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Review article

Rostral medial prefrontal dysfunctions and consummatory pleasure in schizophrenia: A meta-analysis of functional imaging studies

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ABSTRACT

A large number of imaging studies have examined the neural correlates of consummatory pleasure and anticipatory pleasure in schizophrenia, but the brain regions where schizophrenia patients consistently demonstrate dysfunctions remain unclear. We performed a series of meta-analyses on imaging studies to delineate the regions associated with consummatory and anticipatory pleasure dysfunctions in schizophrenia. Nineteen functional magnetic resonance imaging or positron emission tomography studies using whole brain analysis were identified through a literature search (PubMed and EBSCO; January 1990–February 2014). Activation likelihood estimation was performed using the GingerALE software. The clusters identified were obtained after controlling for the false discovery rate at $p < 0.05$ and applying a minimum cluster size of 200 mm^3. It was found that schizophrenia patients exhibited decreased activation mainly in the rostral medial prefrontal cortex (rmPFC), the right parahippocampus/amygala, and other limbic regions (e.g., the subgenual anterior cingulate cortex, the putamen, and the medial globus pallidus) when consummating pleasure. Task instructions (feeling vs. stimuli) were differentially related to medial prefrontal dysfunction in schizophrenia. When patients anticipated pleasure, reduced activation in the left putamen was observed, despite the limited number of studies. Our findings suggest that the medial prefrontal cortex and limbic regions may play an important role in neural dysfunction underlying deficits in consummatory pleasure in schizophrenia.

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1. Introduction

Anhedonia, defined as the inability to experience pleasure, is a core feature of negative symptoms in schizophrenia (Andreason, 1983; Pelizza and Ferrari, 2009). Functional imaging studies have provided researchers the opportunity to examine the neural correlates associated with hedonic experience in schizophrenia (Knutson and Greer, 2008; Kringelbach and Berridge, 2009). Pleasure experience is widely accepted as a construct involving two distinct components, anticipatory pleasure (defined as the emotional state in anticipation of future pleasurable events) and consummatory pleasure (defined as the emotional state while experiencing pleasurable events) (Gard et al., 2006; Knutson and Greer, 2008; Kringelbach and Berridge, 2009). Different brain regions have been proposed to be responsible for these two components (Knutson and Greer, 2008; Kringelbach and Berridge, 2009). Specifically, the ventral striatum (VS) and the ventral tegmental area (VTA) are thought to be primarily responsible for anticipatory (Berridge and Robinson, 1998; de Haan et al., 2004; Knutson and Greer, 2008), while the medial prefrontal cortex (mPFC) and the amygdala are thought to be associated with consummatory pleasure (Knutson et al., 2003; Knutson and Greer, 2008).

For consummatory pleasure, the findings in previous imaging studies provided a mixed picture of mPFC and amygdala activation in schizophrenia patients (Crespo-Facorro et al., 2001; Paradiso et al., 2003; Schlagenhauf et al., 2009; Waltz et al., 2009; Dowd and Barch, 2010; Ursu et al., 2011). For example, some studies reported that patients with schizophrenia exhibited reduced activation in the mPFC in response to the delivery of juice (Waltz et al., 2009), pleasurable odour (Crespo-Facorro et al., 2001) and positive pictures (Paradiso et al., 2003). However, Dowd and Barch (2010) did not find this impairment in schizophrenia patients who viewed positively valenced pictures, faces and words. Likewise, several imaging studies reported that patients with schizophrenia exhibited attenuated activation in bilateral amygdala when they were presented with pictures of happy faces and pleasurable odours (Gur et al., 2002; Schneider et al., 2007; Gradin et al., 2011). However, two other studies found enhanced activation in bilateral amygdala in patients with schizophrenia during the processing of positive affective pictures (Paradiso et al., 2003; Reske et al., 2007).

For anticipatory pleasure, more and more studies in recent years have examined striatal activation associated with the expectation of positive events in patients with schizophrenia. Previous imaging studies in clinical samples suggest that when compared with healthy controls, patients with schizophrenia showed decreased ventral striatal activation in anticipation of reward (Juckel et al., 2006a, 2006b; Schlagenhauf et al., 2008, 2009). Another imaging study reported reduced activation in the dorsal striatum (i.e., the putamen) when schizophrenia patients were presented with unexpected juice deliveries (Waltz et al., 2009). However, these findings have not always been consistent. Some studies only reported reduced activation in the unilateral ventral striatum (left or right) (Juckel et al., 2006a, 2006b; Schlagenhauf et al., 2008) in schizophrenia patients relative to healthy controls. Another study has suggested reduced activation in bilateral ventral striatum in schizophrenia (Schlagenhauf et al., 2009). One study found enhanced activation in this region (Gradin et al., 2011) during expectation of rewarding stimuli. However, other studies did not find any difference in ventral striatal activation between schizophrenia patients and healthy controls (Walter et al., 2009; Simon et al., 2010; Waltz et al., 2010).

To the best of our knowledge, although there have been several recent narrative reviews on the neural mechanism of hedonic experience in patients with schizophrenia (Andreasen et al., 1997; Abler et al., 2008; Craig, 2009; Barch and Dowd, 2010; Kring and Caponigro, 2010), few meta-analyses have been carried out to quantitatively examine the neural correlates associated with hedonic experience. For example, the question of whether there exist brain regions consistently reflecting impairment in response to positive stimuli in schizophrenia is unresolved. Furthermore, we know little about the exact neural basis of anticipatory and consummatory pleasure dysfunction in schizophrenia (Kring and Barch, 2014). One recent meta-analysis demonstrated that patients with schizophrenia showed reduced activation in response to emotional experience in the left occipital pole compared with healthy controls (Taylor et al., 2012). However, the authors mainly focused their attention on negative emotions rather than positive emotions, and hedonic experience, which may be elicited by reward stimuli (Knutson and Greer, 2008; Kringelbach and Berridge, 2009), was not investigated. Therefore, in the present study, we aimed to perform an objective, systematic and quantitative analysis of the imaging literature using activation likelihood estimation (ALE) to investigate the neural correlates of anticipatory and consummatory pleasure in schizophrenia.

