



Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Nonverbal communication remains untouched: No beneficial effect of symptomatic improvement on poor gesture performance in schizophrenia

Florian Wüthrich ^{a,*}, Anastasia Pavlidou ^a, Katharina Stegmayer ^a, Sarah Eisenhardt ^a, Jeanne Moor ^{a,b}, Lea Schäppi ^a, Tim Vanbellingen ^{c,d}, Stephan Bohlhalter ^d, Sebastian Walther ^a

^a Translational Research Center, University Hospital of Psychiatry and Psychotherapy, University of Bern, Switzerland

^b Department of General Internal Medicine, Bern University Hospital, Bern, Switzerland

^c ARTORG Center for Biomedical Engineering Research, Gerontechnology and Rehabilitation Group, University of Bern, Switzerland

^d Neurology and Neurorehabilitation Center, Kantonsspital Luzern, Luzern, Switzerland

ARTICLE INFO

Article history:

Received 17 June 2020

Received in revised form 6 August 2020

Accepted 15 August 2020

Available online xxxx

Keywords:

TULIA

Psychosis

Nonverbal communication

First-degree relatives

Longitudinal

Nonverbal skills

ABSTRACT

Background: Gestures are an important part of communication. Patients with schizophrenia present gesture deficits that tend to deteriorate in the course of the disease and hamper functional outcome. This gesture deficit has been associated with motor abnormalities, cognitive impairment, and psychotic symptoms. Unaffected, first-degree relatives of schizophrenia patients share some subclinical motor and cognitive abnormalities. We aimed to investigate, whether gesture performance changes with symptomatic improvement in patients, and to test the longitudinal performance in unaffected, first-degree relatives.

Methods: In this study, we measured gesture performance using a validated test in 33 patients, 29 first-degree relatives and 38 healthy controls. Measurements were completed shortly after admission and before discharge in patients. Performance was rated blindly by experts using video recordings of the gesture task. Additionally, we evaluated cognitive function and psychotic symptoms at both visits.

Results: Gesture performance was poorer in relatives compared to controls and poorer in patients compared to both relatives and controls. Patients showed an improvement in psychopathology but a significant decrease in gesture performance at follow-up, while performance in the other groups remained stable. Proportional change of gesture performance correlated with change of cognitive function in patients, whereas there were no correlations with change of cognitive function in the other groups.

Conclusion: While symptom severity was reduced, the gesture deficit further deteriorated in schizophrenia. The finding argues for distinct processes contributing to poor nonverbal communication skills in patients, requiring novel alternative treatment efforts.

© 2020 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

1. Introduction

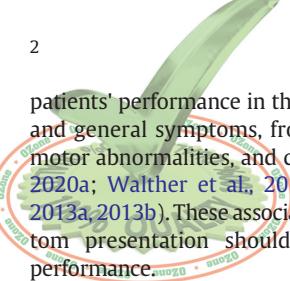
Gestures are important for communication as they carry meaningful information (Cartmill et al., 2012; Goldin-Meadow, 1999). Patients with schizophrenia exhibit deficits in gesture performance, recognition and interpretation when compared to healthy controls, affecting overall communication (Grusser et al., 1990; Troisi et al., 1998; Walther et al., 2015). Patients misinterpret incidental movements as gestures and tend to misattribute meaning to gestures more often than healthy controls (Bucci et al., 2008), produce less gestures while speaking (Lavelle et al., 2013), experience more difficulties registering mismatch of

abstract speech and co-speech gestures (Nagels et al., 2019), show poorer performance in imitation (on demonstrated gesture) of novel, meaningless (Matthews et al., 2013; Park et al., 2008), transitive (object related) and intransitive (communicative, symbolic) gestures (Walther et al., 2013a), as well as pantomime (on verbal instruction) of meaningless, transitive and intransitive gestures (Walther et al., 2013a, 2013b). Previous studies examining isolated gesture production in schizophrenia using the Test of Upper Limb Apraxia (TULIA), a test that measures imitation and pantomime of meaningless, transitive and intransitive gestures, demonstrated overall poorer performance in patients during pantomime versus imitation, and a relevant deficit in 40–67% of patients (Walther et al., 2013a, 2013b).

Negative symptoms have been associated with the frequency of co-speech gestures and imitation of meaningless gestures in schizophrenia (Lavelle et al., 2013; Matthews et al., 2013; Park et al., 2008). Similarly,

* Corresponding author at: Translational Research Center, University Hospital of Psychiatry and Psychotherapy Bern, Bolligenstrasse 111, 3000 Bern 60, Switzerland.

E-mail address: florian.wuethrich@upd.unibe.ch (F. Wüthrich).



patients' performance in the TULIA has been associated with negative and general symptoms, frontal lobe dysfunction, working memory, motor abnormalities, and conceptual disorganization (Walther et al., 2020a; Walther et al., 2016; Walther et al., 2015; Walther et al., 2013a, 2013b). These associations suggest that changes in clinical symptom presentation should be paralleled by changes in gesture performance.

Conversely, gestural deficits have been observed in clinical high risk (CHR) adolescents, exhibiting a higher incidence of semantic mismatches in co-speech gestures (Millman et al., 2014). Gestural performance deficits as measured by TULIA are noticeable in first episode psychosis, but are more pronounced in multiple episode patients (Stegmayer et al., 2016b), indicating deterioration over the course of the illness. However, no significant change in TULIA performance was observed over the course of 6 months, whereas these gesture deficits predicted poor functional outcome (Walther et al., 2016). Thus, it remains unclear if cued gesture performance is a relatively stable marker, only slowly deteriorating over time, or if it is subject to short term change driven by dynamic fluctuations of psychopathology.

