

Original Article

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Neurofunctional representations of instrumental learning in psychosis: a meta-analysis of neuroimaging studies

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Abstract

Background. Establishing appropriate action–outcome associations can allow animals and humans to control behavior and the environment in a goal-directed manner. Deficits in instrumental learning in psychosis have been widely reported in past studies, but the results remain elusive.

Study design. To explore the consistent neural representations of instrumental learning in functional magnetic resonance imaging (fMRI) in individuals with psychosis, a total of 18 studies (458 individuals with psychosis and 454 controls) were included in our coordinate-based meta-analysis.

Study results. Patients with psychosis presented increased activation in the left middle occipital gyrus, insula, and lingual and postcentral gyri; decreased activation in cortico-striato-thalamo-cortical (CSTC) networks, including the dorsal striatum, insula, thalamus, middle cingulate cortex, posterior cingulate cortex, dorsolateral, orbital, and medial prefrontal cortices (DLPFC, OFC, and mPFC), cerebellum, and associated sensory areas, during instrumental learning. Moreover, mPFC hypoactivation was negatively associated with the percentage of first-generation antipsychotic users, and insula hyperactivation was negatively associated with the percentage of medicated individuals.

Conclusions. Our study revealed that the CSTC circuit could facilitate action-based reward learning in psychosis and may help explain the neuropathological mechanisms underlying these deficits in this disorder.

Introduction

Learning the consequences of actions is an adaptive behavior in humans and animals, which allows them to control their environment in a goal-directed manner. Instrumental learning (operant learning) is the ability to learn from consequences and optimize actions by acquiring action–outcome (A–O) associations, which requires both reward processing and causal integration (Dowd & Barch, 2012; Maia, 2009; Miyata, 2019). Reward processing and reinforcement learning impairments are key characteristics of schizophrenia (SZ) and other psychotic disorders and are strongly associated with functional and clinical outcomes (Waltz et al., 2018). In fact, the literature examining reward processing in psychosis has largely relied on instrumental learning tasks, in which participants must make responses first, and rewards only occur after correct and/or rapid response execution (Bouton, Maren, & McNally, 2021; Dowd et al., 2016). In these tasks, the ability to anticipate a reward depends upon the ability to earn the reward by responding appropriately. This requires not only reward processing but also causal integration, either of which may be impaired in individuals with psychosis (Dowd et al., 2016; Waltz et al., 2018). These deficits have been shown across a wide variety of tasks and have been associated with negative symptoms, such as anhedonia and avolition (Dowd & Barch, 2012; Morris et al., 2012). Numerous studies to date have reported an association between A–O learning deficits and the severity of negative symptoms, suggesting, to some extent, that changes in adaptive response to environmental stimuli may play an important part in the onset of SZ. According to ideomotor theories of action control, the anticipation of action goals emerges from the acquisition of bidirectional A–O associations (Hommel, 2009; Shin, Proctor, & Capaldi, 2010); once the capacity is impaired, individuals are unable to generate enough motivation to sustain a behavior pattern for a desired goal, which is associated with amotivation symptoms in SZ (Watson et al., 2015).

The fact that individuals with psychosis exhibit dysfunctional reinforcement processing mechanisms, which may contribute to negative symptoms, is further supported by evidence that the mesolimbic dopamine system, which is known to be important in psychotic symptoms

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and modulates instrumental learning, is disrupted in psychosis (Waltz *et al.*, 2009). As such, investigating the neural representations of instrumental learning will contribute to understanding the relationship between the neurobiology of psychosis and its subjective experience and behavior performance, as well as informing illness diagnosis (Murray *et al.*, 2008). Several studies have attempted to examine the neural basis for A–O learning abnormalities in psychosis and have identified the meso-cortico-limbic circuit, including the ventral (VS) and dorsal striatum (DS), amygdala, insula, dorsolateral prefrontal cortex (DLPFC), orbital prefrontal cortex (OFC), medial prefrontal cortex (mPFC), and anterior cingulate cortex (ACC), as key brain regions involved (Gradin *et al.*, 2013; Juckel *et al.*, 2006a; Liu *et al.*, 2023; Romaniuk *et al.*, 2010; Waltz *et al.*, 2009). These BOLD (blood oxygen level dependent) signal activations in the meso-cortico-limbic reward circuit are thought to communicate information about reward contingencies in the environment that guide action selection and learning. However, the results in individuals with psychosis are still inconsistent. Although most studies have reported reduced VS activity in individuals with psychosis when encoding action value (Gradin *et al.*, 2011; Schlagenhauf *et al.*, 2014; Waltz *et al.*, 2018), some studies have reported no differences between psychosis and healthy control (HC) groups (Culbreth *et al.*, 2016b; Dowd *et al.*, 2016; Waltz *et al.*, 2013). In terms of the prefrontal cortex (PFC), numerous imaging studies have demonstrated altered cortical activity in the mPFC and OFC (Hernaus *et al.*, 2018; Waltz *et al.*, 2018), which is implicated in both valuation and converting value to actions (Balleine & O'Doherty, 2010; Tanaka, Balleine, & O'Doherty, 2008), while other studies have shown intact activity in either the OFC or mPFC during these processes (Culbreth, Gold, Cools, & Barch, 2016a; Koch *et al.*, 2010; Morris *et al.*, 2015). Furthermore, the neural signals of the expected value of the outcome are significantly correlated with negative symptoms (Katthagen *et al.*, 2020; Waltz *et al.*, 2009); however, there is also evidence suggesting correlations with the severity of psychiatric symptoms (Gradin *et al.*, 2011). Additionally, some studies have shown that antipsychotic drugs contribute to the recovery of the activation of different brain regions within the meso-cortico-limbic circuit. The heterogeneity of the included samples and RL (reinforcement learning) paradigms, combined with the bias introduced by including region of interest analyses, may explain the inconsistencies across studies.

