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Nonverbal Social Communication and Gesture Control in Schizophrenia

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Schizophrenia patients are severely impaired in nonverbal communication, including social perception and gesture production. However, the impact of nonverbal social perception on gestural behavior remains unknown, as is the contribution of negative symptoms, working memory, and abnormal motor behavior. Thus, the study tested whether poor nonverbal social perception was related to impaired gesture performance, gestural knowledge, or motor abnormalities. Forty-six patients with schizophrenia (80%), schizophreniform (15%), or schizoaffective disorder (5%) and 44 healthy controls matched for age, gender, and education were included. Participants completed 4 tasks on nonverbal communication including nonverbal social perception, gesture performance, gesture recognition, and tool use. In addition, they underwent comprehensive clinical and motor assessments. Patients presented impaired nonverbal communication in all tasks compared with controls. Furthermore, in contrast to controls, performance in patients was highly correlated between tasks, not explained by supramodal cognitive deficits such as working memory. Schizophrenia patients with impaired gesture performance also demonstrated poor nonverbal social perception, gestural knowledge, and tool use. Importantly, motor/frontal abnormalities negatively mediated the strong association between nonverbal social perception and gesture performance. The factors negative symptoms and antipsychotic dosage were unrelated to the nonverbal tasks. The study confirmed a generalized nonverbal communication deficit in schizophrenia. Specifically, the findings suggested that nonverbal social perception in schizophrenia has a relevant impact on gestural impairment beyond the negative influence of motor/frontal abnormalities.

Key words: social cognition/negative symptoms/pantomime/imitation

Introduction

Social impairments are a central feature of schizophrenia, and social cognition has been suggested as determinant for functional outcome.[1,2] Social cognition includes processes of social interaction, ie, perception, interpretation, and responding to social relevant stimuli.[3] Various domains of nonverbal communication are impaired in schizophrenia, such as facial emotion recognition[4] and imitation,[5] recognition of emotional prosody,[6] use of co-speech gestures,[7,8] and imitation of hand gestures.[9,10]

Successful nonverbal communication relies on both correct perception and expression of information. How nonverbal perception and expression influence each other in schizophrenia is poorly understood, as are the associations with clinical phenomena. Gestures are heterogeneous, complex expressive behaviors that may accompany speech including movements of fingers, hands, and arms. They may substitute or aid language comprehension and provide clues on cognitive action representation.[11–13] Here, we refer to hand and finger gestures related to transitive and intransitive symbolic information. Transitive gestures are tool related and require simulating the specific action in absence of the object (eg, signaling the use of a comb or a hammer). Intransitive gestures convey highly overlearned, emblematic information (eg, signaling stop or waving good bye). Both transitive and intransitive gestures are important components of everyday nonverbal communication. Schizophrenia patients use spontaneous hand gestures less frequently than healthy subjects.[7,8] In hand imitation tasks, patients perform less accurate than controls.[5,9,14] First studies report clear-cut gestural deficits in up to 67% of schizophrenia patients.[14] These gestural deficits encompass spatial and temporal errors as well as body part as object errors (eg, using the index finger when asked to demonstrate how to use a tooth brush).[10,14,15] Gesture deficits in schizophrenia have been linked to

negative symptoms, motor abnormalities (ie, parkinsonism and catatonia), frontal lobe dysfunction, and working memory impairments.[5,8–10,14]

Nonverbal social perception relates to the decoding of social relevant emotional information from various nonverbal cues such as facial affect, prosody, and body gestures.[16] Deficits of nonverbal social perception have been demonstrated in schizophrenia by using multimodal tasks,[16] including poor recognition of hand gestures. In fact, schizophrenia patients tend to misinterpret hand gestures.[17] Poor nonverbal social perception was reported to correlate with conceptual disorganization, but not with negative or positive symptoms.[16]

Correct gesture use is thought to rely on action representation and knowledge of the symbolic content of gestures.[11] Thus, to understand gestural deficits in schizophrenia, we need to test the association between nonverbal social perception, gestural knowledge, and gesture production. As mentioned above, clinical phenomena such as working memory deficits, negative symptoms, and motor abnormalities hamper gesture production in schizophrenia. Their contribution to gestural knowledge and nonverbal social perception requires elucidation. Finally, it has to be clarified whether impairments in the performance of transitive gestures resemble deficits in symbolic representation of action rather than true impairments of action. In other words, do patients suffer from impaired simulation of tool use or from actual defective tool use? For instance, apraxic stroke patients also perform poorly when pantomiming tool use but benefit from the physical properties of the tool during demonstration and actual use.[18]

The present study aimed to investigate whether gesture deficits in schizophrenia were related to nonverbal social perception, gesture knowledge, or actual tool use. Furthermore, we investigated the impact of clinical symptoms such as negative symptoms, working memory impairment, and motor abnormalities (parkinsonism, neurological soft signs [NSS], dyskinesia, and catatonia) on domains of nonverbal communication. We hypothesized that schizophrenia patients were impaired in all tasks on nonverbal communication (nonverbal social perception, gesture performance, gesture knowledge, and tool use). Furthermore, we expected poor nonverbal social perception and presence of motor abnormalities to impair gesture performance in schizophrenia.

Methods

Subjects

In total, 46 patients and 44 healthy control subjects matched for age, gender, and education were included in this study. Subjects were recruited from the inpatient and outpatient departments of the University Hospital of Psychiatry, Bern, Switzerland. Healthy controls were recruited among staff and via advertisement. All subjects were right handed as determined by the Edinburgh handedness inventory.[19] Exclusion criteria included substance abuse or dependence other than nicotine; past or current medical or neurological condition impairing movements, such as dystonia, idiopathic parkinsonism, or stroke; and history of head trauma with concurrent loss of consciousness. Exclusion criterion for patients was a history of electroconvulsive treatment. Exclusion criteria for controls were a history of any psychiatric disorder as well as any first-degree relatives with schizophrenia or schizoaffective disorder.

All participants were interviewed with the Mini International Neuropsychiatric Interview.[20] Patients were further interviewed with the Comprehensive Assessment of Symptoms and History.[21] Diagnoses were given according to Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria ($n = 37$ schizophrenia, $n = 2$ schizoaffective disorder, and $n = 7$ schizophreniform disorder). All but 4 patients received antipsychotic pharmacotherapy. Clinical and demographic data are given in table 1. All participants provided written informed consent. The protocol was approved by the local ethics committee.

Procedures

Nonverbal Communication Tests. Participants underwent behavioral tests on 4 tasks on nonverbal communication related to hand gestures (for detailed

Table 1. Demographic and Clinical Characteristics, Mean (SD)

Characteristic	Controls	Patients	F/X^2	P
No. (%) male	26 (59)	28 (63)	0.15	.83
Age (y)	38.77 (13.58)	37.96 (11.17)	0.10	.99
Education (y)	14.14 (2.66)	13.58 (3.03)	0.87	.99
TONI index	110.60 (10.33)	97.73 (11.03)	31.09	<.001
Digit span	5.36 (0.78)	4.37 (1.22)	20.47	<.001
AIMS	0.15 (0.71)	2.33 (3.86)	10.19	.02
BFCRS	0 (0)	1.63 (3.58)	9.12	.03
UPDRS III	0 (0)	7.09 (7.29)	41.56	<.001
NES	3.94 (4.84)	13.59 (11.45)	21.26	<.001
MRS	0 (0)	2.80 (5.21)	12.72	.006
FAB	17.57 (0.66)	16.16 (2.64)	11.90	.009
TLC		6.20 (7.72)		
SANS		24.87 (16.93)		
CAINS		17.96 (10.67)		
PANSS positive		18.00 (6.13)		
PANSS negative		18.33 (5.13)		
PANSS general		35.43 (8.36)		
CPZ (mg)		403.22 (346.98)		
Duration of illness (y)		12.89 (12.08)		

Note: AIMS, Abnormal Involuntary Movement Scale; BFCRS, Bush Francis Catatonia Rating Scale; UPDRS III, motor part of the Unified Parkinson's Disease Rating Scale; NES, Neurological Evaluation Scale; MRS, Modified Rogers Scale; FAB, Frontal Assessment Battery; TLC, Thought Language and Communication Scale; SANS, Scale for the Assessment of the Negative Syndrome; CAINS, Clinical Assessment Interview for Negative Symptoms; PANSS, Positive and Negative Syndrome Scale; P values adjusted for multiple comparisons.

description, see supplementary material). In all tasks, higher scores indicate superior performance. The test of upper limb apraxia (TULIA)[22] is a comprehensive assessment of gesture production in 2 domains: following demonstration by the examiner (imitation) or on verbal command (pantomime). Performance of 48 items was videotaped. Evaluation rated content and temporal-spatial errors (for details, see supplementary material). Total scores range 0–240. All ratings were performed by a single rater blind to diagnoses and clinical presentation (S.W.), who had been trained by the test developers (T.V. and S.B.). Intraclass correlations exceeded .83.

The Tool-Use test[18] additionally examines the demonstration and actual use of tools. Specifically, 3 conditions using a scoop and a hammer are evaluated: pantomime (without the tool), demonstration (with the tool), and actual use (with a recipient object). Each tool is tested in 3 trials per condition. Performance was videotaped and later evaluated considering grip formation, movement execution, movement direction, and spatial errors. Total scores range 0–72. Tool use was evaluated by 2 raters blind to diagnoses and clinical presentation, who had been extensively trained. Interrater reliability met intraclass correlations of .86.

The modified postural knowledge task (PKT)[23,24] is a gesture recognition task. Participants were presented with cartoons of persons carrying out 10 intransitive and 10 transitive actions, while the distal parts of the executing limbs are not shown. Below each cartoon, 3 images of limb positions are given including the correct one. Participants have to choose the correct match. In addition, 10 images of 3 hands holding objects were presented, again with 2 versions of incorrect grip and position and 1 correct. Total scores range 0–30.

We applied the Mini Profile of Nonverbal Sensitivity (Mini-PONS)[25] to test social perception. The Mini-PONS includes 64 scenes from the original PONS,[26] in which short videos of 2 s each present a white woman with altering facial expression, voice intonation, and/or bodily gestures. Participants had to choose from 2 options the one that best describes the observed situation immediately after watching the video, eg, saying a prayer or talking to a lost child. The total scores range 0–64.

Clinical Assessments. Furthermore, we investigated motor abnormalities in the participants using clinical rating scales to assess abnormal involuntary movements, parkinsonism, NSS, and catatonic behavior. We applied the Abnormal Involuntary Movement Scale (AIMS),[27] the motor part of the Unified Parkinson's Disease Rating Scale (UPDRS III),[28] the Neurological Evaluation Scale (NES),[29] the Bush Francis Catatonia Rating Scale (BFCRS),[30] and the Modified Rogers Scale.[31] In addition, we applied the Frontal Assessment Battery (FAB).[32] Verbal working memory was assessed with the digit span backward from the Wechsler Memory Scale.[33]

In all motor rating scales, higher scores indicate the presence of motor abnormalities. In contrast, in the FAB and digit span, higher scores indicate superior performance. In all subjects, nonverbal intelligence was measured with the Test of Nonverbal Intelligence (TONI).[34]

In the patients, we further assessed the Positive and Negative Syndrome Scale (PANSS)[35] and the Thought Language and Communication scale[36] to monitor formal thought disorder and 2 scales for negative syndrome severity: the Scales for the Assessment of Negative Syndrome (SANS)[37] and the Clinical Assessment Interview for Negative Symptoms (CAINS).[38] The clinical assessments have been performed by a single expert psychiatrist (K.S.), who had been trained by the senior investigator to achieve interrater reliabilities of $\kappa > .80$.

The total assessment had approximately 5 hours duration for patients and approximately 4 hours for controls. In many subjects, tests were performed on 2 consecutive days.

Statistical Analyses

Demographic and clinical data were compared between groups using ANOVAs or chi-square tests where appropriate. In patients, the clinical rating scales were subject to principal component analysis (PCA) extracting components with eigenvalues > 1 and subsequent varimax rotation (for details, see supplementary material). PCA yielded 4 factors explaining a sum of 83.5% of the variance: (1) negative symptoms (30.1%, including PANSS negative, PANSS general, CAINS, and SANS), (2) motor/frontal abnormalities (25.7%, including UPDRS motor part, NES, BFCRS, FAB, and digit span backward), (3) positive symptoms/working memory (14.0%, including PANSS positive, PANSS general, and digit span backward), and (4) dyskinesia/catatonia (13.7%, including AIMS and BFCRS). Factor scores were extracted for further analyses.

First, we compared total scores of the tasks on nonverbal communication (TULIA, PKT, PONS, and Tool-Use) between groups using ANCOVAs controlling for TONI index score and digit span, as groups differed in these variables (table 1). Second, we explored whether performance in one of the nonverbal communication tasks was related to the performance of the other tasks for both groups separately. In controls, we were interested in whether associations were found in the absence of major motor or cognitive impairments. As both medication and age were shown to influence gesture performance and recognition,[10,14,39] we calculated the correlations between the 4 tasks using within-group partial correlations correcting for age and chlorpromazine equivalents (CPZ) in patients and correcting for age in controls. Third, we investigated within-group associations between the 4 nonverbal

communication tasks and the 4 clinical factors, age, and CPZ in stepwise regression analyses. Finally, we explored the association between nonverbal social perception and gesture performance using (1) partial correlations correcting for age, CPZ, and the factor motor/frontal abnormalities, (2) a series of regression models to test whether motor/frontal abnormalities were mediating or moderating this association, and (3) a hierarchical regression analysis, in which motor/frontal abnormalities were the first step and nonverbal social perception was the second step to determine the effect on gesture performance. All analyses were conducted in SPSS22 (IBM). Tests were corrected for multiple comparisons ($P_{corr} = P \times n$), with n being the number of tests.

