

Binding Action and Emotion in First-Episode Schizophrenia

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Key Words

Basic symptoms · Embodiment · Emotions · Intersubjectivity · Neurosciences · Schizophrenia · Functional magnetic resonance imaging

Abstract

Background/Aims: Several components of social cognition are compromised in schizophrenia (SCZ) from the early stage of the illness. In this study we first investigated whether mirror neuron-driven embodied simulation (mnES) is altered in first-episode SCZ. Second, we tested whether emotional cues impact on the mnES in SCZ patients. **Methods:** Twenty-two SCZ patients and 22 healthy controls (HCs) observed goal-related actions in either a neutral or emotional context during functional magnetic resonance imaging scanning. **Results:** Observation of neutral action elicited a lower activity in the frontoparietal network in SCZ patients, as compared to HCs. Particularly, activation in the left inferior parietal lobule in response to the same condition negatively correlated with patients' self-experience disturbances. Moreover, observation of an action performed by an angry

agent produced poorer neural activity in the right anterior insula in SCZ patients as compared to HCs. This difference was mostly due to the negative β -values shown by SCZ patients, which positively correlated with their empathy scores. No differences were found contingent upon the observation of an action performed by a happy agent. **Conclusion:** Our results show that emotional cues allow SCZ patients to partially recover mnES. However, their understanding of the emotional components of the actions of others will likely remain deficient.

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Introduction

Schizophrenia (SCZ) is associated with multifaceted social deficits characterizing different stages of the illness [1]. Behavioural and neuro-imaging investigations showed that SCZ affects different components of social cognition, such as empathy [2–4], mentalizing [5], self/other distinction [6–8], integration of social cue [9, 10] and emotion processing [11].

Mirror neuron-driven embodied simulation (mnES) has been proposed to have a crucial role in human social cognition [12]. Mirror neurons are motor neurons that are activated not only while performing an action, but also while observing someone else executing the same action. This specific class of neurons was first discovered in macaques' premotor area F5 [13, 14] and, later on, also in the posterior parietal cortex [15], in the primary motor cortex [16] and in the anterior cingulate cortex [17]. The potential relevance of mirror neurons for social cognition becomes clear if their interpretation as the expression of direct form of action understanding is taken into account [18]. Specifically, mnES theory proposes that people pre-reflectively [19] reuse their own mental states or processes represented in bodily format to functionally attribute them to others [15, 20].

Empirical investigations exploring mirror neurons in SCZ yielded contrasting results. Evidence of poorer mnES comes from transcranial magnetic stimulation studies [21, 22] and from magneto-encephalography studies [23, 24]. For example, deficient motor facilitation during action observation relative to the resting state was detected in antipsychotic-naïve SCZ patients as compared with medicated SCZ patients and healthy comparison subjects [22]. Accordingly, a magneto-encephalography study demonstrated that untreated SCZ patients exhibit fewer waveforms and equivalent current dipoles in the right parietal lobe than healthy subjects [24]. In contrast, electroencephalography studies reported intact [25] or increased [26] μ -wave suppression (representing greater mnES) in SCZ patients when compared with healthy participants. The contrasting results across these studies may be due to several reasons, such as differing sample sizes and methods used, different impact of positive and negative symptoms within the studied patients' cohort, as well as effect of medications.

However, mnES of action would be only one of different components of social cognition affected by SCZ, as said above. Recent research has focused on another side of social abnormalities in SCZ patients, that is emotional disturbances. Patients experience emotions, particularly negative ones, more than healthy individuals and more than would be expected from their decreased affective expressivity. Deregulated affective states often characterize SCZ patients from the prodromal stages of the disorder and are conceived as an important target for interventions [27]. Moreover, one of the most explored emotional deficits in these patients concerns facial emotion recognition. There is large consensus in the literature that patients are generally less accurate than healthy controls

(HCs) in recognizing emotions [27–30]. Interestingly, however, studies examining emotion/cognition interactions in SCZ – i.e. how much emotional distractors affect task performance [31–33] – have suggested increased effects of emotion interference in SCZ. In other words, while performing a task, patients seem to rely on salient emotional cues more than HCs. Such aberrant responsiveness to affective contextual information likely contributes to patients' impairments in social cognition and behaviour.

During everyday life, emotions play an important role in shaping social interchange. Emotional colouring frequently characterizes motor behaviours. Thus, action and emotion understanding are both crucially relevant for grasping another's intention in social contexts. Finally, emotions are often motivators of (inter-)actions. In a recent functional magnetic resonance imaging (fMRI) study [34] we investigated whether an emotion (happiness, anger or neutral) dynamically expressed by an observed agent modulates brain activity underlying the perception of his/her grasping action. Results showed that the observation of grasping actions embedded in an emotional context elicits a higher neural response at the level of motor frontal cortices, temporal and occipital cortices, bilaterally. Particularly, the dynamic facial expression of anger modulates the re-enactment of a motor representation of the observed action as suggested by the stronger activity in the bilateral precentral gyrus (PCG) and inferior frontal gyrus (IFG). In the present study, we used the same experimental paradigm to investigate the impact of emotional information on action processing in first-episode SCZ patients. Our aim was not to test the patients' ability to recognize emotions (participants were trained to recognize the presented emotions before the scanning session); rather, we wanted to investigate how emotional information is integrated with that pertaining observed action in first-episode SCZ patients. Moreover, we were interested in exploring how action perception is modulated by emotional cues in the same patients, as compared to HCs.

Four possible scenarios could be predicted. (1) Both mnES and responses to emotional cues are not altered in first-episode SCZ patients. No difference should be observed in this case between patients' and HCs' neural responses during the observation of actions embedded in emotional contexts. (2) Only responses to emotional cues are altered in first-episode SCZ patients. In this case, neural responses to actions embedded in a neutral context should not differ between the two groups, whereas neural responses to actions embedded in emotional contexts

Table 1. Demographic information about the SCZ patients and HCs

	HC	SCZ
Age, years	28±3.77	27.45±5.07
Time from psychotic episode, months	n.a.	7.5±5.08
IQ	122±13.08	107±8.43
Handedness score	70.2±15.17	62.43±20.05
Male/female	12/10	14/8
Diagnosis	n.a.	first-episode psychosis
SCID-II cluster A	negative	n.a.
SCID-II cluster B	negative	n.a.
SCID-II cluster C	negative	n.a.
PANSS positive scale	n.a.	13, 14, 13, 8, 11, 10, 12, 9, 13, 11, 10, 9, 13, 17, 19, 16, 16, 17, 12, 0, 18, 15 (12.54±4.17)
PANSS negative scale	n.a.	22, 16, 11, 9, 12, 8, 8, 10, 13, 9, 10, 9, 14, 15, 11, 24, 11, 10, 9, 0, 12, 22 (12.04±5.34)
PANSS general psychopathology scale	n.a.	25, 25, 23, 19, 22, 19, 22, 20, 24, 21, 20, 20, 25, 26, 25, 37, 24, 18, 20, 0, 22, 35 (22.36±6.85)
SPI-A total score	n.a.	127, 70, 91, 71, 3, 91, 34, 23, 97, 15, 6, 19, 12, 15, 56, 73, 35, 21, 27, 72, 74, 81 (50.59±35.52)
Medication	n.a.	6 quetiapine, 7 risperidone, 4 paliperidone, 2 aripiprazole, 3 olanzapine ¹

Data are expressed as means ± SD or numbers. n.a. = Not available; SCID-II = Structured Clinical Interview for DSM-IV Axis II Disorders; SPI-A = Schizophrenia Proneness Instrument.

¹ Chlorpromazine equivalent mean dose = 480 mg/day, SD = 400.22 (calculated on 18 patients because no equivalents are available for paliperidone).

should do. (3) Only mnES is altered in first-episode SCZ patients. In this case, neural responses to actions embedded in a neutral context should differ between the two groups, whereas neural responses to actions embedded in emotional contexts may or may not differ. In particular, it is possible to hypothesize that patients, as they strongly rely on salient emotional cues, can recover their response to action observation when emotional information is available. (4) Both mnES and responses to emotional cues are altered in first-episode SCZ patients. In this case, we should observe entirely different neural response patterns between patients and control participants during the observation of actions embedded both in neutral and emotional contexts. Previous studies have shown a poorer ability of SCZ patients in recognizing both actions [21–24] and emotions [27–30] as compared to HCs. Based on these data we favour the hypothesis that both mnES and responses to emotional cues are altered in first-episode SCZ patients.

