Functional implications and course

Neurocognition and functional outcome in schizophrenia: filling in the gaps

Michael F. Green, William P. Horan, Kristopher I. Mathis, and Jonathan K. Wynn

Acknowledgments

Funding for this project came from NIH grants MH043292 (to MFG).

Introduction and overview

The goal of treatments for schizophrenia has moved beyond management of psychotic symptoms to the goal of “recovery.” Recovery refers to achieving independent living, vocational or educational activities, and satisfying interpersonal relationships (Kopelowicz et al., 2005; Liberman & Kopelowicz, 2005). This goal remains elusive for many patients with schizophrenia, as evidenced by the disappointing statistics on the worldwide level of disability associated with the illness (Murray & Lopez, 1996; WHO, 2008). An important step for public health improvement is to identify the determinants of poor functioning that interfere with successful community adaptation. One of the most consistent correlates and determinants of functional outcome for individuals with schizophrenia has been neurocognition (i.e., episodic memory, attention, working memory, reasoning and problem solving abilities, and speed of processing).

Relationships between neurocognition and functional outcome have been well documented in several reviews of this literature (Green, 1996; Green et al., 2000; Green et al., 2004). The relationships are present in cross-sectional studies, as well as in prospective studies in which neurocognition is assessed at baseline and outcome is assessed one or two years later (Green et al., 2004). The specific types of functional outcome vary across studies, but they usually include aspects of role functioning (work, housekeeping, school), independent living, and/or social functioning with friends and family. Associations between neurocognition and functional outcome are typically stronger than those found between psychotic symptoms and functional outcome, and sometimes even stronger than those between negative symptoms and outcome. Most of the studies in the reviews examined patients with chronic illness, but the linkages are also present in first-episode and prodromal (high-risk) samples (Carrion et al., 2011; Nuechterlein et al., 2011). While the magnitude of these relationships are often modest at the level of individual cognitive domains, a substantial amount of variance in outcome can be explained when summary scores that combine multiple domains are examined (Green et al., 2000).

Given the well-established nature of this literature, this chapter will not conduct a new review. Instead, it will attempt to place this literature in a larger context. Although the
connections between neurocognition and outcome are well established, the mechanisms
through which neurocognition measured in the laboratory ultimately relate to real-world
functioning are not well understood. Over the last decade, investigators have switched from
asking if neurocognition is related to outcome to asking how neurocognition is related to
outcome. In doing so, research has started to identify the intervening steps between
neurocognition and daily living, and also to look to perceptual factors earlier in the
processing stream.

The purpose of the chapter is to sketch out a preliminary integrative model of outcome
that incorporates factors that run from basic perception to functional outcome, with
neurocognition as a lynchpin. We will first consider a close cousin of neurocognition,
namely, social cognition. This area is also considered in Chapter 8 in this book; our focus
here is on how social cognition relates to outcome beyond neurocognition. Neurocognition
and social cognition can collectively be considered types of “ability.” Second, we will move
earlier in the processing stream to examine how early auditory and visual perception help to
explain pathways from brain-based processes to ability measures and subsequently to
community outcome. Third, we will examine motivational factors as promising intervening
steps between ability and daily functioning. Finally, we conclude with recent efforts to
evaluate how these domains (perception, ability, and motivation) can be integrated in a
single model of outcome.

Social cognition and functional outcome in schizophrenia

Although some aspects of social cognition in schizophrenia have been studied for decades
(e.g., facial affect perception), interest in this area has increased substantially in the last
decade. Social cognition refers to the mental operations underlying social interactions,
including perceiving, interpreting, and generating responses to the intentions, dispositions,
and behaviors of others (Fiske & Taylor, 1991; Kunda, 1999). It includes processing a range
of social information from how we identify an emotion on a face to how we draw inferences
about another person’s intentions. At the most basic level, social cognition is what enables
us to understand and effectively interact with other people. Based on a rapidly expanding
data-based literature, we know that schizophrenia is characterized by substantial wide-
ranging social cognitive impairments (Bora et al., 2009; Green et al., 2008; Kohler et al.,
2010). Intuitively, problems with social cognition, such as misperceiving the actions of
other people and reacting in a manner confusing to others, are likely to have an adverse
effect on functioning for patients.

