Relationships between neuropsychological performance, insight, medication adherence, and social metacognition in schizophrenia

Correlates of social metacognition in schizophrenia

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Abstract (231/250)

Background. Social metacognition is still poorly understood in schizophrenia, particularly its neuropsychological basis and its impact on insight and medication adherence. We therefore quantified social metacognition as the agreement between objective and subjective mentalization and assessed its correlates in a sample of individuals with schizophrenia spectrum disorders.

Methods. Participants consisted of 143 patients with schizophrenia or schizoaffective disorders who underwent a metacognitive version of a mentalization task, an extensive neuropsychological battery, and a clinical evaluation to assess their insight into illness and medication adherence. We studied potential interactions between confidence judgments and several neuropsychological and clinical variables on mentalization accuracy with mixed-effects multiple logistic regressions.

Results. Confidence judgments were closely associated with mentalization accuracy, indicative of good social metacognition in this task. Working memory, visual memory, and reasoning and problem-solving were the three neuropsychological dimensions positively associated with metacognition. By contrast, the two measures of medication adherence were associated with poorer metacognition, whereas no association was found between metacognition and clinical insight. The multiple regression model showed a significant positive impact of better working memory, older age at onset, longer duration of hospitalization, and worse medication adherence on social metacognition.

Conclusions. We discuss possible mechanisms underlying the apparent association between social metacognition and working memory. Adherence should be monitored when remediating social metacognition, and psychoeducation should be given to patients with a high level of awareness of their capacity to mentalize.

Keywords

schizophrenia, metacognition, neuropsychological assessment, insight, medication adherence, mentalization, social cognition

Abbreviations

SCID-IV: Structured Clinical Interview for DSM-IV-TR

PANSS: Positive and Negative Syndrome Scale

CGI-S: Clinical Global Impression-Severity

CDS: Calgary Depression Scale

YMRS: Young Mania Rating Scale

BIS: Birchwood Insight Scale

SUMD: Scale to Assess Unawareness of Mental Disorder

MARS: Medication Adherence Rating Scale

BARS: Brief Adherence Rating Scale

fNART: French National Adult Reading Test

WAIS: Wechsler Adult Intelligence Scale

TMT: Trail Making Test

CPT-IP: Continuous Performance Test-identical pairs version

TAP: Test of Attentional Performance

CVLT: California Verbal Learning Test

fmi: fraction of missing information

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1. Introduction

Metacognition refers to a spectrum of mental activities of which the object is one's own thoughts. According to Moritz and Lysaker's account of this concept (Moritz and Lysaker, 2018), it can be defined as the "awareness of one's cognitive performance". This includes the metacognitive experience component, defined as the "conscious reflections about cognitive processes", which was the focus of the present study. In schizophrenia, individuals encompass difficulties in the recognition that one is ill (clinical insight), abnormal cognitive style and beliefs with decreased self-reflectiveness and increased self-certainty (cognitive insight), and deficits in metacognition as defined above (David et al., 2012). One way to evaluate metacognition is to measure the trial-by-trial agreement between objective performance, measured using a first-order neuropsychological task, and subjective cognition, assessed using a self-reported score on a scale (i.e., second-order task). In this framework, good metacognition implies a close relationship between objective and subjective cognition,

whereas their decorrelation reflects metacognitive deficits. However, although the determinants of clinical (Belvederi Murri and Amore, 2019) and cognitive insight (Riggs et al., 2012) have been extensively studied in schizophrenia, they have not yet been sufficiently explored for metacognition.

Investigating the adequacy between confidence and social cognitive performance is of particularly high relevance in schizophrenia, as recent studies reported that social metacognition was associated with social functioning above social cognitive ability and negative symptoms (Silberstein et al., 2018). Moreover, confidence ratings for emotion recognition are significantly associated with real-world functioning reported by high-quality informants (Pinkham et al., 2018a). Very few studies investigated the confidence of individuals with schizophrenia in the attribution of mental states to others, which is an essential component of social cognition. One study reported a deficit especially marked in the case of formal thought disorders, using the Read the mind in The Eyes test (Köther et al., 2012). Another study reported preserved metacognition using animations of moving dots displaying a dyadic interaction demonstrating a chase or no chase (Muthesius et al., 2021).

We aimed to identify the relationship between neurocognition and social metacognition during a mentalization task. A recent meta-analysis reported that metacognitive deficits in schizophrenia were more profound when performance in the first-order task was also impaired, thus suggesting an impact of first-order neuropsychological deficits on metacognitive abilities (Rouy et al., 2021). Thus, the aberrant confidence ratings provided after a first-order neuropsychological task may be due to patients with working memory deficits who cannot remember how difficult this specific task was. In support of this idea, it has been reported that multitasking decreases metacognition in individuals without psychiatric disorders (Konishi et al., 2021). However, the relationships between cognitive performance in the usual neuropsychological domains and metacognition are still underexplored in schizophrenia. Only one study reported in attenuated psychosis syndrome a significant positive association

between metacognition and verbal memory, but not with executive functioning (Koren et al., 2019).

