Prediction of disability in schizophrenia: Symptoms, cognition, and self-assessment

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Abstract
Schizophrenia is associated with wide-ranging disability across multiple functional domains. There are several determinants of disability that have been identified to date, including cognitive and social cognitive impairments, impairments in everyday functional skills and social skills, difficulties in self-assessment of abilities, and negative symptoms. These impairments are related to different elements of disability, and disability and its predictors are not a single global dimension. Further, although psychotic symptoms have limited cross-sectional correlations with everyday functioning, emerging evidence suggests that long-term clinical stability, often induced through treatment with long-acting antipsychotic medications, is also associated with improvements in everyday functioning. This review addresses the characteristics and origins of disability, with treatment implications noted in each disability domain.

Keywords
schizophrenia, disability, cognition, psychosis

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Schizophrenia remains one of the most debilitating diseases despite very good response rates to antipsychotic medication in individuals who are adherent to treatment. Over three fourths of patients display a reduction or elimination of positive psychotic symptoms with antipsychotic medications during their disease course (Anderson et al., 2005; Cassidy, Norman, Manchanda, Schmitz, & Malla, 2010; Levine, Lurie, Kohn, & Levav, 2011; Lieberman et al., 1993; Robinson et al., 1999; Tohen et al., 2000), but recovery rates are still extremely low. Aside from an array of psychiatric symptoms, individuals with schizophrenia experience a spectrum of heterogeneous impairments including cognitive deficits, poor health, and functional skills deficits (Bowie et al., 2010). Unfortunately, treatment-related reduction or even
elimination of positive psychotic symptoms does not guarantee improvement in everyday outcomes, because clinical improvements associated with antipsychotic treatments rarely lead to improved cognition or negative symptoms (Buckley, Harvey, Bowie, & Loebel, 2007). The result is that individuals with schizophrenia continue to struggle with critical areas of everyday functioning such as maintaining employment, social relationships, and living independently while suffering from poor physical health, despite adequate antipsychotic treatment. Specifically, 70–90% of individuals with schizophrenia have vocational and residential challenges (Huxley & Baldessarini, 2007; Lee et al., 2015; Leung, Bowie, & Harvey, 2008; Marwaha, Durrani, & Singh, 2013; Twamley et al., 2002), and live on average 20-years less than the general population (Auquier, Lancon, Rouillon, Lader, & Holmes, 2006; Hennekens, Hennekens, Hollar, & Casey, 2005).

The economic burden associated with schizophrenia is equally staggering, estimated at over $300 billion annually in the U.S. The bulk of this cost is due to reductions in ability to achieve real-world, functional outcomes including independence in residence and employment, rather than direct health-care expenditure on medications and hospitalizations (Insel, 2008). The cost burden of schizophrenia reflects the disease’s chronic and debilitating nature. Consequently, in a large sample of people recently diagnosed with schizophrenia, 80% were found to be either receiving disability compensation or dependent on a relative for financial support within 18 months of diagnosis (Ho, Andreasen, & Flaum, 1997). Ultimately, long-term everyday outcomes of individuals with schizophrenia have changed little from functional outcomes in the 19th century (Hegarty, Baldessarini, Tohen, Waternaux, & Oepen, 1994).

Cognition, skills, and negative symptoms have emerged as well-studied, reliable predictors and are more strongly correlated with outcomes than the severity of psychosis in most studies (Bowie, Reichenberg, Patterson, Heaton, & Harvey, 2006; Bowie et al., 2008; Fett et al., 2011; Green, Kern, Braff, & Mintz, 2000; Harvey et al., 2011; Tabares-Seixasdos et al., 2008). Cognition encompasses neurocognition (e.g., memory, processing, executive functioning) and social cognition (e.g., interpreting emotions/intentions, utilization of social cues to inform behavior). Skills or functional competence refers to the knowledge and ability to complete everyday activities, such as counting change or making an inquiry over the phone, as well as vocational and other self-care skills. Negative symptoms can be divided into reduced emotional expression (absence or blunting of affect, reduced output in speech, and lack of vocal intonation) and reduced emotional experience (reduced interest, hedonic response, and motivation), and determine some elements of disability aside from cognition and skills. Yet despite cognition, skills, and negative symptoms consistently correlating to functional outcomes, studies of the determinants of everyday functional deficits in schizophrenia have stalled at accounting for 50% or less of the variance in real-world functioning (Bowie et al., 2006, 2008, 2010; Harvey et al., 2011).

On the surface, these findings seem disheartening, but promising new leads in the search for transdiagnostic determinants of real-world functional outcome have emerged, including obesity and related health issues, comorbid depression, and impairments in the self-assessment of ability. Further, we have begun to understand with more granularity the predictive components within risk factors domains and how these subdomains diverge for the prediction of different domains of real-world outcomes. For example, social cognition predicts social outcomes but not living independently while neurocognition provides a minimal prediction of social outcomes (Depp et al., 2012; Fett et al., 2011). Improving life outcomes for individuals with schizophrenia hinges on deepening our understanding of the determinants of real-world disability. In this article, we will examine the manifestations of functional disability and delve into the influences various predictive factors have on long-term outcomes. A critical set of findings, associated with greater adoption of longer-acting treatments for psychosis, which reduce relapse and promote general clinical stability, also suggests that there may be a more substantial longitudinal association between control of psychosis and functional outcomes than suggested by cross-sectional or short-term studies focused on oral antipsychotic medications.

**Overview of deficits in everyday functioning**

Achievement of milestones, such as marriage or an equivalent partnership, educational attainment, competitive employment, and independent living, is one way to assess disability. People with schizophrenia typically underperform compared to expectations based on the achievements of family members and
their own functioning before their diagnosis (Wilk et al., 2005). Many individuals with schizophrenia meet certain milestones such as having a history of a stable relationship, employment, or living independently, but only a dismal 6% of patients appear to have concurrent attainment of multiple functional milestones across social, vocational, and residential domains (Harvey et al., 2012).

