Cognition in schizophrenia: Past, present, and future

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Here at last – a journal dedicated to the topic of cognition in schizophrenia: Schizophrenia Research: Cognition. The launch of this journal raises several questions. First: What took so long? Cognition in schizophrenia has been a major focus for a very long time. Exactly how long is somewhat arguable – as seen in the next section, 20, 50, or 100 years are all acceptable answers. From this long-term historical context, it is surprising that it took until 2014 for a publisher to launch a journal focused on cognition in schizophrenia. On the other hand, one could ask provocatively: why do we even need a journal dedicated to this topic? While everyone now agrees that cognition in schizophrenia is an important topic, it is so important that it pervades a wide range of topics. A perusal of schizophrenia-focused journals such as Schizophrenia Bulletin and Schizophrenia Research shows that cognition is a feature of many articles, even those that are not specifically about cognition, including clinical trials, genetics, outcome, and neuroscience.

Schizophrenia Research: Cognition is expected to serve an important function as an international niche journal – a place where interests converge and investigators gather well-packaged information. It is also intended to take scientific risks. Considering that the journal is open access and will have a fast turn-around, this journal will be a place for rapid dissemination of information to people who will make the most of it. Appropriately for this inaugural issue, the two authors of this paper have been asked to comment on how we got here, where we are, and where we are going. That is, the goal of this first article is to place the study of cognition in schizophrenia within a historical and scientific context. In a field as richly textured as ours it is impossible to hit all the important areas, and we hope the reader will forgive our omissions. Phrased in cognitive terms, our limited presentation of the past is a matter of selective memory, the present is a matter of selective attention, and the future is a matter of selective prospection. This broad introduction emphasizes that cognition in schizophrenia provides clues to pathophysiology, treatment, and outcome. In fact, the study of cognitive impairment in schizophrenia has become wholly intertwined with the study of schizophrenia itself.

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1. Where we came from

The history of cognition research in schizophrenia can be roughly carved up into 3 eras: the early clinical observations that occurred in the beginning of the 1900s, the assessment-based approaches that emerged after World War II, and the more recent era (roughly the last 20 years) in which cognition research merged into other disciplines. In many ways the three eras are quite distinct in their emphases and their methods, and all reflect their contemporaneous scientific contexts.

1.1. Clinical observations and formulations in the early 20th century

Until recently, most psychology majors in college were required to take a course on the history of psychology (usually called "History
and Systems). In such a course, students learned historical facts about psychology, one which is that William Wundt is credited with founding the world’s first psychology laboratory in Leipzig, Germany in 1879. Wundt had a long career and trained many students who served as emissaries and conveyed the principles of experimental psychology far and wide. One of his disciples was Emil Kraepelin, who maintained a lifelong interest in psychological phenomena and its applications to psychiatric disorders. It is Kraepelin’s distinction between schizophrenia (dementia praecox) and bipolar disorder that continues to be reflected in the key diagnostic systems (Diagnostic and Statistical Manual, DSM; International Classification of Diseases, ICD) up to the present time. His tendency to label, separate, and divide was not limited to psychiatric disorders; he also noted attentional processing abnormalities in schizophrenia and divided them into two types (Kraepelin, 1971; Nuechterlein and Dawson, 1984). One was a disorder in active attention (aufmerksamkeit) in which patients “lose both inclination and ability on their own initiative to keep their attention fixed for any length of time” (pp. 5–6). The second was an abnormality in passive attention (aufassung) in which there was an “irresistible attraction to casual external impression” (pp. 6–7). In modern parlance, we might call active attention vigilance, and passive attention distractibility. The key point is that his efforts to classify did not stop at diagnoses, but also included efforts to parse cognition.

If Kraepelin was astute and systematic, Eugen Bleuler was downright prescient. Aside from giving schizophrenia its mysterious (and frequently confusing) name, Bleuler understood at an intuitive level that cognitive impairment was a core part of the illness (Bleuler, 1950). He started by making an important distinction between two types of symptoms: fundamental and accessory. Fundamental symptoms are essentially cognitive in nature. They were separated into simple fundamental symptoms, including problems in association, affectivity, and ambivalence. These simple fundamental symptoms are combined to form compound fundamental symptoms, including disturbances in attention. Attention for Bleuler was rather all-encompassing. It included some features that we would call vigilance, but also expanded into areas that we might call social withdrawal: “it is evident that the uninterested or autistically encapsulated patients pay very little attention to the outer world” (p. 68).

In contrast to fundamental symptoms, accessory symptoms were derived from fundamental symptoms and they constitute what we would now call the positive symptoms of schizophrenia: hallucinations, delusions, and behavioral and speech abnormalities. He went on to say that the fundamental symptoms do not necessarily lead to being hospitalized. Instead “it is primarily the accessory phenomena which make his retention at home impossible, or it is they which make the psychosis manifest and give occasion to require psychiatric help” (p. 94).

