Original Investigation | META-ANALYSIS

Ventral Striatal Activation During Reward Processing in Psychosis
A Neurofunctional Meta-Analysis

Joaquim Radua, MD, BStat, PhD; André Schmidt, PhD; Stefan Borgwardt, MD, PhD; Andreas Heinz, MD, PhD; Florian Schlagenhauf, MD; Philip McGuire, MD, PhD; Paolo Fusar-Poli, MD, PhD

IMPORTANCE Abnormal reward processing is suggested to underlie the formation of psychotic symptoms, likely driven by elevated ventral striatal (VS) dopamine levels. Functional magnetic resonance imaging studies reveal alterations of VS activity during reward processing in patients with chronic psychosis and first episode of psychosis, as well as individuals at high risk for psychosis, but findings are inconclusive, conflicting, and difficult to subject to meta-analysis without introducing bias because several studies reported that findings were not statistically significant but did not report statistics.

OBJECTIVE To assess the differences between patients with schizophrenia spectrum disorders and healthy controls in VS activation during reward processing.

DATA SOURCES Web of Knowledge database (incorporating Web of Science and MEDLINE) until July 2015, including references of eligible articles and reviews.

STUDY SELECTION Functional magnetic resonance imaging studies comparing VS activity during monetary reward processing between patients with schizophrenia spectrum disorders or clinical or genetic high-risk state for psychosis and healthy controls.

DATA EXTRACTION AND SYNTHESIS Statistics and thresholds related to the main outcome measures and potential moderators were independently retrieved by 2 investigators. Effect sizes were analyzed using MetaNSUE, a random-effects method that enables the unbiased inclusion of nonstatistically significant unreported effects.

MAIN OUTCOMES AND MEASURES Effect size of the group differences in VS activity, and correlation between VS activity and negative and positive symptom scores in patients.

RESULTS The meta-analysis included 23 studies (917 patients) for reward anticipation, 9 studies (358 patients) for reward feedback, and 8 studies (314 patients) for reward prediction error. We found significant bilateral VS hypoactivation during reward anticipation (23 studies, n = 917) in patients compared with healthy controls (left/right Cohen d, −0.50/−0.70; $P < .001$). Left VS abnormality was more severe in patients with high scores of negative symptoms during reward anticipation ($r = −0.41$; $P < .001$). Patients also showed hypoactivation during reward feedback (left/right d, −0.57/−0.56; $P < .001$). Simulations showed that exclusion of studies with nonstatistically significant unreported effects was associated with a strong bias (d bias = 0.22), whereas estimations using MetaNSUE were unbiased even when statistics were seldom reported (d bias < 0.001).

CONCLUSIONS AND RELEVANCE This meta-analysis provides evidence that patients with psychosis demonstrate VS hypoactivation during reward anticipation. The assessment of VS prediction errors seems to be promising, but more studies are needed to draw valid conclusions.

+ Supplemental content at jamapsychiatry.com

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Joaquim Radua, MD, BStat, PhD, Department of Psychosis Studies, Institute of Psychology, Psychiatry and Neuroscience, PO 63, 16 De Crespigny Park, London SE5 8AF, England (jradua@fidmag.com).

S tudies from more than half a century ago had already reported that patients with schizophrenia often describe how irrelevant stimuli capture their attention and are assigned unduly high significance.[1,2] This phenomenon was suggested to result from abnormal stimulus-reinforcement formations induced by chaotic dopaminergic firing in mesolimbic reward pathways, which could consequently produce psychotic symptoms.[3] The phenomenon was later on framed in terms of "aberrant salience," a phenomenological concept proposing that psychosis may arise from an inappropriate assignment of salience to contextually irrelevant external events and internal mental states.[4,5] In this context, salience refers to the motivational aspect of stimuli, which catch attention because of their association with primary reinforcement,[6] and is mediated by dopamine in the ventral striatum (VS).[6]

Recent proposals link aberrant salience to abnormal prediction error processing, driving the formation of reinforcement learning abnormalities and possibly psychotic symptoms.[7,8] Prediction errors, the discrepancy between the actual inputs and the prediction about it, are mediated via midbrain dopamine neurons and their targets in the VS.[9,10] A contemporary animal model proposed that psychosis may develop as a result of an impaired inhibitory functioning of the medial temporal lobe, leading to elevated VS dopamine level.[11] It was suggested that consequently the number of dopamine neurons participating in providing prediction error signals may be upregulated in schizophrenia, contributing to abnormal salience processing.[11] Whereas diverse neural measures have been interpreted to reflect aberrant salience attribution in psychosis studies[12] up to now, most studies—as meta-analyzed in this article—focused on the processing of reward-indicating cues. In this context, a blunted response between reward-indicating and neutral cues was taken as a measure of aberrant salience.

Positron emission tomography and single-photon emission computed tomography studies have consistently shown that striatal dopamine synthesis capacity is increased in psychosis.[13,14] Functional magnetic resonance imaging (fMRI) studies during monetary reward anticipation have also detected altered VS activation in patients experiencing their first episode of psychosis, patients with chronic psychosis, and individuals at clinical or genetic high risk (HR) for psychosis. However, these fMRI findings seem inconclusive because some studies found reduced VS activation[15-25] whereas others reported no abnormalities.[26-37] Similar conflicts are evident for fMRI reward prediction error studies, with reduced VS activation being found in some studies[38-43] and VS hyperactivation[26] or no VS differences in others.[44] Additionally, the clinical relevance of VS alterations in psychosis is unclear. For example, most of the studies investigated the relation between VS activation and negative symptoms, with some studies revealing significant correlations[15,17,23,28] and others not.[30,32,40] These inconsistencies may be due to small and heterogeneous patient samples, varying tasks and imaging analyses, and/or confounding effects of antipsychotic medication. Unfortunately, these studies are difficult to subject to meta-analysis because several studies state that findings were not statistically significant without reporting statistics, and attempts to retrieve unpublished data by contacting authors have been shown to be mostly (~80%) unsuccessful.[45]

To address these inconsistencies, we present here, to our knowledge, the first systematic review and neurofunctional meta-analysis of VS activation during reward processing in patients at HR, those experiencing their first episode of psychosis, and those with chronic psychosis. In particular, we focused on reward anticipation and feedback, as well as reward prediction error. We investigated the robustness of the meta-analytic findings and the effects of potential clinical and methodological moderators. In addition, we present an innovative methodological approach to include all studies even if they only report that they did not find any statistically significant effect (but not the specific effect size or related statistics).

