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Social Cognition as a Mediator Variable Between Neurocognition and Functional Outcome in Schizophrenia: Empirical Review and New Results by Structural Equation Modeling

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Cognitive impairments are currently regarded as important determinants of functional domains and are promising treatment goals in schizophrenia. Nevertheless, the exact nature of the interdependent relationship between neurocognition and social cognition as well as the relative contribution of each of these factors to adequate functioning remains unclear. The purpose of this article is to systematically review the findings and methodology of studies that have investigated social cognition as a mediator variable between neurocognitive performance and functional outcome in schizophrenia. Moreover, we carried out a study to evaluate this mediation hypothesis by the means of structural equation modeling in a large sample of 148 schizophrenia patients. The review comprised 15 studies. All but one study provided evidence for the mediating role of social cognition both in cross-sectional and in longitudinal designs. Other variables like motivation and social competence additionally mediated the relationship between social cognition and functional outcome. The mean effect size of the indirect effect was 0.20. However, social cognitive domains were differentially effective mediators. On average, 25% of the variance in functional outcome could be explained in the mediation model. The results of our own statistical analysis are in line with these conclusions: Social cognition mediated a significant indirect relationship between neurocognition and functional outcome. These results suggest that research should focus on differential mediation pathways. Future studies should also consider the interaction with other prognostic factors, additional mediators, and moderators in order to increase the predictive power and to target those factors relevant for optimizing therapy effects.

Key words: schizophrenia/social cognition/functional outcome/mediation/review

Introduction

Despite advances in antipsychotic medications as well as psychological treatments, schizophrenia remains one of most disabling disorders worldwide.[1] Functional impairments in living, work, and leisure are essential diagnostic feature of schizophrenia,[2] have a high prevalence[3,4] and are a huge burden for patients as well as their family members.[5] They are associated with high direct and indirect costs[6] and are often present in periods of symptom remission.[7,8] Based on this background, an adequate level of functioning is nowadays part of standardized recovery criteria[9–11] and is a main focus of psychiatric rehabilitation efforts by targeting factors contributing to functional recovery.

A large body of cross-sectional as well as longitudinal studies provides empirical evidence for the link between neurocognition and functional outcome in schizophrenia.[12,13] Neurocognition can be defined as processes of linking and appraising information. It includes abilities like speed of processing, attention, verbal and visual learning and memory, working memory as well as reasoning and problem solving.[14,15] Despite the significant associations between neurocognition and functional deficits, the correlations are generally moderate with composite measures of neurocognition accounting only for 20%–60% of the variance in functional outcome.[13] This has prompted the search for other factors such as mediators that may enhance the understanding of the relationships between neurocognition and functional impairments.

One of the most promising mediators is the area of social cognition as it shows consistent relationships with neurocognition well as with different functional domains.[16,17] The term social cognition is defined in various ways, but generally refers to the mental operations underlying social interactions such as the perception, interpretation, and generation of responses to the intentions, dispositions, and behaviors of others.[18–20] Social cognition encompasses various abilities. The ones most

frequently studied in schizophrenia are emotion perception (perceiving and using emotions), social perception (apprehension of key features of social situations and interactions), social schema/social knowledge (awareness of roles, rules, and goals that guide social interactions and characterize social situations), theory of mind (ToM; the ability to infer intentions, dispositions, and beliefs of others), and social attributions (the ability to infer the causes of particular positive or negative events).[19] Today, consensus exists that social cognition is related to, though distinct from, basic neurocognition and may contribute in a nonredundant way to functional outcome.[21–23] This is consistent with functional neuroimaging research suggesting that the processing of social and nonsocial information relies on semi-independent specialized neural networks.[24–27] Several studies showed that social cognition could explain an additional amount of variance after having controlled for neurocognitive functions.[28–31] It seems to be even a better predictor than neurocognition and clinical symptoms.[32] Psychiatric symptoms have received less attention as predictors of functional outcome. However, in particular, negative symptoms have shown to be consistently associated with functional outcome. The correlations between positive symptoms and functional outcome were generally weaker.[33]

Although there is a growing literature interested in social cognition as a potential mechanism linking neurocognition to functional consequences, a systematic review of current findings has been lacking. In spite of recent advances in testing mediation effects, little attention has been given to quantify the indirect effect across studies. In this paper, we aimed to systematically review the findings and methodology of studies that have investigated social cognition as a mediator variable between neurocognitive performance and functional status in schizophrenia. We estimated the strength of the indirect effect by calculating effect sizes. Many of the reviewed studies comprised small samples and investigated only one social cognitive domain. We carried out a study to evaluate this mediation hypothesis by the means of structural equation modeling (SEM). We included a large sample of schizophrenia patients, a wide array of neurocognitive measures and the social cognitive domains of emotion perception and social knowledge as potential intervening variables.

Review of Social Cognition as a Mediator Variable Between Neurocognition and Functional Outcome in Schizophrenia

Methods of the Review

We identified 15 English language articles published between January 2004 and December 2010 through searches in the databases MEDLINE and PsycINFO. Key words were mediation combined with neurocog*, social cog*, emotion/social perception, theory of mind, attribution, social knowledge, functional outcome, social skills, social competence, quality of life combined with schizophrenia or psychosis. Studies were included 1. if the authors investigated social cognitive domains as a mediator variable between neurocognition and functional outcome, 2. if the sample consisted of patients with a diagnosis of schizophrenia or schizoaffective disorder according to *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) or *International Classification of Diseases, Tenth Version* (ICD-10), and 3. if mediation effects were evaluated by regression analysis, path analysis, or SEM. These statistical techniques seem to be most appropriate to detect mediation effects.[34]

We classified the neuro- and social cognitive measures used in the selected studies according to the MATRICS classification scheme and definitions[14,19] and current neuropsychological literature.[17,35] Functional outcome measures encompassed 4 previously described domains[12,13,16,17]: social skills, social problem solving, social behavior in the milieu, and community functioning (independent living skills, work functioning, social functioning) (see table 1).