Materials and Methods

Participants

Twenty-two SCZ patients and 22 HCs (15 of the HC participants were the same as those reported in our previous study [35]) were included in the present study (table 1). Patients were diagnosed according to the Structured Clinical Interview for DSM-IV. Exclusion criteria for all participants comprised significant medical or neurological illness, substance abuse or dependence in the previous 6 months, IQ <85, and, for the HC group, a personal history of axis I/II disorders or a history of psychosis in first-degree relatives. SCZ and HC groups were matched for age and gender. SCZ patients were recruited from outpatient services at Chieti Mental Health Department. The mean illness duration was 7.5 ± 5.1 months. The SCZ group had intellectual capacities in the range of the average healthy population (IQ mean scores = 107 ± 8.4). Chlorpromazine equivalents were calculated [34, 36] for antipsychotics (table 1). The Ethics Committee of the University of Chieti approved the study. Written informed consent was obtained from all participants after full explanation of the procedure of the study, in line with the Declaration of Helsinki.

Evaluation Scales

SCZ patients were evaluated by the Structured Clinical Interview for DSM-IV axis I disorders [37], rated for symptom severity

with the Positive and Negative Symptom Scale (PANSS) [38] and evaluated for the presence of basic symptoms (BSs) [39] by means of the Schizophrenia Proneness Instrument [39] by two trained psychiatrists. HC participants were evaluated by means of the Structured Clinical Interview for DSM-IV axis II personality disorders [40]. SCZ patients were also required to complete the empathic quotient (EQ) questionnaire [41]. Evidence of the reliability and validity of the EQ has been reported in persons without psychosis [42]. A systematic investigation of the reliability and validity of the EQ in persons with psychosis is still lacking. However, for previous use of the EQ with participants diagnosed with SCZ see, for example: Bora et al. [43], Koelkebeck et al. [44], Konstantakopoulos et al. [45] and Lysaker et al. [46].

fMRI Data Acquisition

All images were collected with a 1.5-tesla Philips Achieva scanner operating at the Institute of Advanced Biomedical Technologies (ITAB G. d'Annunzio, Chieti, Italy). Functional images were acquired with a gradient echo echo-planar imaging sequence. Each subject underwent 4 scans, each including 216 consecutive volumes comprising 26 consecutive ascending 4-mm-thick slices oriented parallel to the anterior-posterior commissure and covering the whole brain (TR = 2.4 s, TE = 50 ms, 64 × 64 image matrix, 4 × 4 mm in-plane resolution; FOV = 256 mm, no gap). A high-resolution structural image was acquired at the end of the session via a 3-dimensional magnetization-prepared rapid acquisition gradient echo pulse sequence (170 sagittal slices, voxel size: 1.25 × 1.25 × 1.20 mm, TR = 8.6 ms, TE = 4.0 ms, 192 × 192 image matrix, FOV = 240 mm).

Stimuli and Conditions

The experimental stimuli consisted of 3 sets of colour videos: (1) 'emotion action', showing an actor (torso, face and arms of either a male or a female) grasping 1 of 4 different objects (bottle, pencil case, receiver or CD case placed on a table) with the right hand and facially expressing anger, happiness or no emotion; (2) 'emotion', showing only the face of the actor (either a male or a female) expressing anger, happiness or no emotion, and (3) 'action', showing only the hand action (the field of view was such that the face did not appear). Hence, the experiment comprised the following 7 conditions: (1a) angry action (AA, the actor grasped an object expressing anger); (1b) happy action (HA, the actor grasped an object expressing happiness); (1c) neutral action (NA, the actor grasped an object with a neutral facial expression); (2a) angry face (AF, expression of anger); (2b) happy face (HF, expression of happiness); (2c) neutral face (NF, a face expressing no emotion); (3) action (one of the objects being grasped). All the emotion and action conditions were dynamic. The actors in the video clips were seen from a frontal point of view. Actors and different types of objects were presented in equal proportions. Two professional actors, a female and a male, were enrolled as models for the videos [47]. The sex of the actor was counterbalanced across conditions. The kinematics of all the presented hand actions was identical in order to avoid that the action emotional context could be inferred by hand kinematics. To obtain such an identity, we applied the blue screen technique, that is a technique for compositing two images or frames together in which a colour (or a small colour range) from one image is removed (made transparent), revealing another image behind it. It was applied to our stimuli in order to superimpose on the same trunk different dynamic facial expressions.

Design and Procedure

The rapid event-related fMRI paradigm consisted of 4 scans. In each scan 12 videos were presented for each of the 7 experimental conditions (AA, HA, NA, action, AF, HF, NF). Each video lasted 1,800 ms and was preceded by a randomized, non-predictable inter-trial interval ranging from 2,000 to 5,000 ms during which a black fixation cross was presented at the centre of a white screen (fig. 1). Participants were instructed to carefully watch the whole scene. To make sure participants paid attention to the experimental stimuli, 8 control trials were randomly inserted in the video sequence of each scan. These unpredictable trials were followed by a question mark lasting 2,000 ms followed by a written request (6,000 ms) to imitate either the action (4 trials) or the emotion (4 trials; fig. 1). In total, our experiment consisted of 336 passive observation trials (48 for each experimental condition) and 32 imitation trials (16 for actions and 16 for emotions), presented in a pseudorandomized order.

Participants lay supine in the scanner with the arms outstretched beside the abdomen. Visual stimuli were projected onto a backprojection screen situated behind the subject's head and were visible in a mirror (10 × 15 cm). Sound-attenuating headphones were used to muffle scanner noise. Participants were instructed to carefully watch the whole scene.

fMRI Data Preprocessing and Analysis

fMRI data were preprocessed and analysed using SPM8 (Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK). For each participant, functional images were first spatially corrected for head movements using a least-squares approach and 6-parameter rigid body spatial transformations [48]. The realigned functional images were then corrected for difference in timing between slices, using the middle slice acquired in time as a reference. The high-resolution anatomical image and the functional images were coregistered and then stereotactically normalized to the Montreal Neurological Institute brain template used in SPM8. Functional images were resampled with a voxel size of 3 × 3 × 3 mm and spatially smoothed with a 3-dimensional gaussian filter of 8 mm full width at half maximum to accommodate anatomical variations between subjects [48]. Images were subsequently analysed using a random-effects approach. At the first stage, the time series of functional MR images obtained from each participant were analysed separately. The effects of the experimental paradigm were estimated on a voxel-by-voxel basis, according to the general linear model extended to allow the analysis of fMRI data as a time series [49]. The onset of each trial constituted a neural event that was modelled through a canonical haemodynamic response function, chosen to represent the relationship between neuronal activation and blood flow changes [50]. Imitation and question mark periods were modelled as separate conditions and then excluded from further analyses.

These single-subject models were used to compute 7 contrast images per subject, each representing the estimated amplitude of the haemodynamic response in 1 of the 7 experimental conditions (AA, HA, NA, action, AF, HF, NF), relative to the inter-trial baseline. These contrast images were used (i) to test the effect of emotional context on action observation in both populations separately and (ii) to directly compare SCZ and HC. The effect of emotional context on action observation in both populations separately was analysed by means of whole-brain voxel-wise contrasts. In particular, in each population we investigated cortical