Methods

Search Strategies
Two investigators (A.S., P.F.-P.) conducted an independent systematic 2-step literature search to identify relevant articles. First, the Web of Knowledge database (incorporating Web of Science and MEDLINE) was searched to detect abstracts in English published through July 2015 (keywords: "psychosis," "schizophrenia," "high-risk psychosis," "salience," "fMRI," "ventral striatum," "reward," "prediction error"). Second, Scopus was used to detect citations of previous systematic reviews and to perform manual searches of the reference lists of the retrieved articles. Identified articles were then screened according to the selection criteria. The Meta-analysis of Observational Studies in Epidemiology (MOOSE) checklist[46] was adopted (eTable 1 in the Supplement).

Selection Criteria
Studies were eligible for inclusion if they (1) were original articles written in English; (2) compared patients with *ICD-10 Classification of Mental and Behavioral Disorders*[47] and/or *DSM-5*[48] diagnosis of schizophrenia spectrum disorders or clinical[49] or genetic[50] HR state for psychosis with healthy controls; and (3) investigated fMRI VS responses explicitly during monetary reward processing, in particular contrasts addressing reward anticipation, feedback of reward, or reward prediction error (**Table**). If available, multiple contrasts from the same study were included. Studies were excluded if they (1) only included anticipation of monetary loss, aversive feedback, and aversive predictive error or other salience-related contrasts (eTables 2 and 3 in the Supplement) or (2) used overlapping data sets[16,21] (we included the original and larger data sets[15,17,18] instead of pooled results[21]).

As detailed in the Statistical Analysis section, we did not exclude studies that did not report effect sizes; note that exclusion of studies with statistically nonsignificant differences would bias the meta-analysis toward those studies with large differences. Literature search was summarized according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (eFigure 1 in the Supplement).[51]

Recorded Variables
Data extraction and quality assessment were independently performed by 2 investigators (A.S., P.F.-P.). The following variables

Table. Description of the Included Samples

		Patients With Psychosis					Controls		
Study	Functional Magnetic Resonance Imaging Contrast/Learning Model	Stage[a]	No.	Age, Mean, y	Males, %	Medicated, %	No.	Age, Mean, y	Males, %
Reward Anticipation (Cue Induced)									
Abler et al,[35] 2008	Anticipation of reward vs neutral	Chronic (SZ, SA)	12	36.7	42	100	12	36.2	58
De Leeuw et al,[23] 2015	Anticipation of reward vs neutral	HR (S)	27	31.7	52	0	29	30.3	41
Diaconescu et al,[19] 2011	Anticipation of reward vs neutral (with or without conditioned stimulus)	Chronic (SZ)	13	37.6	77	100	13	36.5	69
Dowd and Barch,[29] 2012	Anticipation of reward vs neutral	Chronic (SZ, SA)	25	31.4	72	100	20	33.2	70
Esslinger et al,[20] 2012[b]	Anticipation of reward vs neutral	FEP (SZ, SA, D)	27	27.8	74	0	27	27.1	74
Gilleen et al,[31] 2015	Anticipation of reward vs neutral	Chronic (SZ)	20	36.5	100	95	12	30.7	100
Grimm et al,[22] 2014	Anticipation of reward vs neutral	HR (FGR)	54	33.6	43	0	80	33.5	49
Juckel et al,[15] 2006	Anticipation of reward vs neutral	Chronic (SZ), FGA	10	31.5	80	100	10	30.6	80
		Chronic (SZ), SGA	10	37.6	60	100			
Juckel et al,[34] 2012	Anticipation of reward vs neutral	HR (BS, SIPS)	13	25.5	85	46	13	25.7	85
Mucci et al,[30] 2015	Anticipation of reward vs neutral	Chronic (SZ)	28	33.1	64	100	22	31.9	45
Nielsen et al,[24] 2012	Overall salience contrast (uncertain reward + uncertain loss greater than certain neutral + certain neutral)	FEP (SZ, SA)	31	25.9	71	0	31	25.7	71
Nielsen et al,[25] 2012	Overall salience contrast (uncertain reward + uncertain loss greater than certain neutral + certain neutral)	FEP (SZ)	23	26.0	70	0	24	25.7	83
Roiser et al,[32] 2013	Adaptive salience (high-probability rewarding vs low-probability rewarding cues	HR (ARMS)	18	25.7	39	0	18	26.5	56
Schlagenhauf et al,[17] 2008	Anticipation of reward vs neutral	Chronic (SZ), FGA	10	30.5	90	100	10	31.8	90
Schlagenhauf et al,[18] 2009	Anticipation of reward vs neutral	Chronic (SZ)	15	30.1	80	0	15	30.1	80
Silva Alves et al,[36] 2013	Anticipation of reward vs neutral	Chronic (SZ)	10	22.7	100	100	12	34.5	100
Simon et al,[27] 2010	Anticipation of reward vs neutral	Chronic (SZ, SA)	15	26.3	67	100	15	25.2	67
Smieskova et al,[37] 2015[b]	Adaptive salience (high-probability rewarding vs low-probability rewarding cues)	FEP (P)	29	25.9	66	41	19	26.4	53
		HR (ARMS)	34	24.3	76	0			
Walter et al,[26] 2009	Anticipation of reward vs neutral	Chronic (SZ)	16	38.0	50	100	16	33.0	44
Waltz et al,[28] 2010	Anticipation of reward vs loss	Chronic (SZ)	17	37.8	76	100	17	37.8	71
Wotruba et al,[33] 2014	Anticipation of reward vs neutral	HR (BS, SIPS)	21	25.1	71	0	24	23.3	54
Total			478	30.2	67	42	439	30.2	64
Reward Feedback (Outcome Induced)									
Abler et al,[35] 2008	Feedback of reward vs omission of reward	Chronic (SZ, SA)	12	36.7	42	100	12	36.2	58
De Leeuw et al,[23] 2015	Feedback of reward vs omission of reward	HR (S)	27	31.7	52	0	29	30.3	41
Dowd and Barch,[29] 2012	Feedback of reward vs omission of reward	Chronic (SZ, SA)	25	31.4	72	100	20	33.2	70
Gilleen et al,[31] 2015	Feedback of reward vs loss	Chronic (SZ)	20	36.5	100	95	12	30.7	100
Nielsen et al,[24] 2012	Feedback of reward vs omission of reward	FEP (SZ, SA)	31	25.9	71	0	31	25.7	71
Schlagenhauf et al,[18] 2009	Feedback of reward vs omission of reward	Chronic (SZ)	15	30.1	80	0	15	30.1	80
Simon et al,[27] 2010	Feedback of reward vs omission of reward	Chronic (SZ, SA)	15	26.3	67	100	15	25.2	67
Waltz et al,[28] 2010	Feedback of reward vs omission of reward	Chronic (SZ)	17	37.8	76	100	17	37.8	71
Wotruba et al,[33] 2014	Feedback of reward vs omission of reward	HR (BS, SIPS)	21	25.1	71	0	24	23.3	54
Total			183	30.8	70	48	175	29.6	65