The second question we addressed is whether clinical insight is associated with social metacognition in schizophrenia. It has been hypothesized that poor insight in schizophrenia stems from a failure of metacognition, i.e., patients' lack of ability to reflect on their mental content accurately and a systematic bias in assessing it (David et al., 2012). Thus, poor insight should be associated with low social metacognition in schizophrenia. However, this has received no experimental confirmation, despite a promising initial report (Koren et al., 2004).

We also aimed to explore the relationship between medication adherence and social metacognition. Medication adherence is a crucial determinant of prognosis in schizophrenia (Lindenmayer et al., 2009). As medication adherence is positively associated with clinical insight in schizophrenia (Czobor et al., 2015), we hypothesized that better social metacognition would also be associated with better medication adherence, and, to the best of our knowledge, this study is the first to investigate this link. Adherence is influenced by several sociodemographic (age, education level), clinical (age at onset, substance abuse, duration of hospitalization, insight, and depression), and neuropsychological characteristics (see (García et al., 2016) et al. for a review). We aimed to control for these potential confounders when exploring the association between social metacognition and medication adherence.

In summary, we aimed to identify the neurocognitive and clinical correlates of social metacognition in a sample of individuals with schizophrenia spectrum disorders, focusing on insight and medication adherence, by analyzing the effect of the interaction between confidence in mentalization and clinical or cognitive variables on mentalizing accuracy.

2. Materials and methods

2.1. Study design and characteristics of the recruiting network

In this multicenter longitudinal cohort (previously registered at ClinicalTrials.gov under number NCT02901015), patients were recruited from seven centers of expertise for schizophrenia (Clermont-Ferrand, Créteil, Grenoble, Marseille, Montpellier, Strasbourg, and Versailles), making up a network established by the FondaMental Foundation. For this ancillary and exploratory study, only the baseline data were analyzed. General practitioners or psychiatrists referred patients. The local medical ethics committee (*Comité de Protection des Personnes Ile-de-France XI*) approved the study (2012-A00387-36). Each participant provided written informed consent before inclusion and received an indemnity.

2.2. Participants

The primary criterion for inclusion was the presence of schizophrenia or schizoaffective disorder, for which the diagnosis was based on a structured clinical interview according to DSM-IV-TR (SCID-IV) (First et al., 1997). The patients were between 18 and 65 years of age. The exclusion criteria were actually hospitalized under constraint, substance dependence at the time of assessment (except tobacco), electroconvulsive therapy (within the last six months), serious head trauma, significant or evolutive epilepsy or neurological disorder, and significant sensory impairment. Other inclusions and exclusion criteria are reported in Supplementary Information 1.

2.3. Assessment tools

Data were collected on two different days that were separated by less than two weeks.

2.3.1. Clinical assessments

The severity of schizophrenic symptoms was assessed using the total score of the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Medication adherence was assessed using both a self-report scale and a clinician-rated instrument. The first instrument was the Medication Adherence Rating Scale (MARS) (Thompson et al., 2000), a self-reported questionnaire that assesses medication adherence behavior, subjective experiences of negative side effects, and attitudes and beliefs toward antipsychotic medication. The second instrument was the Brief Adherence Rating Scale (BARS) (Byerly et al., 2008), in which a clinician assessed the proportion of antipsychotic doses effectively taken by the patient in the previous month. Details of the other clinical assessments are reported in Supplementary Information 2.

2.3.2. Premorbid level of cognitive functioning

Education level was assessed by the total duration of education in years. The French version of the National Adult Reading Test (fNART) (Nelson and O'Connell, 1978) provided an estimate of premorbid IQ.

2.3.3. Neuropsychological assessment: battery of cognitive tests

Details of the neuropsychological assessment are reported in Supplementary Information 3. Experienced neuropsychologists administered the tests in a fixed order. The standardized test battery evaluated seven cognitive domains. Six complied with the recommendations concerning the neurocognitive domains that should be represented in a cognitive battery for schizophrenia, according to a consensus of international experts (Green et al., 2004): processing speed, attention/vigilance, working memory, verbal memory, visual memory, and

reasoning and problem-solving. The battery also investigated a seventh neurocognitive dimension, executive functioning.

2.3.4. The social metacognition task

We assessed social metacognition by testing the confidence in the attribution of intentions to others. We designed a new paradigm derived from the V-COMICS test, an attribution of intention tasks using comic-strips (Brunet et al., 2000; Sarfati et al., 1997). The social metacognition task was performed with other social cognitive tests included in the EVACO battery, described elsewhere (Brunet-Gouet et al., 2021). The test consisted of 10 attribution-of-intention cartoons and two training trials administered before the task to check the patients' understanding (see Figure 1 & Supplementary Figure 1). Each self-paced trial required the subject to look at three-picture stories placed in the upper half of the sheet and then select the correct ending among three possible answers in the lower half of the sheet. The possible answers were designed following the same pattern: one correct answer satisfying the intentional logic of the story and two incorrect answers that depict actions that are either absurd or frequent but with no link to the story's context. In each comic strip, one of the answer pictures was masked. The correct answer was covered in one half of the trials and the frequent situation in the other half. The participant had to choose one of three responses (including the masked response) as the logical ending to the story at his/her own pace. Then, he/she was asked to rate his/her degree of confidence among four levels: totally sure (coded 4), almost sure (coded 3), not sure (coded 2), not sure at all (coded 1). The comic strips were presented in the same order to all subjects. Covering up one of the images prompted the subject to consider alternative endings to the story and formulate mentalistic hypotheses under conditions of increased uncertainty.