To address this issue, we performed a voxel-based meta-analysis to investigate the neural representations elicited by instrumental learning in individuals with psychosis compared to HCs. Our current work aimed to investigate the neural representations of aberrant behavior–outcome associations, which is different from several previous meta-analysis studies. One meta-analysis focused on prediction errors (PRs) in patients with SZ and patients with major depressive disorder (Yaple, Tolomeo, & Yu, 2021). Another meta-analysis compared reward anticipation signals in individuals with schizophrenia using several paradigms, such as the monetary incentive delay (MID) task and instrumental reward learning task (Leroy *et al.*, 2020). Our recent meta-analysis focused on reward processing in individuals with schizophrenia during the anticipation and outcome stages using the MID task (Zeng *et al.*, 2022). To minimize the heterogeneity of functional imaging paradigms, we included only studies that employed the instrumental learning task, where subjects obtain A–O associations via their own selections with subsequent feedback (see Description of the reinforcement learning task in the [Supplementary Materials](#)). Specifically, in the instrumental learning paradigm, participants earn rewards via their correct actions first, and they repeat the same actions in subsequent

trials when the situation is similar. If there is a stimulus before the individual responds, this learning is called discriminated operant; if there is no stimulus, it is called free operant (Bouton *et al.*, 2021) (see [Supplementary Table S1](#)). From the literature reviewed above, we could expect that individuals with psychosis may show blunted activation within meso-cortico-limbic pathways during instrumental learning. Moreover, we expect that abnormal neural activations during instrumental learning would be closely related to the severity of symptoms and clinical variables.

Methods

See the Methods in the [Supplementary Materials](#).

Results

Brain activation differences between individuals with psychosis and HCs during instrumental learning

Included studies and sample characteristics

During the instrumental learning task, a total of 18 studies involving 456 individuals with psychosis and 454 HCs met the meta-analysis inclusion criteria ([Figure 1](#)). The mean age of individuals with psychosis (35.83 years) and HCs (34.93 years) was not significantly different ($t = 0.4645$, $p = 0.6453$). There was no significant difference ($\chi^2 = 32.0000$, $p = 0.232$) in the percentage of males between individuals with psychosis (69.57% male) and controls (63.77% male) ([Table 1](#)).

Included paradigms and behavioral indicators

As illustrated in [Supplementary Table S2](#), after checking all the studies, we found that the experimental paradigms used in the included studies can be summarized into the following three types: the probabilistic instrumental learning (PIL) task (in 12 studies), the probabilistic reversal learning (PRL) task (in 5 studies), and the probabilistic trial-and-error task (in 1 study).

Additionally, we have summarized some behavioral indicators related to instrumental learning deficits in psychosis in [Supplementary Table S2](#). Among them, 'correct choice' (available in 6 datasets) refers to the percentage of trials in which participants choose the commonly rewarded stimuli in the PIL and PRL paradigms. 'Total reward' (available in 3 datasets) indicates the total amount of money that participants earned through correct responses during the whole task. The 'learning rate' (available in 6 datasets) is an important parameter in RL models for evaluating participants' ability to learn from PE and to impact the updated expected value. In addition, 'win-stay' and 'lose-shift' (available in 5 datasets) are used in the PIL and PRL paradigms, respectively, and refer to the percentage of trials in which the participants selected the rewarded stimuli or avoided the unrewarded stimuli in the last trial. 'Reversals' (available in 4 datasets) are only used in the PRL task and refer to the number of reward contingency reversals during the whole task.

Summarizing the behavioral indicators we extracted, compared to HCs, we found that individuals with psychosis required more trials to learn the reward contingencies, achieved fewer reversals, showed less responsivity to positive feedback (win-stay and lose-shift probability), had fewer correct choices and total rewards, and showed attenuated learning rates. In brief, individuals with psychosis showed reduced task performance compared with HCs, which may reflect a cognitive decline when instrumental associations are built and value representations are created.

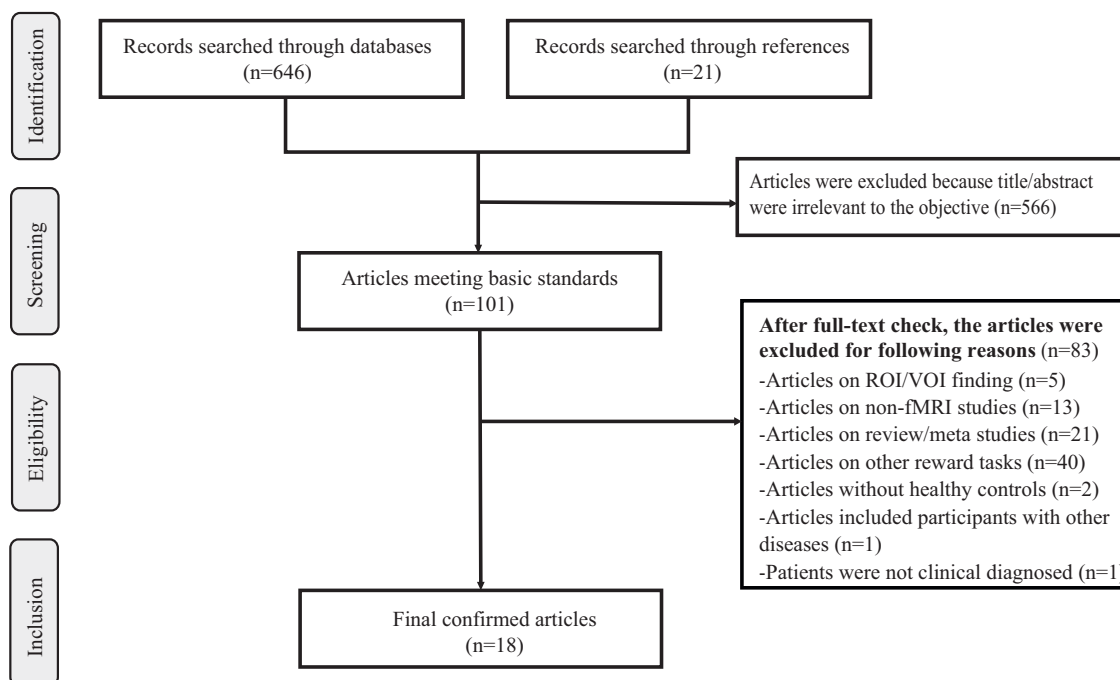


Figure 1. Flow diagram of the inclusion and exclusion process of selected articles. Of 667 articles initially identified, a total of 18 studies were enrolled in the meta-analysis. Notes: fMRI, 'functional magnetic imaging'; ROI, 'regions of interest'; VOI, 'volume of interest'.