(continued)

Table. Description of the Included Samples (continued)

Study	Functional Magnetic Resonance Imaging Contrast/Learning Model	Patients With Psychosis					Controls		
		Stage[a]	No.	Age, Mean, y	Males, %	Medicated, %	No.	Age, Mean, y	Males, %
Reward Prediction Error									
Gradin et al,[40] 2011	State action reward state action	Chronic (SZ)	14	42.5	79	79	17	40.6	41
Koch et al,[43] 2010	Temporal difference learning (positive prediction error/positive vs negative prediction error)	Chronic (SZ)	19	35.2	63	95	20	29.7	60
Morris et al,[41] 2012	Reward[c] surprise interaction (incorrectly predicted reward greater than correctly predicted reward; correctly predicted nonreward greater than incorrectly predicted nonreward)	Chronic (SZ, SA)	16	33.0	56	100	16	32.9	50
Murray et al,[38] 2008[b]	Standard reinforcement learning algorithm (prediction error on reward vs prediction error on neutral)	FEP (SZ, BD, PNOS)	13	26.0	69	62	12	26.0	75
Schlagenhauf et al,[42] 2014	Rescorla-Wagner model	FEP (SZ)	24	27.5	92	0	24	27.2	92
Walter et al,[26] 2009	Receipt of high greater than receipt of low greater than receipt of no greater than omission of low greater than omission of high reward	Chronic (SZ)	16	38.0	50	100	16	33.0	44
Waltz et al,[39] 2009	Temporal difference errors (positive-negative contrast)	Chronic (SZ, SA)	18	37.7	72	100	18	37.1	78
Wolf et al,[44] 2014	Unpredictable reward vs loss outcomes	Chronic (SZ, SA)	41	41.7	54	98	37	39.2	49
Total			155	35.7	66	78	159	33.9	61

Abbreviations: ARMS, at-risk mental state; BD, bipolar disorder with psychosis; BS, basic symptoms; D, delusional disorder; FEP, first-episode psychosis; FGA, first-generation antipsychotic; FGR, first-grade relatives of schizophrenic patients; HR, high risk; SGA, second-generation antipsychotic; SIPS, structured interview for prodromal symptoms; P, psychosis of unspecified type; PNOS, psychosis not otherwise specified; S, siblings of schizophrenic patients; SA, schizoaffective; SZ, schizophrenia.

[a] Individuals were deemed to have genetic risk if they were (1) FGRs or (2) Ss.

The clinical HR state was defined according to international and well-validated criteria detailed elsewhere,[50] which include (1) attenuated psychotic symptoms, (2) brief and limited intermittent psychotic symptoms, (3) genetic risk and deterioration syndrome, and (4) BS.

[b] These studies (may have) included patients with diagnoses other than SZ, SA, or schizophreniform disorders.

were recorded from each article: reference, sample sizes, age, sex, illness stage, antipsychotic treatments, type of analysis ("region of interest" [ROI] vs whole-brain), statistical thresholds, VS group differences (eg, *t* values), publication year, clinical and methodological items objectively used to calculate quality scores (eTable 4 in the Supplement), and correlations between VS activity and negative and/or positive symptoms.

Notably, whole-brain studies did not report the mean VS effect but the peak VS effect. This latter effect is larger than the mean VS effect, and its use would thus bias the meta-analysis. To address this issue, whole-brain coordinates and *t* values of the maxima were introduced into anisotropic effect-size signed differential mapping[52,53] in order to recreate the image of effect size based on the correlations between adjacent voxels, and the mean effect of all voxels with any probability of being located in the nucleus accumbens according to the Harvard-Oxford atlas[54] was then extracted. To overcome the potential downward bias associated to this estimation,[53] maps were scaled to make differences with ROI studies minimal. Also, analyses were repeated after only including the latter.
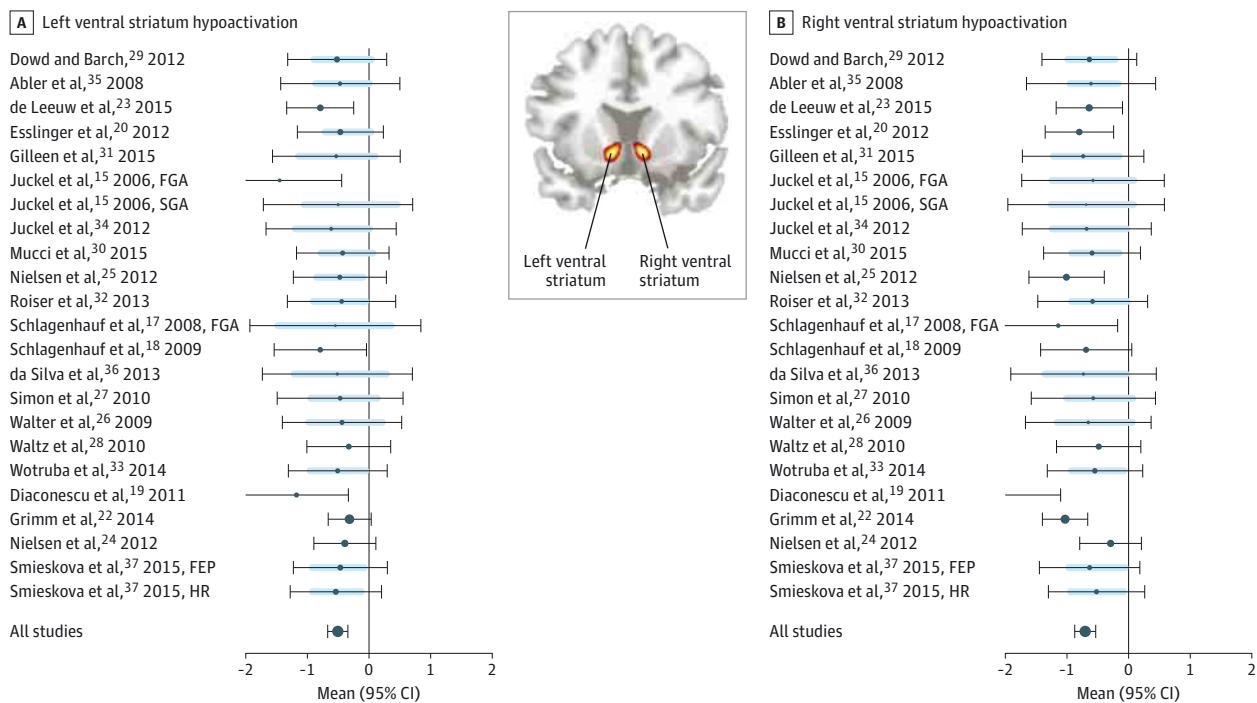
Statistical Analysis