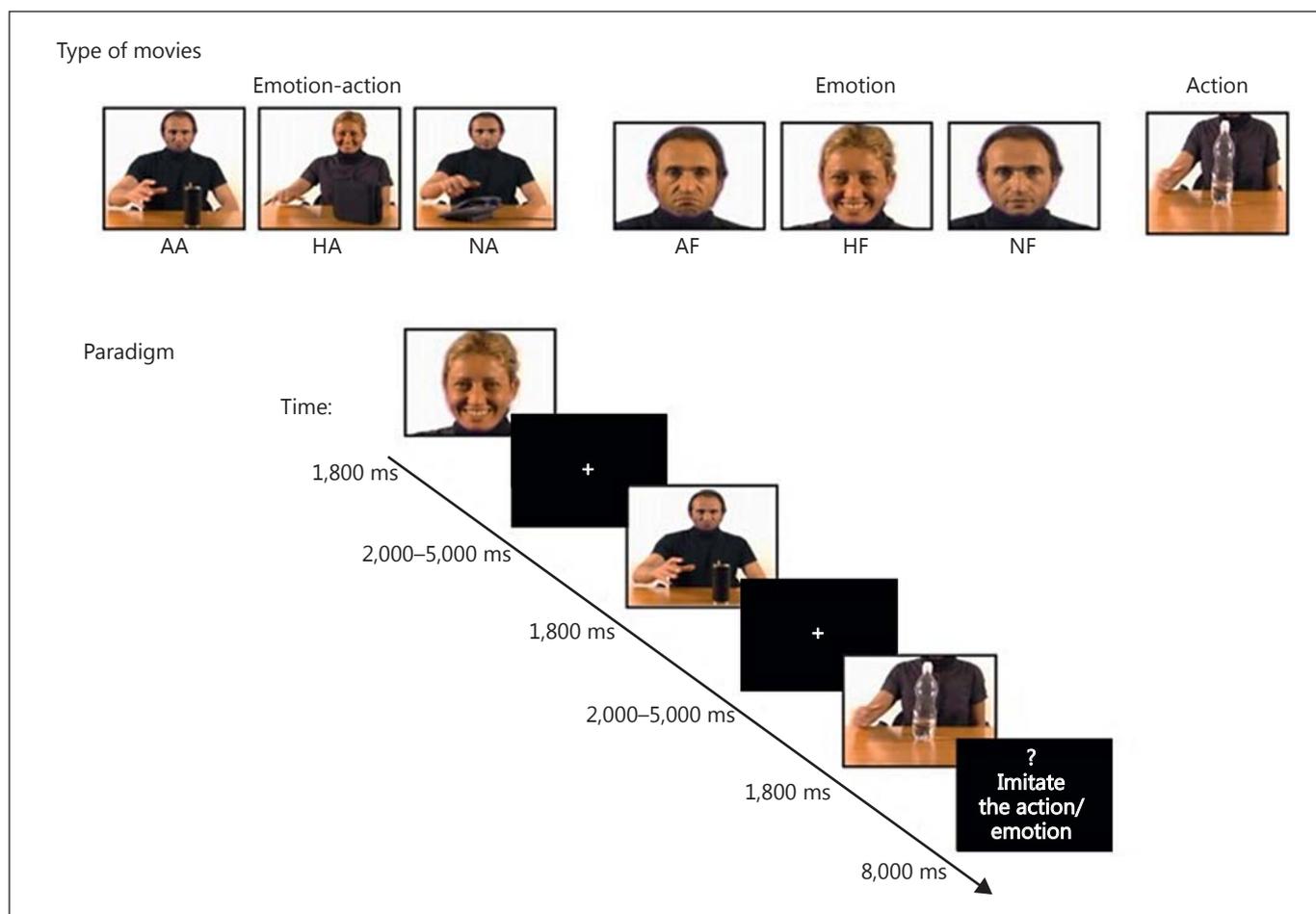


Fig. 1. Examples of the 3 sets of colour videos used in the visual stimulation. Lower panel: description of the experimental paradigm.

regions differentiating between observation of actions embedded in emotional contexts as compared to actions embedded in neutral context. To this aim, AA \neq NA and HA \neq NA comparisons were performed ($p < 0.05$ false discovery rate). It should be noted that such contrasts also control for low-level visual activations.

To test for group differences in the integration of the action with the emotion, we compared, across populations, the neural responses to the observation of AA, HA and NA, relative to the intertrial baseline.

To further investigate whether the difference between SCZ and HC controls relies more on the neural response to the observation of the action alone, the emotion alone or the integration between the two, we adopted the procedure described below. For each area showing differential responses to AA, HA and NA conditions, between SCZ and HC, we extracted the β -values contingent upon the observation of the action alone, and the emotion alone (anger, happy and neutral, respectively). Then, we performed 2-sample t test analyses (action vs. emotion) on regionally averaged estimated β -values. The aim of this analysis was to make sure that response patterns to action and emotion did not show between-group dif-

ferences. Only in this case any differential responses to AA, HA and NA conditions, between SCZ and HC, would not be confounded by between-group differences in the response to either a body alone, as tested in action, or a face alone, as tested in emotion. Note that there is no circularity (i.e. double dipping) [51] in this analysis, because t tests were performed between conditions we did not use for region of interest selection. We also performed 1-sample t tests on the same regions to test whether the single experimental conditions were significantly different from the intertrial fixation baseline.

Then, β -values of the individual patients extracted from the brain regions showing differential activation patterns between the HC and SCZ were correlated with the EQ score, the Schizophrenia Proneness Instrument scores and PANSS. To test for independence of PANSS and Schizophrenia Proneness Instrument, we ran partial correlations between the two scales. To control for possible outliers, robust regressions [52] implemented in Matlab were also performed. Robust regression methods are indeed less sensitive than ordinary least squares, to large changes in small parts of the data. Finally, β -values of the individual patients extracted from the

Table 2. Montreal Neurological Institute coordinates of peaks of relative activation in the cortical regions where the blood oxygen level-dependent signal was significantly different during observation of action-emotion versus NA in HCs and SCZ patients

Anatomical region	Side	Main local maxima							
		HC				SCZ			
		x	y	z	z-score	x	y	z	z-score
<i>AA versus NA</i>									
OC	L/R	-24	-99	-3	9.97				
MTG/STS	R	57	-45	3	4.60	66	-45	9	3.45
	L	-51	-45	9	5.05	-60	-45	18	4.31
PCG	R	51	6	39	3.84				
SMA/pre-SMA	L	-3	6	66	4.35	-6	-3	72	3.78
IFG – insula	L	-36	12	24	3.78	-51	9	-6	4.60
						-39	-36	30	4.25
						51	24	33	4.16
MFG/IFG (opercular-triangular)	R					33	54	0	4.03
						33	24	-9	3.40
SFG	L					-15	12	63	3.45
IPL	L					-48	-42	45	3.66
<i>HA versus NA</i>									
OC	R	33	-93	-6	3.52				
LG	R	21	-66	-6	4.27				
FG	L	-36	-63	-12	4.50				
MTG/STS	R	54	-45	9	5.28				
	L	-54	-42	9	5.27				

SMA = Supplementary motor area; MFG = middle frontal gyrus; SFG = superior frontal gyrus; IPL = inferior parietal lobe; LG = lingual gyrus; FG = fusiform gyrus.

brain regions showing differential activation patterns between the HCs and SCZ patients were also correlated with chlorpromazine equivalence values to test for unspecific drug-driven effects.

Results

Neural Mapping of Observing AAs and HAs Compared to NAs in HCs and SCZ Patients

Due to data corruption 1 HC was discarded from the analysis. When contrasting the effect of observing either AA or HA with NA in HCs (AA ≠ NA or HA ≠ NA, respectively), the following activation differences were found. Regarding AA relative to NA, higher activation was found in the left IFG (pars triangularis and pars opercularis), left pre-supplementary motor area (SMA), right inferior PCG, middle temporal gyrus/superior temporal sulcus (MTG/STS) bilaterally and left middle optic chiasm (OC). Regarding HA, relative to NA, higher activation was

found in the MTG/STS, left fusiform gyrus, right lingual gyrus, middle and inferior OC bilaterally (table 2; fig. 2).

The same contrasts while comparing AA relative to NA in SCZ patients revealed the following: higher activation in the left IFG encompassing the insula, the SMA, MTG/STS, the right middle frontal gyrus encompassing the pars opercularis and triangularis of the IFG, the left superior frontal gyrus and the left inferior parietal lobe. No voxels turned out to be significant in the contrast HA ≠ NA.

Group Differences in the Neural Activity while Observing NAs

While comparing the neural activity contingent upon the observation of an actor grasping the object with an NF, HCs showed higher activation, as compared to SCZ patients in the following areas: bilateral middle frontal gyrus, the right IFG (parts orbitalis, opercularis and triangularis), the left PCG and the left inferior parietal lobe (table 3; fig. 3).

