Generalized and Specific Neurocognitive Deficits in Psychotic Disorders: Utility for Evaluating Pharmacological Treatment Effects and as Intermediate Phenotypes for Gene Discovery

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A growing body of research suggests that schizophrenia and bipolar disorder share overlapping clinical, neurobiological, and genetic features, raising important questions about the boundaries and distinctiveness of these 2 major psychiatric disorders. A generalized cognitive impairment has long been understood to be a core feature of schizophrenia. More recently, it has become apparent that cognitive impairment also occurs in bipolar disorder, particularly in those patients with a history of psychotic symptoms. Whether a generalized deficit exists across a spectrum of psychotic disorders is less clearly established. Additionally, in the context of a broad impairment, it remains a significant challenge to identify deficits in specific cognitive processes that may have distinct neurochemical or regional brain substrates and linkages to particular risk-associated genetic factors. In this article, we review the findings from neuropsychological studies across a spectrum that includes schizophrenia, schizoaffective and bipolar disorders, and conclude the available evidence strongly supports that a generalized deficit is present across psychotic disorders that differs in severity more so than form. We then consider the implications of generalized and specific deficits in psychosis for 2 areas of research—the evaluation of pharmacological treatments targeting cognitive deficits, and the investigation of cognitive intermediate phenotypes in family genetic studies. Examples from the literature that touch on the relevance of the generalized deficit in these contexts are provided, as well as consideration for the continued need to identify specific impairments that are separable from the generalized deficit in order to advance drug and gene discovery.

Key words: schizophrenia/schizoaffective disorder/bipolar disorder/neuropsychology/cognition/endophenotype/treatment effects

Introduction

Despite long-held distinctions in psychiatric nosology and diagnostic systems, there is an emerging literature that supports shared aspects of psychopathology, treatment response, genetics, and neurobiology in schizophrenia and bipolar disorder.1–4 Cognitive impairments, considered core features of schizophrenia, are present at illness onset, remain relatively stable over the course of illness, do not change substantially with antipsychotic medications effective at treating other symptoms, and account for much of the functional disability associated with the illness.5–9 It was recently demonstrated that the broad cognitive impairment in schizophrenia is not attributable to reduced general intellect.10 It is now also understood that cognitive functioning is impaired in bipolar disorder, particularly when there is a history of psychotic symptoms. These impairments are present early in the course of illness and between mood episodes, with no indications of appreciable change with available treatments.11–16 For these reasons, cognitive deficits have been increasingly identified over the last 2 decades as critical targets for the development of new treatments for psychotic disorders.17 Concurrently, demonstrations that cognitive impairment is heritable and present among nonpsychotic first-degree relatives of psychotic probands12,18 suggest that it may also be a useful intermediate phenotype for identifying neurobiological and genetic factors that are important to understanding the etiology of psychotic disorders.

Cognitive impairment has both generalized and specific aspects. Conceptually, the generalized deficit is an impairment present across cognitive domains, whereas specific deficits impact a particular domain of function above and beyond what would be predicted by the severity of the generalized deficit.19 There has been much
consideration for which of these types of deficit are most important to evaluate and study, and the difference in emphasis can be seen depending on the line of work being conducted. For example, interest in the generalized deficit has been prominent in studies of treatment-related functional outcome and of treatment efficacy with cognitive enhancement as a target as reflected in many industry trials and criteria for decisions about treatment indications by the Food and Drug Administration. For studies that focus on the neurochemical and regional brain basis of cognitive impairments, interest has typically been on specific cognitive processes believed to be linked to the neurobiological processes of interest. These specific deficits can be evaluated by a number of assessment methods including clinical neuropsychological measures, neurophysiologic recordings, functional brain imaging, and experimental cognitive neuroscience paradigms all of which have their benefits and limitations. As specific deficits are essentially residual variance from the generalized deficit, clarifying the degree to which their examination can better assess treatment outcomes or advance gene discovery is among the greatest challenges for clinical cognitive neuroscience field.

In the schizophrenia literature, there are well-established findings that demonstrate cognitive functioning, when measured by neuropsychological measures, is broadly impaired across domains with deficits on the order of 1–2 SD often being reported. These findings have been widely regarded to reflect a generalized cognitive deficit in the disorder. In neuropsychological studies, verbal memory and processing speed are domains that current evidence suggests may be most disproportionately impaired, yet their differential deficits are relatively small against the backdrop of the overall generalized deficit. Whether a generalized deficit exists across a spectrum of psychotic disorders is less clearly established but important to consider as questions about the boundaries between diagnostic syndromes are raised.