Results of the Review

Description of Sample Characteristics and Methodology of the Included Studies. Table 1 gives an overview of the 15 included studies,[36–50] their corresponding sample, and methodological characteristics as well as the key findings. Most samples consisted of multiepisode psychosis patients with a diagnosis of schizophrenia or schizoaffective disorder according to DSM-IV or ICD-10. The mean age was 39.09 years (SD = 6.59) and the majority was male (mean: 69%, SD = 9.79). Only one sample[36,37,49] explicitly comprised first-episode psychosis patients as well as participants with a diagnosis of other nonaffective psychotic disorders.

There was considerable variability in the reported statistical parameters (eg, R^2, R^2 change, partial r, standardized regression coefficients β) and the applied statistical methods, with 6 studies using regression analysis,[36–41] 5 studies path analysis,[37–46] and 5 studies SEM.[47–50] Moreover, studies differed in the applied statistical procedure to test mediation effects: Nine studies estimated the parameters of the mediation model while controlling for the direct effect of neurocognition on functional outcome.[47,48] Others excluded the estimation of the direct effect a priori or in the final mediation model.[44,45] Although being the most important criterion for a mediation effect,[51] only 8 studies[39,48] reported size and significance level of the indirect effect.

Evidence for Social Cognition as a Mediator Variable. Even with wide variation among the studies in the selection of measures and in the applied statistical methods, some general conclusions are warranted. In summary, all but one study[38] found evidence for the mediating role of social

Table 1. Sample and Methodological Characteristics and Key Findings of the 16 Included Studies

Study	Sample	Age Mean (SD)	Design	Method	NC	SC	FO	Key Findings
1. Addington et al[36]	103 SZ, SA, PD	FE: 25.1 (8.0) ME: 35.5 (7.2)	CS	Regression-analysis	PS, A, VM, VSM, WM, R, M, C	EP	CF	EP mediated the relationship between NC and CF at baseline (a = .56****, b = .22*, c = .27**, c' = .21 (ns) and at 1-year follow-up (a = .59****, b = .42****, c = .36****, c' = .18 (ns).
2. Addington et al[37]	103 SZ, SA, PD	FE: 25.1 (8.0) ME: 35.5 (7.2)	CS	Regression-analysis	PS, A, VM, VSM, WM, R, M, C	SP/SK	CF, SPS	SP mediated the relationship between NC and CF at baseline (a = .47****, b = .28**, c = .27**, c' = .18 ns) and at 1-year follow-up (a = .50****, b = .39****, c = .36****, c' = .22*). SP mediated the relationship between NC and SPS at baseline (a = .47****, b = .44****, c = .33**, c' = .16 ns) and at 1-year follow-up (a = .50****, b = .49****, c = 34****, c' = .13 ns).
3. Nienow et al[38]	56 SZ, SA	41.5 (7.8)	CS	Regression analysis	A	EP	SPS	EP moderated the relationship between A and SPS. No evidence for EP as a mediator between A and SPS, as EP was no significant predictor of SPS (β_1 = .19 and p_1 = .13 and β_2 = .15 with p_2 = .27) controlling for the influence of A on SPS.
4. Horton and Silverstein[39]	65 SZ, SA	Hearing: 45.0 (8.9) Deaf: 47.0 (9.2)	CS	Regression analysis	A, VM, VSM	EP, ToM	CF	Differential pattern of mediation: EP (identification) as mediator between VM and CF (a = .34**, b = .31**, c = .38**, c' = .29*, R^2 = 34%), A (early visual processing) and CF (a = .36**, b = .30*, c = .37**, c' = .26*, R^2 = 31%), VSM and CF (a = .48**, b = .33*, c = 30, c' = .20 with P = .11, R^2 = 24%). EP (discrimination) as mediator between A (early visual processing) and CF (a = .33*, b = .35*, c = .37*, c' = .27*, R^2 = 34%). ToM as mediator between VM and CF (a = .36**, b = .38**, c = .38**, c' = .29*, R^2 not reported) and VSM and CF (a = .30*, b = .45**, c = .40**, c' = 31**, R^2 = 48%). All indirect effects were significant ($P \leq .05$). A (vigilance) was not significantly correlated with EP or ToM. Patterns of mediation varied between deaf and hearing participants.