Main meta-analysis

According to the instrumental learning meta-analysis, the psychosis group presented increased activity in the left middle occipital gyrus (MOG), insula, lingual gyrus (ING), and postcentral gyrus (PoCG) and decreased activity in the cortico-striato-thalamo-cortical (CSTC) circuit, including the right DS, insula, thalamus, middle and posterior cingulate cortices (MCC and PCC), dorsolateral frontal gyrus (DLPFC), OFC, left cerebellum, mPFC, and associated sensory areas (inferior and middle temporal gyrus and inferior [IFG] and superior parietal gyrus [SPG]) (Table 2 and Figure 2).

Sensitivity analysis

Whole-brain jackknife sensitivity analysis revealed that the results in the left MOG, left ING, right SPG, left cerebellum, right PCC, right IFG, right precentral gyrus, right middle frontal gyrus (MFG), right DLPFC, and right thalamus activity were highly replicable and preserved in all combinations of datasets. The increased activation in the left insula and PoCG remained significant in all but one and three combinations, respectively. The decreased activation in the right striatum, left mPFC, and right OFC remained significant in all but one study (Supplementary Table S2).

Subgroup analysis

The subgroup analyses for instrumental learning meta-analysis were repeated for studies that included individuals with chronic SZ only, those involving patients receiving medication, those using money stimulus, those including psychosis patients diagnosed by the DSM, those using a 3.0-T MR scanner, and those including only English-speaking individuals. The above results remained largely unchanged when the analyses were repeated, except for studies that included individuals with chronic SZ only, studies involving patients receiving medication, and studies that included individuals with SZ diagnosed by the DSM (Supplementary Table S2).

Meta-regression analysis

We explored information on the mean age, duration of illness, percentage of male patients, symptom severity, dose equivalent, medication, and task performance variables using meta-regression analysis. Notably, meta-regression analyses revealed that the percentage of first-generation antipsychotic (FGA) users was negatively associated with mPFC hypoactivation (Montreal Neurological Institute [MNI] coordinates: $x = 6$, $y = 24$, $z = 60$, $r = -0.473$, $p = 0.035$), and the percentage of medicated individuals was associated with insula hyperactivation (MNI coordinates: $x = -34$, $y = -8$, $z = 8$, $r = -0.480$, $p = 0.048$) (Figure 3).

Discussion

In the coordinate-based meta-analysis, we found a widely distributed reduced brain response during instrumental learning in the CSTC circuit, including the DS, insula, thalamus, MCC, PCC, cerebellum, mPFC, dorsolateral frontal gyrus (DLPFC), OFC, and associated sensory areas, and higher activity in the left MOG, insula, ING, and PoCG. Moreover, mPFC hypoactivation was negatively associated with the percentage of first-generation antipsychotic (FGA) users, and insula hyperactivation was negatively associated with the percentage of medicated patients. These findings in the psychosis group confirmed reward processing abnormalities when the subjects performed the instrumental learning task, providing further evidence of impaired action–outcome (A–O) learning in psychosis. Additionally, summarizing the behavioral indicators we extracted, compared to HCs, we found that the psychosis groups required more trials to learn the A–O contingencies and achieved fewer rewards in these tasks, which perhaps reflects a cognitive decline when building instrumental associations and creating value representations.

Table 1. Demographic and clinical characteristics of the studies included in the meta-analysis

Studies	Phase of illness	Psychosis								Healthy controls					Experiment paradigm
		No. (male)	Mean age	Medicated	Diagnosis criteria	Olanzapine Equivalents (mg)	Education (years)	IQ	Parental education	No. (male)	Mean age	Education (years)	IQ	Parental education	
Culbreth, Westbrook, et al. (2016b)	SZ or schizoaffective disorder	57 (38)	37.0	Y (T & A)	DSM-IV	NA	13.0	95.1 ^a	12.9	36 (19)	36.6	14.2	98.7 ^a	12.8	PRL
Culbreth, Gold, et al. (2016a)	Chronic SZ	29 (24)	39.6	Y (A)	DSM-IV	NA	13.4	101.3 ^a	14.2	21 (15)	39.6	15.1	109.7 ^a	14.2	PRL
Deserno et al. (2020)	Chronic SZ	46 (32)	35.0	Y	DSM-IV	12.68	NA	98.22 ^a	NA	43 (30)	35.07	NA	103.81 ^a	NA	PIL
Dowd et al. (2016)	SZ or schizoaffective disorder	38 (24)	35.00	Y (T & A)	DSM-IV	23.93	12.95	NA	14.00	37 (16)	36.43	14.14	NA	13.78	PIL
Ermakova et al. (2018)	FEP	14 (7)	23.57	N	ICD–10	0	NA	103.46 ^b	NA	39 (19)	23.23	NA	113.47 ^b	NA	PIL
Gradin et al. (2011)	Chronic SZ	14 (11)	42.50	NA	DSM-IV	NA	NA	111.60 ^c	NA	17 (7)	40.64	113.13	113.13 ^c	NA	PIL
Hernaus et al. (2018)	SZ or schizoaffective disorder	22 (16)	39.61	Y (T & A)	SCID-I	14.63	13.19	103.93 ^d	14.08	22 (13)	34.92	15.39	114.04 ^d	13.70	PIL
Katthagen et al. (2020)	Chronic SZ	19 (12)	33.2	N	ICD–10	0	NA	96.7 ^e	NA	23 (16)	32.2	105.2	105.2 ^e	NA	PRL
Koch et al. (2010)	Chronic SZ	19 (12)	35.2	Y	DSM-IV	24.54	10.58	>70 ^e	NA	20 (12)	35.2	12.70	>70 ^f	NA	Probabilistic trial-and-error learning task
Lee et al. (2019)	Chronic SZ	27 (16)	45.8	NA	DSM-V	NA	13.4	NA	14.0	25 (17)	47.2	14.5	NA	15.2	PIL
Murray et al. (2008)	FEP	13 (5)	26	Y (A)	DSM-IV	6.03	NA	113 ^c	NA	12 (9)	26	NA	116 ^c	NA	PIL
Reinen et al. (2016)	SZ, schizoaffective or schizophreniform disorder	16 (9)	34.3	NA	DSM-IV	NA	NA	NA	NA	23 (10)	33.7	NA	NA	NA	PIL
Schlagenhauf et al. (2014)	FEP or SZ	22 (20)	25.4	N	DSM-IV& ICD–10	0	NA	97.7 ^e	NA	24 (22)	27.2	NA	103.6 ^e	NA	PRL
Segarra et al. (2016)	Chronic SZ	21 (18)	32.24	Y (T & A)	DSM-IV	12.57	13.5	107.08 ^b	NA	21 (17)	34.33	14.85	114.24 ^b	NA	PIL
Vanes et al. (2018)	Chronic SZ	21 (18)	41.3	Y	ICD–10	9.34	NA	91.86 ^d	NA	24 (18)	38.4	NA	115.8 ^d	NA	PIL
Waltz et al. (2013)	Chronic SZ	29 (24)	39.6	Y (A)	SCID-I	NA	13.4	102.9 ^d	14.2	21 (15)	39.6	15.1	116.6 ^d	14.2	PRL
Waltz et al. (2018)	Chronic SZ	27 (17)	38.1	Y (T & A)	SCID-I	13.16	13.2	104.1 ^d	14.1	27 (18)	38.3	15.0	118.8 ^d	14.6	PIL
White, Kraguljac, Reid, and Lahti (2015)	SZ or schizoaffective disorder	22 (17)	39.41	Y (T & A)	NA	NA	NA	NA	NA	19 (11)	36.47	NA	NA	NA	PIL