2.4. Statistical analyses

Social metacognition was quantified using mixed-effects logistic regression between mentalizing accuracy (binary categorical variable) and confidence (continuous variable). We first ran successive analyses, including a fixed effect of moderators belonging to the variables listed above, the interaction between the moderator and confidence, random intercepts by participants, and a full random effects structure. We applied an optimization by quadratic approximation (BOBYQA) with a set maximum of 200,000 iterations. Standardized β coefficients are reported. Assuming that social metacognition reflects the strength of the association between mentalization performance and confidence, a variable was interpreted as a moderator of metacognition if its interaction with mentalizing confidence had a significant effect on mentalizing accuracy. After this first stage of variable selection, missing data were estimated using multivariate imputations by chained equations (50 imputations, mice package of R). The fraction of missing information (fmi) and the proportion of total variance due to missingness (λ) are reported in the results. We then ran a mixed-effects multiple logistic regression on imputed datasets with several independent variables to check whether the potential neurocognitive and clinical moderators identified in the simple regressions remained significant while simultaneously accounting for all the effects. Beyond the main effect of confidence, the independent variables were included in this multiple model if:

- the level of significance of their interaction with confidence was $p < 0.25$. This threshold is usual for selecting variables for multiple regressions (Hosmer Jr et al., 2013; Mickey and Greenland, 1989). In this case, both the interaction term and the main effect of the covariate were included in the model.

- the level of significance of their interaction with confidence was $p \geq 0.25$ and the level of significance of their main effect was $p < 0.25$. In this case, only the main effect of the covariate was included in the model.

To avoid the selection of redundant variables, which would have led to the cancellation of their effect on social metacognition in the multiple regression model, we discarded variables that strongly correlated with another one ($|r| > 0.4$) within the same group of variables (clinical characteristics, premorbid level of cognitive functioning, and neurocognition). In this case, we retained in the multiple regression the variable for which the interaction with confidence had the highest effect on mentalization accuracy (for variables for which the interaction with confidence was $p < 0.25$) or the variable which had the highest direct effect on mentalization accuracy (for variables for which the interaction with confidence was $p \geq 0.25$ and the level of significance of their main effect on mentalization accuracy was $p < 0.25$).

3. Results

3.1. Characteristics of the participants

The study included 143 outpatients with schizophrenia (n = 104) or schizoaffective disorder (n = 39), who were included between April 2013 and June 2017. Socio-demographic, clinical, and neuropsychological characteristics of the sample are presented in Table 1, along with

premorbid levels of cognitive functioning. Their detailed neuropsychological performance is reported in Supplementary Table 1.

The participants were mostly men with schizophrenia. The average total PANSS score indicated mild symptoms and the average severity of illness was moderate. The average BARS score was in the range of previous studies, including outpatients with schizophrenia, with a lower bound of 70% (Xu et al., 2018) and a higher bound above 90% (Stip et al., 2013, p. 2013; Triveni et al., 2021). The average MARS score was also near that reported for another sample of French individuals with schizophrenia spectrum disorders (Verdoux et al., 2020).

The most strongly affected cognitive dimension was memory. Reasoning and problem-solving were less strongly affected. The average accuracy on the mentalization task across the 10 items was 0.76 ± 0.20 SD and the average confidence score 3.3 ± 0.45 (between almost sure and totally sure). Accuracy and confidence distributions are reported in Supplementary Figure 2.

3.2. Interaction analyses

The bivariable mixed-effects logistic regression between mentalizing accuracy and confidence was significant ($\beta = 0.66 \pm SD\ 0.07$, $z = 9.1$, $p < 0.001$), indicating that participants were able to adjust their confidence ratings to the accuracy of their responses.

3.2.1. Tri-variable mixed-effects logistic regressions

The results of the mixed-effects logistic regressions between mentalizing accuracy and confidence, with several successive moderators, are presented in Table 2 for the interaction between confidence and moderators and Supplementary Tables 2 & 3 for the main effect of moderators and confidence, respectively.

Significant interactions with confidence were found for age at onset, duration of hospitalization, MARS, BARS, duration of education duration, fNART, working memory, visual memory, and reasoning and problem solving (see Table 2). The plots of the fixed effect model estimate of confidence on mentalizing accuracy according to the level of the significant moderator are presented in Figure 2. Metacognition, assessed as the strength of the association between accuracy and confidence, was greater for individuals who were older at onset. Metacognition was also better for individuals with longer hospitalizations. Metacognition was worse for individuals with high MARS and BARS. Metacognition was also better for individuals with a longer duration of education and high fNART, working and visual memory, and reasoning and problem-solving.

The variables significantly associated with better mentalizing accuracy were lower PANSS total and MARS scores, higher education and premorbid IQ, better processing speed, attention/vigilance, working memory, verbal memory, reasoning and problem-solving, and executive functioning (see Supplementary Table 2).

3.2.2. Multiple mixed-effects logistic regression

3.2.2.1. Variable selection

The variable selection process is detailed in Supplementary Information 4. The following independent variables were included in the final multiple mixed-effects logistic regression: age at onset, duration of hospitalization, CGI-S, BARS, fNART, attention, working memory, visual memory (their main effect and their interaction with confidence), and the main effect of confidence, PANSS total score, CDS, and processing speed.