There has been much discussion regarding the challenge a broad neuropsychological deficit brings to understanding the cognitive dysfunction in schizophrenia and whether there are additional specific impairments which are measurable beyond this deficit that could shed light on underlying pathophysiology. This matter holds relevance for 2 areas of active research in psychosis: (1) the evaluation of pharmacological treatment effects on cognition, which may be difficult to detect on broad neuropsychological measures due to considerable shared variance and conflation of multiple specific cognitive processes on many tests; and (2) the evaluation of potential cognitive intermediate phenotypes whose relative value for elucidating risk mechanisms along genotype-to-phenotype pathways may be dependent upon the unique phenotypic characterization they provide beyond that of the broad cognitive impairment.

In this article, we consider evidence for a broad neuropsychological impairment across a psychosis spectrum that includes schizophrenia, schizoaffective disorder, and psychotic bipolar disorder, with an emphasis on cross-diagnostic studies in which psychotic groups were studied in parallel. We then consider the implications of a broad impairment for the evaluation of pharmacological treatment effects on cognitive deficits in psychosis and for the evaluation of cognitive intermediate phenotypes for psychosis. Examples from the literature that illustrate the importance for consideration of generalized and specific deficits in these contexts are provided.

Neuropsychological Impairment in Schizophrenia, Schizoaffective Disorder, and Bipolar Disorder

Lewandowski et al recently completed a thoughtful and comprehensive review of studies evaluating neuropsychological impairment in schizophrenia, schizoaffective, and bipolar disorders. Although studies vary widely with respect to sample size and the neuropsychological measures used, virtually all studies demonstrated impaired performance of patient groups compared to healthy individuals on most neuropsychological measures and across cognitive domains. The majority of studies found that schizophrenia patients had greater deficits compared to bipolar patients, whereas fewer studies, typically of smaller sample size and perhaps reduced power to detect group effects, reported equivalent performances between these groups. Whether bipolar patients in cross-diagnostic comparisons have a history of psychosis is not always specified, which could influence the extent of neuropsychological impairment reported in studies involving these groups; among those studies that do, greater cognitive deficits have been observed among bipolar patients with a history of psychosis than those without. The few studies examining impairment in schizoaffective disorder reported deficits generally comparable or somewhat reduced relative to those of schizophrenia. We know of no reasonably powered studies in which bipolar or schizoaffective disorder patients evidenced greater neuropsychological impairment than schizophrenia patients.

The Bipolar Schizophrenia Network on Intermediate Phenotypes (BSNIP) consortium recently reported on neuropsychological findings using the Brief Assessment of Cognition in Schizophrenia (BACS) neuropsychological battery in the largest cross-diagnostic cognitive study of schizophrenia (n = 293), schizoaffective disorder (n = 165), and psychotic bipolar disorder (n = 227) conducted to date. We observed robust neuropsychological impairment among all patient groups on a composite score, with schizophrenia having significantly greater impairment than either schizoaffective or bipolar disorder, and schizoaffective disorder in turn demonstrating greater impairment than bipolar disorder. Thus, the severity of neuropsychological impairment in these individuals...
dimensionally scaled with the extent of enduring psychotic symptoms and lesser prominence of mood symptoms (ie, impairment increased from psychotic bipolar patients with a history of psychosis only present during mood episodes to schizoaffective and schizophrenia patients whose course is marked by more persistent psychotic symptoms). Examining the profile of scores across specific neuropsychological domains on the BACS revealed a highly similar pattern of deficits across diagnostic groups. The similarity of the neuropsychological profile between these disorders is also observed during the acute phase of illness.\(^{14}\)

In contrast to the consistent literature indicating that a generalized deficit quantitatively differentiates diagnostic groups (schizophrenia > or equivalent to schizoaffective disorder > bipolar disorder), there is limited evidence to support selective neuropsychological impairment in particular cognitive domains between these disorders based on the existing literature, though of course future studies of specific cognitive processes may yet discover such differences. These findings are consistent with the notion that a broad generalized cognitive impairment is characteristic of psychosis in general, and that it is the magnitude of this impairment that varies across diagnostic categories.