Meanwhile, since different tasks and stimuli were used and different types of patients (e.g., with regard to medication status and severity of negative symptoms) were recruited in different studies, we have further examined whether these confounding factors affected the ALE findings.

2. Methods

2.1. Selection of articles

PubMed and EBSCO (PsycARTICLES, PsycINFO, PsycEXTRA, PsycCRITIQUES) online database searches were conducted between January 1990 and February 2014. Search terms included “emotion,” “emotional experience,” “affective experience,” “pleasure,” “anhedonia”, “positive emotion”, “positive affect”, “reward”, and

"happiness", with different combinations of "schizophren*" and "brain mapping", "fMRI" or "PET". Six hundred and seven articles were identified through the literature search. Eleven articles were added based on our previous meta-analysis (Yan et al., 2012). Thus, a total of 618 articles were identified.

Articles were excluded according to the following criteria (see Fig. 1):

(1) Articles that appeared more than once (270 articles excluded).
(2) Articles that were not experimental reports or not published in peer-reviewed journals (143 articles excluded).
(3) Articles not written in English (five articles excluded).
(4) Paradigms that did not capture emotional experience using fMRI (functional magnetic resonance imaging) or PET (positron emission tomography) (108 articles excluded).
(5) Articles not reporting the coordinates of neural activation associated with hedonic experience (i.e., positive condition–neutral condition) (26 articles excluded).
(6) Articles that did not focus on schizophrenia patients (22 articles excluded).
(7) The data of the articles were either not available or not applicable (i.e., studies reporting results using correlation analysis (Harvey et al., 2010) or functional connectivity analysis (Anticevic et al., 2012a) (16 articles excluded).
(8) Articles that did not report whole brain results (nine articles excluded).

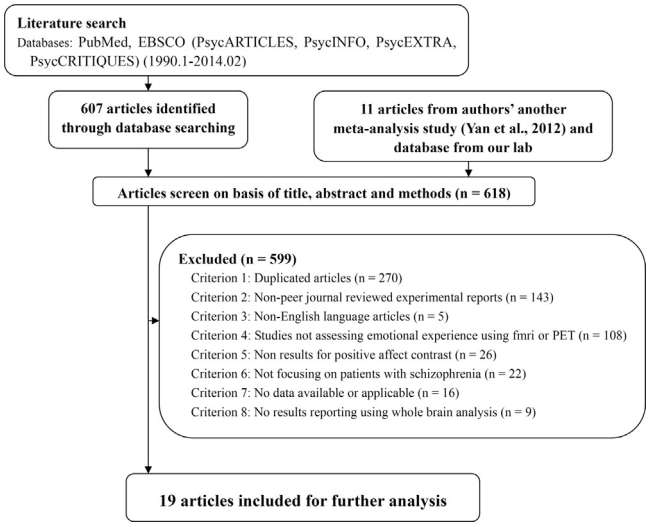

Fig. 1. The flow chart for the meta-analysis.

2.2. Studies included into the ALE meta-analysis

A total of 19 studies were included in the ALE meta-analysis with a total of 316 patients with schizophrenia (214 males) and 299 healthy controls (186 males) (see details in Table 1). There were 107 foci from 14 studies (anticipatory pleasure:11 foci from four studies; consummatory pleasure: 96 foci from 10 studies) that were included in the meta-analysis statistically comparing regions where schizophrenia patients had significantly decreased brain activation relative to healthy controls (healthy controls (HC) > schizophrenia (Sz)), and 19 foci from four studies (anticipatory pleasure: 0 study; consummatory pleasure: 19 foci from four studies) were included to examine the reverse contrast (Sz > HC). Eight studies reported activation with a total of 55 foci (anticipatory pleasure: five foci from three studies; consummatory pleasure: 50 foci from six studies) for schizophrenia patients alone while 10 studies reported activation with a total of 122 foci (anticipatory pleasure: 56 foci from six studies; consummatory pleasure: 66 foci from seven studies) for healthy controls alone. We performed ALE analysis for anticipatory and consummatory pleasure contrasts, respectively.

Since the analyses were conducted in Talairach space, activation coordinates which were originally reported in Montreal Neurological Institute (MNI) coordinates were converted using Lancaster's transform before the ALE analysis. For articles using Brett's formulation to convert from MNI to Talairach, the data was first converted back to MNI coordinates using Brett's transform, and then transformed into Talairach space using Lancaster's transform.

2.3. Activation likelihood estimation

A random-effects meta-analysis was carried out using the up-to-date version of the GingerALE software (GingerALE 2.3.1) (Turkeltaub et al., 2002; Laird et al., 2005; Eickhoff et al., 2009). The idea behind the ALE analysis is that the peak coordinates reported in studies should be viewed as probability distributions around themselves (Turkeltaub et al., 2002). In practical terms, an ALE map was constructed based on foci from studies included, and then convolved with a 3D Gaussian kernel. We chose to use the ALE algorithm described by Eickhoff et al. (2009). In this algorithm, full-width at half-maximum (FWHM) was automatically provided to compute the ALE value

Table 1
Summary of articles included in the meta-analysis (19 published imaging studies including 316 schizophrenia patients and 299 healthy controls).

