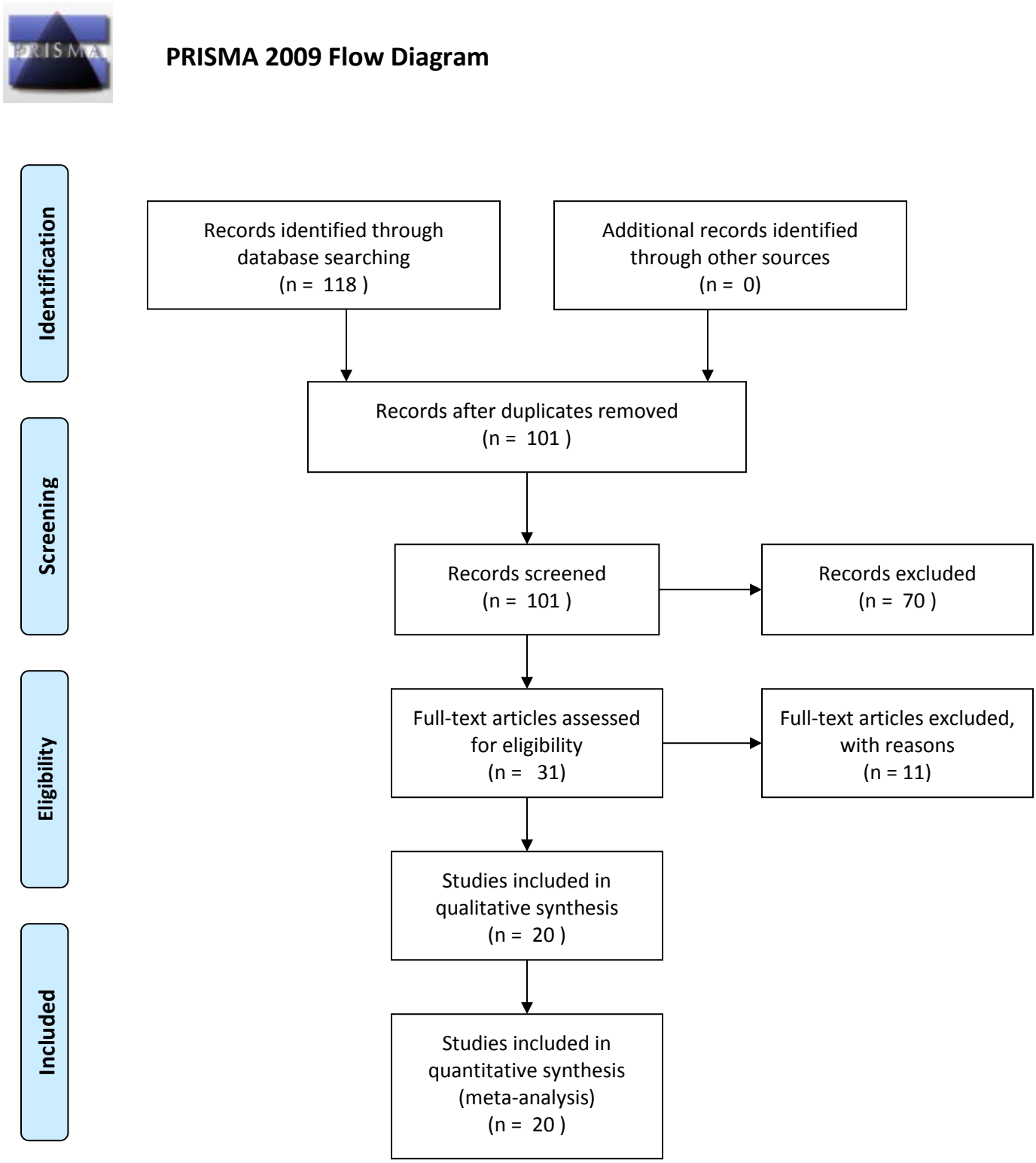
Tables:

Table 1: PRISMA diagram describing the selection of studies for the meta-analysis.



	Antipsychotic Medication	Subject numbers (HC / SCZ)	Foci (Ant / Out)	Reward Type	Anticipation	Outcome
Arrondo, et al., (2015)	Medicated	21 / 22	1	Money	HC > SCZ	
Chung and Barch, (2016)	Medicated	36 / 27	2	Money	HC>SCZ (sustained across anticipation and outcome)	
Culbreth, et al., (2016a)	Most medicated	57 / 36	18	Performance feedback		HC > SCZ
da Silva Alves, et al., (2013)	Medicated	10 /12	2	Money	HC>SCZ	
Dowd and Barch, (2012)	Medicated	20 / 25	4 /3	Money	HC>SCZ	HC>SCZ
Dowd, et al., (2016)	All but 3 medicated	37 / 38	8/2	Money	SCZ>HC (Q values)	SCZ>HC (RPE)
Gradin, et al., (2013)	Medicated	18 / 14	- /4, 1	Water		HC > SCZ, SCZ > HC
Koch, et al., (2010)	All but one medicated	20 / 19	4	Money		RPE (HC>SCZ)
Koch, et al., (2015)	Mixed	44 / 44	21	Money	HC > SCZ	
Morris, et al., (2012)	Medicated	16 / 16	16	Money		SCZ/HC interaction (Ant/RPE)
Murray, et al., (2008)	Most medicated	12 / 13	24	Money		HC>SCZ (RPE)
Reinen, et al., (2016)	Unmedicated	23 / 16	50	Money		SCZ/HC interaction (RPE)
Schlagenhauf, et al., (2014)	Unmedicated	24 / 24	-/4,3	Performance Feedback		SCZ> HC and

