



Review article

Pathways to functional outcomes in schizophrenia spectrum disorders: Meta-analysis of social cognitive and neurocognitive predictors



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ABSTRACT

The current meta-analysis explored relationships between functional outcomes in schizophrenia spectrum disorders and different domains of neurocognition and social cognition. Literature searches were conducted in PsycINFO, PubMed, and ProQuest to identify articles reporting correlations between cognition domains and functional outcomes. Of 1361 articles identified, 166 met all inclusion criteria (12,868 participants; 518 correlations). Fifty-three random-effects meta-analyses yielded mean correlation estimates for relationships between neurocognition and social cognition and functional outcomes. Overall, associations between social cognition and neurocognition, and functional outcomes demonstrated significant small-to-medium effect sizes. Social cognition explained more unique variance in functioning than neurocognition (7.3% vs. 4.4%; 9.2% total average variance). Social cognition also mediated the relationship between neurocognition and functional outcomes. A significant proportion of the variance in the relationships between cognition and functional outcomes remained unexplained. These findings suggest that integrated interventions targeting both neurocognition and social cognition may optimally improve functional outcomes. Standardized measurement of cognition and functioning, longitudinal studies, and tests of additional moderators (e.g., first episode samples) in future research were identified as important future directions.

1. Introduction

Decades of research have established a strong link between functional outcomes in schizophrenia and impairments in both social cognition (SC) and neurocognition (NC) (Couture et al., 2006; Fett et al., 2011; Ludwig et al., 2017; Green et al., 2011). As a result, interventions targeting NC (McGurk et al., 2007; Prikken et al., 2018; Reeder et al., 2017) or SC (Grant et al., 2017; Kurtz et al., 2016; Kurtz and Richardson, 2012), are widely disseminated yielding improvements in specific NC and SC abilities but equivocal effects on functional outcomes (e.g., Grant et al., 2017; Prikken et al., 2018). More nuanced understanding of interrelationships between NC and SC and effects on functioning is needed to clarify how to best target NC and SC to improve treatment development, implementation, and outcomes (Horan and Green, 2017).

Although both NC and SC exhibit some overlap (i.e., strong

relationships with one another), they are demonstrably separate constructs that differentially relate to functional outcomes (Allen et al., 2007; Ludwig et al., 2017; Nuechterlein et al., 2004). Pinkham et al. (2016) demonstrated that SC has incremental validity in explaining the variance in functional outcomes beyond NC in both first-episode and chronic schizophrenia populations, possibly as a mediator between NC and functional outcomes. Several studies support the role of SC as a mediator, providing additional evidence of a related but distinct relationship between NC, SC, and functional outcomes (Brekke et al., 2005; Schmidt et al., 2011; Vauth et al., 2004).

Despite support for SC as a mediator between NC and functional outcomes, the majority of interventions target either NC or SC impairments (Paquin et al., 2014). Interventions targeting only one domain of cognition may be one explanation for small or null effects on functional outcomes in schizophrenia (Horan and Green, 2017). A better understanding of the relationships between NC, SC, and functioning is

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necessary to inform development and dissemination of optimally effective interventions in schizophrenia.

We therefore undertook a meta-analysis of the relationships between functional outcomes in schizophrenia and social cognition and neurocognition. Meta-analysis is needed because the only previous quantitative review is 10 years old (studies reviewed up to 2007) and examined just 55 studies (Fett et al., 2011). Fett et al. (2011) found small to large mean correlations between NC and SC and functional outcomes. Interpreting the strongest individual correlations, the data suggested that SC explains more variance in functional outcomes than NC, with the strongest individual correlations observed between theory of mind and community functioning ($\hat{u}_p = .48$; 23% variance explained) and attention and vigilance and social skills ($\hat{u}_p = .39$; 15% variance explained), respectively. A search of PsychINFO indicated that more than 2000 papers with “neurocognition” or “social cognition” and “functioning” in the title have been published during the interim. It is also the case that new work has emerged on SC domains such as attributional style and for participants in the early stages of schizophrenia (“first-episode psychosis” or FEP). Understanding how SC and NC relate to outcomes for FEP samples is important given the (a) qualitative differences between first-episode and chronic schizophrenia (e.g., Braw et al., 2008), (b) increased focus on FEP treatments (e.g., RAISE Early Treatment Program, Kane et al., 2015), and (c) need for intervention before impairments in social functioning stabilize (Velthorst et al., 2017).

The present meta-analysis will review all eligible studies published up to July 2017 to improve our current understanding of inter-relationships between NC and SC with functional outcomes in schizophrenia by: (1) quantifying the relationships between functional outcomes and domains of NC and SC, (2) comparing the strength of relationships between NC and SC with functional outcomes, while accounting for important moderator variables; (3) analyzing the associations between specific NC and SC cognitive domains and functional outcomes in FEP samples; and (4) formally testing mediation of the NC-functional outcome relation by SC.

