

## Limbic Interference During Social Action Planning in Schizophrenia

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Schizophrenia is characterized by social interaction deficits contributing to poor functional outcome. Hand gesture use is particularly impaired, linked to frontal lobe dysfunction and frontal grey matter deficits. The functional neural correlates of impaired gesturing are currently unclear. We therefore investigated aberrant brain activity during impaired gesturing in schizophrenia. We included 22 patients with schizophrenia and 25 healthy control participants matched for age, gender, and education level. We obtained functional magnetic resonance imaging data using an event-related paradigm to assess brain activation during gesture planning and execution. Group differences in whole brain effects were calculated using factorial designs. Gesture ratings were performed by a single rater, blind to diagnoses and clinical presentation. During gesture planning and execution both groups activated brain areas of the praxis network. However, patients had reduced dorsolateral prefrontal cortex (DLPFC) and increased inferior parietal lobe (IPL) activity. Performance accuracy was associated with IPL activity in patients. Furthermore, patients activated temporal poles, amygdala and hippocampus during gesture planning, which was associated with delusion severity. Finally, patients demonstrated increased dorsomedial prefrontal cortex activity during planning of novel gestures. We demonstrate less prefrontal, but more IPL and limbic activity during gesturing in schizophrenia. IPL activity was associated with performance accuracy, whereas limbic activity was linked to delusion severity. These findings may reflect impaired social action planning and a limbic interference with gestures in schizophrenia contributing to poor gesture performance and consequently poor social functioning in schizophrenia.

*Key words:* nonverbal communication/social cognition/delusions/gesture performance/fMRI/amygdala

### Introduction

Schizophrenia is characterized by impaired social interaction contributing to poor functional outcome.<sup>1</sup> Particularly nonverbal communication is disturbed including gesture performance in both patients and subjects at risk for psychosis.<sup>2-8</sup> Gestures are skilled movements critical for social interaction,<sup>9,10</sup> conveying relevant nonverbal information. Gesture deficits have been linked to impaired frontal lobe function, working memory deficits and altered motor behavior.<sup>3,4</sup> Gesture impairments in schizophrenia predict poor functional outcome after 6 months.<sup>11</sup> Furthermore, poor nonverbal social perception and impaired gesture performance are strongly associated.<sup>4</sup> Finally, alterations in the mirror neuron system may lead to poor gesture performance.<sup>12,13</sup>

Three key aspects of gesturing may be investigated: gesture perception, interpretation and production.<sup>14</sup> Recent functional magnetic resonance imaging (fMRI) studies indicated aberrant neural processing in the language network in schizophrenia during perception of abstract metaphoric gestures.<sup>15,16</sup> Behavioral data suggests misinterpretation of incidental movements as gestures in patients with delusions.<sup>17</sup> Delusions in turn are associated with altered brain activity in the limbic system.<sup>18,19</sup> Therefore, functional alterations in the limbic system may foster misinterpretation of gestures in schizophrenia. Two recent fMRI studies investigated the imitation of meaningless finger movements in schizophrenia: One reported preserved neural activity,<sup>20</sup> while the other found reduced right parietal lobe activation in patients.<sup>21</sup> Imitation of finger movements may be related to imitation of gestures, yet lacking the communicative context. Even though performance of gestures on command (termed pantomimes) is defective in up to 67% of schizophrenia patients,<sup>2-4</sup>

the underlying pathophysiology is unknown and their functional neural correlates have not been studied yet. Pantomimes represent a critical nonverbal component of real-life social encounters, for instance as co-speech gestures.<sup>9,22</sup>

Current neurocognitive models<sup>23–25</sup> including evidence from fMRI studies in healthy subjects<sup>26–28</sup> as well as lesion studies<sup>29–32</sup> suggest a widespread, left lateralized, fronto-temporo-parietal cortical network for planning pantomime gestures and imitation of tool use. According to these models distinct ventral and dorsal streams of this so called praxis network are relevant for motor control. In detail, the dorso-dorsal stream provides “online” control of actions and is running from the primary visual cortex, the superior parietal lobe to the dorsal premotor area.<sup>23,24,33</sup> In contrast, the ventro-dorsal stream is relevant for action semantics connecting medial superior temporal areas with the inferior parietal cortex and dorsal premotor cortex.<sup>24</sup> Finally, visual object processing and object semantics is processed in the ventral stream running from the visual cortex through the temporal lobe to the inferior frontal gyrus.<sup>28</sup>

Investigating gesture performance in schizophrenia provides further information on the contribution of the praxis network. In fact, schizophrenia patients with defective pantomime performance had reduced gray matter (GM) in the ventral-dorsal pathway, most prominent in the left IFG in contrast to patients with correct gesture performance.<sup>34</sup>

Despite the growing evidence and clinical relevance of gesture abnormalities in schizophrenia, the neural correlates of impaired gesture performance are currently unclear. However, this pathophysiological knowledge may stimulate the development of treatment approaches. Therefore, we tested functional correlates of gesture performance on visual verbal command (pantomime) in schizophrenia patients and healthy controls with fMRI. We hypothesized aberrant activation of the praxis network in schizophrenia during both planning and actual performance of gestures and altered prefrontal cortex activation during gesture planning. In particular, we hypothesized planning of novel gestures to be demanding and to be associated with prominent alterations in the frontal lobe in schizophrenia. In contrast, brain activity during planning of familiar, highly overlearned gestures (such as tool related gestures) may be more preserved in schizophrenia. Finally, we tested a possible association of defective social action planning with delusional experience in patients.

