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Reward-related decision-making in schizophrenia: A multimodal neuroimaging study

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ABSTRACT

Schizophrenia is a severe psychiatric disorder characterized by important cognitive deficits, which ultimately compromise the patients' ability to make optimal decisions. Unfortunately, the neurobiological bases of impaired reward-related decision-making in schizophrenia have rarely been studied. The objective of this study is to examine the neural mechanisms involved in reward-related decision-making in schizophrenia, using functional magnetic resonance imaging (fMRI). Forty-seven schizophrenia patients (DSM-IV criteria) and 23 healthy subjects with no psychiatric disorders were scanned using fMRI while performing the *Balloon Analogue Risk Task* (BART). A rapid event-related fMRI paradigm was used, separating decision and outcome events. Between-group differences in grey matter volumes were assessed with voxel-based morphometry. During the reward outcomes, increased activations were observed in schizophrenia in the left anterior insula, the putamen, and frontal subregions. Reduced grey matter volumes were observed in the left anterior insula in schizophrenia which spatially overlapped with functional alterations. Finally, schizophrenia patients made fewer gains on the BART. The fact that schizophrenia patients had increased activations in sub-cortical regions such as the striatum and insula in response to reward events suggests that the impaired decision-making abilities of these patients are mostly driven by an overvaluation of outcome stimuli.

1. Introduction

Schizophrenia is a severe and complex psychiatric disorder associated with poor social and occupational functioning (Green, 1996). The disorder is characterized by significant cognitive and affective impairments (Bora et al., 2010; Habel et al., 2000), which ultimately compromise the patients' ability to make practical decisions. Clinical manifestations of impaired decision-making in schizophrenia are numerous, and include substance misuse (Hartz et al., 2017), occupational and financial problems (Marson et al., 2006), proneness to pathological gambling (Desai and Potenza, 2009), self-harm (Haddock et al., 2013), as well as interpersonal problems (McGuire et al., 2017). Unfortunately, the pathophysiological bases of impaired reward-related decision-making in schizophrenia have been rarely studied, and thereby remain poorly understood.

Optimal decision-making requires to adapt choices based on the outcomes (rewards and punishments) of previous choices. Several cognitive studies have examined reward related decision-making in schizophrenia. Recently, Brown et al. (2015) performed a meta-analysis of 8 studies that have addressed this question using the *Iowa Gambling Task* (IGT) (Bechara et al., 1994), whereby participants need to choose between 4 decks offering small rewards and smaller punishments (i.e. advantageous decks) or large rewards and larger punishments (i.e. disadvantageous decks). The results of the meta-analysis showed that schizophrenia patients have moderate deficits in reward related decision-making as illustrated by an increased selection of disadvantageous decks over advantageous ones. Despite this, a paucity of studies have examined the neurobiological mechanisms involved in suboptimal reward related decision-making in schizophrenia. Preliminary functional neuroimaging studies on reward-related decision-making in this

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population have highlighted impairments in the ventral striatum (Brown et al., 2015; Rausch et al., 2014; Richter et al., 2015), a key region of the brain reward system. The neuroanatomical bases of sub-optimal reward related decision-making in schizophrenia have also been explored. In a study from Premkumar et al. (2008) overall performance on the IGT was positively correlated with the left orbito-frontal cortex in healthy subjects, but not in schizophrenia patients.

Thus far, the IGT has been the most frequently employed task to assess reward-related decision-making in schizophrenia (Brown et al., 2015). Despite its importance, the task is complex and requires associative learning of the representations of expectancies (Brambilla et al., 2013). Therefore, poor performance on the IGT in schizophrenia patients may be linked to impaired learning or erroneous calculation of expected value rather than impaired reward-related decision-making. Indeed, the difference between schizophrenia patients and controls on the IGT is mostly apparent for the decks with infrequent punishments, which typically require repeated calculations (Brown et al., 2015). This suggests that the IGT may not entirely be adapted to assess reward-related decision-making in this population, which is characterized by learning difficulties (Horan et al., 2008). A relevant alternative to assess reward-related decision-making in schizophrenia is the *Balloon Analogue Risk Task* (BART) (Bogg et al., 2012), in which participants are presented with a balloon and each time they click on a button, the balloon is incrementally inflated and virtual money is added up to a threshold at which point the balloon explodes. For each balloon, participants must choose whether to cash out or to take the risk of potentially earning more money. The BART has excellent psychometric properties and predictive validity for real-life behavior (Lejuez et al., 2002; Rao et al., 2008; White et al., 2008). It is simple, easy to understand, and less dependent on repeated calculations, which are all important features when assessing reward-related decision-making in schizophrenia. The functional neuroimaging adaptation of the BART allows the investigation of decision and outcome periods separately, as well as the examination of associations between brain responses and objective risk, based on predetermined probabilities of explosions (Bogg et al., 2012).