2. Method

The meta-analysis was registered through Prospero (CRD42018092456) and followed PRISMA guidelines, see Supplementary Table 1 for concordance with PRISMA Checklist for meta-analyses (Moher et al., 2009).

2.1. Search strategy

Articles for potential inclusion were identified through searches completed in July 2017 in the databases PsychINFO and PubMed. To address the file-drawer effect (Rosenthal, 1979), unpublished findings were identified through dissertations published on ProQuest and pre-prints published on PsyArXiv (searches yielded no pre-prints). All studies from Fett et al. (2011) were also included. Searches spanned August 2009, the most recent time period included by Fett et al. (2011) to July 2017. Search terms were identified through consultation with an academic librarian and included: *schizophrenia spectrum and other psychotic disorders* (PubMed MeSH term) or (*schizophrenia, psychosis, psychotic, schizophrenia spectrum, prodrome*) combined with functional outcome search terms (*functional outcome, independent living skills, skills of daily living, community functioning, social functioning, work functioning, occupational functioning, vocational functioning, social skill, quality of life, community behavior, social behavior, life satisfaction, social adjustment, social dysfunction, employment*) and neurocognition search terms (*neuropsych*, neurocog**) or social cognition search terms (*emotional perception, affect perception, emotional recognition, attribution*, theory or mind, mentalizing, mentalising, social cognition, prosody, social knowledge, mind reading, social cue, social judgment*). Search terms were identical to Fett et al. (2011) with the addition of: *schizophrenia spectrum* and

prodrome and the use of PubMed MeSH term (*schizophrenia spectrum and other psychotic disorders*).

2.2. Article inclusion criteria

Articles were inspected for the following inclusion criteria: a) the article was written in English b) the sample consisted of individuals with a diagnosis of non-affective psychosis according to well established diagnostic criteria (e.g., *Diagnostic and Statistical Manual of Mental Disorder* and the *International Classification of Diseases*), c) at least one cross-sectional correlation between a cognitive domain and functional outcome measure was reported, d) established and reproducible outcome measures were used that could be classified into domains of cognition and functioning. Correlations with study-specific factor scores and partial correlations were excluded as these indices could not meaningfully be combined across studies. Samples with special characteristics (e.g., geriatric and forensic) were excluded to minimize potential bias in effect size estimates; low statistical power precluded using special sample characteristics as moderators.

2.2.1. Neurocognition domains

Domains of NC included: attention and vigilance, processing speed, reasoning and problem solving, verbal comprehension, verbal fluency, verbal learning and memory, visual learning and memory, working memory, and combined neurocognition – a composite score based on two or more NC domains (Supplementary Table 3). NC domains were based on NC factors identified by the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Committee (Nuechterlein et al., 2004).

2.2.2. Social cognition domains

Five domains of SC were included: attribution bias, emotion perception and processing, social knowledge and perception, theory of mind, and combined social cognition – a composite score based on two or more SC domains (Supplementary Table 3). SC domains were based on SC factors identified by the MATRICS Committee (Green et al., 2005). The present review included attribution bias and combined social cognition domains, previously omitted in Fett et al. (2011), because new studies reported relationships between these SC domains and functional outcomes.

2.2.3. Domains of functional outcome

Four domains of functional outcomes were included in line with Fett et al. (2011): community functioning (e.g., activities of daily life and relationships), social behavior in the milieu (e.g., observed behaviors in a specific context), social problem solving (e.g., abilities to address a social problem or generate solutions), and social skills (e.g., social interaction abilities like eye contact and conversation skills, Supplementary Table 4). Functional outcomes are typically based on observer ratings (e.g., Quality of Life Scale; Heinrichs et al., 1984), performance on a task meant to simulate real-world scenarios and responsibilities (e.g., UCSD Performance Based Skills Assessment; Patterson et al., 2001), ratings of social interaction during role-play tasks (e.g., Role Play Test; Penn et al., 1995), or observations made in vivo such as work performance or behavior in a treatment setting (e.g., Work Personality Profile; Bolton and Roessler, 1986). In general, domains of community functioning and social behavior in the milieu are based on ratings of perceived real-world performance while domains of social problem solving and social skill are considered measures of functional capacity measured by task-based performance (Bowie et al., 2006). Hence, measures of functional capacity are not the same as measures of community functioning and we would not expect the same pattern of effects.