3.2.2.2. Model output

The results are reported in Table 3. Four variables remained significant moderators of the relationship between confidence and mentalization accuracy: age at onset, duration of hospitalization, BARS, and working memory. The variables that were significantly associated with better mentalization were confidence, CDS, and processing speed.

We ran an additional analysis with a more conservative threshold for variable selection ($p<0.05$), to lower the number of variables included in the final model and to check the consistency of our results (see Supplementary Information 5). The results remained consistent, except for CDS which was not included in the model. Moreover, the interaction between BARS and confidence became marginally significant.

4. Discussion

We aimed to gain greater insight into the nature of intention attribution in schizophrenia by investigating confidence for mentalization judgments. In addition, we aimed to test whether social metacognition is associated with neurocognition, insight, and medication adherence in

a sample of outpatients with schizophrenia spectrum disorders by analyzing the interaction between mentalizing accuracy and confidence.

First, the data reported here showed that the participants adjusted their confidence according to the accuracy of their responses, which suggests they were capable of metacognitive monitoring. Whether metacognition is preserved or disrupted in schizophrenia remains a debated topic: a recent meta-analysis reported that metacognition varies across domains in schizophrenia, with more pronounced impairment for metamemory than metaperception in comparison to matched healthy volunteers (Rouy et al., 2021). Data were insufficient to conclude about a deficit in social metacognition, with some studies reporting a deficit in patients (Jones et al., 2019; Moritz et al., 2012), whereas others did not (Pinkham et al., 2018b). Of note, we cannot determine whether social metacognition was preserved or impaired in the present data sample, as our study does not include a control group.

Several neuropsychological dimensions were associated with social metacognition in the tri-variable analyses: working memory, visual memory, and reasoning and problem-solving. The strongest association was found for working memory, which remained significant in the multiple regression. By contrast, the association between social metacognition and visual memory became non-significant in the multiple regression analysis. This result suggests that working memory is a crucial function involved in correctly reporting judgments about performance in mentalization in schizophrenia. Previous studies identified other neuropsychological bases of social metacognition in schizophrenia: verbal memory and attention, which partially explained the lower social metacognition performance for emotion perception found in schizophrenia (Köther et al., 2012); and verbal reasoning, processing speed, and working and verbal memories, which were associated with the difference between confidence and performance in emotion recognition (Perez et al., 2020). One interpretation of this result is that neuropsychological performance, such as working memory and executive function, is involved in the metacognitive task, which implies keeping track of the difficulty of the first-level task to produce an accurate confidence judgment a few seconds later. This result

also suggests that remediating working memory may improve social metacognition, although working memory training has shown limited generalizability to other domains in schizophrenia (Cassetta et al., 2019; Cella et al., 2017).

Clinical insight was not associated with social metacognition in this study. This result confirms the lack of association between clinical insight and metacognition shown in previous studies (Faivre et al., 2021; Kircher et al., 2007) and suggests that poor insight may not be domain-general in schizophrenia, i.e., it may not be the consequence of a single impairment in monitoring information processing at the cognitive level. Alternative conceptions of clinical insight have been proposed in the literature, in which insight may be a defense mechanism, a coping strategy that protects patients from depressive symptoms arising from awareness of having a chronic mental illness (Mintz et al., 2003), or a disturbance of the basic sense of minimal selfhood, i.e., an altered experience of being a self (Henriksen and Parnas, 2014).
Better social metacognition was not associated with better adherence. Medication adherence was in fact associated with poor metamentalization performance. As we had hypothesized a reverse relationship, this association might have occurred by chance, and we believed this result needs replication as it was only marginally significant in the sensitivity analysis using another p-value threshold for variable selection. Performing well in metacognition may imply that individuals with schizophrenia are aware of their cognitive deficits. Patients may thus attribute these deficits to their medication, leading to lower adherence. However, it was not possible to confirm this hypothesis as we did not measure cognitive insight. It is also possible that medication directly impairs metacognition. The Health Belief Model proposes that adherence emerges when patients are aware of the vulnerability and seriousness of their condition and when they know and interiorize the benefits of treatment adherence (Lacro et al., 2002). Our results suggest that social metacognition may interfere with interiorizing such medication benefits. Metacognitive remediation for schizophrenia should include psychoeducation about the causes of cognitive deficits, primarily due to the disorder itself, rather than appropriate antipsychotic medication. Such complementary psychoeducation

should help patients to identify and modify automatic negative thoughts about medications and strengthen their belief that taking their medication is a step toward recovery.

This study identified other clinical variables associated with social metacognition. First, being younger at onset was associated with lower social metacognition, which remained after controlling for neuropsychological performance, clinical severity, and duration of hospitalization. Younger age at onset is usually associated with a more severe form of schizophrenia, with more negative symptoms (Ballageer et al., 2005), a worse functional prognosis (Immonen et al., 2017), and more pronounced cognitive impairments (Rajji et al., 2009). Second, prolonged hospitalization was surprisingly associated with better social metacognition. It is possible that patients gain insight into their cognitive deficit through psychoeducation during more prolonged hospitalizations. Another explanation could be the mediation of depressive symptoms, as they are associated with more frequent hospitalization (Conley et al., 2007) and weaker overestimation of performance (Jones et al., 2021, p. 202) in schizophrenia. However, this explanation seems unlikely, as the association between social metacognition and the duration of hospitalization remained significant when the CDS score was introduced as a covariate in the multiple regression model. Moreover, social metacognition was not significantly associated with depression in our study, which contradicts a previous report showing that patients who manifested extreme overconfidence in emotion recognition had the least depression (Jones et al., 2019).