No.	Articles	Imaging device	Task instruction	Stimuli	Sample size (Sz–HC)	% Male	Age Sz	% Drug	Estimated NS	Pleasure type	Contrast
1	Crespo-Facorro et al. (2001)	PET	Stimuli	Odorant	18-16	68	30.00	0	0.51*	Consummatory	√[a, b]
2	Gur et al. (2002)	fMRI	Stimuli	Face	14-14	71	28.80	93	0.32	Consummatory	√[a, c, d]
3	Paradiso et al. (2003)	PET	Stimuli	Pictures	18-17	66	30.00	0	0.51*	Consummatory	√[a, b]
4	Taylor et al. (2005)	PET	Stimuli	Pictures	18-10	61	33.02	75	0.32	Consummatory	√[a, c, d]
5	Juckel et al. (2006b)	fMRI	Feeling	Money	10-10	100	26.80	0	0.47*	Anticipatory	√[a, d]
6	Reske et al. (2007)	fMRI	Feeling	Pictures	10-10	60	37.40	100	0.30	Consummatory	√[a, b]
7	Schlagenhauf et al. (2008)	fMRI	Feeling	Money	10-10	90	30.50	100	0.44*	Anticipatory	√[a, c, d]
8	Schlagenhauf et al. (2009)	fMRI	Feeling	Money	15-15	63	30.10	0	0.54*	Anticipatory Consummatory	√[d] √[d]
9	Walter et al. (2009)	fMRI	Feeling	Money	16-16	47	38.00	100	0.45*	Anticipatory Consummatory	√[a, c, d] √[b, c, d]
10	Waltz et al. (2009)	fMRI	Feeling	Drink	18-18	75	37.70	100	0.19	Consummatory	√[a]
11	Simon et al. (2010)	fMRI	Feeling	Money	15-15	67	26.30	100	0.37*	Anticipatory Consummatory	√[d] √[c, d]
12	Gradin et al. (2011)	fMRI	Feeling	Water	14-17	58	42.50	60	0.25	Anticipatory	√[c, d]
13	Holt et al. (2011)	fMRI	Stimuli	Sentence	14-18	82	42.90	79	0.31	Consummatory	√[a]
14	Morris et al. (2012)	fMRI	Feeling	Money	16-16	53	33.00	100	0.28	Consummatory	√[c, d]
15	Surguladze et al. (2011)	fMRI	Stimuli	Face	32-16	53.1	43.15	100	0.21	Consummatory	√[c, d]
16	Koch et al. (2010)	fMRI	Feeling	Money	19-20	61.5	35.20	94.7	0.38*	Consummatory	√[a]
17	Li et al. (2010)	fMRI	Stimuli	Face	12-12	50	29.80	100	0.27	Consummatory	√[a]
18	da Silva Alves et al. (2013)	fMRI	Feeling	Money	10-12	100	22.70	100	0.29	Anticipatory	√[a]
19	Lakis and Mendrek (2013)	fMRI	Feeling	Pictures	37-37	51	32.46	100	0.26	Consummatory	√[a]

Note: Sz=schizophrenia; HC=healthy controls; Stimuli=stimuli oriented task requiring participants to response to the emotional stimuli itself (i.e. happy facial expression); Feeling=feeling oriented task using emotional stimuli to evoke participants' mood.

[a] HC > Sz.
[b] Sz > HC.
[c] Sz alone.
[d] HC alone; NS=negative symptom.
* Indicated elevated level of negative symptom.

based on the number of subjects recruited. Lastly, GingerALE performed cluster analysis on the threshold map, based on the minimum volume that is specified in the previous step. Clusters identified in the meta-analysis were obtained after controlling for the false discovery rate (FDR) at $p < 0.05$ and applying a minimum cluster size of 200 mm^3 (about 7 voxels with size of $3 \times 3 \times 3$ mm). The reason for applying this cluster threshold was to lower the false-positive error rate. This threshold has been frequently used in previous studies (Li et al., 2010; Jardri et al., 2011; Sugranyes et al., 2011). The brain maps of ALE values were imported to mango software 2.4 (http://ric.uthscsa.edu/mango/).

A number of confounding factors such as medication status, severity of negative symptoms, task instruction type, and stimulus characteristics might affect the neurobiological activity associated with hedonic experience in schizophrenia (da Silva Alves et al., 2008; Barch and Dowd, 2010; Kring and Caponigro, 2010). We performed subsidiary analyses (HC > Sz, and Sz > HC contrasts) for neural responses in medicated (defined as all the patients taking antipsychotic medications) and unmedicated schizophrenia patients (defined as 0% patients taking antipsychotic medication) compared with healthy controls. For negative symptoms, the symptom score in each study was transformed first by dividing the total score of the negative symptom scale used in that study (Yan et al., 2012). Then we averaged the transformed score of all the studies. If the transformed score in one study was higher than the averaged score, this study was considered as a study recruiting patients with relatively elevated negative symptoms, and vice versa. Since the averaged score of the present study was 0.35, which was within the range of the established cut-off score in previous studies (transformed cut-off score: from 0.22 to 0.38) (Bell et al., 2013; Gold et al., 2013; Oorschot et al., 2013), our high/low categorization was considered valid. Similar subsidiary analyses were performed for these two types of studies. For task instruction type, since different task instructions (feeling-oriented vs. stimuli-oriented) might activate different parts of the medial prefrontal cortex (dorsal/rostral vs. ventral) (Ochsner et al., 2004; Olsson and Ochsner, 2008), this factor was also taken into consideration. Stimuli-oriented tasks required participants to rate the emotional stimulus itself. On the other hand, feeling-oriented tasks required participants to provide their feelings about or be passively exposed to emotional stimuli. Lastly, we also performed subsidiary analyses on studies using different kinds of stimuli such as positively valenced pictures, money, odourants, drinks, faces, and words.