Furthermore, first-degree relatives of patients with schizophrenia, which are unaffected by psychosis, also exhibit slight deficits or signs similar to patients, but to a lesser extent. This includes, among other features, prospective memory (Saleem et al., 2018), executive function (Aydin et al., 2017), and emotion recognition (Allott et al., 2015), as well as, motor abnormalities (Burton et al., 2016; Kent et al., 2020; Schappi et al., 2018). The conception of schizophrenia as a neurodevelopmental or neurodegenerative disorder (Knoll et al., 1998; Rapoport et al., 2012) and the high heritability of the disease (Cannon et al., 1998) suggest that these deficits represent endophenotypes – illness associated traits that can be observed in patients before onset of the disease and in unaffected relatives (Lenzenweger, 2013). Likewise, gesture performance requires cognitive and motor skills, which might be endophenotypes and compromised in subjects with a genetic risk of psychosis. Therefore, if gesture performance does change in patients depending on state psychopathology and if gesture deficits were present but stable in unaffected relatives, gesture performance could be a behavioral marker of psychosis risk, potentially predicting the transition in young subjects at risk for psychosis. Indeed, while relatives may share gesture impairments with patients, we would need to know whether there are changes of gesture performance over time.

Since gesture deficits have been observed in CHR individuals, become more noticeable over the course of the disease, and can predict outcome, it is crucial to expand our knowledge about intra-individual variability and its relation to psychopathology. Consequently, this study aims to investigate short term changes in gesture performance and their relation to psychopathology in patients with schizophrenia, their first-degree relatives and healthy controls. We employed the TULIA to measure imitation and pantomime of meaningless, transitive and intransitive gestures. We anticipated no significant test-retest training effects, as previous studies reported some learning effects after 48 h (Walther et al., 2020b), but not after 1 week (Vanbellingen et al., 2020) in healthy subjects and we planned test-retest intervals to be longer than 1 week. As gesture performance has been associated with psychopathological factors in schizophrenia, we expected patients' performance to change according to changes in symptom presentation, i.e. gesture deterioration with symptom progression. Consequently, we anticipated stable performance in first-degree relatives and controls, for they present no psychosis.

2. Methods

2.1. Participants

The current study included 33 patients (11 males, 22 females), 29 first-degree relatives (parents, siblings or children; 6 males, 23

females), and 38 controls (19 males, 19 females). Patients and controls were matched for age, gender and education. All participants were right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971) and were native German speakers. Demographic and clinical characteristics of all participants are presented in Table 1. Written informed consent was obtained from all participants, and the study was approved by the local Ethics Committee (KEK-BE 025/13) and complies with the tenants of the Declaration of Helsinki.

Patients were recruited from the University Hospital of Psychiatry in Bern, Switzerland, and diagnosed with schizophrenia in accordance to the structured clinical interview (SCID) and DSM-5 criteria. During the study, they received treatment as usual, which did not include any specific therapy to improve communication skills. Most patients received atypical antipsychotics ($N = 26$). A minority received typical ($n = 3$), a combination of typical and atypical ($n = 3$), or no antipsychotics ($n = 1$). First-degree relatives were contacted by the patients and/or the Association of Schizophrenia Patients' Relatives in Bern, Switzerland. Controls were recruited among staff and other volunteers of the community without any family history of schizophrenia. Exclusion criteria for all participants were substance abuse (except nicotine), and no history or current medical or neurological disorders associated with movement impairments.

2.2. Assessments

Hand and finger gesture performance for both baseline and follow-up visits was assessed for all participants using the Test of Upper Limb Apraxia (TULIA) (Vanbellingen et al., 2010). We pursued a pragmatic approach with recruitment shortly after admission and follow-up just before expected discharge of patients. For relatives and controls we aimed at 2–4 week intervals between measurements. The TULIA performance was videotaped and later examined by an independent rater according to the TULIA manual. The rater was blind to both the group membership of the participants and the timing of the tests. The maximum total score for TULIA is 240 based on 48 items in two different domains: imitation, which requires performance after demonstration by the examiner, and pantomime, which requires performance following verbal instruction. Within the two domains, three semantic categories of gestures are present: transitive (tool or object related), intransitive (communicative symbolic) and meaningless (novel gestures without semantic content). Higher score designates superior performance. In addition, frontal lobe dysfunction, verbal working memory, and psychopathology (in patients only) were assessed using the Frontal Assessment Battery (FAB) (Dubois et al., 2000), Digit Span Backwards (DSB) (Hilbert et al., 2015), and Positive And Negative Syndrome Scale (PANSS) (Kay et al., 1987) respectively for both baseline and follow-up visits.

2.3. Data analysis

Mean TULIA scores for each domain (imitation and pantomime) were calculated and presented separately for each group (patients, first-degree relatives and controls) and visit (baseline and follow-up) using scripts written in R (version 3.6.1). Demographic data were compared using one-way ANOVA. Statistical analysis of the mean TULIA scores, FAB and DSB were carried out using repeated measures ANCOVAs covaried for age and gender. Antipsychotic medication (in chlorpromazine equivalents, CPZ), PANSS total and subscale scores were compared between visits in patients using paired *t*-tests. In addition, we calculated the proportional change of participants' TULIA scores between the two visits and correlated them with the proportional change of FAB and DSB across all groups and CPZ and PANSS in patients using Pearson partial correlations in R with age and gender as covariates (follow-up/baseline; higher numbers of proportional change indicate improvement in TULIA, FAB, DSB and deterioration in PANSS). Additionally, we correlated time to follow-up with proportional change of TULIA

Table 1

Demographic characteristics.

	Patients N = 33	First-degree relatives N = 27	Controls N = 38	ANOVA	Post-hoc
Age (years)	35.8 ± 10.2	45.3 ± 15.1	39.9 ± 13.4	$F_{2,95} = 4.0$ $p < .05$	Patients-controls $p = .374$ Relatives-controls $p = .231$ Relatives-patients $p = .016$
Gender (% female)	33.3%	77.8%	44.7%	$F_{2,95} = 6.9$ $p < .01$	Patients-controls $p = .572$ Relatives-controls $p = .018^*$ Relatives-patients $p = .001^*$
Time to follow-up (days)	28.6 ± 30.1	10.3 ± 6.1	19.8 ± 19.5	$F_{2,95} = 5.4$ $p < .01$	Patients-controls $p = .092$ Relatives-controls $p = .081$ Relatives-patients $p = .001^*$
Education (years)	13.8 ± 3.0	13.8 ± 2.6	13.8 ± 2.6	$F_{2,95} = 0.0012$ $p > .1$	

Mean ± Standard Deviation.