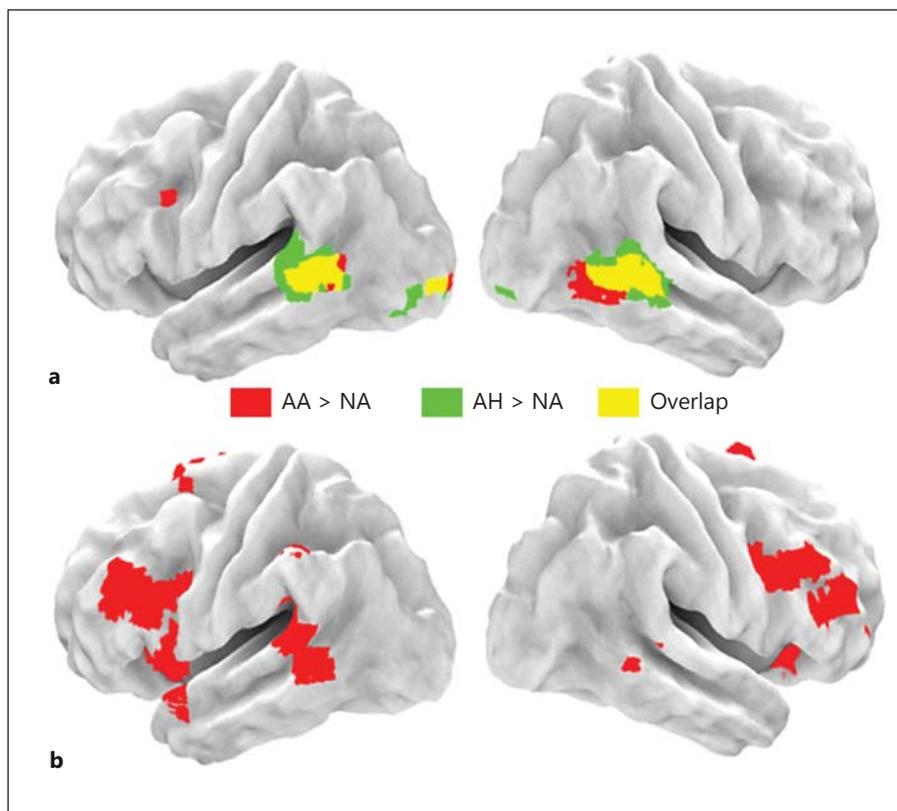


Fig. 2. Regions activated either in AA versus NA contrast (red; colours in the online version only) or in HA versus NA (green) contrast in HCs (a) and SCZ patients (b). $p < 0.05$, false discovery rate corrected.

Table 3. Montreal Neurological Institute coordinates of peaks of differential activation between HCs and SCZ patients

Anatomical region	Side	Main local maxima			
		x	y	z	z-score
AA					
IFG – insula	R	39	24	-9	4.85
NA					
Middle frontal gyrus	R	33	45	18	4.36
	L	-30	45	33	4.57
		-45	51	0	4.48
IFG – orbital	R	36	24	-9	4.56
	L	-33	30	-6	3.91
IFG – triangular	R	48	36	15	3.64
IFG – opercular	R	48	15	30	4.28
PCG	L	-45	6	42	4.21
Inferior parietal lobe	L	-45	-33	36	4.38

Increased activations in HCs were generally due to negative β -values in SCZ patients, which significantly differed from baseline (table 4), except for the PCG.

Two-sample t tests aimed at identifying the source of the difference between HC and SCZ patients are described below for each area. Detailed statistics are reported in table 4.

Right Middle Frontal Gyrus

In both HCs and SCZ patients the activation due to observation of the action alone did not differ from that of the observation of the NF alone. Visual inspection of the data though suggested higher activation in HCs as compared to SCZ patients. To statistically examine this observation, we tested whether estimated β -values in the two conditions of interest were significantly activated with respect to the intertrial fixation baseline in both populations. The estimated β -value in the NF alone condition was higher than zero in HCs but not in SCZ patients (fig. 3; table 4). Differently, estimated β -values in the action alone condition did not differ from the intertrial fixation baseline in both populations.

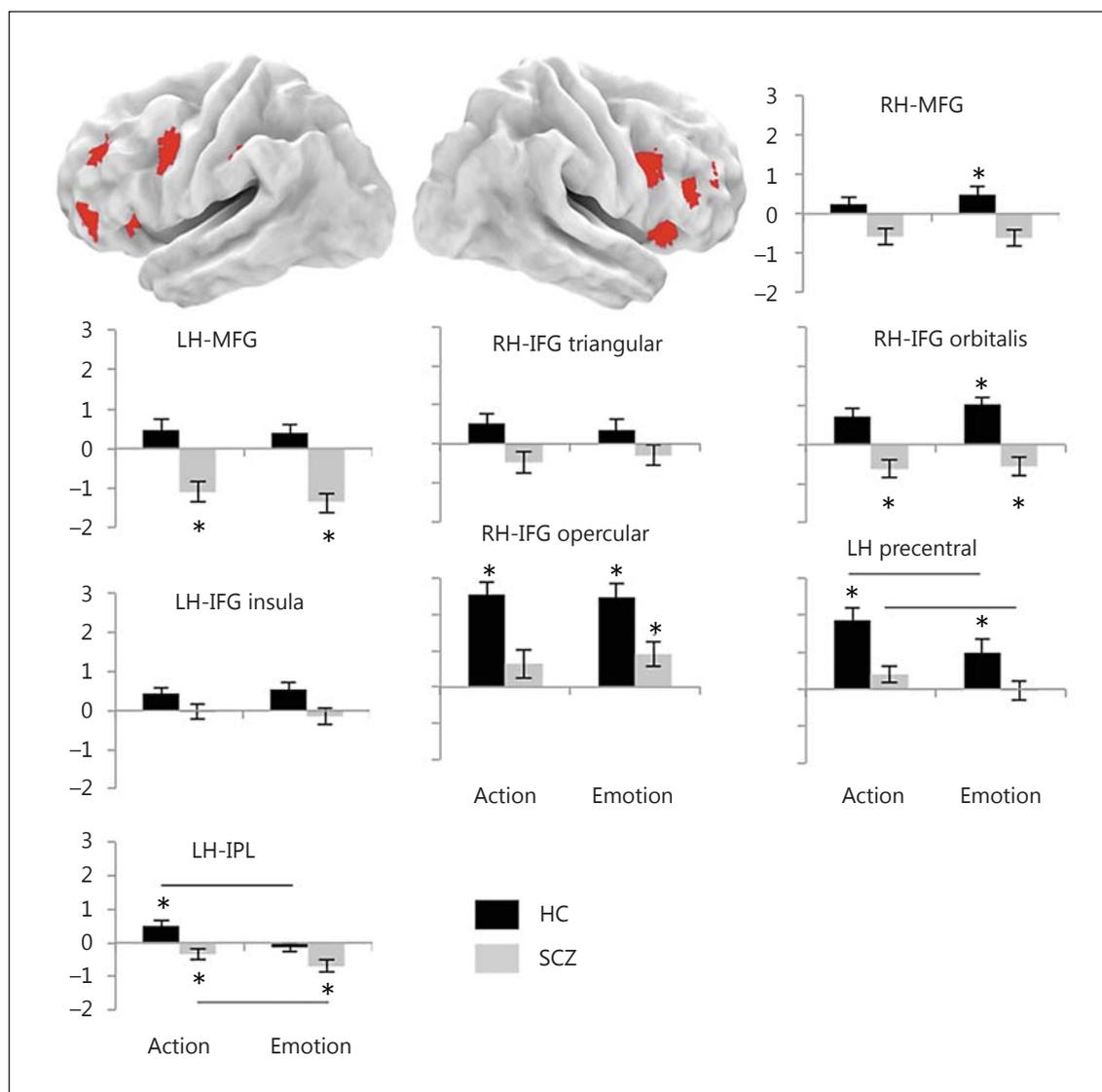


Fig. 3. Regions of relatively higher activation (and estimated β -values) in HCs as compared to SCZ patients during observation of the NA. Group activation data are rendered on the cortical surface of a 'canonical' brain [81]. MFG = Middle frontal gyrus; LH = left hemisphere; RH = right hemisphere; IPL = inferior parietal lobe. Asterisks indicate β -values significantly higher than the intertrial fixation baseline. Bars indicate significant differences between conditions.

Left Middle Frontal Gyrus

In both HCs and SCZ patients the activation due to observation of the action alone did not differ from that of the observation of the NF alone. The difference between the two groups was due to the fact that only in SCZ patients was the activity in this area significantly lower in both the action alone condition and the NF alone condition with respect to the intertrial fixation baseline (fig. 3; table 4).

Right IFG – Opercular

In both the HCs and the SCZ patients the activation due to observation of the action alone did not differ from that of the observation of the NF alone. However, while in HCs both experimental conditions activated this region with respect to the intertrial fixation baseline, in SCZ patients only the observation of the NF alone produced a reliable activation as compared to baseline (fig. 3; table 4).