Failure to meet milestones in social relationships, employment, and independent living produce cyclical disability and poverty. A discussion of the manifestations of impairment across social, work, residential, and physical health will help depict the complex nature of disability and the barriers to functional recovery. Impairments in everyday functional outcomes are present early in the course of the illness (Reichenberg et al., 2009) and can be detectable at the time of the diagnosis (Caspi et al., 2003). Functional deficits remain present throughout the disease course, even when psychosis symptoms are temporarily controlled (Keefe et al., 2006), and the majority of people with schizophrenia receive at least some disability compensation indefinitely (Harvey et al., 2012; Rosenheck et al., 2006).

Social functioning
Deficits in social functioning are pervasive among individuals with schizophrenia. There are elements of both reduced social motivation and reduced social competence, both of which have the potential to influence social outcomes. Patients often live socially isolated lives and display behaviors incompatible with interpersonal interaction. They have evidence of both active and passive avoidance of social contact. This may relate to limitations in identifying or articulating their own emotions, expressing their needs, and manifest appropriate interpersonal behavior, as evidenced by making inappropriate remarks (Harvey, Velligan, & Bellack, 2007; Patterson, Moscona, McKibbin, Davidson, & Jeste, 2001). Some individuals with schizophrenia may also manifest social impairment by acting disruptively, making intrusive requests, misjudging personal space, and manifesting dysregulation in speech volume or tone (Wykes & Stuart, 1986). Overall, patients with schizophrenia have smaller social networks than the general population (Horan, Subotnik, Snyder, & Nuechterlein, 2006; Patterson, Semple, & Shaw, 1997). The majority of individuals with schizophrenia form few long-term, stable relationships. A large study (n = 1,400) found that only 12% of patients were married. Almost two thirds of the small minority with a spouse or child are challenged in the ability to fulfill essential familial responsibilities (Rosenheck et al., 2006).

Independent living
In the U.S., approximately 25–40% of people with schizophrenia live without supervision and were financially responsible for their bills (Harvey et al., 2012; Leung et al., 2008). The rate of independent living among people with schizophrenia differs drastically by country, due to the varying degrees of social supports available. For example, three times more people with schizophrenia live independently in Sweden than in the U.S. despite similar levels of objectively measured functional skill (Harvey et al., 2009). In the Swedish sample, the rate of governmental social support for independent residence was essentially 100%. Disability benefits still play a critical role in independent living in the U.S. despite less structured governmental, residential supports than in Sweden. Over 75% of the independently residing patients in the U.S. received disability compensation (Harvey et al., 2009), but the overall rate of social support was considerably less in the U.S. Similarly, a study of people with schizophrenia 2 years after their first episode found that the only patients who lived independently were receiving disability benefits or supported by their families (Ho, Nopoulous, Flaum, Arndt, & Andreasen, 1998).

Individuals with schizophrenia also struggle with higher-level functional skills. Examples of advanced self-care include a person actively participating in their medical care, managing their medications, or utilizing transportation successfully. Patients often fail to access routine health care, regardless of insurance status. A study of veterans found that distance to a medical facility substantially decreased utilization of preventative care services for veterans with psychosis while veterans without severe mental illness overcame the barrier distance created by scheduling multiple appointments on the same day (McCarthy, Piette, Fortney, Valenstein, & Blow, 2006). Only 50% of people with schizophrenia had a valid driver’s license, and approximately 40% reported that they currently were drivers. Comparatively, only 4% of the healthy controls in this study, based in California, reported not having driver’s licenses (Palmer et al., 2002).
Vocational outcomes

Chronic unemployment produces repercussions across many domains. Unemployed individuals, especially with limited or no disability benefits, often cannot afford to live independently. Residential and financial instability, in turn, may make accessing care and medications more difficult, promoting symptom relapse and cyclical hospitalizations for acute stabilization. Very few individuals with schizophrenia can financially support themselves. Before the first episode of psychosis, upwards of 80% of patients report they participated in part-time or full-time premorbid employment or education (Harvey et al., 2012). Rates of competitive employment plummet to 10–20% after a diagnosis of schizophrenia (Harvey et al., 2012; Rosenheck et al., 2006). Supportive employment programs, which help individuals find and maintain employment, are useful in marginally increasing vocational stability. Employment rates rise to a median of 60% for people involved in programs with higher levels of support (Bond, 2004). However, elevated rates of employment are contingent on continuous services. The majority of individuals fail to maintain employment upon cessation or closure of services (Bell, Bryson, Greig, Fiszdon, & Wexler, 2005).

Overlapping functional deficits, milestone impairments, and disincentive structures make competitive employment a challenge for individuals with schizophrenia. People with schizophrenia often struggle to navigate the array of interim steps required to achieve vocational milestones. For example, obtaining a job may require a person to complete an application, prepare a resume, seek a job, and go on interviews. Once a person has a job, they must successfully navigate transportation to and from work, fulfill job requirements, and communicate effectively.

Poor educational outcomes and disability benefits play a role in the chronic unemployment associated with schizophrenia. People with schizophrenia receive less education than would be expected based on their demographic factors, which further impedes their chance to secure a job (Rosenheck et al., 2006; Sharma & Antonova, 2003). Additionally, disability benefits may disincentivize employment. People with schizophrenia who receive disability payments are less likely to be competitively employed than were those who do not receive these payments (Rosenheck et al., 2006). Social security provides reliable, albeit minimal, financial support. Benefits often additionally link individuals with health-care coverage. Thus, seeking employment in the absence of health insurance might reduce or eliminate a patient’s medical support. Moreover, although theoretically, people with severe mental illness should be covered on the basis of the presumptive disability, seeking such coverage requires proactive actions that many people with schizophrenia find challenging, leading to high rates of under- and uninsured.