* Denotes a significant difference.

and CPZ. We applied Benjamini-Hochberg procedure to account for multiple comparisons in correlation analyses (Benjamini and Hochberg, 1995). Finally, as sensitivity analyses, we removed subjects who had excessively long time to follow-up (>50 days) and repeated all analyses, and removed two outliers with extreme improvements in TULIA and positive symptoms and repeated correlations.

3. Results

3.1. Clinical and demographic data

Groups differed in age and gender but not education. Post-hoc analysis revealed a significant difference in age only between patients and first-degree relatives, while first-degree relatives had significantly higher number of female participants compared to patients and controls. Both differences are due to including mothers as first-degree relatives (Table 1). Mean time interval between visits was shorter in the first-degree relatives than patients.

3.2. TULIA change over time

A 3 (Group) x 2 (Domain) x 2 (Visits) repeated measures ANCOVA (covaried for age and gender) revealed a significant interaction between Group and Visits ($F_{2,378} = 3.6, p < .05$; Fig. 1). Post-hoc analysis using the Benjamini-Hochberg procedure indicated lower mean TULIA scores during the follow-up visit vs baseline for patients ($p = .003$), but not for first-degree relatives ($p = .428$) or controls ($p = .462$). Additionally, patients had poorer performance during the baseline visit compared to first-degree relatives ($p = .002$) and controls ($p < .001$). Furthermore, first-degree relatives had poorer performance at trend level ($p = .051$) compared to controls at baseline. Likewise, during the follow-up visit patients again exhibited poorer performance compared to first-degree relatives ($p < .001$) and controls ($p < .001$). Similarly, first-degree relatives also displayed poorer performance than controls ($p = .001$) during the follow-up visit.

No other significant interactions between Group x Domain, Domain x Visits, as well as Group x Domain x Visits were observed (all $F < 1.5$ and $p > .28$). Moreover, a significant main effect of Group ($F_{2,378} = 60.5, p < .001$) and Domain ($F_{1,378} = 12.6, p < .001$) was also observed, while the main effect of Visits was at trend level ($F_{2,378} = 3.28, p = .071$). Since the triple interaction was not significant, we refrained from including categories into the model (quadruple interaction).

3.3. Clinical changes over time

A 3 (Group) x 2 (Visit) repeated measures ANCOVA (covaried for age and gender) revealed a significant main effect of Group and Visit for both FAB (Group: $F_{2,378} = 27.0, p < .0001$; Visit: $F_{1,378} = 5.7, p <$

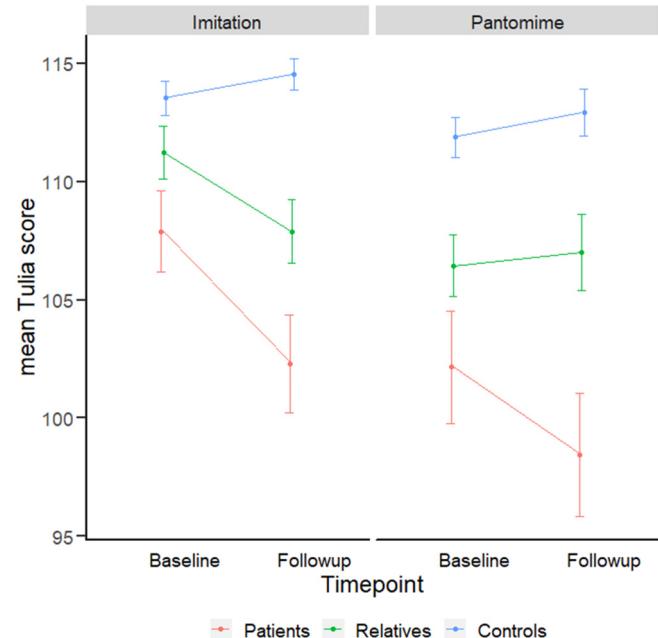


Fig. 1. TULIA performance by group and domain for both visits. Higher score indicates better performance.

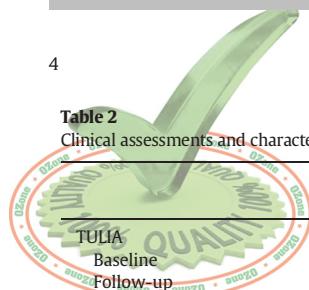
.05) and DSB (Group: $F_{2,378} = 35.9, p < .0001$; Visit: $F_{1,378} = 5.6, p < .05$). In contrast, no significant interaction between Group and Visit was observed for FAB ($F_{2,378} = 1.7, p = .17$) or DSB ($F_{2,378} = 1.8, p = .15$). Patients performed poorer than controls in both, FAB ($p \leq .001$) and DSB ($p \leq .001$). Patients also scored lower than relatives in DSB ($p \leq .001$). In contrast, we found no significant differences between relatives and controls ($p = .159$) and between relatives and patients ($p = .174$) in FAB or between relatives and controls in DSB ($p = .989$).

In addition, paired *t*-tests of PANSS in patients revealed significant improvement in all subscales and total scores (positive $T = -3.9, p < .001$; negative $T = -4.5, p < .001$; general $T = -5.3, p < .001$, total $T = -5.4, p < .001$), as well as a significant increase in antipsychotic medication dosage ($T = 2.1, p = .047$). Means and standard deviations of clinical measures are presented in Table 2.

