Cognitive Impairment in Schizophrenia and Affective Psychoses: Implications for DSM-V Criteria and Beyond

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It has recently been suggested that the diagnostic criteria of schizophrenia should include specific reference to cognitive impairments characterizing the disorder. Arguments in support of this assertion contend that such inclusion would not only serve to increase the awareness of cognitive deficits in affected patients, among both clinicians and researchers alike, but also increase the “point of rarity” between schizophrenia and mood disorders. The aim of the current article is to examine this latter assertion in light of the recent opinion piece provided by Keefe and Fenton (Keefe RSE, Fenton WS. How should DSM-V criteria for schizophrenia include cognitive impairment? Schizophr Bull. 2007;33:912–920). Through literature review, we explore the issue of whether cognitive deficits do in fact differentiate the major psychoses. The overall results of this inquiry suggest that inclusion of cognitive impairment criteria in Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition) (DSM-V) would not provide a major advancement in discriminating schizophrenia from bipolar disorder and affective psychoses. Therefore, while cognitive impairment should be included in DSM-V, it should not dictate diagnostic specificity—at least not until more comprehensive evidence-based reviews of the current diagnostic system have been undertaken. Based on this evidence, we consider several alternatives for the DSM-V definition of cognitive impairment in schizophrenia, including (1) the inclusion of cognitive impairment as a specifier and (2) the definition of cognitive impairment as a dimension within a hybrid categorical-dimensional system. Given the state of current evidence, these possibilities appear to represent the most parsimonious approaches to the inclusion of cognitive deficits in the diagnostic criteria of schizophrenia and, potentially, of mood disorders.

Key words: schizophrenia/psychosis/bipolar disorder/depression/cognition

Introduction

Cognitive deficits are common and clinically relevant features of schizophrenia and are important indices of functional and treatment outcomes in patients.1–8 There is a growing consensus regarding the importance of incorporating cognitive deficits into the major diagnostic systems, including Diagnostic and Statistical Manual of Mental Disorders and International Classification of Diseases. Recently, it has been suggested that the diagnostic criteria for schizophrenia should specifically include a criterion pertaining to cognitive ability. One such possibility would require “a level of cognitive functioning suggesting a consistent severe impairment and/or a significant decline from premorbid levels considering the patient’s educational, familial and socioeconomic background.”1,6 Clearly, inclusion of such a criterion would increase the awareness of the importance of cognitive dysfunction in schizophrenia and would ideally lead to routine administration of brief cognitive assessment tools by clinical providers. There is little doubt that this represents a desirable outcome that would help stimulate the development of new treatment methods and promote better management of cognitive impairments in this disorder.

The advantages of this approach have been thoroughly discussed in 2 recent opinion articles by Keefe6 and by Keefe and Fenton.1 One of the main arguments supporting the inclusion of cognitive impairment as a diagnostic criterion is the expectation that such qualification of the clinical picture would help define a “point of rarity” between schizophrenia and closely associated affective disorders. Keefe and Fenton1 discuss the existing literature on cognitive differences between schizophrenia and bipolar disorder (BD) and conclude that these 2 clinical entities may be cognitively separable. Moreover, Keefe and Fenton1 suggest that schizoaffective (SA) disorders may also be cognitively differentiated from BD. However, we...
disagree with this contention on the basis of the available literature, including the results of our own recent meta-analytic studies in each of these disorders. This issue is of critical importance as the outcome of this discussion will impact on the awareness and understanding of the nature of cognitive impairment in schizophrenia and affective disorders among both research and clinical communities alike. How then should we define cognitive impairment in schizophrenia? What are the consequences of different definitions of cognitive impairment to the development of valid diagnostic systems? And what should be done regarding the recognition of cognitive impairment in affective disorders?

In this article, we first discuss the evidence regarding cognitive distinctions that discriminate schizophrenia from mood disorders in the context of the reviews provided by Keefe and Fenton. We provide an updated viewpoint on this issue due to the inclusion of several meta-analyses focusing on cognitive deficits in affective disorders that have been published since the Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition) (DSM-V) meeting on deconstructing psychosis, upon which Keefe and Fenton based their recent work. Our group has also conducted 3 relevant meta-analyses that further elaborate and help to characterize the cognitive profile of BD, affective psychoses, and their distinction from the cognitive profile of schizophrenia.