Physical health and longevity deficits

Health deficit exacerbates the vicious cycle of disability and has been shown to directly impair everyday outcomes (Strassnig & Harvey, 2013; Strassnig, Newcomer, & Harvey, 2012; Strassnig, Signorile, Gonzalez, & Harvey, 2014; Strassnig et al., 2015a, 2017, 2018; Vankampfort et al., 2012). Poor physical health and associated comorbid chronic conditions primarily lead to the disease’s life-shortening course (Auquier et al., 2006). The ineffectiveness of antipsychotic medication at targeting negative symptoms means that current pharmacologic treatment does little to attenuate deficits associated with reduced levels of social, vocational, and physical motivation. Sedentary behavior and lack of physical activity interact with the metabolic side effects of antipsychotic medication to further worsen an individual’s health, with functional implications.

Patients’ avolition, apathy, and maladaptive lifestyles coupled with the adipogenic medication lead to higher rates of obesity and comorbidities including diabetes, hypertension, and cardiovascular disease in individuals with schizophrenia than general populations (Allison et al., 2009; Hennekens et al., 2005). Compared to the general population, people with schizophrenia smoke more, exercise less, and eat more poorly (Megna et al., 2011). We recently conducted a study that sought to evaluate how people with schizophrenia spend their days compared to healthy controls. Nearly 200 participants reported their daily activities via text messages on provided electronic devices. Initial findings showed that 88% of the time patients with schizophrenia were not engaged in any activity that involved more than sitting. The most frequent activities were eating, watching TV, and just sitting. Comparatively, healthy controls were three times more active. Healthy controls were engaged in activities that involved standing or moving 60% of the time (Strassnig et al., 2019).
Poor physical fitness makes completing activities of daily living more challenging and has a direct impact on functional outcomes (Strassnig & Harvey, 2013; Strassnig et al., 2012, 2014, 2015a, 2017, 2018; Vankampfort et al., 2012). A person must have the physical capacity to stand, walk, and lift light objects without substantial shortness of breath. Without this minimum level of physical capacity, a person cannot complete basic self-care tasks such as cleaning, bathing, and cooking as well as more advanced self-care tasks such as walking to a bus stop or standing in line to pick up prescriptions. In addition to the high prevalence of chronic conditions, poor lifestyle and medication side effects weaken the physiological capacity in people with schizophrenia. Individuals with schizophrenia have been found to have decreased rates of oxygen consumption (VO\textsubscript{2Max}) (Strassnig, Brar, & Ganguli, 2011; Strassnig et al., 2014).

Reduced physical capacity has direct repercussions on real-world outcomes. Recent studies found that increased waist circumference and reduced performance on repeated standing from a chair were associated with decreased success in obtaining gainful employment. Importantly, these simple measures of physical limitations significantly correlated to employment and independence in living (Strassnig et al., 2017, 2018). Exercise regimens strikingly have shown an association with enhanced cognitive performance, particularly in memory and processing speed, a decrease in composite positive and negative symptoms, improved mood, and better physical capacity (Malchow et al., 2015; Strassnig & Harvey, 2013; Strassnig et al., 2012, 2015b). Fortunately, interventions aimed at physical fitness may have the potential to improve both functional outcomes and other significant risk factors for debility such as cognition and symptomatology (Strassnig & Harvey, 2013; Strassnig et al., 2012, 2015b).

**Most consistent predictors of functional outcomes**

Identifying the predictors of everyday outcomes is essential to developing treatments that break through the current treatment ceiling of symptom remission to reach functional recovery. Pervasive yet heterogeneous deficits span across social, residential, vocational, and health-related milestones. Domains of functional deficits appear to be mostly independent (Harvey et al., 2012). For example, a previously unemployed patient in a supportive employment program might show no improvement in his ability to live independently despite a steady job. Further, the independence of functional domains appears to grow with the course of the illness making functional recovery more challenging.

Distinct functional domains also appear to have divergent predictors. A growing body of research has shown that constitutive subdomains of the most consistently significant factors of functional status (cognition, functional skills, and negative symptoms) predict different domains of real-world outcomes in people with schizophrenia. Independence between the severity of positive symptoms and risk factors for debility, such as cognitive deficits, further complicate the already complex phenomenon that underlies impaired functional outcomes. In the following sections, we will delve into the predictors of functional outcome. We will focus on the most consistent predictors (cognition, skills, and negative symptoms) and discuss the influence of antipsychotic medication, clinical stability, self-assessment, and health on functional recovery.

**Cognition**

Substantially, 70–75% of individuals with schizophrenia perform below general population standards on neurocognitive tasks including processing speed, attention, learning and memory, and problem-solving and working memory (Kremen, Seidman, Faraone, Toomey, & Tsuang, 2000; Mojtabai et al., 2000; Reichenberg et al., 2009; Wilk et al., 2005). The prevalence of cognitive impairments is consistent throughout the disease, detectable at the time of the first episode (Mojtabai et al., 2000; Reichenberg et al., 2009; Saykin et al., 1994) and generally independent of symptom remission (Heaton et al., 2001). Cognitive deficits among individuals are evident even when IQ scores are matched with healthy controls (Wilk et al., 2005). Detection of cognitive deficit can occur before the onset of psychotic symptoms (Casi et al., 2003). Cognitive metrics including IQ scores, reading level, and achievement of other academic milestones are lower in premorbid patients with schizophrenia than healthy individuals (Palmer et al., 1997; Woodberry, Giuliano, & Seidman, 2008). Neurocognitive ability declines with age and might be associated with functional decline and exaggerated aging hypothesized to occur among subsets of individuals with schizophrenia (Harvey et al., 2013). Cognitive limitations are pervasive among...
individuals with schizophrenia and correlate with debility from premorbid to chronic schizophrenia.