3.4. Correlations

We calculated the proportional change of individual TULIA scores for both visits and correlated them separately with the proportional change of FAB, DSB and PANSS (Fig. 2; Supplementary Fig. S1) independently

Table 2
Clinical assessments and characteristics.



	Patients N = 33	Relatives N = 27	Controls N = 38
TULIA			
Baseline	210.0 ± 21.2	217.6 ± 11.1	225.4 ± 7.9
Follow-up	200.7 ± 25.9	214.8 ± 14.4	227.4 ± 8.1
FAB			
Baseline	16.3 ± 1.7	16.7 ± 1.6	17.5 ± 0.7
Follow-up	16.5 ± 2.1	17.4 ± 1.0	17.6 ± 0.6
DSB			
Baseline	4.3 ± 1.2	5.2 ± 0.8	5.3 ± 0.7
Follow-up	4.7 ± 1.1	5.5 ± 0.6	5.3 ± 0.8
Characteristics (only patients)		Baseline	Follow-up
PANSS positive		18.3 ± 6.7	14.1 ± 4.6
PANSS negative		17.7 ± 4.7	15.5 ± 5.3
PANSS general		34.9 ± 8.6	29.5 ± 9.4
PANSS total		71.0 ± 17.4	59.2 ± 17.7
CPZ (mg)		418.3 ± 395	500 ± 472

Mean ± Standard Deviation; TULIA: Test of Upper Limb Apraxia; FAB: Frontal Assessment Battery; DSB: Digit Span Backwards; PANSS: Positive And Negative Syndrome Scale; CPZ: Chlorpromazine equivalent.

for each domain. For imitation, patients showed a significant correlation between change in TULIA and FAB ($r = 0.48, p < .01$), as well as DSB ($r = 0.51, p < .001$), but not with change in symptom severity. In contrast, no significant correlation in first-degree relatives or controls was observed (all $|r| < 0.22$ and $p > .15$). For pantomime, in patients proportional change correlated between TULIA and FAB ($r = 0.55, p < .001$), and positive symptoms ($r = -0.47, p = .008$), but not for DSB ($r = 0.20, p = .28$) and negative symptoms ($r = -0.01, p = .94$). The correlations between proportional changes of pantomime and total PANSS ($r = -0.41, p = .021$) and general subscale of PANSS ($r = -0.39, p = .03$) were the only correlations with uncorrected $p < .05$ to not pass the Benjamini-Hochberg procedure. Similarly to imitation, no significant correlations were observed for first-degree relatives or controls in pantomime (all $|r| < 0.22$ and $p > .19$). We found no correlations of proportional change of TULIA with time to follow-up in any of the groups and no correlation of CPZ with time to follow-up or TULIA in patients (all $|r| < 0.3$ and $p > .1$).

3.5. Sensitivity analyses

We removed 4 patients and 2 control subjects who had times to follow-up longer than 50 days. Results of repeated analyses are presented in Supplementary Tables S1 and S2, and Supplementary Figs. S2 and S3. In contrast to our main analyses, mean time to follow-up of relatives was shorter than those of patients and controls. The repeated measures ANCOVA revealed significant main effects for Group and Domain, but in contrast to our main analysis, the Group x Visits interaction was only at trend level ($p = .07$). The 3 (Group) x 2 (Visit) ANCOVA for FAB yielded similar results as before, the ANCOVA for DSB showed a significant effect for Group, but in contrast to our main analysis, the effect for Visit was only at trend level ($p = .07$). Paired *t*-tests in patients confirmed improvements in all subscales and total score of the PANSS. Conversely, the increase in medication dosage was not significant anymore after removal of patients with time to follow-up >50 days. Correlation analyses without the two subjects with extreme

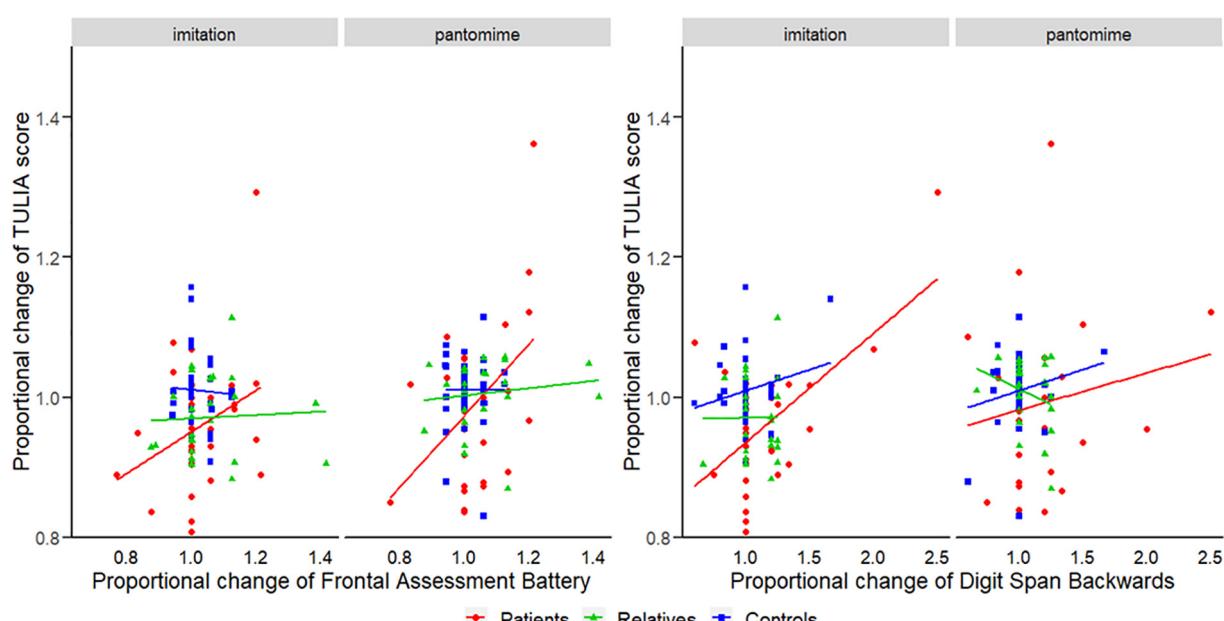


Fig. 2. Correlations of proportional change of TULIA with proportional changes of Frontal Assessment Battery and Digit Span Backwards by group and domain. Higher proportional change indicates improvement.

improvement in TULIA and positive symptoms resulted in no significant correlations, i.e. removal of the outliers rendered the correlation insignificant (Supplementary Table S3).