Our second objective will be to discuss alternative approaches to the inclusion of cognitive impairment in the diagnostic classification of schizophrenia and affective disorders.

Diagnostic Differences in Cognition

Cognitive Deficits in Schizophrenia, Affective Psychoses, and Remitted BD

A number of meta-analyses have examined the magnitude of cognitive impairment in schizophrenia. Large effect sizes (ESs; between 1.0–1.5; see figure 1a), representing robust impairments, have been reported across a multitude of cognitive domains, including current IQ, category fluency, verbal memory, sustained attention, and response inhibition. In particular, the symbol coding task yields some of the most robust impairments, with very large ESs reported (between 1.5–1.6).

Several meta-analyses have also examined cognitive deficits in remitted BD. Results of the most recent of these studies is summarized in figure 1a and 1b. It should be noted that while figure 1a and 1b substantially differ from the relevant figure presented by Keefe and Fenton, this is due to the inclusion of more updated information, including the results of recent meta-analyses, rather than inclusion of additional individual studies. As can be seen in these figures, pronounced deficits (ESs between 0.70–0.86) in verbal memory, response inhibition, sustained attention, executive functions, working memory, and symbol coding are in evidence. A meta-analysis undertaken by our group (Bora et al) additionally examined cognitive differences between patients with affective psychoses (BD or major depressive disorder [MDD] with history of psychosis) and healthy controls. In this analysis, impairment in symbol coding was found to be the most robust deficit in patients with affective psychoses (ES of 1.0), alongside large impairments in a number of other domains including response inhibition, verbal learning, and category fluency. Interestingly, when the analysis was restricted specifically to psychotic BD, the magnitude and pattern of impairments remained very similar.

These results suggest that cognitive impairment is apparent not only in schizophrenia but also in affective psychoses and BD. Comparing across the 3 groups, very similar profiles and levels of impairment are apparent in a number of the reported cognitive domains. The most notable difference between these groups appears to be a greater general impairment in patients with schizophrenia, particularly given indices of current and premorbid IQ, symbol coding, and category fluency.

Diagnostic Differences in Severity of Cognitive Impairment

One prominent argument supporting the inclusion of cognitive impairment in the diagnostic criteria of...
schizophrenia has been the suggestion that cognitive deficits are more severe in this disorder than in BD. A recent meta-analysis investigating this issue concluded that cognitive deficits in schizophrenia were indeed about 0.3–0.6 ES greater across a number of cognitive domains as compared with BD.12 This between-group difference was found to be most pronounced for verbal fluency, working memory, verbal and visual memory, mental speed, and executive control (ES = 0.4–0.6). However, these differences were not sufficiently large to differentiate the 2 disorders because an average difference of ES of 0.5 would indicate that 31% of patients with BD would perform worse than the average patient with schizophrenia.12

Furthermore, it could be argued that differences between schizophrenia and psychotic mood disorders may be even smaller in magnitude due to evidence suggesting that psychosis might have a negative impact on cognition in BD.13–16 In a recent meta-analysis, we examined cognitive differences between major psychoses by comparing the cognitive functioning of patients with schizophrenia, SA disorder, and affective psychoses (BD or MDD patients with a history of psychotic features).17 The most pronounced differences between schizophrenia and psychotic mood disorders were in the domains of verbal learning and current IQ (approximately 0.4 ES), while the between-group differences for working memory, processing speed, executive control, and verbal fluency were minimal (0.2–0.3 ES). In this meta-analysis, demographic variability of the schizophrenia cohort investigated between studies was also found to be an important determinant of the extent of the between-group differences. Specifically, studies that included a greater proportion of male patients and patients with more severe negative symptoms, as compared with the affective psychosis group, were more likely to find between-group cognitive differences. Associations between cognitive deficits, negative symptoms, and younger onset of the illness were also apparent. These findings could be explained in 3 ways: Firstly, they may simply reflect a general gender bias in cognition. Secondly, consistent with dimensional approaches, there may be a simple gradient of severity running across the major psychoses. If this were the case, poor cognition and more severe negative symptoms would be more common in schizophrenia due to the fact that a patient with a poor prognosis receives a diagnosis of schizophrenia. However, one potential argument refuting this view contends that gender does not appear to be a marker of poor prognosis in BD or major depression.18–20 Moreover, there is little evidence that cognitive impairment in males with affective disorders is of any greater magnitude than their female counterparts. Additionally, a meta-analytic review did not find any negative effect of an increased male ratio in BD.11,21 Finally, these results might suggest that the observed group differences between schizophrenia and affective psychoses were driven by a subgroup of schizophrenia patients (more commonly males) with a poor prognosis. If this were the case, there would be no substantive evidence to support the notion that magnitude of cognitive impairment can differentiate between affective psychoses and most schizophrenia patients.