## Methods

### Subjects

This study included 22 patients with schizophrenia spectrum disorders according to the Diagnostic and Statistical Manual of Mental Disorders (DSM5) criteria and 25 healthy control subjects matched for age, gender, and

duration of education. Patients were recruited between December 2013 and November 2014 at the inpatient and outpatient departments of the University Hospital of Psychiatry, Bern. Healthy controls were recruited via advertisement and among staff and students. All participants were right-handed. General exclusion criteria were substance abuse or dependence other than nicotine, history of motor impairments such as dystonia, idiopathic parkinsonism or stroke, history of head trauma with concurrent loss of consciousness and history of electroconvulsive treatment. Exclusion criteria for controls were history of any psychiatric disorder, as well as any first-degree relatives with schizophrenia or schizoaffective disorder. All participants provided written informed consent. The study protocol adhered to the declaration of Helsinki and was approved by the local Ethics Committee.

All patients received antipsychotic medication, average daily chlorpromazine equivalents (CPZ) during the last 5 years were calculated.<sup>35</sup> Symptom severity in patients was assessed with the Comprehensive Assessment of Symptoms and History (CASH)<sup>36</sup> and the Positive And Negative Syndrome Scale (PANSS).<sup>37</sup> All participants were further interviewed with the Mini International Neuropsychiatric Interview (MINI).<sup>38</sup> In addition, frontal lobe function, verbal working memory and nonverbal intelligence were assessed using the Frontal Assessment Battery (FAB),<sup>39</sup> the digit span backwards (DSB) task (subtest from the Wechsler Memory Scale [WMS-III])<sup>40</sup> and the Test of nonverbal Intelligence [TONI].<sup>41</sup> Assessment of symptoms was conducted on the day of MRI scan.

### Experimental Procedures

**Task: Gesture Performance on Verbal Command.** We employed a modified instructed delay paradigm<sup>26,42,43</sup> for pantomime gestures (figure 1). Participants performed 20 novel and 20 familiar gestures in random order with their right hand in 2 runs. Instructions were presented visually as written commands. Familiar gestures included 10 transitive (tool related, eg. use of scissors) and 10 intransitive

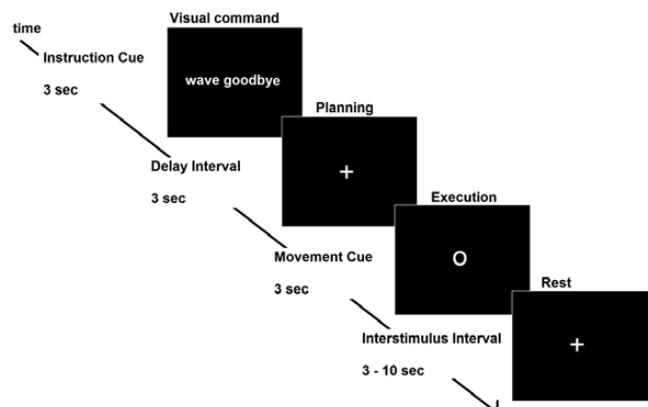


Fig. 1. Pantomime gesture task.

symbolic actions (eg, waving good bye). Novel gestures are meaningless actions, such as spreading the little finger outward. During the linguistic control condition trials (10 neutral sentences, eg, “The weather is cold during winter.”),<sup>44</sup> participants were asked to relax and neither plan nor undertake any movements. Thus, linguistic control was matched for attention and visual processing, but lacked any specific demands in motor planning (figure 1). Within runs, gesture condition and linguistic control condition were intermixed. Each command was presented twice. Each run started with the rest instruction followed by written movement commands or linguistic control for 3 seconds (figure 1). Next, a fixation cross was presented for 3 seconds, during which participants had to plan movements. Immediately after the planning phase, a round symbol indicated the execution phase of 3 seconds, which in turn was followed by a jittered inter-stimulus interval of 3–10 seconds. The total duration of the fMRI task was 13 minutes.

Participants performed gestures with the right hand and arm. Subjects lay horizontal in the MR scanner and their arms rested beside their trunk. To reduce head motion foam pads were placed around the participants’ head and we explicitly instructed participants to avoid head motion, in particular while performing gestures. Furthermore, most of the gestures involved the hand and forelimb in proximity to the hand. In case of movements including the arm participants were explicitly asked to mainly use the forelimb.

An independent rater blinded for diagnosis and clinical status evaluated the video-recorded gesture performance according to the Test of Upper Limb Apraxia (TULIA)<sup>45</sup> criteria (eg, according to spatial, temporal or content errors, higher scores indicating better performance accuracy; full criteria see supplementary material).

*Functional Magnetic Resonance Imaging.* Imaging was performed on a 3T MRI scanner (Siemens Magnetom Trio; Siemens Medical Solutions) with a 12-channel radio frequency headcoil for signal reception. 3D-T1-weighted (Modified Driven Equilibrium Fourier Transform Pulse Sequence; MDEFT) images for each subject have been obtained,<sup>46</sup> providing 176 sagittal slices with  $256 \times 256$  matrix points with a non-cubic field of view (FOV) of 256 mm, yielding a nominal isotropic resolution of 1 mm<sup>3</sup> (ie, 1 mm  $\times$  1 mm  $\times$  1 mm). Further scan parameters for the anatomical data were 7.92 ms repetition time (TR), 2.48 ms echo time (TE) and a flip angle of 16° (FA).

For functional sequences, 390 T2\*-weighted echo planar single-shot images (EPI) were acquired. Further scan parameters for the functional images were 38 slices, and slice thickness = 3 mm,  $64 \times 64$  matrix size, 3.59 mm  $\times$  3.59 mm  $\times$  3 mm voxel dimension, FOV 230 mm, TR = 2 seconds and TE = 30 ms. In addition the acquisition of a  $B_0$  image was performed in order to quantify inhomogeneity within the echo planar imaging (EPI) images. The following parameters were used: 38 axial slices with

slice thickness = 3.0 mm, interslice distance = 0 mm, FOV =  $230 \times 230$  mm<sup>2</sup>, matrix size =  $64 \times 64$ ; TR = 488 ms, TE<sub>short</sub> = 4.92 ms, TE<sub>long</sub> = 7.38 ms, gradient-EPI readout, interleaved order, acquisition time 65 seconds, number of measurements  $N = 1$ , Flow compensation pulse, Bandwidth 260 Hz/Px and effective Echo spacing 0.215 ms. These images were positioned exactly as the fMRI images.