Research in social cognition in schizophrenia has tended to cluster around four types of
social cognitive processes: emotion processing, social perception, attributional style, and
mental state attribution (i.e., theory of mind). Emotion processing includes perceiving and
using emotion to facilitate adaptive functioning. One influential model of emotional
processing (also called emotional intelligence) includes four components: identifying emo-
tions, using emotions to facilitate cognition, understanding emotions, and managing
emotions (Mayer et al., 2002; Mayer et al., 2003). Of these components, perceiving emotions
(e.g., identifying emotions in faces) has been the most extensively studied social cognitive
process in schizophrenia. Social perception refers to the ability to judge social cues from
textual information and communicative gestures (Corrigan & Green, 1993; Sergi &
Green, 2002). In social perception tasks, participants typically process nonverbal, paraver-
bal, and/or verbal cues to make inferences about the social situations that contained such
cues. **Attributional style** refers to how individuals characteristically explain the causes for positive and negative events in their lives (Bentall et al., 2001). Key distinctions are typically made between external personal attributions (i.e., causes attributed to other people), external situational attributions (i.e., causes attributed to situational factors), and internal attributions (i.e., causes attributed to oneself). In schizophrenia research, attributional style has been studied primarily to understand psychological mechanisms of persecutory delusions and paranoid beliefs in which there is a bias for patients with these symptoms to perceive malicious intent in other people. **Mental state attribution** (also called theory of mind, or mentalizing) involves inferring the intentions, dispositions, and beliefs of others (Baron-Cohen et al., 2001; Brune, 2005; Frith and Corcoran, 1996). This process includes the ability to understand false beliefs, hints, intentions, humor, deceptions, metaphor, and irony. This process requires one to “stand in someone’s shoes.” Mental state attribution studies in schizophrenia have relied heavily on measurements that were borrowed from the developmental literature, such as those used with autism spectrum disorders. The use of tests that were developed for children and adolescents means that the psychometric characteristics of mental state attribution measures used in schizophrenia are often problematic, but some newer measures have better psychometric properties in this population (Kern et al., 2009).

A growing literature has examined relationships between the domains of social cognition described earlier and various aspects of community functioning in schizophrenia (e.g., work, social, independent living). A previous review of this literature concluded that there were consistent functional correlates of social perception and emotion perception (Couture et al., 2006). A recent meta-analysis examined the amount of variance in functioning explained by neurocognition and social cognition in 52 studies that included 2692 subjects (Fett et al., 2011). The associations across studies between outcome and key social cognitive domains were all relatively strong: mental state attribution/theory of mind, 0.48; social perception, 0.41; emotion processing, 0.31. When the explanatory value of neurocognition and of social cognition were compared, the neurocognitive factor accounted for 6% of variance in community functioning, whereas the average of social cognitive domains explained 16%. Hence, social cognition is not related to functional outcome only—the strength of that relationship appears to be greater than for neurocognition.

The distinction between neurocognitive and social cognitive tasks depends mainly on the types of stimuli (e.g., people/faces vs. objects) and the types of responses (e.g., judgments about mental states to other people vs. simple speed and accuracy). Neurocognitive and social cognitive tasks often share cognitive demands, such as working memory and perception. Hence, one might question whether neurocognition and social cognition are truly different constructs. However, several data sets have shown that neurocognitive tests and social cognitive tests are only partially interrelated. Studies using confirmatory factor analysis with schizophrenia patients (Allen et al., 2007; Bell et al., 2009; Sergi et al., 2007) or exploratory factor analysis in participants with psychosis or heightened vulnerability to psychosis (van Hooren et al., 2008; Williams et al., 2008) indicate that models fit better when the two domains are separated compared to when they are combined. The general conclusion from these studies is that social cognition in schizophrenia is associated with neurocognition, but is not redundant to it. The relative distinctiveness of neurocognition and social cognition supported by the schizophrenia literature has also been found using healthy samples.
The conclusion that there is both partial overlap and relative distinctiveness between neurocognition and social cognition is consistent with studies from the social neuroscience literature that reveal partially overlapping and partially distinct patterns of neural activation associated with nonsocial and social cognitive activation tasks (van Overwalle, 2009).

The observation that neurocognition and social cognition are separable raises the question of how these domains work together to determine outcome. We previously found social cognition to be a mediator between neurocognition and functioning (Brekke et al., 2005). Being a mediator means that social cognition is associated with neurocognition, social cognition is related to functional outcome after controlling for its relationship to neurocognition, and the direct pathway between neurocognition and functional outcome becomes significantly smaller when social cognition is included in the model. This role of social cognition as a mediator is supported by a large number of data sets: out of 15 studies that considered whether social cognition was a significant mediator between neurocognition and functional outcome, 14 studies supported that role (Schmidt et al., 2011). The fact that social cognition is a mediator between neurocognition and functional outcome is additional evidence that the two domains are not redundant. If they were, it would not be possible for social cognition to have a significant relationship with outcome while controlling for its relationship to neurocognition.