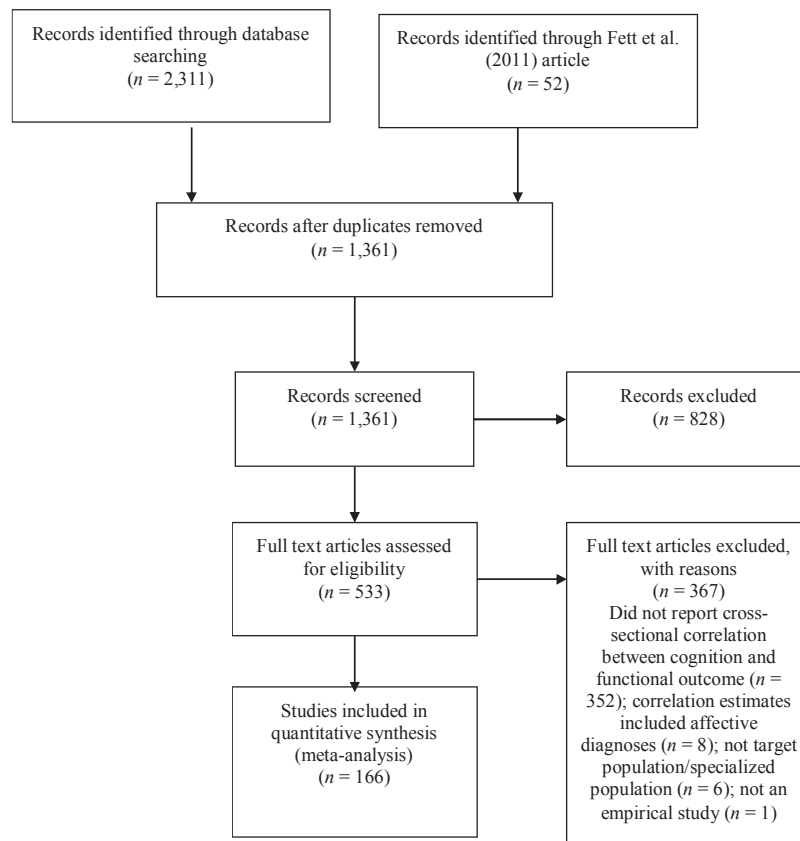


Fig. 1. Consort diagram for article inclusion.

2.3. Effect size relationships

Potential articles were pooled from all sources and duplicates were removed resulting in 1361 articles (see Fig. 1 for the flow of information through phases of the present review). Article titles were inspected for inclusion, followed by abstracts, resulting in 533 articles reviewed at the full-text level. Reasons for exclusion at the full-text level included (a) study did not report a cross-sectional correlation between a cognitive domain and functional outcome ($n = 352$); (b) sample included affective diagnoses ($n = 8$); (c) sample was a specialized population ($n = 6$); (d) article was not an empirical study ($n = 1$). Penn et al. (1995), previously included in Fett et al. (2011), was excluded during full-text review since the Conversation Role Play Test, previously categorized as a measure of social cognition, is now considered a functional outcome and thus a correlation between a cognition domain and functional outcome was not present.

One hundred and sixty-six articles met inclusion criteria for the present review (see Supplementary Materials for full reference list and Supplementary Table 2 for sample characteristics). If studies reported multiple cognition-outcome correlations within the same domain (e.g., working memory and community functioning), correlations were pooled. Studies were allowed to contribute multiple cognition-outcome correlations across unique domains (e.g., working memory and community functioning and working memory and social skills) resulting in a total of 518 effect sizes.

2.4. Coding procedure

Article coding categories were defined prior to article review and were based on categories included by and recommendations by PRISMA (Moher et al., 2009). Articles were coded for: year of publication, country of publication, inpatient percentage, schizophrenia spectrum diagnoses, illness duration, chlorpromazine (CPZ) equivalent dosage,

percent of sample taking medication, age, percent male, percent white, years of education, cognitive measure and classification, functional measure and classification, and risk of bias. Risk of bias was evaluated by adapting items for correlational studies from Downs and Black (1998) and generating a summary score of 1 (low risk of bias) to 3 (high risk of bias). Socioeconomic status, reliability of measures, and diagnostic standard were included in the coding procedure but not discussed here due to infrequent reporting. Supplementary Table 2 provides coding categories and corresponding study values.

All articles were double-coded by TFH and CCM or MOP (doctoral students in clinical psychology). Discrepancies in objective categories (e.g., sample size) were reconciled by consulting original articles; discrepancies in subjective categories (e.g., risk of bias) were reconciled through a consensus meeting. Intraclass correlation coefficients (ICCs) prior to collation were excellent for objective coding categories ($ICC = .99$ for correlation effect sizes; $M_{ICC} = .97$ (range .84–.99) for study characteristic categories). The reliability for coding of article quality was satisfactory, $M_{PABAK} = .78$ (Koo and Li, 2016).

2.5. Overlapping samples

Overlapping samples were identified through (1) cross-referencing all authors and research groups, (2) cross-referencing grant numbers, and (3) cross-referencing committee members for unpublished dissertations. Samples with potential overlap underwent a second-round of full-text inspection. Samples with a probable degree of overlap were dealt with in the following ways: estimates from smaller sample sizes were deleted in the case of overlapping samples presenting identical cognition-outcome relationships (13 studies); overlapping studies were included if they presented unique cognition-outcome relationships (37 studies); identical overlapping samples presenting the same cognition-outcome pairs were averaged (7 studies; see Supplementary Table 2).