4. Discussion

The present study investigated short term changes of gesture performance in patients with schizophrenia, their first-degree relatives and healthy controls, as well as their relation to working memory, frontal lobe function, and psychopathology.

Gesture performance was significantly poorer in patients compared to the other groups during both visits while relatives performed significantly poorer than controls during the follow-up visit. Patients were the only group to show a significant change in gesture performance between visits with decreased performance at follow-up. Pantomime performance was inferior compared to imitation across all groups and visits. Patients presented a significant improvement in PANSS scores at follow-up. In addition, change in gesture performance correlated with change in frontal function (both domains), and working memory (imitation) in patients, but not in the other groups.

The gradually poorer performance of relatives and patients compared with controls is consistent with our hypotheses. The current results corroborate previous reports on gesture performance in patients (Martin et al., 1994; Matthews et al., 2013; Park et al., 2008; Walther et al., 2013a), and observations in relatives in various other signs and symptoms of schizophrenia (Allott et al., 2015; Aydin et al., 2017; Burton et al., 2016; Saleem et al., 2018). Prior studies reported a gesture deficit in up to 67% of patients with schizophrenia and veritable apraxia in 27% of patients. They presented errors resembling those in apraxia, such as body-part-as-object errors or impaired spatial orientation (Walther et al., 2020a; Walther et al., 2013b).

In line with our hypotheses, no significant training effects were observed in gesture performance across groups. Against our predictions, gesture performance deteriorated in the patients, while concurrent symptoms improved. We had assumed that gestures improve with less psychopathology. Indeed, we found decreases in positive symptoms to correlate with improved TULIA performance in our main analysis. However, a sensitivity analysis showed that the correlation was mainly driven by two outliers. This large effect of outliers might be explained by the high variance in TULIA scores in patients, indicating massive heterogeneity in the course of gesture performance.

While first degree relatives exhibited a gesture deficit compared with controls, they showed no significant change in performance and no correlation of cognitive function and gesture performance, similar to healthy controls. This observation is in line with reports on neurological soft signs, which change within the course of psychosis but are also seen in unaffected first-degree relatives (Bachmann and Schroder, 2017; Schappi et al., 2018). Therefore, the gesture performance deficit may qualify as a behavioral marker of the risk for psychosis.

In accordance with our hypotheses, partial correlations revealed associations of gesture performance with cognitive function in patients. Conversely, we did not find any correlations of frontal lobe function and working memory with performance in controls or relatives. The associations showed a differential pattern across domains in patients. Frontal lobe function correlated positively with both, imitation and pantomime. However, working memory only correlated positively with imitation, while positive score of the PANSS correlated negatively with pantomime in our main analysis but not in our sensitivity analysis. Thus, in general, improved cognitive function predicts better gesture performance in patients. It remains unclear if ameliorated psychotic symptoms can predict improvement in gesture performance. Imitation requires more information to be recalled, e.g. amplitudes, timing, and speed of demonstrations, possibly explaining its association with working memory. In contrast, pantomime depends on a more elaborate planning process that could be hampered by psychotic symptoms such as conceptual disorganization and motor disturbance. The lack of

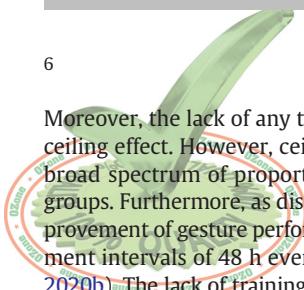
correlations in controls and relatives is likely to be attributed to the stable gesture performance in these groups. Furthermore, there was no association of cognitive abilities at baseline with change of gesture performance in any of the groups (data not shown).

Patients improved significantly in all subscales of the PANSS between baseline and follow-up. Since patients were recruited shortly after admission and received treatment as usual (represented by the significant increase in antipsychotic dosages), we notice that treatment generally ameliorated psychotic symptoms. However, as outlined above, patients showed a deterioration of the gesture deficit despite the improvement of the psychotic syndrome. Moreover, neither time intervals between visits, nor dosage of antipsychotics correlated with the change of performance. This implies that the gesture deficit in schizophrenia, as represented by TULIA, is a distinct disruption of non-verbal communication. Given that gesture only improved with the amelioration of positive symptoms in some outliers, we suggest that there is a need for additional, complementary therapies targeting improvement of (nonverbal) communication and social functioning in patients with schizophrenia who present a persistent gesture deficit.

Future research will find and evaluate such therapies. Previous findings suggest the importance of motor symptoms, frontal function, positive symptoms, and working memory for various tests of social functioning, including gesture performance (Dutschke et al., 2018; Walther et al., 2020a; Walther et al., 2015; Walther et al., 2013a, 2013b). Novel therapies could therefore either aim at gestures and communication directly or at working memory and motor abnormalities (Lefebvre et al., 2020). Moreover, brain areas of the praxis network have been linked to impaired social skills including gesture performance and perception (Bohlhalter et al., 2009; Stegmayer et al., 2016a; Stegmayer et al., 2018; Straube et al., 2014; Viher et al., 2018; Wroblewski et al., 2020; Wüthrich et al., 2020). Therefore, a possible approach for new therapies might be non-invasive brain stimulation of the praxis network. Indeed, studies applying transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS) to improve gesture performance and processing in healthy subjects as well as in patients with schizophrenia have reported promising effects, but broader evidence is still needed (Bolognini et al., 2015; Schulke and Straube, 2019; Vanbellingen et al., 2020; Walther et al., 2020b; Weiss et al., 2013). Psychotherapeutic approaches to improve communication skills in schizophrenia have been present for decades, but are not commonly integrated in standard treatment of schizophrenia and have strongly focused on verbal communication (Joyal et al., 2016). However, trainings including nonverbal communication are being developed and tested (Riedl et al., 2020). Future studies should examine the combination of brain stimulation and psychotherapy.