Results

Between-Group Differences in Nonverbal Communication

Controls had superior performance in the nonverbal intelligence test and the digit span backward and less motor abnormalities and frontal lobe dysfunction compared with schizophrenia patients (table 1). Patients had inferior performance in all tasks of nonverbal communication (table 2) when controlling for nonverbal intelligence and working memory. Applying the cutoff scores,[14,18] 45.7% of schizophrenia patients had gesture performance deficits (47.8% pantomime and 32.6% imitation) and 37.8% were impaired in the Tool Use task (37.8% pantomime, 11.1% demonstration, and 11.1% use).

Within-Group Correlations

Controls. In controls, none of the nonverbal communication tasks correlated significantly with any other. Partial correlations corrected for age indicated that gesture performance, gestural knowledge, and nonverbal social perception were related to higher IQ (supplementary table S2). In contrast, gestural knowledge and nonverbal social perception were correlated with longer duration of education, and gesture performance was correlated with better working memory performance. Finally, tool use performance was unrelated to any of the descriptive variables.

Patients. In patients, the performance between each of the nonverbal communication tasks was strongly correlated (table 3), except the correlation between nonverbal social perception (PONS) and tool use at trend level. Particularly, gesture performance was closely linked to gestural knowledge, tool use, and nonverbal social perception. The correlations between communication tasks remained significant even when correcting for verbal working memory impairments, age, and CPZ (supplementary table S3). Furthermore, nonverbal communication task performances demonstrated significant partial correlations with clinical variables when correcting for age and CPZ (supplementary tables S4 and S5).

Next, the contributions of age, CPZ, and the 4 clinical factors to the 4 nonverbal communication tasks were tested using stepwise linear regression models (table 4). All 4 tasks were associated with motor/frontal abnormalities. Beyond these associations, gesture performance was related to age, positive symptoms, and the dyskinesia/catatonia factor. Furthermore, nonverbal social perception was explained by positive symptoms/working memory and tool use by dyskinesia/catatonia. The negative symptom factor and CPZ were excluded in each model.

Finally, we explored whether intact nonverbal social perception was critical for correct performance of hand gestures and whether motor/frontal abnormalities may hamper this association. Partial correlations suggested that nonverbal social perception was associated with better performance of hand gestures ($r = 0.34$, $P = .04$) when correcting for age, CPZ, and the factor motor/frontal abnormalities. Figure 1 depicts the mediator analysis. In patients, superior nonverbal social perception is associated with correct performance of hand gestures (top panel). Although adding motor/frontal abnormalities to the model decreased the effect of nonverbal social perception on gesture performance, the association still remained significant, while the explained variance was increased (lower panel). In other words, motor/frontal abnormalities only partially mediated the effect of nonverbal social perception on gesture performance. In addition, there was no interaction effect of

Table 2. Group Comparisons of Task Performance, Mean (SD) With Covariates TONI and Digit Span Backward

	Controls ($n = 44$)	Patients ($n = 46$)	F ($df = 3$)	P
TULIA	225.67 (7.75)	206.13 (28.12)	13.88	<.001
PKT	27.31 (1.44)	24.41 (4.34)	10.98	<.001
PONS	46.67 (4.42)	41.42 (6.03)	19.88	<.001
Tool Use	71.93 (0.46)	69.59 (4.28)	8.77	<.001

Note: TONI, Test of Nonverbal Intelligence; TULIA, test of upper limb apraxia; PKT, postural knowledge task; PONS, Profile of Nonverbal Sensitivity; P values adjusted for multiple comparisons.

Table 3. Partial Correlations Between Tasks in Patients ($n = 46$), Corrected for Age and CPZ

	PONS		PKT		Tool Use	
	r	P	r	P	r	P
TULIA	.57	<.001	.76	<.001	.75	<.001
PONS			.52	.003	.38	.07
PKT					.51	.005

Note: Abbreviations are explained in the first footnote to table 2. P values adjusted for multiple comparisons.

Table 4. Factors Impacting Nonverbal Communication Tasks

Model	R^2_{corr}	*df*	*F*	*P*	Predictor	β	*T*	*P*
TULIA	.60	4, 41	17.80	<.001	Motor/frontal	−.56	−5.39	<.001
					Age	−.27	−2.60	.01
					Positive/WM	−.22	−2.33	.03
					Dyskinesia/catatonia	−.22	−2.28	.03
PONS	.46	2, 43	20.06	<.001	Motor/frontal	−.53	−4.81	<.001
					Positive/WM	−.45	−4.08	<.001
PKT	.23	1, 44	14.37	<.001	Motor/frontal	−.50	−3.79	<.001
Tool use	.54	2, 43	27.41	<.001	Motor/frontal	−.69	−6.78	<.001
					Dyskinesia/catatonia	−.26	−2.53	.02

Note: Abbreviations are explained in the first footnote to table 2. WM, working memory. Collinearity statistics: tolerance > 0.82, variance inflation factor < 1.22.

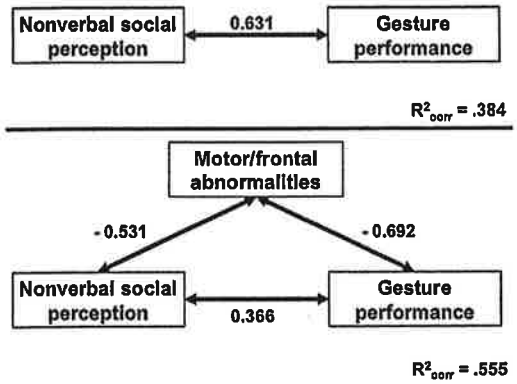

Fig. 1. Association of social perception, motor/frontal abnormalities, and gesture performance. Upper panel: direct association between nonverbal social perception (PONS) and gesture performance (TULIA). Lower panel: inclusion of the mediator motor/frontal abnormalities (motor/frontal factor). Numbers indicate beta-weights. Note that the association between nonverbal social perception and gesture performance is weaker in the lower panel, suggesting a partial mediator effect of motor/frontal abnormalities.

nonverbal social perception and motor/frontal abnormalities on gesture performance (data not shown). Hierarchical regression analysis indicated that nonverbal social perception had an effect on gesture performance beyond motor/frontal abnormalities (model 1: motor/frontal abnormalities $R^2 = .48$, $F_{(change)}[1, 44] = 40.39$, $P_{(change)} < .001$, motor/frontal abnormalities $\beta = -.69$, $P < .001$; model 2: nonverbal social perception $\Delta R^2 = .10$, $F_{(change)}[2, 43] = 9.75$, $P_{(change)} = .003$, motor/frontal abnormalities $\beta = -.50$, $P < .001$, nonverbal social perception $\beta = .37$, $P = .003$).

Discussion

The present study on nonverbal communication deficits in schizophrenia yielded 4 main findings. First, we confirmed impairments in nonverbal social perception and gesture production in schizophrenia.[1,10,14,16,40] In addition, patients had deficits in gestural knowledge and actual tool use. Second, as hypothesized, in schizophrenia, deficits in gesture performance were associated with impairments in nonverbal social perception, gesture knowledge, and tool use. In contrast, performance in these tasks was not correlated in controls. Third, motor/frontal abnormalities were the common factors associated with poor performance in all 4 nonverbal tasks in patients. Still, beyond motor abnormalities, the tasks were associated with distinct clinical factors. Fourth, poor nonverbal social perception was associated with impaired gesture performance and this association was only partially mediated by motor/frontal abnormalities. In contrast, a smaller ecological study failed to find an association between nonverbal social perception and spontaneous gesture use in schizophrenia.[8]

Motor Abnormalities Impaired Nonverbal Communication

Motor abnormalities are an intrinsic dimension of schizophrenia present even before the onset of the full blown disorder and often deteriorated by antipsychotic treatment.[41–44] The motor phenomena include catatonia, parkinsonism, abnormal involuntary movements, and NSS.[42] We hypothesized that motor abnormalities would contribute to nonverbal social communication, particularly to expressive gestures or body posture and action imitation. Indeed, the factor motor/frontal abnormalities (including parkinsonism, NSS, catatonia, frontal dysfunction, and working memory) correlated inversely with all tasks. In addition, the dyskinesia/catatonia factor also correlated inversely with gesture production and tool use. Thus, the presence of motor/frontal abnormalities impairs perception and expression of nonverbal communication in schizophrenia. Impaired gesture performance has been linked to motor abnormalities and frontal lobe dysfunction before.[10] Consequently, patients with motor abnormalities are prone to impairments in nonverbal communication. This is not only relevant for chronic schizophrenia but also for subjects at risk for psychosis and first episode patients with schizophrenia. Both groups may experience motor abnormalities[45,46]

and deficits in social cognition.[47] Therefore, it is conceivable that some of the social cognitive impairments are related to motor abnormalities. Indeed, young patients with schizotypal disorder use gestures less frequently than controls.[48] Furthermore, subjects at ultrahigh risk of psychosis demonstrate content errors of spontaneous co-speech gestures.[49]

Link of Social Perception and Gesture Control: Mirror Neurons and Theory of Mind

Part of the strong relationship of social perception and gesture control was independent of motor/frontal abnormalities as demonstrated by the mediation analysis. Furthermore, hierarchical regression confirmed that the impact of nonverbal social perception on gesture performance was greater than the negative impact of motor/frontal abnormalities although regression models are not suited to finally prove causal relationships. In case a patient had sufficient nonverbal social perception abilities, the presence of significant motor/frontal abnormalities would, therefore, impair but not perish gesture performance.

A possible link between social perception and gesture control may be viewed in the light of embodied cognition, in which gestures were suggested to mediate between action and its mental representation.[11] Particularly, the mirror mechanism indicates that motor acts of others are understood by the same mechanism underlying the execution of these motor acts. Furthermore, the mirror mechanism of motor behavior is critical for the interpretation of goals and intentions of others.[50] Another model claims that action semantics, ie, knowledge on specific actions and their meaning, is critical to understand action of others.[51] Thus, the knowledge of the abstract meaning of gestures along with the action representation must, therefore, be critical for correct gesture performance.

The brain areas involved in gesture production, gesture observation, action imitation, and action observation are broadly the same: inferior frontal gyrus (IFG), insula and inferior parietal lobule (IPL).[24,52–55] Imitation and observation of hand gestures activate the right IPL and the medial prefrontal cortex, thus engaging the mirror neuron system and the mentalizing system.[55] In schizophrenia, aberrant neural activation was detected during the processing of metaphoric gestures in the left IFG and left superior temporal sulcus (STS).[56,57] Likewise, patients had abnormal activation during imitation and observation of finger movements within the IPL and STS.[58] Therefore, the cerebral motor system including cortical premotor areas may contribute to social cognitive deficits in schizophrenia during the perception, interpretation, and production of actions such as hand gestures and body postures.

Current psychological treatment programs to enhance social cognition efficiently improve emotion recognition but fail to impact more complex measures of nonverbal social perception.[59] A specific add-on training of hand gestures may increase and generalize the effects of current social skills training approaches. Furthermore, our data suggest considering some aspects of motor behavior when assessing social cognition. In fact, hand gestures and head and body movements are used for nonverbal expression in social interactions.

Negative Symptoms and Working Memory in Nonverbal Communication

Negative symptoms could have impact on social interaction, thus impair social cognition.[3,60] The results of our study were conflicting: the negative factor of the PCA failed to correlate with any nonverbal communication task. However, in line with previous reports, impaired gesture performance, tool use, and gestural knowledge correlated with increased ratings in CAINS, SANS, and PANSS negative.[5,9,10,14] Still, nonverbal social perception (PONS) lacked correlation with negative symptoms, as in other studies.[1,16] The discrepancy between tests might be due to the composition of the negative factor in the PCA. In sum, our results argue against a general impact of negative symptoms on nonverbal communication in schizophrenia. Instead, negative symptoms may impact expression but not perception of nonverbal social interaction.

Schizophrenia has been associated with a generalized supramodal impairment in working memory.[61] In fact, imitation of hand gestures was linked to working memory in schizophrenia before.[9] However, our results argue against a specific effect on gesture production and in favor of a generalized effect on nonverbal communication. Indeed, the test of verbal working memory correlated with each of the 4 tasks (supplementary table S4). Furthermore, working memory was part of the factor motor/frontal abnormalities that correlated with all nonverbal tasks. The correlations between the tasks remain significant in schizophrenia even when controlling for working memory (supplementary table S3).

In controls, we found no correlation between the 4 nonverbal communication tasks. This lack of association would argue for distinct processes and abilities between gesture performance, gesture knowledge, tool use, and social perception. The scores of the gesture knowledge (PKT) and the Tool Use task clearly demonstrate a ceiling effect because these tests were developed for use in elderly subjects with apraxia.[18,23,39,62] However, tasks of nonverbal social perception (PONS) and gesture performance (TULIA) were designed to avoid ceiling effects and have sufficient variance in our sample. Still, nonverbal social perception and gesture performance were unrelated in healthy subjects in contrast to patients with schizophrenia.

Patients and controls were well matched for age, gender, and educational level. However, they still differed in nonverbal IQ and working memory performance. Therefore, we had to include these parameters as covariates in the group comparisons. We investigated a heterogeneous group of

patients concerning age, duration of illness, and symptom severity. Therefore, gesture performance was better in this sample than in our previous study.[14] In order to account for effects of treatment and age, CPZ and age were control variables in partial correlation analyses. Of course, controlling for antipsychotic medication dose will not exclude medication effects. Furthermore, although we excluded patients with current comorbid disorders based on diagnostic interviews, we cannot completely exclude comorbidity effects of subsyndromal disturbances or undeclared past disorders.