### Statistical Analysis

Statistical tests of behavioral, clinical and demographic data were performed using SPSS 22.0 (IBM SPSS Statistics: IBM Corp). Two-sample *t* tests and chi-square tests ( $\chi^2$ ) were used to test for group differences in clinical and demographic data. Gesture performance data were normally distributed. A repeated measure ANOVA tested the effects of category, group and their interaction on gesture performance applying Greenhouse-Geisser correction. Level of significance was set at  $P < .05$ , 2-tailed.

Missing trials and trials with severe gesture errors (eg, unrecognizable or movement present, but hard to decipher) were excluded from further fMRI analysis. To assess planning- and execution-related increases in blood oxygenation level dependent (BOLD) signal we used Statistical Parametric Mapping (SPM8) software (Wellcome Department of Imaging Neuroscience, University of London). Preprocessing included slice time correction, realignment, coregistration, normalization, and spatial smoothing with a Gaussian kernel of 8 mm full-width at half-maximum. In addition, preprocessing included correction of distortion of EPI images due to possible regional variations of the static magnetic field (eg,  $B_0$ ).

Statistical analysis of the preprocessed data was conducted via a 2-stage mixed effects model. At the single subject level, the activity for planning and execution of familiar and novel gestures as well as the linguistic controls was modeled in one General Linear Model (GLM) using the standard SPM canonical hemodynamic response function. For each participant, realignment parameters were included in the GLM as regressors of no interest to correct for residual motion. In order to identify brain areas specifically associated with planning and execution of familiar and novel gestures, gesture conditions (familiar and novel) were contrasted against the linguistic control condition at the single subject level (eg, planning familiar gestures vs linguistic control; execution novel gestures vs linguistic control).

Next, contrasts from each single subject were entered into second-level random effects analyses. Whole brain effects were calculated using 2 flexible factorial designs with the factors group, planning and execution for each of the 2 gesture categories (familiar and novel) separately. Between group effects were calculated comparing both conditions (planning and execution) between patients and controls within the factorial designs (eg, patients vs controls:

planning familiar gestures; controls vs patients: planning familiar gestures). We report results with a uniform threshold of  $P \leq .001$  and a minimum cluster size of 180 voxels.

We explored potential influences of motion on the BOLD signal. Neither group nor phase of the experiment had an influence on head motion during the scan (see supplementary material: Analysis S1, table S1). Finally, we calculated post hoc Spearman's rank correlations (2-tailed) to assess the relationship between performance ratings (TULIA scores), psychopathological characteristics of delusional experience from the CASH present state and neural activity during gesture planning. Therefore, we extracted mean beta estimate values of full brain clusters differentially activated during the planning condition as regions of interest (ROIs) for each subject using a toolbox for SPM (MarsBaR).<sup>47</sup>

## Results

### Behavioral and Clinical Data

Demographic and clinical data are given in table 1. Patients performed poorer than controls in both gesture categories (familiar and novel, see table 1 and supplementary

material: figure S1). The gesture deficit comprised temporal, spatial, semantic and content errors. We found significant effects of gesture category ( $F_{(1/45)} = 67.1, P < .001$ ), and group ( $F_{(1/45)} = 20.0, P < .001$ ), but no category  $\times$  group interaction ( $F_{(1/45)} = .1, P = .70$ ). However, the proportion of excluded trials (missing trials and trials with severe errors) did not differ between patients and controls (table 1).