This study had several limitations. Because the study lacks a sample of healthy controls, it was impossible to establish whether there was a deficit in social metacognition in the participants with schizophrenia and whether the relationship between working memory and social metamentalization was specific to schizophrenia or characterized a more generalizable phenomenon. One was that the participants' profile may have influenced certain results, which may not be generalizable to all individuals with schizophrenia. Indeed, our sample included mostly males, and participants had slightly better clinical insight relative to previous reports that included outpatients (Braw et al., 2012; Cavelti et al., 2016; Novick et al., 2015), whose

level was compatible with that previously found in a group of participants who recovered from an acute episode of schizophrenia (Birchwood et al., 1994). Such a good level of clinical insight could explain the lack of its association with social metacognition reported here. The lack of association between insight and social metacognition may also be explained by the fact that we only investigated global insight scores. A previous study, indeed, reported the absence of a correlation between metacognition and overall insight, but a significant positive association between metacognition and awareness of current symptoms (Koren et al., 2004). A measure of cognitive insight was absent from our study. We could not thus confirm the results of the previous report showing an association between cognitive insight and social metacognitive performance for emotion perception (the subscale self-certainty of the BCIS correlated with the number of high-confidence incorrect responses) in schizophrenia (Köther et al., 2012). Another limitation comes from the methodology used to assess adherence: an objective measure of adherence with pill counting, blood or urine analysis, electronic monitoring, and electronic refill records may be preferable to the subjective methods we used. Investigating metamemory rather than social metacognition may be a better option for medication adherence (Hargis and Castel, 2018). Our study was also limited in terms of the number of items used to quantify social metacognition. Further studies investigating social metacognition in schizophrenia may benefit from improved measures of metacognition over hundreds of trials, such as metacognitive efficiency (Maniscalco and Lau, 2012). Finally, the selection strategy for variables retained in the multiple model can lead to the impression that a more limited set of variables is associated with metacognition than is actually the case. This analysis provides information about which variables have the greatest association with social metacognition.

5. Conclusion

This exploratory study investigated several neuropsychological and clinical correlates of social metacognition in schizophrenia using interaction analysis. We found that working memory and reasoning and problem-solving were positively associated with better social metacognition. Better medication adherence was associated with poorer social metacognition. Poorer social metacognition was also associated with a younger age at onset and a shorter duration of hospitalization. In addition to revealing important cognitive and clinical factors of social metacognition in schizophrenia, our results suggest that future metacognitive remediation strategies should focus on working memory, as well as providing psychoeducation to avoid a decrease in medication adherence for individuals with improved metacognition. Moreover, individuals with early-onset schizophrenia spectrum disorders may particularly benefit from metacognitive remediation.

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Declaration of interest

None

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Figure legends

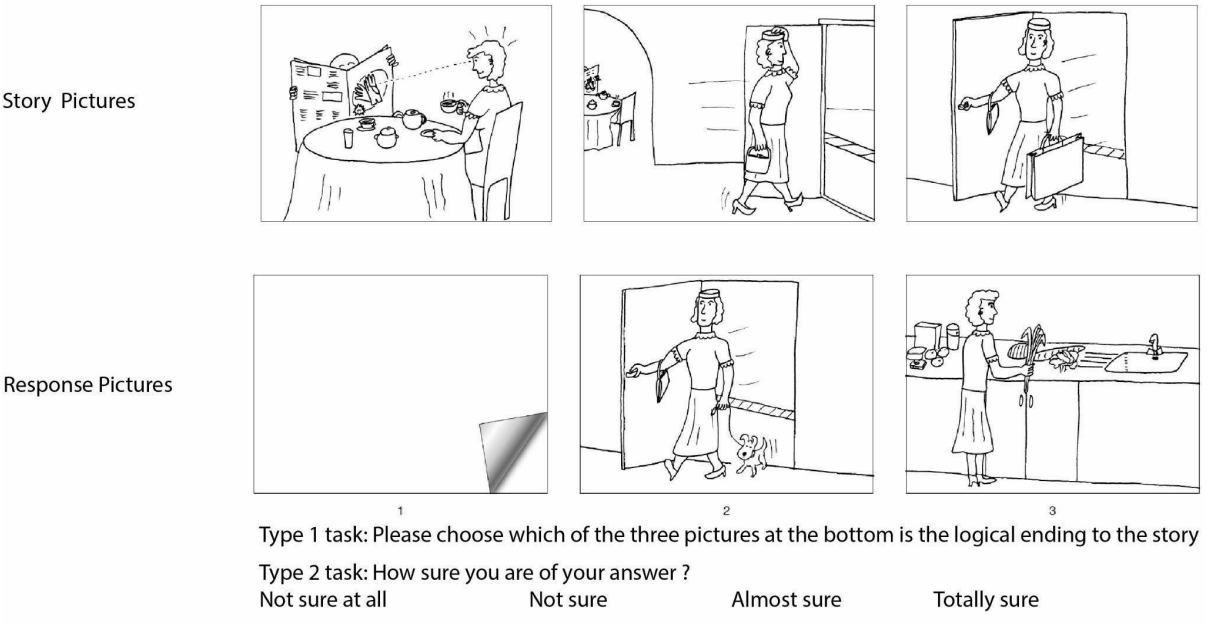


Figure 1. Example of a comic strip for which the correct answer was masked (1: bottom left). The middle answer (2) is only visually related to the cartoon but makes no sense. The answer on the right (3: frequent situation) represents a familiar situation (buying vegetables when one