Bleuler made many conceptual contributions, but perhaps most relevant to this discussion is his view that psychotic symptoms were secondary to fundamental symptoms, including attentional problems. His hierarchy of symptoms is counter-intuitive, and unfortunately would soon be forgotten. He specifically proposed that the features of illness that were most dramatic, and that necessitated treatment, were somewhat removed from the disease process. He even went on to say that their manifestation was arbitrary: “almost the totality of the heretofore described symptomatology of dementia praecox is a secondary, in a certain sense, an accidental one” (p. 349). Along these lines he proposed that the fundamental symptoms were stable over time, whereas the accessory symptoms waxed and waned.

In the brilliant, ground-breaking, works of Kraepelin and Bleuler we see the conceptual building blocks of modern studies of cognition. If scientific history was linear and progressive, the field would have moved right along to examine the implications of these insights into the cognition of schizophrenia – but that did not happen. A few notable thinkers (e.g., K. Goldstein, N. Cameron) continued to focus on psychological/cognitive phenomenon in schizophrenia with difficult-to-define concepts such as “abstraction” and “over-inclusive thinking” but it was a niche interest (Bolles and Goldstein, 1938; Cameron, 1939). Instead, much of the focus shifted to the more noticeable and more dramatic “accessory” psychotic symptoms and the importance of cognition was largely forgotten, temporarily.

1.2. Competing approaches to cognition 1950 – 1980

The post-World War II era was characterized by two distinct, highly empirical, views of the cognitive problems in schizophrenia. One view was shaped by experimental psychology and it tried to characterize and understand schizophrenia in terms of basic psychological phenomenon (shades of Wundt). This approach is probably best represented by the famous Biometrics Research Unit at the New York State Psychiatric Institute at Columbia University, which was founded by Joseph Zubin in 1954 (Zubin, 1950; Zubin and Spring, 1977). (No less than 3 organizations bestow awards named after Joseph Zubin.) The scientific approach that Zubin and others from the Biometrics program defined was experimental psychopathology and it sought a theoretical understanding of the etiology of schizophrenia. Their approach to schizophrenia emphasized objective measurement and strong experimental methodology. It also relied on the assumption that the most fruitful way to study the etiology of psychiatric disorders lies in integrative frameworks that use multiple levels of analysis simultaneously (i.e., genetic, biological and psychosocial). This integrative approach is taken for granted now, but was remarkable in the 1960s when it was proposed. As an example of this integrative approach, Zubin, Samuel Sutton, and others examined event related potentials (ERPs) in combination with cognitive tasks (Sutton et al., 1965). This led to a long-standing productive examination of ERP abnormalities in schizophrenia, including the P300, a waveform that is used to reflect allocation of attentional processes.

To better decompose psychological processes, a substantial amount of effort during this era was devoted to understanding very simple performance-based tasks, such as reaction time (Nuechterlein and Dawson, 1984). Indeed, reaction time was described as the “closest thing to a north star of schizophrenia research” (Cancro et al., 1971). Many studies examined cued reaction time tests in which subjects received trials with regular and irregular intervals between a warning signal (instructing the subject to get ready) and the imperative stimulus (instructing the subject to respond). David Shalow and colleagues noticed that, unlike controls, patients were unable to benefit from temporal regularity of the intervals (called a set index) once they exceeded a few seconds (Rodnick and Shalow, 1940; Shalow, 1962). Surprisingly, at the longer intervals, the patients were faster for the irregular versus regular trials, a pattern called the cross-over effect. This pattern of performance was perplexing and it never received a clear explanation (aside from largely descriptive explanations of failure to maintain set), but it occupied a prominent role in experimental research, partly because it was unexpected and wonderfully measurable.

This line of highly empirical research set the stage for clinical psychopathology researchers who unabashedly borrowed from experimental psychology, a practice that is commonplace now. This type of translational research took many forms, including borrowing from models of attention, perception, sensory gating, or emotional actions (Braff, 1993; Green et al., 2011a; Kring and Neale, 1996; Nuechterlein and Dawson, 1984; Nuechterlein et al., 1994). The goal was to closely measure deficits in schizophrenia in precise experimental paradigms, and then infer what the results mean about underlying deficits in the disorder based on existing experimental models. By using normal cognition models as the framework, the results in patients may implicate one visual process or one type of attentional abnormality more than another.