Moreover, longitudinal studies of social skills in first-degree relatives of patients with schizophrenia are sparse. Finally, longitudinal data on relatives and CHR individuals might shed light onto the mechanisms of conversion from predisposition/high risk into psychosis. While altered gesture behavior has been described in CHR individuals (Millman et al., 2014; Osborne et al., 2017), to date, the predictive potential of deterioration of gesture behavior for subsequent transition into psychosis remains unknown.

There are some limitations to this study. First, the relatives were significantly older and included more females than the other groups because this group consisted largely of patients' mothers. This ensures exclusion of subjects at clinical high risk who could later convert to psychosis, potentially biasing the findings. Additionally, we accounted for the differences by covarying our analyses with age and gender. Relatives also had significantly shorter time to follow-up. As there was no association of the interval between visits and the clinical variables in any of the groups, this is unlikely to influence our results. Second, we did not record extrapyramidal symptoms at both visits. Although change in antipsychotic dosage did not correlate with change in TULIA performance, we cannot exclude a non-linear increase in (motor) side-effects as a potential cause of deterioration of gesture performance in patients.



Moreover, the lack of any training effects in controls might indicate a ceiling effect. However, ceiling effects seem unlikely considering the broad spectrum of proportional change that we observed across all groups. Furthermore, as discussed above, healthy controls showed improvement of gesture performance in a TMS-study with shorter assessment intervals of 48 h even in the placebo condition (Walther et al., 2020b). The lack of training effect is to be attributed to the rather long interval between baseline and follow up, as well as the complexity of the task, the low number of repetitions, and the lack of feedback on performance. Consequently, healthy subjects showed no test-retest training effects in the TULIA after one week in a prior report (Vanbellingen et al., 2020). Moreover, this study took place in an inpatient setting. More change and a variable course of symptoms are to be expected shortly after admission. Therefore, it is unlikely that the decrease in performance continues linearly in a more stable outpatient setting. Indeed, the fact that there was no significant change in TULIA performance in a 6 months follow-up (Walther et al., 2016), and a more prominent gesture deficit in multiple episode compared with first episode patients (Stegmayer et al., 2016b) suggests either a slow decline with temporary disturbances or an episodic development with incomplete remission. Finally, the gesture deficit is not a universal feature in schizophrenia. Depending on cut-offs, it is present in 40–67% of patients (Walther et al., 2015; Walther et al., 2013a, 2013b). Patients exhibiting a gesture deficit might particularly benefit from interventions targeting communication skills. Indeed, patients with gesture deficits tend to have impaired social skills and eventually, poorer functional outcome (Walther et al., 2016). Therefore, patients need to be screened and treated for gesture deficits to effectively improve their outcome and lower the burden of the disease. However, further research is needed to examine whether gesture behavior changes over longer periods of time, i.e. years and decades.

5. Conclusion

Gesture performance was gradually poorer between controls, relatives, and patients with schizophrenia. In controls and relatives, gesture performance remained stable at follow-up. While symptoms improved compared to baseline, the gesture performance decreased in patients with schizophrenia. This indicates a distinct disturbance of nonverbal communication in schizophrenia with insufficient effects of the standard treatment. Therefore, new therapeutic approaches such as non-invasive brain stimulation, trainings to improve nonverbal communication or the combination of both should be explored.

Role of the funding source

This study was supported by the Swiss National Science Foundation (SNF grants #152619 to SW and SB, #184717 to SW), the National Institutes of Health (NIH grant R01-MH118741 to SW), and the Gottfried and Julia Bangerter-Rhyner Foundation (to SW). The funding sources had no influence on study design, data analysis or interpretation, or the content or publication of the manuscript.

CRediT authorship contribution statement

SW wrote the protocol, acquired funding and supervised the study. AP analyzed the data. FW wrote the first draft of the manuscript. KS, LS and JM recruited participants and performed measurements. SE and SW rated video-based data. All authors contributed to data interpretation and edited the manuscript. All authors approved the final manuscript.

Declaration of competing interest

Dr. Walther received honoraria from Janssen, Lundbeck, and Sunovion. Dr. Stegmayer received honoraria from Lundbeck and Sunovion Pharmaceuticals. All other authors report no competing interests.

Acknowledgement

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.schres.2020.08.013>.