Conclusion

In conclusion, schizophrenia patients presented generalized impairments in 4 tasks of nonverbal communication. In addition, patients with motor/frontal abnormalities had more difficulties in the tasks. Finally, irrespective of the negative influence of motor/frontal impairments, there was a strong association between nonverbal social perception and gesture performance pointing to a mirror mechanism of gesture behavior. Future studies should focus on the underlying brain alterations and establish whether specific interventions on motor abnormalities may aid social cognition.

Supplementary Material

Supplementary material is available at http://schizophreniabulletin.oxfordjournals.org.

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Supplemental material to "Nonverbal social communication and gesture control in schizophrenia"

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Methods

Nonverbal communication tasks

TULIA

The Test of Upper Limb Apraxia (TULIA)[1] is a comprehensive assessment of gesture production in two domains: either following demonstration by the examiner (imitation) or on verbal command (pantomime). Both domains include three semantic categories of hand gestures: meaningless (e.g. „lay your hand flat on your head", transitive (tool related, e.g. „demonstrate how to use a toothbrush") and intransitive (symbolic and non-tool related, e.g. „salute like a soldier"). The order of the domains was randomized across participants. The participants performed the TULIA with their right hand. The TULIA includes 48 items, each rated on a scale from 0-5, with higher scores indicating better performance (total score 0-240). Performance was recorded on video and rated by one rater (SW) blind to diagnosis and clinical presentation. The rater had been previously trained by the test developers (TV and SB). Intraclass correlations exceeded .83. The TULIA has excellent internal consistency, strong test-retest reliability and excellent interrater reliability with intraclass correlations ranging .89 - .99[1].

Evaluation rated content (e.g. substitutions or perseverations) as well as temporal-spatial errors (e.g. hesitations, wrong movement trajectories or final positions, omissions, body-part-as-object errors). Perseverations are wrong movements that have previously been tested. Body-part-as-object errors relate to use of fingers to represent tools instead of simulating the tool use, e.g. moving the index finger horizontally in front of the mouth when ask to demonstrate how to use a toothbrush.

Tool Use

The Tool-Use test[2] examines the use of a scoop and a hammer in three conditions: pantomime (without the tool), demonstration (with the tool) and actual use (with a recipient object). The participants are sitting on a table with all relevant objects on top, but the tools are in reverse position in order to test the correct grip. Each tool is tested in three trials per condition. Ratings include grip formation, movement execution, direction of movement, and space. If performed correctly, the condition is rated with 4 points. The total score is the sum of all ratings of all trials in all conditions with both tools (total score 0-72 points). The order of conditions was randomized across participants. The Tool Use performance was recorded on video. Videos contained no information on clinical presentation or diagnoses and were rated by two independent raters (KS and NS, interrater reliability: intraclass correlations .86). Participants performed the Tool Use test with their right hand. The Tool-Use test was developed to test the difference between impaired simulation of tool use (pantomime) and actual tool use in patients with apraxia. Applying this test in schizophrenia we can disentangle whether patients have problems with abstract use of tool-related gestures (pantomime condition), or problems with the haptic properties of the tools (demonstration condition) or problems during actual tool use with recipient objects (e.g. hammer and nail).

PKT

The modified postural knowledge task (PKT)[3, 4] is a gesture recognition task administered on paper sheets. Participants were presented with cartoons of persons carrying out 10 intransitive and 10 transitive actions, while the distal parts of the executing limbs are not shown. Below each cartoon, three images of limb positions are given including the correct one. The participants had to choose as quickly as possible the correct matching image. In addition, 10 images of three hands holding objects were presented, again with two versions of incorrect grip and position and one correct. Participants had to choose the correct one. Before the PKT was run, two test images per condition were presented. The examiner entered the response on the scoring sheet. The total score is derived from the sum of correct responses (0-30).

Mini-PONS

We applied the Mini Profile of Nonverbal Sensitivity (Mini-PONS)[5] as a comprehensive test of social perception. The Mini-PONS includes 64 scenes from the original PONS[6], in which short videos of 2 s each present a white woman with altering facial expression, voice intonation and/or bodily gestures. The Mini-PONS contains 50%

scenes with positive and 50% with negative affective valence. It has good agreement with the original PONS but the advantages of reduced administration time (15 min) and more focused assessments, because it is limited to scenes with average levels of difficulty. The Mini-PONS includes 16 stimuli of each of the following: voice, face and voice, face, and body gestures. We used E-prime software to present stimuli in randomized order. Participants had to choose from two options the one that best describes the observed situation immediately after watching the video, e.g. saying a prayer or talking to a lost child. Participants entered the responses using a keyboard with no time limit. The total score corresponds to the number of correct responses (0-64). The original PONS contains 220 stimuli, but in previous studies with schizophrenia patients, shorter versions with 110 stimuli were used in order to sustain attention throughout the test[7].

Verbal working memory

Digit span backwards

Verbal working memory was assessed with the digit span backwards from the Wechsler Memory Scale[8] in which the participant is presented with digits at a rate of one per second. The backward test requires the participant to repeat the digits in reverse order. The number of digits increases by one until the participant consecutively fails two trials of the same digit span length.

Principal component analysis of the clinical rating scales

The clinical rating scales were entered in a principal component analysis (PCA). We entered the PANSS subscores, two rating scales for negative symptoms (CAINS and SANS), four scales for motor signs (UPDRS motor, NES, AIMS, BFCRS), the FAB and the digit span as well as a scale for the assessment of formal thought disorder (TLC). The TLC, however, had to be removed from the PCA because of insufficient association with the other variables as indicated by a low Kayser-Mayer-Olkin measure (< .5). Thus, we finally entered PANSS positive, PANSS negative, PANSS general, CAINS, SANS, TLC, FAB, Digit span, AIMS, UPDRS motor part, BFCRS, and NES. The overall Kayser-Mayer-Olkin measure (.785) for the whole model was good. We extracted components with an Eigenvalue > 1. The screeplot indicated 4 components. Afterwards, a varimax rotation was performed. This resulted in 4 factors that explained a sum of 82.5% of the variance.

1st factor: negative symptoms – 30.08% of the variance; 2nd factor: motor/frontal abnormalities - 25.71% of the variance; 3rd factor: positive symptoms/working memory - 13.97% of the variance; 4th factor: dyskinesia/catatonia – 13.71% of the variance. The 4 factors were not correlated with each other (r-range: -.029 - .064). The pattern matrics of the rotated factor loadings is given below.

Table S1. Pattern matrics of the four components

Pattern matrics[a]				
	Components			
	negative	motor/frontal	positive	dys/cat
PANSS positive			.879	
PANSS negative	.890			
PANSS general	.775		.432	
AIMS				.863
UPDRS motor part		.790		
BFCRS		.570		.649
NES		.862		
SANS	.919			
CAINS	.849			
FAB		-.774		
Digit span backwards		-.547	-.676	
Principal component analysis, varimax rotation with Kaiser-normalization[a]				
[a] Rotation converged in 7 iterations. coefficients < 0.4 suppressed				

Results

Table S2. Partial correlations in controls

	TULIA		PONS		PKT		Tool Use	
	r	p	R	p	r	p	r	p
Duration of education	.27	.08	**.41**	**.007**	**.31**	**.04**	.06	.72
TONI index score	**.36**	**.02**	**.31**	**.05**	**.42**	**.006**	- .14	.37
Digit span backwards	**.41**	**.006**	.15	.35	.17	.28	.06	.70
Motor Assessments								
AIMS	- .01	.98	- .24	.20	.14	.45	.05	.80
BFCRS								
MRS								
NES	- .21	.24	- .18	.32	- .06	.74	.12	.52
UPDRS III								

Partial correlations correcting for age. Note that partial correlations for BFCRS, MRS and UPDRS in controls are impossible to calculate as the scores are all 0. p-values uncorrected for multiple comparisons.

Table S3. Partial correlations of Tasks controlling for age, CPZ and digit span in 46 schizophrenia patients

	PONS		PKT		Tool Use	
	r	p	r	p	r	p
TULIA	**.40**	**.02**	**.65**	**< .001**	**.70**	**< .001**
PONS			**.40**	**.02**	.18	.31
PKT					**.40**	**.01**

Uncorrected p-values

Table S4. Partial correlations of task performance and descriptive measures in patients (n = 46).

	TULIA		PONS		PKT		Tool Use	
	r	p	r	p	r	p	r	p
Duration of education	.16	.29	**.34**	**.03**	.07	.66	.16	.32
TONI index score	.11	.49	**.33**	**.03**	.23	.14	.08	.63
Digit span backwards	**.47**	**.003**	**.62**	**< .001**	**.36**	**.03**	**.42**	**.01**
Motor Assessments								
AIMS	- .29	.05	.06	.72	- .03	.84	**- .31**	**.04**
BFCRS	**- .67**	**< .001**	- .26	.09	**- .34**	**.02**	**- .63**	**< .001**
MRS	**- .49**	**.001**	- .02	.88	- .16	.29	**- .52**	**< .001**
NES	**- .61**	**< .001**	**- .49**	**.001**	**- .50**	**.001**	**- .68**	**< .001**
UPDRS III	**-0.50**	**.001**	- .17	.27	**- .38**	**.01**	**- .58**	**< .001**
Clinical Rating Scales								
FAB	**.74**	**< .001**	**.51**	**.001**	**.77**	**<.001**	**.60**	**< .001**
TLC	- .21	.17	- .19	.23	- .08	.62	- .01	.98
SANS	**- .35**	**0.02**	.03	.87	- .20	.20	**- .35**	**.02**
CAINS	**- .39**	**.01**	- .12	.45	**- .34**	**.03**	**- .37**	**.02**
PANSS negative	**- .47**	**.001**	- .11	.50	**- .31**	**.04**	**- .46**	**.002**
PANSS positive	- .19	.22	- .31	.05	- .07	.65	- .08	.61
PANSS general	**- .32**	**.03**	- .11	.50	- .17	.28	- .20	.19

Partial correlations correcting for age and CPZ. P-values uncorrected for multiple comparisons

Table S5. Partial correlations of communication tasks and clinical factors correcting for age and CPZ.

	TULIA		PONS		PKT		Tool Use	
	r	p	r	p	r	p	r	p
Factor negative	-0.171	0.298	0.123	0.470	-0.111	0.499	-0.153	0.359
Factor motor/frontal	**-0.687**	**< 0.001**	**-0.514**	**< 0.001**	**-0.557**	**< 0.001**	**-0.729**	**< 0.001**
Factor positive/WM	-0.303	0.061	**-0.549**	**< 0.001**	-0.247	0.129	-0.139	0.404
Factor dyskinesia/catatonia	-0.294	0.069	0.123	0.468	-0.008	0.962	-0.282	0.086

Uncorrected p-values

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Gesture Performance in Schizophrenia Predicts Functional Outcome After 6 Months

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The functional outcome of schizophrenia is heterogeneous and markers of the course are missing. Functional outcome is associated with social cognition and negative symptoms. Gesture performance and nonverbal social perception are critically impaired in schizophrenia. Here, we tested whether gesture performance or nonverbal social perception could predict functional outcome and the ability to adequately perform relevant skills of everyday function (functional capacity) after 6 months. In a naturalistic longitudinal study, 28 patients with schizophrenia completed tests of nonverbal communication at baseline and follow-up. In addition, functional outcome, social and occupational functioning, as well as functional capacity at follow-up were assessed. Gesture performance and nonverbal social perception at baseline predicted negative symptoms, functional outcome, and functional capacity at 6-month follow-up. Gesture performance predicted functional outcome beyond the baseline measure of functioning. Patients with gesture deficits at baseline had stable negative symptoms and experienced a decline in social functioning. While in patients without gesture deficits, negative symptom severity decreased and social functioning remained stable. Thus, a simple test of hand gesture performance at baseline may indicate favorable outcomes in short-term follow-up. The results further support the importance of nonverbal communication skills in subjects with schizophrenia.

Key words: nonverbal communication/negative symptoms/psychosis/hand gestures/social perception

Introduction

The outcome of schizophrenia is very heterogeneous, ranging from functional recovery to substantial decline.[1–3] While remission, that is, a low level of positive and negative symptoms, is frequently achieved with adequate treatment in the first episodes, only 40% of patients may achieve social or functional recovery, that is, vocational and social functioning in the normal range.[2] The achievement of functional recovery is not necessarily linked to remission of symptoms.[4] Meta-analyses demonstrated poor functional outcome to be related to impaired cognition, with slightly stronger effects of social cognition than neurocognition on outcomes.[5] The poor long-term outcome observed in some patients with schizophrenia is a result of several factors, including the course of the illness, social adversities, and availability of mental health care.[2] In addition, severe negative symptoms in the early course have frequently been reported in subjects with poor outcome.[3] Clinicians today have no reliable and readily available markers of treatment outcomes in schizophrenia. However, to truly individualize treatment efforts, markers are clearly needed.[6]

Two symptom domains share a putative association with poor outcome in schizophrenia, that is, negative symptoms and impaired social cognition. Indeed, negative symptoms contribute to poor functional outcome and may also moderate the effect of cognitive impairment on functional outcome.[7] This is particularly true for the early course of schizophrenia.[8] Among negative symptoms, motivational deficits are particularly relevant for poor functional outcome in schizophrenia.[9–11] Negative symptoms tend to be stable over time, also in the early course.[12–14] Even though, findings of a recent meta-analysis suggest that negative symptoms may substantially improve in outpatient settings.[15]

Social cognition is another important factor contributing to functional outcome in schizophrenia.[16] It includes processes involved in social interaction, such as perceiving, interpreting, and reacting to social cues. Besides

deficits in perceiving and imitating affective facial expression[17,18] or emotional prosody,[19] schizophrenia patients also share impaired perception, interpretation, and performance of gestures.[20–23]

Schizophrenia patients and subjects at risk for psychosis use hand gestures less frequently during social interaction.[24–26] In addition, up to 67% of patients present with clear deficits performing gestures.[21,27,28] Perception and performance of gestures are tightly coupled in schizophrenia, that is, poor perception is linked to impaired performance.[21] In subjects at risk for psychosis, gesturing is more frequently associated with wrong content.[29] These deficits in gesture perception and performance in schizophrenia are likely to impair real-life social interaction and therefore hamper social functioning. Cross-sectionally, hand gesture performance was linked to positive and negative symptoms,[18,21,22,25,29] while nonverbal social perception was predominantly associated with positive symptoms.[21,30] Whether gesture deficits are predictive of poor functional outcome or negative symptom severity, however, remains unknown.