A distinctly different slant on cognition in schizophrenia was taking hold at the same time as the experimental psychology/
psychopathology approach. Although similarly measurement focused, this other approach had its roots in clinical neuropsychology. Human clinical neuropsychology emerged in the post-war era, fortified by numerous illustrative case studies of focal lesions from combat injuries (Luria, 1980). In this context, it is not surprising that a cottage industry of studies emerged that compared schizophrenia to neurological patients on standardized clinical neuropsychological assessments. These types of comparisons were in keeping with the common referral questions for psychiatric patients, which were for the purpose of differential diagnosis. Typically the neuropsychologist was asked to determine whether cognitive impairments in a patient were "organic" meaning neurological versus "functional" meaning not neurological. This type of question sounds jarring from a modern viewpoint – it assumes that cognitive deficits are not a core part of schizophrenia, that cognitive deficits for psychiatric patients are not brain-based, and that this distinction between organic and functional is both meaningful and informative. The demise of the word "organic" in the research literature reflects a fundamental shift in assumptions.

Beyond the conceptual problems, the endeavor to distinguish two types of cognitive impairment was largely futile. After a very large number of studies, the inescapable conclusion was neuropsychological tests could not distinguish cognitive impairments that accompany schizophrenia from those that accompany head injury (Goldstein, 1986; Heaton et al., 1978). In retrospect, it is an unsurprising conclusion and the efforts to discriminate schizophrenia from head injury reflect a time-limited zeitgeist. Although problems in differential diagnosis could be attributed to the tests themselves, the problem in this line of research was the conceptual framing and the stated goals, not the assessment methods. The measures for the most part were reliable and would have been informative for different types of research questions, such as those considered in the next section.

Neither of these approaches paid much attention to clinical symptoms. We can speculate about the reasons for the omission. First is that the people conducting the studies were mainly clinical and experimental psychologists and not directly involved in treating schizophrenia. Second is that the overlap between cognition and psychotic symptoms tend to be rather modest (Gold, 2004; O'Leary et al., 2000). Third is that, at least for the experimental psychology approach, the emphasis was on cognitive vulnerability factors that would be relatively impervious to changes in clinical state (remains a cent of Bleuler). Fourth is that there was not much effort to parse different types of clinical symptoms until the re-focusing on negative and disorganized symptoms in the 1980s (Andreasen and Olsen, 1982; Crow, 1980). Although cognition and clinical symptoms can safely be considered different domains of schizophrenia, we learned later that there is value in considering areas of shared variance, such as negative and disorganized symptoms.

1.3. Ramping up to the present: 1980s and 1990s

It is impossible to adequately summarize the ferment and the excitement that characterized the research in cognition in schizophrenia during the latter part of the 20th century. In a selective review such as this one, many key findings and research directions unfortunately will be omitted. For the purposes of illustration, we have selected 3 themes that took root in this period and will also be discussed in terms of current research.

1.3.1. Cognition and neuroscience

Nothing makes a point quite like a picture of the brain. And what made a very big impression were the initial pictures of the brains of people with schizophrenia (Johnstone et al., 1976; Weinberger et al., 1979). Their brains simply looked different – for example the ventricles appeared to be larger in schizophrenia (Raz and Raz, 1990; Weinberger et al., 1979). The larger ventricles reflected the relative reduction of brain tissue to cerebral spinal fluid. Further, the brain changes were often associated with cognitive impairment, thereby giving cognitive deficits firm neural footing. Consider how the world view for cognition in schizophrenia changed with these neuroimaging applications. Only a few years previously, investigators were administering tests to separate the organic from functional origins of impairment. Suddenly it was obvious that many schizophrenia patients have brains that are not entirely normal and these give rise to cognitive problems. Nonetheless, the inferences were limited from these early studies: for one, the ratio of ventricle to brain is entirely non-specific regarding the affected brain regions, as well as diagnosis. Also the spatial resolution of these imaging techniques (computerized tomography) was very limited compared with later methods.

The early structural findings were soon followed by functional neuroimaging studies. Initially these were studies of positron emission tomography (PET) in schizophrenia (Berman et al., 1986; Weinberger et al., 1986). Similar to the effects of the early structural imaging, the functional neuroimaging studies forced a reconsideration of brains in schizophrenia. Not only did the brains look different from healthy brains, they functioned differently as well. A common observation was that schizophrenia patients did not activate their frontal lobes as much, and as reliably, as control samples (i.e. hypofrontality) (Andreasen et al., 1992; Buchsbaum et al., 1992; Gur and Pearson, 1993). Much like the findings of enlarged ventricles, hypofrontality was wholly non-specific for diagnosis (other disorders also showed it), and for mechanisms (there are too many different ways to have reduced frontal activity). Also, functional magnetic resonance imaging (fMRI) would soon replace PET for cognitive activation studies in schizophrenia, although PET is still the method of choice for other types of studies, such as those assessing drug receptor occupancy. The variety of neuroscientific methods used currently to study schizophrenia is huge, and ranges from molecular neurobiology to genomics, to a focus on systems and networks. But this research direction was launched with the early neuroimaging studies and the striking realization that the brain in schizophrenia (as well as its cognitive processes) is available for rigorous study – just as it is in any other brain-based disorder.