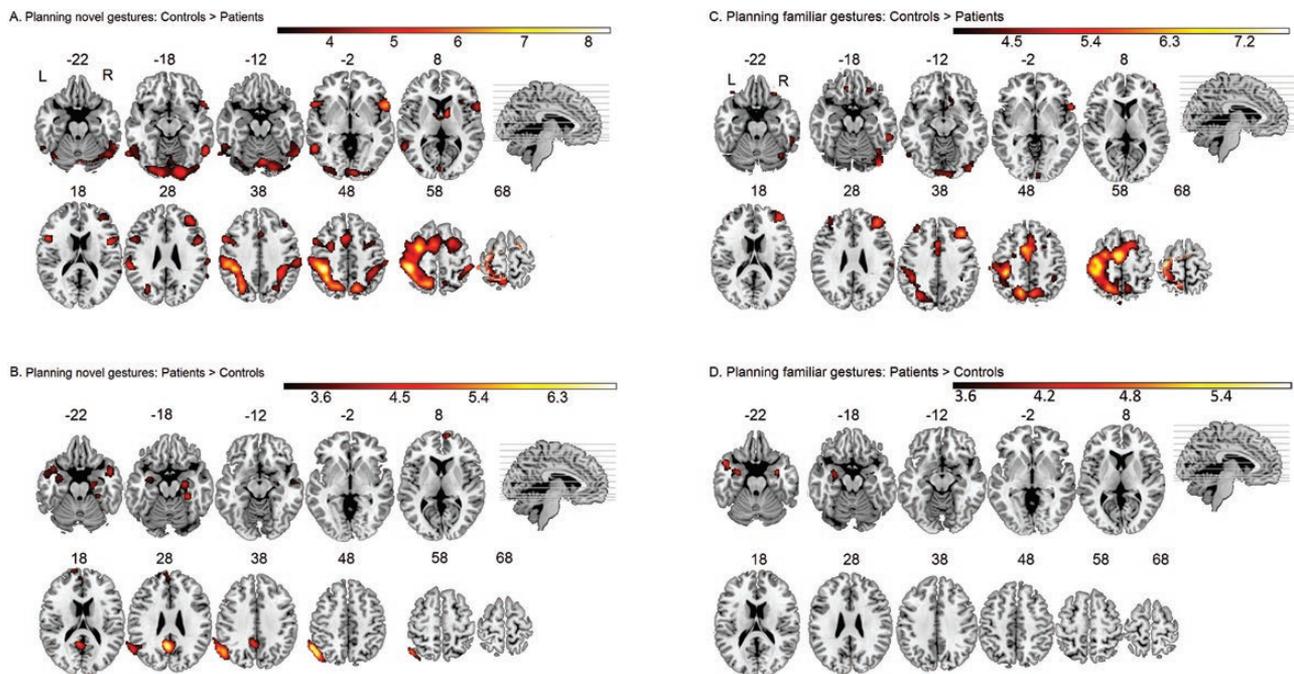
### fMRI Results

*Planning Novel and Familiar Gestures.* Within-group results are given in the supplementary material (supplementary material: Analyses S2 and S3, figure S2 and table S2). During planning of novel gestures between-group contrasts indicated reduced activation in patients in brain areas commonly related to gesture planning, ie, in the ventral and dorsal stream, the motor cortex and the right dorsolateral prefrontal cortex (DLPFC) (controls > patients) (figure 2A and table 2A). Furthermore, we detected abnormal bilateral activation in temporal pole, amygdala and hippocampus in schizophrenia

**Table 1.** Demographic and Clinical Data

	Controls		Patients		Tests
	Men/Women		Men/Women		<i>P</i>
Gender (No [%])	13 (52%)/ 12 (48%)		14 (64%)/ 8 (36%)		.421
	<i>M</i>	SD	<i>M</i>	SD	<i>P</i>
Age (y)	39.2	14.0	37.5	9.8	.63
Education (y)	14.1	2.7	13.5	3.1	.68
TONI index score	109.8	10.9	99.7	9.1	.002
DSB	5.5	0.7	4.6	0.9	.003
FAB	17.5	0.7	16.7	0.9	<.001
Gesture performance total	163.4	15.9	137.6	21.8	<.001
Familiar gestures	89.5	7.8	77.3	16.8	<.001
Novel gestures	74.0	10.1	60.4	9.8	.004
Gestures missing (%)	1.6	2.5	1.5	8.4	.45
CPZ (mg)	—	—	397.5	406.1	—
Schizophrenia patients ( <i>n</i> )	—	—	16	—	—
Schizophreniform disorder ( <i>n</i> )	—	—	4	—	—
Schizoaffective disorder ( <i>n</i> )	—	—	2	—	—
PANSS total (range)	—	—	73.0 (43–103)	17.8	—
PANSS pos (range)	—	—	17.5 (7–26)	6.7	—
PANSS neg (range)	—	—	18.8 (11–27)	4.5	—
CAINS Expression (range)	—	—	4.2 (0–10)	3.6	—
CAINS Motivation/Pleasure (range)	—	—	16.5 (4–29)	7.3	—
CASH delusions (range)	—	—	2.3 (0–5)	2.0	—
Number of episodes	—	—	5.7	6.3	—
DOI (y)	—	—	11.2	9.3	—

*Note:* TONI index score, Test of nonverbal Intelligence index score; DSB, digit span backwards; FAB, Frontal Assessment Battery; Gesture performance total, total scores of gesture performance; Familiar gestures, performance scores of performance of familiar gestures; Novel gestures, performance scores of performance of novel gestures (performance ratings refer to gesture performance inside the scanner); CAINS, Clinical Assessment Interview for Negative Symptoms (Factor 1 Expression; Factor 2 Motivation/Pleasure); CPZ, chlorpromazine equivalents; PANSS, Positive And Negative Syndrome Scale; pos, positive; neg, negative; CASH, comprehensive assessment of schizophrenia history (delusions, global rating of severity of delusions); DOI, duration of illness. *P* values correspond to 2-sample *t* tests for continuous variables and  $\chi^2$  tests for categorical variables.



**Fig. 2.** Neural activity during gesture planning in schizophrenia patients and healthy controls. Between group effects of planning novel (A and B) and familiar (C and D) gestures. The bars indicate  $T$ -values. The images are depicted at standard MNI-templates (threshold of  $P < .001$ , minimum voxel size 180).

(patients > controls). In addition, patients demonstrated increased activation in the middle frontal gyrus (dorsomedial frontal cortex: DMPFC; patients > controls) (figure 2B and table 2A). Likewise, during planning of familiar gestures patients showed hypoactivation in the praxis network, the motor cortex and the DLPFC, while again patients presented abnormal bilateral activation in the temporal pole and amygdala (figures 2C and 2D). The full list of between group results (controls > patients and patients > controls) is given in table 2A. To rule out the putative effects of frontal lobe function on our whole brain findings we provide additional analyses with frontal lobe function (FAB) as covariate. The analyses yielded substantially the same results independent of frontal lobe function (see supplementary material, table S3).

*Execution Novel and Familiar Gestures.* We analyzed between group effects during gesture execution to determine the relationship of actual gesturing and brain activity. Groups did not differ in neural activation during performance of novel gestures (controls > patients and patients > controls). However, patients displayed hypoactivation during execution of familiar gestures within the premotor cortices (bilateral SMA, pre-SMA and cingulate motor areas; see table 2C).

*Association of Gesture Behavior With Neural Activation During Gesture Planning.* Accuracy of gesture performance was associated with the right DLPFC (middle frontal gyrus) activation during gesture planning in controls but with left inferior parietal lobe (IPL) activation in

patients (figure 3 and supplementary material: table S4). Moreover, the abnormal BOLD activity in limbic regions (right temporal pole, amygdala and hippocampus) during planning was significantly associated with the level of delusions in patients (figure 3 and supplementary material: table S4).

## Discussion

Defective gesture performance in schizophrenia substantially hampers social interaction, predicting poor functional outcome.<sup>11</sup> Thus, investigating gesture behavior provides a window to social communicative impairments in schizophrenia.<sup>14</sup> During social interaction gestures substitute or support verbal information. When encountering subjects with schizophrenia, both faulty or reduced nonverbal expression and biased nonverbal perception may contribute to poor understanding. While gesture impairments are currently being explored in schizophrenia spectrum disorders, very little is known on the neural underpinnings of this deficit.<sup>14</sup> Here we investigated neural correlates of gestural deficits in schizophrenia patients and well-matched healthy controls using fMRI. Results indicate aberrant neural activity most prominent during planning of gestures, which may contribute to poor gesture performance.