Cognition has reemerged as a central feature of schizophrenia, particularly in terms of the role cognitive limitations have in the development and maintenance of deficits in everyday living. Performance on tests of cognition and of the ability to perform everyday functional skills appear to be more relevant to impairments in functioning than the severity of psychosis in most studies (Bowie et al., 2006, 2008, 2010; Fett et al., 2011; Green et al., 2000; Harvey et al., 2011; Tabares-Seisdedos et al., 2008). Two large meta-analyses found impairments in cognition to be the most consistent determinant of functional outcomes (Green et al., 2000). Global neurocognition appears more strongly related to disability than cognitive subdomains in that individual domains (e.g., learning, attention, executive functioning) have small to moderate correlations with global functional outcome in schizophrenia while composite scores manifest a moderate to large correlation with disability. Indices of global neurocognitive ability can be developed with small subsets of tests that account for upwards of half the variance in overall performance (Keefe et al., 2006). The reason for this is merely the more cognitive domains that a specific measure predicts, the more globally sensitive it is to functional outcome. The classic example is that of various coding tests. These tests require intact functioning in several domains in order to be performed efficiently, including visual perception, problem-solving, working memory, and speed (Knowles et al., 2015). The vast majority of individuals with schizophrenia exhibit persistent global neurocognitive deficits, independent of life stage or change in symptoms, which strongly correlates to chronic disability.

Social cognition has more recently been identified as a candidate domain to understand functional outcomes in healthy and impaired populations. An individual’s ability to identify and interpret other’s emotions or intentions, and to use these social signals to guide informed conclusions or behaviors fall under the broad category of social cognition. The majority of individuals with schizophrenia display impairments in multiple social cognitive domains (Savla, Vella, Armstrong, Penn, & Twamley, 2013). Similar to neurocognition, social cognitive deficits can be detected before disease onset and persist during periods without active psychosis (Fett et al., 2011). The social cognitive domain Theory of Mind, describing the ability to understand the mental states of others and oneself, has been most strongly correlated to real-world outcomes (Fett et al., 2011). A recent study found that global functional deficits had a linear relationship to whether a person with schizophrenia had unimpaired, impaired, or very impaired performance on Theory of Mind indices (Rocca et al., 2016). More broadly, global social cognition has been shown to explain a small to moderate amount of the variance in functional outcomes (Pinkham, Penn, Green, & Harvey, 2016; Schmidt, Mueller, & Roder, 2011).

Evidence suggests a divergence of neurocognition and social cognition for the prediction of different domains of real-world outcomes, such that social cognition predicts social outcomes but not living independently, and neurocognition provides a minimal prediction of interpersonal relationships (Depp et al., 2012; Fett et al., 2011). A study by Pinkham, Penn, Green, and Harvey (2016) found that combined neurocognition and social cognition accounted for 13% of the variance in global functional outcomes as rated by high-quality informants. When the outcomes domains were differentiated, neurocognition accounted for only 5% of the variance in social outcomes (Pinkham et al., 2016). The differing predictive value of neurocognition and social cognition has led to an exploration of potential mediators, associated factors, and cognitive subdomains that interact with cognition to influence everyday outcomes across the three main domains of functioning.

**Introspective accuracy**

There has been a recognition that the ability to evaluate one’s own cognition, referred to often as “metacognition,” is an important cognitive ability on its own. Over- and underestimation of one’s ability are both manifestations of impaired metacognitive functioning. A newly defined component of the larger metacognition construct addresses how well individuals evaluate their own abilities and performance (Koren, Seidman, Goldsmith, & Harvey, 2006), and we refer to this type of self-awareness as “introspective accuracy” (IA). Self-reports lie at the crux of the clinically assessing IA. Impairments in IA can be easily defined by discrepancies between how one evaluates abilities and achievements, and his/her objective performance or a high-contact informant’s rating of his/her ability. Poor performers could be helped to attempt to match their aspirations to accomplishments and improve over time. Good performers could have their functioning bolstered by recognizing
their competence. Thus, even a population whose performance often is poor could benefit from accurate self-assessment or experience additional challenges from inaccurate self-evaluation (Gould et al., 2015).

Importantly, a growing body of research has found that IA deficits across various domains have negative consequences on morbidity and mortality as these impairments impact medication adherence, suicidality, everyday activities, vocational functioning, and social outcomes (Green et al., 2011; Holshausen, Bowie, Mausbach, Patterson, & Harvey, 2014; McKibbin, Patterson, & Jeste, 2004; Patterson et al., 1997). One study asked 214 individuals with schizophrenia to self-evaluate their cognitive ability on a validated rating scale. Concurrently, high-contact clinicians rated the patient’s cognitive abilities on the same rating scale. Participants with schizophrenia took performance-based tests to assess their cognitive abilities and everyday functional skills. The findings were striking. Global impairments in IA of overall cognitive functioning and everyday functioning were more strongly correlated than objective ability indexed by performance-based cognitive and functional skills indices (Gould, Sabbag, Duran, Patterson, & Harvey, 2013).

Further, IA of neuro- and social cognition appear to predict everyday functional outcomes differentially. IA of neurocognition preferentially predicts nonsocial everyday functional outcomes while IA of social cognition predicts real-world social outcomes. Information obtained regarding IA of performance can be clinically helpful, regardless of whether performance is objectively good or bad (Silberstein & Harvey, 2019). IA can extend to how self-aware a person is of their functional disability. Patient judgments regarding their own level of everyday functioning have been shown to have almost no correlational relationship with either performance-based assessments or high contact clinician reports (Sabbag et al., 2011, 2012) nor did these judgments relate to objective data regarding attaining functional milestones such as employment or residential status (Harvey et al., 2012). Such results are consistent with findings of multiple meta-analyses reporting a lack of correlation between objective and subjective ratings of functioning and quality of life, with these results suggesting wide-ranging impairments (Tolman & Kurtz, 2012). A recent study found that a patient who misestimates their overall impairments is less likely to be employed than a patient who more accurately assesses their disability. Conversely, independent living status has no association with how well a person with schizophrenia assesses the severity of their disability (Strassnig et al., 2018).