comes back home with a bag) if the whole story and the woman's intention are ignored. Concerning the intention of the character, the correct answer could be that the woman comes back from shopping with brand new gloves.

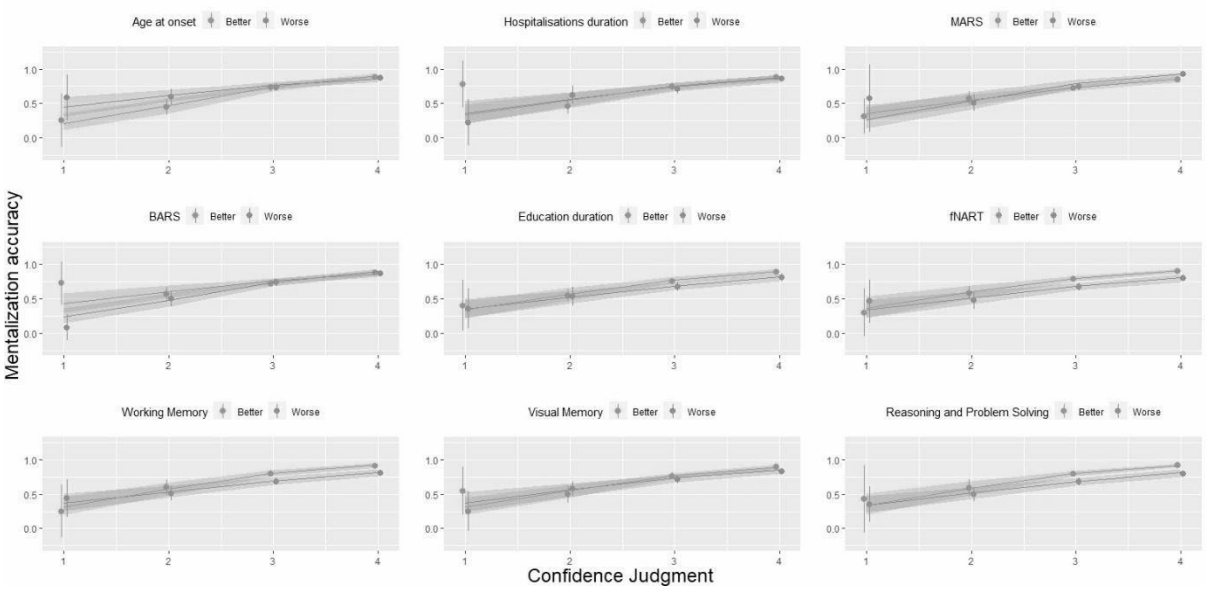
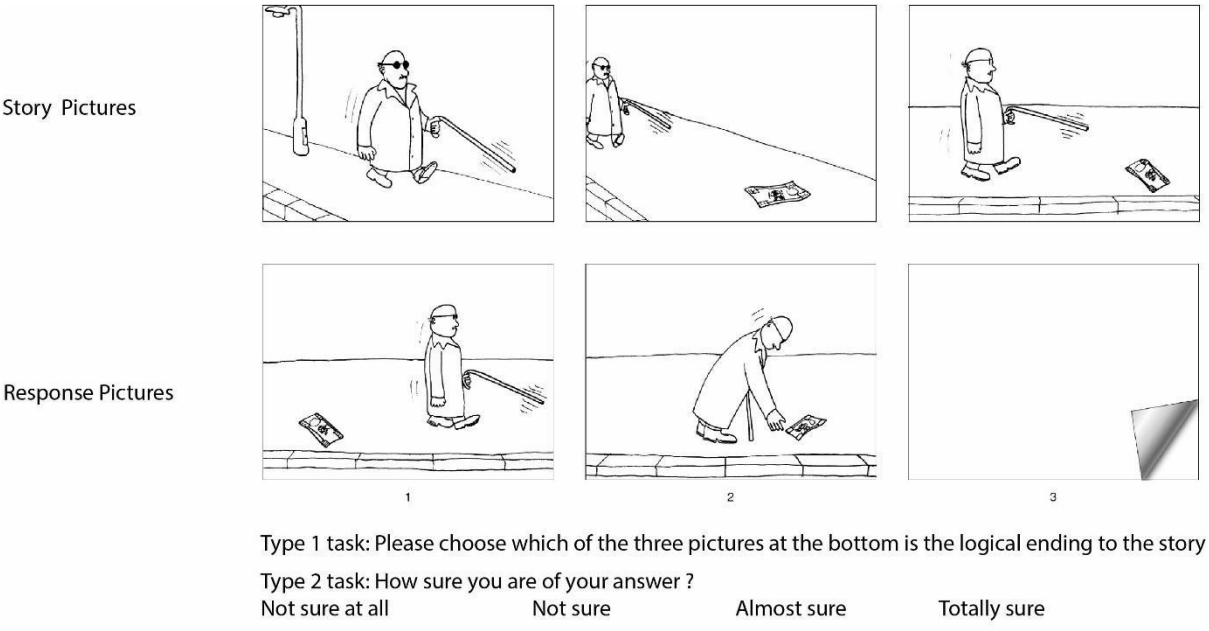
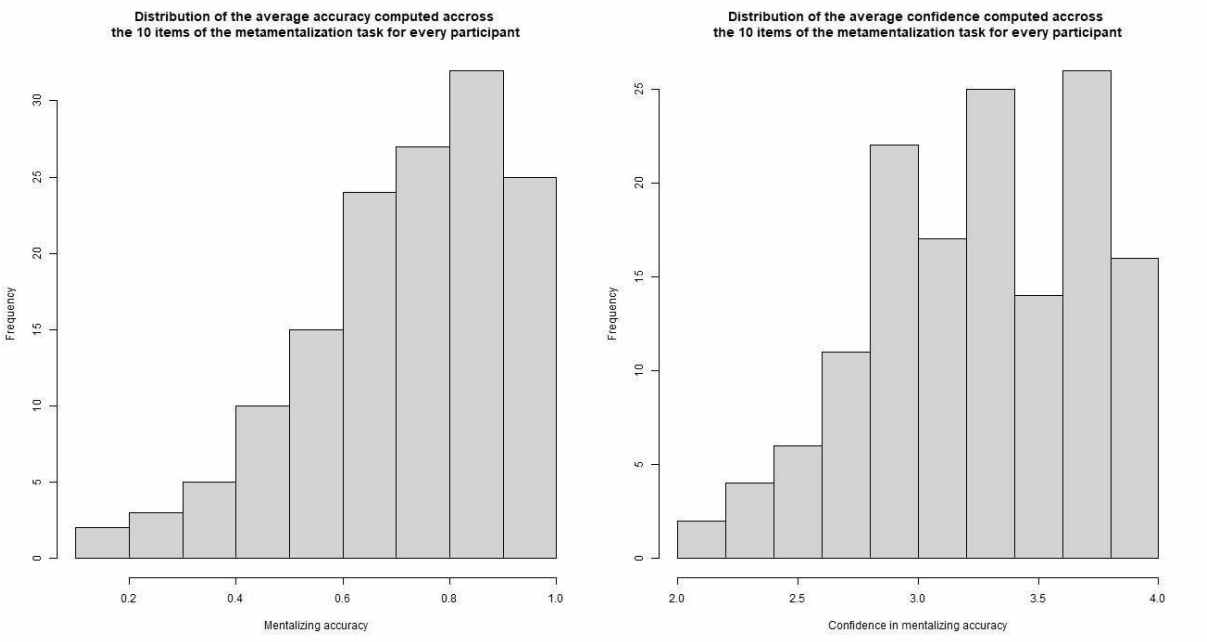