Table 1. Continued

Study	Sample	Age Mean (SD)	Design	Method	NC	SC	FO	Key Findings
5. Vaskinn et al[40]	26 SZ	32.3 (9.3)	CS	Regression analysis	PS, VM, R	EP	SPS	EP mediated NC and SPS. $b = .21$ ($P = .37$), $c = .57$**, $c' = .43$ ($P = .07$). $R^2 = 35\%$ in SPS.
6. Meyer and Kurtz[41]	53 SZ, SA	35.1 (11.6)	CS	Regression analysis	A, VM, R	EP	SSK	EP mediated the direct relationship between A and R and SSK. $b = .29$*, $c = .30$*, $c' = .22$ ($P = .10$). VM was no significant predictor of SSK. $R^2 = 46\%$ in SSK. Additional predictors: age and duration of illness.
7. Brekke et al[42]	139 100 (L) SZ, SA	38.2 (9.0)	CSL	Path analysis	PS, A, VM, R	EP	CF, SBM	EP mediated the relationship between NC and FO at baseline and at 1-year follow-up. This relationship between EP and FO was mediated by social competence and social support. $R^2 = 21\%$ (CS) and $R^2 = 14\%$ (L) in FO.
8. Bell et al[43]	151 SZ, SA	42.8 (8.9)	L	Path analysis	PS, A, VM, WM; R, TD	EP, ToM,E, RA	SBM	Simple mediation model: SC mediated the relationship between NC and SBM, but the model fit was not adequate. $a = .47$*** ($R^2 = 22\%$), $b = .23$*** ($R^2 = 5\%$). Distal mediation model: The influence of social cognition on SBM in the simple mediation model was mediated by social discomfort. $R^2 = 18\%$ in SBM.
9. Gard et al[44]	91 SZ, SA	39.9 (11.4)	CS	Path analysis	PS, A, VM, VSM, WM	EP	CF	Simple mediation model: Direct relationship NC and CF ($c = .22$*; $R^2 = 5\%$) was mediated by EP. This resulted in a nonsignificant direct relationship NC and CF ($c' = -.06$, $P = .64$). $a = .66$**, $b = .39$** ($R^2 = 15\%$). Distal mediation model: Motivation mediated the relationship between EP and CF showed in the simple mediation model. $R^2 = 21\%$ in CF.
10.Brittain et al[45]	64 SZ	41.9 (11.1)	CS	Path analysis	A	SP	CF	SP mediated a significant indirect effect (.16**) between attention (“biological motion”) and CF. $a = .44$** ($R^2 = 20\%$), $b = .37$* ($R^2 = 14\%$ in FO).
11. Couture et al[46]	178 SZ, SA	45.9 (10.9)	CS	Path analysis	PS, WM, VM, VSM, R	ToM	CF	ToM mediated the relationship between NC and CF with negative symptoms and social competence serving as additional mediators. $R^2 = 7\%$ in CF.
12. Vauth et al[47]	133 SZ	28.8 (7.1)	CS	SEM	A, VM, WM, R	SK	SPS	SK mediated the relationship between NC and SPS. $a = .91$, $b = .31$, $c' = .16$. $R^2 = 25\%$ in SPS.

Table 1. Continued

Study	Sample	Age Mean (SD)	Design	Method	NC	SC	FO	Key Findings
13. Sergi et al[48]	75 SZ	46.7(9.5)	CS	SEM	A	SP	CF	SP mediated the relationship between A and CF. a = .57* (R^2 = 32%), b = .44*, c = .35* (R^2 = 12%), c' = .03 (P = .46). R^2 = 18% in CF. Significant indirect effect (β = .25*).
14. Addington et al[49]	103 SZ, SA, PD	FE: 25.1 (8.0) ME: 35.5 (7.2)	CS	SEM	PS, A, VM, VSM, WM, R, M, C	EP, SP	CF, SPS	The distal mediation model explained 80% of the variance in FO with group status as predictor variable. SC mediated the relationship between NC and FO. NC and SC partially mediated the relationship between group status and FO.
15. Rassovsky et al[50]	174 SZ	44.5 (9.9)	CS	SEM	A	SP	CF	SP and negative symptoms mediated the relationship between A and CF. R^2 = 41% in CF.
16. Schmidt et al (this study)	148 SZ, SA	35.3 (9.8)	CS	SEM	PS, A, VM, VSM, WM	EP, SK	CF	SC mediated the relationship between NC and CF. a = .67***, b = .35*, c = .38** (R^2 = 14%), c' = .15 (P = .37). R^2 = 21% in CF. Significant indirect effect (β = .23*).

Note: SZ: schizophrenia; SA: schizoaffective disorder; PD: other nonaffective psychotic disorder; FE: first-episode psychosis; ME: multiple-episode psychosis; CS: cross-sectional; L: longitudinal; SEM: structural equation modeling; PS: processing speed; A: attention; VM: verbal memory; VSM: visual memory; WM: working memory; R: reasoning and problem solving; M: motor skills; C: construction and visuo-spatial skills; TD: thought disorder; EP: emotion perception; SP: social perception; ToM: theory of mind; SK: social knowledge/social schema; E: egocentricity; RA: ability to establish rapport; CF: community functioning; SPS: social problem solving skills; SBM: social behavior in the milieu; SSK: social skills; NC: neurocognition; SC: social cognition; FO: functional outcome; *a*: standardized coefficient of the relationship between the independent variable (neurocognition) and the mediator variable (social cognition); *b*: standardized coefficient of the relationship between the mediator variable and the dependent variable (functional outcome) controlling for the independent variable; *c*: standardized coefficient of the relationship between the independent variable and the dependent variable; *c′*: standardized coefficient of the relationship between the independent variable and the dependent variable controlling for the mediator variable. *$P < .05$; **$P < .01$; ***$P < .001$; ****$P < .0001$.

cognition (see table 1). Findings from these independent data sets show consistent patterns, even when key demographic variables like duration of illness and age were controlled.[41] In accordance with a mediation effect, the direct relationship between neurocognition and functional status has been reduced, when social cognition was added. Furthermore, social cognition appears to contribute incremental validity on functional outcome beyond neurocognition.[42,47] However, Nienow et al[38] concluded that emotion perception performed as a moderator, rather than a mediator variable in the relationship between attention and social problem solving. Additionally, 2 studies[39,41] could not confirm all hypothesized mediating relationships because some of them failed to meet the conditions for mediation. More precisely, Meyer and Kurtz[41] found evidence that deficits in recognizing happy faces acted as a mediator between visual vigilance as well as problem solving and social skills. In contrast, verbal memory was not related to the social skills performance assessment. Differential mediation patterns were found in the study of Horton and Silverstein[39] as well: Only 6 of 15 possible mediation relationships met the requirements for mediation with emotion perception being associated with the highest number of cognitive domains. Vigilance was neither correlated with emotion perception nor with ToM. However, no further consistent patterns of relationships could be derived from these results. In summary, recent studies mainly supported a mediation effect through social cognitive domains, but some of them needed to make additional choices in the selection of cognitive domains.