2.6. Statistical methods

Correlation coefficients between SC, NC, and functional outcomes formed the indices of effect size. Correlation coefficients were converted using Fisher's *r*-to-*z* transformation to stabilize variance and estimate confidence intervals prior to all analyses (Fisher, 1922). All analyses were conducted in R using the 'metafor' package (Viechtbauer, 2010).

Random effects meta-analyses were conducted for each domain of cognition and functional outcome pair (e.g., processing speed and community functioning, theory of mind and social problem-solving) whenever there were three or more relevant observations. Random effects meta-analyses account for heterogeneity introduced by different methods or samples and allow for multiple effect estimates from a single sample (Hasselblad and Hedges, 1995; Hedges and Vevea, 1998; Viechtbauer, 2010). Relationships between functional outcomes and overall NC domains (i.e., estimation of effect size across all neurocognitive domains) and overall SC domains were also conducted to provide overall effect estimates in addition to specific cognition-outcome pair estimates. Sample-weighted average effect sizes (\hat{u}_p), and heterogeneity statistics (I^2 , Q) were calculated for each meta-analysis. Additionally, moderators (e.g., age, illness duration) were examined utilizing a mixed-effects model.

Funnel plots and regression tests for funnel plot asymmetry were generated for each meta-analysis to examine publication bias (Egger et al., 1997). For the subset of studies that reported relationships between all three domains (i.e., NC, SC, and functional outcomes), a random effects mediation analysis was conducted utilizing the 'metaSEM' package (Cheung, 2015) to examine SC as a potential mediator of the relationship between NC and functional outcome.

3. Results

3.1. Sample characteristics

The sample of studies in the present review included 12,868 participants with non-affective psychosis with a mean age of 39.84 ($SD = 6.85$); 69.3% of the sample was male, 48.2% white, and had completed an average of 12.18 years of education ($SD = 1.10$). Participants had a diagnosis of schizophrenia (87.9%), schizoaffective disorder (8.0%), psychosis NOS (0.2%), or other diagnoses within the non-affective psychosis spectrum (3.9%). Twenty-four studies reported aggregate schizophrenia spectrum sample sizes but did not report frequency of specific diagnoses (see Supplementary Table 2).

The majority of samples (78.9%) were outpatients, and average illness duration was 16 years (range: 0.44–34.45 years; $SD = 7.64$). Most patients were taking psychotropic medication (95.8%) and the average CPZ equivalence was 549.2 mg ($SD = 231.9$). Samples with an average illness duration less than or equal to five years ($n = 11$) were classified as a FEP sample (Breitborde et al., 2009).

Seventeen studies included in the review were unpublished (10%). A meta-regression indicated publication status did not significantly predict effect sizes ($\beta = -.01$, $SE = .04$, $p = .78$). Likewise, coder ratings of bias risk were not associated with relationship estimates ($\beta = -.01$, $SE = .03$, $p = .67$). Meta-regression indicated effects were not characterized by small sample bias ($\beta = -.04$, $SE = .03$, $p = .09$), where small sample bias was defined as possessing sufficient power to detect a medium-sized effect (i.e., $N \geq 48$) or not ($N < 48$).

Fifty-three random effects meta-analyses were conducted to quantify the relationship between the four functional outcomes (behavior in the milieu, community functioning, social problem-solving, and social skills) and each SC and NC domain, as well as overall SC (e.g., multi-level model providing weighted average for all individual domains of SC combined) and NC (i.e., see Fig. 2 for estimated effects organized by functional outcome). An additional 15 relationships had fewer than 3 studies contributing effects so meta-analyses could not be conducted

(see Supplementary Table 7 and relationships presented without effect sizes in Fig. 2). Moderator analyses were conducted for overall SC and NC only, to ensure adequate power to detect moderation.

The majority of samples reported information for at least one moderator variable: mean age (99.2%), sex (100%), race or ethnicity (46%), mean years of education (75.8%), specific diagnosis (86.3%), duration of illness (75.8%), inpatient status (94.4%), and mean CPZ dosage (35.5%). Few studies included information for all moderators of interest, so moderators were applied to all overall models individually with Bonferroni correction for multiple comparisons rather than incrementally to maximize observations included in each analysis.

3.2. Publication bias

Publication bias was examined through funnel plot inspection (see Supplementary Figure 1) and Egger's regression. Out of 41 tests for funnel plot asymmetry, only two regression equations for associations between cognition and functional outcomes were significant: the association between reasoning and problem solving and social skills ($z = 2.42$, $p = .02$), and between theory of mind and community functioning ($z = 2.84$, $p < .01$). The associations between reasoning and problem solving and social skills included only 4 observations, therefore any interpretation about funnel plot asymmetry should be made cautiously. A significant Egger's test with regards to the association between theory of mind and community functioning was due to a single observation (-0.4). Removal of this observation from the model results in a non-significant Egger's test. Taken together, these findings suggest that publication bias is not a concern in the current analysis.