1.3.2. Cognition and outcome in schizophrenia

The introduction of antipsychotic medications in the 1950s carried great promise and high expectations. Some of that promise was realized: the antipsychotic medications did indeed reduce psychotic symptoms in the majority of patients with schizophrenia (Braslows, 1997). It was natural to expect that psychotic symptom reduction would be accompanied by functional improvements and community integration. But that did not happen – in fact, the introduction of these powerful medications made rather little difference for community integration (Hegarty et al., 1994; Jaakskelainen et al., 2013). The reasons were elusive; if the clinical psychotic symptoms were not holding patients back from community reentry, then what was? This puzzle highlighted the difference between remission, meaning the reduction of symptoms, versus recovery, meaning full community participation.

We know from numerous studies that cognitive impairment is an important correlate and determinant of functioning in schizophrenia (Green, 1996; Green et al., 2000, 2004). Though perhaps not intuitive, cognition is a much better correlate of outcome than psychotic symptoms. We also know that antipsychotic medications have minimal effects on cognition (Keefe et al., 2007a,b). Herein lies the explanation for the discrepancy – antipsychotic medications treat psychotic symptoms, but not cognition. Cognition is related to outcome, but psychotic symptoms are not consistently related. That is why the introduction of antipsychotic medications changed the level of symptomatology for inpatient units, but did little for overall recovery rates.

This association between cognition and outcome is robust – it was replicated and extended in many in countries, using many different types of assessments, in different patient groups across phase of
illness, including prodromal (Carrion et al., 2011; Horan et al., 2012). The findings from the last couple of decades established the link between cognition and functioning. As will be seen in the next section on current studies, the questions have shifted from whether cognition is related to outcome to how cognition is related to outcome. Further, not all types of cognition are equally important when it comes to navigating the real world.

1.3.3. Cognition and interventions

Once it was established that cognition is a core feature of schizophrenia and that it is related to functional recovery, it followed naturally to ask whether treatments can enhance cognition. After all, if cognition was holding people with schizophrenia back from full participation in their daily lives, then cognition enhancement should eliminate this barrier. Intervention studies for cognition in schizophrenia can be grouped into two general categories that we will consider separately: cognitive remediation and psychopharmacology.

The studies on cognitive remediation from the 1980s and 1990s included highly focused experimental manipulations on a particular task, as well as broad rehabilitation programs that borrowed heavily from cognitive rehabilitation with brain-injured patients (Ben-Yishay et al., 1985; Green, 1993, 1998). For experimental manipulations, investigators explored the modifiability of performance on cognitive tasks (e.g., reaction time, problem solving, vigilance, verbal memory) using a range of approaches (such as coaching, monetary reinforcement, or instructions on performance strategies). For example, the Wisconsin Card Sorting Test was the testing ground for a variety of manipulations – results usually showed that patients’ performance can be improved (Goldberg et al., 1987; Green et al., 1992). These studies demonstrated that the performance deficits were not fixed, and also that the improvements sometimes persisted over time.

In contrast to the focused efforts to demonstrate modifiability on a task, more comprehensive and longer-lasting cognitive programs were also applied to schizophrenia patients (Brenner et al., 1990; Hogarty et al., 2004; van der Gaag et al., 2002). These programs were usually applied to small groups of patients and were extensions of the psychiatric rehabilitation programs. Beyond the typical procedures and structure of psychiatric rehabilitation, they included cognitive exercises that could be done in the group format.

These early approaches might appear overly focused (for the task manipulations) and less than novel (for the rehabilitation programs), but they established the ground work for later studies by demonstrating: 1) that task performance for schizophrenia patients can be modified, even on tasks that reflected core and relatively enduring impairments, and 2) the training exercises were well tolerated by patients, similar to other ongoing psychosocial interventions.

Regarding psychopharmacological approaches to cognition enhancement in schizophrenia – it started with a mirage. With the introduction of second-generation antipsychotic medications, many people (including the authors of this article) thought they had cognitive benefits when compared to first-generation medications. Initial suggestions of this effect came from examining patients who were placed on clozapine, and who showed cognitive benefits in some cognitive domains and not others (Goldberg et al., 1993; Hagger et al., 1993). Evaluations of the cognitive effects of risperidone and olanzapine followed as they were introduced to market (Green et al., 2002; Purdon et al., 2000). Comparisons of second- to first-generation medications (some controlled and some not) added support to the idea that the more recent medications had cognitive benefits (Harvey and Keefe, 2001; Woodward et al., 2005). However, there were also some warning signs. First, the interpretation of the results was limited by relatively small sample sizes, and many of the earlier studies were uncontrolled. Second, concerns persisted that the doses of the medications were not well-matched (with relatively higher, and perhaps more sedating, dosing for the first-generation medication). These problems were addressed more directly in recent studies that are covered in the next section.