We used an effect size measure outlined by Preacher and Kelley[52] to estimate the magnitude of the indirect effect in simple mediation models: the standardized indirect effect, which is the product a × b (*a*: standardized regression coefficient of the relationship between the independent variable (neurocognition) and the mediator variable (social cognition); *b*: standardized regression coefficient of the relationship between the mediator (social cognition) and the dependent variable (functional outcome) controlling for the independent variable (neurocognition).). This effect size has the advantage that it is standardized and independent from sample size thereby allowing to compare the strength of the indirect effect across multiple studies.[52] The mean standardized indirect effect for the 9 studies providing sufficient information was 0.20 (see table 2). This indicates that functional outcome is expected to increase by 0.20 SDs for every SD change in neurocognition through social cognition.

An additional criterion to consider in evaluating mediation models is the amount of explained variance in functional outcome.[5] In simple mediation models,[36–41,43–45,47,48] 5%–48% (mean: 25%, SD = 11.73) of the variance in functional outcome was due to the influence of neuro- and social cognition. Studies using path analysis or SEM could explain a larger proportion of variance (range: 7%–41%, mean: 20%, SD = 11.41) than simple mediation models (range: 5%–25%; mean: 16%, SD = 6.86), if additional mediators were included. In these distal mediation models, social cognition mediated the link between neurocognition and functional outcome. Furthermore, motivation,[44] social discomfort,[43] social support,[42] and social competence[42,46] mediated again the impact of social cognition on functional status. Negative symptoms functioned independently from social cognition as a mediator variable.[46,50] In one model,[49] group status (schizophrenia patients vs healthy controls) had an indirect effect on functional status through neuro- and social cognition thereby explaining 80% of the variability in functional outcome.

Table 2. Effect Sizes for the Indirect Effect

Study	ES Standardized Indirect Effects
Vauth et al[47]	.28
Addington et al[36,37] (mean)	.20
Sergi et al[48]	.25
Horton et al[39]	.13
Bell et al[43]	.11
Gard et al[44]	.26
Brittain et al[45]	.16
Schmidt et al (this study)	.23

Only 2 studies[42,43] examined mediation effects longitudinally. The viability of the mediation model in predicting functional outcome was generally supported. However, there was some degradation in the model fit as well as in the amount of explained variance in comparison to the cross-sectional model (21% cross-sectional vs 14% at 1-year follow-up).[42] Brekke et al[42] identified social cognition, social competence as well as social support as important intervening variables between neurocognition and both concurrent and 12-month global functional outcome in a distal mediation model. In the study of Bell et al,[43] social cognition and social discomfort mediated the relationship between basic neurocognitive variables and work rehabilitation outcome after 6 months. The model with social cognition as the only intervening variable revealed an inadequate model fit. Notably, up to now only distal mediation models including additional intervening variables could validate the relevance of social cognition longitudinally.

Differential Mediation Patterns Between Neuro-, Social Cognition, and Functional Outcome. It is largely unclear which social cognitive functions are the most effective mediators. With regard to the social cognitive MATRICS domains, emotion perception was examined most frequently as a mediator variable (45%) and to a lesser extent social perception (20%), ToM (15%) as well as social knowledge (15%). No study included social attributional style. Seven studies investigated only one single social cognitive domain and provided enough data to calculate indirect effects: emotion perception,[36,38,39,44] social

perception,[45,48] ToM,[39] and social knowledge.[47] Social knowledge revealed the strongest mean standardized indirect effect (.28) followed by social perception (.21), emotion perception (.19), and ToM (.14). Most of the studies computed global composite scores for neurocognition and functional outcome as the mean of several cognitive and functional subdomains. Five studies assessed attention, more precisely vigilance[38,39] and early visual processing,[38,39,45,48,50] as a single neurocognitive predictor variable. Interestingly, none of them could confirm an association between vigilance, social cognition (emotion perception, ToM), and community functioning or social problem solving skills. However, all studies, which investigated the relationship between early visual processing and community functioning, found evidence for the mediating role of social and emotion perception.

In the next 2 sections (see "Methods" and "Results"), we present our own data investigating the hypothesis that social cognition acts as a mediator between neurocognition and functional outcome in schizophrenia. All study results are discussed together in the last part of the article (see "Discussion".)

Methods

Participants

The sample comprised 148 outpatients with a diagnosis of schizophrenia or schizoaffective disorder according to DSM-IV-TR or ICD-10. Diagnosis was confirmed by their treating clinician and by chart review. We included patients if they were aged between 18 and 50 years, had an illness-duration of more than 2 years, and an intelligence quotient of at least 80 (Reduced Wechsler Intelligence Test,[53] WIP). Subjects were excluded if they met the criteria for substance dependence, an organic brain syndrome, or for an acute psychotic episode. All participants provided written informed consent under protocols approved by the ethics committee at the University of Bern.