Overall, social cognition appears to be a consistent correlate of functional outcome. In addition, it helps to provide a mechanism through which problems in neurocognition lead to problems in functional outcome. Social cognition acts as a mediator between the two; variance from neurocognition “flows through” social cognition to impact functional outcome. Consistent with this view, social cognition explains unique variance in functional outcome (Brekke et al., 2005; Poole et al., 2000; Vauth et al., 2004). That is, it has incremental validity that accounts for variance in outcome above and beyond that provided by neurocognition. Both neurocognition and social cognition can be considered reflections of integrative cognitive processes and are both reflections of the general category of ability. The next section covers what happens if we move earlier in processing and consider perceptual processes.

**Perception as a correlate and predictor of social cognition and outcome**

As opposed to later (more integrative) stages, such as neurocognition or social cognition, many studies of functional outcome have moved earlier in the processing stream to examine the effects of visual and auditory perception. Individuals with schizophrenia have abnormalities in both of these modalities and starting with perceptual measures in mechanistic models of outcome has some interpretive advantages for two reasons (Javitt, 2009). First, perceptual variables have rather direct and established ties to neural processes. Neural models of perception are better specified than they are for many of the neurocognitive domains that depend on integrating information from different sources. Second, perceptual variables are relatively less influenced by later-stage processes. Although top-down processes influence some early perceptual variables, their effects tend to be relatively small. Hence, early perceptual variables, in a model of outcome, are much more likely to influence later variables than later-stage variables (e.g., neurocognition, social cognition, motivation, etc.) are to influence perception.
Several studies in schizophrenia have found associations between lower-level perceptual processing and higher-level variables. In previous publications from our laboratory we found that early visual perception is a contributor in models of functional outcome (Rassovsky et al., 2011; Sergi et al., 2006). Perceptual variables can contribute to outcome either directly, or indirectly via social cognition. Our studies used versions of visual masking in which the processing of a visual target is disrupted by a visual mask that is briefly presented shortly before (forward masking) or after (backward masking) the target. The visual masking paradigm provides excellent temporal resolution by manipulating the interval between the target and mask, and can be used to assess the first 100 ms of visual processing. Other early visual processing measures, including visual evoked potentials assessed using electroencephalography, have shown similar connections to functional outcome (Butler et al., 2005). In addition, more integrative visual tasks have been used to examine visual integration. In these tasks, subjects are asked to detect a contour in an array of separate small visual elements. This ability to integrate visual elements into contours is related to higher-level social cognitive processes, such as mental state attribution (Schenkel et al., 2005; Uhlhaas et al., 2006).

In addition to the role played by visual processing impairments in leading to social cognitive deficits, impaired early auditory processing leads to problems in emotion detection from the prosody of voices (Javitt, 2009; Leitman et al., 2005, 2010). Basic auditory processing in schizophrenia, assessed with tasks such as simple tone matching, was correlated with poor prosody detection (Leitman et al., 2005). In a follow-up study, poor early auditory processing was associated with poorer ability to detect complex pitch changes inherent in prosodic speech (Leitman et al., 2010).

In addition to behavioral measures, early auditory processing can be assessed with specific event-related potentials (ERPs). Mismatch negativity (MMN) is one ERP index of early auditory discrimination that reflects the difference in neural response to an expected (standard) tone and an unexpected (rare) tone. Mismatch negativity can be evoked even when stimuli are not directly or fully attended, making it an ideal measure of early auditory processing without any cognitive or effortful processing by the participant. Reduced MMN (meaning less of a difference between standard and rare tones) is indicative of dysfunctional early auditory processing. Mismatch negativity is related to lower levels of functioning and independent living in schizophrenia patients (Light & Braff, 2005). In addition, MMN has been shown to be related to an aspect of social cognition, namely, social perception that is heavily reliant on processing brief perceptual cues (Wynn et al., 2010).

The connections between auditory and visual perceptual processes and later processes (e.g., social cognition, and eventually community outcome) are typically viewed within a “cascade” model. In such models, early impairments produce perceptual information that is eroded, partial, or unstable in some way. This poorly formed perceptual information is fed forward to higher-level processing stages. However, because the perceptual information is imperfect initially, subsequent processing of this information is impaired as well (Javitt, 2009).