Figure 2. Tri-variable mixed-effects logistic regressions of mentalization accuracy on confidence judgment according to the level of various moderators. Regression lines and the 95% confidence intervals around them represent the model fit. Data are split according to the median of the moderator for illustrative purposes only.



Supplementary Figure 1. Example of a comic strip for which the correct answer was unmasked (1: bottom left). The middle answer (2) is a wrong answer (nonsense condition). The answer on the right (3) is masked (frequent condition) and considered to be incorrect.



Supplementary Figure 2. Distributions of mentalizing accuracy and confidence.

Tables

Table 1. Participant characteristics.

Variables	Mean or %	sd
Sociodemographic characteristics		
Age (years)	31.4	8.2
Sex (% men)	77.6	
Clinical characteristics		
Diagnostic (% schizophrenia)	72.7	
Age at onset (years)	21.4	5.6
Hospitalization duration (months)	5.8	7.1
Chlorpromazine equivalents (mg/24h)	460.7	386.4
PANSS total	25.3	9.1
PANSS negative	19.5	7.7
PANSS positive	14.5	5.5
PANSS general	33.6	9.7
CGI-S	4.1	1.4
CDS	3.8	4.3
YMRS	2.1	3.8
BIS	9.1	2.5
SUMD	1.6	0.6
MARS	6.2	2.3
BARS	88.8	22.1
Premorbid level of cognitive functioning		
Education duration (years)	12.6	2.5
fNART	104	8.1
Neurocognition		
Type of WAIS (% WAIS-III)	63.6	
Processing speed	-0.8	0.7
Attention/vigilance	-0.7	0.7
Working memory	-0.5	0.7
Verbal memory	-1	1.1
Visual memory	-1.2	1
Reasoning and problem solving	-0.4	0.9
Executive functioning	-1	1.5

PANSS: Positive and Negative Syndrome Scale, CGI-S: Clinical Global Impression-Severity Scale, CDS: Calgary Depression Scale, YMRS: Young Mania Rating Scale, BIS: Birchwood Insight Scale, SUMD: Scale to assess Unawareness of Mental Disorders, MARS: Medication Adherence Rating Scale, BARS: Brief Adherence Rating Scale, fNART: French National Adult Reading Test, WAIS: Wechsler Adult Intelligence Scale

Table 2. Results for the tri-variable mixed-effects logistic regressions between mentalizing accuracy and confidence, with several successive moderators. This table reports only the interaction effect between confidence and the moderators (the main effects of the confidence and the clinical moderators are reported in Supplementary Tables 2 & 3, respectively).