The current study tested whether the performance of hand gestures was predictive of symptomatic and functional outcome after 6 months. We hypothesized poor gesture performance at baseline to be associated with poor functioning (social and global), impairments in performance-based measures of outcome, and increased negative symptoms at follow-up. Furthermore, we tested whether nonverbal social perception was predictive of symptomatic and functional outcome after 6 months. Here, we hypothesized poor nonverbal perception at baseline to be associated with poor functioning but not with increased negative symptoms at follow-up.

Methods

Participants

This study was part of a larger investigation on gesture control in schizophrenia. Baseline data have already been reported.[21] In total, 28 patients with schizophrenia spectrum disorders participated in the 6-month follow-up tests. All patients were treated within an outpatient program, except one who was completely remitted and did not receive any treatment at the longitudinal assessment. Patients received continued outpatient treatment including pharmacotherapy, visits with psychiatrists, and case management. No specific psychosocial intervention was offered during outpatient care. Exclusion criteria were substance abuse or dependence other than nicotine; past or current medical conditions impairing motor function such as idiopathic parkinsonism, dystonia, or stroke; history of head trauma with concurrent loss of consciousness; and history of electroconvulsive treatment. Patients were interviewed using the Mini International Neuropsychiatric Interview[31] as well as the Comprehensive Assessment of Symptoms and History.[32] According to DSM-5 at baseline, 25 patients suffered from schizophrenia and 3 from schizophreniform disorder. All participants provided written informed consent. The protocol had been approved by the local ethics committee.

Procedures

Comprehensive assessment of psychopathology, gesture performance, and nonverbal social perception has been conducted at baseline.[21] Baseline measures of negative symptoms included the Clinical Assessment Interview for Negative Symptoms (CAINS)[33] and the Scale for the Assessment of Negative Symptoms (SANS).[34] Follow-up assessments included gesture performance, nonverbal social perception, the Positive And Negative Syndrome Scale (PANSS),[35] as well as measures of functional outcome. All clinical and psychopathological assessments at any time point were performed by one experienced clinical psychiatrist (K.S.), who had previously been trained by the senior (S.W.) to achieve interrater reliability of $\kappa \geq .8$. In order to attain high attrition rates during follow-up, patients were approached by telephone up to five times to schedule assessment at 6 months. Furthermore, they received financial compensation for travel costs and participation in the follow-up assessments.

TULIA

The Test of Upper Limb Apraxia (TULIA) is a comprehensive assessment of gesture performance in two domains: following demonstration by the examiner (imitation) or on verbal command (pantomime).[36] Evaluation of the 48 items rated content and temporal-spatial errors from video recordings. Total scores range from 0 to 240. All ratings were performed by a single rater (S.W.), blind to diagnoses, clinical presentation, and assessment time point, who had been trained by the test developers (T.V. and S.B.). Intraclass correlations prior to the start of the study exceeded .83. Based on cutoff scores,[28] patients were classified into those with gesture deficits and those without gesture deficits at baseline (demographic and clinical data are given in supplementary table S1). The original cutoff score of 194 (2 SD below the mean of controls) separated patients with apraxia from healthy older adults (mean age 61 years).[36] We have determined a cutoff score of 210 from an age- and gender-matched control group that fit to typical samples of schizophrenia patients (mean age 40 years).[28] The cutoff is across both TULIA domains, thus may balance clear deficits in one domain. Patients with gesture deficits demonstrate content or temporospatial errors in the majority of gestures. In addition, patients with gesture deficits are older, are chronic, and have more impaired frontal lobe function and more motor symptoms.[27,37]

PONS

We applied the Mini Profile of Nonverbal Sensitivity (Mini-PONS)[38] to test nonverbal social perception.

The Mini-PONS includes 64 scenes from the original PONS,[39] in which short videos of 2 s each present a white woman with altering facial expression, voice intonation, and/or bodily gestures. Patients had to choose from two options the one that best describes the observed situation immediately after watching the video, for example, saying a prayer or talking to a lost child. The total scores range from 0 to 64. In one participant, PONS was not assessed at baseline.

Outcome

Functioning was assessed with the Social and Occupational Functioning (SOFAS)[40] and the Global Assessment of Functioning (GAF) from DSM-IV, mainly based on self-report. In addition, we assessed functional capacity, that is, the ability to adequately perform everyday skills that are relevant to functioning. Functional capacity was measured with the brief version of the University of California San Diego Performance-Based Assessment (UPSA brief).[41] The brief version of the UPSA is limited to 10- to 15-min administration and consists of role-play tasks focusing on finances (eg, counting change or writing a check) and communication (eg, calling to reschedule an appointment). Scores range from 0 to 100, with higher scores indicating superior real world functioning. The UPSA brief has proven great validity in clinical samples.[41,42]

Statistical Analyses

Descriptive and clinical characteristics were compared between time points using paired *t*-tests. Simple correlation analyses were performed between psychopathological and outcome measures as well as TULIA and PONS scores at baseline. To test the categorical impact of gesture performance at baseline (patients with or without gesture deficits) on the course of psychopathology and outcome, we conducted repeated measures ANCOVAs testing the effects of time, group, and the Time × Group interaction including age and duration of illness as covariates.

To test the dimensional impact of gesture behavior on functional and symptomatic outcome (GAF, SOFAS, UPSA brief, and PANSS scores at follow-up), simple linear regression analyses were applied. Finally, we tested the additional contribution of baseline TULIA or PONS scores on the course of PANSS negative, PANSS positive, GAF, and SOFAS, applying hierarchical regression analyses. Here, we explored the effect of the baseline values (first step) and the additional contribution of baseline TULIA or PONS scores (second step) on follow-up values of the same rating scales. Within this approach, the magnitude of the R^2 change (ΔR^2) was tested for significance. All analyses were performed with SPSS-22.

Results

Over the course of 6 months, positive symptoms (PANSS positive), total PANSS scores, and nonverbal perception (PONS) improved (table 1). No changes were noted in negative symptoms (PANSS negative), GAF, SOFAS, medication dose, or gesture performance (TULIA). When classifying subjects according to the proportional change of scores into those with improving (≥10% better), declining (≥ 10% worse), or stable course (within 10% change), 14 patients (50%) improved, 5 (18%) declined, and 9 (32%) remained unchanged in the PANSS negative. Likewise, for the SOFAS course, 7 (25%) improved, 13 (46%) declined, and 8 (29%) remained unchanged.

Typical hand gesture errors included body-part-as-object errors (eg, use of the extended index finger to indicate the use of a toothbrush instead of the correct hand position during brushing the teeth) and errors of spatial orientation (ie, incorrect hand/finger posture relative to

Table 1. Clinical and Demographic Characteristics

	Baseline	6 Months	Range of Proportional Change From Baseline (%)	Statistic	*P* Values
Gender (men / women)	20 / 8				
Age (years)	38.4 (10.8)				
Education (years)	13.8 (3.1)				
Duration of illness (years)	13.5 (11.5)				
PANSS positive	18.8 (5.7)	15.0 (6.2)	43–167	$t(27) = 3.1$	.004
PANSS negative	18.3 (5.4)	16.7 (7.0)	48–139	$t(27) = 1.7$	.09
PANSS total	73.0 (16.4)	64.2 (21.0)	52–135	$t(27) = 3.0$	.006
CPZ (mg)	294.8 (262.3)	327.5 (314.9)		$t(27) = .9$	.38
GAF	53.2 (18.2)	48.5 (22.5)	40–175	$t(27) = 1.4$	.17
SOFAS	53.9 (18.0)	49.6 (21.9)	40–184	$t(27) = 1.4$	.18
TULIA	201.5 (33.1)	195.1 (35.8)	78–142	$t(27) = 1.8$	.09
PONS	42.6 (5.9)	44.8 (5.7)	78–135	$t(26) = -2.5$	.02

Note: CPZ = chlorpromazine equivalents; GAF = Global Assessment of Functioning; PANSS = Positive And Negative Syndrome Scale; PONS = Profile of Nonverbal Sensitivity; SOFAS = Social and Occupational Functioning; TULIA = Test of Upper Limb Apraxia.

body or face). Furthermore, we observed errors of wrong content and incorrect movement sequences.

Poorer baseline gesture performance and nonverbal perception correlated with higher symptom severity at follow-up and with impaired functional outcome at 6-month follow-up (table 2). In fact, patients with a gesture deficit at baseline experienced decline in SOFAS and stable PANSS negative syndrome scores (figure 1 and supplementary table S2). Furthermore, performance-based measures of functional capacity at 6-month follow-up were worse in patients with gesture deficits at baseline, particularly in the communication domain (table 3).

Table 2. Correlations of Baseline Gesture Performance and Clinical Measures

	Baseline			
	TULIA (n = 28)		PONS (n = 27)	
	r	P Values	r	P Values
Baseline measures				
PANSS negative	−.59	<.001	−.26	.18
CAINS	−.45	.02	−.25	.20
SANS	−.48	.01	−.18	.38
GAF	.67	<.001	.57	.002
SOFAS	.63	<.001	.59	.001
Follow-up measures				
PANSS negative	−.74	<.001	−.50	.01
GAF	.65	<.001	.51	.01
SOFAS	.71	<.001	.52	.01
UPSA brief	.74	<.001	.59	.001

Note: Abbreviations are explained in the first footnote to table 1. CAINS = Clinical Assessment Interview for Negative Symptoms; SANS = Scale for the Assessment of Negative Symptoms; UPSA = University of California San Diego Performance-Based Assessment.
Measures of clinical rating scales for each assessment (baseline or follow-up) were correlated here.

Functional outcome was associated with gesture performance in both categorical and dimensional ratings of gesture performance. Linear regression analyses indicated that TULIA at baseline predicted UPSA brief at 6 months (R^2_{adj} = .53, F = 32.3, β = .74, P < .001), GAF at 6 months (R^2_{adj} = .40, F = 18.6, β = .65, P < .001), SOFAS at 6 months (R^2_{adj} = .49, F = 26.7, β = .71, P < .001), and PANSS negative at 6 months (R^2_{adj} = .53, F = 32.3, β = .74, P < .001). Hierarchical linear regression analyses tested whether TULIA at baseline predicted the course of functioning and psychopathology (table 4, top). Better TULIA performance at baseline accounted for 8% of the variance for 6-month GAF, 13% of the variance for 6-month SOFAS, and 14% of the variance for 6-month PANSS negative.

Likewise, PONS at baseline predicted UPSA brief at 6 months (R^2_{adj} = .32, F = 13.0, β = .59, P = .001), GAF at 6 months (R^2_{adj} = .23, F = 8.8, β = .51, P = .007), SOFAS at 6 months (R^2_{adj} = .25, F = 9.5, β = .52, P = .005), and PANSS negative at 6 months (R^2_{adj} = .22, F = 8.2, β = −.50, P = .009). Hierarchical regression analyses also tested whether PONS at baseline predicted the course of functioning and symptoms (table 4, bottom). Better PONS performance at baseline accounted for 10% of the variance for 6-month PANSS negative. But PONS had no predictive value for functioning at follow-up.

Discussion

The outcome of schizophrenia is a complex issue for which there are currently no predictive markers available. The results of this study indicate that gesture performance and nonverbal social perception at baseline

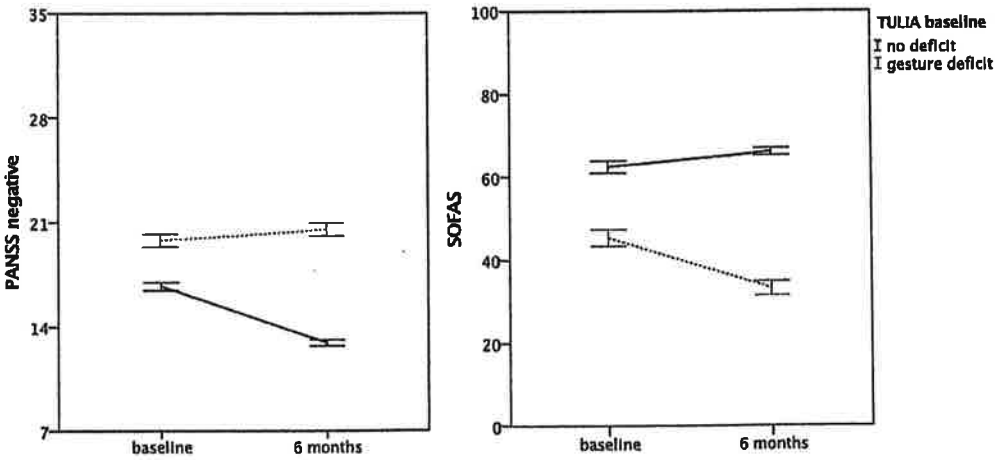

Fig. 1. Baseline gesture performance and course of social functioning and negative symptoms. Lines indicate means and standard errors of the mean (SEM). Baseline TULIA scores were used to dichotomize subjects into those with gesture deficits (n = 14) and those without gesture deficits (n = 14). Group × Time interactions were detected for PANSS negative ($F_{2,28}$ = 7.0, P = .01) and SOFAS ($F_{2,28}$ = 9.8, P = .004), both co-varied for age and duration of illness. PANSS = Positive And Negative Syndrome Scale; SOFAS = social and occupational functioning; TULIA = Test of Upper Limb Apraxia.

were associated with symptoms, functional capacity, and functional outcome after 6 months. Furthermore, hierarchical regression analyses demonstrated that both gesture performance and nonverbal social perception predicted the course of negative symptoms. But only gesture performance at baseline predicted functional outcome beyond the baseline measures. Thus, if these findings are replicated, a bedside test of hand gesture accuracy may become a marker of functional outcome in schizophrenia spectrum disorders after 6 months.