In line with previous studies, participants activated the praxis network when planning and executing hand gestures.<sup>26–28</sup> However, neural activation was generally less prominent and more left-lateralized in patients, which may explain behavioral gestural deficits. Furthermore, patients demonstrated aberrant activation of the bilateral

**Table 2.** Neural Activity During Planning and Execution of Novel and Familiar Gestures in Schizophrenia Patients and Healthy Controls

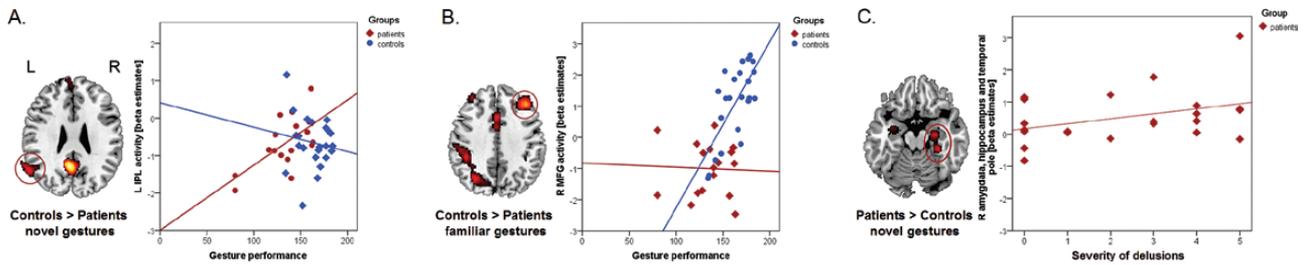
A Planning Novel Gestures							
Controls > Patients							
Brain Region	Cluster		Peak		MNI Coordinates		
	$P_{(FWE-corr)}$	$k$	$P_{(FWE-corr)}$	$T_{(90)}$	$x$	$y$	$z$
L IPL extending to SPL, L/R SMA, L IFG and STG	<.001	15 297	<.001	8.3	-38	-36	48
R IFG extending to STG	<.001	1522	<.001	6.6	58	16	-4
Left MTG and ITG/STG	<.001	1079	.001	6.3	-58	-52	2
R/left occipital gyrus/lingual gyrus/V1	<.001	3732	.03	5.5	20	-94	-10
L/R thalamus and L/R caudate head	.002	317	.04	5.4	10	2	8
R MFG (DLPFC) and IFG	<.001	738	.10	5.2	38	42	28
Patients > controls							
Brain region	Cluster		Peak		MNI coordinates		
	$P_{(FWE-corr)}$	$k$	$P_{(FWE-corr)}$	$T_{(90)}$	$x$	$y$	$z$
L IPL	<.001	1705	<.001	6.9	-58	-58	46
L mid cingulum/precuneus	<.001	1014	<.001	6.8	-4	-56	26
L temporal pole	<.001	1059	.001	6.3	-38	16	-34
R hippocampus, temporal pole	<.001	1383	.04	5.4	46	-4	-34
L hippocampus/amygdala	.001	349	.69	4.4	-30	-34	-18
L superior frontal gyrus (DMPCF) extending to the ACC	<.001	439	.77	4.4	-8	64	10
B Planning familiar gestures							
Controls > patients							
Brain region	Cluster		Peak		MNI coordinates		
	$P_{(FWE-corr)}$	$k$	$P_{(FWE-corr)}$	$T_{(90)}$	$x$	$y$	$z$
L/R SMA	<.001	19 257	<.001	7.7	36	-18	66
L STG extending to MTG and IFG	.004	290	.008	5.8	-58	16	-4
L IOG and MOG	<.001	2762	.02	5.6	-42	-86	-16
R MFG (DLPFC)	<.001	1186	.25	4.8	32	42	42
R IFG and OFG	<.001	804	.28	4.8	10	34	-18
Left IPL	.02	227	.4	4.7	-60	-26	32
R ITG and MTG	<.001	525	.67	4.4	58	-66	-14
Patients > controls							
L temporal pole extending to hippocampus and amygdala	<.001	1487	.04	5.4	-46	10	-28
R temporal pole extending to hippocampus and amygdala	<.001	919	.06	5.3	46	0	-30
C Execution familiar gestures							
L/R SMA, pre-SMA and mid cingulum	<.001	510	.50	4.578	-12	4	46
R/L cingulate motor areas	.006	269	.92	4.170	6	22	40

*Note:* (A) Between group effects of planning of novel and familiar gestures; (B) Between group effects of execution of familiar gestures. MOG, middle occipital gyrus; IOG, inferior occipital gyrus; IPL, inferior parietal lobe; SPL, superior parietal lobe; MTG, middle temporal gyrus; ITG, inferior temporal gyrus; STG, superior temporal gyrus; IFG, inferior frontal gyrus; SMA, supplementary motor area; PMv, ventral premotor area; OFG, orbitofrontal gyrus; MFG, middle frontal gyrus; DLPFC, dorsolateral prefrontal cortex; DMPCF, dorsomedial prefrontal cortex; ACC, anterior cingulate cortex; M1, primary motor cortex.

amygdala, hippocampus and temporal pole during gesture planning. Involvement of limbic areas such as amygdala in gesture performance has not been reported before, neither in studies in healthy subjects<sup>26,28</sup> nor in lesion studies.<sup>29,30</sup> Strikingly, limbic activation was associated with delusion severity in patients.