**Social competence and functional capacity**

Impairment of skills or abilities may lead to an adverse impact on interpersonal relationships, employment, and residential stability (Evans et al., 2004; Patterson et al., 2001). The ability to perform the skills required for activities of daily living or social communications is referred to as functional capacity (nonsocial skills) or social competence (social skills) (Green et al., 2011; McKibbin et al., 2004). Social competence includes the ability to greet another person or call a landlord to inquire about rent. Writing a check, cooking, or utilizing public transportation are examples of functional capacity. Individuals with schizophrenia perform functional skills (i.e., skills required for social, vocational, and independent living functioning) at lower levels than the general populations (Patterson et al., 2001). Functional skills appear similarly across populations despite cultural differences and proportionally lower across premorbid functionality (Harvey et al., 2009).

College-educated individuals with a diagnosis of schizophrenia have been found to perform functional skills at a similar proficiency to healthy people who completed only middle school (McIntosh et al., 2011). These measures also have excellent measurement characteristics (Leifker, Bowie, & Harvey, 2009).

Recent findings suggest that functional capacity (nonsocial skill) and social competence (social skill) do not align with the divergent pattern of prediction for functional outcomes as shown by neuro- and social cognition. Evidence suggests that functional capacity and social competence are most strongly associated with the same domain of real-world deficits: vocational outcomes. A person must have the skills to communicate effectively (i.e., social competence) and perform vocational tasks adequately (i.e., functional capacity) to be a success in the workplace. Surprisingly, social competence has shown less consistent and weaker associations to independent living and social functioning (Pinkham et al., 2014; Silberstein, Pinkham, Penn, & Harvey, 2018), while independent living is consistently predicted by functional capacity indices in targeted studies (Bowie et al., 2010). Overall, the delineation between nonsocial and social capacity and outcome may not be as
demarcated as the divergent pattern of prediction shown by neuro- and social cognition. These results translate into the clinical care of individuals with schizophrenia. Importantly, clinicians can utilize both functional capacity and social competence to predict work outcomes.

The ease of objective measurement of functional capacity has made it widely employed in evaluating individuals with severe mental illness. A clinician can assess whether a patient can pay a bill, count correct change, make a phone call, or brush their teeth through controlled simulations (Mausbach et al., 2008), including computerized assessments of technology-based functional skills (Czaja et al., 2017; Keefe et al., 2016). The simplicity of assessment allows clinicians to utilize competence as a reliable clinical endpoint. However, capacity is not a proxy for functional outcomes. Demonstration of paying a bill in a role-play does not predict that a person would have the motivation and ability to locate the correct bill, pay by the due date, acquire necessary materials such as stamps, or place the check in a mailbox in the real world. As such, performance on functional capacity/social competence measures has consistently not fully accounted for high-contact informant reports of functional outcomes and measurable achievement of functional milestones (Bowie, McGurk, Mausbach, Patterson, & Harvey, 2012; Gupta, Holshausen, Mausbach, Patterson, & Bowie, 2012). The ability to demonstrate skills in a controlled environment differs from performing the same task in real-world settings. Hence, assessment of functional capacity and social competence remains essential. As noted below, negative symptoms are a powerful intervening factor for prediction of the failure to engage in skills in the repertoire.

Functional capacity and social competence are highly and consistently related to both cognitive ability and real-world functioning. As such, these skills have been proposed to be an important mediator of the influence of cognitive functioning on real-world functioning (Bowie et al., 2006, 2008; McClure et al., 2007). Neurocognition preferentially predicts functional capacity, but social cognition does not always preferentially predict social competence. A recent study found that neurocognition accounted for 31% of the variability in functional capacity and only 15% of the variance in social competence. Interestingly, in that study, social cognition failed to account for unique variance in social competence (Pinkham et al., 2016). These findings were extended when jointly assessing neurocognition and social cognition. Global cognition more strongly predicted functional capacity (adjusted $R^2 = .37$, $p < .001$) than social competence (adjusted $R^2 = .19$, $p = .032$). Neurocognitive ability can inform clinicians of a patient’s functional capacity and nonsocial outcomes; however, social cognition cannot provide insight into an individual’s social competence despite significantly correlating to social outcomes.

### Negative symptoms

Negative symptoms alone can hypothetically explain the independence of cognition and social competence. Negative symptoms encompass reduced social drive and motivation, blunted affect, and anhedonia. A particular part of negative symptoms, social amotivation, plays a key role in social outcomes. Reduced social motivation is a classic feature of schizophrenia. Social amotivation can present in a patient through lack of interest or active avoidance of interpersonal interactions across social, public, and work settings. Upwards of 40% of individuals with schizophrenia display reduced social motivation (Kirkpatrick, Buchanan, Ross, & Carpenter, 2001). Decreased motivation stems from errors embedded in the brain’s behavior and reward pathways rather than deliberate choice (Tamminga, Buchanan, & Gold, 1998). Social amotivation, either associated with the reduced experience of positive reinforcement from interactions or impairments in the ability to recall that pleasure probably factor into anhedonia, which is another pervasive negative symptom in schizophrenia (Gard, Kring, Buchanan, Ross, & Carpenter, 2001). Decreased motivation stems from errors embedded in the brain’s behavior and reward pathways rather than deliberate choice (Tamminga, Buchanan, & Gold, 1998). Social amotivation, either associated with the reduced experience of positive reinforcement from interactions or impairments in the ability to recall that pleasure probably factor into anhedonia, which is another pervasive negative symptom in schizophrenia (Gard, Kring, Buchanan, Ross, & Carpenter, 2001). Decreased motivation stems from errors embedded in the brain’s behavior and reward pathways rather than deliberate choice (Tamminga, Buchanan, & Gold, 1998). Social amotivation, either associated with the reduced experience of positive reinforcement from interactions or impairments in the ability to recall that pleasure probably factor into anhedonia, which is another pervasive negative symptom in schizophrenia (Gard, Kring, Buchanan, Ross, & Carpenter, 2001). Decreased motivation stems from errors embedded in the brain’s behavior and reward pathways rather than deliberate choice (Tamminga, Buchanan, & Gold, 1998). Social amotivation, either associated with the reduced experience of positive reinforcement from interactions or impairments in the ability to recall that pleasure probably factor into anhedonia, which is another pervasive negative symptom in schizophrenia (Gard, Kring, Buchanan, Ross, & Carpenter, 2001).
worse functional outcomes (Ventura et al., 2015). Negative symptomatology early in the illness has significant functional implications. The severity of negative symptom 1 year after the first episode of psychosis was associated with multiple elements of impaired everyday functioning 7 years later. Persistent negative symptoms present early in schizophrenia probably correlate with long-term debility, including real-world deficits that were not apparent early in the disease course.