References

- Allott, K.A., Rice, S., Bartholomeusz, C.F., Klier, C., Schlogelhofer, M., Schafer, M.R., Amminger, G.P., 2015. Emotion recognition in unaffected first-degree relatives of individuals with first-episode schizophrenia. *Schizophr. Res.* 161 (2–3), 322–328.
- Aydin, E., Cansu Ulgen, M., Tabo, A., Devrim Balaban, O., Yesilyurt, S., Yumrukcal, H., 2017. Executive function and genetic loading in nonpsychotic relatives of schizophrenia patients. *Psychiatry Res.* 248, 105–110.
- Bachmann, S., Schroder, J., 2017. Neurological soft signs in schizophrenia: an update on the state- versus trait-perspective. *Front. Psychiatry* 8, 272.
- Benjamini, Y., Hochberg, Y., 1995. Controlling the false discovery rate - a practical and powerful approach to multiple testing. *Journal of the Royal Statistical Society Series B-Statistical Methodology* 57 (1), 289–300.
- Bohlhalter, S., Hattori, N., Wheaton, L., Friedman, E., Shamim, E.A., Garraux, G., Hallett, M., 2009. Gesture subtype-dependent left lateralization of praxis planning: an event-related fMRI study. *Cereb. Cortex* 19 (6), 1256–1262.
- Bolognini, N., Convento, S., Banco, E., Mattioli, F., Tesio, L., Vallar, G., 2015. Improving ideo-motor limb apraxia by electrical stimulation of the left posterior parietal cortex. *Brain* 138 (Pt 2), 428–439.
- Bucci, S., Startup, M., Wynn, P., Baker, A., Lewin, T.J., 2008. Referential delusions of communication and interpretations of gestures. *Psychiatry Res.* 158 (1), 27–34.
- Burton, B.K., Hjorthoj, C., Jepsen, J.R., Thorup, A., Nordentoft, M., Plessen, K.J., 2016. Research review: do motor deficits during development represent an endophenotype for schizophrenia? A meta-analysis. *J. Child Psychol. Psychiatry* 57 (4), 446–456.
- Cannon, T.D., Kaprio, J., Lonnqvist, J., Huttunen, M., Koskenvuo, M., 1998. The genetic epidemiology of schizophrenia in a Finnish twin cohort. A population-based modeling study. *Arch. Gen. Psychiatry* 55 (1), 67–74.
- Cartmill, E.A., Beilock, S., Goldin-Meadow, S., 2012. A word in the hand: action, gesture and mental representation in humans and non-human primates. *Philos. Trans. R. Soc. Lond. Ser. B Biol. Sci.* 367 (1585), 129–143.
- Dubois, B., Slachevsky, A., Litvan, I., Pillon, B., 2000. The FAB: a frontal assessment battery at bedside. *Neurology* 55 (11), 1621–1626.
- Dutschke, L.L., Stegmayer, K., Ramseyer, F., Bohlhalter, S., Vanbellingen, T., Strik, W., Walther, S., 2018. Gesture impairments in schizophrenia are linked to increased movement and prolonged motor planning and execution. *Schizophr. Res.* 200, 42–49.
- Goldin-Meadow, S., 1999. The role of gesture in communication and thinking. *Trends Cogn. Sci.* 3 (11), 419–429.
- Grusser, O.J., Kirchhoff, N., Naumann, A., 1990. Brain mechanisms for recognition of faces, facial expression, and gestures: neuropsychological and electroencephalographic studies in normals, brain-lesioned patients, and schizophrenics. *Res. Publ. Assoc. Res. Nerv. Ment. Dis.* 67, 165–193.
- Hilbert, S., Nakagawa, T.T., Puci, P., Zech, A., Buhner, M., 2015. The digit span backwards task verbal and visual cognitive strategies in working memory assessment. *Eur. J. Psychol. Assess.* 31 (3), 174–180.
- Joyal, M., Bonneau, A., Fecteau, S., 2016. Speech and language therapies to improve pragmatics and discourse skills in patients with schizophrenia. *Psychiatry Res.* 240, 88–95.
- Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr. Bull.* 13 (2), 261–276.
- Kent, J.S., Disner, S.G., Van Voorhis, A.C., Urosevic, S., Caligiuri, M.P., Sponheim, S.R., 2020. Exploring the relationship of transdiagnostic mood and psychosis symptom domains with motor dysfunction. *Neuropsychobiology* 79 (4–5), 301–312.
- Knoll, J.L.T., Garver, D.L., Ramberg, J.E., Kingsbury, S.J., Croissant, D., McDermott, B., 1998. Heterogeneity of the psychoses: is there a neurodegenerative psychosis? *Schizophr. Bull.* 24 (3), 365–379.
- Lavelle, M., Healey, P.G., McCabe, R., 2013. Is nonverbal communication disrupted in interactions involving patients with schizophrenia? *Schizophr. Bull.* 39 (5), 1150–1158.
- Lefebvre, S., Pavlidou, A., Walther, S., 2020. What is the potential of neurostimulation in the treatment of motor symptoms in schizophrenia? *Expert. Rev. Neurother.* 20 (7), 697–706.
- Lenzenweger, M.F., 2013. Endophenotype, intermediate phenotype, biomarker: definitions, concept comparisons, clarifications. *Depress. Anxiety* 30 (3), 185–189.
- Martin, P., Tewesmeier, M., Albers, M., Schmid, G., Scharfetter, C., 1994. Investigation of gestural and pantomime performance in chronic schizophrenic inpatients. *Eur. Arch. Psychiatry Clin. Neurosci.* 244 (2), 59–64.
- Matthews, N., Gold, B.J., Sekuler, R., Park, S., 2013. Gesture imitation in schizophrenia. *Schizophr. Bull.* 39 (1), 94–101.
- Millman, Z.B., Goss, J., Schiffman, J., Mejias, J., Gupta, T., Mittal, V.A., 2014. Mismatch and lexical retrieval gestures are associated with visual information processing, verbal production, and symptomatology in youth at high risk for psychosis. *Schizophr. Res.* 158 (1–3), 64–68.
- Nagels, A., Kircher, T., Grosvald, M., Steines, M., Straube, B., 2019. Evidence for gesture-speech mismatch detection impairments in schizophrenia. *Psychiatry Res.* 273, 15–21.
- Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 9 (1), 97–113.