We applied two sets of outcome measures. First, the performance-based measure UPSA brief, which evaluates actual problem solving. UPSA brief performance was predicted by both baseline measures TULIA and PONS, which explained different proportions of the UPSA brief variance (53% vs 32%). The UPSA brief scores are well in line with those reported in the literature from Swedish or US samples.[41,43,44] Second, we applied the GAF and SOFAS, which are rated mainly based on patients' self-report. TULIA and PONS at baseline predicted a substantial proportion of GAF and SOFAS variance at follow-up, with better performance at baseline indicating superior functioning at follow-up. GAF and SOFAS were entered into hierarchical regression analyses and were predicted by gesture performance but not nonverbal social perception. Therefore, our results not only suggest that nonverbal communication skills were predictive of functional outcome, but further indicate that nonverbal performance skills are more useful than nonverbal perceptual skills when predicting the functional outcome at 6-month follow-up.

The main finding of our study is well in line with reports on the contribution of social cognitive impairments to poor functional outcome in schizophrenia.[5,16,45–47] One has to keep in mind that we applied rather direct measures of social cognition, that is, hand gesture performance and nonverbal social perception, both of which tended to slightly improve over time in our sample. However, more complex measures of social cognition demonstrated temporal stability in a 12-month longitudinal study as well as in a cross-sectional study in first episode schizophrenia.[47,48] While poor social functioning at baseline predicted poor social function at 6-month follow-up, the baseline ability to perform hand gestures correctly added further information on social functioning at follow-up. Thus, an actual performance measure of nonverbal social skills may become a useful predictor of functional outcome. Indeed, those with poor gesture performance at baseline faced a decline of social functioning during follow-up.

Both gesture performance and nonverbal social perception at baseline predicted negative symptom severity at follow-up, even when controlling for baseline negative symptoms. This is in line with the notion that negative symptoms comprise two main factors, one of which is diminished expression[49] that should be related to poor gesture performance, the other is avolition. In fact, the association of gesture performance and negative symptom severity has been reported before,[22,29] even though the correlation between impaired gesture performance and negative symptom severity was weak in some

Table 3. Performance-Based Measures at Follow-up and Baseline TULIA Performance

	Gesture Deficit	No Deficit	*t*	*P* Values
UPSA finances	39.0 (12.9)	46.4 (4.1)	2.1	.06
UPSA communication	26.2 (9.4)	35.3 (9.6)	2.5	.02
UPSA brief total	65.1 (20.1)	81.7 (11.2)	2.7	.01

Note: Abbreviations are explained in the first footnote to tables 1 and 2.

Table 4. Hierarchical Regression Analyses

	Block I: Baseline Variables					Block II: TULIA at Baseline				
	R^2	*df*	*F*	β	*P* Values	ΔR^2	*df*	*F*	β	*P* Values
Variables at 6 months										
PANSS positive	.19	1, *26*	6.21	.44	.02	.04	1, *25*	1.25	−.20	.27
PANSS negative	.55	1, *26*	32.01	.74	<.001	.14	1, *25*	10.88	−.46	.003
GAF	.42	1, *26*	19.00	.65	<.001	.08	1, *25*	4.01	.38	.06
SOFAS	.46	1, *26*	22.51	.68	<.001	.13	1, *25*	8.15	.47	.01
	Block I: Baseline Variables					Block II: PONS at Baseline				
	R^2	*df*	*F*	β	*P* Values	ΔR^2	*df*	*F*	β	*P* Values
Variables at 6 months										
PANSS positive	.19	1, 25	6.21	.44	.02	.04	1, 24	1.25	−.20	.27
PANSS negative	.55	1, 25	30.32	.74	<.001	.10	1, 24	6.58	−.32	.02
GAF	.43	1, 25	18.61	.65	<.001	.03	1, 24	1.28	.21	.27
SOFAS	.47	1, 25	22.08	.69	<.001	.02	1, 24	1.08	.19	.31

Note: Abbreviations are explained in the first footnote to table 1.
Hierarchical regression analyses applied the same instruments at baseline and follow-up.

studies.[21,27,28] In contrast, nonverbal social perception was unrelated to negative symptoms in cross-sectional studies.[50,51] However, broader measures of social cognition correlated with negative symptom severity.[47,48] In the present study, TULIA correlated with several negative symptom ratings at baseline and follow-up, while PONS was only associated with negative symptoms at follow-up. Thus, negative symptom severity seems to be linked to nonverbal communication skills. Strikingly, poor baseline gesture performance indicated a group of patients with stable course of negative symptoms, while good performance was associated with amelioration of negative symptoms during follow-up.

The correct performance of hand gestures may critically contribute to nonverbal communication and therefore benefit social skills.[20] In addition, incorrect interpretation of hand gestures would interfere with communication, particularly, as schizophrenia patients are more likely to interpret accidental gestures as threatening or self-referential.[23,30] Importantly, gesture performance and nonverbal social perception are strongly correlated in schizophrenia, that is, deficits in one domain are associated with impairments in the other.[21] Previous work of our lab and others has established that correct hand gesture performance relies on motor abilities, frontal lobe functions, and to some extent on working memory performance.[18,21,22,27,28] The cross-sectional analysis indicated that both impairments in gesture performance and poor nonverbal social perception were associated with the factor motor/frontal lobe dysfunction and with the factor positive symptoms/working memory.[21] In the course of 6-month treatment, positive symptoms significantly improved. At the same time, scores on the Mini-PONS increased, suggesting that nonverbal social perception may improve as positive symptoms are controlled. However, at group level we failed to observe changes in gesture performance. Neither gesture performance nor nonverbal social perception at baseline explained any variance of PANSS positive at follow-up when controlling for the baseline PANSS positive score. Thus, any association between positive symptoms and nonverbal skills was cross-sectional.

The baseline TULIA scores were used to separate patients without gesture deficits from patients with gesture deficits based on cutoff scores.[28] In line with our previous studies, patients with gesture deficits were older and had been suffering longer from schizophrenia (supplementary table S1).[27] Gesture deficits are more frequently observed in patients with multiple episodes of the disorder.[37] Still, the Group × Time interactions for negative symptoms and social functioning (figure 1 and supplementary table S2) in the repeated measures ANCOVAs remained significant even when controlling for age and duration of illness. Furthermore, the dimensional assessment of gesture performance yielded similar results as the categorical one in the hierarchical regression analyses. Findings hold also true when restricting analyses to subjects with less than 15 years of illness duration (supplementary table S5).

If these findings can be replicated in larger studies with rigorous longitudinal statistics accounting for various associated clinical factors, baseline performance of hand gestures may help to identify subjects who require even more effort in treating or preventing negative symptoms and functional decline. Schizophrenia patients with clear gesture deficits have reduced gray matter within the left inferior frontal gyrus compared to schizophrenia patients without gesture deficits.[52] Thus, structural brain alterations within the semantic networks implicated in gesture and speech processing[53,54] may contribute to poor hand gesture performance.

Social cognitive training has been effective in the domains of facial affect recognition and theory of mind.[55] Future studies need to establish whether the hand gesture deficits may be alleviated with specific nonverbal communication training.[20] Our findings suggest that this could also improve functional outcome.

Some limitations of the current study require discussion. First, the assessment of functional capacity with the UPSA brief has only been performed at follow-up. Baseline measures would have enabled hierarchical regression analyses also for this important outcome variable. However, linear regression analyses clearly supported an association of baseline gesture performance and social perception with follow-up functional capacity. Second, we applied the Mini-PONS to assess the accuracy of nonverbal perception. It contains various nonverbal stimuli that are not gestures. In future studies, a specific test of gesture perception should be applied. Third, the small sample size limits the number of factors that may be entered in the regression analyses. Thus, the potential contribution of other clinical factors to social outcome in schizophrenia could not be explored. Fourth, due to the exploratory nature, analyses were uncorrected for multiple comparisons. Thus, findings have to be interpreted with caution and require replication. Fifth, this was a naturalistic longitudinal study in which patients received treatment as usual. Therefore, we cannot infer whether particular treatment strategies may have improved social functioning or outcome of negative symptoms. However, no single specific treatment option has emerged to effectively target negative symptoms or social outcome. Finally, a common problem to longitudinal studies is decline in attrition rate, ultimately leading to selection bias. However, at baseline no relevant differences emerged between patients completing the study and patients lost to follow-up (supplementary table S4).

Conclusion

In a longitudinal study, two tasks of nonverbal communication, that is, hand gesture performance and nonverbal social perception, predicted negative symptoms,

functional capacity, and functional outcome after 6 months. The performance of hand gestures at baseline was of added value predicting social functioning at follow-up beyond the baseline measure. Further longitudinal studies need to test whether simple tests of nonverbal communication skills may have the potential to become readily available outcome markers in schizophrenia.

Supplementary Material

Supplementary material is available at http://schizophreniabulletin.oxfordjournals.org.

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Supplementary Material

Gesture performance in schizophrenia predicts functional outcome after 6 months

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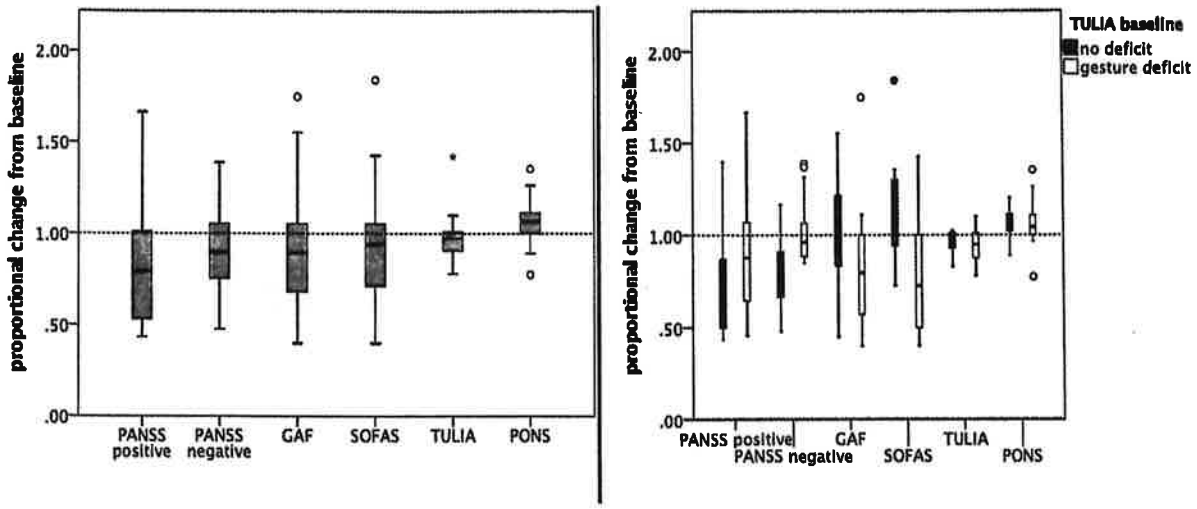
Supplementary Table S1. Comparison of baseline demographic and clinical variables between patients with and without gesture deficits at baseline.

	no deficit	TULIA defict	Statistic	P
Age (years)	32.4 (7.8)	44.4 (10.1)	$t(26) = -3.5$	.002
Duration of illness (years)	7.6 (6.8)	19.4 (12.3)	$t(26) = -3.2$	.004
PANSS negative	16.7 (4.4)	19.8 (6.0)	$t(26) = -1.6$	.13
CPZ (mg)	255.9 (192.4)	333.6 (320.3)	$t(26) = -.8$	.44
SOFAS	62.4 (16.3)	45.4 (15.7)	$t(26) = 2.8$	.01
PONS	45.4 (4.1)	38.6 (6.4)	$t(22.2) = 3.3$	.003

PANSS – positive and negative syndrome scale, CPZ –chlorpromazine equivalents, GAF – Global Assessment of Functioning, SOFAS – Social and occupational functioning assessment scale, TULIA – Test of Upper Limb Apraxia, PONS – Profile of Nonverbal Sensitivity (Mini-PONS)

Supplementary Figure. Proportional change from baseline



Left panel: proportional change from baseline for all patients. Right panel: proportional change from baseline for the groups according to TULIA baseline performance. Boxplots indicate median, 25th and 75th percentiles. Horizontal dashed line indicates no change. Lower values represent improvement over time for PANSS positive and negative, but deterioration for GAF, SOFAS, TULIA and PONS.

Supplementary Table S2. Repeated measures in patients with (14) or without (14) gesture deficits at baseline.

	Group effect		Time effect		Group x Time effect	
TULIA	9.1	.01	.4	.52	.2	.68
GAF	5.6	.03	.4	.53	1.9	.19
PANSS positive	· .9	.34	3.8	.06	0.1	.79

All analyses are co-varied for age and duration of illness.