Negative symptoms have consistently been shown to be a significant contributor to disability and a stronger cross-sectional risk factor than positive symptoms (Rabinowitz et al., 2012). Some evidence suggests that negative symptoms more strongly predict impairments in social functioning than independent living or employment (Kalin et al., 2015; Strassnig et al., 2015a). However, chronic negative symptoms probably have a longitudinal impact on domains of everyday outcome beyond interpersonal relationships. Amotivation, anhedonia, and reduced reward sensitivity likely limits a patient’s desire to seek and maintain employment. The cumulation of social and financial withdrawal probably contributes to later homelessness (Ventura et al., 2015).

Recent research has suggested that negative symptoms can be considered in terms of two subdomains: diminished expression (i.e., blunted affect) and reduced experience (i.e., avolition and anhedonia) (Blanchard & Cohen, 2006; Foussias & Remington, 2010; Jang et al., 2016; Kring, Gur, Blanchard, Horan, & Reise, 2013). Lack of motivation (experience deficit) can lead to deficits in everyday functioning regardless of other elements of ability. Further, individuals with schizophrenia often exhibit dysfunctional attitudes. Defeatist thoughts substantially contribute to amotivation (Beck, Himelstein, Bredemeier, Silverstein, & Grant, 2018). It is entirely possible to possess the social cognition and social competence required to engage socially but lacked the motivation or attitude to initiate interpersonal relationships because of misestimation of the likely outcomes of the social interactions. Likewise, a person with a defeatist attitude may lack motivation to perform at their neurocognitive potential (Beck et al., 2018). As such, defeatist attitudes have been shown to not only explain variance in negative symptoms (i.e., motivation) but also in neurocognition and functional outcome (Beck et al., 2018). Recent evidence suggests that the negative symptoms of reduced emotional experience (i.e., avolition-asociality) have a more potent impact on social outcomes than a reduced expression of emotions (Harvey, Khan, & Keefe, 2017).

The findings further align with evidence that negative symptoms have a minimal association with nonsocial outcomes in individuals with chronic schizophrenia. In a recent study, reduced emotional experience accounted for 19% of the variance in social outcomes, but only accounted for 1% of the variance in nonsocial outcomes (Harvey et al., 2017). This research also suggested that deficits in emotional experience predicted social impairments better than the total negative symptoms scores on the Positive and Negative Syndrome Scale (Kay, Fiszbein, & Opler, 1987) and that deficits in emotional expression accounted for virtually no variance in either social or nonsocial outcomes.

Clinically, these findings emphasize the importance of gauging a patient’s motivation to engage in potentially reinforcing activities, social and otherwise, when attempting to understand functional outcomes. It is entirely possible that a person with blunted affect who is motivated to maintain relationships will have less everyday social impairment than a person who lacks the motivation to engage in social outcomes but can laugh and smile.

Revisiting clinical stability as a predictor of long-term functional outcomes

In order to evaluate the predictors of functional outcomes, recent data suggest that it is important to consider clinical outcomes on a longitudinal basis. Levels of clinical outcomes can be defined in terms of clinical response, stability, remission, and recovery. Recent evidence suggests that promotion of clinical stability alone can predicate remission and possible recovery. Clinical stability refers to maintenance at a decreased level of symptomatology, not necessarily full symptomatic remission (Andreasen et al., 2005). Approximately 40% of individuals with schizophrenia reach clinical remission, meaning they experience at least 6 months of no more than mild psychotic symptoms (De Hert et al., 2007; Kahn et al., 2015). The stability of clinical remission is tenuous, and nearly 60% of patients will relapse in their lifetime (Kahn et al., 2015). Most people with schizophrenia experience periods when they are either entirely or partially nonadherent with their medication regimen (Fenton, Blyer, & Heinssen, 1997) and
this is a substantial predictor of relapse. Antipsychotic medications have been shown to reduce the risk of relapse by 60–65% compared to placebo (Kahn et al., 2015; Leucht et al., 2012). Relapse in nonadherent patients occurs at a rate of slightly more than 10% per month (Robinson et al., 1999). Rates of medication nonadherence do not differ significantly from other chronic conditions (Christensen et al., 2010). However, clinically visible symptomatology often presents more quickly in schizophrenia than in chronic diseases like hypertension (Christensen et al., 2010). Analyses of the causes of nonadherence in schizophrenia have suggested that illness-related causes including a limited clinical response to treatment, cognitive impairments, and unawareness of illness account for the majority of nonadherence (Velligan et al., 2009).

The route of antipsychotic medication also influences long-term clinical and behavioral stability. Some antipsychotics come in long-acting injectable (LAI) versions which reduce daily oral pills to a shot lasting several weeks. The majority of long-acting therapeutic options are delivered in the office and allow clinicians to know with certainty that a patient is compliant. LAIs also remove several barriers to drug adherence for patients. Such barriers include the ability to take medication as prescribed, motivation for daily compliance, and difficulty navigating the pharmacy prescription process.