The Generalized Deficit and Evaluation of Pharmacological Treatment Effects in Psychosis

The need to develop new treatments targeting cognitive deficits has been a major focus of research in recent years with stakeholders from academia, the National Institute of Mental Health, and industry working on this problem. The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative\(^{48}\) was undertaken to identify a cognitive battery that would be useful in clinical trials targeting cognition in schizophrenia, the result of which was the MATRICS Cognitive Consensus Battery (MCCB).\(^{49}\) The MCCB is comprised of standardized neuropsychological measures that were selected based upon their ability to detect impairments in schizophrenia and their established reliability, minimal practice effects, and associations with functional outcome.\(^{50}\) The battery generates a composite score, like the BACS battery, and such indices of generalized function have most commonly been the outcome of primary interest in clinical trials.

Given the evidence for a broad cognitive impairment in psychosis when measured with neuropsychological tests, a question arises as to what is the optimal cognitive assay to evaluate pharmacological treatment effects. Although not without important advantages, including the ease with which it can be efficiently measured\(^{51}\) and its established relation to daily functioning,\(^{7}\) a concern with use of a composite index from a battery of neuropsychological tests to measure pharmacological treatment effects is that performance on most measures are highly intercorrelated (ie, share substantial amounts of variance) and are dependent upon multiple higher order cognitive processes. This may limit their utility if drug effects impact specific processes based upon their receptor targets in ways that change some processes significantly with minimal impact on most processes and therefore a modest impact on the generalized deficit. Approaches from the cognitive neurosciences, in which paradigms are developed based upon an understanding of and intent to assess function in specific underlying neurophysiology and neural systems, allow for the evaluation of more specific and distinct cognitive processes. In addition, such paradigms are more directly related to those used in behavioral pharmacology studies in which manipulations of specific neurotransmitter systems yield circumscribed effects on cognition in animal and human models (eg,\(^{52,53}\)). It is, therefore, possible that in this context, treatment effects on specific cognitive operations, selected based on the understanding of drug action, may be more readily observable.

As an example, in our prior work we have demonstrated that measures of oculomotor neurophysiology were sensitive to detecting deficits in attentional control,\(^{50}\) response inhibition,\(^{55,56}\) and working memory,\(^{57,58}\) among first-episode psychosis patients prior to treatment that were of similar magnitude of deficits detected on standardized neuropsychological measures,\(^{59}\) many of which were similar to the neuropsychological measures comprising the MCCB. When patients were evaluated after a short course of antipsychotic treatment, mostly with second-generation antipsychotic medication, we observed minimal changes on neuropsychological measures in patients that were of a similar magnitude to practice effects in healthy individuals. These findings are consistent with those observed with several larger clinical trials using neuropsychological measures that sought to compare different medication effects on cognitive outcomes.\(^{60,61}\) In contrast, on several oculomotor tasks, we found changes after antipsychotic treatment that exceeded practice effects observed in healthy individuals who were studied in parallel and that suggested improvement in aspects of automatic and voluntary attentional control,\(^{54,55}\) and a worsening of working memory performance\(^{57,58}\) similar to effects observed in nonhuman primates exposed to antipsychotic drugs.\(^{62}\) Thus, a pattern of both beneficial and adverse treatment-related effects were observed on oculomotor performance measures. Furthermore, correlations among oculomotor measures, or between oculomotor and neuropsychological measures, were minimal suggesting little shared variance, which may have increased their sensitivity to specific effects to a greater degree than was detectable by neuropsychological measures. Last, it is noteworthy that while the effect size of the generalized deficit is typically similar to or greater than deficit on specific measures in clinically stable patients with psychotic disorders, detecting drug effects using specific tests that
are selected according to drug pharmacology may provide for a considerably more powerful approach to measuring pharmacological treatment response.

Although such experimental tasks have proven useful to identify differential pharmacological effects on cognition in psychotic patients, an important limitation is that the association of performance on measures more closely aligned with cognitive neuroscience methods to functional outcomes is less well established, and often less robust, than for neuropsychological measures. Although they may prove useful in early phase studies for demonstrating proof of concept and establishing translational platforms, for establishing engagement of the targeted neural circuit, or for dose optimization, they may prove less useful in phase 3 registration trials in terms of predicting patients’ functional outcomes that seem primarily driven by generalized rather than specific deficits thus far.