3.3. Neurocognition

3.3.1. Overall neurocognition-functional outcome associations

A random-effects meta-analysis yielded a medium-sized average correlation between overall NC (i.e., across all NC domains) and functional outcomes and ($\hat{u}_p = 0.21$, 95% CI [0.18, 0.24], $p < .01$) based on 399 effect sizes; 60.88% of the variation in effect sizes was due to heterogeneity between studies ($Q = 1556.36$, $p < .001$; $I^2 = 60.88$). Random-effects meta-analyses examining relationships between summary NC and specific functional outcome domains also yielded medium correlations (\hat{u}_p s = .14–.26) based on 32–264 relationships. Significant variation (31–73%) due to heterogeneity between studies (Q s 108.9–988.9, $ps < .001$) was present for functional outcomes of community functioning, social behavior in the milieu and social skills but not for social problem solving ($Q = 31.3$, $p = .45$; see Supplementary Table 5).

3.3.2. Associations between specific neurocognition domains and functional outcomes

Mean correlation estimates across specific NC functional outcome relationships were small to medium in size ($\hat{u}_p = .06$ –.33). The smallest effect was observed between verbal comprehension and social behavior in the milieu ($\hat{u}_p = .06$, $p = .60$). The largest effect was observed between overall neurocognition and social skills ($\hat{u}_p = .33$, $p < .001$). All relationships between specific NC domains and respective functional outcomes are presented in Supplementary Table 6, as well as in Fig. 2.

3.3.3. Moderators of the neurocognition-functional outcomes association

Random-effects meta-regression analyses were conducted to examine potential influence of moderator variables on NC – functional outcome relationships (see Supplementary Table 5). Most moderators did not significantly influence relationships between NC and functional outcomes, with some exceptions: samples with more males showed weaker relationships between NC and summary functional outcomes ($\beta = -.0038$, $SE = .001$, $p < .001$) and more racially diverse samples showed weaker relationships between NC and summary functional outcomes ($\beta = -.0030$, $SE = .001$, $p = < .001$). Moderators should