3. Results

3.1. Contrast of anticipatory, and consummatory pleasure

3.1.1. Consummatory pleasure

For healthy controls alone, seven studies reported activation, resulting in 66 foci. ALE scores and cluster size in these brain locations are summarized in Table 2 and Fig. 2. Healthy controls activated the left amygdala, the pregenual anterior cingulate cortex (pgACC, BA 32), the left putamen, the left insula (BA 13), the medial prefrontal cortex (mPFC, BA 6), and the right red nucleus (RN) (when consummating pleasure).

For schizophrenia patients, 50 foci from six studies revealed significant activations associated with positive emotion (see Table 2 and Fig. 2 for details of ALE value and cluster size). It yielded four clusters indicating activation at the left postcentral gyrus (PostG, BA 3), the left insula (BA 13), the right fusiform gyrus (FG, BA 19), and the left declive during consummatory pleasure processing in schizophrenia patients.

For the group contrast of HC > Sz, 10 studies reported a total of 96 foci of relative decrease in activation in schizophrenia patients compared with healthy controls. The brain map, ALE value, and cluster size are presented in Table 2 and Fig. 3. It consistently revealed eight clusters indicating activation reductions in the rostral medial prefrontal cortex (rmPFC, BA 9), the right parahippocampal gyrus/amygdala (BA 20), the left precental gyrus (PreG, BA 6), the left putamen, the right inferior frontal gyrus (IFG, BA 9), the left middle temproal gyrus (MTG, BA 21),the left medial globus pallidus (MGP), and the subgenual ACC (sgACC, BA 32) in schizophrenia patients relative to healthy controls. Activation in the rmPFC remained significant when we applied a more conservative statistic threshold of FDR-corrected p-value < 0.01 and a minimum cluster size of 200 mm^3.

For the group contrast of Sz > HC, four studies found a total of 19 foci of relative increase in activation at the right culmen in Sz patients compared with HC, although the number of studies was small (Table 2 and Fig. 3).

3.1.2. Anticipatory pleasure

As expected, 55 foci from six studies revealed enhanced acitivation in the right caudate head, the left lateral globus pallidus, and the red neucleus (RN) associated with anticipatory pleasure in healthy samples (see Table 2 and Fig. 2).

For the group contrast of HC > Sz, four studies found a total of 11 foci of relative decrease in activation in schizophrenia patients compared with healthy controls. It revealed only one cluster indicating an activation reduction in the left putamen in patients with schizophrenia (see Table 2 and Fig. 3).

For schizophrenia patients alone and the group contrast of Sz > HC, the number of studies and foci was too small for meaningful ALE analysis.

3.2. Confounding factors

For anticipatory pleasure, since the number of studies with between-group contrasts was small, we were not able to perform the subsidiary analyses on all four confoundings factors. Here, we mainly reported the findings of confounding factor analysis for consummatory pleasure. Eleven studies included between-group contrasts (either HC > Sz or Sz > HC).

3.2.1. Task instruction

Studies using a feeling-oriented task (n of study=4; n of foci=50) demonstrated attenuated activation in the rmPFC (BA 9) and the left putamen in Sz patients. On the other hand, studies using stimuli-oriented tasks (n of study=6; n of foci=46) showed decreased activation in the sgACC (BA 32), the left MGP, and the anterior middle cingulate cortex (aMCC, BA 32) in patients with Sz compared with HC (Table 3).

3.2.2. Medication status, negative symptoms and stimulus type

For these three confounding factors, due to the limited number of studies, confounding analyses were asymmetrical. For example, studies including patients taking medications (n=4) and with a mild level of negative symptoms (n=7) both demonstrated reduced activation in the left PreG (BA 6) and the left MTG. However, for studies comprising unmedicated patients and patients with a high level of negative symptoms, the number of studies (unmedicated: n=2; high level of negative symptoms: n=3) were too small for meaningful analyses for the Sz > HC or HC > Sz comparison. For stimulus type, we attempted to seperately perform analyses for studies using pictures, faces, money, words, drinks, and odourants as stimuli. However, the number of studies for almost all types of stimuli was also too small to perform subsidiary analyses.

4. Discussion

The present meta-analysis showed that schizophrenia patients exhibited reduced activation associated with consummatory pleasure mainly in the rmPFC (BA 9), the right parahippocampal gyrus/amygdala and other related regions such as the left PreG (BA 6), the right IFG (BA 9), the sgACC, the left MTG (BA 21), the left putamen, and the left MGP compared with healthy controls. Attenuated activation in the left putamen was found in patients with schizophrenia when processing anticipatory pleasure relative to healthy controls. For consummatory pleasure, dsyfunction in the rmPFC and the sgACC in schizophrenia was differetially elicited by feeling-oriented instructions and stimuli-oriented instructions.

Table 2
ALE results of neural response abnormality for consummatory and anticipatory pleasure contrasts ($p_{(FDR\text{-}corrected)} < 0.05$; volume size $> 200\ mm^3$).