LAI s have consistently been shown to reduce rates of relapse and hospitalization across populations and throughout the disease (Alphs et al., 2015; Kishimoto, Agarwal, et al., 2013; Olivares, Rodriguez-Martinez, Buron, Alonso-Escolano, & Rodriguez-Morales, 2008; Olivares et al., 2009; Tiihonen et al., 2011). LAIs provide an avenue to prevent frequent cycles of relapse and decline among first-episode psychosis patients. A study of 2,588 first-episode psychosis patients in Finland found that LAI antipsychotic drugs reduced relapse rates by 64% (Tiihonen et al., 2011). The reduction of relapse among patients recently diagnosed with schizophrenia is particularly significant because upwards of 70% of first-episode psychosis patients discontinue oral medication within months of initiation and relapses are frequent in the first year of the illness (Emsely et al., 2012; Tiihonen et al., 2011).

Reduced hospitalizations and relapse rates occur in patients with chronic schizophrenia who were switched from oral antipsychotics to LAIs. The Electronic Schizophrenia Treatment Adherence Registry (e-STAR), a prospective, observational study of 1,345 patients, demonstrated the effectiveness of LAIs among patients with more chronic disease. One year after switching from oral to LAI antipsychotics, fewer patients on LAI compared to oral medication required hospitalization (89.1% vs. 67.0%) or experienced symptom relapse (14.6% vs. 52.2%) (Olivares et al., 2008). After 2 years, patients on LAIs were significantly more likely than patients on oral medication to be treatment adherent (81.8% vs. 63.4%, p < .0001) and to have improved symptomatology (p = .0165) (Olivares et al., 2009). A meta-analysis of 25 mirror studies, which compares outcomes of patients on oral antipsychotics against the outcome of the same patients on LAIs, found that injectables significantly reduced the risk of hospitalization, the number of hospitalizations, and decreased the length of stay (Kishimoto, Nitta, Bornstein, Kane, & Correll, 2013).

Importantly, the impact of LAIs appears to extend to functional outcomes. Research has consistently shown associations between LAIs and improved global, real-world outcomes (Lambert, De Marinis, Pfeil, Naber, & Schreiner, 2010; Llorca, Bouhours, Moreau-Mallet, & French investigators, 2008; Lloyd, Latif, Simpson, & Shrestha, 2010; Marinis et al., 2007; Peuskens et al., 2010; Schreiner et al., 2014). The global functioning of patients in the e-STAR study receiving LAIs improved significantly from patients’ baseline on oral antipsychotics (p < .001). Additionally, the average rating on the Global Assessment of Functioning was significantly higher for those who adhered to LAIs for the 24-month trial than those who discontinued use (67.2 vs. 55.4) (Peuskens et al., 2010). Many of the same studies that showed improved Global Assessment of Functioning ratings in patients on LAIs versus oral medications also showed an association between LAIs and improved quality of life ratings, reduced symptomatology, and higher treatment satisfaction (Llorca et al., 2008; Lloyd et al., 2010; Marinis et al., 2007; Schreiner et al., 2014). About 1 in 5 patients in a sample of 529 European patients who switched to LAI from oral antipsychotics experienced combined improvement in symptomatology, functional outcome, and quality-of-life measures (Lambert et al., 2010). Evidence suggests that first-episode psychosis, acutely ill, and stable patients with schizophrenia all globally benefit from LAI antipsychotic treatment.

Beyond global measures of quality of life and everyday functioning, LAIs have been associated with
improved social and vocational functioning. A randomized trial examined the difference in real-world outcomes after 24 months of treating clinically stable patients with either risperidone LAI \((n = 329)\) or oral quetiapine \((n = 337)\), a second-generation antipsychotic. Participants receiving LAIs showed significantly increased social/occupational functioning and quality of life than participants taking oral antipsychotics (Rouillon et al., 2013). A similar pattern of improvement has been suggested among acutely ill individuals. A randomized, double-blind, placebo-controlled trial of 404 inpatients with schizophrenia showed LAI compared to placebo significantly improved ratings of social functioning, vocational functioning, and motivation in only 8 weeks (Witte, Case, Schuh, & Ascher-Svanum, 2012). Better social functioning could be detected by 3 months after 532 individuals with schizophrenia switched to LAIs from oral medications and persisted at the 24-month endpoint (Macfadden et al., 2011).

LAI s have also correlated with improved self-care. A study of 924 veterans with chronic schizophrenia found that switching to LAIs increased health-care utilization. The number of attended outpatient visits increased from 24.6 to 39.1 \((p < .001)\) after initiation of LAIs (Ren et al., 2011).

The Paliperidone Palmitate Research in Demonstrating Effectiveness (PRIDE) evaluated the effects of the once-monthly injectable, paliperidone, compared to daily oral antipsychotic in patients at high risk for nonadherence. The 444 participants had a history of schizophrenia and recent incarceration or arrest. Half of the patients that encounter the criminal justice system require multiple psychiatric hospitalizations and nearly three quarters experience recidivism. (Alphs et al., 2015; Harris & Koepsell, 1996; Kunz et al., 2004). Rates of recidivism or hospitalization were significantly lower in the participants who received the LAI medication, paliperidone palmitate, than the oral antipsychotic. One third of individuals on monthly injections were reinstitutionalized during the 15-month study compared to 45% of individuals on daily oral medications. (Alphs et al., 2015). The median time of arrest/incarceration or hospitalization was 190 days later among patients taking LAI than those taking oral antipsychotics \((446 \text{ vs. } 216)\). The PRIDE study aimed to reflect real-world management by enrolling patients with high rates of nonadherence; thus, the results suggest that LAIs can improve relapse rate and behavioral stability among most people with schizophrenia.

Despite the multitude of positives, there are some drawbacks to using LAIs that merit consideration. Injections need to be skillfully administered, LAIs have the potential to accumulate over time unless properly monitored, there is less dosing flexibility as usually only a few different doses are available (especially for the second-generation LAIs), and LAIs can be costly which can become relevant in low-reimbursement settings and limit accessibility (Seeman, 2017).