In recent years, there has been substantial progress in the development of cognitive neuroscience-based paradigms to evaluate specific cognitive processes that can and have been used in clinical trials. The Cognitive Neuroscience Test Reliability and Clinical Applications for Schizophrenia (CNTRACS) Consortium, which followed the Cognitive Neuroscience Treatment to Improve Cognition in Schizophrenia (CNTRICS), was designed to develop measures of discrete cognitive processes linked to neural systems believed to be altered in schizophrenia, and probably have relevance to psychotic disorders more broadly. CNTRACS has addressed several of the challenges that the use of experimental paradigms developed from the cognitive neurosciences pose with respect to practical implementation in clinical research, including psychometric issues, use in multisite clinical studies, and relationship to functional outcomes. The CNTRACS Consortium battery comprises tasks that assess visual processing, episodic memory, and goal maintenance, and deficits among schizophrenia and schizoaffective patients using these measures have been observed. Importantly, in a study examining the association between tasks on the CNTRACS and selected subtests from the MCCB, both common and unique deficits were detectible and shown to relate to functional impairments, albeit modestly. Pharmacological treatment effects on the CNTRACS battery, and their association with changes in functional outcomes, have not yet been reported to our knowledge. Nevertheless, preliminary findings demonstrate that these tasks reliably measure specific cognitive processes separable from the generalized cognitive impairment suggesting that they hold promise for detecting pharmacological effects on discrete neural systems.

The Generalized Deficit and Evaluation of Cognitive Intermediate- or Endo-Phenotypes in Psychosis

In addition to evaluating treatment effects on cognition in clinical trials, the identification of genetic factors conferring susceptibility to psychotic disorders has remained a major challenge for the field despite substantial heritability for both schizophrenia spectrum and bipolar disorders. Intermediate phenotypes are measurable traits that are more proximal to liability genes and their impact on related neural substrates than are clinical signs and symptoms, and thus they may help in resolving heterogeneity within the broad syndromes of psychosis and thereby with identification of risk genes related to psychosis. There are established criteria against which potentially useful intermediate phenotypes are considered including that they are associated with the illness, do not vary with clinical state, heritable, overrepresented among unaffected family members relative to the general population, and co-segregate with illness within families. Generalized cognitive functioning has long been regarded as a promising intermediate phenotype for schizophrenia. Findings from the Consortium on the Genetics of Schizophrenia lent additional support for this position, and the BSNIP consortium extended this across the psychosis spectrum to include schizoaffective and psychotic bipolar disorders, as deficits were detected among all proband and relative groups and estimates of their familiality across pedigrees were significant.

Considering the evidence for generalized neuropsychological impairment observed across these psychotic proband groups and their first-degree relatives, and the significant heritability estimates, a question arises of whether specific cognitive deficits are detectible and remain heritable after accounting for this general deficit. By including the BACS battery as a measure of generalized deficit as well as specific neuropsychological measures in the protocol used in the BSNIP cohort, we have started examining putative-specific cognitive deficits in this way. For example, we examined the elevation in antisaccade error rate, a measure of impaired executive inhibitory control heavily dependent on prefrontal systems, in proband and relative groups before and after co-varying for generalized neuropsychological impairment as indexed by the BACS composite score. Across the entire sample, we observed significant, albeit small negative associations between BACS performance and antisaccade error rate. Among probands, antisaccade error rate was robustly elevated in all groups, with schizophrenia probands demonstrating impairment greater than schizoaffective disorder probands who in turn had the greater impairments than bipolar probands, similar to the group effects observed on the BACS composite. In the family members of these case probands, elevated error rate was also observed, even among those relatives without a personal history of psychosis or elevated psychosis spectrum personality traits; unlike findings in patient probands, these effects were similar across schizophrenia, schizoaffective and bipolar pedigrees. After accounting for the shared variance with the BACS composite score, significant
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control comparisons, will not likely be incrementally useful for identifying discrete neurobiological systems and substrates that are relevant to genotype-to-phenotype pathways important for understanding the complex mechanisms of illness liability across individuals with psychotic disorders.

Concluding Remarks
Considerable evidence supports the notion that broadly impaired cognitive functioning is central to the pathophysiology of psychosis, and that it is likely the magnitude, rather than the presence of impairment, which differentiates syndromes within the psychosis spectrum. This broad impairment can be reliably captured by neuropsychological measures with linkages to important functional outcomes for patients. The detection of specific effects in the setting of this broad impairment is challenging yet critical if the field is to further advance development of pharmacological treatments targeting cognitive deficits or identify genes conferring liability to psychosis. Any impairment that is only a marker for the generalized deficit, even if robustly impaired in patient control comparisons, will not likely be incrementally useful for evaluation of drug effects or for gene discovery. As has been suggested by others, pursuing research that includes measures of broad and specific deficits collected and evaluated simultaneously in the same subjects is needed. In so doing, the relative contributions of broad vs specific deficits for identifying relevant genes and monitoring pharmacological treatment effects on cognition and functional outcome may be fairly and empirically considered.

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