#### *Altered Activation of the Action Network and Mirror System in Patients*

Several factors may contribute to poor gesture processing in schizophrenia, eg, impaired action planning, working memory deficits, and motor abnormalities.<sup>14</sup> Therefore, one would expect aberrant brain activity in patients



**Fig. 3.** Association between gesture performance, delusion severity and neural activity in differentially activated brain areas. Spearman's rank correlation analysis of the neural activity in (A) the left IPL, (B) the right middle frontal gyrus and (C) association of neural activity in the right amygdala, hippocampus and temporal pole and severity of delusions within patients. MFG—middle frontal gyrus (DLPFC), IPL—inferior parietal lobe.

particularly in the IPL and frontal lobe including premotor cortex and areas of cognitive control. Here, patients demonstrated a relative hyperactivation of the IPL and the DMPFC as well as a relative hypoactivation of the DLPFC when planning novel gestures. In fact, this pattern contributed to the actual gesture accuracy: in patients performance was associated with left IPL activation, but in controls performance relied on right DLPFC activation. Thus, patients seem to engage the parietal components of the action network instead of the DLPFC. The frontal lobe is relevant for higher order motor control including action planning and execution.<sup>48</sup> In line with this, impaired gesturing in schizophrenia was linked to impaired frontal lobe function.<sup>3,4</sup> The DMPFC has been suggested to elaborate the meaning of communicative and social ambiguous stimuli.<sup>49,50</sup> Thus, the DMPFC hyperactivity in patients planning novel gestures may indicate the unsuccessful search for meaning in meaningless gestures.

Our results substantiate earlier findings demonstrating aberrant mirror neuron activation within the IPL during both action observation and action execution in schizophrenia.<sup>21</sup> The IPL contains so-called mirror-neurons.<sup>51</sup> Gesture performance and gesture perception are tightly coupled in schizophrenia.<sup>4</sup> In order to perform a gesture correctly, we need to integrate action planning and the semantic meaning. The mirror neuron system provides topographical overlap of motor and semantic representations.<sup>52</sup> Therefore, our results suggest that defective mirror system contributes to gestural deficits in schizophrenia.

Furthermore, our results complement reports investigating gesture perception in schizophrenia. In particular, gesture perception and planning of gesture performance engage overlapping brain areas (ie, the inferior frontal gyrus).<sup>13,16,34</sup> However, gesture execution demonstrated hypoactivation within the cingulate motor areas in patients, which is in contrast to previous reports on gesture perception. Finally, previous work suggested hand gesture performance to be linked to general severity of positive or negative symptoms with some inconsistency.<sup>4-6,11-13</sup> However, we detected no such association in our study. In conclusion, the combined investigation of neural correlates during gesture perception and

performance would be the next endeavor. Furthermore, we need to test whether aberrant neural activity in schizophrenia during gesture processing would indicate subjects with particularly poor social outcome.

#### *Aberrant Limbic Activation in Patients*

Our main results extend previous findings by showing that patients activate amygdala and temporal pole not only in response to affective stimulation<sup>53-55</sup> but also during gesture planning. We may speculate that the pathological activation of key emotion processing areas may distract gesture performance. Likewise, amygdala activity may drive emotional interference on cognitive processing.<sup>56</sup> Furthermore, the limbic cluster of activity including amygdala was associated with delusion severity. Limbic brain areas are critical for incentive salience and the evolution of delusions in schizophrenia.<sup>18,57-60</sup> Thus, our findings suggest incentive salience even during planning of socially relevant action. Indeed, perception and interpretation of gestures may be biased by delusions of reference or hallucinatory experience, particularly in socially ambiguous situations.<sup>17,61</sup>

The aberrant activation of limbic brain areas in patients was exclusively correlated with delusion severity but unrelated to gesture performance.

#### *Limitations*

In addition to patient status, other factors may have influenced brain activation in the current fMRI study including differences in task performance and medication effects. In order to account for performance differences, we excluded trials with major errors in both groups. Major errors comprised movements without temporal or spatial association with the requested gesture. Medication effects on the fMRI signal are equivocal, eg, antipsychotics may normalize limbic neural activity or have no effect at all.<sup>62,63</sup> In addition, medication may affect gesture performance. However, in our study gesture performance was not associated with dosage of antipsychotic medication (data not shown).

The group of schizophrenia patients presented with typical neurocognitive impairments which may affect gesture performance.<sup>4,64</sup> However, introducing frontal lobe function as a covariate to our imaging analyses, yielded substantially the same results. Our task was designed to investigate action planning and the execution of hand gestures, but does not allow contrasting the 2 conditions, as the execution phase directly followed the planning phase without jittering interval. Therefore, we do not directly compare brain activation during planning and execution. In fact, hemodynamic response functions in the bilateral SMA as shown in the supplementary material indicate that both conditions may elicit a neural response at single-subject level regardless of the absent jittering interval between the 2 experimental conditions (supplementary material: Analysis S4, figure S3).

Finally, our paradigm included a linguistic control task. While this control was useful to correct for unspecific semantic associations, it may at the same time hamper the detection of relevant neural signal in brain areas of the language network. In fact, some brain areas are active during both language and gesture processing, eg, the IFG.<sup>10,34,65</sup> Despite the linguistic control task, we detected brain activity during gesture planning in the IFG in both groups.

## Conclusion

In summary we demonstrated an aberrant pattern of brain activation during social action planning in schizophrenia, ie, gesture planning and execution. Patients' gesture performance relied on IPL instead of DLPFC activity, which is in line with the association of poor gesture performance and frontal lobe dysfunction. Finally, we observed aberrant limbic activity in patients during gesture planning, which was linked to delusion severity. Thus, the pathophysiology of gesture performance in schizophrenia involves reduced DLPFC impact and limbic interference. These functional alterations may contribute to poor gesture performance, poor social interaction and poor functional outcome in schizophrenia.

## Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin* online.

## Funding

This work was supported by the Bangerter-Rhyner Foundation (to S.W.) and the Swiss National Science Foundation (SNF grant 152619/1 to S.W., A.F., and S.B.).

## Acknowledgment

The authors have declared that there are no conflicts of interest in relation to the subject of this study.