Overall, evidence strongly indicates that LAIs improve relapse rates, quality of life, global/social/vocational functioning, and behavioral stability in patients with schizophrenia.

**Treatment resistance and outcome**

A substantial minority of patients develop an inadequate response to antipsychotic medications despite adherence, referred to as treatment-resistant schizophrenia. Upwards of 75–90% of patients in their first-episode psychosis show a positive response to antipsychotic medications (Anderson et al., 2005; Cassidy et al., 2010; Levine et al., 2011; Lieberman et al., 1993; Robinson et al., 1999; Tohen et al., 2000). However, the robust remission of positive symptoms in first-episode patients wanes with successive medication discontinuations and subsequent relapses. Approximately 30% of people with schizophrenia manifest a minimal response to conventional and atypical antipsychotic medications (Kane, Honigfeld, Singer, & Meltzer, 1988; Levine et al., 2011; Lieberman et al., 1996). The increased rate of treatment resistance seen in the chronic course of the disease may have some relationship to nonadherence. After each relapse, a proportion of patients fail to respond to the same or different antipsychotic medication than they did previously (Emsley, Chiliza, & Asmal, 2013; Emsley, Nuamah, Hough, & Gopal, 2012; Kahn et al., 2015).

Finally, the degree of clinical response to medications even at illness onset appears related to their premorbid level of functioning. A study of 467 drug-naïve individuals with schizophrenia found that those who were married, in long-term relationships, employed, or lived independently had a faster response to medication than patients with poorer premorbid social functioning. For instance, current employment increased the probability of rapidly responding to the antipsychotic medication by 150% (Nordon et al., 2014). Better premorbid social functioning appears to be predictive of better response
throughout the disease including the treatment response, lower relapse rates, and improved long-term outcomes (Levine & Rabinowitz, 2010; Levine, Rabinowitz, Case, & Ascher-Svanum, 2010; Santesteban-Echarri et al., 2017).

Although substantial failure to respond to antipsychotic medications is commonly associated with significant disability, data on wide-ranging disability reduction with clozapine treatment are not as clear as could be hoped. Randomized trials have suggested that clozapine reduced inpatient costs markedly and total costs minimally (Rosenheck et al., 1998, 1999), but that patients treated with haloperidol and clozapine did not differ in scores on clinical ratings of disability Heinrichs-Carpenter Quality of Life Scale (QLS) or in community role functioning (p = .06), family relationships (p = .23), social relationships (p = .30), and daily activities (p = .20). A recent small cross-sectional study found that clozapine responders manifested better cognitive performance and functional capacity than nonresponders (Nucifora et al., 2019). Many studies of clozapine did not examine disability as much as they focused on reduced hospitalization and reduced violence. Even the large-scale Clinical Antipsychotic Trials Of Intervention Effectiveness (CATIE) clozapine study reported on symptoms and did not report on disability, even though clozapine was effective at symptom reduction in previously refractory patients (McEvoy et al., 2006).

Conclusion

Patients with schizophrenia struggle to maintain social relationships, sustain employment, and live independently. Functional deficits persist throughout the chronic course of schizophrenia. Achievement of initial emission from positive psychotic symptoms does little to impact real-world functioning and very few individuals with schizophrenia reach functional recovery early in their illness. Research has shown that functional outcomes are most consistently predicated by neurocognition, social cognition, and negative symptoms. IA, functional skills, health impairments, duration of untreated first-episode psychosis, premorbid functioning, and behavioral instability contribute to poor community functioning. Table 1 outlines the most influential and promising predictive factors for the three major domains of real-world outcomes: social, vocational, and residential functioning.

The pervasiveness of disability and the complex factors leading to these deficits should not make functional recovery seem like an impossible feat. As a way forward, multiple therapies have shown promise in improving risk factors for functional decline, suggesting potential targets for future research, perhaps alone or in combination: (1) Early treatment of psychotic symptoms may lead to fewer relapses and diminish both early and late functional decline (Santesteban-Echarri et al., 2017). (2) Increased use of LAIs can facilitate medical adherence and help with behavioral stability (Alphs et al., 2015; Kishimoto, Agarwal, et al., 2013; Tiibonen et al., 2011). (3) Supportive employment programs provide people with schizophrenia the environment to succeed and maintain work (Bond, 2004). (4) Exercise programs improve the physical and mental states. Also, regimens such as circuit training have also been shown to enhance cognitive performance and lessen the severity of symptomatology (Strassnig & Harvey, 2013; Strassnig et al., 2012, 2015b). (5) Finally, a broad range of therapies including cognitive behavioral therapy, cognitive remediation, metacognitive behavior therapy, and skills training have shown promise in increasing neurocognition, social cognition, IA, and functional skills (Hofmann, Asnaani, Vonk, Sawyer, & Fang, 2012; Kurtz & Mueser, 2008; Moritz et al., 2014; Wykes, Huddy, Cellard, McGurk, & Czobor, 2011). It would be important to delineate the most effective combination of these interventions.

Table 1. Functional domains and their most consistent predictors.

| Functional domain               | Predictors                                                                 |
|--------------------------------|---------------------------------------------------------------------------|
| Social functioning             | Social cognition, Social competence (modest predictor), IA of social cognition, Negative symptoms, Long-term clinical stability |
| Vocational functioning         | Neurocognition, Impaired IA of neurocognition, Disability, Physical capacity, Functional capacity, Social competence, Long-term clinical stability |
| Residential functioning        | Neurocognition, Impaired IA of neurocognition, Functional capacity, Physical capacity, Long-term clinical stability |

Note: IA = introspective accuracy.

Table 1. Functional domains and their most consistent predictors.
perhaps with an emphasis on matching the prevailing symptoms/deficits with an individual treatment plan. Personalization of treatment according to the predominant presentation may yield the best results and provide the most (cost)effective way forward.

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