Procedure

Data were collected within the context of an international randomized controlled trial in Switzerland, Germany, and Austria evaluating the efficacy of a recently developed cognitive behavioral group therapy program, the Integrated Neurocognitive Therapy (INT).[54] Participants were randomly assigned to either INT or to Treatment As Usual (TAU). A comprehensive battery of measures was administered at baseline prior to randomization. Interviewers for the assessment of functional outcome were blind to cognitive results and vice versa.

Measures

Neurocognition. The neurocognitive test battery included commonly used measures in schizophrenia research[55]: Speed of processing was assessed with the Controlled Oral Word Association Test[56] (COWAT) (mean value of produced words per minute for category (animals) and word fluency (letter "S")); attention with the Continuous Performance Test[57] (CPT) (total number of omission errors during the test; test duration: 20 minutes); working memory with the Letter-Number Span[58] (LNS) (total number of correctly remembered items); verbal memory with the Auditory Verbal Learning Test[59] (AVLT) (delayed recall: number of remembered words after a delay of 20 minutes); and visual memory with the Wechsler Memory Scale-Revised Third Edition[60] (WMS-R) (total number of correctly recognized items).

Social Cognition. Social cognition comprised the domains of emotion perception and social schema. We assessed emotion perception with 2 facial affect recognition tasks: the computerized Picture of Facial Affect Test[61] (PFA) and the Emotion Recognition Questionnaire (V. Roder, D. R. Mueller, unpublished data) (Emorec). In both of them, participants need to view photographs of faces. They have either to identify specific basic emotions (PFA) or to rate their intensity on a 5-point Likert scale (Emorec). The series of photographs has been developed and validated by Ekman and Friesen.[62] The Emorec has been validated by an independent sample of 50 healthy control subjects that rated the emotional intensity of these facial expressions and showed adequate reliability and validity. The test score of both measures was the total number of correct judgments.

The computerized Social Component Sequencing Task-Revised[47,63] (SCST-R) evaluates the availability of social knowledge that influences the processing of social information and the generation of interpersonal responses. The task is to order the component actions of 12 social situations in the right temporal sequence. The test score was the sum of the correctly juxtaposted pairs over all situations.

Functional Outcome. Functional outcome was measured using the Global Assessment of Functioning (GAF) Scale of the DSM-IV. One major limitation of the GAF is that it is a global measure for 3 distinct domains of functioning.[64] This is why we modified the GAF by rating the information of participants and their caregivers separately for vocational, social, and psychological functioning. These 3 subscales comprise 10 intervals and include criteria for scoring within each interval. All raters received training and revealed intraclass correlation coefficients of .92. Studies indicate that the GAF is a valid measure of global psychological, vocational, and social functioning[65] given that patients are clinically stable.[66] The present sample consisted of schizophrenia outpatients with the symptom ratings being in the medium range (see table 3).

Table 3. Sample Characteristics and Means and Standard Deviations of Study Measures

	Mean	SD
Age (y)	35.3	9.8
Male (%)	66.9	
Education (y)	11.7	1.6
IQ[a]	105.5	10.8
Duration of illness (y)	10.3	7.7
Number of hospitalizations	3.9	3.9
Symptoms[b]		
PANSS Positive Symptoms	15.6	4.9
PANSS Negative Symptoms	16.9	5.9
PANSS General Symptoms	35.2	8.7
Neurocognition		
COWAT	13.0	4.0
CPT	2.2	5.1
LNS	12.7	4.1
AVLT	8.8	3.3
WMS-R	6.1	1.6
Social cognition		
PFA	22.2	3.8
Emorec	6.3	0.9
SCST-R	62.0	12.3
GAF		
Vocational	48.1	12.3
Social	51.2	11.0
Psychological	48.1	9.7

Note: COWAT: Controlled Oral Word Association Test,[56] CPT: Continuous Performance Test,[57] LNS: Letter Number-Span,[58] AVLT: Auditory Verbal Learning Test,[59] WMS-R: Wechsler Memory Scale-Revised,[60] PFA: Picture of Facial Affect Test,[61] Emorec: Emotion Recognition Questionnaire, (V. Roder, D. R. Mueller, unpublished data) SCST-R: Social Component Sequencing Test-Revised,[63] GAF: Global Assessment of Functioning Scale.
[a]Reduced Wechsler Intelligence Test (WIP; Dahl, 1986[53]).
[b]Positive and Negative Syndrome Scale (PANSS; Kay et al[93]).

Statistical analyses

We employed SEM with maximum likelihood estimation of the AMOS 17.0 package to estimate and test mediation effects. SEM evaluates multiple hypothesized relationships between latent and observed variables simultaneously by combining confirmatory factor analysis with multiple regression analysis.[67] This allows to explicitly model measurement errors and may thereby result in less biased parameter estimations, which is an advantage over multiple regression and path analysis[68]. Factor loadings specify the association between an unobservable construct (ie, a latent variable) and its theoretically linked measures (ie, indicator variables). Regression analyses determine the associations between latent variables and are indexed by standardized partial regression coefficients.

Prior to evaluating the mediation hypothesis, we checked raw data for normality and outliers, replaced missing values (1.7% of the data set) by regression imputation and calculated zero-order correlations of the study measures. Confirmatory factor analyses should ensure that the 3 latent variables neurocognition, social cognition, and functional outcome are assessed with sufficient reliability and validity.