Group contrast	Pleasure type	Foci Num.	Cluster Num.	Regions label	BA	Volume	Peak ALE	Talairach coordinates			Contributed Num. of foci
								x	*y*	*z*	
HC > Sz	**Anticipatory pleasure[5, 7, 9, 18] (*N*=4)**	11	**1***	**L. putamen**		**816**	**0.011**	**−18**	**10**	**0**	**3**
	Consummatory pleasure[1, 2, 3, 4, 6, 10, 13, 16, 17, 19] (*N*=10)	96	**1***	**rmPFC**	**9**	**824**	**0.02**	**12**	**44**	**18**	**3**
			2	L. PreG	6	584	0.015	−36	4	30	3
			3	L. putamen		368	0.014	−22	10	12	2
			4	R.IFG	9	360	0.013	48	12	26	2
			5	R. parahippocampal gyrus/ amygdala	20	352	0.014	40	−18	−20	2
			6	L.MTG	21	296	0.009	−56	−32	−6	3
			7	L.MGP		280	0.012	−14	−6	−8	2
			8	sgACC	32/ 11	272	0.012	−6	32	−10	2
Sz > HC	**Anticipatory pleasure (*N*=0)**	0	–								
	Consummatory pleasure[1, 3, 6, 9] (*N*=4)	19	**1***	**R. culmen**		**416**	**0.011**	**0**	**−56**	**−22**	**2**
Sz alone	**Anticipatory pleasure[7, 9, 12] (*N*=3)**	5	–								
	Consummatory pleasure[2, 4, 9, 11, 14, 15] (*N*=6)	50	**1***	**L. PostG**	**3**	**832**	**0.021**	**−36**	**−28**	**48**	**4**
			2	L. insula	13	416	0.013	−32	22	6	3
			3	R. fusiform gyrus	19	352	0.015	36	−70	−12	2
			4	L. declive		200	0.013	−36	−78	−16	2
HC alone	**Anticipatory pleasure[5, 7, 8, 9, 11, 12] (*N*=6)**	55	**1***	**R. caudate head**		**3064**	**0.035**	**10**	**4**	**2**	**11**
			2*	**L. LGP**		**1944**	**0.027**	**−16**	**4**	**0**	**7**
			3*	**R. RN**		**896**	**0.018**	**6**	**−24**	**−8**	**4**
	Consummatory pleasure[2, 4, 8, 9, 11, 14, 15] (*N*=7)	66	**1***	**L. amygdala**		**1400**	**0.026**	**−20**	**−6**	**−10**	**5**
			2	pgACC	32	432	0.016	−2	44	2	3
			3	L. putamen		232	0.014	−18	6	0	2
			4	L. inusla	13	224	0.013	−30	20	6	2
			5	mPFC	6	224	0.013	−2	−6	48	2
			6	R. RN		216	0.014	4	−22	−8	2

Note: R.=right; L.=left; Sz=schizophrenia; HC=healthy control; N=number of studies involved in the ALE analysis; rmPFC=rostral medial prefrontal cortex; IFG=inferior frontal gyrus; PreG=precentral gyrus; MTG=middle temporal gyrus; sgACC=subgenual anterior cingulate cortex; pgACC=pregenual anterior cingulate cortex; postG=postcentral gyrus; LGP=lateral globus pallidus; RN=red neucleus; SN=substania nigra.; "−" refers that we did not perform the subsidiary analysis because of the number of studies was less than four.

* Refers that the findings remained significant after a more conservative correction ($p < 0.01$ FDR-corrected, cluster size $> 200\ mm^3$); the number listed beside the pleasure type (i.e. Anticipatory Pleasure) refers to the serial number of study listed in Table 1.

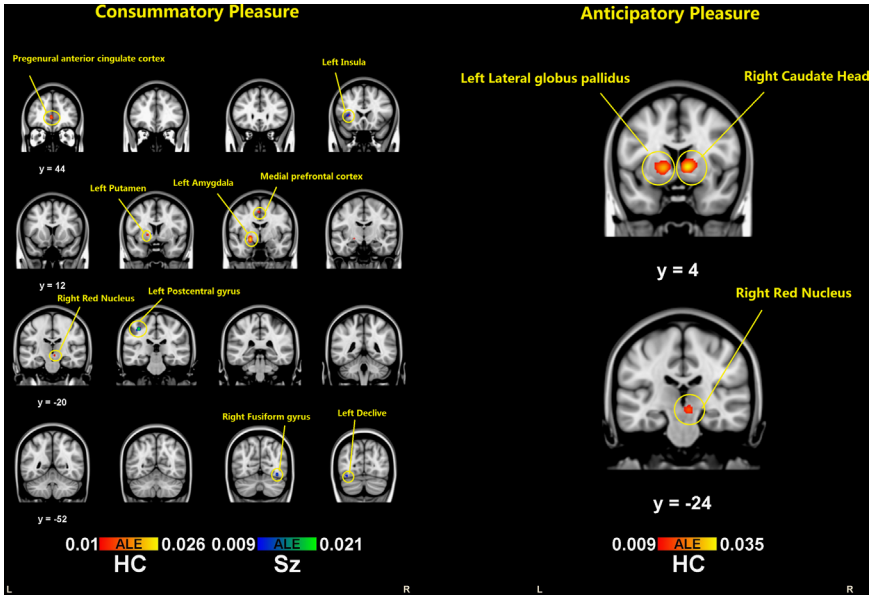

Fig. 2. Results from an activation likelihood estimation meta-analysis of studies investigating neural response changes related with consummatory and anticipatory pleasure in healthy controls and schizophrenia alone, respectively. Light regions represent increasing brain activity in the contrast of consummatory and anticipatory pleasure in healthy controls and schizophrenia patients, respectively.