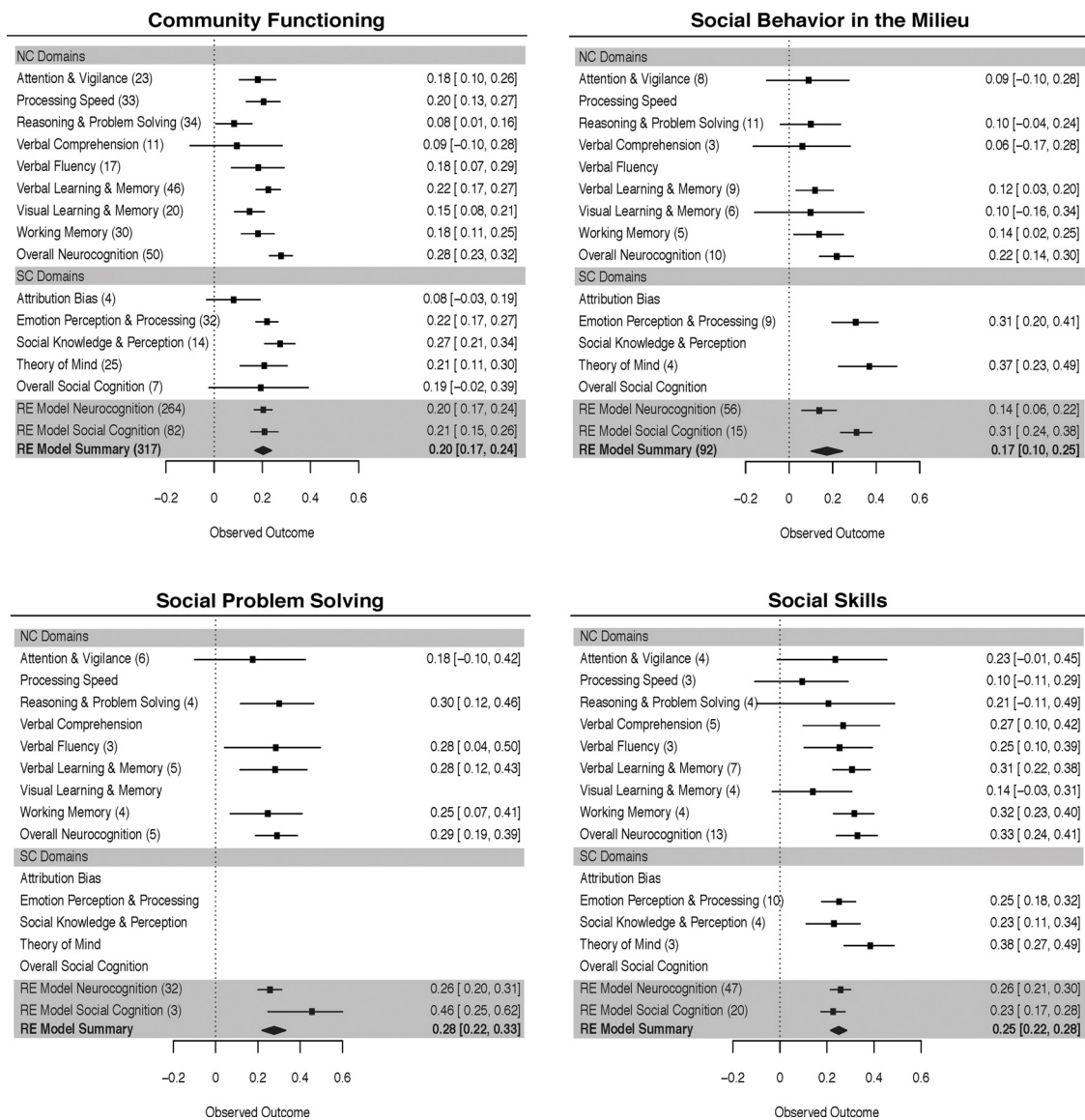


Fig. 2. Forest plots displaying correlation coefficients [95% CI] by functional outcome. Diamond polygons represent summary correlation coefficient estimates among all cognition domains. Note: (n) = number of studies (K) included in estimates, RE = random effects, relationships with K ≤ 3 not presented. RE Model Social Cognition based on effect estimates from emotion perception & processing (K = 2) and social perception and knowledge (K = 1), specific SC domains not presented since K ≤ 3, RE model effect estimate presented for comparison with NC but should be interpreted with caution.

be interpreted with caution given the small observed associations and modest variance explained by moderators (all pseudo R²s for significant moderators < 1%).

3.4. Social cognition

3.4.1. Overall social cognition-functional outcome associations

A random-effects meta-analysis yielded an overall medium correlation between all domains of social cognition and functional outcomes, ($\hat{u}_p = 0.24$, 95% CI [0.19, 0.28], $p < .01$) based on 119 relationships with 62.29% of the variation in effect sizes due to heterogeneity between studies ($Q = 300.10$, $p < .001$; $I^2 = 62.29$). Random-effects meta-analyses examining relationships between summary SC and specific functional outcome domains also yielded medium correlations ($\hat{u}_{ps} = .21-.46$, $ps < .01$) based on 3 – 82 relationships. Significant variation (2–67%) due to heterogeneity between studies (Qs 39.2–227.9, $ps < .01$) was present for functional outcomes of community functioning and social skills but not social problem solving and social skills ($Qs = 2.6-13.2$, $p > .05$; see Supplementary Table 5).

Caution is warranted with interpretation of the overall relationship between SC and social problem solving ($\hat{u}_{ps} = .46$). This estimate is based on only three relationships (two from emotion perception and processing and one from social perception and knowledge) and is presented only for comparison with overall NC relationships.

3.4.2. Associations between specific social cognition domains and functional outcomes

Mean correlation estimates across specific SC-functional outcome relationships were small to medium in size ($\hat{u}_p = .08-.38$). The smallest effect was observed between attribution bias and community functioning ($\hat{u}_p = .08$, $p = .16$). The largest effect was observed between theory of mind and social skills ($\hat{u}_p = .38$, $p < .001$). Relationships between specific SC domains and respective functional outcomes are presented in Supplementary Table 6 and Fig. 2.

No significant differences emerged when directly comparing effect estimates between domains of NC and SC with functional outcomes. Eighty percent of the observed relationships (8 out of 10) between SC and functional outcomes were significant, compared with 68% (21 out

of 31) of the observed relationships between NC and functional outcomes (proportion not significantly different between NC and SC ($X^2(1) = 0.52, p = 0.48$)).

3.4.3. Moderators of the social cognition-functional outcomes association

Random-effects meta-regression meta-analyses were conducted to examine potential influence of moderator variables on SC – functional outcome relationships (see Supplementary Table 5). Most moderators did not significantly influence relationships between SC and functional outcomes, with one exception: samples with more inpatients were associated with weaker relationships between SC and community functioning ($\beta = -.0024, SE = .001, p < .001$). However, caution in interpretation is warranted since inpatient status explained less than 1% of the variance in this relationship (pseudo $R^2 < 1\%$).

3.5. Hierarchical regression of functional outcomes on social cognition and neurocognition

To better understand incremental variance explained by NC and SC, respectively, hierarchical regressions utilizing the subset of studies that reported relationships between NC, SC, and functional outcomes were conducted ($n = 32$; 153 correlation matrices). NC and SC both has significant beta coefficients in respective equations and together explained 9.2% of variance in functional outcomes. However, NC explained an additional 1.9% of variance (4.4% total variance) in functional outcomes after accounting for SC, $F(1, 2417) = 50.401, p < .01$, whereas SC explained an additional 4.8% of variance (7.3% total variance) in functional outcomes after accounting for NC, $F(1, 2417) = 127.05, p < .01$.