In recent years, the BART has become one of the most widely used task to study the neurobiological bases of reward-related decision-making. Thus far, the several functional magnetic resonance imaging (fMRI) studies performed in the field have shown that the dorso-lateral prefrontal cortex, medial prefrontal cortex, anterior cingulate cortex, insula, and striatum play a key role in reward-related decision-making in healthy volunteers, with prefrontal regions being more closely involved in decision-making, and sub-cortical regions, in reward processing (Forster et al., 2016; Galvan et al., 2013; Kohno et al., 2015; Schonberg et al., 2012). In schizophrenia, preliminary studies using the BART have shown that patients make smaller gains on the task, compared to controls (Cheng et al., 2012; Reddy et al., 2014), suggesting that patients make suboptimal decisions characterized by risk avoidance. Unfortunately, no fMRI study has examined the neural bases of impaired reward-related decision-making in schizophrenia using the BART, at least to our knowledge.

The main objective of the current multimodal neuroimaging study is to examine both the neurofunctional and neuroanatomical bases of suboptimal reward-related decision-making in schizophrenia, using the BART. We hypothesized that schizophrenia patients will make smaller gains on the BART, and that their decisions will be characterized by risk avoidance. At the neural level, we expected to observe, in patients, frontal alterations during decision events and alterations in sub-cortical regions (e.g. striatum and insula) during reward outcomes.

2. Methods

2.1. Participants

Forty-seven male outpatients with schizophrenia or schizoaffective disorder (Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria) were recruited at the *Institut Universitaire en Santé Mentale de Montréal* and the *Institut Philippe-Pinel de Montréal*. Diagnoses were established with the *Structured Clinical Interview for DSM-IV* (First and Gibbon, 2004). Schizophrenia patients reported no comorbid substance use disorders within the last 12 months, and were stabilized on antipsychotic medication (i.e. reported no changes in the 2 months preceding the fMRI session). Schizophrenia participants were treated with one or more of the following antipsychotics: aripiprazole (n = 5); clozapine (n = 20); olanzapine (n = 9); quetiapine (n = 10); risperidone (n = 6); fluphenazine (n = 2); loxitane (n = 1); paliperidone (n = 5); ziprasidone (n = 1). The influence of antipsychotics in patients was examined by calculating olanzapine equivalents (Leucht et al., 2014). Twenty-three heathy men were also recruited, who reported no psychiatric disorder (including substance use disorder), and were not treated with centrally-acting medication. Participants in both groups had no concomitant neurological disorders, unstable medical condition, or MRI contra-indications. Furthermore, all participants had an estimated intelligence quotient (IQ) over 70, as evaluated by the Wechsler Abbreviated Scale of Intelligence (Wechsler, 2011), and tested negative at an urine drug screenings administered before the fMRI session.

After a discussion of the study and its implications, all participants gave written consent in accordance with the Declaration of Helsinki. The study was approved by the local ethic committees.

2.2. Clinical assessments

In schizophrenia patients, psychiatric symptoms were assessed with the *Positive And Negative Syndrome Scale* (PANSS) (Kay et al., 1987), which yields five subscores (positive, negative, disorganization/cognitive, excitation, depression) according to Lindenmayer et al. (1995)'s five factor model of schizophrenia.

2.3. Balloon analogue risk task

A slightly modified version of the BART described by Bogg et al. (2012) was employed in this study (see Fig. 1). Prior to the fMRI scanning session, participants completed an abbreviated 5 min block on a laptop to familiarize themselves with the task. The instructions given to the participants were to inflate the balloon without having it explode, and to maximize the total amount of cash earned. The participants were informed that the compensation they received for taking part in the study was not changed in function of the BART outcome. For a given balloon trial, 12 successive inflation responses were possible. The probability of explosion over successive inflation responses increased parametrically (see Bogg et al. (2012)). While in the scanner, participants completed two 8 min runs. Each run began and ended with the display of a fixation cross at the center of the screen. The fixation cross at the beginning lasted 60 s, to establish baseline activity. At the beginning of each trial, the screen displayed an image of a balloon, a square decision cue (green = *a* response is allowed, red = responses are disallowed), the current wager amount, and the total earnings. Participants had no time restrictions to make a decision (i.e. to choose to Inflate the balloon or Cash In the wager by selecting the appropriate button). The inter-stimuli interval was jittered and randomized, lasting 0 to 6 s after each response. During this delay, no feedback was given, to allow for a separate estimation of the Blood Oxygen Level Dependent (BOLD) response during choice and outcome periods. Following an inflation of the balloon, the outcome could either be a successful inflation (Success) or an explosion (Explosion). If the balloon was inflated, the decision cue turned red (for 1500, 2000, or 2500 ms) after which the decision cue turned green with the image showing an inflated balloon. If the balloon exploded, the participants were presented with an image showing an exploded balloon (500 ms) and then the words "You Lose!" (1000 ms). After a decision to Cash In, the balloon was replaced by the words "You Win!" (for 1000 ms). After