Table 4. Estimated β -values (SD in parentheses) in the action and emotion (NF) experimental conditions

Anatomical region	Side	HC			SCZ		
		action	emotion	p value	action	emotion	p value
Middle frontal gyrus	R	0.26 (0.75)	<i>0.48 (1.03)</i>	0.15	-0.59 (0.99)	-0.61 (1.02)	0.87
	L	0.45 (1.37)	0.38 (1.06)	0.77	<i>-1.12 (1.07)</i>	<i>-1.36 (1.25)</i>	0.23
IFG – opercular	R	<i>2.56 (1.61)</i>	<i>2.47 (1.72)</i>	0.11	<i>-0.62 (1.08)</i>	<i>-0.55 (1.11)</i>	0.71
IFG – orbital	R	<i>0.71 (0.92)</i>	<i>1.01 (0.93)</i>	0.75	0.63 (1.81)	<i>0.89 (1.58)</i>	0.38
	L	<i>0.43 (0.74)</i>	<i>0.53 (0.95)</i>	0.58	-0.03 (0.91)	-0.15 (1.01)	0.53
IFG – triangular	R	0.52 (1.20)	0.37 (1.18)	0.39	-0.46 (1.32)	-0.30 (1.23)	0.58
PCG	L	<i>1.85 (1.66)</i>	<i>0.98 (1.79)</i>	<i>0.012</i>	0.40 (1.03)	-0.05 (1.18)	<i>0.015</i>
Inferior parietal lobe	L	<i>0.49 (0.75)</i>	-0.14 (0.54)	<i>0.001</i>	-0.33	-0.70	<i>0.007</i>

Values in italics are significantly different from the intertrial fixation baseline (1-sample t tests); p values refer to the statistics of the 2-sample t tests (action vs. emotion) performed for each group.

Right IFG – Orbitalis

In both the HCs and the SCZ patients the activation due to observation of the action alone did not differ from that of the observation of the NF alone. Similarly, in both populations neural activity was significantly different in the experimental conditions as compared to the intertrial fixation baseline. Differently, though, while in HCs this activity was positive, in SCZ patients it was negative (fig. 3; table 4).

Right IFG – Triangularis

In both the HCs and the SCZ patients the activation due to observation of the action alone did not differ from that of the observation of the NF alone. The difference between HCs and SCZ patients consisted in an opposite pattern of activation. Indeed, while HCs had positive β -values in both experimental conditions, SCZ patients had negative β -values (fig. 3; table 4).

Left PCG

In HCs the left PCG was more activated by the observation of action alone as compared to the observation of the NF alone. Differently, in SCZ patients the two conditions did not differ from each other. Also, only in SCZ patients did neither the observation of the action nor the observation of the face activate this area (fig. 3; table 4).

Left IFG

In both the HCs and the SCZ patients the activation due to observation of the action alone did not differ from that of the observation of the NF alone. However, while

in HCs both experimental conditions activated this region with respect to the intertrial fixation baseline, in SCZ patients β -values did not differ from the intertrial fixation baseline (fig. 3; table 4).

Left Inferior Parietal Lobe – Supramarginal Gyrus

In both the HCs and the SCZ patients the activation due to observation of the action alone differed from that of the observation of the NF alone. Different patterns of activation were observed though. Indeed, in HCs the inferior parietal lobe was activated by the observation of action alone but not by the observation of the NF alone. Conversely, in SCZ patients it was significantly deactivated in both experimental conditions (fig. 3; table 4).

Group Differences in the Neural Activity while Observing AAs and HAs

IFG – Insular Cortex

While comparing the neural activity contingent upon the observation of an actor grasping the object with an AF, we found higher activation in the right IFG insular cortex in HCs as compared to SCZ patients. Two-sample t tests aimed at identifying the source of this difference revealed that in HCs the observation of the AF (β -value = 1.18) activated this area more than the observation of the action alone (β -value = 0.46, $p < 0.05$). Conversely, in SCZ patients the two conditions did not differ from each other (fig. 4). Also, note that in SCZ patients β -values were negative as compared to the intertrial fixation baseline, while in HCs they were positive. No other voxels turned out to be significant (fig. 4).

Fig. 4. **a** Group differences in the neural activity while observing AA. **b** Estimated β -values in the action alone and emotion alone conditions in HCs and SCZ patients. **c** Correlation between estimated β -value in the right anterior insula and EQ scores in SCZ patients. The line represents the linear best fit; r refers to the coefficient of correlation. The correlation survived also the robust fit correlation. Asterisks indicate β -values significantly higher ($p < 0.05$) than the intertrial fixation baseline. Bars indicate significant differences between conditions.

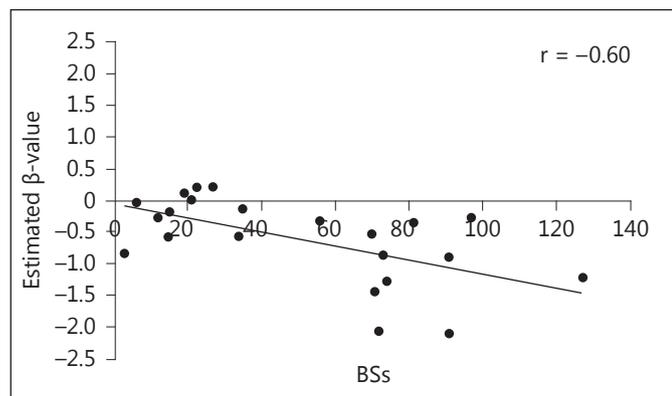
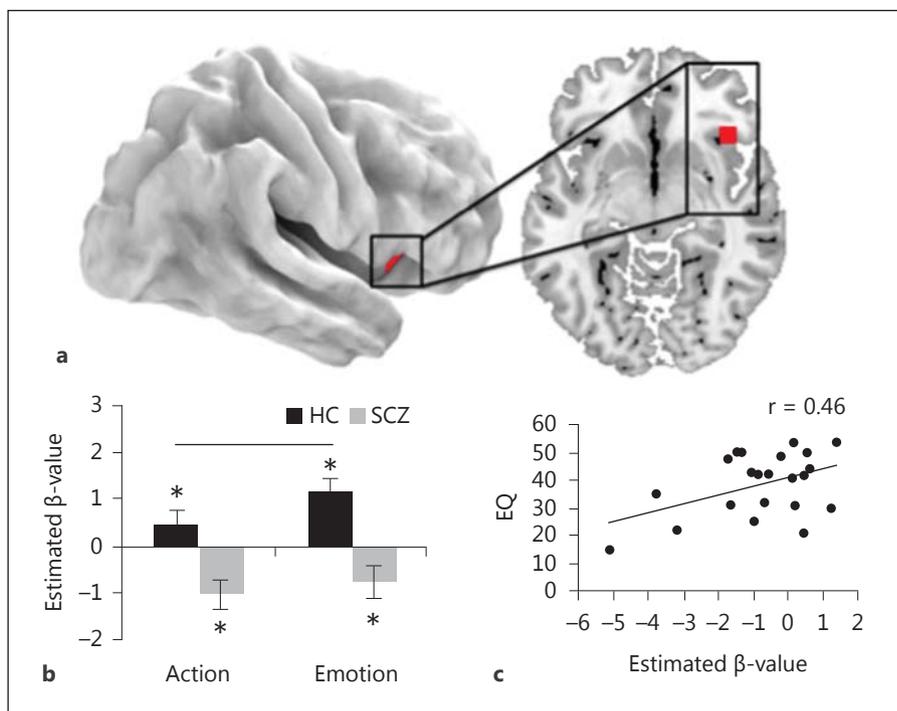


Fig. 5. Correlation between estimated β -value in the left inferior parietal lobe and the Schizophrenia Proneness Instrument scores. The correlation survived also the robust fit correlation.

No differences were found contingent upon the observation of HAs.

Correlations between Differential Brain Activity with EQ Scores, Schizophrenia Proneness Instrument Scores, PANSS and Chlorpromazine Equivalences

Discovering the possible relation between measures of empathy and symptomatology as measured by the Schizo-

phrenia Proneness Instrument scores and PANSS, and neural activity contingent upon the observation of actions performed in either a neutral or an emotional context is crucial for understanding the nature of the phenomena called into play in our experimental conditions. We found that the activation of the left inferior parietal lobe (i.e. supramarginal gyrus), while observing the NA, was negatively correlated with the total score to the Schizophrenia Proneness Instrument ($r = -0.60$, $p < 0.01$; fig. 5). This correlation remained significant also controlling for the PANSS score, thus suggesting that the two scales operationalize different aspects of the psychopathology. PANSS scores did not correlate with the blood oxygen level-dependent signal in any activated cortical region.

We also found that the activation of the right anterior insula while observing the AA was positively correlated with the EQ ($r = 0.46$, $p < 0.05$; fig. 4). Both correlations survived the robust regression analysis.