Notes: ICD-10, international classification of diseases, 10th Edition; DSM-IV, diagnostic and statistical manual of mental disorders, 4th Edition; SZ, schizophrenia; FEP, first episode psychosis; HC, healthy control; T, Typical psychotic drugs; A, Atypical psychotic drugs; Olanzapine Equivalents are calculated according to the DDD(defined daily doses) method; PRL, Probabilistic Reversal learning task; PIL, Probabilistic instrumental learning task; Y, Yes; N, No; NA, not available. The IQ scores were respectively assessed using the ^aWechsler Test of Adult Reading(WTAR), ^bCulture Fair matrices test, ^cNational Adult Reading Test, ^dWechsler Abbreviated Scale of Intelligence-II(WASI), ^eWortschatztest(WST), ^fverbal IQ test.

Table 2. Results of the meta-analyses for brain activation difference between individuals with psychosis and HCs during instrumental learning

Brain regions	MNI	SDM value	p value	Number of voxels	Breakdown
	coordinates				
SZ > HC					
Left MOG	−46,−74,4	1.4	0.000030994	661	Left middle occipital gyrus, BA 19, BA 37, BA 39, BA 18 Left middle temporal gyrus, BA 37, BA 39, BA 19 Left inferior occipital gyrus, BA 19, BA 37
Left insula	−48,−20,0	1.075	0.000314832	715	Left insula, BA 48 Left superior temporal gyrus, BA 48, BA 22 Left rolandic operculum, BA 48 Left heschl gyrus, BA 48 Left middle temporal gyrus, BA 22,BA 48
Left ING	−26,−94,−16	1.011	0.00043869	112	Left lingual gyrus, BA 18 Left inferior occipital gyrus, BA 18
Left PoCG	−38,−36,64	1.173	0.000149667	103	Left postcentral gyrus, BA 3, BA 4, BA 2
SZ < HC					
Right SPG	36,−68,46	−2.961	~0	2114	Right superior parietal gyrus, BA 7, BA 40, BA 5 Right middle temporal gyrus, BA 21, BA 22, BA 20, BA 37 Right angular gyrus, BA 39, BA 7, BA 40, BA 22, BA 48, BA 19 Right inferior parietal (excluding supramarginal and angular) gyri, BA 40, BA 39, BA 7 Right superior occipital gyrus, BA 7 Right precuneus, BA 7, BA 5 Right supramarginal gyrus, BA 48, BA 40, BA 42, BA 22 Right superior temporal gyrus, BA 21, BA 22, BA 42, BA 48 Right inferior temporal gyrus, BA 20 Right middle occipital gyrus, BA 19
Left cerebellum	−26,−76,−30	−2.465	0.000046432	1459	Left cerebellum, crus II, crus I Left cerebellum, hemispheric lobule VIIIB, VIII, VI Left cerebellum, crus I, BA 19, BA 18 Left cerebellum, hemispheric lobule VI, BA 19, BA 18
Right striatum	30,−8,6	−2.6	0.000015497	805	Right lenticular nucleus, putamen, BA 48 Right striatum Right insula, BA 48 Right Rolandic operculum, BA 48
Right PCC & MCC	6,−42,24	−2.471	0.000046432	825	Right median cingulate/paracingulate gyri, BA 23 Left posterior cingulate gyrus, BA 23, BA 30, BA 26 Right posterior cingulate gyrus, BA 23, BA 26 Left median cingulate/paracingulate gyri Right precuneus, BA 23, BA 30, BA 26
Right IFG & insula	54,20,8	−2.47	0.000046432	568	Right inferior frontal gyrus, opercular part, BA 48, BA 44, BA 45, BA 6, BA 38, BA 47 Right inferior frontal gyrus, triangular part, BA 45, BA 48, BA 47, BA 38 Right rolandic operculum, BA 48, BA 6 Right insula, BA 48, BA 47, BA 45 Right temporal pole, superior temporal gyrus, BA 48
Right IFG	44,4,32	−2.314	0.000180602	254	Right inferior frontal gyrus, opercular part, BA 44, BA 6 Right precentral gyrus, BA 44, BA 6 Right middle frontal gyrus, BA 44, BA 6, BA 9 Right superior longitudinal fasciculus II, III
Right MFG	46,36,34	−2.063	0.000887632	74	Right middle frontal gyrus, BA 46, 45
Left mPFC	−4,22,60	−1.959	0.001491487	67	Left superior frontal gyrus, medial, BA 8 Right superior frontal gyrus, medial, BA 8 Left supplementary motor area, BA 8 Right supplementary motor area, BA 8
Right ITG	58,−60,−12	−2.036	0.001006365	62	Right inferior temporal gyrus, BA 37
Right dIPFC	22,24,54	−2.012	0.001130223	41	Right superior frontal gyrus, dorsolateral, BA 8
Right OFC	46,48,−6	−1.839	0.00281781	35	Right inferior frontal gyrus, orbital part, BA 46, BA 47 Right middle frontal gyrus, orbital part, BA 46, BA 47
Right thalamus	16,−20,12	−2.065	0.000887632	27	Right thalamus Right anterior thalamic projections