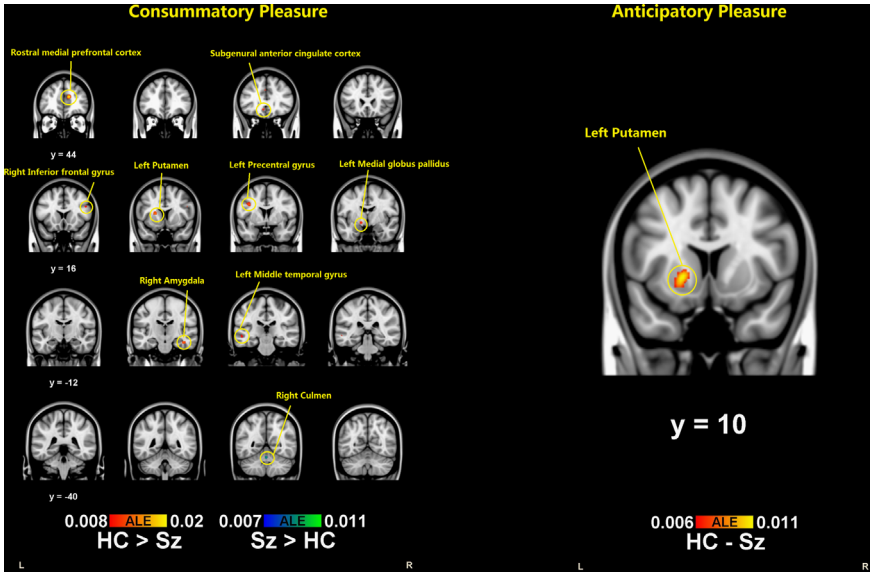

Fig. 3. Results from an activation likelihood estimation meta-analysis of studies investigating neural response changes related with consummatory and anticipatory pleasure in healthy controls compared with schizophrenia and vise versa. Light regions represent brain activity decrease in patients with schizophrenia relative to healthy comparison participants. Dark regions represent brain activity increase in patients with schizophrenia relative to healthy controls.

Table 3
ALE results for consummatory pleasure contrasts (including HC > Sz and Sz > HC) within confounding factors (i.e. task instruction (feeling oriented/stimuli oriented)) ($p_{FDR} < 0.05$; volume size > 200 mm^3).

Confounding factors		Group contrast	Foci Num.	Cluster Num.	Regions label	BA	Volume (mm^3)	Peak ALE	Talairach coordinates		
									x	*y*	*z*
Task Instruction	***Feeling Oriented***	HC > Sz[6, 10, 16, 19] (***N*=4**)	50	**1***	**rmPFC**	**9**	**840**	**0.020**	**12**	**44**	**18**
				2	L. putamen		432	0.014	−22	10	12
		Sz > HC[6, 9] (***N*=2**)	2	–							
	Stimuli Oriented	HC > Sz[1, 2, 3, 4, 13, 17] (***N*=6**)	46	1	L. MGP		424	0.012	−14	−6	−8
				2	sgACC/vmPFC	32/11	392	0.011	−6	32	−10
				3	aMCC	32	272	0.009	−2	30	32
		Sz > HC[1, 3] (***N*=2**)	17	–							

Note: R.=right; L.=left; Sz=schizophrenia; HC=healthy control; N=number of studies involved in the ALE analysis; rmPFC=rostral medial prefrontal cortex; MGP=medial globus pallidus; sgACC=subgenual anterior cingulate cortex; aMCC=anterior middle cingulate cortex; "–" refers that we did not perform the subsidiary analysis because of the number of studies was less than four.

* Refers that the findings remained significant after a more conservative correction ($p < 0.01$ FDR-corrected, cluster size > 200 mm^3); the number listed beside the group contrast refers to the serial number of study listed in Table 1.

4.1. Consummatory pleasure dysfunction in schizophrenia

4.1.1. Reduced rostral medial prefrontal activation in schizophrenia

In our study, deceased activation in the rmPFC, which has been considered by Knutson and his colleagues as a key brain region involved in "in the moment" hedonic processing or positive feedback (Knutson et al., 2003; Knutson and Greer, 2008), was robustly observed in patients with schizophrenia. Similar to our finding, medial prefrontal dysfunction was also observed in previous studies mainly investigating consummatory negative emotions in patients with schizophrenia (Taylor et al., 2012) and especially in those with blunted affect (Fahim et al., 2005; Stip et al., 2005). In Taylor's recent meta-analysis (Taylor et al., 2012), 121 foci from 28 contrasts for general negative emotions were included. The meta-analysis revealed that schizophrenia patients exhibited attenuated neural activation in the right dorsal medial frontal gyrus (BA 32), the right medial prefrontal gyrus (BA 6) and bilateral anterior cingulate (BA 24 and BA 32) during negative emotion processing. Our study underscores that the medial prefrontal cortex plays an important role in the consummatory processing of both positive and negative information. It is of interest, however, that the rmPFC in this study is distinct from those regions reported in the study of Taylor et al. Specifically, deficit in consummatory pleasure in schizophrenia patients might be represented rostrally in the mPFC, whereas consummtory negative emotion might be represented more dorsally in the mPFC. Dissociable dysfunction in the rostral and dorsal mPFC might improve our understanding of the neural correlates of the consummatory emotional deficit in schizophrenia and provide clues for intervention of negative symptoms (e.g., repetitive transcranial magnetic stimulation (rTMS) in schizophrenia (Dlabac-de Lange et al., 2010).