Cognitive Impairment and Clinical State

Keefe and Fenton1 argue that one of the main differences between the cognitive profiles of schizophrenia and mood disorders is the more state-dependent nature of cognitive deficits in the latter. For that reason, it was suggested that cognitive impairment criteria should emphasize the consistency of cognitive deficits in schizophrenia in order to increase the point of rarity between the disorders.

There is sufficient evidence showing long-term stability of cognitive deficits in schizophrenia.22–24 Also, a significant number of longitudinal studies have examined the relationship between symptomatic improvement and cognition in schizophrenia, and, as Keefe and Fenton1 have suggested, these studies do not support a substantial association between improvements in symptoms and recovery of cognitive functioning.24–27 For example, in the recent European First Episode Schizophrenia Trial study, which included 498 first-episode patients with schizophrenia or schizophreniform disorder, cognitive improvement, and symptoms were only weakly correlated.26 This is also the case for chronic schizophrenia patients, and a recent meta-analysis of longitudinal studies did not find a significant effect of changes in symptoms on cognitive improvements.27

However, the results of previous meta-analyses clearly demonstrate that cognitive impairment also persists throughout euthymic states in BD.9–11 While only a few longitudinal studies have examined cognitive deficits in BD, recent evidence suggests that cognitive impairment might also be stable over the long term.28,29 These results, as in schizophrenia, suggest that cognitive impairment is not simply a by-product of other symptom domains in BD. The findings of recent studies in unaffected first-degree relatives of BD also suggest that cognitive impairment might be a trait-related feature of BD.10,11,30,31 Unlike BD, however, there is less evidence for cognitive impairments in remitted patients with a history of depression.32 Further studies are needed to examine cognitive deficits in remitted patients with major depression, especially psychotic depression because there is clear evidence showing that the cognitive profiles of patients with psychotic depression are unique in comparison with those of their nonpsychotic counterparts.33 We believe that evidence at least in BD argues against the utility of using stability of cognitive impairment as a tool for increasing the point of rarity between schizophrenia and mood disorders. However, we share Keefe and Fenton’s1 opinion regarding the importance of emphasizing the consistency of cognitive impairments when operationalizing the impairment criteria because
Prevalence of Cognitive Impairments in Schizophrenia and Mood Disorders

Without doubt, cognitive impairment is a common and cardinal feature of schizophrenia, with more than 80% of patients showing significant impairment (according to a 1 SD impairment criterion). However, studies investigating cognitive impairment in affective disorders also provide evidence for a substantial prevalence of such deficits. As detailed above, in BD, the negative ES across several cognitive domains is approximately 0.8. Similarly, in a recent meta-analysis, we examined the magnitude of neuropsychological impairment in affective psychoses (MDD or BD with psychotic features), yielding a mean impairment ES of approximately 1 SD across several cognitive domains. Given such evidence, if a 1.0 SD impairment criterion were to be applied, almost 40% of remitted BD patients and half of patients with affective psychoses would meet criteria for impairment (figure 2). The results of a recent study undertaken by Reichenberg et al corroborate our estimations. In this study, the authors defined cognitive impairment as 1 SD below normal in 2 or more cognitive domains, resulting in 84% of their schizophrenia patients, 58.3% of psychotic major depression patients, and 57.7% of psychotic BD patients meeting impairment criteria. These results suggest that there is a significant overlap between the major psychoses when 1 SD is used as the diagnostic threshold.