Notes: Results were threshold at $p = 0.005$, peak height threshold of 1, extent threshold of 10. BA, Brodmann area; MOG, middle occipital gyrus; ING, lingual gyrus; PoCG, postcentral gyrus; SPG, superior parietal gyrus; PCC, posterior cingulate cortex; MCC, middle cingulate cortex; IFG, inferior frontal gyrus; MFG, middle frontal gyrus; mPFC, medial prefrontal cortex; ITG, inferior temporal gyrus; dIPFC, dorsolateral prefrontal cortex; OFC, orbital prefrontal cortex; SDM, signed differential mapping; MNI, Montreal Neurological Institute.

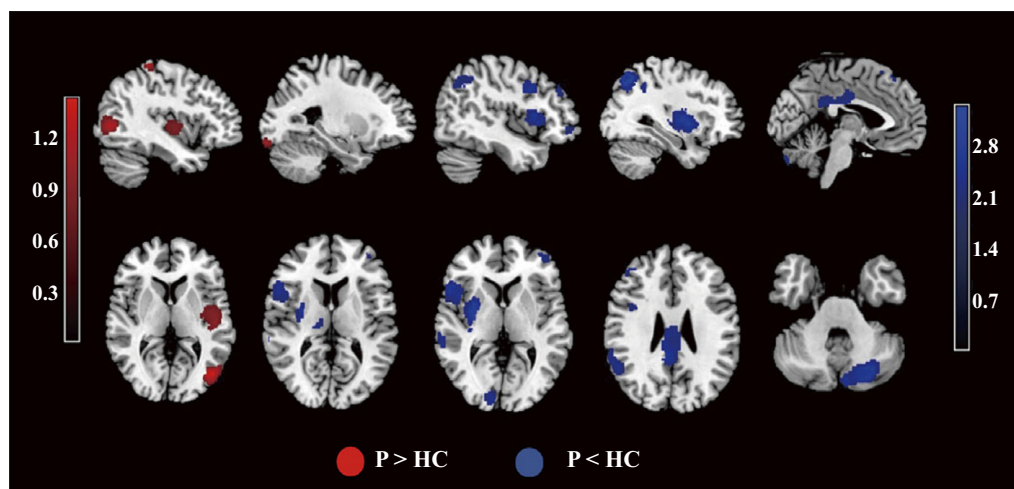


Figure 2. Instrumental learning-evoked activation differences between individuals with psychosis and HCs in the meta-analysis. Brain regions that showed significant differences in instrumental learning-related activation in individuals with psychosis relative to HCs. Red and blue indicate hyperactivity and hypoactivity, respectively, in individuals with psychosis compared to HCs, and the color scale represents probability values from statistical randomization testing (z values). For the instrumental learning, the psychosis group showed hyperactivation in the middle occipital gyrus (MOG), insula, lingual gyrus, postcentral gyrus, and hypoactivation in the CSTC circuit, including the dorsal striatum (DS), insula, thalamus, middle and posterior cingulate cortex (MCC/PCC), dorsolateral prefrontal cortex (DLPFC), orbital prefrontal cortex (OFC), cerebellum, medial prefrontal cortex (mPFC), and association sensory area (inferior and middle temporal gyrus, inferior and superior parietal gyrus). Notes: P, 'individuals with psychosis'; HC, 'healthy control'.

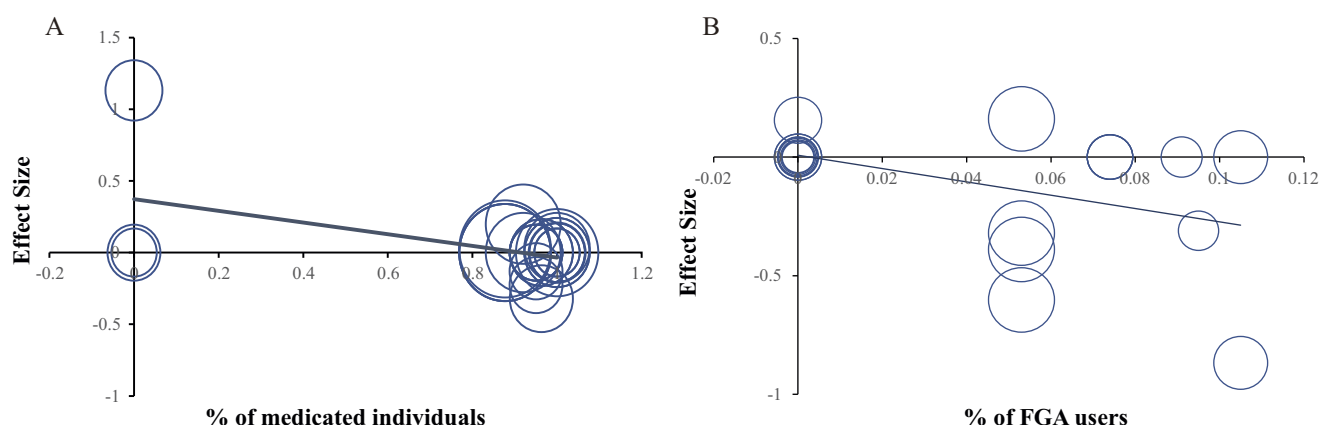


Figure 3. (A–B). Meta-regression analyses between clinical symptoms and brain activity during instrumental learning. (a) Scatter plot showing a significantly negative association between instrumental learning-evoked activity in the mPFC (MNI coordinates: $x = 6$, $y = 24$, $z = 60$, $r = -0.473$, $p = 0.035$) and the % (percentage) of medicated individuals (the proportion of individuals with psychosis who had ever received medicated treatment). (b) Scatter plot showing a significantly negative association between instrumental learning-evoked activity in the insula (MNI coordinates: $x = -34$, $y = -8$, $z = 8$, $r = -0.480$, $p = 0.048$) and the % (percentage) of FGA users (the proportion of individuals with psychosis who had ever received FGA). Notes: mPFC, 'medial prefrontal cortex'; MNI, 'Montreal Neurological Institute'.