3.6. Mediation analyses

A random effects mediation analysis explored the potential role of SC as a mediator between NC and functional outcomes in the same subset of studies. Correlations between NC and SC allowed for modeling of dependency between these two domains. Results suggest SC is a partial mediator between NC and functional outcomes (Fig. 3). Prior to mediation, NC was significantly correlated with SC ($\hat{u}_p = .29, p < .01$), SC was significantly correlated with functional outcomes ($\hat{u}_p = .23, p < .01$), and NC was significantly correlated with functional outcomes ($\hat{u}_p = .23, p < .01$). When SC was included as a mediator in the model, the relationship between NC and functional outcome decreased but was still significant ($\hat{u}_p = .14, p < .01$).

4. Discussion

4.1. Current findings

With respect to a priori aims, (1) domains of NC and SC demonstrated small to medium relationships with functional outcomes. Specific domains of cognition exhibited a range of effect estimates based on functional outcome. This range likely reflects differences in the type of functional outcome (e.g., community functioning and social

behavior in the milieu measure real-world functional performance while social problem solving and social skills measure task-based functional capacity). Specific NC domains of verbal learning and memory (community functioning), working memory (social behavior in the milieu and social skills) and reasoning and problem solving (social problem solving) demonstrated the strongest relationships with specific functional outcomes (2–10% variance explained). For SC, the strongest associations were present for social knowledge and perception (community functioning) and theory of mind (social behavior in the milieu and social skills) explaining 7–14% of variance in functioning; (2) Relationships between overall NC and SC with functional outcomes were not significantly different in bivariate analyses. However, SC did explain more *unique* variance in functioning (4.8%) than NC (1.9%) in a subset of studies examining both domains, suggesting distinct relationships for respective domains of cognition with functional outcomes; (3) Relationships were not moderated by FEP sample status, suggesting similar associations between NC and SC with functional outcomes are already present in the early stages of illness; 4) Consistent with previous theoretical and empirical work, the role of SC as a partial mediator between NC and functional outcomes was substantiated (Addington et al., 2010; Green and Nuechterlein, 1999; Schmidt et al., 2011; Vaskinn et al., 2008).

In line with previous findings of Fett et al. (2011), specific domains of NC and SC generally demonstrated small to medium relationships with functional outcomes irrespective of sample characteristics. Results of the present review substantiate the previous finding that SC explains more unique variance in functional outcomes than NC with the inclusion of 18 previously unreported cognition-functional outcome relationships (see Supplementary Table 7). Whereas theory of mind exhibited the strongest SC association with community functioning, the current results show that social knowledge and perception exhibits the strongest relationship with community functioning. Verbal learning had the strongest NC association with community functioning, which replicates Fett et al.'s (2011) results.

Of note, relationships between NC, SC, and functional outcomes were generally weaker (i.e., smaller effect estimates) than relationships presented in Fett et al. (2011). The present review includes three times the number of studies with a sample size almost five times bigger, spanning an additional ten years of published and unpublished results. The phenomenon of observing decreasing, but more robust, effect sizes over time with the expansion of areas of research (i.e., the “in silico effect”; Monsarrat and Vergnes, 2018) may be one explanation for the present results. Many of the smaller effect sizes observed also exhibited smaller confidence intervals in line with the in silico effect. Another potential explanation for smaller effect estimates may be the novel inclusion of unpublished findings to address the file-drawer effect (Rosenthal, 1979). Although publication status did not significantly predict effect size, effect estimates from unpublished work were slightly smaller than published estimates and likely contributed to overall smaller effect estimates. Finally, whereas Fett et al. (2011) only presented individual effect estimates (e.g., verbal learning and community functioning), the present review utilized random effects approaches to model summary estimates between NC, SC, and functional domains for the first time (e.g., all domains of NC with community functioning). When combining these individual effect estimates to produce summary effect estimates across domains of functional outcomes, the average variance explained by NC (2–7%) and SC (4–10%) is smaller than individual relationship estimates. However, the largest individual effect estimates do replicate Fett et al. (2011) in terms of variance explained.

This meta-analysis is the first to investigate the relationships between specific NC and SC domains with functional outcomes in a large sample of 166 studies in conjunction with a mediation analysis that is vital for the comprehensive understanding of cognition-outcome relationships. Mediation results demonstrated SC is a mediator in the relationship between NC and functional outcomes. According to the proximal-distal approach (e.g., Brenner et al., 1995; Green et al., 2019;

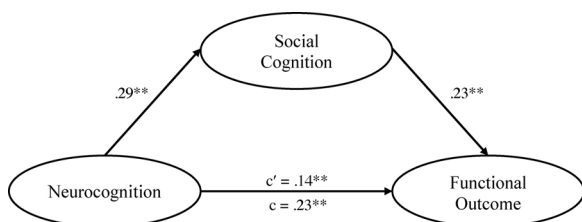


Fig. 3. Mediation analysis examining NC, SC, and functional outcome relationships. Note: c = direct effect, c' = mediated (i.e., partial) effect. $**p < .01$.