Almost all of the focus on psychopharmacology was on second-generation medications, as opposed to novel drugs with distinctly different mechanisms of action. In retrospect, this tunnel vision was unfortunate. However, there are several possible reasons for it: First, the introduction of second-generation medications generated genuine optimism about previously unmet treatment needs, including cognition and negative symptoms. There was a hope (or even an expectation) that the clinicians could get all the treatment needs for schizophrenia met in a single pill. Second, because these drugs were on the market (or close to coming on the market), pharmaceutical companies had an interest in funding investigator-initiated grants to demonstrate the full range of effects. Finally, there was a scientific basis to expect cognition enhancement. For example, animal studies indicated that second-generation medications could reverse induced cognitive deficits in a way that first-generation medications could not (Young et al., 2009). So, it was not entirely a mirage; but it turned out to be overly optimistic.

2. Cognition in schizophrenia: present

Current research on cognition in schizophrenia naturally has grown out of its past. There are many areas of investigation at the present that clearly define the field. These include the definition and assessment of social cognition, cognitive and affective neuroscience, treatment of cognitive and social cognitive deficits, and the influences of genomic factors on cognition and its end-product in schizophrenia; everyday disability, and phase of illness. We will discuss each of these domains briefly.

2.1. Social cognition

Social cognition refers broadly to the domains of cognitive functions that are employed in socially relevant situations (Harvey and Penn, 2010). These include emotion processing, social perception, theory of mind/mental state attribution, and attributional style/bias, as well as more complex and developing concepts such as social metacognition (Pinkham et al., in press). It is clear that social cognition is of considerable importance for understanding social outcomes (Couture et al., 2006), with the correlation between impairments in social cognitive processes and functional outcomes more substantial than the correlations between neurocognitive deficits and these same outcomes (Fett et al., 2011). The study of social cognition is quite robust, in that more articles on social cognition are submitted to journals such as this one than articles focused only on neurocognition.

At the same time, the study of social cognition is in some ways less developed than that of neurocognition. A National Institute of Mental Health (NIMH) task force concluded that the domains of social cognition were less well defined than in neurocognition and that, as outcomes measures, many social cognitive tasks have some major deficiencies (Green et al., 2008). These include poor psychometric properties, and apparently similar outcome measures with minor variations, but few comparisons among them. In fact, an expert survey of social cognition produced 168 different domains and 108 different outcomes measures, with many of these domains and measures being very closely related to each other (Pinkham et al., in press). The similarity of many of these measures to each other has led to challenges in direct comparisons of their usefulness, as many of these assessments have overlapping content. Several efforts are underway to identify optimal social cognition measures and these studies will add clarity to the field.
2.2. Cognitive, social, and affective neuroscience

Considerable progress has been made regarding the functional and structural neuroimaging of cognition in healthy samples. The increased understanding of normal regional brain activity and functionally connected neural networks has been applied to developments in schizophrenia research. For example, the Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) initiative attempted to validate selective cognitive tests that are tied to specific neural networks and subprocesses (Carter and Barch, 2007). A data-collection extension of this initiative developed 4 performance-based tasks and examined their correlation with measures of both everyday functioning and performance-based measures of functional capacity (Gold et al., 2012). Although the correlations among indices of disability and performance on these measures were modest, the fact that this initiative could identify highly selective cognitive measures that were linked to specific neural systems reflects the substantial progress in this area.

Aside from cognitive neuroscience, the rapid emergence of social and affective neuroscience is now influencing schizophrenia research (Ochsner, 2008). These domains of inquiry focus on the neural substrates of social and emotional processes in healthy and impaired populations. For example, considerable work has gone into the patterns of neural activation during identification of facial emotion in schizophrenia (Anticevic et al., 2012; Taylor et al., 2012). Given the prominence of social processing and affective impairments in schizophrenia, this research direction can help to identify underlying neural abnormalities that give rise to social and emotional functioning. There are also rich possibilities to examine the intersection of cognition and emotion, including whether emotion dysregulation is associated with difficulties regulating cognitive efforts, the cognitive impact of negative or traumatic emotional experiences, and the impact of differences in emotional reactivity on the ability to perform cognitive operations. In addition, examination of underlying commonalities and differences in brain activation during emotional and cognitive tasks could inform treatments jointly aimed at emotional factors and cognitive deficits. Overall, social and affective neuroscience are expanding rapidly in basic behavioral science, and they are well positioned to shed light on the neural basis of both social and motivational problems associated with schizophrenia (Green et al., 2013).

2.3. Treatment of cognitive and functional deficits

Interventions targeting the disability of schizophrenia have been attempted for decades as described above. However, many interventions were aimed at social, vocational, and residential skills deficits in the absence of any interventions aimed at cognition. As cognitive impairments are primary correlates of functional deficits, it stands to reason that cognitive deficits might well underlie the skills deficits that lead to disability and might be “rate limiters” of treatment improvements. Meta-analyses of interventions aimed at disability reduction have suggested that, in general, treatment of cognitive and skills deficits should proceed in parallel to yield functional benefits (Wykes et al., 2011).