						HC>SCZ (RPE)
Segarra, et al., (2016)	Medicated	21 / 21	10	Money		HC>SCZ
Subramaniam, et al., (2015)	Medicated	20 / 37	2	Money	HC > SCZ	
Walter, et al., (2009)	Atypical medication	16 / 16	1	Money	HC > SCZ	HC>SCZ (RPE)
Waltz, et al., (2009)	Medicated	18 / 18	26	Juice		HC>SCZ (RPE)
Waltz, et al., (2013)	Medicated	21 /29	2	Money		HC > SCZ
White, et al., (2015)	Medicated	22 / 19	5	Money		SCZ > HC (RPE)
Wolf, et al., (2011)	All but one	26 / 25	8	Performance feedback		HC>SCZ
Summary	18 (most/all) Medicated / 2 Unmedicated	482 / 471	221	17 Money / 3 Performance feedback / 1 Juice	7 HC>SCZ, 1 SCZ>HC	11 HC>SCZ, 4 SCZ>HC, 2 interaction

Table 2: Studies included in the present meta-analysis (Ant=Anticipation; Out=Outcome; RPE=Reward Prediction Error), their characteristics and the contrasts selected.

Main Effect	K	MNI (X Y Z)	Studies contributing
Right Ventral Striatum	181	10 12 -2	Arrondo, et al., (2015) 14.68% (Ant, HC>SCZ) Gradin, et al., (2013) 0.47% (Out: HC>SCZ) Morris, et al., (2012) 28.61% (Out: PE*group) Reinen, et al., (2016) 14.35% (Out: PE*group) Segarra, et al., (2016) 12.28% (Out: HC>SCZ) White, et al., (2015) 14.65% (Out: SCZ>HC) Wolf, et al., (2011) 14.88% (Out: HC>SCZ)

Table 3: Table describing location of significant main effect across all (HC>SCZ and SCZ > HC) studies. Percentages in the final column show the percentage contribution made by each study to the final cluster, and the contributing contrast is listed.

Conjunction of rsfMRI and MACM (CCN)	*k*	MNI co-ordinates (x, y, z)	*t*
Bilateral Striatum (caudate, putamen), thalamus, anterior insula	5062	12 10 -2 14 6 -2 -12 10 -2 4 -14 10 -24 20 -4 -6 -20 10	9.09 9.00 8.72 8.36 7.82 7.66
Superior medial frontal cortex/preSMA: two clusters	185 170	-2 24 42 -4 8 54 4 24 40 6 24 32 4 16 48	6.04 4.63 6.11 4.42 3.58
Midbrain	44	2 -18 -14 -2 -16 -14	4.17 4.16
Left Dorsolateral Prefrontal Cortex	17	-48 8 36 -50 12 36	3.54 3.51
Left Inferior Parietal Lobule (hIP1)	17	-38 -56 44	3.75

Conjunction of CCN [rsfMRI/MACM] and [HC>SCZ] structure			
Thalamus (PFC/temporal subregions)	131	0 -16 4	
Left Ventral Striatum	86	-6 9 -7	
Left Frontal Operculum	6	-39 25 -4	
Conjunction of CCN [rsfMRI/MACM] and [SCZ>HC] structure			
Left Putamen	107	-26 3 4	

Table 4: Table describing the co-ordinates of the CCN, and its overlap with the structural meta-analysis of comparisons of HC and SCZ. A cluster threshold of 5 voxels was applied.

Region	P(Activation / Domain)	P(Activation / Paradigm)	P(Domain / Activation)	P(Paradigm / Activation
Right ventral striatum cluster	Gustation Cognition Emotion	Reward Taste	Emotion Cognition	Reward
CCN	Olfaction Gustation Sadness Happiness Pain Cognition Emotion	Olfactory monitor, discrimination Taste Reward	Pain Emotion Cognition	Reward Pain monitor, discrimination Delay Match to Sample Theory of mind Passive listening Mediation Overt naming Mental rotation Estimation

Table 5. Table describing decoding analyses for the Right Ventral Striatum cluster identified by the meta-analysis, and the associated CCN.

Figures:

Figure 1: Right ventral striatal region identified by ALE meta-analysis.

Figure 2: Location of CCN derived from right ventral striatum seed.

Figure 3: Regions in brain in which functional connectivity, as estimated with rsfMRI, is less than zero (blue), greater than zero but less than z=0.1146 (red), greater than z=0.1146 (green). Note location of the significant right ventral striatum cluster is omitted. MA values in these three regions were significantly different from one another.