From the behavioural perspective, a number of previous narrative reviews and meta-analyses did not find significant differences in pleasantness or arousal rating to positive stimuli between schizophrenia patients and healthy controls (Kring and Moran, 2008; Cohen and Minor, 2010; Cohen et al., 2010; Kring and Caponigro, 2010; Yan et al., 2012). Two factors might account for the difference between findings from behavioural and imaging studies. One is that fMRI may be a more sensitive tool than behavioural assessments to detect the affective dysfunction in schizophrenia. The other possibility is that there may be a compensatory neural mechanism which is able to

account for the seemingly intact behavioural response to positive stimuli in patients with schizophrenia when there is an underlying activation deficit detectable only by fMRI. In this study, we observed that schizophrenia patients showed enhanced activation at the right culmen, which plays an important role in emotional experience (Schmahmann, 2000; Goel and Dolan, 2001; Turner et al., 2007). Moreover, previous studies have found that schizophrenia patients showed increased activation in the cerebellum but decreased activation in the prefrontal gyrus (Andreasen et al., 1997; Stip et al., 2005), which suggests the presence of compensatory mechanisms in various cortical and subcortical (including cerebellar) circuits.

4.1.2. Attenuated amygdala activation in schizophrenia

We observed decreased amygdala activation with consummatory pleasure in patients with schizophrenia compared with healthy controls. Consistent with our findings on positive affect, a number of previous studies have traditionally suggested that schizophrenia patients exhibit decreased amygdala activation during negative affective processing (Shayegan and Stahl, 2005; Rosenfeld et al., 2011; Anticevic et al., 2012b). For example, in one meta-analysis (not ALE), Anticevic et al. (2012b) specifically focused on amygdala function and found that patients with schizophrenia showed moderate under-recruitment of bilateral amygdala (effect size = −0.20) in response to aversive emotional stimuli, suggesting that under-recruitment of the amygdala might underlie the neural mechanism of consummatory affective processing in schizophrenia. Consistent with this hypothesis, another meta-analysis by Li et al. (2010) specifically measured the neural response to facial emotion in patients with schizophrenia and found decreased activation in bilateral amygdala (ALE value = 0.052 to 0.060; cluster size = 272 to 368 mm^3). Furthermore, failure of amygdala activation has been observed in patients with schizophrenia during the performance of both explicit and implicit tasks (an explicit design refers to tasks directly requiring participants to discriminate, judge, or evaluate the property of a facial expression; an implicit design refers to tasks indirectly measuring patients' emotion processing by asking them to evaluate the unrelated properties of a stimulus (e.g., gender, age detection). Meanwhile, a number of structural MRI studies have also observed significant bilateral reduction of amygdala volume (6–10%) in schizophrenia patients compared with healthy controls (Lawrie and Abukmeil, 1998; Wright et al., 2000), which might establish an important role for the amygdala in understanding the affective deficit in consummatory pleasure experience in patients with schizophrenia. However, the impact of anhedonic symptoms on amygdala activity during hedonic experience processing (Barch and Dowd, 2010) should also be noted because some studies did not report significantly decreased activity in this region in patients with schizophrenia (Paradiso et al., 2003; Reske et al., 2007; Dowd and Barch, 2010). For example, Dowd and Barch (2010) reported intact amgydala response to positively valenced stimuli in schizophrenia patients, but they did find that the magnitude of this response was negatively correlated with the physical anhedonia score. Therefore, more research his needed to specifically delineate how negative symptoms of schizophrenia like anhedonia modulate activation in these brain regions.

Decreased activations were also observed in other brain regions such as the sgACC, the putamen, and the MGP, all of which have been considered important limbic hot spots in the processing of consummatory pleasure in healthy controls (Knutson and Greer, 2008; Kringelbach and Berridge, 2009). In line with this finding, one recent review has stated that patients with schizophrenia exhibited dysfunction in the limbic system (i.e., the anterior cingulate cortex, the orbitofrontal cortex, and the striatum) in response to positive stimuli, even though these results were mixed with an equal number of studies finding intact activation in these regions (Kring and Barch, 2014). In addition, cognitive processing (i.e., cognitive control and affective maintenance) might contribute to the finding of differences in activation of the ACC in patients with schizophrenia (Kring and Barch, 2014; Ursu et al., 2011). Taken together, the findings suggest that limbic functional abnormality might also play arole in consummatory pleasure processing in schizophrenia.

4.1.3. Confounding factors

For task instruction, our subsequent confounding factor analysis showed that patients with schizophrenia exhibited reduced activation in the rmPFC in studies with feeling-oriented instructions. It suggests that studies using feeling-oriented instructions might contribute to the rmPFC dysfunction during processing of consummatory pleasure in patients with schizophrenia. As is known, the mPFC has been considered a key brain region where activation is correlated with consummatory pleasure in healthy populations (Knutson and Greer, 2008). Furthermore, reporting on feeling of one's own feeling has been found to be associated with dorsal/rostral mPFC activation (Ochsner et al., 2004; Olsson and Ochsner, 2008). Patients with schizophrenia have been found to have difficulty in identifying and describing their own feeling compared with their unaffected siblings and healthy controls (van 't Wout et al., 2007; Kimhy et al., 2012). One functional neuroimaging study has found that patients with schizophrenia showed similar hypoactivation in the rostral/dorsal mPFC during self-evaluation of their own emotional, mental and physical traits (relative to evaluating the traits of others) (Bedford et al., 2012). From the perspective of brain structure, one multimodal neuroimaging study combining both voxel-based morphometry (VBM) and diffusion tensor imaging (DTI) to detect grey matter volume and white matter integrity and connectivity identified the medial prefrontal cortex as a prominent site of abnormality in schizophrenia. This region also corresponds to the anterior midline node of the default mode network, a brain system which is believed to support the maintenance of one's sense of self (Pomarol-Clotet et al., 2010).