## References

- Green MF, Horan WP, Lee J. Social cognition in schizophrenia. *Nat Rev Neurosci*. 2015;16:620–631.
- Walther S, Vanbellingen T, Müri R, Strik W, Bohlhalter S. Impaired gesture performance in schizophrenia: particular vulnerability of meaningless pantomimes. *Neuropsychologia*. 2013;51:2674–2678.
- Walther S, Vanbellingen T, Müri R, Strik W, Bohlhalter S. Impaired pantomime in schizophrenia: association with frontal lobe function. *Cortex*. 2013;49:520–527.
- Walther S, Stegmayer K, Sulzbacher J, et al. Nonverbal social communication and gesture control in schizophrenia. *Schizophr Bull*. 2015;41:338–345.
- Lavelle M, Healey PG, McCabe R. Is nonverbal communication disrupted in interactions involving patients with schizophrenia? *Schizophr Bull*. 2013;39:1150–1158.
- Millman ZBG, Goss J, Schiffman J, Mejias J, Gupta T, Mittal VA. Mismatch and lexical retrieval gestures are associated with visual information processing, verbal production, and symptomatology in youth at high risk for psychosis. *Schizophr Res*. 2014. In press.
- Stegmayer K, Moor J, Vanbellingen T, et al. Gesture performance in first- and multiple-episode patients with schizophrenia spectrum disorders. *Neuropsychobiology*. 2016;73:201–208.
- Mittal VA, Tessner KD, McMillan AL, Delawalla Z, Trotman HD, Walker EF. Gesture behavior in unmedicated schizotypal adolescents. *J Abnorm Psychol*. 2006;115:351–358.
- McNeill D. *Hand and Mind: What Gestures Reveal About Thought*. Chicago, IL: University of Chicago Press; 1992.
- Cartmill EA, Beilock S, Goldin-Meadow S. A word in the hand: action, gesture and mental representation in humans and non-human primates. *Philos Trans R Soc Lond B Biol Sci*. 2012;367:129–143.
- Walther S, Eisenhardt S, Bohlhalter S, et al. Gesture performance in schizophrenia predicts functional outcome after 6 months. *Schizophr Bull*. 2016;42:1326–1333.
- Park S, Matthews N, Gibson C. Imitation, simulation, and schizophrenia. *Schizophr Bull*. 2008;34:698–707.
- Matthews N, Gold BJ, Sekuler R, Park S. Gesture imitation in schizophrenia. *Schizophr Bull*. 2013;39:94–101.
- Walther S, Mittal VA. Why we should take a closer look at gestures. *Schizophr Bull*. 2016;42:259–261.
- Straube B, Green A, Sass K, Kircher T. Superior temporal sulcus disconnectivity during processing of metaphoric gestures in schizophrenia. *Schizophr Bull*. 2014;40:936–944.
- Straube B, Green A, Sass K, Kirner-Veselinovic A, Kircher T. Neural integration of speech and gesture in schizophrenia: evidence for differential processing of metaphoric gestures. *Hum Brain Mapp*. 2013;34:1696–1712.
- Bucci S, Startup M, Wynn P, Baker A, Lewin TJ. Referential delusions of communication and interpretations of gestures. *Psychiatry Res*. 2008;158:27–34.
- Pinkham AE, Liu P, Lu H, Kriegsmann M, Simpson C, Tamminga C. Amygdala hyperactivity at rest in paranoid individuals with schizophrenia. *Am J Psychiatry*. 2015;172:784–792.
- Stegmayer K, Horn H, Federspiel A, et al. Ventral striatum gray matter density reduction in patients with schizophrenia and psychotic emotional dysregulation. *Neuroimage Clin*. 2014;4:232–239.