TULIA –Test of Upper Limb Apraxia, PONS – Profile of Nonverbal Sensitivity (Mini-PONS), GAF – Global Assessment of Functioning, SOFAS – Social and occupational functioning assessment scale, PANSS – positive and negative syndrome scale

Supplementary Table S3. Hierarchical regression analyses of TULIA domains pantomime and imitation.

	Block I: baseline variables				Block II: TULIA pantomime at baseline				
PANSS	.19	1, 26	6.2	.44	.02	.02	1, 25	.5	-.13	.49
Positive										
GAF	.40	1, 26	19.0	.65	<.001	.06	1, 25	2.9	.34	.10

	Block I: baseline variables				Block II: TULIA imitation at baseline				
PANSS	.19	1, 26	6.2	.44	.02	.07	1, 25	2.4	-.26	.14
Positive										
GAF	.40	1, 26	19.0	.65	<.001	.07	1, 25	3.6	.33	.07

Supplementary Table S4. Comparison of the group investigated with subjects lost to follow-up (baseline variables).

	Completer	Lost to Follow-up	Statistic	P
Gesture group Deficit/nondeficit	14/14	8/14	$Chi^2 = .3$	.77
Education (years)	13.8 (3.1)	13.0 (3.0)	$t(45) = -.9$	.38
PANSS positive	18.8 (5.7)	17.6 (7.3)	$t(45) = -.6$	.54
PANSS total	73.0 (16.4)	72.0 (18.6)	$t(45) = -.2$	.84
GAF	53.2 (18.2)	59.3 (18.9)	$t(45) = 1.1$	.28
TULIA	201.5 (33.1)	210.6 (16.8)	$t(45) = 1.1$	.27

Baseline total sample n = 47, PANSS – positive and negative syndrome scale, CPZ –chlorpromazine equivalents, GAF – Global Assessment of Functioning, SOFAS – Social and occupational functioning assessment scale, TULIA –Test of Upper Limb Apraxia, PONS – Profile of Nonverbal Sensitivity (Mini-PONS)

Supplementary Table S5. Hierarchical regression analyses of TULIA performance at baseline in subjects with less than 15 years illness duration (n = 18).

	Block I: baseline variables				Block II: TULIA at baseline					
PANSS Positive	.32	1, 16	7.6	.57	.01	.02	1, 15	.4	-.14	.54
GAF	.37	1, 16	9.4	.61	.01	.11	1, 15	3.3	.36	.09

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

Three key aspects of gesturing may be investigated: gesture perception, interpretation and production.[14] Recent functional magnetic resonance imaging (fMRI) studies indicated aberrant neural processing in the language network in schizophrenia during perception of abstract metaphoric gestures.[15,16] Behavioral data suggests misinterpretation of incidental movements as gestures in patients with delusions.[17] Delusions in turn are associated with altered brain activity in the limbic system.[18,19] 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,[20] while the other found reduced right parietal lobe activation in patients.[21] 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,[2–4]

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.[9,22]

Current neurocognitive models[23–25] including evidence from fMRI studies in healthy subjects[26–28] as well as lesion studies[29–32] 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.[23,24,33] 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.[24] 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.[28]

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.[34]

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.[35] Symptom severity in patients was assessed with the Comprehensive Assessment of Symptoms and History (CASH)[36] and the Positive And Negative Syndrome Scale (PANSS).[37] All participants were further interviewed with the Mini International Neuropsychiatric Interview (MINI).[38] In addition, frontal lobe function, verbal working memory and nonverbal intelligence were assessed using the Frontal Assessment Battery (FAB),[39] the digit span backwards (DSB) task (subtest from the Wechsler Memory Scale [WMS-III][40] and the Test of nonverbal Intelligence [TONI]).[41] 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[26,42,43] 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

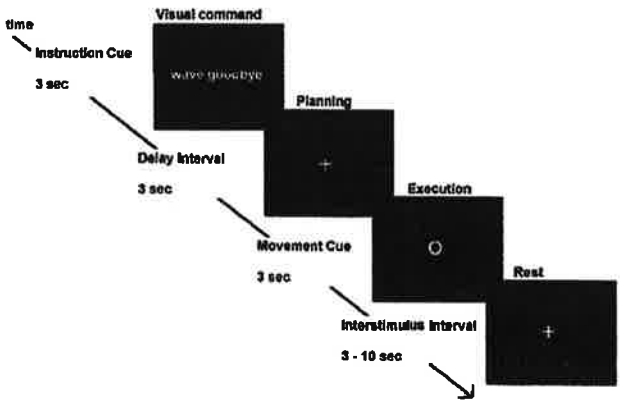

Fig. 1. Pantomime gesture task.

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."),[44] 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 interstimulus 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)[45] 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,[46] providing 176 sagittal slices with 256 × 256 matrix points with a non-cubic field of view (FOV) of 256 mm, yielding a nominal isotopic resolution of 1 mm3 (ie, 1 mm × 1 mm × 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 × 64 matrix size, 3.59 mm × 3.59 mm × 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 × 230 mm^2, matrix size = 64 × 64; TR = 488 ms, TEshort = 4.92 ms, TElong = 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 (χ^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).[47]

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 × 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		*P*
Gender (No [%])	13 (52%)/ 12 (48%)		14 (64%)/ 8 (36%)		.421
	M	SD	*M*	SD	*P*
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 (*n*)	—	—	16		—
Schizophreniform disorder (*n*)	—	—	4		—
Schizoaffective disorder (*n*)	—	—	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 χ^2 tests for categorical variables.

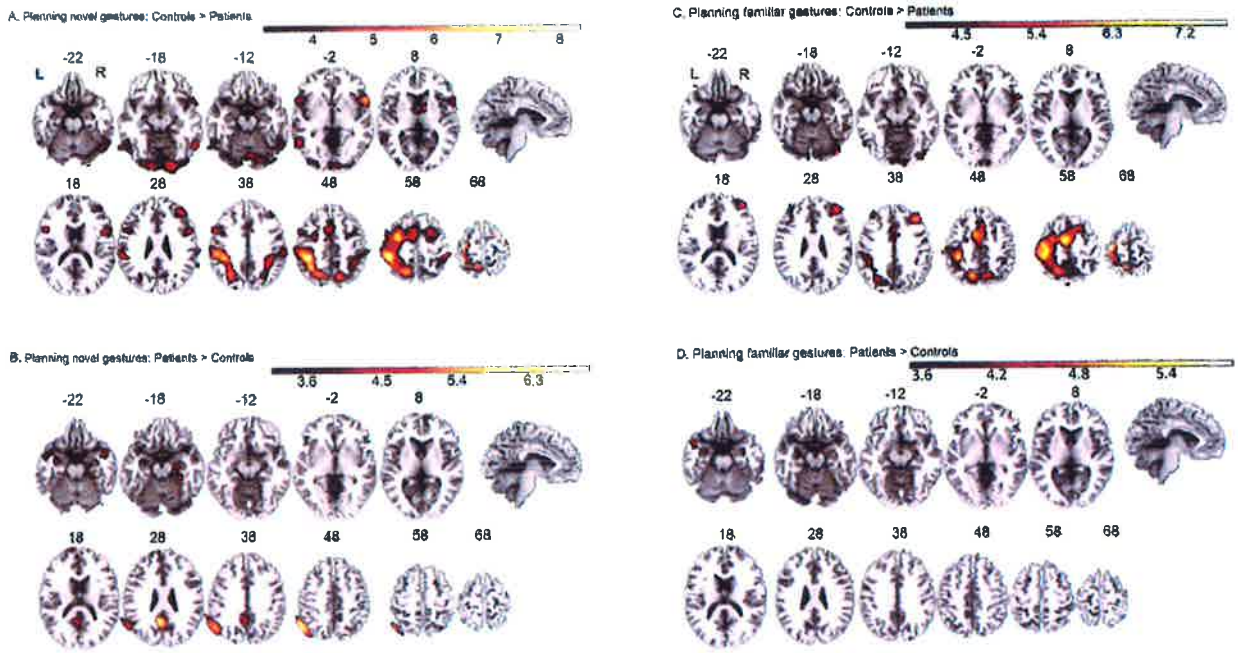

Fig. 2. Neural activity during gesture planning in schizophrenia patients and healthy controls. Between group effects of planning novel (A and B) and familiar (C and D) gestures. The bars indicate *T*-values. The images are depicted at standard MNI-templates (threshold of $P < .001$, minimum voxel size 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.[11] Thus, investigating gesture behavior provides a window to social communicative impairments in schizophrenia.[14] 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.[14] 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.[26–28] 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							
	Cluster		Peak		MNI Coordinates		
Brain Region	$P_{(FWE-corr)}$	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							
	Cluster		Peak		MNI coordinates		
Brain region	$P_{(FWE-corr)}$	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							
	Cluster		Peak		MNI coordinates		
Brain region	$P_{(FWE-corr)}$	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; DMPFC, 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[26,28] nor in lesion studies.[29,30] 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.[14] Therefore, one would expect aberrant brain activity in patients

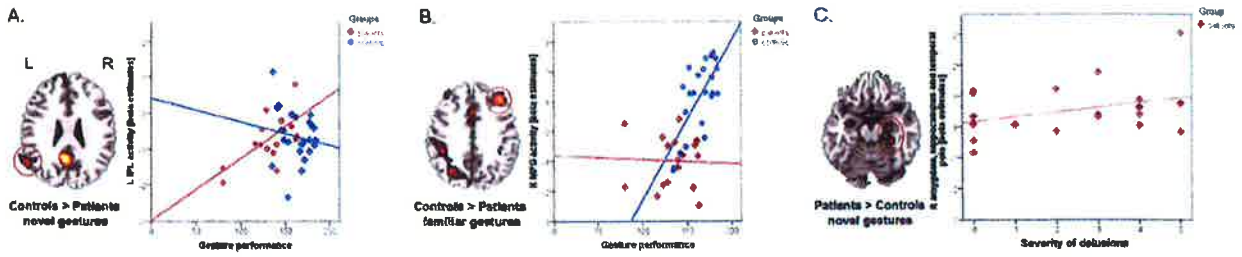

Fig. 3. Association between gesture performance, delusion severity and neural activity in differentially activated brain areas. Spearman's rank correlation analysis of the neural activity in (A) the left IPL, (B) the right middle frontal gyrus and (C) association of neural activity in the right amygdala, 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.[48] In line with this, impaired gesturing in schizophrenia was linked to impaired frontal lobe function.[3,4] The DMPFC has been suggested to elaborate the meaning of communicative and social ambiguous stimuli.[49,50] 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.[21] The IPL contains so-called mirror-neurons.[51] Gesture performance and gesture perception are tightly coupled in schizophrenia.[4] 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.[52] 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).[13,16,34] 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.[4–6,11–13] 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[53–55] 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.[56] 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.[18,57–60] 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.[17,61]

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.[62,63] 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.[4,64] 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.[10,34,65] 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.

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

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Supplementary material:

Limbic interference during social action planning in schizophrenia

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List of elements in the supplementary material

Method S1 Scoring method of gesture performance according to the Test of Upper Limb Apraxia (TULIA)[1]

Performance ratings of 20 novel gestures, 20 familiar (10 transitive and 10 intransitive) gestures were assessed (40 gestures, max 200 points)

5: Normal movement or identical to the demonstrated movement.

4: Goal of the movement is achieved, but errors occur not affecting trajectory (normal movement plane relative to goal object [tool or own body], normal joint coordination and movement shape). Movement is too slow, hesitating, robot-like, sloppy with minor spatial errors such as reduced amplitudes.

3: Goal of the movement is achieved, errors subtly affecting trajectory occur, but are corrected. Extra movements and omissions are present (mainly distal), even brief content errors (substitutions, perseverations) may occur; however, corrections are made in the ongoing movement.

2: Goal of the movement is achieved, errors subtly affecting trajectory occur, but are not corrected. Body-part-as-object errors, extra movements and omissions (mainly distal) occur without correction.

1: Goal of the movement is not achieved, errors grossly affecting trajectory occur or semantic content is incorrect. Final position is false, major errors in spatial orientation, overshoot and extra movements (particularly proximal), however, overall movement pattern remains recognizable. Persisting substitutions (related or unrelated) and perseverations occur.
0: No movement, unrecognizable movement. Seeking and amorphous movements, no temporal or spatial relationship to the requested gesture.

Analysis S1. Analysis of motion parameters in schizophrenia patients and healthy controls

Gestures (familiar and novel) were balanced for repetitive (e.g. lift two times the middle finger) and nonrepetitive (e.g. spreading the little finger outward) as well as proximal and distal movements. Most of the performed gestures were distal in nature (involving movements of the distal arm or hand: e.g. spreading the little finger outward). However, to test whether systematic differences may be present in motion parameters across the phases of the experiment and whether groups differed in motion parameters may be present we extracted six motion parameters from realignment (x, y and z vector [mm] and roll = α, pitch = β *and* yaw = γ [degrees]). For each of the six motion parameters we calculated an average of the total motion across the four phases of the experiment (cue, control, planning and execution). This was done by individually summing the six absolute displacement estimates for each image compared with the reference image and then dividing by the number of images of the task phase. Neither in head translation (Table S1 A), nor in head rotation (Table S1 B) did we detected systematic differences between the cue, control, planning and execution phase in the average absolute values of the estimated motion parameters. Furthermore, no significant effect of group (translation: $F_{(1, 45)}$ 0.081, $P = 0.777$; rotation: $F_{(1, 45)} = 0.005$; $P = 0.944$) or interaction between phase of experiment x group (translation: $F_{(1.0, 45)} = 1.287$; $P = 0.255$; rotation: $F_{(1.5, 45)} = 2.297$, $P = 0.123$) appeared applying Greenhouse-Geisser correction. When

planning and execution phase were exclusively compared, there was again no effect of group (translation: $F_{(1, 45)} = 2.153$, $P = 0.149$; rotation: $F_{(1, 45)} = 0.020$, $P = 0.888$) and no interaction of phase of experiment x group (translation: $F_{(1.0, 45)} = 2.122$; $P = 0.152$; rotation: $F_{(1.0, 45)} = 0.010$; $P = 0.921$) applying Greenhouse-Geisser correction.