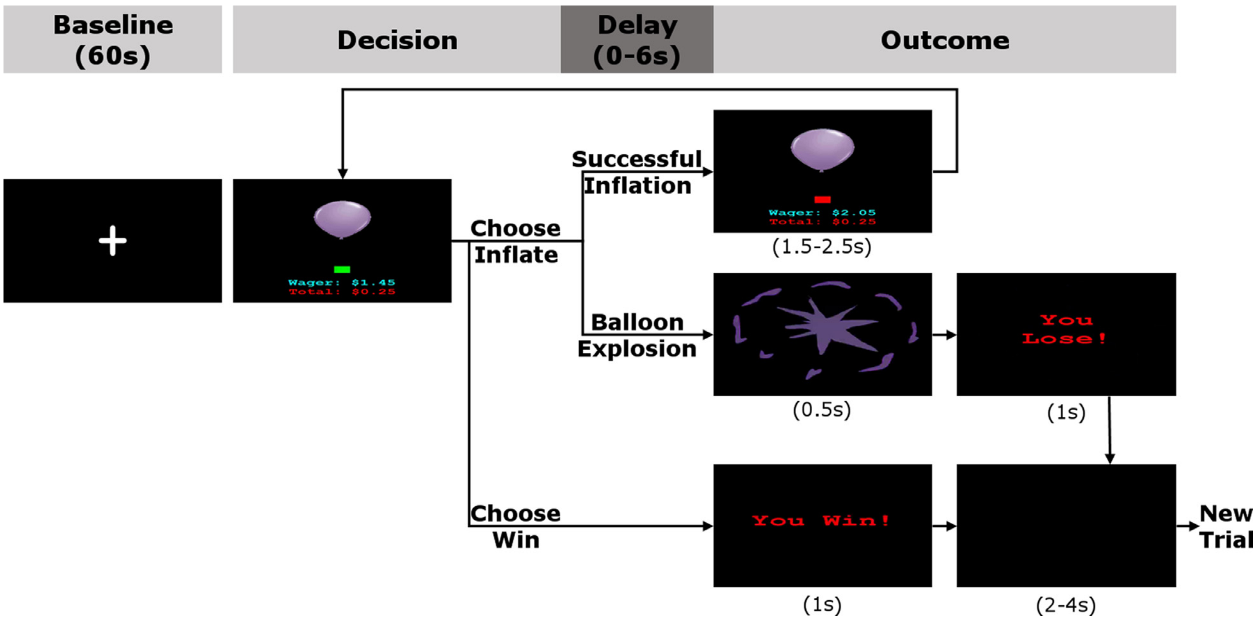

Fig. 1. Schematic representation of the modified Balloon Analogue Risk Task (BART) adapted from Bogg et al. (2012).

a Win or an Explosion, the screen became black (for 2000, 3000, or 4000 ms), and a new trial was presented.

2.4. MRI data acquisition parameters

BOLD signal was recorded using a T2-weighted gradient echo-planar imaging (EPI) sequence (TR: 2090 ms; TE: 30 ms; Flip Angle: 90°; matrix: 64 × 64; voxel size = 3.5 mm^3; 38 axial slices) on a 3.0 Tesla Siemens TRIO MRI system, using a 32-channel, high-resolution, transmit/receive brain volume coil. An inline retrospective motion correction algorithm was employed while the EPI images were acquired. Individual high-resolution co-planar anatomical images were also acquired using a three-dimensional, ultrafast gradient echo sequence (TR: 2300 ms, TE: 2.98 ms, Flip Angle: 9°, matrix: 256 × 240; voxels size: 1 mm^3; 176 sagittal slices).

2.5. fMRI data analysis

fMRI data was analyzed with Brain Voyager QX 2.8 (Brain Innovation, Maastricht, Netherlands) software. Functional images were slice-time corrected, corrected for motion artifacts (≤ 2 mm), high-pass filtered, co-registered to the corresponding anatomical image, spatially normalized to the stereotaxic Talairach space (Talairach and Tournoux, 1988), and spatially smoothed with a 3D isotropic Gaussian kernel (8 mm FWHM).