Cognitive remediation therapies have made substantial gains in the past two decades. Advancing past repetitive drill and practice interventions, the current cognitive remediation interventions share several critical features. They include dynamic difficulty titration, elimination of focus on “training the test”, feedback and encouragement, and a user-friendly interface with visually appealing graphics. These features combine to promote engagement and levels of adherence with treatment that are greater than before.

Training on specific cognitive skills is consistently found to be effective for improving cognition, but not necessarily for improving functioning. Studies of both comprehensive rehabilitation interventions and targeted skills training programs show that short term treatments generally show functional gains only when additional skills training is included (e.g., Bell et al., 2008; McGurk et al., 2007). This situation may be offset by findings that substantial doses of cognitive remediation (50 hours or more) are associated with both substantial cognitive changes (cognition change of up to d > 0.80) and improvements in functional skills (Fisher et al., 2009). Clearly an important issue to be resolved is whether a substantial dose of cognitive remediation can by itself improve daily life. In other words, does an improvement of 10 IQ points yield functional gains if the time frame for detecting these gains is long enough? It will be important for regulatory approval (and payer participation) to know whether concomitant skills training programs are necessary to realize the full benefits of cognitive remediation.

An important related issue concerns approval by regulatory agencies for treatments for cognition in schizophrenia. The overall goal of the NIMH Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Initiative was to construct a regulatory pathway for cognitive enhancement (Marder and Fenton, 2004). Although MATRICS was aimed at pharmacological treatments, there does not appear to be a substantial distinction in the approval process for pharmacological and remediation-oriented interventions. At present both pharmacological and remediation-oriented strategies are under consideration for approval, though none have been approved so far. Pharmacological interventions would be considered as therapies added to a foundation of antipsychotic treatment for symptom management. Cognitive remediation interventions delivered with a computer, in person, or remotely would be considered to be medical devices and would be approved accordingly. As treatments are approved for cognition, one of the critical issues is the extent to which payers or regulators will expect to see functional gains to maintain approval for treatments with pharmacological or remediation-focused cognitive enhancing treatments.

2.4. Genomic influences on cognition

Studies of the genomic influences on schizophrenia represent a large share of the research effort on the condition, with samples of patients in the tens of thousands. Cognitive deficits are clearly central to the illness and meet several critical criteria for being considered as important ‘endophenotypes’ (Bravd et al., 2007). They are stable, present in attenuated form in relatives, presumed to be genetically simpler than the illness phenotype, and measured with high reliability. In addition, they are among the most heritable of all illness-related traits, at least in families affected by severe mental illness.

The heritability of a variety of cognitive functions in families of people with schizophrenia has been demonstrated in a multiple studies (Gur et al., 2007). Memory, attention, and executive functions seem to have a strong familial component that is substantially inheritable. In addition, while disability is a complex phenotype, the skills underlying disability may be less complex. The components of disability, including everyday living skills and employment appear to be quite heritable behavioral traits (McGrath et al., 2009). The skills that underlie disability include cognition, as well as the ability to perform cognitively demanding everyday living skills.

Previous studies have identified genomic variation associated with cognitive endophenotypes (Greenwood et al., 2011). These include verbal memory, working memory, indices of attention / vigilance, and social cognitive processes. Further, sensory gating endophenotypes, such as P50 suppression and startle blink responses, also have strong genomic linkages. The full value of these findings will depend on their replication, and several related studies are in process.

2.5. Functional capacity

The study of functional capacity has increased substantially in the last decade. This concept refers to the ability to perform functionally
relevant skills, including those relevant to social, vocational, and residential functions (Harvey et al., 2009; McKibbin et al., 2004). Multiple sophisticated performance-based assessments have been developed (Green et al., 2011b), including computerized assessments described for the first time in this issue. Several studies have suggested that these skills may be more proximal to real-world disability than cognitive deficits and they share features with cognitive deficits that suggest they are core features of the illness: stability over time, minimally associated with symptoms, and similarities cross-culturally.

Further, impairments in functional capacity performance meet criteria for an endophenotype, including substantial temporal stability (Light et al., 2012) and low levels of correlation with clinical symptoms (e.g., Bowie et al., 2008). Further, functional capacity scores appear to be minimally related to environmental support (Harvey et al., 2009), suggesting that having more support while performing these skills does not influence the likelihood that people with severe mental illness can perform them with competence. However, as shown recently, limited opportunities for experience in demonstrating skills can contribute to functional skill deficits on these tasks (Holshausen et al., in press).