In accordance with the "causal steps approach"[69] by Baron and Kenny, we used 2 models to evaluate potential mediation effects: A basic model postulating a direct relationship between neurocognition and functional outcome (ie, total effect) and a mediation model which posits a small nonsignificant link between neurocognition and functional outcome (ie, direct effect) and significant associations of social cognition with neurocognition as well as functional outcome (ie, indirect effect). However, this approach has been criticized due to its low power in detecting intervening variable effects and due to its lack of quantification of the indirect effect. Therefore, it seems necessary to test the significance of the indirect effect itself. The path coefficient for the indirect effect represents the change in functional outcome for every unit change in neurocognition that is mediated through social cognition. Simulation research shows that bootstrapping the mediated effect tends to have the highest power and the best type I error control. A bootstrap approximation with 2000 iterations yielded a percentile-based confidence interval. If zero is not between the lower and upper bound, one can conclude that the indirect effect is significantly different from zero and that mediation is present.[34,70]

Model fit, the degree to which a structural equation model fits the sample data, was assessed by 3 commonly used indices: the chi-square test (χ^2), the comparative fit index (CFI), and the root mean-squared error of approximation (RMSEA). A good-fitting model requires a nonsignificant chi-square test, which means that the model-implied covariance matrix and the observed data matrix are not significantly different from each other. CFI and RMSEA use cut-off scores: Values higher than .9 for the CFI and smaller than .08 for the RMSEA indicate an adequate model fit.[71,72]

Recommendations for the sample size using SEM vary widely between at least 100 and several thousands.[73,74] Hair et al[75] suggest that the minimum sample size for SEM must be greater than the minimum ratio of at least 5 participants for each estimated parameter. Our mediation model comprised 23 parameters that had to be estimated. Therefore, a sample size of 148 participants can be considered as adequate.

Results

Sample characteristics as well as means and SDs of all indicator variables are listed in table 3. All but 4 participants were taking antipsychotic medication (92% atypical neuroleptics, 6% typical neuroleptics, 2% mixed).

Table 4 shows the zero-order correlations of all study measures. All neuro- and social cognitive measures had significant associations with social and/or psychological

Table 4. Zero-Order Correlations Among Study Measures

Measure	1	2	3	4	5	6	7	8	9	10
1 COWAT	—									
2 CPT	.30**	—								
3 LNS	.42**	.41**	—							
4 AVLT	.37**	.34**	.41**	—						
5 WMS	.27**	.30**	.35**	.31**	—					
6 PFA	.29**	.26**	.23**	.21*	.24**	—				
7 Emorec	.10	.02	.02	.14	.15	.44**	—			
8 SCST	.37**	.29**	.46**	.31**	.30**	.48**	.31**	—		
9 GAF_v	.15	−.01	.11	.14	−.09	.00	.01	.15	—	
10 GAF_s	.26**	.19*	.19*	.16	.24**	.23**	.28**	.22**	.32**	—
11 GAF_p	.20*	.15	.17*	.19*	.18*	.22**	.23**	.30**	.35**	.67**

Note: COWAT: Controlled Oral Word Association Test, CPT: Continuous Performance Test, LNS: Letter Number-Span, AVLT: Auditory Verbal Learning Test, WMS-R: Wechsler Memory Scale-Revised, PFA: Picture of Facial Affect Test, Emorec: Emotion Recognition Questionnaire, SCST-R: Social Component Sequencing Test-Revised, GAF_v: Global Assessment of Functioning vocational functioning, GAF_s: social functioning, GAF_p: psychological functioning.
*$P < .05$; **$P < .01$.

functioning, but none was significantly correlated with vocational functioning. This violates the requirements for mediation.[69] Consequently only the 2 GAF subscales social and psychological functioning were used as indicators of the latent variable functional outcome in the following statistical procedure. Confirmatory factor analyses revealed that all included indicators were reliable and valide measures of their respective latent variable, as suggested by their significant moderate to high factor loadings ($\beta = .46–.83$, $P < .001$).

The basic model (see figure 1) depicts the direct relationship between neurocognitive performance and functional status. This path was statistically significant (standardized coefficient $\beta = .38$, $P < .01$). Neurocognition accounted for 14% of the variance in functional outcome. The basic model provided a very good fit for the observed data indicated by the nonsignificant chi-square test ($\chi^2 = 6.54$, $df = 13$, $P = .92$), a CFI of 1.00 and an RMSEA value smaller than .05. These results satisfy Baron and Kenny's[69] first step of testing mediation.

The mediation model intends to evaluate the strength of the indirect relationship while controlling for the direct effect of neurocognition on functional outcome (see figure 1). The direct path from neurocognition to functional outcome was no longer significant, as soon as the mediator was entered into the model ($\beta = .15$, $P = .37$). Instead, social cognition encompassing emotion perception and social schema was significantly associated with neurocognition ($\beta = .67$, $P < .001$) and was predictive of functional status itself ($\beta = .35$, $P < .05$). The model explained 21% of the variance in functional outcome. All of the model fit indices were very good ($\chi^2 = 42.85$, $df = 32$, $P = .10$, CFI = .97, RMSEA = .04). The bootstrapping estimate revealed a significant indirect effect ($\beta = .23$, 95% CI = .037 to .85, $P < .05$). These data are consistent with a complete mediation effect through social cognition.

Discussion

This study aimed to further shed light on the complex mechanisms through which neurocognition influences functional outcome in schizophrenia. We systematically reviewed studies investigating the mediating role of social cognition and conducted a mediation analysis by the means of SEM. Despite wide variations in the selection of cognitive and outcome domains and measures, the most consistent finding was that at least part of this relationship is mediated by a pathway through social cognitive domains (ES = .20 for the mean standardized indirect effect). This implies that neurocognitive impairments may have an adverse effect on social cognition and thereby exert a negative influence on functional status. The results of our own statistical analysis are in line with these conclusions: Social cognition comprising emotion perception and social knowledge completely mediated a significant indirect relationship between neurocognition and functional outcome.