An event-related approach was employed for data analysis. Predictors of interest, corresponding to the experimental events, were convolved with the hemodynamic response function estimated using the double-gamma model. The BART model included five experimental events, namely the decision to Inflate or to Cash In, and the Success, Win and Explosion outcomes. The Explosion event was modelled but was treated as predictor of no interest, due to its low incidence (< 5% of outcome events). The predictors were entered as fixed factors in a single-subject general linear model (GLM), and an auto-regressive AR (2) model was used to account for serial correlations. Explosion probabilities (z-transformed) were included as parametric modulators for the Inflate and Success events (Bogg et al., 2012; Fukunaga et al., 2012). Then, the parameters of the first-level analysis were entered into a second-level of analysis corresponding to a random-effect GLM that was used for group comparisons (Penny and Holmes, 2003). As in previous fMRI studies, the focus of the group-level analyses were the Inflate and Success events (Bogg et al., 2012; Fukunaga et al., 2012; Schonberg et al., 2012). Knowing that schizophrenia patients tend to attribute motivational value to irrelevant stimuli (Strauss et al., 2014), the Win event was also considered as an event of interest. As our version of the BART comprised 120 s of baseline activity, we analyzed the events with and without their parametric modulation. The statistical threshold for significance was determined by computing a Monte Carlo simulation (Ward, 2000). Assuming a per voxel probability threshold of $p = 0.001$, after 10 000 simulations, a cluster size of 343 re-sampled voxels (i.e. 343 mm^3) was indicated to correct for multiple comparisons at $p < 0.05$. Regional beta-values were extracted and used to perform correlation analyses between BOLD responses and clinical variables (e.g. psychiatric symptoms, IQ and antipsychotic dosage).

2.6. MRI data analyses

Between-group differences in grey matter (GM) volumes were investigated using voxel-based morphometry (VBM) (Ashburner, 2007; Ashburner and Friston, 2000). We used the *Diffeomorphic Anatomic Registration Through an Exponentiated Lie Algebra* algorithm of the *Statistical Parametric Mapping*-12 software (SPM-12; Wellcome Department of Cognitive Neurology), which provides improved registration accuracy compared with conventional VBM (Klein et al., 2009). Analyses were made according to the steps proposed by Ashburner (2015). Magnetic resonance images were segmented into GM, white matter and cerebrospinal fluid. GM population templates were generated from the entire image dataset, and were normalized to the *Montreal Neurological Institute* (MNI) stereotaxic space. Images were modulated to ensure that relative GM volume was preserved following spatial normalization. The voxel sizes for spatially normalised images were 1.5 mm^3. Images were smoothed with an 8 mm Gaussian kernel (FWHM). Between-group differences in GM volumes were assessed using independent-samples *t*-test. VBM data was corrected for participants' total intracranial volume using proportional scaling. The participants' age and IQ were entered as covariates in the model. An initial threshold of $p_{(uncorr.)} < 0.001$ was used for the statistical parametric maps of GM between-group comparisons. Based on the inverse of the icbm2tal affine transformation matrix (Laird et al., 2010; Lancaster et al., 2007), fMRI clusters of interests were converted from the Talairach to the MNI (as implemented in SPM) stereotaxic space. These fMRI data-driven ROIs were applied to GM between-group differences using a small volume correction (SVC, as

Table 1
Participant characteristics.

	SCZ (*n* = 47)	Healthy (*n* = 23)	Significance
Age, mean years (SD)	34.4 (9.6)	31.9 (8.2)	$t = -1.10$; $p = 0.28$
Handedness,% right	89.5	95.5	$\chi^2 = 1.22$; $p = 0.54$
Ethnicity,% Caucasian	80.9	87.0	$\chi^2 = 1.54$; $p = 0.82$
IQ, (SD)	89.2 (10.8)	100.7 (15.3)	**$t = 3.00$; $p = 0.005$**
BART Total, $ (SD)	17.0 (5.2)	19.3 (5.1)	$t = 1.77$, $p = 0.08$
Rate of exploded balloon,% (SD)	23.2 (13.6)	31.3 (15.9)	**$t = 2.20$, $p = 0.03$**
Diagnoses	12 SA, 1SZP	–	–
Age of onset, mean years (SD)	22.2 (5.8)	–	–
PANSS – 5 factors, (SD)			
Positive	9.7 (2.5)	–	–
General	14.6 (4.8)	–	–
Disorganized	7.5 (2.1)	–	–
Excited	7.2 (2.7)	–	–
Depressed	7.9 (2.2)	–	–
Clozapine,%	42.5	–	–
Olanzapine equivalents mg, (SD)	14.6 (8.7)	–	–

BART = Balloon Analogue Risk Task; PANSS = Positive And Negative Syndrome Scale; IQ = Intelligence quotient; SA = Schizo-affective disorder; SZP = Schizophreniform; SD = standard deviation. Bold font indicates significant between-group differences.

implemented in SPM12) family-wise error (FWE) $p_{(FWE)} < 0.05$ corrected threshold. The MATLAB NeuroElf toolbox (http://neuroelf.net) was used for visualization. The open-source image editor GIMP was used to build the figures (http://www.gimp.org).