An important consideration is the suggestion that functional capacity and neurocognitive skills may both reflect a larger common trait that we can call "ability." Several studies with different samples have suggested that there may be one ability trait that cuts across tasks labeled "neurocognitive" and those designated as "functional" (Harvey et al., 2011). Although the types of tasks are quite different, they can be modeled in a way that both connect to one underlying trait in statistical models (Green et al., 2012). Further, cognitive and functional capacity indices were equivalently stable and similarly associated with the single factor over 6-week and 6-month follow-up assessments using sophisticated statistical analyses (Harvey et al., 2013).

### 2.6. Phase of illness

Previously, there was little need to discriminate the phase of illness of the patients. If schizophrenia developed, it stayed around and it may have actually worsened. Now we can detect risk states earlier, although imprecisely, and are better able to differentiate the effects of treatment, duration of illness, and are early course of illness on cognitive functioning (Cannon et al., 2008). Now we clearly know that the signature of cognitive impairment is not markedly different prior to the onset of diagnosable illness. We also know that, in the absence of the relatively rare phenomenon of nearly complete treatment resistance in older age, there is little consistent evidence of cognitive decline (Harvey et al., 2010).

Groups are also working on identifying cognitive predictors of conversion from what looks like a schizophrenia prodrome to a psychotic state. The literature suggests that probably we are looking too late: individuals who are considered to be prodromal and already have cognitive deficits seem more likely to convert to psychosis; those without the deficits seem at lower risk (Seidman et al., 2010). One of our goals in the next decade will be in closing the gap on convergence between clinical and cognitive deficits in cases who are about to convert to psychosis and to "get there earlier" in the cognitive prediction side.

### 3. The future – educated guesses

The baseball manager Yogi Berra famously observed that “It’s tough to make predictions, especially about the future.” Hence, the authors of this article have little to gain, and can only be proved wrong, by sticking our necks out and making predictions, especially about the future. Undaunted, we will make some general guesses at this point. The subsequent trend lines for research in cognition and schizophrenia will be played out in the pages of this new journal, and we will eventually know what we got right and what we got wrong.

One general rule is that research into cognition in schizophrenia follows, often closely in time, developments in basic biological science. Hence, as advances in basic science (e.g., inflammatory markers, optogenetics, epigenetics, pluripotent stem cells, advanced neuroimaging paradigms, etc.) are applied to schizophrenia, they will also be applied to the cognition of schizophrenia. Once a biomarker is found to be associated with the disease, the next step frequently is to evaluate whether it is related to cognitive impairment. Herein lies one of the advantages of cognition compared with other features of the illness – it is seen as more directly related to known brain circuits. Beyond this general tendency to essentially travel on the coat tails of neuroscience advances, we can identify a few promising directions.

#### 3.1. Treatment – a 3rd path

Treatments for cognition in schizophrenia fall into two categories: training interventions (such as cognitive remediation), and psycho-pharmacology. However, we may soon see a focus on a third approach: neurostimulation. Such approaches include transcranial magnetic stimulation (TMS), and transcranial direct current stimulation (tDCS) (Minzenberg and Carter, 2012). These approaches attempt to change cognition by directly stimulating the brain. In TMS a strong, transient magnetic field is applied to the scalp from a hand-held coil. That application creates electric current in the brain, which alters the membrane potential and leads to neuronal firing. In tDCS a low-intensity direct current is applied to the scalp, which modulates neuronal excitability (either higher or lower, depending on polarity), but does not cause firing directly. The beneficial effects of these methods sometimes appear to be long lasting, but the results are variable (Guse et al., 2010). The value of these approaches alone, or in combination with other treatment modalities, is likely to be a focus in coming years.

#### 3.2. The interface of motivation and cognition

It is common to view cognition and motivation as separate spheres. Indeed, motivation is much more linked to negative symptoms, such as asociality and avolition. But recent formulations suggest that the two domains may be linked. For example, self-reported intrinsic motivation has an effect on the benefits of cognitive remediation (Medalia and Brekke, 2010). In addition, it is possible that impairments in cognition and social cognition, lead over time to decreases in motivation that we see as negative symptoms, including asociality and anhedonia (Green et al., 2012). Recent developmental models suggest that the two largest unmet treatment needs in schizophrenia, cognition and motivational negative symptoms, are related, and may emerge at different points in development (Beck et al., 2009; Grant and Beck, 2009). That is, long-standing cognitive and social cognitive problems could lead to expectations (dysfunctional beliefs) in which the person learns to not expect to be successful or to enjoy interactions. These beliefs, in turn, lead to motivational negative symptoms. The interaction and overlap between the science of cognition and the science of motivation present wide open areas of exploration for psychopathology.