As noted, some studies with nonsignificant group differences did not report any statistics (eg, *t*, *F*, or *P* values) that could be converted into effect sizes. Exclusion of these findings ("nonstatistically significant unreported effects" [NSUEs]) would bias the meta-analysis—taken to the extreme, including only the 3 studies reporting differences but excluding the 1000 studies not detecting any difference (as detailed in the eMethods section in the Supplement, we also empirically test this bias with simulations). Inclusion of studies with NSUEs by assuming them to have a null effect size would be a more conservative option but still not free from bias.[53]

To correctly include studies with NSUEs into meta-analyses, we developed a new method, called MetaNSUE, based on multiple imputations algorithms.[55] First, the MetaNSUE calculates the bounds of nonstatistical significance of each study with NSUEs (ie, the unreported *t* value or *r* coefficient must be within these bounds) and converts them to unbiased effect sizes (Cohen *d* or *z*) using a standard formula.[53] Second, an estimation of the parameters for subsequent imputations is conducted by maximizing the likelihood that the reported effect sizes have those values, as well as the likelihood that the unreported effect sizes are within those bounds. Relevantly, these parameters include the between-study heterogeneity (ie, random differences between studies beyond those due to sampling) and potential covariates used to individually predict the expected effect size of each study (with or without NSUEs). Third, multiple imputations

Figure. Forest Plots of the Ventral Striatum Response to Reward Anticipation in Psychosis

A Left ventral striatum hypoactivation

Dowd and Barch,[29] 2012
Abler et al,[35] 2008
de Leeuw et al,[23] 2015
Esslinger et al,[20] 2012
Gilleen et al,[31] 2015
Juckel et al,[15] 2006, FGA
Juckel et al,[15] 2006, SGA
Juckel et al,[34] 2012
Mucci et al,[30] 2015
Nielsen et al,[25] 2012
Roiser et al,[32] 2013
Schlagenhauf et al,[17] 2008, FGA
Schlagenhauf et al,[18] 2009
da Silva et al,[36] 2013
Simon et al,[27] 2010
Walter et al,[26] 2009
Waltz et al,[28] 2010
Wotruba et al,[33] 2014
Diaconescu et al,[19] 2011
Grimm et al,[22] 2014
Nielsen et al,[24] 2012
Smieskova et al,[37] 2015, FEP
Smieskova et al,[37] 2015, HR

All studies

Left ventral striatum   Right ventral striatum

B Right ventral striatum hypoactivation

Dowd and Barch,[29] 2012
Abler et al,[35] 2008
de Leeuw et al,[23] 2015
Esslinger et al,[20] 2012
Gilleen et al,[31] 2015
Juckel et al,[15] 2006, FGA
Juckel et al,[15] 2006, SGA
Juckel et al,[34] 2012
Mucci et al,[30] 2015
Nielsen et al,[25] 2012
Roiser et al,[32] 2013
Schlagenhauf et al,[17] 2008, FGA
Schlagenhauf et al,[18] 2009
da Silva et al,[36] 2013
Simon et al,[27] 2010
Walter et al,[26] 2009
Waltz et al,[28] 2010
Wotruba et al,[33] 2014
Diaconescu et al,[19] 2011
Grimm et al,[22] 2014
Nielsen et al,[24] 2012
Smieskova et al,[37] 2015, FEP
Smieskova et al,[37] 2015, HR

All studies

In studies with known measures, symbols show the mean, and error bars, the 95% confidence interval (CI). Studies with nonstatistically significant unreported effects are distinguished by the presence of a shaded bar around the mean showing the interval containing 95% of the imputed effect sizes; the central symbol shows the mean, and the error bars, the 95% CI. Size of the data

marker corresponds to the relative weight assigned in the pooled analysis. FEP indicates first episode of psychosis; FGA, first-generation antipsychotic; HR, individuals at high risk for schizophrenia; and SGA, second-generation antipsychotic. The location of the ventral striatum is indicated for reference.

of the unreported effect sizes are randomly created according to the expected value (within- and between-study), variance, and statistical significance bounds of each study with NSUEs. This step is needed to create realistic "noisy" imputations because imputing the unreported effect sizes using their *expected* value would mean assuming that within-study variability and between-study heterogeneity are null. Finally, a standard meta-analysis is separately conducted for each set of imputed effect sizes using restricted maximum-likelihood random-effect models,[56] and results from these meta-analyses are pooled using a standard formula for multiple imputations.[57]

Empirical validation using simulations showed that estimations were strongly biased when conducting a standard meta-analysis without NSUEs (d bias = 0.22), moderately negatively biased when converting NSUEs to zeros (d bias = −0.07), and nearly unbiased when using MetaNSUE (d bias < 0.001, even when statistics were seldom reported). See eMethods in the Supplement for details of the procedure and the validation.

A separate meta-analysis was conducted for group differences in left and right VS activation. Robustness of these differences was assessed by studying the between-study heterogeneity, estimating the potential reporting bias (metaregression by standard error to detect whether results from small imprecise studies might have been reported only if they were significant[58-60]), and conducting jackknife analyses (ie, iteratively repeating the meta-analysis with all studies but 1 in or-

der to detect whether results may be driven by a single study). Differences between left and right group differences in activation were also investigated, along with subgroups (medication-free, patients, HR individuals, ROI studies) and metaregressions by mean age, percentage of males, percentage of medicated patients, publication year, and quality score. Meta-analysis of the correlations between psychotic symptoms and VS activation was also conducted. Finally, we performed an exploratory analysis treating all 3 domains (anticipation/feedback and prediction error) together.

On the basis of the results of the empirical validation, moderator variables were included in the maximum-likelihood step. All findings with $P < .05$ are reported as trends, but given the multiple tests conducted (3 different reward processing domains and 2 brain sides), only those at $P \le .05/6 = .008$ were considered statistically significant.