3. Results

3.1. Clinical data

Men with schizophrenia had a lower IQ than healthy men (see Table 1). The two groups did not differ in terms of age, handedness, and ethnicity. There was a non-significant trending effect in the performance on the BART, where schizophrenia patients gained less money than healthy subjects and exploded significantly fewer balloons. Moreover, schizophreniform or schizoaffective subjects did not differ significantly on these variables from the rest of the SCZ sample.

3.2. fMRI data

For the decision to Inflate event (main effect), increased activations were observed in the left superior frontal gyrus in schizophrenia patients, relative to healthy subjects (Table 2; Fig. 2). A trending between-group difference was observed in the left superior frontal gyrus for the Inflation event with *parametric modulation* (see Supplementary Material Figure S1). For the Success outcome event (main effect), increased activations were observed in schizophrenia patients, relative to healthy subjects, in the bilateral occipital, left putamen, left precentral and postcentral gyrus (Table 2; Fig. 2). For the Success event *with parametric modulation*, all these regions (including the putamen) were found to be significantly activated across groups (*both* schizophrenia patients and healthy subjects), but no between-group differences were observed (see Supplementary Material Figure S2).

For the Win outcome event, increased activations were observed in schizophrenia patients, relative to healthy subjects, in the bilateral putamen, bilateral cingulate gyrus, left middle and superior frontal gyrus, left claustrum, left insula, and the left supramarginal gyrus (Table 2; Fig. 2).

Finally, no associations were found between activations and psychiatric symptoms, olanzapine equivalents, or IQ in schizophrenia. Schizophreniform or schizoaffective subjects did not differ significantly in activations from the rest of the SCZ sample.

3.3. MRI data

VBM analyses revealed a widespread decrease in gray matter volume in schizophrenia patients compared to healthy subjects in several bilateral frontal, cingular, insular, and cerebellar regions (see Supplementary Material Table S1). Of the regions significantly impaired in schizophrenia as determined by the functional analyses, we used the putamen, insula, and cingulate gyrus as fMRI data-driven ROIs for subsequent neuroanatomical analyses, given that previous fMRI studies using the BART have shown that these regions are reliably involved in reward-related decision-making (Forster et al., 2016; Galvan et al., 2013; Kohno et al., 2015; Schonberg et al., 2012). The ROI analysis of the left putamen/insula [Win event] revealed a significant decrease in insular GM volume in schizophrenia patients compared with healthy subjects (SVC peak $p_{(FWE)} = 0.007$, $p_{(uncor.)} < 0.001$, $t = 3.98$, peak-coordinate (MNI) −35,15,8l; cluster-level

Table 2
Differences in activations between schizophrenia patients and controls during reward-related decision-making.

Region	L/R	BA	Talairach			T-max	Voxels (mm³)
			x	y	z		
Decision to Inflate							
[SCZ > Healthy]							
Superior frontal gyrus	L	8	−12	44	34	4.1	654
[Healthy > SCZ]							
-							
Success							
[SCZ > Healthy]							
Inferior occipital gyrus	R	19	36	−76	−5	4.4	1517
Middle occipital gyrus	R	18	18	−88	16	4.9	1980
Putamen	L	–	−24	2	16	4.4	1981
Inferior occipital gyrus	L	18	−36	−85	−2	4.1	466
Inferior frontal gyrus/ Precentral gyrus	L	44	−48	−1	16	4.4	1384
Postcentral gyrus	L	40	−63	−25	19	4.3	358
[Healthy > SCZ]							
-							
Win							
[SCZ > Healthy]							
Putamen	R	–	24	8	7	4.4	894
Cingulate gyrus	R	32	9	11	34	4.3	1067
Cingulate gyrus	L	24	−9	2	37	4.7	1831
Superior frontal gyrus	L	6	−9	−13	67	4.1	439
Putamen/Insula	L	–	−24	11	13	4.3	1947
Inferior frontal gyrus	L	47	−30	8	−14	4.0	438
Middle frontal gyrus	L	9	−30	26	34	4.6	1050
Supramarginal gyrus	L	40	−42	−40	31	4.5	1626
[Healthy > SCZ]							
-							

L/R = left/right hemisphere, BA = Brodmann area; SCZ = schizophrenia.