Overall, support for starting outcome models very early in the processing stream has become increasingly persuasive, because perceptual factors are seen to relate to higher-level ability factors (neurocognition and social cognition). Further, there are benefits to constructing models that begin at a perceptual level due to the well-established links to neural substrates. The following section addresses the question of how the perception-to-ability linkages eventually lead to community functioning.
Role of negative symptoms with cognition and functional outcome

A key unresolved question in this area is how motivation and negative symptoms fit with ability factors to lead to functional outcome. Negative symptoms reflect a decrease or absence of normal functions within two broad domains: (1) internal experience-related impairments, including diminished emotional experience (anhedonia), motivation to engage in productive activities (avolition), and desire for social affiliation (asociality); (2) expressive or communicative impairments, including diminished facial expressivity, gestures, prosody, and speech production (Blanchard et al., 2011; Kirkpatrick et al., 2006). In general, motivation and negative symptoms are highly overlapping and can be considered reflections of the same underlying avolitional state (Nakagami et al., 2008, 2010). It has been known for a long time that, like neurocognition, negative symptoms are consistent predictors of daily functioning (Breier et al., 1991; Fenton & McGlashan, 1994). What is less clear is how neurocognition and negative symptoms interact so that they are both determinants of outcome. There is surprisingly little theoretical discussion about this issue in the literature (see Harvey et al., 2006, for an example).

There are two general possibilities. One is that two independent paths to functional outcome exist: one that flows through neurocognition and a separate one that is based on motivation. Such a model is depicted in Figure 5.1. In this model, problems start with impaired perception, as in the cascade models mentioned earlier. Next, a variety of performance-based skills, including neurocognition, social cognition, and functional capacity that can be collectively called measures of ability are diminished (Harvey et al., 2011). We have already discussed neurocognition and social cognition. Functional capacity (also called competence) refers to the ability to demonstrate activities of daily living or social communications in a simulated setting (Green et al., 2011; McKibbin et al., 2004). Measures of functional capacity are performance-based simulations in which a participant demonstrates how he/she would conduct daily activities such as paying a bill, taking their medication, or planning an outing to a local recreational site (Patterson et al., 2001, 2002). Similar to social cognition, functional capacity can act as a mediator between

Two pathways to functional outcome

![Diagram of two pathways to functional outcome](image_url)
neurocognition and functional outcome (Bowie et al., 2006, 2010). These three types of measures, neurocognition, social cognition, and functional capacity, are distinctive but typically they are intercorrelated. Hence, they are shown as part of the same category of ability.

Alternative models can be formally tested with statistical techniques such as structural equation modeling, or path analysis. In this two pathway model (Figure 5.1), the ability path reflects what one can do, whereas the motivational path reflects what one wants to do. The two pathway model is reflected in everyday speech; people commonly describe others (e.g., their family members, or even themselves) as being fully capable of accomplishing tasks, but not having enough motivation to give it a try. A clinical example would be a patient who appears to have the skills and competence to function at work or college, but does not get out of bed early enough to catch the bus on a regular basis. We might attribute that problem to decreased motivation in the presence of good ability.

Instead of two pathways, there could be a single path in which ability helps to determine motivation. An example of a single path model that includes both cognitive (i.e., ability) variables and negative symptoms comes from the work of Beck and colleagues (Beck & Rector, 2005). This theory proposes that ability (e.g., neurocognition and functional capacity) and functional outcome are related via intervening variables in a causal pathway involving dysfunctional beliefs (Figure 5.2). According to this model, reduced ability leads to discouraging life circumstances as individuals find themselves repeatedly failing at basic life tasks. These discouraging experiences engender negative attitudes and beliefs about one’s self. For example, patients may start to feel that they are likely to fail before they even undertake daily activities. These dysfunctional attitudes, in turn, contribute to decreased motivation, energy, and interest; which manifest clinically as negative symptoms. The theory by Beck and colleagues proposes a single indirect pathway that runs from impaired ability (and its resulting discouraging experiences) to dysfunctional attitudes to negative symptoms to functional outcome.

This provocative theory regarding the connection between dysfunctional beliefs and negative symptoms has received some empirical support. Studies have shown connections between ability and dysfunctional beliefs (Horan et al., 2010), dysfunctional beliefs and negative symptoms (Grant & Beck, 2009), and dysfunctional beliefs and social functioning.
A study from our laboratory found that one type of dysfunctional attitudes, “defeatist beliefs,” was connected to a measure of functional capacity and to negative symptoms (Horan et al., 2010). Defeatist beliefs refer to overgeneralized conclusions about one's ability to perform tasks (e.g., “If you cannot do something well, there is little point in doing it at all.” “Taking even a small risk is foolish because the loss is likely to be a disaster.”). A variety of dysfunctional beliefs exist, such as maladaptive beliefs about one's ability to communicate effectively (Beck et al., 2009), but defeatist beliefs has been a focus of research in schizophrenia.