Results

Reward Anticipation

This meta-analysis included 23 studies (n = 917) (see Table), with reported group differences in 7 (left) and 9 (right) studies, and NSUEs in the remaining studies. Patients showed significant hypoactivation in both left and right VS (d left/right = −0.50/−0.70; $P < .001$ in both cases) (**Figure**). No

residual heterogeneity or potential reporting bias was observed (P = .12-.92). Jackknife analyses showed similar hypoactivation when any single study was discarded (left d range, −0.45 to −0.58; right d range, −0.66 to −0.77; P < .001 in all cases) or when the meta-analysis was restricted to studies in medication-free patients or to studies using ROIs (left/right d = −0.45/−0.72 and −0.59/−0.65, respectively; P < .001 in all cases). No differences were detected between left and right VS (P = .18). No effects of age, sex, antipsychotic medication use, publication year, or quality score were observed (P = .14 to >.99). Similar hypoactivation was found in patients and HR individuals (left/right d = −0.55/−0.67 vs −0.44/−0.78; P = .53/.57).

Eleven studies analyzed the correlation between VS activation and negative symptoms,[15,17,23,24,27-30,32,33] and we were able to retrieve the correlation coefficient in 5 (left) and 2 (right) studies, with the remaining studies reporting NSUEs. Left hypoactivation was more pronounced in patients with higher negative symptoms (r = −0.41; P < .001), an effect that was not evident at the right VS (P = .86). No residual heterogeneity or potential reporting bias was observed (P = .35-.96). Jackknife analyses (only conducted for left VS) showed similar correlations when any single study was discarded (r range, −0.36 to −0.45; P < .003 in all cases).

Six studies had investigated the relationship with positive symptoms[20,23,24,27,32,33] and we were able to retrieve the correlation coefficient in 2 (left) and 3 (right) studies, with the remaining studies reporting NSUEs. No relationship between VS activation and positive symptoms could be detected (P = .47-.79), although this result should be taken with caution because only 6 studies could be included and there was residual heterogeneity among them (left/right: I^2 = 63%/72%; P = .03/.003, probably due to studies reporting opposite findings).

Reward Feedback

This meta-analysis included 9 studies (n = 358) (Table), with reported group differences in 1 study, and NSUEs in the remaining studies. Patients showed significant hypoactivation in both left and right VS (left/right d= −0.57/−0.56; P < .001) (eFigure 2 in the Supplement), and no residual heterogeneity or potential reporting bias was observed (P = .89-.93). One may wonder that a single study makes the meta-analysis statistically significant. However, it must be noted that the empirical validation showed that MetaNSUE's false-positive rate is not increased when only 1 study reports significant differences. That said, jackknife analyses showed similar hypoactivation when any study with NSUEs was discarded (left d range, −0.59 to−0.64; right d range, −0.57 to −0.62; P < .001 in all cases) but no differences if the only study detecting group differences[23] was discarded (P = .95-.96), indicating a lower replicability of this finding, which should thus be taken with caution. No differences were detected between left and right VS (P = .72). No meta-regression analyses were conducted because of the high probability that the study detecting differences behaved as a leverage point. No relationship with negative or positive symptoms could be observed (eResults in the Supplement).

Reward Prediction Error

This meta-analysis included 8 studies (n = 314) (Table), with reported between-group differences in 4 (left) and 6 (right) studies, and NSUEs in the remaining studies. Patients showed hypoactivation in both left and right VS (left/right d = −0.28/ −0.53) (eFigure 3 in the Supplement), although not statistically significant at the left and only at trend level (.008 < P < .05) at the right side (left/right P = .37/.01). This lack of significance should be taken with caution because only 8 studies were included, and there was residual high heterogeneity (which decreases the precision and thus the statistical significance of the estimates) among them (I^2 = 83% and 64%; P < .001 and .02). No potential reporting bias was observed (P = .12-.76). Jackknife analyses (only conducted for right VS) showed relatively similar hypoactivation when any single study was discarded (d range, −0.39 to −0.62; all P < .06). Differences between left and right VS were not statistically significant (P = .53). No metaregression analyses were conducted because of the paucity of studies. No relationship with negative or positive symptoms could be observed (eResults in the Supplement).

Combination of Reward Anticipation, Feedback, and Prediction Error

Results of this exploratory analysis are explained in the eResults in the Supplement.

Discussion

Our meta-analysis revealed that psychosis was robustly associated with VS hypoactivation during reward anticipation, including 23 studies with 917 participants, whereas no residual heterogeneity, potential reporting bias, or jackknife abnormalities have been detected. Meta-analyses of reward feedback and prediction error also showed VS hypoactivation but should be carefully considered, because findings were driven by a single study in the first (although validation showed an excellent control of the false-positive rate) and were not statistically significant in the second (probably due to between-study heterogeneity). No differences were observed between left and right VS in any of the reward processes. Our meta-analysis further showed that left VS activation during reward anticipation was negatively correlated with negative symptoms in patients.

The robust finding of VS hypoactivation during reward anticipation may support that psychosis is characterized by impaired learning of stimulus-reinforcement associations.[7,61] However, studies of reward anticipation did not investigate the learning process directly but rather the neural response to reward-indicating cues learned before scanning, and thus our finding may reflect a more general blunting of VS responsivity rather than a specific deficit during reinforcement learning. The attribution of incentive salience to rewarding cues has been proposed to be mediated by phasic dopamine increase in the striatum and contributes to the wanting of reward.[6] A recent meta-analysis has shown that striatal presynaptic dopaminergic markers are consistently altered in psychosis.[13,62]

In chronic psychosis,[13,63] and already in clinical HR subjects,[64] striatal dopamine levels are elevated in the absence of incoming stimuli, which may steer the assignment of salience to normally irrelevant stimuli whose presence happens to temporally coincide with dopamine release.[4,65] Moreover, a chaotic stress-associated striatal dopamine release[5,7] may also impede a phasic dopamine release in response to contextually relevant (eg, reward indicating) cues, leading to decreased differentiation between the responses to relevant and irrelevant stimuli.[65] In this framework, the VS hypoactivation during reward anticipation can be taken as a measure of altered salience processing because it reflects a blunted response toward reward-indicating compared with neutral cues. However, general caution is recommended in relating dopamine release to neural activation because they are often not measured in the same region (elevated dopamine levels have been found in the associative striatum[63,64] and different VS definitions are used across studies) and also because fMRI signals have limited statistical relationships to neurochemical markers.[66] For example, sophisticated attempts to relate VS fMRI signals during reward anticipation with measures of dopamine release induced by monetary incentive delay task have revealed mixed results.[67,68] The Discussion section should be read with this caveat in mind.