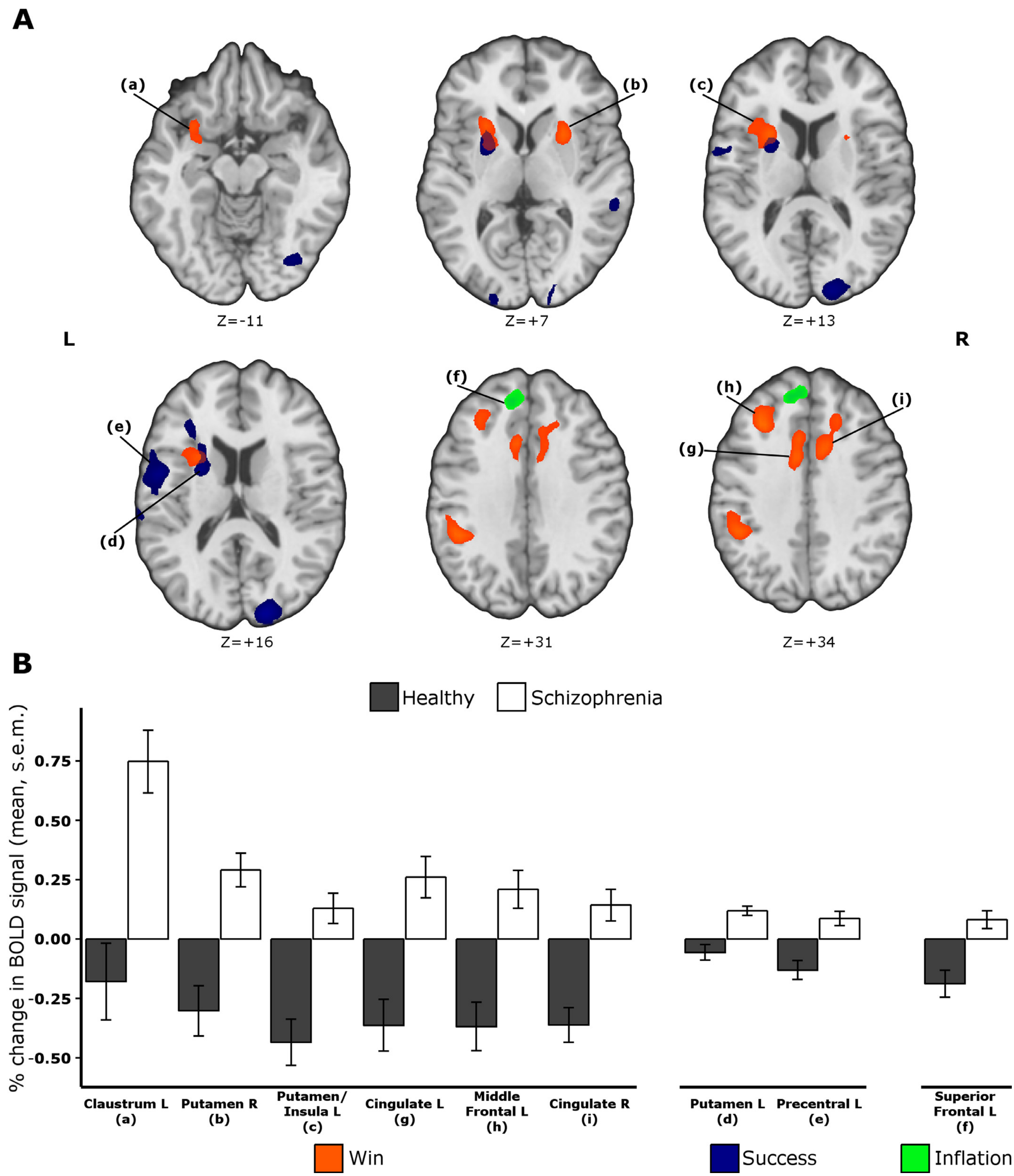

Fig. 2. Hyperactivations in schizophrenia patients in comparison to healthy subjects during risky decision-making. **A.** Between-group differences during the Win event, and **B.** the associated percent change in BOLD signal by group.
Abbreviations: BOLD, blood oxygen dependent signal; L/R, left/right hemisphere.

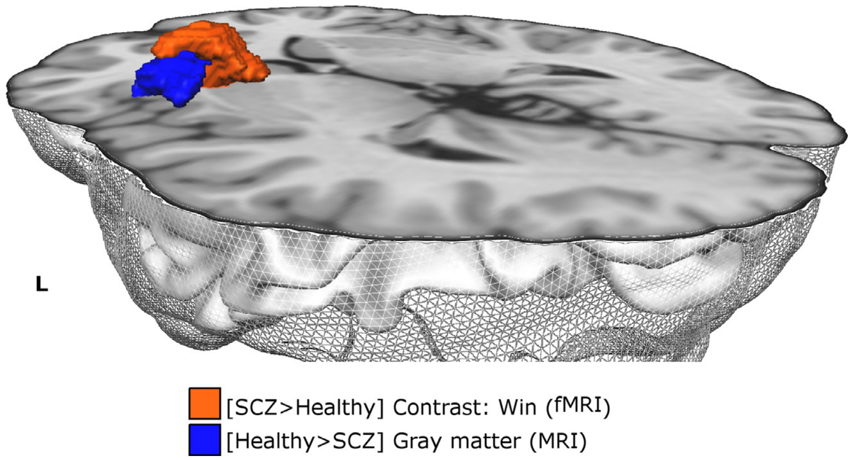

Fig. 3. Left anterior insular structural and functional alteration overlap in schizophrenia.
Abbreviations: MRI, magnetic resonance imaging; fMRI, functional MRI; SCZ, schizophrenia, L, left hemisphere.