On the other hand, our subsidiary analysis for studies employing stimulus-oriented instructions showed that patients with schizophrenia had attenuated activation in cortical regions such as the sgACC when they were required to report on affective properties of the stimuli. Since the sgACC is located adjacent to the ventral portion of the mPFC, its activation is more likely to be associated with reporting on the affective properties of a stimulus (Ochsner et al., 2004; Olsson and Ochsner, 2008). Previous studies have suggested that patients with schizophrenia may have difficulties in distinguishing properties of emotional stimuli (e.g., facial emotion; see meta-analysis in Kohler et al., 2010). Therefore, this might partially explain the observation of sgACC dysfunction during reporting of the affective properties of a stimulus. Taken together, in line with the hypothesis by Kring and Elis (2013), Kring and Moran (2008), our finding supports the differential role of task instruction in measuring mPFC dysfunction associated with consummatory pleasure in patients with schizophrenia.

4.2. Altered striatal response associated with anticipatory pleasure in schizophrenia

Recently, more and more researchers have suggested that impairment in anticipatory pleasure experience might underlie the phenomenon of anhedonia in schizophrenia (Kring and Caponigro, 2010; Cohen et al., 2011). The striatum, including the ventral and dorsal striatum, is critical for reward prediction/anticipatory pleasure (Groenewegen and Trimble, 2007; Knutson and Greer, 2008). At the level of brain morphometry in schizophrenia, numerous studies have found reduced grey matter

volume in the ventral and dorsal striatum in patients with schizophrenia (Gaser et al., 2004; Mamah et al., 2007), including medication-naïve patients (Keshavan et al., 1998; Ebdrup et al., 2010). In fMRI studies, there is growing evidence suggesting that activation in the striatum reflecting reward prediction/wanting may be affected in schizophrenia patients (Barch and Dowd, 2010). Consistent with these findings, our results indicate activation reduction in the left putamen (dorsal striatum) during anticipatory pleasure processing in schizophrenia. However, we did not observe decreased ventral striatal activation in patients with schizophrenia. One reason to explain this negative finding is the small number of studies reporting findings using whole brain analysis. A number of previous neuroimaging studies analyzed regions of interest (ROIs) and performed the between-group contrast in a pre-defined region (such as ventral striatum) (Juckel et al., 2006a; Schlagenhauf et al., 2009; Gradin et al., 2011). As is known, these ROI studies are not amenable to ALE analysis. Our ALE analysis only included four studies with 11 foci reporting group comparison contrasts (HC > Sz). Therefore, more work is needed before any conclusion can be made about the role of the striatal region in anticipatory pleasure dysfunction in schizophrenia. For example, it is worthwhile to investigate how negative symptoms moderate activation in the striatal region during the processing of anticipatory pleasure in schizophrenia. On the other hand, social anhedonia has been considered a potential vulnerability marker for schizophrenia spectrum disorders (Meehl, 1990; Kwapil, 1998). As far as we know, no study has examined the neural basis of anticipatory pleasure in schizophrenia in the social interaction context. More studies are needed to examine the neural response associated with anticipatory pleasure carrying social information in schizophrenia patients to improve our understanding of social anhedonia and social withdrawal in schizophrenia.

4.3. Limitations

There are several limitations in the present study. First, relative to HC > Sz comparison, the Sz > HC comparison yielded only four studies for consummatory pleasure and no study for anticipatory pleasure, suggesting that our meta-analytic study might be better able to identify reduced rather than increased activation in patients with schizophrenia. Similar asymmetries were also present in the subsidiary analyses. We originally intended to find out how stimulus type, level of negative symptoms, and medication affect neural activation associated with consummatory pleasure in schizophrenia patients, but the number of studies for each confounding factor was too small for meaningful analysis. Second, since only positive findings could be applied to ALE analysis, some negative findings were inevitably excluded in our analysis. Moreover, ALE does not readily allow for multiple regression analysis to tease out the separate influences of different variables (such as medication status and negative symptom). More sophisticated methods of analysis combining both behavioural and imaging data should be developed to examine the underlying mechanism of hedonic experience in schizoophrenia. Third, we acknowledge the possibility that the predominance of males in the included studies might have biased the results.

5. Conclusion

Taken together, our findings suggest that the medial prefrontal cortex and the limbic regions may play an important role in the neural dysfunction associated with consummatory pleasure processing and support the differential role of task instruction in affecting mPFC dysfunction in schizophrenia. It may provide researchers relatively solid evidence to understand the neural correlates of anhedonia (especially consummatory pleasure) in schizophrenia and to develop more effective and specific clinical interventions (such as repetitive transcranial magnetic stimulation or real-time fMRI training) to alleviate negative symptoms in schizophrenia.

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Appendix A

See citations of appendix references (Crespo-Facorro et al., 2001; da Silva Alves et al., 2013; Gradin et al., 2011; Gur et al., 2002; Holt et al., 2011; Juckel et al., 2006; Koch et al., 2010; Lakis, Mendrek 2013; Li et al., 2010; Morris et al., 2012; Paradiso et al., 2003; Reske et al., 2007; Schlagenhauf et al., 2008; Schlagenhauf et al., 2009; Simon et al., 2010; Surguladze et al., 2011; Taylor et al., 2005; Walter et al., 2009; Waltz et al., 2009).

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