We found that patients also showed a trend for right VS hypoactivation during reward prediction error processing. However, the robustness of this meta-analysis was limited by a relevant between-study heterogeneity, which is probably due to the different reinforcement learning algorithm,[38,40,42] and the diverse psychological task designs and contrasts used across studies.[26,39,41,43] Previous studies in healthy participants combining fMRI and positron-emission tomography measures showed that the right VS prediction error signal is negatively associated with VS presynaptic dopamine level.[69,70] We could thus speculate that the elevated striatal dopamine level in psychosis[14] might be associated with the right VS hypoactivation during prediction error processing that we found. In line with this argumentation, a behavioral measure of aberrant salience attribution (derived from the salience attribution task), which is heightened in patients with schizophrenia,[71] was found to be positively correlated with striatal dopamine synthesis capacity and negatively correlated with fMRI striatal prediction errors signal in health controls.[72]

Current antipsychotic drug use was not found to moderate the reduced VS activation during reward anticipation. However, most studies included patients treated with both typical and atypical antipsychotics, and it has been proposed that the effect of several atypical drugs may result from a dopamine-mediated attenuation of aberrant salience processing,[4,65] whereas typical but not atypical drugs have been shown to reduce the VS response to reward-indicating stimuli.[15] In line with this finding, a recent meta-analysis in psychosis did not find a significant modulation of antipsychotics on striatal dopamine synthesis capacity.[13,62]

We found that left VS hypoactivation during reward anticipation was more pronounced in patients with higher negative psychotic symptoms in accordance with evidence from a previous meta-analysis.[73] Our correlation findings

thus suggest that VS hypoactivation may impair the positive and motivational effect of rewarding events and in turn promote negative symptoms.[5] This corresponds with a first pilot study, which suggested that decreased left VS activation is inversely correlated with the severity of negative symptoms in antipsychotic-free patients.[16] The authors suggested that high striatal dopamine turnover may increase the "noise" in the reward system, thus interfering with the neuronal processing of reward-predicting cues by phasic dopamine release.[16] This, in turn, may lead to negative symptoms, which group in 2 factors, one involving diminished expression of affect and alogia and the second involving avolition including anhedonia and asociality.[74] Our findings may also have some translational effects, given that negative psychotic symptoms are refractory to all available treatments.[75] However, this conclusion requires further research given that there is also evidence showing that dopamine function in the VS was inversely correlated with negative symptom severity.[63] Furthermore, the relation between VS activation during reward anticipation and positive symptoms requires further investigation because only 6 studies were available and there was residual heterogeneity among them.

This study has some limitations. Findings of VS hypoactivation during reward feedback and prediction error, as well as the correlation with positive symptoms, are less robust than the hypoactivation during reward anticipation or the correlation with negative symptoms and should be taken with caution until more studies are available; the first finding might also reflect that VS activation is not crucially involved during the feedback phase in the monetary incentive delay task.[76] We could not explore whether group differences may be due to negative symptoms. Region of interest delimitation was slightly heterogeneous across studies, resulting in different VS definitions. Similarly, recreation of images from peak *t* values may not be free from downward bias,[53] although maps were scaled and analyses were repeated after only including the latter. To contain consistency in fMRI contrasts, we focused on rewarding stimuli without considering anticipation of monetary loss, aversive feedback, and aversive predictive error or other salience-related contrasts due to the high heterogeneity of these contrasts; however, a preliminary meta-analysis during loss anticipation revealed bilateral VS hypoactivation in psychotic patients, suggesting that VS hypoactivation in psychosis may be associated with a general deficit in salience processing (eTable 2 in the Supplement). More studies are needed to support this finding. The present analysis was restricted to the VS given its relevance during reward processing and psychosis.[12] However, the VS does not function in isolation during reward processing and future studies should consider this process from a network perspective.[77] A whole-brain analysis will be of interest when more whole-brain studies are available. Finally, the lack of a significant effect in the moderator variable for disease stage does not necessarily mean that no differences exist between the groups. More studies for each group, particularly for the HR group, are needed to draw robust inferences.

Conclusions

This meta-analysis demonstrates reduced VS activation during reward anticipation in psychosis, which supports altered processing of salient reward-indicating stimuli. We further showed that the VS dysfunction during reward prediction is correlated with negative symptoms. More studies are needed to assess whether the abnormality also affects reward feedback and prediction error.

REFERENCES

1. McGhie A, Chapman J. Disorders of attention and perception in early schizophrenia. *Br J Med Psychol.* 1961;34:103-116.

2. Chapman J. The early symptoms of schizophrenia. *Br J Psychiatry.* 1966;112(484): 225-251.

3. Miller R. Schizophrenic psychology, associative learning and the role of forebrain dopamine. *Med Hypotheses.* 1976;2(5):203-211.

4. Kapur S. Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. *Am J Psychiatry.* 2003;160(1):13-23.

5. Heinz A. Dopaminergic dysfunction in alcoholism and schizophrenia—psychopathological and behavioral correlates. *Eur Psychiatry.* 2002;17 (1):9-16.

6. Berridge KC, Robinson TE. What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? *Brain Res Brain Res Rev.* 1998;28(3):309-369.

7. Heinz A, Schlagenhauf F. Dopaminergic dysfunction in schizophrenia: salience attribution revisited. *Schizophr Bull.* 2010;36(3):472-485.

8. Fletcher PC, Frith CD. Perceiving is believing: a Bayesian approach to explaining the positive symptoms of schizophrenia. *Nat Rev Neurosci.* 2009;10(1):48-58.

9. Schultz W, Apicella P, Scarnati E, Ljungberg T. Neuronal activity in monkey ventral striatum related to the expectation of reward. *J Neurosci.* 1992;12(12):4595-4610.

10. Schultz W, Dayan P, Montague PR. A neural substrate of prediction and reward. *Science.* 1997; 275(5306):1593-1599.

11. Lodge DJ, Grace AA. Hippocampal dysregulation of dopamine system function and the pathophysiology of schizophrenia. *Trends Pharmacol Sci.* 2011;32(9):507-513.

12. Winton-Brown TT, Fusar-Poli P, Ungless MA, Howes OD. Dopaminergic basis of salience dysregulation in psychosis. *Trends Neurosci.* 2014; 37(2):85-94.

13. Fusar-Poli P, Meyer-Lindenberg A. Striatal presynaptic dopamine in schizophrenia, part II: meta-analysis of [^{18}F/^{11}C]-DOPA PET studies. *Schizophr Bull.* 2013;39(1):33-42.

14. Howes OD, Kambeitz J, Kim E, et al. The nature of dopamine dysfunction in schizophrenia and what this means for treatment. *Arch Gen Psychiatry.* 2012;69(8):776-786.