Our findings were consistent with the positive valence system within the Research Domain Criteria (RDoC) project, which is a framework for research on mental disorders that focuses on dimensions of behavioral and psychological functioning and their implementation of neural circuits (Cuthbert & Insel, 2013; Insel *et al.*, 2010). In the RDoC, functions associated with processing reward-related information are fundamental drivers of motivation, learning, and goal-directed behavior and have been classified as positive valence systems under the RDoC (Dexter *et al.*, 2025). As is central to the RDoC framework, identifying the distinct mechanisms underlying instrumental learning task performance may provide a better understanding of the antecedents and processes that lead to different forms of psychopathology (Michelini *et al.*, 2021). In addition, in a system that proposes a hierarchical dimension classification of mental health, called Hierarchical Taxonomy of Psychopathology (HiTOP), reward learning is also associated with the distress and substance abuse subfactor and the thought disorder

spectrum, which has been proven by a series of behavioral and neuroimaging experiments; thus, identifying the aberrant brain mechanisms of instrumental learning is also highly important for further understanding potential biobehavioral systems underlying psychopathology and ultimately informing future classifications (Kotov *et al.*, 2021; Michelini *et al.*, 2021; Ruggero *et al.*, 2019).

In instrumental learning, reward and punishment exist as opposite behavioral outcomes, enabling animals to build associations between stimuli, action, and outcomes, providing information for future decisions, and adapting to the changing environment (Bouton *et al.*, 2021; Dexter *et al.*, 2025; Taylor, Pearlstein, & Stein, 2020). It is a biological instinct to seek benefits and avoid harm, so the action will be reinforced if it results in reward and suppressed if it results in punishment. However, a decline in the reward learning ability of individuals with schizophrenia has been confirmed in many previous studies and is correlated with reduced working memory, impaired executive function, and increased negative

symptoms (Nestor et al., 2014; Woodberry, Giuliano, & Seidman, 2008). The disruption in reward learning makes it difficult for participants with psychosis to develop goal-directed behavior toward a specific outcome, ultimately leading to amotivation in clinical practice, which is also considered a core symptom of psychosis (Waltz et al., 2009). Taken together, these results suggest that impaired motivational processes, induced by reward learning deficits, may represent a common denominator uniting the neuropsychological and clinical manifestations of psychosis. Summarizing our findings from the perspective of reward processing, we also propose a network neurobiological model, including the prefrontal cortex and striatal dopamine circuit. Within the prefrontal cortex circuit, when an action is planned in a given context, the medial prefrontal cortex first signals an outcome prediction, and then, after the action is executed, the prediction is updated by comparing it to the actual outcome to produce a discrepancy (PE) (Krawitz, Braver, Barch, & Brown, 2011). Indeed, current evidence suggests a role of the thalamus in schizophrenia. For example, thalamo-cortical connections would be reflected in poor cognitive focus, e.g., impaired attention (Liu et al., 2023; Paul et al., 2024). In the striatal reward system, the striatal dopaminergic activity signal receives unexpected rewards, and reciprocal feedback loops with frontal regions such as the DLPFC and OFC facilitate the formation of value representations (Robinson et al., 2012; Robinson, Frank, Sahakian, & Cools, 2010). Understanding the brain mechanisms of deficits in reward learning may provide insight into important motivational deficits that may be a future target for the treatment of SZ-spectrum disorders.

Compared with HCs, individuals with psychosis presented hyperactivity in the visual centers and somatosensory areas, including the MOG, ING, and PoCG. Consistent with our results, Tu and colleagues reported elevated functional connectivity in the post-central, precentral, and lateral occipital gyri (Tu et al., 2019). In fact, abnormally increased activation related to A–O associations in sensory areas would imply a heightened salience of irrelevant stimuli and impair goal-directed behavior through associations with reinforcing events (Zeng et al., 2022). The hyperactivation in the left insula was also reported in our meta-analysis. As an important part of the salience network (SN), the insula is widely involved in marking salient stimuli for additional processing and increasing the incentive salience of irrelevant or inappropriate stimuli (Manoliu et al., 2014; Palaniyappan & Liddle, 2012; Singer, Critchley, & Preusschoff, 2009), which, in turn, leads to delusions and hallucinations (Kapur, 2003). Our findings suggest that overactivation of salience processing in psychosis may cause inappropriate associations or delusions.

We detected hypoactivation in the PFC, including the mPFC, DLPFC, and OFC, in the psychosis groups, revealing a central role of the PFC in A–O learning and motivated behavior in dynamic environments. Furthermore, the PFC has been divided into multiple subregions that play complementary roles in reward-based A–O learning (Brown & Bowman, 2002; Buckley et al., 2009; Gläscher et al., 2012; Luk & Wallis, 2013). Specifically, the OFC has been implicated in encoding outcome/state representations (Fellows, 2011; Morrison & Salzman, 2009) and changes quickly after changes in reward contingencies (Fiuzat, Rhodes, & Murray, 2017), which contributes to the brain's representation of a 'cognitive map' (Whyte et al., 2019). A cognitive map is analogous to a spatial map in that it organizes knowledge about the relationships between an action and a possible outcome in a particular state (Behrens et al., 2018; Niv, 2019; Wilson, Takahashi, Schoenbaum, & Niv, 2014), which plays an important role in guiding individual

selection. Experiments across rodent and primate species also suggest that OFC lesions cause damage in adapting their choices based on updated valuations (Bradfield et al., 2015; Rhodes & Murray, 2013). The mPFC is generally considered to be involved in processing and monitoring behaviors by predicting the outcomes of actions (Matsumoto, Matsumoto, Abe, & Tanaka, 2007; Rudebeck et al., 2008); afterward, it detects discrepancies between actual and predicted outcomes to generate PE and update the outcome anticipation appropriately (Alexander & Brown, 2014, 2011). Consistent with our findings, a series of studies revealed reduced activation in the mPFC in individuals with psychosis when processing PE (Jessup, Busemeyer, & Brown, 2010; Krawitz et al., 2011). Finally, the DLPFC is directly involved in the use of value information to guide action selection and the production of the 'sense of agency' (SoA) (Khalighinejad, Di Costa, & Haggard, 2016), which refers to the experience of being in control of one's own actions and their consequences (Moore & Fletcher, 2012). In addition, SoA has also been related to many neurological and psychiatric disorders, especially the positive symptoms (delusions and hallucinations) of psychosis, which means misattributing one's own thoughts, feelings, and actions to external factors (Moore & Fletcher, 2012; Penton et al., 2018). The observed dysfunction may suggest the impairment of value representation and A–O learning in individuals with psychosis.