$p_{(FWE)} = 0.025$) (Fig. 3). No between-group differences were observed in other ROIs. Schizophreniform or schizoaffective subjects did not differ significantly insular volume from the rest of the SCZ sample.

4. Discussion

To our knowledge, this is the first multimodal neuro-imaging study to employ the BART to investigate both the functional and structural alterations underlying impaired reward-related decision-making in schizophrenia. At the behavioral level, schizophrenia patients displayed risk avoidance, as they made slightly fewer gains and made significantly fewer explosions. Our fMRI analyses revealed functional alterations in schizophrenia patients, notably in the superior frontal gyrus during decision-making, the putamen and precentral gyrus following successful trials, and the bilateral putamen, left insula, bilateral cingulate, superior left claustrum, and middle frontal gyrus when receiving an expected reward [Win event]. We did not observe between-group differences in cerebral activity when assessing Success events *modulated* by the probability of explosion. When examining the Success *modulated* events, we did observe, however, activations across groups in regions such as in the left putamen that are consistent with the results of previous fMRI studies using the BART (Forster et al., 2016; Galvan et al., 2013; Kohno et al., 2015; Schonberg et al., 2012). Structural analyses revealed widespread gray matter volume loss in schizophrenia patients when compared to healthy subjects, especially in medial frontal/orbital as well as bilateral cingular and insular regions. We assessed the conjunction between structural and functional alterations, and found a spatial overlap in the left anterior insula specifically, where decreased gray matter volume corresponded with an altered activation in schizophrenia patients during reward processing, when compared to healthy subjects.

Our results show neuro-functional alterations in schizophrenia in brain regions (i.e. putamen, insula, and cingular cortex) that have been consistently found to be involved in reward-related decision-making in several fMRI studies using the BART (Forster et al., 2016; Galvan et al., 2013; Kohno et al., 2015; Schonberg et al., 2012). These results are coherent with abundant literature in neuroimaging showing striatal alterations during reward processing in schizophrenia, independently of decision-making processes (Strauss et al., 2014). Interestingly, most of the functional differences were observed during the reward outcome events (Success & Win), and not during the choice/decision periods. Furthermore, the differences in activations were observed in the Success event that was not modulated by the probability of explosion. Increased activations were also observed in sub-cortical regions (e.g. striatum & insula) in schizophrenia during the Win event in the BART, which is a well-predicted outcome having reduced rewarding value, since the participants know they have banked the amount of money that was wagered (Schonberg et al., 2012). Taken together, these observations suggest that between-group differences were mostly driven by an overvaluation of outcome stimuli having little biological significance that is present from the start (main event), regardless of gain increases. Although the results of the current study might echo the aberrant salience hypothesis of psychosis (Howes and Nour, 2016; Kapur, 2003), it is important to point out that this hypothesis states that psychosis results from the attribution of motivational value to *irrelevant* stimuli, whereas the current results highlight an over-valuation of stimuli having *low* motivational value. Regardless of these subtle differences, the current results are novel in that they may explain why schizophrenia patients tend to avoid risk in tasks such as the BART (Cheng et al., 2012; Reddy et al., 2014). That is, reward seeking in these patients may be fulfilled more quickly, even by stimuli with low motivational value. Finally, during the decision to Inflate events, schizophrenia patients displayed increased activations in the medial superior frontal gyrus. Previous fMRI studies have shown that this part of the dorso-medial prefrontal cortex plays a key role in action selection (Rushworth et al., 2004), suggesting that increased neurophysiologic effort is required to make reward-related decisions in schizophrenia.