15. Juckel G, Schlagenhauf F, Koslowski M, et al. Dysfunction of ventral striatal reward prediction in schizophrenic patients treated with typical, not atypical, neuroleptics. *Psychopharmacology (Berl).* 2006;187(2):222-228.

16. Juckel G, Schlagenhauf F, Koslowski M, et al. Dysfunction of ventral striatal reward prediction in schizophrenia. *Neuroimage.* 2006;29(2):409-416.

17. Schlagenhauf F, Juckel G, Koslowski M, et al. Reward system activation in schizophrenic patients switched from typical neuroleptics to olanzapine. *Psychopharmacology (Berl).* 2008;196(4):673-684.

18. Schlagenhauf F, Sterzer P, Schmack K, et al. Reward feedback alterations in unmedicated schizophrenia patients: relevance for delusions. *Biol Psychiatry.* 2009;65(12):1032-1039.

19. Diaconescu AO, Jensen J, Wang H, et al. Aberrant effective connectivity in schizophrenia patients during appetitive conditioning. *Front Hum Neurosci.* 2011;4:239.

20. Esslinger C, Englisch S, Inta D, et al. Ventral striatal activation during attribution of stimulus saliency and reward anticipation is correlated in unmedicated first episode schizophrenia patients. *Schizophr Res.* 2012;140(1-3):114-121.

21. Hägele C, Schlagenhauf F, Rapp M, et al. Dimensional psychiatry: reward dysfunction and depressive mood across psychiatric disorders. *Psychopharmacology (Berl).* 2015;232(2):331-341.

22. Grimm O, Heinz A, Walter H, et al. Striatal response to reward anticipation: evidence for a systems-level intermediate phenotype for schizophrenia. *JAMA Psychiatry.* 2014;71(5):531-539.

23. de Leeuw M, Kahn RS, Vink M. Fronto-striatal dysfunction during reward processing in unaffected siblings of schizophrenia patients. *Schizophr Bull.* 2015;41(1):94-103.

24. Nielsen MØ, Rostrup E, Wulff S, et al. Alterations of the brain reward system in antipsychotic naïve schizophrenia patients. *Biol Psychiatry.* 2012;71(10):898-905.

25. Nielsen MO, Rostrup E, Wulff S, et al. Improvement of brain reward abnormalities by antipsychotic monotherapy in schizophrenia. *Arch Gen Psychiatry.* 2012;69(12):1195-1204.

26. Walter H, Kammerer H, Frasch K, Spitzer M, Abler B. Altered reward functions in patients on atypical antipsychotic medication in line with the revised dopamine hypothesis of schizophrenia. *Psychopharmacology (Berl).* 2009;206(1):121-132.

27. Simon JJ, Biller A, Walther S, et al. Neural correlates of reward processing in schizophrenia—relationship to apathy and depression. *Schizophr Res.* 2010;118(1-3):154-161.

28. Waltz JA, Schweitzer JB, Ross TJ, et al. Abnormal responses to monetary outcomes in cortex, but not in the basal ganglia, in schizophrenia. *Neuropsychopharmacology.* 2010;35 (12):2427-2439.

29. Dowd EC, Barch DM. Pavlovian reward prediction and receipt in schizophrenia: relationship to anhedonia. *PLoS One.* 2012;7(5): e35622.

30. Mucci A, Dima D, Soricelli A, et al. Is avolition in schizophrenia associated with a deficit of dorsal caudate activity? a functional magnetic resonance imaging study during reward anticipation and feedback. *Psychol Med.* 2015;45(8):1765-1778.

31. Gilleen J, Shergill SS, Kapur S. Impaired subjective well-being in schizophrenia is associated with reduced anterior cingulate activity during reward processing. *Psychol Med*. 2015;45(3): 589-600.

32. Roiser JP, Howes OD, Chaddock CA, Joyce EM, McGuire P. Neural and behavioral correlates of aberrant salience in individuals at risk for psychosis. *Schizophr Bull*. 2013;39(6):1328-1336.

33. Wotruba D, Heekeren K, Michels L, et al. Symptom dimensions are associated with reward processing in unmedicated persons at risk for psychosis. *Front Behav Neurosci*. 2014;8:382.

34. Juckel G, Friedel E, Koslowski M, et al. Ventral striatal activation during reward processing in subjects with ultra-high risk for schizophrenia. *Neuropsychobiology*. 2012;66(1):50-56.

35. Abler B, Greenhouse I, Ongur D, Walter H, Heckers S. Abnormal reward system activation in mania. *Neuropsychopharmacology*. 2008;33(9): 2217-2227.

36. da Silva Alves F, Bakker G, Schmitz N, et al. Dopaminergic modulation of the reward system in schizophrenia: a placebo-controlled dopamine depletion fMRI study. *Eur Neuropsychopharmacol*. 2013;23(11):1577-1586.

37. Smieskova R, Roiser JP, Chaddock CA, et al. Modulation of motivational salience processing during the early stages of psychosis. *Schizophr Res*. 2015;166(1-3):17-23.

38. Murray GK, Corlett PR, Clark L, et al. Substantia nigra/ventral tegmental reward prediction error disruption in psychosis. *Mol Psychiatry*. 2008;13(3):239, 267-276.

39. Waltz JA, Schweitzer JB, Gold JM, et al. Patients with schizophrenia have a reduced neural response to both unpredictable and predictable primary reinforcers. *Neuropsychopharmacology*. 2009;34(6):1567-1577.

40. Gradin VB, Kumar P, Waiter G, et al. Expected value and prediction error abnormalities in depression and schizophrenia. *Brain*. 2011;134 (pt 6):1751-1764.

41. Morris RW, Vercammen A, Lenroot R, et al. Disambiguating ventral striatum fMRI-related BOLD signal during reward prediction in schizophrenia. *Mol Psychiatry*. 2012;17(3):235, 280-289.

42. Schlagenhauf F, Huys QJ, Deserno L, et al. Striatal dysfunction during reversal learning in unmedicated schizophrenia patients. *Neuroimage*. 2014;89:171-180.

43. Koch K, Schachtzabel C, Wagner G, et al. Altered activation in association with reward-related trial-and-error learning in patients with schizophrenia. *Neuroimage*. 2010;50(1): 223-232.

44. Wolf DH, Satterthwaite TD, Kantrowitz JJ, et al. Amotivation in schizophrenia: integrated assessment with behavioral, clinical, and imaging measures. *Schizophr Bull*. 2014;40(6):1328-1337.

45. Gibson CA, Bailey BW, Carper MJ, et al. Author contacts for retrieval of data for a meta-analysis on exercise and diet restriction. *Int J Technol Assess Health Care*. 2006;22(2):267-270.