Finally, no significant covariance effect was found for chlorpromazine equivalences in the SCZ patients, suggesting that there was no linear relationship between medication dose and differential activation between the HCs and SCZ patients.

Discussion

The present study aimed at investigating whether and how emotional cues modulate brain activity underlying action processing in first-episode SCZ patients, as compared to HCs. Facial expression of emotions, in particular, may cue intentions behind actions. That might facilitate embodied simulation and trigger an appropriate reaction [35]. In the present study we presented grasping actions either associated (HA, AA) or not (NA) with emotional cues (i.e. dynamic facial expression of emotions). These experimental conditions allowed us to test whether mnES per se or its modulation by contextual information is impaired in SCZ patients.

mnES in SCZ

Previous studies investigating potential alterations of mnES in SCZ showed contrasting results [53–58]. Possible explanations of such incongruities may relate to differing sample sizes, medications, different impact of positive and negative symptoms within the studied patients' cohort, and methods used across studies. Other critical sources of conflicting findings might concern different tasks and stimuli used in each investigation, as well as different contexts in which actions were presented. Indeed, mnES seems to be modulated by contextual information, for example, pragmatic [59] and emotional [35].

We found differences in mnES between SCZ patients and healthy participants already for the observation of NA, that is when emotional cues were not provided by the context. Such differences mainly involved the frontoparietal network critical for action representation [60–62], such as the IFG, PCG and inferior parietal lobe.

Imaging data in humans suggest a role of the IFG and PCG in coding the motor goal of the action [63] and, from another perspective, in the understanding of the agent's motor intention, driven by the context in which the action is embedded [59]. Moreover, data from action imitation and observation studies [59, 64] demonstrate that the inferior parietal lobe, in addition to the IFG, is involved in coding the abstract aspects of actions (such as their motor intention). According to the previous literature and based on our data, we would then conclude that all these aspects of action processing are affected in SCZ patients.

Interestingly, activation in the inferior parietal lobe in these patients correlated negatively with BS severity, as assessed by the Schizophrenia Proneness Instrument: activation in the inferior parietal lobe decreased with augmented symptom severity. This relationship was found between NA observation conditions and BS severity, but

not with observation of actions embedded in emotional contexts. The detected relationship between cortical processes and BSs highlights the clinical relevance of the results, especially concerning preventive approaches and early diagnosis. BSs can occur and have been reported in every stage of the illness, i.e. in the prodrome to the first psychotic episode, in prodromes to relapse, in residual states and even during psychotic episodes per se [65]. Moreover, BSs represent a link between a phenomenological approach to psychopathology and a categorical approach based on positive and negative symptoms. Specifically, BSs could gradually increase in number and severity, even many years before psychosis onset, and finally develop into psychotic symptoms, such as negative and positive symptoms [39, 65]. Interestingly, we did not detect any relationship between activation patterns and positive and negative symptoms, and the correlation between altered activation patterns in SCZ and BSs was independent of positive and negative symptoms. This may underscore the relevance and specificity of BSs, tapping into distinct neural mechanisms. A possible alternative explanation is that the included SCZ patients had a very recent illness onset and relatively low PANSS scores.

Finally, as BSs represent subjective experiential disturbances in the domains of cognition, perception, bodily experience, action and affective states [66, 67], our results support a close and specific link between self-experience anomalies and mnES, which supports intersubjective relationships in social everyday life [20, 68, 69].

All these findings are consistent with those previously obtained by Ebisch et al. [6], which showed activation in the ventral premotor cortex for the observation of interpersonal touch decreasing with increased BS severity. A subsequent study [70] demonstrated a link between BS severity and functional connectivity of the ventral premotor cortex with the posterior cingulate cortex, a brain region central in mediating self-experience, further suggesting a deranged relationship between an afflicted self and its social environment underlying certain social cognition deficits in SCZ.

Interestingly, however, embodied simulation and BS severity have not always been found to negatively correlate in first-episode SCZ patients. Ferri et al. [71] indeed found that patients with severer symptomatology show a prolonged higher efficiency than HCs, in processing action-related verbs. According to the authors, this result would indicate that neural activity supporting embodied simulation during action-verb understanding is not itself reduced in SCZ. Possible alterations may be related to hierarchically higher-order processes, involved in the cog-

nitive top-down control of action representations [62, 72, 73].

However, evidence about the relation between BS severity and embodied simulation in SCZ is not necessarily conflicting. Rather, it can be explained by considering the multifaceted nature of embodied simulation itself. Embodied simulation theory endorses the emphasis on reuse as the core notion of mental simulation. It posits that brain and cognitive resources typically used for one purpose are reused for another purpose [74]. The same concept would apply to different states, such as action observation, motor imagery, language, perception of emotion or sensation of another. Reuse of different brain and cognitive resources in all these conditions might be differently affected by SCZ. SCZ, thus, might also represent an appropriate model to evaluate possible relations/dissociations between the manifold facets of embodied simulation.

Effect of Emotional Cues on mnES in SCZ

Between-group comparisons of the responsiveness to actions embedded in emotional contexts indicate that emotional cues enhance mnES in SCZ patients. Indeed, differently from what we found for the observation of NAs, we did not find any between-group difference concerning neural responses to actions performed by an actor expressing happiness, and only small differences for the observation of actions performed by an angry actor. These results can be interpreted in the sense that both positive (happiness) and negative (anger) emotional cues might stimulate a kind of compensation process that compensates for the reduced activity in the neutral condition. Moreover, our results are consistent with neurobiological models implying that SCZ patients are more inclined than HCs to utilize emotional cues as response determinants during cognitive tasks [32, 75]. The outcome of such 'aberrant salience processing' can be that, if emotional cues are provided, SCZ patients' and healthy controls' performance during a cognitive task may not differ. For example, Herbener et al. [75] using emotional pictorial stimuli demonstrated that memory enhancement for negative images did not differ between SCZ patients and healthy volunteers. Our results show a similar effect of emotional cues on neural response to action observation. That is, when actors expressed either happiness or anger while performing an action mnES occurred at comparable levels between SCZ patients and controls. We found only one between-group difference, which concerned activity in the right insula during the observation of AA. SCZ patients showed negative responses in this region,

which also positively correlated with the EQ score: 'deactivation' in the right insula decreased with reduced EQ. This evidence is in line with previous studies consistently showing that the insula (a) is engaged in the perception or experience of emotion [76, 77] and angry hand movements [78] and (b) is likely responsible for inducing a resonance in the visceromotor centers of the observer while watching emotion in other people [76], thus playing a key role in empathy. Our results further suggest that 'pure motor resonance', involving frontoparietal regions, and empathy, involving the insula, are two aspects of mnES that can dissociate, at least in part, in SCZ patients. Indeed, when action and emotional cues were simultaneously presented, patients recovered activity in the frontoparietal network critical for action representation [60–62]. However, differences between SCZ patients and HCs still remained at the level of a region, the anterior insula, which is known to connect action representation networks with limbic areas [79]. Communication between these two systems in the human brain is thought to support empathy. Why? Because we need to invoke the representation of the actions associated with the emotions we are witnessing in order to empathize. Our results seem to suggest that when patients witness actions associated with anger, representation of action becomes as efficient as in HCs, but its link to limbic areas via the insula might be impaired. Such impairments would predict the reduced empathy, a well-known feature of schizophrenia [80].

In conclusion, our study supports previous evidence of poorer mnES during action observation in schizophrenia [21–24]. Moreover, it goes further by showing that emotional cues might allow patients to recover mnES, at least in part. However, their understanding of the emotional components of others' actions will likely remain deficient.