Furthermore no participant had to be excluded from data analysis due to head motion. Maximum allowed head motion of 3.6 mm was set during the experiment. One single image of one patient extending the set maximal amplitude and was therefore excluded from imaging analysis.

Table S1. Average absolute values of the estimated motion parameters of head rotation and head translation during the cue, control, planning and execution phase (conditions).

Average absolute values of the estimated motion parameters			
Head translation	**x (mm)**	**y (mm)**	**z (mm)**
Cue	0.0239 ± 0.3502	0.2089 ± 0.2997	-0.0739 ± 0.5789
Control	0.0267 ± 0.3553	0.2138 ± 0.2986	-0.0761 ± 0.5989
Planning	0.0213 ± 0.3494	0.2109 ± 0.3063	-0.0640 ± 0.5769
Execution	0.0122 ± 0.3519	0.2131 ± 0.3062	-0.0675 ± 0.5766
Head rotation	**α (degrees)**	**β (degrees)**	**γ (degrees)**
Cue	0.0038 ± 0.0120	-0.0018 ± 0.0047	-0.0011 ± 0.0060
Control	0.0039 ± 0.0121	-0.0018 ± 0.0047	-0.0011 ± 0.0060
Planning	0.0039 ± 0.0121	-0.0018 ± 0.0048	-0.0012 ± 0.0060
Execution	0.0040 ± 0.0122	-0.0018 ± 0.0048	-0.0014 ± 0.0060

[a] Head translation x condition: $F_{(2.503/43)} = 1.562$, $P = 0.209$; head rotation x condition: $F_{(2.5/43)} = 2.241$, $P = 0.099$.

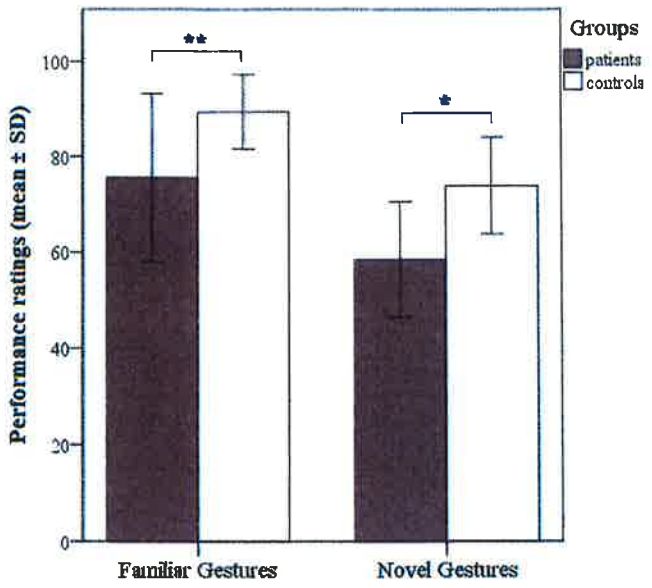


Figure S1. Gesture Performance of schizophrenia patients and healthy controls during fMRI. Patients performed poorer than controls in both gesture categories (familiar and novel). Note: $^{**}P < 0.001$; $^{*}P < 0.01$.

Analysis S2. Within-group analysis: Planning of Familiar and Novel Gestures

In healthy controls planning of both gesture categories (familiar and novel) induced activation in the ventral and dorsal stream, the motor cortex and the right dorsolateral prefrontal cortex (DLPFC) (Figure S2 A, C and Table S2 A). In addition planning of novel gestures relied on activity in bilateral striatum, insula, inferior frontal gyrus (IFG), ventral premotor area (PMv) and left DLPFC (Table S2 A). This grossly parallels previous reports investigating gesturing in healthy subjects [2-6]. Likewise, in schizophrenia patients planning of both gesture categories relied on activation in the ventral and dorsal stream and the motor cortex but activation of the two streams was less prominent and more left lateralized (Figure S2 B, D and Table S2 A). Moreover patients failed to activate ventral motor areas (cingulate motor area, pre-SMA) and DLPFC when planning familiar gestures (Table S2 A). Most interestingly, planning of both gesture types yielded additional activation of the bilateral temporal poles, right hippocampus and amygdala in patients (Figure S2 B, D and Table S2 A).

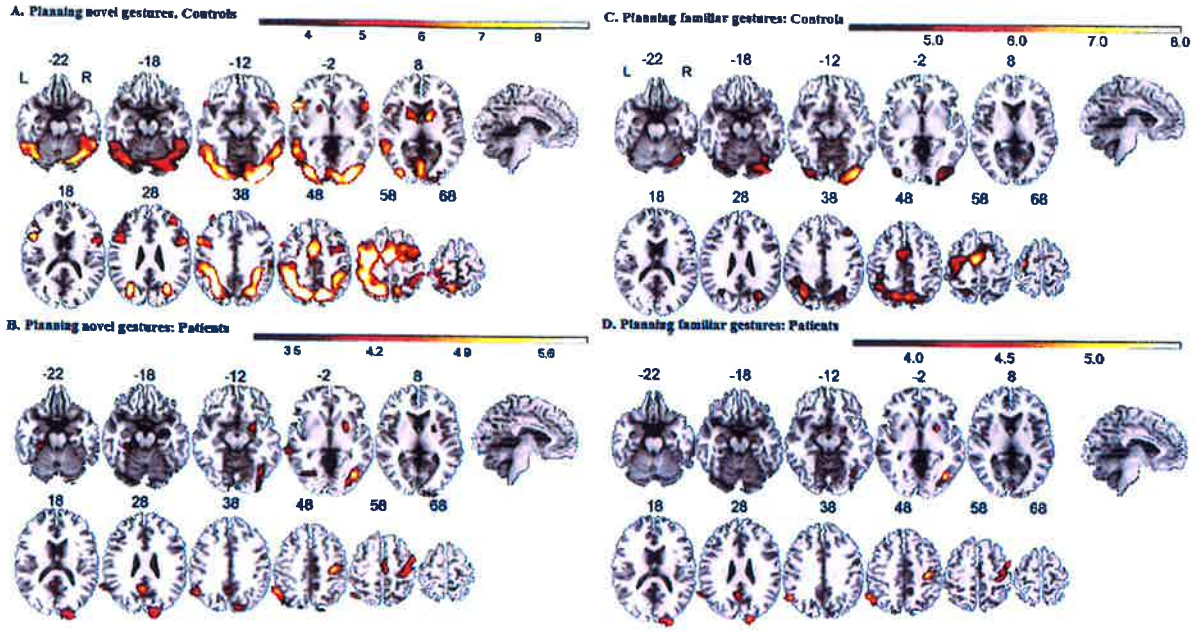


Figure S2. Neural activity during gesture planning in schizophrenia patients and healthy controls. Within group effects of planning of novel (A, B) and familiar (C, D) gestures. The bars indicate T-values. The images are depicted at standard MNI-templates (threshold of $P <$ .001, minimum voxel size 180); all depicted brain areas reached whole brain significance at a family wise error (FWE) corrected level $P < .05$ (peak or cluster).

Analysis S3: Within-group analysis: Execution of Familiar and Novel Gestures

In healthy controls actual gesture performance (execution) of both gesture categories engaged bilateral brain activity in the two streams, the motor cortex, the cerebellum and the thalamus (Table S2 B). A very similar pattern of brain activity was detected in patients performing gestures. However, patients failed to demonstrate significant hemodynamic response in bilateral thalamus and the inferior and middle temporal gyrus when producing novel gestures (Table S2 B.1). In addition performance of familiar gestures exclusively relied on left-lateralized brain activation in patients (Table S2 B.2).

Table S2. Neural activity during planning and execution of novel and familiar gestures in schizophrenia patients and healthy controls. (A) Within group effects of gesture planning. (B) Within group effects of gesture execution.

A.1 Planning novel gestures	**Controls**							**Patients**						
	cluster		peak					cluster		peak				
	$P_{(FWE-corr)}$	k	$P_{(FWE-corr)}$	$T_{(90)}$	x	y	z	$P_{(FWE-corr)}$	k	$P_{(FWE-corr)}$	$T_{(90)}$	x	y	z
L MOG, IOG	< .001	37541	< .001	8.8	36	-88	-10	.02	207	.89	4.2	-26	-68	-4
R MOG, IOG								< .001	1303	.44	4.6	16	-92	26
L IPL and SPL , MTG, ITG, STG								< .001	1125	.09	5.2	-54	-56	48
								.005	271	.95	4.1	-66	-34	-2
R temporal lobe (MTG, ITG, STG)								<.001	979	.006	5.9	40	-72	0
R IPL and SPL, M1								< .001	1183	.008	5.8	38	-20	50
L/R IFG, insular								*n.s.*						
L/R SMA								< .001	409	.61	4.5	6	-20	58
L/R thalamus								*n.s.*						
L striatum/putamen								*n.s.*						
R striatum/putamen								< .001	628	.04	5.4	26	6	-8

R precuneus , mid cingulum								< .001	771	.18	5.0	-4	-56	28
L/R cingulate motor areas, PMv								*n.s.*						
L OFG, MFG (DLPFC) and ACC								*n.s.*						
R MFG (DLPFC)	< .001	485	.355	4.7	36	42	28	*n.s.*						
L cerebellum								.023	202	.86	4.3	-30	-32	-20
L temporal pole	*n.s.*							< .001	645	.36	4.7	-36	18	-36
R temporal pole	*n.s.*							< .001	574	.45	4.6	54	6	-26
R ; amygdala, hippocampus	*n.s.*							< .001	628	.04	5.4	26	6	-8
A.2 Planning familiar gestures	**Controls**							**Patients**						
	cluster		peak					cluster		Peak				
	$P_{(FWE\text{-}corr)}$	k	$P_{(FWE\text{-}corr)}$	$T_{(90)}$	x	y	z	$P_{(FWE\text{-}corr)}$	k	$P_{(FWE\text{-}corr)}$	$T_{(90)}$	x	y	z
L/R SMA	< .001	12968	< .001	8.0	-4	-10	56	< .001	374	.87	4.2	6	-20	58
L IPL and SPL, M1								< .001	1185	.06	5.3	-54	-58	44
R IPL and SPL , M1								< .001	1205	.05	5.3	36	-22	48
L precuneus, mid cingulum								< .001	703	.42	4.7	-4	-58	30
L STG and MTG								.01	232	.90	4.2	-66	-32	0
L/R pre-SMA and cingualate motor areas								*n.s.*						

R MTG and ITG	< .001	578	.085	5.2	56	-42	-20	< .001	945	.03	5.5	40	-70	-2
R IOG and MOG,cerebellum, ITG and MTG	< .001	4104	< 0.001	7.7	34	-90	-12	< .001	808	.30	4.8	16	-92	28
L IOG and MOG,cerebellum, ITG and MTG	< .001	2304	.005	5.9	-32	-86	-14	*n.s.*						
R MFG (DLPFC)	< .001	771	.033	5.4	40	32	40	*n.s.*						
L temporal pole	*n.s.*							< .001	633	.28	4.8	-34	18	-34
R temporal pole	*n.s.*							< .001	477	.89	4.2	54	10	-26
R striatum/putamen; amygdala, hippocampus	*n.s.*							< .001	511	.14	5.0	26	4	-8
B.1 Execution novel gestures	**Controls**							**Patients**						
	cluster		peak					cluster		Peak				
	$P_{(FWE-corr)}$	k	$P_{(FWE-corr)}$	$T_{(90)}$	x	y	z	$P_{(FWE-corr)}$	k	$P_{(FWE-corr)}$	$T_{(90)}$	x	y	z
L/R SMA, M1 and STG; L IPL, SPL	< .001	10570	< 0.001	9.2	-2	-6	56	< .001	1317	.04	5.4	-8	-14	50
L/R cingulate motor areas, IFG, insular, PMv								< .001	3915	.008	5.8	-54	-24	50
Right IPL, SPL, M1 and STG	< .001	3713	.002	6.2	58	-22	42	< .001	2472	.09	5.2	44	-36	54
R/L Thalamus	< .001	639	< 0.001	6.8	-2	-20	-4	*n.s.*						
R cerebellum	< .001	1390	< 0.001	6.6	22	-48	-26	< .001	1090	.01	5.7	20	-48	-26

L putamen, extending to insular, IFG and PMv	< .001	1510	.004	6.0	-28	0	0	< .001	1401	.36	4.7	-46	4	12
R putamen extending to insula, STG and PMv	< .001	855	.017	5.6	24	2	4	< .001	613	.90	4.2	56	6	34
L cerebellum	< .001	529	.057	5.3	-28	-50	-28	< .001	531	.06	5.3	-32	-46	-30
R MTG and ITG	.003	311	.196	4.9	50	-60	-2	*n.s.*						
B.2 Execution familiar gestures	**Controls**							**Patients**						
	cluster		Peak					cluster		Peak				
	$P_{(FWE-corr)}$	k	$P_{(FWE-corr)}$	$T_{(90)}$	x	y	z	$P_{(FWE-corr)}$	k	$P_{(FWE-corr)}$	$T_{(90)}$	x	y	z
L IPL and SPL, M1, cingulate motor areas, IFG, STG, PMv	< .001	22210	< .001	9.322	-4	-6	56	< .001	3200	.005	5.9	-40	-16	56
R IPL and SPL, M1, cingulate motor areas, IFG, STG, PMv								*n.s.*						
L/R pre-SMA								*n.s.*						
L/R SMA								< .001	1112	.02	5.6	-8	-16	50
L putmane/striatum , insular and IFG								< .001	764	.26	4.8	-26	0	6
R putamen/striatum; insular and IFG								.03	189	> .99	3.6	24	8	-2
L thamalum								.011	240	.88	4.2	-6	-20	-6
R thalamus								*n.s.*						
R cerebellum	< .001	2227	< .001	7.90	28	-46	-30	< .001	845	.09	5.2	-24	-50	-28

				8										
L cerebellum	< .001	664	.06	5.297	-30	-48	-28	< .001	1461	.007	5.9	22	-46	-26
R temporal lobe ITG, MTG	< .001	460	.08	5.193	50	-60	-2	*n.s.*						
R inferior temporal gyrus	.001	349	.85	4.263	42	-10	-34	*n.s.*						
L temporal pole extending to amygdala and hippocampus	*n.s.*							.003	293	.58	4.5	-32	8	-32

[a] 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, ACC – anterior cingulate cortex, M1 – primary motor cortex.