#### 3.3. Technology as a problem and a solution

Perhaps the most ubiquitous feature of worldwide culture in the 21st century is technology. Television shows for children feature dogs who have blogs and nearly every aspect of life is technology driven. As a result, elderly individuals and people with severe mental illness are expected to perform on-line banking and ATM tasks, and to engage in internet or phone voice menu tasks to schedule appointments and refill predictions (Harvey and Keefe, 2012). In many
cases there are no alternatives offered other than internet-based services. This relentless change creates a disadvantage for those with less experience or less ability, but may, paradoxically, offer opportunities. Technology can be less expensive and in an era when health costs are a paramount concern, technology may offer an opportunity for service delivery that would never be possible if in-person interventions were required. For instance, remotely delivered cognitive enhancement interventions have recently been shown to have clinical efficacy (see this issue). Thus, in contrast to the classical model of bricks and mortar clinic, receptionist, therapist, and group interventions, people with severe mental illness could be provided with a low priced device loaded with software and be prompted and cued remotely to self-administer the intervention. This type of intervention has been applied with success for years in aging populations with low levels of experience with technology (Czaja et al., 2006).

3.4. Applications of animal models

It is obvious that animal models of cognition have had a profound impact on our understanding of human cognition. However, they have had a limited impact on the study of cognitive impairment in schizophrenia. To understand the multitude of genetic and molecular mechanisms associated with cognitive impairment in schizophrenia, neural circuit assays (i.e., behavioral tasks known to depend on specific circuits) are needed, and those often come from animal models (Moore et al., 2013). Such models are valuable for neural demonstrations of construct validity (whether the identified cognitive processes are homologous between species), as well as pre-clinical indications of predictive validity (whether a drug is likely to have a therapeutic benefit in human patients) (Keeler and Robbins, 2011). Given an increasing focus on construct validity at the neural level, and increasing examples of successful translation and back-translation, this area could assume a much larger emphasis for the study of cognition in schizophrenia in coming years.

3.5. Diagnoses

An intriguing, though perhaps unsettling, thought about the future of cognition research in schizophrenia is that it might not exist at all. That is, it might not be on schizophrenia per se. One of the implications of the NIMH Research Domains Criteria (RDoC) Project is that specific diagnoses, such as schizophrenia, will not fit into the growing knowledge from neuroscience, and instead the field will move to brain-based constructs that cut across diagnostic boundaries (Cuthbert and Insel, 2010; Insel et al., 2010). A better understanding of these domains might lead to a reorganization of the diagnostic groupings in a way that better carves psychopathology at its neuroscientific joints. In such a reorganization, schizophrenia as a separate disorder could be clumped into a mixed category of psychoses, or split into the meaningful and biologically validated subtypes.

It is easy for this pendulum to swing too far in either direction. A narrow focus on biomarkers or RDoC dimensions risks an overreliance on reductionism that overlooks important higher-order and functional aspects of the disease. In contrast, a narrow focus on clinical syndromes and traditional diagnostic categories risks an overreliance on surface-level clinical features and a continued failure to identify neurobiologically meaningful dimensions or subtypes.

Resolving this balancing act will not occur immediately, and schizophrenia is not disappearing as a diagnosis any time soon. Instead, there will be continued efforts to start with existing diagnoses and to revise them incrementally. In this mode, cognition might become a more central part of schizophrenia in diagnostic systems. That very nearly happened for the latest version of the Diagnosis and Statistical Manual (DSM-5) in which cognition was one of several dimensions that was initially slated for inclusion, but ultimately moved out of the main body of the text to Section 3, meaning that it requires additional study (Barch et al., 2013). In contrast to DSM, the proposed revision for the International Classification of Diseases (ICD-11) includes level of cognitive impairment as a specifier (Gaebel, 2012). If that change in ICD-11 is maintained through the field trials and revision process, it will mark the first time that clinicians internationally will be asked to note and record the cognitive status of schizophrenia patients as a routine part of evaluation.

4. Conclusions

Schizophrenia in the past was a grim diagnosis with a poor prognosis. At the present time, it can probably be better described as a serious condition, with plenty of reasons to be hopeful. The breadth and depth of valuable information on this disease, as in other areas of science, is experiencing rapid, almost exponential, growth. We probably learned more about schizophrenia in the past 10 years than we learned in the previous 100. Like any other area of biomedical science, the sheer volume of the scientific output, as well as the rate of change, is daunting and intimidating. Most of us are conducting research on topics that did not exist, or were not discussed, when we were in training. The future holds both considerable promise and substantial challenge. This new journal will track those developments, help to organize the massive amount of information, and provide a forum for their dissemination and impact.

Role of Funding Source
Nil

Contributors
There are no other contributors other than the authors.

Conflict of interest
Dr. Green has been a consultant to AbbVie, Biogen, DSP, and Roche, and he is on the scientific advisory board of Mnemosyne. He has received research funds from Amgen. Dr. Harvey has received a contract research grant from Genentech, and has received honoraria for consulting or travel support from AbbVie, Boehringer Ingelheim, En Vivo, Genentech, Otsuka America, Roche, Sunovion, Shire, and Takeda.

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