Some issues warrant caution when interpreting these findings. One[38] of 15 studies found only support for a moderation but not for a mediation effect between early visual processing and social problem solving skills through emotion perception. Another research group[48] used the same neurocognitive measure but revealed evidence for mediation. However, they differed in that they focused on other levels of functioning and on other social cognitive aspects. At a conceptual level, these different results could be attributable to the existence of differential mediation patterns: Each neuro- and social cognitive domain may provide a separate mediating pathway and may be differentially predictive of functional status at different points of time (eg, early visual processing-social perception and community functioning). Therefore, a critical question is which social cognitive domains are effective

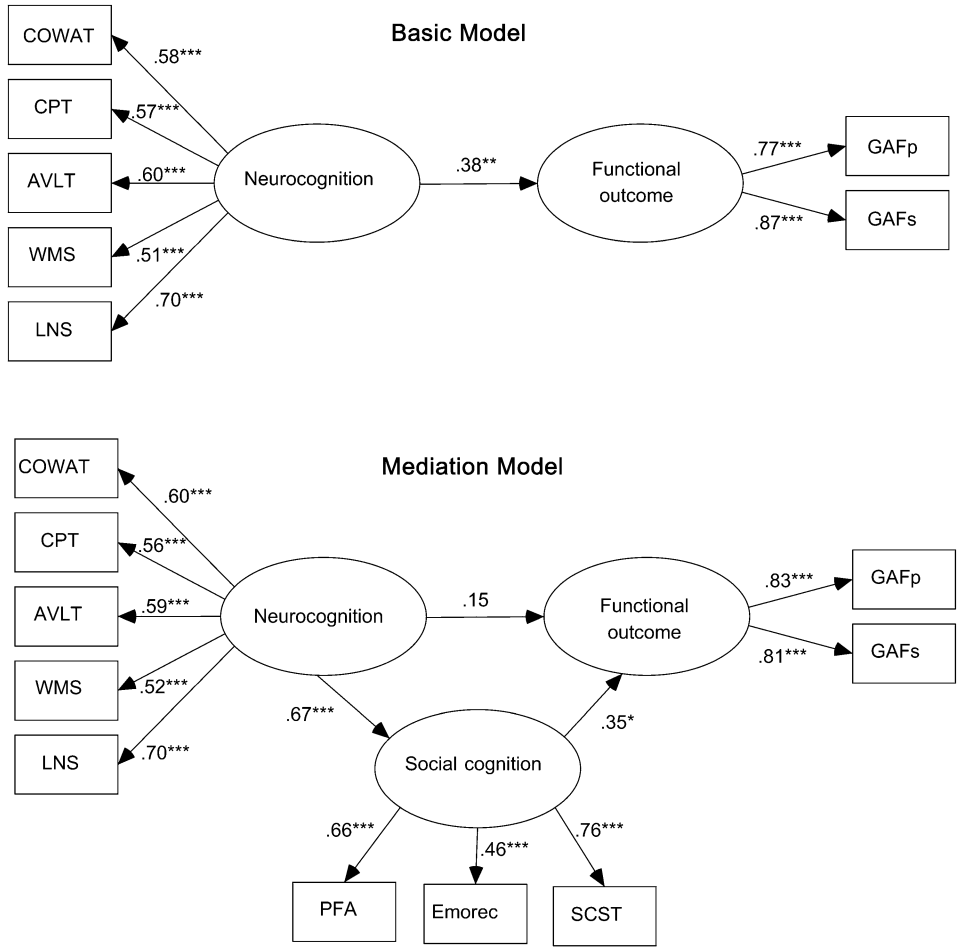

Fig. 1. Basic model and mediation model. *Note*: $*P < .05$; $**P < .01$; $***P < .001$. Circles represent unobserved latent variables. Rectangles represent observed measured variables. Values are standardized path coefficients. COWAT: Controlled Oral Word Association Test, CPT: Continuous Performance Test, LNS: Letter-Number Span, AVLT: Auditory Verbal Learning Test, WMS-R: Wechsler Memory Scale-Revised, PFA: Picture of Facial Affect Test, Emorec: Emotion Recognition Questionnaire, SCST-R: Social Component Sequencing Test-Revised, GAF_s: social functioning, GAF_p: psychological functioning.

mediators and with regard to which time period. In our review, most studies that reported mediation effects investigated emotion perception and to a lesser degree social perception. This corresponds well with a recent research finding suggesting that the social cognitive factor comprising emotion and social perception showed the highest correlation with neurocognition and functional outcome compared with both other dimensions named "attributional style" and "higher level inferential and regulatory processes".[31] In contrast, other studies identified ToM to have the highest correlations with functional outcome[17] and to be the most potent mediator.[39] Calculating the standardized indirect effects in our review revealed the largest effect sizes for social knowledge (ES = .28) and social perception (ES = .21). However, these results are only preliminary as they are based on few studies differing in the number and type of employed measures. Clearly, more research is needed to assess a wide range of social cognitive domains to unravel their differential relationships with neurocognition and functional outcome. Yet, most studies used neurocognitive composites scores in order to reduce model complexity. This may mask specific predictor-mediator-outcome links. Another reason for the varying patterns of relationships may be the differential validity of the postulated mediation model. Therefore, it may be crucial to determine whether or not the mediation effect remains constant across various contexts or subgroups of schizophrenia patients. This effect is called moderated mediation.[76] Additionally, recent innovations in SEM technique allow evaluating how well models fit at the level of the individual participant.[77] These analyses could sharpen current mediation models by identifying clinical and demographic characteristics of subgroups that do fit the model to a high degree or that do not fit the model (yet) (eg, education, duration of illness, premorbid social functioning). These results may be important with regard to a differential indication of integrated cognitive remediation therapy approaches.