Table S3. Neural activity during planning and execution of novel and familiar gestures in schizophrenia patients and healthy controls co-varied for frontal lobe function. (A) Between group effects of planning of novel and familiar gestures. (B) Between group effects of execution of familiar gestures.

A.1 Planning novel gestures							
controls > patients							
	cluster		**peak**		**MNI coordinates**		
Brain region	$P_{(FWE\text{-}corr)}$	k	$P_{(FWE\text{-}corr)}$	$T_{(89)}$	x	y	z
L IPL extending to SPL, L/R	<.001	15353	<.001	7.8	-38	-38	48
R IFG extending to STG	<.001	2496	<.001	6.5	48	6	22
R IPL extending to SPL	<.001	3037	<.001	6.3	14	-70	50
L/R thalamus and L/R caudate	<.001	617	.008	5.8	10	2	8
R MFG (DLPFC) and IFG	<.001	602	.266	4.8	36	44	26
patients > controls							
	cluster		**peak**		**MNI coordinates**		
Brain region	$P_{(FWE\text{-}corr)}$	k	$P_{(FWE\text{-}corr)}$	$T_{(89)}$	x	y	z
L IPL	< .001	1372	< .001	6.2	-50	-66	46
L temporal pole	< .001	1012	.003	6.0	-38	16	-34
L mid cingulum/precuneus	< .001	601	.009	5.9	-4	-56	26
R hippocampus, temporal pole	< .001	1069	.076	5.2	46	-4	-34
L superior frontal gyrus (DMPCF)	.012	231	1.00	3.8	-8	64	10
A.2 Planning familiar gestures							
controls > patients							
	cluster		**Peak**		**MNI coordinates**		
Brain region	$P_{(FWE\text{-}corr)}$	k	$P_{(FWE\text{-}corr)}$	$T_{(89)}$	x	y	z
L/R SMA	<.001	14325	<.001	7.7	36	-20	64
L MFG (DLPFC) extending to	<.001	2033	.018	5.6	-40	46	22
L STG extending to MTG and IFG	.014	230	.040	5.4	-58	16	-4
L IOG and MOG	<.001	2638	.042	5.4	-42	-86	-16
R MFG (DLPFC) extending to	<.001	627	.798	4.3	40	44	22

Left IPL	.006	267	.4	4.7	-60	-26	32
patients > controls							
	cluster		**Peak**		**MNI coordinates**		
Brain region	$P_{(FWE\text{-}corr)}$	k	$P_{(FWE\text{-}corr)}$	$T_{(89)}$	x	y	z
L temporal pole extending to	<.001	689	.14	5.0	-46	-4	-34
R temporal pole extending to	<.001	1259	.06	5.3	36	10	-32
B Execution familiar gestures							
controls > patients							
	Cluster		**peak**		**MNI coordinates**		
Brain region	$P_{(FWE\text{-}corr)}$	k	$P_{(FWE\text{-}corr)}$	$T_{(89)}$	x	y	z
L/R SMA, pre-SMA and mid	< .001	544	.50	4.6	-12	4	46
R/L cingulate motor areas	.005	271	.92	4.2	6	22	40

[a] 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, DMPFC – dorsomedial prefrontal cortex, ACC – anterior cingulate cortex, M1 – primary motor cortex.

Table S4. Association of performance ratings, psychopathological characteristics and brain activation during planning gestures in brain regions with significant between group effects.

		Performance		Psychopathology
Brain regions		Gesturing		CASH delusion
Novel gestures schizophrenia patients > controls				
L temporal pole, hippocampus, amygdala	Patients	$r_{(21)} = .002$; $P = >.99$		$r_{(21)} = .41$; $P = .06$
	Controls	$r_{(24)} = .32$; $P = .13$		
R temporal pole, hippocampus, amygdala	Patients	$r_{(21)} = .21$; $P = .42$		**$r_{(21)} = .46$; $P = .04$**
	Controls	**$r_{(24)} = .41$; $P = .05$**		
Novel gestures controls < schizophrenia patients				
L hippocampus	Patients	$r_{(21)} = .33$; $P = .20$		$r_{(21)} = .25$; $P = .28$
	Controls	$r_{(24)} = .13$; $P = .56$		
L IPL	Patients	**$r_{(21)} = .64$; $P = .006$**	**$Z = -1.9$, $P_{(\text{two tailed})} = .06$**	$r_{(21)} = .006$; $P = .98$
	Controls	$r_{(24)} = .15$; $P = .50$		
L SFG (DMPFC)	Patients	$r_{(21)} = .23$; $P = .37$		$r_{(21)} = .21$; $P = .37$
	Controls	$r_{(24)} = .34$; $P = .11$		
Familiar gestures controls > schizophrenia patients				
L/R SMA	Patients	$r_{(21)} = .10$; $P = .71$		$r_{(21)} = .31$; $P = .18$
	Controls	$r_{(24)} = .38$; $P = .38$		
R MFG (DLPFC)	Patients	$r_{(21)} = -.04$; $P = .88$	**$Z = 2.9$, $P_{(\text{two tailed})} = .004$**	$r_{(21)} = .04$; $P = .86$
	Controls	**$r_{(24)} = .70$; $P < .001$**		

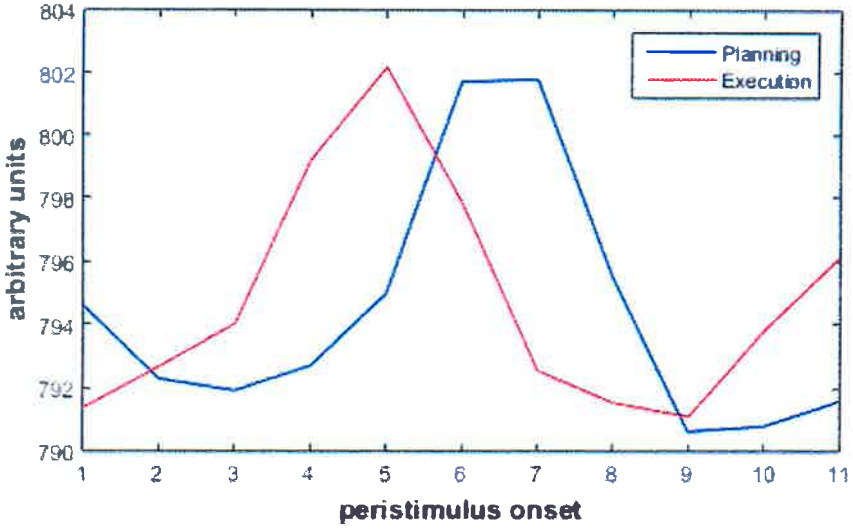
[a]IPL – inferior parietal lobe, SFG – superior frontal gyrus, SMA – supplementary motor area, MFG – middle frontal gyrus, DLPFC – dorsolateral prefrontal cortex, DMPFL – dorsomedial prefrontal cortex, Z – Fisher Z transformation.

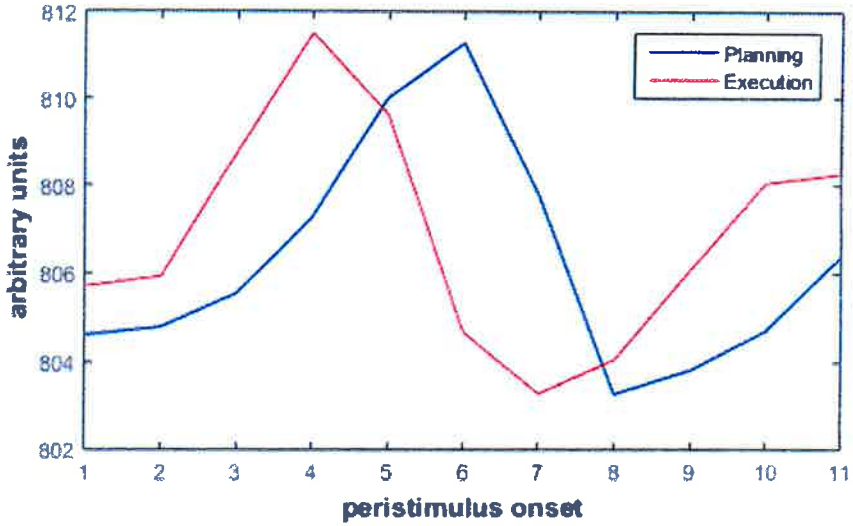
Analysis S4. Hemodynamic response function during planning and execution in the SMA

In our study design the execution phase directly follows the planning phase without jittering interval. Therefore we do not directly compare brain activation during the two experimental conditions. To illustrate whether specific increases in blood oxygenation level dependent (BOLD) signal can still be detected between the two experimental conditions, we explored the

hemodynamic response functions in one brain region (the supplementary motor area: SMA). The extracted mean hemodynamic response functions during planning and execution have been plotted against peristimulus onset time for four subjects (Figure S3). In fact, within the SMA a separable increase of the BOLD signal was identified (see Figure S3: red and blue line) arguing for a signal which can be detected despite the missing jittering interval between the two experimental conditions.

Figure S3. Mean hemodynamic response function for four single cases in the supplementary motor area (SMA) during planning and execution. Blue = hemodynamic response during planning of gesture performance; red = hemodynamic response during execution of gesture performance.


Planning
Execution
arbitrary units
peristimulus onset
804
802
800
798
796
794
792
790
1
2
3
4
5
6
7
8
9
10
11


Planning
Execution
arbitrary units
peristimulus onset
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810
808
806
804
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1
2
3
4
5
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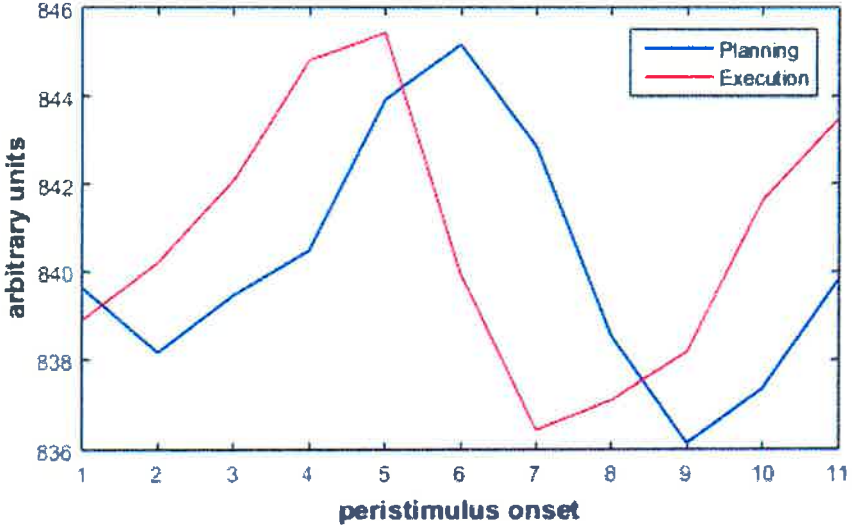
9
10
11


Planning
Execution
arbitrary units
peristimulus onset
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842
840
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836
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3
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5
6
7
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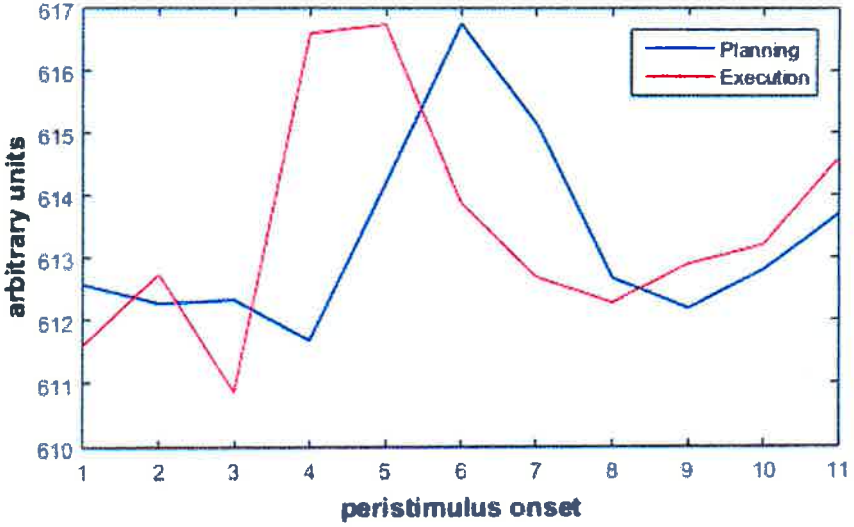
9
10
11


Planning
Execution
arbitrary units
peristimulus onset
617
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