Ryan, 2009), the proximity of SC to functional outcomes offers support for SC as a primary treatment target for optimal improvement in functioning. However, correlation analyses based on the entire sample of studies demonstrated medium effect sizes from both NC and SC domains and seem to support the increasing focus on integrated interventions targeting both domains of NC and SC in schizophrenia populations (Fisher et al., 2017; Green et al., 2019; Peña et al., 2016).

Additionally, results recommend consideration of the desired type of functional outcome improvement when planning interventions. Perhaps unsurprisingly, SC was particularly more strongly associated with measures of outcome that are social skill and behavior-related (e.g., social behavior in the milieu and social skills) while NC and SC seemed to be equally associated with community functioning which is more related to activities of daily living. SC may be particularly important with respect to social behavior, which in turn may improve community outcomes through better helping networks, while NC may be particularly important for independent living which makes these networks possible. Overall, results suggest integrated approaches to interventions targeting both NC and SC may engender optimal improvements in functioning.

4.2. Limitations

The effect size estimates are correlations between functional outcomes and NC and SC which means that caution is warranted in drawing causal conclusions. Longitudinal research examining cognitive domains and functional outcomes will be important to delineate directional relationships between these domains. Second, a surprisingly small proportion of studies ($n = 11$) included FEP populations; thus, the effect estimates for this population need to be considered with caution. The lack of significant moderators observed in the relationship between cognitive domains and functional outcomes also leaves a significant amount of heterogeneity in the observed relationships between NC, SC, and functional outcomes unexplained. Routine reporting of clinical factors such as symptoms (Ventura et al., 2009), as well as motivation and social competence (Schmidt et al., 2011) would allow for investigation of these as moderators and may explain more heterogeneity between cognition and outcomes.

4.3. Future directions

Notwithstanding these limitations, results from this meta-analysis point to important areas for future development and research. Although measures were grouped into categories of respective NC, SC, and functional outcomes, a wide range of methods and measures were used to quantify these different domains. Categorization of cognitive domains and functional outcomes allows for taxonomic organization of relationships in a meaningful way, but these classifications were defined in different ways across studies. The sheer number of different measures precludes the inclusion of moderators specific to each instrument, but future research should continue the work of the MATRICS and SCOPE studies to examine psychometric properties (e.g., reliability, internal and external validity) of cognition measures within schizophrenia populations (Nuechterlein et al., 2008; Pinkham et al., 2014). The large number of studies included in the present meta-analysis suggests we *are* measuring SC, NC, and functional outcomes in schizophrenia populations but more research into *how* we measure these domains is an important future direction. Focusing not just on capturing these domains, but doing so in a way that is accurate, reliable, and standardized may reduce heterogeneity related to measurement methods and allow for meaningful discoveries regarding why relationships between cognitive domains vary across studies and individuals. Investigation of the relationships between domains of functional outcomes (e.g., social behavior in the milieu and social skills) and real-world functioning is also needed to better understand which relationships are essential treatment targets for genuine improvements in

functioning.

Finally, the relationships between NC, SC, and functional outcomes leaves much of the variance in functional outcomes unexplained. One implication of this finding may be to shift focus away from NC and SC to identify factors that are more closely linked with functioning (e.g., motivation; Green et al., 2019). Alternatively, examining NC and SC in isolation may be overly simplistic and may underestimate the role of cognition. More complex models examining relationships between NC, SC, and functioning with intervening variables (e.g., motivation, metacognition) may provide a more comprehensive understanding of this relationship via identification of indirect effects of NC and SC on functional outcomes (Galderisi et al., 2014; Grant and Beck, 2009; Green et al., 2019; Lysaker et al., 2010).

4.4. Conclusions

NC and SC exhibit reliable relationships with different functional outcomes within schizophrenia spectrum populations with SC accounting for greater unique variance. Importantly, findings demonstrate SC mediates the relationship between NC and functional outcomes. Future research is needed to explain significant heterogeneity observed within these relationships and more research on additional moderators such as clinical factors and measurement methods may provide a promising next step. Findings suggest observed cognition-outcome relationships are already established in FEP, highlighting the importance of early intervention, but more research with FEP populations is needed. Additionally, longitudinal studies and experimental studies that improve NC and SC and assess change in functioning will provide more comprehensive understanding of the direction and strength of the relationships among NC, SC, and functional outcomes.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.neubiorev.2019.07.020>.

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