Variable	β	sd	z	p
Sociodemographic characteristics				
Sex (women)	0.02	0.17	0.1	0.889
Age	0.06	0.07	0.9	0.374
Clinical characteristics				
Diagnosis (schizoaffective)	0.11	0.18	0.6	0.517
Chlorpromazine equivalents	-0.03	0.08	-0.4	0.661
Age at onset	**0.18**	**0.08**	**2.3**	**0.021**
Duration of hospitalizations	**0.22**	**0.11**	**2.1**	**0.039**
PANSS total	0.03	0.07	0.4	0.722
CGI-S	-0.09	0.07	-1.3	0.2
CDS	0.06	0.07	0.9	0.364
YMRS	-0.08	0.09	-0.9	0.345
BIS	0.02	0.08	0.2	0.83
SUMD	0.03	0.08	0.4	0.668
MARS	**-0.19**	**0.08**	**-2.4**	**0.015**
BARS	**-0.27**	**0.1**	**-2.6**	**0.01**
Premorbid level of cognitive functioning				
Duration of education	**0.14**	**0.07**	**2**	**0.049**
fNART	**0.15**	**0.06**	**2.4**	**0.017**
Neurocognition				
Processing speed	0.07	0.07	0.9	0.352
Attention/vigilance	0.13	0.07	1.8	0.07
Working memory	**0.24**	**0.08**	**3.2**	**0.001**
Verbal memory	0.13	0.07	1.7	0.088
Visual memory	**0.19**	**0.08**	**2.4**	**0.018**
Reasoning and problem solving	**0.21**	**0.07**	**3.1**	**0.002**
Executive functioning	0.08	0.06	1.3	0.197
Type of WAIS (WAIS-III)	0.04	0.15	0.2	0.809

PANSS: Positive and Negative Syndrome Scale, CGI-S: Clinical Global Impression-Severity Scale, CDS: Calgary Depression Scale, YMRS: Young Mania Rating Scale, BIS: Birchwood Insight Scale, SUMD: Scale to assess Unawareness of Mental Disorders, MARS: Medication Adherence Rating Scale, BARS: Brief Adherence Rating Scale, fNART: French National Adult Reading Test, WAIS: Wechsler Adult Intelligence Scale.

Table 3. Results for the multiple analysis with a mixed-effects logistic regression.

Independent variable	β	Statistic	p	λ	fmi
Confidence	**0.74 (0.08)**	**t(1303.2)=9.3**	**<0.001**	0.037	0.038
Age at onset	0.09 (0.1)	t(1033.3)=0.9	0.375	0.094	0.096
Duration of hospitalizations	-0.01 (0.12)	t(416.8)=-0.1	0.916	0.265	0.268
CGI-S	0.09 (0.12)	t(1099.5)=0.7	0.468	0.081	0.083
BARS	0.06 (0.11)	t(1174.7)=0.6	0.562	0.066	0.067
fNART	0.15 (0.1)	t(1267.6)=1.5	0.144	0.045	0.047
Attention	0.19 (0.1)	t(1037.9)=1.8	0.071	0.093	0.095
Working memory	0.13 (0.11)	t(1302.1)=1.1	0.26	0.037	0.038
Visual memory	0.1 (0.1)	t(1162.9)=1	0.341	0.068	0.07
PANSS total	-0.1 (0.11)	t(1256)=-0.9	0.366	0.048	0.05
CDS	**0.22 (0.09)**	**t(1315.7)=2.3**	**0.02**	0.033	0.035
Processing speed	**0.23 (0.11)**	**t(1215.3)=2.1**	**0.032**	0.057	0.059
Diagnostic (schizo-affective)	0.06 (0.21)	t(1346.4)=0.3	0.768	0.024	0.026
Confidence : Age at onset	**0.18 (0.08)**	**t(1183.4)=2.3**	**0.019**	0.064	0.066
Confidence : Duration of hospitalizations	**0.26 (0.11)**	**t(467.4)=2.4**	**0.019**	0.242	0.246
Confidence : CGI-S	-0.05 (0.09)	t(1086.5)=-0.6	0.575	0.084	0.085
Confidence : BARS	**-0.22 (0.11)**	**t(814.4)=-2**	**0.045**	0.14	0.142
Confidence : fNART	0 (0.08)	t(1208.5)=0	0.988	0.059	0.06
Confidence : Attention	0.01 (0.09)	t(905.4)=0.2	0.873	0.12	0.122
Confidence : Working memory	**0.25 (0.1)**	**t(1196.5)=2.6**	**0.009**	0.061	0.063
Confidence : Visual memory	0.12 (0.09)	t(1002.7)=1.4	0.165	0.1	0.102

FMI: fraction of missing information, CDS: Calgary Depression Scale, CGI-S: Clinical Global Impression Scale - Severity, BARS: Brief Adherence Rating Scale, fNART: French National Adult Reading Test