The published data are inconclusive on the question of one versus two pathways. Some studies suggest that negative symptoms lie on a separate pathway from ability (Bowie et al., 2006, 2008), whereas other studies suggest it lies on the same pathway as perceptual or ability measures (Couture et al., 2011; Grant & Beck, 2009; Rassovsky et al., 2011). Most studies have not had enough variables and subjects to formally test one versus two causal pathways, so there is little way to arbitrate between the possibilities.

**From perception to community functioning: trying to put it all together**

The final section of this chapter is more speculative and it includes our best guess for a useful integrative model of outcome that incorporates perception, ability, and motivation. In describing this model, we will rely on the published data mentioned earlier, and unpublished data from our laboratory. Our findings are generally supportive of a single pathway model, similar to that proposed by Beck and colleagues. The data suggest that functional outcome in schizophrenia can be considered the result of a relatively linear and streamlined series of steps from perception to ability to beliefs/motivation to functional outcome (see Figure 5.3). This figure has several connections that are largely expected based on previous data and theories. For example, there are considerable data to support the linkages between perception and ability, and between negative symptoms and daily functioning. Less data exist on the idea that ability leads to motivation (via dysfunctional attitudes), although that is predicated by the theoretical framework of Beck and colleagues.

**Figure 5.3.** Single pathway to functional outcome.
The model shown in Figure 5.3 is relatively parsimonious compared to the two pathway model, but it also raises some questions. For example, negative symptoms are a multi-faceted construct composed of two separable subdomains: diminished expression (affective flattening and alogia) and diminished experience (avolition/apathy and anhedonia/asociality) (Blanchard & Cohen, 2006). Experiential negative symptoms are particularly close to concepts of motivation; they refer to a reduction in internal drive and emotion, as opposed to a reduction in outward expressions and communication. Additionally, experiential negative symptoms appear to be more closely related to outcome than expressive symptoms (Horan et al., 2006; Orsel et al., 2004; Rassovsky et al., 2011). It will be important to determine whether negative symptoms in general or experiential negative symptoms in particular are relevant for models of functional outcome in schizophrenia. The initial findings suggest the functional implications of experiential symptoms are greater.

A second consideration is that the association between experiential negative symptoms and functional outcome might be influenced by the degree of overlap in how the two are assessed. Interviews for functional outcome and those for negative symptoms ask similar types of questions regarding the extent to which a patient is engaged in activities in daily life. This issue of measurement overlap has provided a rationale for the development of new scales that assess experiential negative symptoms independently from current community functioning (Blanchard et al., 2010). Such a scale, the Clinical Assessment Interview for Negative Symptoms (CAINS), was recently developed through an NIMH sponsored consortium (Blanchard et al., 2011) and will be a valuable addition for future studies of outcome.

Conclusions
In summary, research on outcome in schizophrenia has moved beyond the question of whether neurocognition is related to outcome and has started asking how the relationship works. Although the pathway(s) through which neurocognition leads to outcome are complex, we are beginning to understand how ability variables (including neurocognition, social cognition, and functional capacity) interface with more fundamental processes (perception) on the one hand, and motivational factors on the other, to impact functioning. These models emphasize the importance of considering both what a person can do and what the person wants to do, as both can limit one’s successful adaptation. Models of outcome will become more complex as additional relevant factors are considered. Such factors would include additional within-person factors (e.g., insight, metacognition, premorbid history), as well as external factors (e.g., social and family support, opportunities for supported employment). In addition, future research will consider factors that influence outcome at a particular phase of illness (prodromal, first-episode, and chronic).

A better understanding of the mechanisms and intervening steps through which neurocognition ultimately impacts outcome is critical for the development of new recovery oriented treatments. It is notable that all of the components of the final model in Figure 5.3 are also targets for interventions. Recovery oriented treatments are showing promise on several fronts, including neurocognitive and social cognitive remediation, cognitive behavioral therapy for negative symptoms, and drug development for both neurocognition and negative symptoms. A greater understanding of how neurocognition and other factors contribute to outcome can help guide the implementation of these promising treatment approaches.
References


Chapter 5: Neurocognition and functional outcome in schizophrenia


Sergi, M. J., Rassovsky, Y., Widmark, C., et al. (2007). Social cognition in schizophrenia: relationships with neurocognition and...
negative symptoms. *Schizophrenia Research, 90*, 316–324.