In the current review, a moderate amount of variance (25%) in functional outcome was accounted for by neuro- and social cognition. In accordance with a recent meta-analysis[17] and our own study (21%), a large proportion of variance in functional outcome is therefore left unexplained by neuro- and social cognitive performance. These results and the small effect size of the indirect effect indicate that functional disability is multiply determined by a host of other factors. Accordingly, models including additional mediators had a better fit to the observed data[43] and could explain more variability in functional outcome.[43,44] Recent studies found, for example, support for a mediating effect of motivation,[77] metacognition,[78] dysfunctional attitudes,[79,80] and negative symptoms.[46,50,81,82] Moreover, most of the reviewed studies assessed global levels of community functioning as outcome variable (eg, social and work functioning). In contrast, performance-based measures of functional outcome seem to be less influenced by environmental factors as they evaluate what an individual is capable of doing in specific situations and not what it actually performs in real world. Therefore, they are theoretically and empirically more closely related to cognitive measures. Recent studies found evidence that such functional capacity measures mediate the relationship between cognitive variables and global functional outcome.[81,82] This may lead to higher amounts of explained variance in functional outcome.

Investigating mediator variables allows directing and refining the development of Cognitive Remediation Therapy (CRT) approaches by identifying elements crucial for enhancing generalization of therapy effects on functional outcome. Therefore, these study findings have important clinical implications. They suggest that a combined treatment of neuro- and social cognition may reveal synergistic effects and be integral to creating and maintaining change in functional outcome domains.[83,84] An adequate level of functional outcome may first require rehabilitation of rudimentary neuro- and social cognitive functions.[42] Such multimodal CRT approaches like the Integrated Psychological Therapy[15] (IPT), the Cognitive Enhancement Therapy[85,86] (CET), and the Neurocognitive Enhancement Therapy[87,88] (NET) found improvements both in the proximal outcome of neuro- and social cognitive performance and in the more distal areas of psychopathology and functional outcome.[15,89] The underlying therapy rationale was also supported by an analysis of IPT interventions indicating that the combined treatment of neuro- and social cognitive subprograms had superior effects in proximal and distal outcomes than neurocognitive intervention alone.[90] Eack et al[91] investigated the mechanism of change during integrated cognitive remediation therapy more directly. They found that changes in neurocognition and social cognition separately mediated functional improvements in schizophrenia patients. The authors came to the same conclusion that CRT may need to target neuro- and social cognition to achieve an optimal functional response.

There are several limitations to our study. First, we used only a cross-sectional design, which does not allow firm conclusions about the causality between the investigated variables. It seems possible that functional deficits may have an adverse effect on cognitive domains as well. For example, negative social interactions at work may drive the development of biases in perceiving and evaluating other persons. Although we used a theory-driven approach, clearly more long-term studies are needed. Second, global measures like the GAF may not be precise enough to detect individual differences in functional status. This could lead to a restriction in the range of functional deficits. This seems to be one explanation why we found no significant associations between vocational functioning and cognitive variables in our study and why we had to exclude vocational functioning from all further analysis. Due to this post hoc model modification, the final model should be cross-validated using other samples. Third, our study participants were willing to engage in a 12-month long intervention. Moreover, according to our inclusion criteria, they had an IQ of at least 80 and no comorbid diagnosis of substance dependence. Therefore, our sample may not be representative of all individuals with schizophrenia. Fourth, it would have been very interesting to explore differential pathways between neuro-, social cognitive, and functional domains. However, our sample comprised 148 schizophrenia patients and it was necessary to reduce the number of parameter estimated in the model by forming latent variables.

The current review raises a number of issues that need to be considered in future research. All but 2 studies[42,43] used a cross-sectional design. Therefore, future studies should employ a longitudinal design in order to investigate the temporal order of causation suggested by the mediator model. This could clarify if the mediation model is also valid in predicting long-term functional outcome or if other factors become more influential. Furthermore, there was an extensive range of cognitive tests and functional outcome measures administered across the studies. Due to the heterogeneous assessment, we were unable to draw any firm conclusions about which tests are the most powerful predictors and mediators. Therefore, future studies should use multiple assessments of functional status that range from functional capacity to more distal real-world performance measures.[92] Additionally, it seems an important next step to develop or select a social cognitive test-battery with adequate psychometric properties, which can be applied to schizophrenia patients and which measures a broad range of social cognitive domains. Clearly, more guidelines with regard to the statistical procedure to assess mediation effects are needed. This could increase the comparability of study results. Providing information about the correlations among

study measures, the regression coefficients, indirect effects as well as the amount of explained variance in each dependent variable would allow calculating more reliable effect sizes based on a larger number of studies.[52]

Despite these limitations, it seems clear that certain social cognitive domains are one of the key mediators of the cognition-outcome relationship. Research should focus on differential mediation pathways between neurocognition and functional outcome. Future studies should also consider the interaction with other prognostic factors, additional mediators, and moderators in order to increase the predictive power and to target those factors relevant for optimizing therapy effects.

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