We also found reduced neural activation in the striatal reward system, including the DS, insula, and thalamus, which are associated with reward processing during instrumental learning, in the psychosis groups. The striatum is a key structure of the basal ganglia that projects to frontal regions through dopamine neurotransmitters, collectively participating in A–O learning and reward processing (Delgado, Miller, Inati, & Phelps, 2005; Haber, 2003). Previous studies on reward processing have focused mainly on the VS, with more reward-related neurons found here, and the role of the DS in reward learning has gradually been confirmed in recent years (Ravel, Legallet, & Apicella, 2003; Takikawa, Kawagoe, & Hikosaka, 2002; Watanabe, Lauwereyns, & Hikosaka, 2003). Many neuroimaging studies have supported the impact of the DS on the processing of all types of rewards and punishments, such as money, liquids, and odors (O'Doherty et al., 2004; O'Doherty et al., 2003). The DS, which connects with frontal and sensory cortices, is critical for acquiring and executing motivated behavior, which shifts to selection or action strategies if the state value changes (Burton, Nakamura, & Roesch, 2015; Foerde, 2018; Kesby, Eyles, McGrath, & Scott, 2018); the VS, which projects to the PFC and ACC regions, is required for creating value representations that form associations between the predictive outcome and action (Patterson & Knowlton, 2018; Porrino et al., 2004). The reward circuit provides necessary value information for the formation of A–O associations and voluntary actions, and impairment of the reward circuit leads to poor performance in instrumental learning behaviors in individuals with psychosis, which has been confirmed in many neuroimaging and meta-analysis studies (Katthagen et al., 2020; Vanes et al., 2018; Yang et al., 2024; Zeng et al., 2022). For example, our previous meta-analyses revealed hypoactivity in the reward circuit in individuals with SZ during the reward anticipation and PE processing phases (Yang et al., 2024; Zeng et al., 2022). Furthermore, there is a correlation between abnormal activation related to reward processing in the striatum and the severity of negative symptoms in individuals with unmedicated SZ (Katthagen et al., 2020). In summary, our results revealed that reward processing dysfunction is an important factor for aberrant A–O learning in psychosis individuals.

Attenuated activation in the MCC, PCC, and cerebellum was also found in individuals with psychosis during the instrumental learning task. Owing to the connectivity of the cingulate cortex, they participate as a whole in A–O learning (Rolls, 2019). The outcome inputs from the OFC to the ACC and the action information from the parietal cortex to the PCC are brought together to the MCC, after which A–O associations are integrated to guide behavior for the desired goal (Bush, 2011; Rolls & Wirth, 2018; Vogt, 2016). Additionally, recent anatomical work has revealed bidirectional connections between the cerebellum and the basal ganglia, which possibly indicates a critical role of the cerebellum in reinforcement learning (Bostan & Strick, 2010). It has been proposed that the cerebellum could contribute to anticipating action outcomes by predicting and transmitting the action state to the basal ganglia (Miall & Galea, 2016). This evidence supports the involvement of the MCC, PCC, and cerebellum in A–O learning during instrumental learning tasks.

Correlations between instrumental learning-related responses and medication status

Our meta-analysis revealed that hypoactivity in the mPFC during instrumental learning was negatively associated with the percentage of FGA users. Dysfunction in the mPFC may result in hallucinations and delusions (Schlagenhauf *et al.*, 2008). For example, previous studies revealed that hyperconnectivity between the mPFC and default mode network was correlated with more severe positive symptoms in individuals with psychosis (Whitfield-Gabrieli *et al.*, 2009). Brent and colleagues reported that delusional thinking was negatively correlated with connectivity between the lateral temporal cortex and ventral mPFC, which was possibly mediated by social cognition dysfunction (Brent *et al.*, 2014). Notably, as potent antagonists of D2-class dopamine receptors (Del'guidice & Beaulieu, 2008), FGAs are effective for positive symptoms (hallucinations and delusions) (Garver, 2006). Consistent with this, a systematic review revealed the superiority of FGA over second-generation antipsychotics (SGAs) in terms of the pharmacological treatment of delusional disorders (Muñoz-Negro & Cervilla, 2016). In conclusion, these results may suggest that FGA plays a key role in the treatment of positive symptoms and that the relevant physiological function is related to the mPFC.

We also found that insula hyperactivation was negatively associated with the percentage of medicated individuals with psychosis. In line with this finding, previous studies have reported that left insula activation is negatively correlated with cumulative antipsychotic medication (Walter *et al.*, 2016), and anatomical evidence has also indicated an association between antipsychotic exposure and reduced insula volume in individuals with psychosis (Palaniyappan & Liddle, 2012). According to the aberrant incentive salience hypothesis, dysfunction in the insula would cause inappropriate assignment of motivational salience and novelty and contribute to delusion and hallucination symptoms (Kapur, 2004; White, Joseph, Francis, & Liddle, 2010). A meta-analysis of data from 7450 individuals with SZ who were treated with common, typical, and atypical antipsychotics revealed improvements in core psychotic symptoms such as hallucinatory behavior (Bertolino *et al.*, 2004; Mendrek *et al.*, 2004). Our meta-regression results suggest that antipsychotic drugs have a positive influence on the abnormal salience attribution and positive symptoms of psychosis. Notably, although the regression analysis results during instrumental learning are statistically

significant, they remain preliminary and require confirmation through longitudinal studies.