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References

- 1 Green MF, Bearden CE, Cannon TD, Fiske AP, Helleman GS, Horan WP, Kee K, Kern RS, Lee J, Sergi MJ, Subotnik KL, Sugar CA, Ventura J, Yee CM, Nuechterlein KH: Social cognition in schizophrenia. 1. Performance across phase of illness. *Schizophr Bull* 2012; 38:854–864.
- 2 Fujino J, Takahashi H, Miyata J, Sugihara G, Kubota M, Sasamoto A, Fujiwara H, Aso T, Fukuyama H, Murai T: Impaired empathic abilities and reduced white matter integrity in schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry* 2014;48:117–123.
- 3 Sestito M, Umiltà MA, De Paola G, Fortunati R, Raballo A, Leuci E, Maffei S, Tonna M, Amore M, Maggini C, Gallese V: Facial reactions in response to dynamic emotional stimuli in different modalities in patients suffering from schizophrenia: a behavioral and EMG study. *Front Hum Neurosci* 2013;7:368.
- 4 Ripoll LH, Zaki J, Perez-Rodriguez MM, Snyder R, Strike KS, Boussi A, Bartz JA, Ochsner KN, Siever LJ, New AS: Empathic accuracy and cognition in schizotypal personality disorder. *Psychiatry Res* 2013;210:232–241.
- 5 Bora E, Pantelis C: Theory of mind impairments in first-episode psychosis, individuals at ultra-high risk for psychosis and in first-degree relatives of schizophrenia: systematic review and meta-analysis. *Schizophr Res* 2013;144:31–36.
- 6 Ebisch SJ, Salone A, Ferri F, De Berardis D, Romani GL, Ferro FM, Gallese V: Out of touch with reality? Social perception in first-episode schizophrenia. *Soc Cogn Affect Neurosci* 2013;8:394–403.
- 7 Ferri F, Frassinetti F, Mastrangelo F, Salone A, Ferro FM, Gallese V: Bodily self and schizophrenia: the loss of implicit self-body knowledge. *Conscious Cogn* 2012;21:1365–1374.
- 8 Liepelt R, Schneider JC, Aichert DS, Westmann N, Dehning S, Moller HJ, Riedel M, Dolk T, Ettinger U: Action blind: disturbed self-other integration in schizophrenia. *Neuropsychologia* 2012;50:3775–3780.
- 9 Dalmaso M, Galfano G, Tarqui L, Forti B, Castelli L: Is social attention impaired in schizophrenia? Gaze, but not pointing gestures, is associated with spatial attention deficits. *Neuropsychology* 2013;27:608–613.
- 10 Van't Wout M, van Rijn S, Jellema T, Kahn RS, Aleman A: Deficits in implicit attention to social signals in schizophrenia and high risk groups: behavioural evidence from a new illusion. *PLoS One* 2009;4:e5581.
- 11 Kring AM, Elis O: Emotion deficits in people with schizophrenia. *Annu Rev Clin Psychol* 2013;9:409–433.
- 12 Gallese V: Mirror neurons, embodied simulation and a second-person approach to mind-reading. *Cortex* 2013;49:2954–2956.
- 13 Di Pellegrino G, Fadiga L, Fogassi L, Gallese V, Rizzolatti G: Understanding motor events: a neurophysiological study. *Exp Brain Res* 1992;91:176–180.
- 14 Gallese V, Fadiga L, Fogassi L, Rizzolatti G: Action recognition in the premotor cortex. *Brain* 1996;119:593–609.
- 15 Gallese V, Gernsbacher MA, Heyes C, Hickok G, Iacoboni M: Mirror neuron forum. *Perspect Psychol Sci* 2011;6:369–407.
- 16 Vigneswaran G, Philipp R, Lemon RN, Krasov A: M1 corticospinal mirror neurons and their role in movement suppression during action observation. *Curr Biol* 2013;23:236–243.
- 17 De Araujo MF, Hori E, Maior RS, Tomaz C, Ono T, Nishijo H: Neuronal activity of the anterior cingulate cortex during an observation-based decision making task in monkeys. *Behav Brain Res* 2012;230:48–61.
- 18 Rizzolatti G, Fogassi L, Gallese V: Neurophysiological mechanisms underlying the understanding and imitation of action. *Nat Rev Neurosci* 2001;2:661–670.
- 19 Pineda JA: *Mirror Neuron Systems*. New York, Humana Press, 2009.
- 20 Gallese V: The roots of empathy: the shared manifold hypothesis and the neural basis of intersubjectivity. *Psychopathology* 2003;36:171–180.
- 21 Enticott PG, Hoy KE, Herring SE, Johnston PJ, Daskalakis ZJ, Fitzgerald PB: Reduced motor facilitation during action observation in schizophrenia: a mirror neuron deficit? *Schizophr Res* 2008;102:116–121.
- 22 Mehta UM, Thirithalli J, Basavaraju R, Gangadhar BN, Pascual-Leone A: Reduced mirror neuron activity in schizophrenia and its association with theory of mind deficits: evidence from a transcranial magnetic stimulation study. *Schizophr Bull* 2014;40:1083–1094.
- 23 Schurmann M, Jarvelainen J, Avikainen S, Cannon TD, Lonnqvist J, Huttunen M, Hari R: Manifest disease and motor cortex reactivity in twins discordant for schizophrenia. *Br J Psychiatry* 2007;191:178–179.
- 24 Kato Y, Muramatsu T, Kato M, Shibukawa Y, Shintani M, Mimura M: Magnetoencephalography study of right parietal lobe dysfunction of the evoked mirror neuron system in antipsychotic-free schizophrenia. *PLoS One* 2011;6:e28087.
- 25 Horan WP, Pineda JA, Wynn JK, Iacoboni M, Green MF: Some markers of mirroring appear intact in schizophrenia: evidence from mu suppression. *Cogn Affect Behav Neurosci* 2014;14:1049–1060.
- 26 McCormick LM, Brumm MC, Beadle JN, Paradiso S, Yamada T, Andreasen N: Mirror neuron function, psychosis, and empathy in schizophrenia. *Psychiatry Res* 2012;201:233–239.
- 27 Ventura J, Wood RC, Jimenez AM, Helleman GS: Neurocognition and symptoms identify links between facial recognition and emotion processing in schizophrenia: meta-analytic findings. *Schizophr Res* 2013;151:78–84.
- 28 Ventura J, Wood RC, Jimenez AM, Helleman GS: Neurocognition and symptoms identify links between facial recognition and emotion processing in schizophrenia: meta-analytic findings. *Schizophr Res* 2013;151:78–84.
- 29 Saracco-Alvarez R, Fresan A, Escamilla-Orozco R: Facial emotion recognition in schizophrenia: a comparison with siblings and control subjects. *Schizophr Res* 2013;151:291–292.
- 30 Simpson C, Pinkham AE, Kelsven S, Sasson NJ: Emotion recognition abilities across stimulus modalities in schizophrenia and the role of visual attention. *Schizophr Res* 2013;151:102–106.
- 31 Hahn B, Robinson BM, Kaiser ST, Harvey AN, Beck VM, Leonard CJ, Kappenman ES, Luck SJ, Gold JM: Failure of schizophrenia patients to overcome salient distractors during working memory encoding. *Biol Psychiatry* 2010;68:603–609.
- 32 Patrick RE, Christensen BK: Reduced directed forgetting for negative words suggests schizophrenia-related disinhibition of emotional cues. *Psychol Med* 2013;43:2289–2299.
- 33 Henik A, Salo R: Schizophrenia and the Stroop effect. *Behav Cogn Neurosci Rev* 2004;3:42–59.
- 34 Woods SW: Chlorpromazine equivalent doses for the newer atypical antipsychotics. *J Clin Psychiatry* 2003;64:663–667.
- 35 Ferri F, Ebisch SJ, Costantini M, Salone A, Arciero G, Mazzola V, Ferro FM, Romani GL, Gallese V: Binding action and emotion in social understanding. *PLoS One* 2013;8:e54091.
- 36 Lehman AF, Lieberman JA, Dixon LB, McGlashan TH, Miller AL, Perkins DO, Kreyenbuhl J; American Psychiatric Association Steering Committee on Practice Group: Practice guideline for the treatment of patients with schizophrenia, second edition. *Am J Psychiatry* 2004;161:1–56.
- 37 First MB, Spitzer RL, Gibbon M, Williams JBW: *Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version (SCID-CV)*. Washington, American Psychiatric Press, 1996.
- 38 Kay SR, Fiszbein A, Opler LA: The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull* 1987;13:261–276.
- 39 Klosterkötter J, Hellmich M, Steinmeyer EM, Schultze-Lutter F: Diagnosing schizophrenia in the initial prodromal phase. *Arch Gen Psychiatry* 2001;58:158–164.