46. Stroup DF, Berlin JA, Morton SC, et al; Meta-analysis of Observational Studies in Epidemiology (MOOSE) group. Meta-analysis of

observational studies in epidemiology: a proposal for reporting. *JAMA*. 2000;283(15):2008-2012.

47. World Health Organization. *The ICD-10 Classification of Mental and Behavioral Disorders: Clinical Descriptions and Diagnostic Guidelines*. Geneva, Switzerland: World Health Organization; 1992.

48. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Washington, DC: American Psychiatric Association; 2013.

49. Fusar-Poli P, Borgwardt S, Bechdolf A, et al. The psychosis high-risk state: a comprehensive state-of-the-art review. *JAMA Psychiatry*. 2013;70 (1):107-120.

50. Johnstone EC, Abukmeil SS, Byrne M, et al. Edinburgh high risk study—findings after four years: demographic, attainment and psychopathological issues. *Schizophr Res*. 2000;46(1):1-15.

51. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009;339:b2535.

52. Radua J, Rubia K, Canales-Rodríguez EJ, Pomarol-Clotet E, Fusar-Poli P, Mataix-Cols D. Anisotropic kernels for coordinate-based meta-analyses of neuroimaging studies. *Front Psychiatry*. 2014;5:13.

53. Radua J, Mataix-Cols D, Phillips ML, et al. A new meta-analytic method for neuroimaging studies that combines reported peak coordinates and statistical parametric maps. *Eur Psychiatry*. 2012;27 (8):605-611.

54. Desikan RS, Ségonne F, Fischl B, et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage*. 2006;31(3): 968-980.

55. Rubin DB. *Multiple Imputation for Nonresponse in Surveys*. New York, NY: John Wiley and Sons; 1987.

56. Viechtbauer W. Conducting meta-analyses in R with the metafor package. *J Stat Softw*. 2010;36(3): 1-48.

57. Li KH, Meng XL, Raghunathan TE, Rubin DB. Significance levels from repeated p-values with multiply-imputed data. *Stat Sin*. 1991;1(1):65-92.

58. Fusar-Poli P, Radua J, Frascarelli M, et al. Evidence of reporting biases in voxel-based morphometry (VBM) studies of psychiatric and neurological disorders. *Hum Brain Mapp*. 2014;35 (7):3052-3065.

59. David SP, Ware JJ, Chu IM, et al. Potential reporting bias in fMRI studies of the brain. *PLoS One*. 2013;8(7):e70104.

60. Ioannidis JP, Munafò MR, Fusar-Poli P, Nosek BA, David SP. Publication and other reporting biases in cognitive sciences: detection, prevalence, and prevention. *Trends Cogn Sci*. 2014;18(5):235-241.

61. Deserno L, Boehme R, Heinz A, Schlagenhauf F. Reinforcement learning and dopamine in schizophrenia: dimensions of symptoms or specific features of a disease group? *Front Psychiatry*. 2013;4:172.

62. Fusar-Poli P, Meyer-Lindenberg A. Striatal presynaptic dopamine in schizophrenia, part I: meta-analysis of dopamine active transporter (DAT) density. *Schizophr Bull*. 2013;39(1):22-32.

63. Kegeles LS, Abi-Dargham A, Frankle WG, et al. Increased synaptic dopamine function in associative regions of the striatum in schizophrenia. *Arch Gen Psychiatry*. 2010;67(3):231-239.

64. Egerton A, Chaddock CA, Winton-Brown TT, et al. Presynaptic striatal dopamine dysfunction in people at ultra-high risk for psychosis: findings in a second cohort. *Biol Psychiatry*. 2013;74(2):106-112.

65. Howes OD, Egerton A, Allan V, McGuire P, Stokes P, Kapur S. Mechanisms underlying psychosis and antipsychotic treatment response in schizophrenia: insights from PET and SPECT imaging. *Curr Pharm Des*. 2009;15(22):2550-2559.

66. Singh KD. Which "neural activity" do you mean? fMRI, MEG, oscillations and neurotransmitters. *Neuroimage*. 2012;62(2):1121-1130.

67. Schott BH, Minuzzi L, Krebs RM, et al. Mesolimbic functional magnetic resonance imaging activations during reward anticipation correlate with reward-related ventral striatal dopamine release. *J Neurosci*. 2008;28(52):14311-14319.

68. Urban NB, Slifstein M, Meda S, et al. Imaging human reward processing with positron emission tomography and functional magnetic resonance imaging. *Psychopharmacology (Berl)*. 2012;221(1): 67-77.

69. Deserno L, Huys QJ, Boehme R, et al. Ventral striatal dopamine reflects behavioral and neural signatures of model-based control during sequential decision making. *Proc Natl Acad Sci U S A*. 2015;112(5):1595-1600.

70. Schlagenhauf F, Rapp MA, Huys QJ, et al. Ventral striatal prediction error signaling is associated with dopamine synthesis capacity and fluid intelligence. *Hum Brain Mapp*. 2013;34(6): 1490-1499.

71. Pankow A, Katthagen T, Diner S, et al. Aberrant salience is related to dysfunctional self-referential processing in psychosis. *Schizophr Bull*. 2015;sbv098.

72. Boehme R, Deserno L, Gleich T, et al. Aberrant salience is related to reduced reinforcement learning signals and elevated dopamine synthesis capacity in healthy adults. *J Neurosci*. 2015;35(28): 10103-10111.

73. Goghari VM, Sponheim SR, MacDonald AW. The functional neuroanatomy of symptom dimensions in schizophrenia: a qualitative and quantitative review of a persistent question. *Neurosci Biobehav Rev*. 2010;34(3):468-486.

74. Blanchard JJ, Cohen AS. The structure of negative symptoms within schizophrenia: implications for assessment. *Schizophr Bull*. 2006; 32(2):238-245.

75. Fusar-Poli P, Papanastasiou E, Stahl D, et al. Treatments of negative symptoms in schizophrenia: meta-analysis of 168 randomized placebo-controlled trials. *Schizophr Bull*. 2015;41(4): 892-899.

76. Knutson B, Fong GW, Bennett SM, Adams CM, Hommer D. A region of mesial prefrontal cortex tracks monetarily rewarding outcomes: characterization with rapid event-related fMRI. *Neuroimage*. 2003;18(2):263-272.

77. Rothkirch M, Schmack K, Deserno L, Darmohray D, Sterzer P. Attentional modulation of reward processing in the human brain. *Hum Brain Mapp*. 2014;35(7):3036-3051.