Clinical implications

From the RDoC perspective, the biological markers of instrumental learning may help elucidate the complex and multifaceted symptoms as well as the neurobehavioral disruptions observed in individuals with psychosis. Instrumental learning behavior depends on multiple component processes, including reward processing, the integration of action–outcome, and the signaling of mismatches between expected and obtained outcomes, called PE (Waltz *et al.*, 2018; Yang *et al.*, 2024). Dysfunction in reward processing is regarded in DSM-5 as a key factor in the anhedonic symptoms of schizophrenia (Francesmonneris, Pincus, & First, 2013). This relationship is consistent with the findings of several instrumental learning studies in psychosis, which have shown that increased negative symptoms, particularly anhedonia and avolition, are associated with reduced striatal responses to reward-predicting cues (Dowd & Barch, 2012; Juckel *et al.*, 2006b; Simon *et al.*, 2010). In other words, the structure of anhedonia is closely related to the process of reward evaluation, prediction, and motivation. In addition, within the RDoC framework, which aims to identify pathophysiological mechanisms that are common across multiple psychiatric disorders as well as those that are unique to specific psychiatric symptoms, reward processing abnormalities in the dopaminergic system could account for neurobiological dysfunctions observed in psychotic disorders (Cuthbert, 2022; Insel *et al.*, 2010). In our meta-analysis, we found that reward learning deficits in patients with psychosis were associated with reduced activation in the CSTC circuitry. As psychosis is linked to changes in reward processing, probing neural processes of the reward system may improve the present understanding of the different profiles of motivational deficits and related neurobiological abnormalities associated with psychosis. Therefore, identifying specific profiles of abnormal reward processing during instrumental learning may be useful for identifying the brain–behavior dimensions of psychopathology and for supporting broader definitions of psychiatric symptoms.

Furthermore, our findings of abnormal neural representations of instrumental learning can help to better understand the effects of antipsychotic drugs in psychosis. Our study suggested that dysfunction of the mPFC and insula was associated with the medication state in psychosis, which may explain the antipsychotic medication effect on reinforcement learning. In patients responding to a treatment-induced blockade of dopamine D2 receptors, psychotic symptoms may be ameliorated by normalizing salience abnormalities in the reward system. In line with this, longitudinal studies have shown an improvement in attenuated striatal signaling in patients with antipsychotic-naïve SZ when they receive monotherapy with a selective dopamine D2/3 antagonist (Nielsen *et al.*, 2012). One recent study revealed that reward processing in the caudate was normalized only after 6 weeks of aripiprazole monotherapy in individuals with FEP (Tangmose *et al.*, 2023). Findings have also shown that patients with SZ treated with SGA drugs exhibit normalization of reward-related nucleus accumbens activation (Juckel, Schlagenhauf, Koslowski, Wüstenberg, *et al.*, 2006b). These findings suggest that antipsychotic drugs may have a positive influence on abnormal salience attribution, which will help clarify the mechanisms of instrumental learning in psychosis, thereby guiding the development of effective interventions.

Limitations and future directions

Some limitations of this study need to be highlighted. First, publication bias was almost inevitable despite our comprehensive literature search (Cheung & Vijayakumar, 2016), and our meta-analyses, which were based on peak and effect sizes, were based on coordinates from published studies rather than raw statistical brain maps. Second, the correlation between brain activity and behavioral performance could not be determined due to insufficient data, and exploring the relationship between the brain and behavior will be our future research direction. Similarly, different subcategorical diagnoses in groups may affect between-subject variability, potentially affecting our findings. We also cannot rule out the potential influence of illness severity and stage on our results. Third, we did not distinguish studies based on the types of stimuli used, which is likely to affect our results. For example, some studies give only rewards to participants when they respond correctly, while others also punish participants when they make mistakes; the rewards they use include money, liquids, and scores. Fourth, the complicated effects of treatment, such as drug types, clinical response, and side effect profiles, cannot be ignored in our meta-analysis, and future longitudinal studies need to investigate the effects of medication and illness stage on neurological dysfunction in reward learning. Fifth, our study included only adult participants, so care should be taken when applying our research results to the child/adolescent population. Finally, diverse imaging acquisition techniques (e.g., different MRI field strengths, MRI scanners, and imaging parameters) may lead to methodological heterogeneity and potentially limit our ability to detect robust group differences.

In this study, we used a voxel-wise meta-analysis to investigate the neural responses during instrumental learning in participants with psychosis. Within the RDoC system, identifying the pathophysiological mechanisms that are unique to specific psychiatric symptoms, such as reward processing abnormalities in the dopaminergic system, could account for neurobiological dysfunctions observed in psychotic disorders. Our findings of functional alterations in psychosis may serve as state markers of psychosis that reflect the pathophysiological processes of the illness. Notably, although the meta-regression analysis results of brain activation and medicated states are statistically significant, they are only preliminary, and further large-scale longitudinal studies are needed in the future to understand the effects of and changes in antipsychotic drugs on brain activity. Moreover, the direct correlation between behavioral responses and brain activation in participants with SZ needs further exploration, especially with respect to the relationships between different behavioral stages and brain activity, to better investigate the relationships among the efficacy of drugs, patients' behavior, and brain activity. Additionally, it would be interesting to explore the relevant concepts of reward learning and its neural representations, including the learning rate, reward sensitivity, and PE, in the future using theories and models of reinforcement learning, such as model-free versus model-based decision-making.

Conclusion

The present study examined the neural mechanisms during A–O learning in individuals with psychosis and their relevance to clinical symptomology. Our meta-analysis revealed hyperactivity in sensory areas and hypoactivity in the CSCT circuit in patients with psychosis during instrumental learning tasks. Additionally,

instrumental learning-evoked mPFC hypoactivation was linked to the percentage of FGA users, and insula hyperactivation was linked to the percentage of medicated individuals. Our findings provide evidence for dysfunctions in value representation and A–O association integration in psychosis and have the potential to clarify the complex brain–behavior relationships in psychosis.

Supplementary material. The supplementary material for this article can be found at <http://doi.org/10.1017/S0033291725101323>.

Data availability statement. The data supporting the findings in this study might be requested via the corresponding author of this article upon reasonable request.

Author contribution. J. Zeng and X. Yang contributed to the study conception and design and supervised the study. Y. Song, B. Cheng contributed significantly to the analysis and manuscript preparation. Y. Song and H. Cao perform the analysis with constructive discussions. X. Yang, Y. Song, and J. Zeng wrote the manuscript, which was reviewed by all authors and approved for publication.

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