- 40 First MB, Gibbon M, Spitzer RL: Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II, Version 2.0). New York, Biometric Research Department, New York State Psychiatric Institute, 1996.
- 41 Baron-Cohen S, Wheelwright S: The empathy quotient: an investigation of adults with Asperger syndrome or high functioning autism, and normal sex differences. *J Autism Dev Disord* 2004;34:163–175.
- 42 Lawrence EJ, Shaw P, Baker D, Baron-Cohen S, David AS: Measuring empathy: reliability and validity of the empathy quotient. *Psychol Med* 2004;34:911–919.
- 43 Bora E, Gokcen S, Veznedaroglu B: Empathic abilities in people with schizophrenia. *Psychiatry Res* 2008;160:23–29.
- 44 Koelkebeck K, Pedersen A, Suslow T, Kueppers KA, Arolt V, Ohrmann P: Theory of mind in first-episode schizophrenia patients: correlations with cognition and personality traits. *Schizophr Res* 2010;119:115–123.
- 45 Konstantakopoulos G, Oulis P, Ploumpidis D, Patrikelis P, Nikitopoulou S, Papadimitriou GN, David AS: Self-rated and performance-based empathy in schizophrenia: the impact of cognitive deficits. *Soc Neurosci* 2014;27:1–11.
- 46 Lysaker PH, Hasson-Ohayon I, Kravetz S, Kent JS, Roe D: Self perception of empathy in schizophrenia: emotion recognition, insight, and symptoms predict degree of self and interviewer agreement. *Psychiatry Res* 2013; 206:146–150.
- 47 Mazzola V, Vuilleumier P, Latorre V, Petit A, Gallese V, Popolizio T, Arciero G, Bondolfi G: Effects of emotional contexts on cerebello-thalamo-cortical activity during action observation. *PLoS One* 2013;8:e75912.
- 48 Friston KJ, Ashburner J, Frith CD, Poline JB, Heather JD, Frackowiak RSJ: Spatial registration and normalization of images. *Hum Brain Mapp* 1995;2:165–189.
- 49 Worsley KJ, Friston KJ: Analysis of fMRI time-series revisited – again. *Neuroimage* 1995;2:173–181.
- 50 Friston KJ, Fletcher P, Josephs O, Holmes A, Rugg MD, Turner R: Event-related fMRI: characterizing differential responses. *Neuroimage* 1998;7:30–40.
- 51 Kriegeskorte N, Simmons WK, Bellgowan PSF, Baker CI: Circular analysis in systems neuroscience: the dangers of double dipping. *Nat Neurosci* 2009;12:535–540.
- 52 Huber PJ: Robust estimation of a location parameter. *Ann Stat* 1964;35:73–101.
- 53 Piefke M, Kramer K, Korte M, Schulte-Rüther M, Korte JM, Wohlschläger AM, Weber J, Shah NJ, Huber W, Fink GR: Neurofunctional modulation of brain regions by distinct forms of motor cognition and movement features. *Hum Brain Mapp* 2009;30:432–451.
- 54 Sato W, Kochiyama T, Yoshikawa S, Naito E, Matsumura M: Enhanced neural activity in response to dynamic facial expressions of emotion: an fMRI study. *Cogn Brain Res* 2004;20:81–91.
- 55 Thioux M, Gazzola V, Keysers C: Action understanding: how, what and why. *Curr Biol* 2008;18:R431–R434.
- 56 Van de Riet WA, Grezes J, de Gelder B: Specific and common brain regions involved in the perception of faces and bodies and the representation of their emotional expressions. *Soc Neurosci* 2009;4:101–120.
- 57 Gallese V: Mirror neurons, embodied simulation, and the neural basis of social identification. *Psychoanal Dialog* 2009;19:519–536.
- 58 Rizzolatti G, Sinigaglia C: Further reflections on how we interpret the actions of others. *Nature* 2008;455:589.
- 59 Iacoboni M, Molnar-Szakacs I, Gallese V, Buccino G, Mazziotta JC, Rizzolatti G: Grasping the intentions of others with one's own mirror neuron system. *PLoS Biol* 2005;3:e79.
- 60 Buccino G, Binkofski F, Fink GR, Fadiga L, Fogassi L, Gallese V, Seitz RJ, Zilles K, Rizzolatti G, Freund HJ: Action observation activates premotor and parietal areas in a somatotopic manner: an fMRI study. *Eur J Neurosci* 2001;13:400–404.
- 61 Buccino G, Lui F, Canessa N, Patteri I, Lagravinese G, Benuzzi F, Porro CA, Rizzolatti G: Neural circuits involved in the recognition of actions performed by nonconspecifics: an fMRI study. *J Cogn Neurosci* 2004;16:114–126.
- 62 Buccino G, Vogt S, Ritzl A, Fink GR, Zilles K, Freund HJ, Rizzolatti G: Neural circuits underlying imitation learning of hand actions: an event-related fMRI study. *Neuron* 2004;42: 323–334.
- 63 Johnson-Frey SH, Maloof FR, Newman-Norlund R, Farrer C, Inati S, Grafton ST: Actions or hand-object interactions? Human inferior frontal cortex and action observation. *Neuron* 2003;39:1053–1058.
- 64 Hamilton AF, Grafton ST: Goal representation in human anterior intraparietal sulcus. *J Neurosci* 2006;26:1133–1137.
- 65 Schultze-Lutter F: Subjective symptoms of schizophrenia in research and the clinic: the basic symptom concept. *Schizophr Bull* 2009; 35:5–8.
- 66 Huber G: The concept of substrate-close basic symptoms and its significance for the theory and therapy of schizophrenic diseases (in German). *Nervenarzt* 1983;54:23–32.
- 67 Klosterkötter J: The meaning of basic symptoms for the genesis of the schizophrenic nuclear syndrome. *Jpn J Psychiatry Neurol* 1992; 46:609–630.
- 68 Gallese V: The manifold nature of interpersonal relations: the quest for a common mechanism. *Philos Trans R Soc Lond B Biol Sci* 2003;358:517–528.
- 69 Gallese V: Motor abstraction: a neuroscientific account of how action goals and intentions are mapped and understood. *Psychol Res* 2009;73:486–498.
- 70 Ebisch SJ, Mantini D, Northoff G, Salone A, De Berardis D, Ferri F, Ferro FM, Di Gianantonio M, Romani GL, Gallese V: Altered brain long-range functional interactions underlying the link between aberrant self-experience and self-other relationship in first-episode schizophrenia. *Schizophr Bull* 2014;40: 1072–1080.
- 71 Ferri F, Salone A, Ebisch SJ, De Berardis D, Romani GL, Ferro FM, Gallese V: Action verb understanding in first-episode schizophrenia: is there evidence for a simulation deficit? *Neuropsychologia* 2012;50:988–996.
- 72 Badre D: Cognitive control, hierarchy, and the rostro-caudal organization of the frontal lobes. *Trends Cogn Sci* 2008;12:193–200.
- 73 Vogt S, Buccino G, Wohlschläger AM, Canessa N, Shah NJ, Zilles K, Eickhoff SB, Freund HJ, Rizzolatti G, Fink GR: Prefrontal involvement in imitation learning of hand actions: effects of practice and expertise. *Neuroimage* 2007;37:1371–1383.
- 74 Gallese V, Sinigaglia C: How the body in action shapes the self. *J Consc Stud* 2011;18: 117–143.
- 75 Herbener ES, Rosen C, Khine T, Sweeney JA: Failure of positive but not negative emotional valence to enhance memory in schizophrenia. *J Abnorm Psychol* 2007;116:43–55.
- 76 Wicker B, Keysers C, Plailly J, Royet JP, Gallese V, Rizzolatti G: Both of us disgusted in my insula: the common neural basis of seeing and feeling disgust. *Neuron* 2003;40:655–664.
- 77 Phillips ML, Williams LM, Heining M, Herba CM, Russell T, Andrew C, Bullmore ET, Brammer MJ, Williams SC, Morgan M, Young AW, Gray JA: Differential neural responses to overt and covert presentations of facial expressions of fear and disgust. *Neuroimage* 2004;21:1484–1496.
- 78 Grosbras M-H, Paus T: Brain networks involved in viewing angry hands or faces. *Cereb Cortex* 2006;16:1087–1096.
- 79 Carr L, Iacoboni M, Dubeau M-C, Mazziotta JC, Lenzi GL: Neural mechanisms of empathy in humans: a relay from neural systems for imitation to limbic areas. *Proc Natl Acad Sci* 2003;100:5497–5502.
- 80 Derntl B, Finkelmeyer A, Toygar TK, Hulsman A, Schneider F, Falkenberg DI, Habel U: Generalized deficit in all core components of empathy in schizophrenia. *Schizophr Res* 2009;108:197–206.
- 81 Mazziotta JC, Toga AW, Evans A, Fox P, Lancaster J: A probabilistic atlas of the human brain: theory and rationale for its development. The International Consortium for Brain Mapping (ICBM). *Neuroimage* 1995;2: 89–101.