20. Horan WP, Iacoboni M, Cross KA, et al. Self-reported empathy and neural activity during action imitation and observation in schizophrenia. *Neuroimage Clin*. 2014;5:100–108.
21. Thakkar KN, Peterman JS, Park S. Altered brain activation during action imitation and observation in schizophrenia: a translational approach to investigating social dysfunction in schizophrenia. *Am J Psychiatry*. 2014;171:539–548.
22. Mcneill D. So you think gestures are nonverbal. *Psychol Rev*. 1985;92:350–371.
23. Goodale MA, Milner AD. Separate visual pathways for perception and action. *Trends Neurosci*. 1992;15:20–25.
24. Binkofski F, Buxbaum LJ. Two action systems in the human brain. *Brain Lang*. 2013;127:222–229.
25. Rizzolatti G, Matelli M. Two different streams form the dorsal visual system: anatomy and functions. *Exp Brain Res*. 2003;153:146–157.
26. Bohlhalter S, Hattori N, Wheaton L, et al. Gesture subtype-dependent left lateralization of praxis planning: an event-related fMRI study. *Cereb Cortex*. 2009;19:1256–1262.
27. Vry MS, Tritschler LC, Hamzei F, et al. The ventral fiber pathway for pantomime of object use. *Neuroimage*. 2015;106:252–263.
28. Brandi ML, Wohlschläger A, Sorg C, Hermsdörfer J. The neural correlates of planning and executing actual tool use. *J Neurosci*. 2014;34:13183–13194.
29. Buxbaum LJ, Shapiro AD, Coslett HB. Critical brain regions for tool-related and imitative actions: a componential analysis. *Brain*. 2014;137:1971–1985.
30. Hoeren M, Kümmerer D, Bormann T, et al. Neural bases of imitation and pantomime in acute stroke patients: distinct streams for praxis. *Brain*. 2014;137:2796–2810.
31. Martin M, Nitschke K, Beume L, et al. Brain activity underlying tool-related and imitative skills after major left hemisphere stroke. *Brain*. 2016;139:1497–1516.
32. Manuel AL, Radman N, Mesot D, et al. Inter- and intra-hemispheric dissociations in ideomotor apraxia: a large-scale lesion-symptom mapping study in subacute brain-damaged patients. *Cereb Cortex*. 2013;23:2781–2789.
33. Goodale MA. Separate visual systems for perception and action: a framework for understanding cortical visual impairment. *Dev Med Child Neurol*. 2013;55(suppl 4):9–12.
34. Stegmayer K, Bohlhalter S, Vanbellinghen T, et al. Structural brain correlates of defective gesture performance in schizophrenia. *Cortex*. 2016;78:125–137.
35. Woods SW. Chlorpromazine equivalent doses for the newer atypical antipsychotics. *J Clin Psychiatry*. 2003;64:663–667.
36. Andreasen NC, Flaum M, Arndt S. The Comprehensive Assessment of Symptoms and History (CASH). An instrument for assessing diagnosis and psychopathology. *Arch Gen Psychiatry*. 1992;49:615–623.
37. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull*. 1987;13:261–276.
38. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry*. 1998;59(suppl 20):22–33;quiz 34–57.
39. Dubois B, Slachevsky A, Litvan I, Pillon B. The FAB: a Frontal Assessment Battery at bedside. *Neurology*. 2000;55:1621–1626.
40. Wechsler D. *Wechsler Memory Scale (WMS-III)*. San Antonio, TX: Psychological Corporation; 1997.
41. Ritter N, Kilinc E, Navruz B, Bae Y. Test Review: L. Brown, R. J. Sherbenou, & S. K. Johnsen Test of Nonverbal Intelligence-4 (TONI-4). Austin, TX: PRO-ED, 2010. *J Psychoeduc Assess*. 2011;29:484–488.
42. Fridman EA, Immisch I, Hanakawa T, et al. The role of the dorsal stream for gesture production. *Neuroimage*. 2006;29:417–428.
43. Króliczak G, Frey SH. A common network in the left cerebral hemisphere represents planning of tool use pantomimes and familiar intransitive gestures at the hand-independent level. *Cereb Cortex*. 2009;19:2396–2410.
44. Russ JB, Gur RC, Bilker WB. Validation of affective and neutral sentence content for prosodic testing. *Behav Res Methods*. 2008;40:935–939.
45. Vanbellinghen T, Kersten B, Van Hemelrijk B, et al. Comprehensive assessment of gesture production: a new test of upper limb apraxia (TULIA). *Eur J Neurol*. 2010;17:59–66.
46. Deichmann R, Schwarzbauer C, Turner R. Optimisation of the 3D MDEFT sequence for anatomical brain imaging: technical implications at 1.5 and 3 T. *Neuroimage*. 2004;21:757–767.
47. Brett M, Anton JL, Valabregue R, Poline JB. Region of interest analysis using an SPM toolbox [abstract]. Presented at the 8th International Conference on Functional Mapping of the Human Brain, Sendai: June 2–6, 2002 Vol 16, No 2 2002.
48. Miller EK, Cohen JD. An integrative theory of prefrontal cortex function. *Annu Rev Neurosci*. 2001;24:167–202.
49. Jenkins AC, Mitchell JP. Mentalizing under uncertainty: dissociated neural responses to ambiguous and unambiguous mental state inferences. *Cereb Cortex*. 2010;20:404–410.
50. Iacoboni M, Lieberman MD, Knowlton BJ, et al. Watching social interactions produces dorsomedial prefrontal and medial parietal BOLD fMRI signal increases compared to a resting baseline. *Neuroimage*. 2004;21:1167–1173.
51. Molenberghs P, Cunnington R, Mattingley JB. Brain regions with mirror properties: a meta-analysis of 125 human fMRI studies. *Neurosci Biobehav Rev*. 2012;36:341–349.
52. Rizzolatti G, Craighero L. The mirror-neuron system. *Annu Rev Neurosci*. 2004;27:169–192.
53. Anticevic A, Van Snellenberg JX, Cohen RE, Repovs G, Dowd EC, Barch DM. Amygdala recruitment in schizophrenia in response to aversive emotional material: a meta-analysis of neuroimaging studies. *Schizophr Bull*. 2012;38:608–621.
54. Marwick K, Hall J. Social cognition in schizophrenia: a review of face processing. *Br Med Bull*. 2008;88:43–58.
55. Taylor SF, Kang J, Brege IS, Tso IF, Hosanagar A, Johnson TD. Meta-analysis of functional neuroimaging studies of emotion perception and experience in schizophrenia. *Biol Psychiatry*. 2012;71:136–145.
56. Dolcos F, McCarthy G. Brain systems mediating cognitive interference by emotional distraction. *J Neurosci*. 2006;26:2072–2079.
57. Bracht T, Horn H, Strik W, et al. White matter pathway organization of the reward system is related to positive and negative symptoms in schizophrenia. *Schizophr Res*. 2014;153:136–142.
58. Winton-Brown TT, Fusar-Poli P, Ungless MA, Howes OD. Dopaminergic basis of salience dysregulation in psychosis. *Trends Neurosci*. 2014;37:85–94.
59. Menon M, Schmitz TW, Anderson AK, et al. Exploring the neural correlates of delusions of reference. *Biol Psychiatry*. 2011;70:1127–1133.

60. Heinz A, Schlagenhauf F. Dopaminergic dysfunction in schizophrenia: salience attribution revisited. *Schizophr Bull.* 2010;36:472–485.
61. White TP, Borgan F, Ralley O, Shergill SS. You looking at me?: Interpreting social cues in schizophrenia. *Psychol Med.* 2016;46:149–160.
62. Medoff DR, Holcomb HH, Lahti AC, Tamminga CA. Probing the human hippocampus using rCBF: contrasts in schizophrenia. *Hippocampus.* 2001;11:543–550.
63. Pankow A, Friedel E, Sterzer P, et al. Altered amygdala activation in schizophrenia patients during emotion processing. *Schizophr Res.* 2013;150:101–106.
64. Barch DM, Ceaser A. Cognition in schizophrenia: core psychological and neural mechanisms. *Trends Cogn Sci.* 2012;16:27–34.
65. Chang EF, Raygor KP, Berger MS. Contemporary model of language organization: an overview for neurosurgeons. *J Neurosurg.* 2015;122:250–261.