- Osborne, K.J., Bernard, J.A., Gupta, T., Dean, D.J., Millman, Z., Vargas, T., Ristanovic, I., Schiffman, J., Mittal, V.A., 2017. Beat gestures and postural control in youth at ultra-high risk for psychosis. *Schizophr. Res.* 185, 197–199.
- Park, S., Matthews, N., Gibson, C., 2008. Imitation, simulation, and schizophrenia. *Schizophr. Bull.* 34 (4), 698–707.
- Rapoport, J.L., Giedd, J.N., Gogtay, N., 2012. Neurodevelopmental model of schizophrenia: update 2012. *Mol. Psychiatry* 17 (12), 1228–1238.
- Riedl, L., Nagels, A., Sammer, G., Straube, B., 2020. A multimodal speech-gesture training intervention for patients with schizophrenia and its neural underpinnings – the study protocol of a randomized controlled pilot trial. *Front. Psychiatry* 11, 110.
- Saleem, S., Kumar, D., Venkatasubramanian, G., 2018. Prospective memory in first-degree relatives of patients with schizophrenia. *Clin. Neuropsychol.* 32 (5), 993–1001.
- Schappi, L., Stegmayer, K., Viher, P.V., Walther, S., 2018. Distinct associations of motor domains in relatives of schizophrenia patients—different pathways to motor abnormalities in schizophrenia? *Front. Psychiatry* 9, 129.
- Schulke, R., Straube, B., 2019. Transcranial direct current stimulation improves semantic speech-gesture matching in patients with schizophrenia spectrum disorder. *Schizophr. Bull.* 45 (3), 522–530.
- Stegmayer, K., Bohlhalter, S., Vanbellingen, T., Federspiel, A., Moor, J., Wiest, R., Muri, R., Strik, W., Walther, S., 2016a. Structural brain correlates of defective gesture performance in schizophrenia. *Cortex* 78, 125–137.
- Stegmayer, K., Moor, J., Vanbellingen, T., Bohlhalter, S., Muri, R.M., Strik, W., Walther, S., 2016b. Gesture performance in first- and multiple-episode patients with schizophrenia spectrum disorders. *Neuropsychobiology* 73 (4), 201–208.
- Stegmayer, K., Bohlhalter, S., Vanbellingen, T., Federspiel, A., Wiest, R., Muri, R.M., Strik, W., Walther, S., 2018. Limbic interference during social action planning in schizophrenia. *Schizophr. Bull.* 44 (2), 359–368.
- Straube, B., Green, A., Sass, K., Kircher, T., 2014. Superior temporal sulcus disconnectivity during processing of metaphoric gestures in schizophrenia. *Schizophr. Bull.* 40 (4), 936–944.
- Troisi, A., Spalletta, G., Pasini, A., 1998. Non-verbal behaviour deficits in schizophrenia: an ethological study of drug-free patients. *Acta Psychiatr. Scand.* 97 (2), 109–115.
- Vanbellingen, T., Kersten, B., Van Hemelrijk, B., Van de Winckel, A., Bertschi, M., Muri, R., De Weerdt, W., Bohlhalter, S., 2010. Comprehensive assessment of gesture production: a new test of upper limb apraxia (TULIA). *Eur. J. Neurol.* 17 (1), 59–66.
- Vanbellingen, T., Pastore-Wapp, M., Kubel, S., Nyffeler, T., Schupfer, A.C., Kiefer, C., Zilzperger, L., Lutz, K., Luft, A.R., Walther, S., Bohlhalter, S., 2020. Interhemispheric facilitation of gesturing: a combined theta burst stimulation and diffusion tensor imaging study. *Brain Stimul.* 13 (2), 457–463.
- Viher, P.V., Stegmayer, K., Kubicki, M., Karmacharya, S., Lyall, A.E., Federspiel, A., Vanbellingen, T., Bohlhalter, S., Wiest, R., Strik, W., Walther, S., 2018. The cortical signature of impaired gesturing: findings from schizophrenia. *Neuroimage Clin.* 17, 213–221.
- Walther, S., Vanbellingen, T., Muri, R., Strik, W., Bohlhalter, S., 2013a. Impaired gesture performance in schizophrenia: particular vulnerability of meaningless pantomimes. *Neuropsychologia* 51 (13), 2674–2678.
- Walther, S., Vanbellingen, T., Muri, R., Strik, W., Bohlhalter, S., 2013b. Impaired pantomime in schizophrenia: association with frontal lobe function. *Cortex* 49 (2), 520–527.
- Walther, S., Stegmayer, K., Sulzbacher, J., Vanbellingen, T., Muri, R., Strik, W., Bohlhalter, S., 2015. Nonverbal social communication and gesture control in schizophrenia. *Schizophr. Bull.* 41 (2), 338–345.
- Walther, S., Eisenhardt, S., Bohlhalter, S., Vanbellingen, T., Muri, R., Strik, W., Stegmayer, K., 2016. Gesture performance in schizophrenia predicts functional outcome after 6 months. *Schizophr. Bull.* 42 (6), 1326–1333.
- Walther, S., Alexaki, D., Stegmayer, K., Vanbellingen, T., Bohlhalter, S., 2020a. Conceptual disorganization impairs hand gesture performance in schizophrenia. *Schizophr. Res.* 215, 467–468.
- Walther, S., Kunz, M., Muller, M., Zurcher, C., Vladimirova, I., Bachofner, H., Scherer, K.A., Nadesalingam, N., Stegmayer, K., Bohlhalter, S., Viher, P.V., 2020b. Single session transcranial magnetic stimulation ameliorates hand gesture deficits in schizophrenia. *Schizophr. Bull.* 46 (2), 286–293.
- Weiss, P.H., Achilles, E.I., Moos, K., Hesse, M.D., Sparing, R., Fink, G.R., 2013. Transcranial direct current stimulation (tDCS) of left parietal cortex facilitates gesture processing in healthy subjects. *J. Neurosci.* 33 (49), 19205–19211.
- Wroblewski, A., He, Y., Straube, B., 2020. Dynamic causal modelling suggests impaired effective connectivity in patients with schizophrenia spectrum disorders during gesture-speech integration. *Schizophr. Res.* 216, 175–183.
- Wüthrich, F., Viher, P.V., Stegmayer, K., Federspiel, A., Bohlhalter, S., Vanbellingen, T., Wiest, R., Walther, S., 2020. Dysbalanced resting-state functional connectivity within the praxis network is linked to gesture deficits in schizophrenia. *Schizophr. Bull.* 46 (4), 905–915.