Another relevant finding of this study is the spatial overlap between structural and functional alterations, as measured by VBM and fMRI respectively, in the left anterior insula in schizophrenia patients. Our results are consistent with recent studies investigating reward-related decision-making in healthy subjects using the BART. Indeed, Helfinstein et al. (2014) have observed that BOLD activity patterns in bilateral anterior insula were reliable predictors of the ability to make safe versus risky choices during the BART. Moreover, Nasiriavanaki et al. (2015) reported a positive correlation between the performance on the BART and gray matter volume specifically in the right anterior insula. These studies suggest that reward-related decision-making, as measured by the BART, is related to both structural and functional features of the anterior insula, which is involved in emotion awareness and has connections with structures implicated in reward processing such as the anterior cingulate cortex, prefrontal cortex and the limbic system (i.e. amygdala and striatum) (Namkung et al., 2017). In comparison, the posterior insula has been associated with somatosensory/nociceptive (Segerdahl et al., 2015) and motor information processing (Namkung et al., 2017). The spatial overlap between the functional and structural alterations in this limbic region suggest that anterior insula alterations also pay a key role, along with the striatum, in the impaired ability of schizophrenia patients to make reward-related decisions (Ouzir, 2013). This is an important result given that the spatial overlap is determined within the same pool of participants, especially when a majority of individual neuroimaging studies employing a multimodal approach are unable to establish a spatial correspondence between structure and function in schizophrenia (Isobe et al., 2016). Our main result is coherent with results from Radua et al. (2012) who reported spatially conjoint structural and functional alterations in the anterior insula of first episode psychosis patients in a multimodal neuroimaging meta-analysis of 43 studies (1427 psychosis patients and 1403 healthy subjects).

This study presents certain limitations, as all participants recruited in this study were male. Although this inclusion criterion limits the generalizability of our findings, this choice was based on literature showing sex-differences in decision-making (Reber and Tranel, 2017) and on our objective to reduce sources of heterogeneity. Furthermore, schizophrenia patients were taking antipsychotic medications, which could be a potential confound, as studies have reported that antipsychotic treatment can influence both brain structure (Smieskova et al., 2009) and function (Fusar-Poli et al., 2007). For instance, it has been shown that antipsychotics block dopamine-D_2 receptors in the striatum (Kapur et al., 2000). Therefore, some of our results could be explained by the confounding effects of antipsychotics. To account for the potential effect of antipsychotic medication on our results, olanzapine equivalents were calculated and applied in covariance analyses, and we found that antipsychotics had no influence on our results. In addition, over the quarter of the SCZ sample recruited for this study were schizophreniform or schizoaffective subjects. However, we did not observe significant differences in BART performance and neural activations between these individuals and the rest of the SCZ sample. As for the BART task itself, participants were aware that there were no actual monetary incentives associated with the outcome of the task, although this could have influenced the level to which participants were invested in the task. Unfortunately, no data was gathered on smoking status in the current study. Given that risk-taking is higher in cigarette smokers (Lejuez et al., 2003), the potential confounding effect of smoking status on our result cannot be ruled out. Finally, we could not perform analyses on the explosion events, simply because of their low prevalence. Despite these limits, the results of this study are substantial as they are based on a large sample of schizophrenia patients, using a task that is considered an ecologically valid model to assess reward-related decision-making (Rao et al., 2008), simple to understand, and that allows for the investigation of decision and outcome periods separately (Bogg et al., 2012). Our results are also reinforced by the multimodal coherence of an insular alteration in schizophrenia, which is noteworthy considering the paucity of non-meta-analytic neuroimaging studies that report a spatial overlap between functional and structural dysfunctions in schizophrenia.

To conclude, this is the first multimodal imaging study to investigate reward-related decision-making processing in a large sample of male schizophrenia patients, using the BART. The results indicate increased sub-cortical activations of the striatum and insula during outcome events in schizophrenia patients when compared to healthy subjects, as well as spatially convergent structural alteration in the left anterior insula. As such, these results may underlie the sub-optimal ability to make reward-related decisions in schizophrenia, which is characterized by risk avoidance. Future studies on risky decision-making in schizophrenia will need to pay attention to uncertainty, since decision-making has been shown to be influenced by uncertainty in healthy population, and decision-making under uncertainty has been shown to be impaired in schizophrenia (Fujino et al., 2016). Finally, future studies should seek to compare and/or replicate our results in women.

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Contributors

AT wrote the manuscript, did the brain imaging analysis; AD was involved in study design, patient recruitment and assessment, as well as provided critical comments about the manuscript. OLipp was involved in patient recruitment and assessment, as well as provided critical comments about the manuscript; ES was involved in patient recruitment and assessment, as well as provided critical comments about the manuscript; PL was involved in patient recruitment and assessment, as well as provided critical comments about the manuscript; ML was involved in patient recruitment and assessment, as well as provided critical comments about the manuscript; OLungu was involved in brain imaging analysis and provided critical comments about the manuscript; SP was involved in study design, brain imaging analyses, writing the manuscript, as well as provided critical comments about the manuscript.

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Conflict of interest

A. D. and S. P. are holders of grants from Otsuka Pharmaceuticalsand HLS Therapeuticsunrelated to the current study. A.T., O. Lipp, E. S., P. L., M. L., O. Lungu reported no biomedical financial interests or potential conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pscychresns.2019.03.007.

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