As discussed by Gold, one alternative approach to increasing the diagnostic specificity of cognitive impairment would be to use a more conservative criterion (eg 2 SDs below the norm). Gualtieri and Morgan reported that only 30% of patients with BD and 4% of normal controls fell below the 2 SD impairment threshold in at least 2 cognitive domains. However, more stringent criteria would also decrease the sensitivity of detecting cognitive impairments in clinical populations. Even in the severely impaired sample of Wilk et al, only half of the patients performed below 2 SDs from the norm. In fact, results of meta-analyses conducted in schizophrenia would estimate that an even smaller percentage of patients would meet impairment criteria given such a stringent threshold. However, use of a more stringent cognitive impairment criterion would also effectively cause a division of schizophrenia into 2 entities (cognitively impaired and cognitively unimpaired).

Early Cognitive Decline in Schizophrenia

There is evidence indicating that subjects who later develop schizophrenia have cognitive impairment during their childhood and adolescence. However, there is less evidence for a similar premorbid intellectual impairment in affective disorders. While few studies have compared premorbid intellectual impairments in patients who later develop schizophrenia or BD, most of these studies report premorbid IQ impairments only in the schizophreniform group. There is also evidence of early progressive preonset cognitive impairment from childhood to late adolescence in schizophrenia. As discussed by Keefe, these findings are somewhat specific to schizophrenia, with a general lack of similar evidence regarding preonset intellectual impairments in affective disorders.

Nevertheless, early cognitive decline may not differentiate between schizophrenia and affective psychoses due to the fact that IQ deficits in early adolescence are observed only in a subgroup of patients who later go on to develop schizophrenia. The most compelling study regarding premorbid IQ in schizophrenia is based on a population-based cohort of 555 326 adolescents who were assessed prior to recruitment into the army. In this study, while 1856 of these adolescents (76% male) were later diagnosed with schizophrenia, only 33% had low IQ (<85) prior to illness onset. Also, among patients with apparently normal IQ, a subgroup (23%) still had lower than expected intellectual capacity based on a discrepancy between actual and expected IQ scores. Nevertheless, according to this study, only half of the patients could be considered to have had a premorbid intellectual impairment. Furthermore, this ratio was probably an overestimate because the study sample was biased toward inclusion of more severe cases and male patients. These findings suggest that while early cognitive decline is potentially specific to schizophrenia, it is not common enough to reliably differentiate between most cases of schizophrenia and affective psychoses.
Summary of Case for Diagnostic Differences in Cognition

As discussed above, defining the severity and prevalence of cognitive impairment would not help to differentiate schizophrenia from other major psychoses due to the significant overlap of cognitive performance between syndromes. Further, because early intellectual decline is a characteristic limited to a subgroup of patients with schizophrenia, it would also serve little use in differentiating between these disorders. Emphasizing stability of the cognitive impairment would not be a solution either, as cognitive deficits persist regardless of symptom state in both schizophrenia (ie, following resolution of first-rank symptoms) and BD (ie, during periods of euthymia). Therefore, we suggest that introducing cognitive impairment as an inclusion criterion for diagnostic purposes would not serve to increase the point of rarity between the major psychoses.

How to Define Cognitive Impairment in Schizophrenia?

Keefe and Fenton’s Proposal

As Keefe and Fenton1 have suggested, it could still be desirable to include cognition in the diagnostic criteria of schizophrenia as this may effectively increase the awareness of cognitive dysfunction in clinical practice. Inclusion of cognitive impairment criteria could also pave the way for research efforts to focus more explicitly on treatment avenues targeting cognitive remediation. The emphasis that Keefe and Fenton1 place on recognizing the stability of cognitive deficits over time and the importance of decline from premorbid levels of cognitive functioning is also important.

Keefe and Fenton’s1 recommendations regarding the inclusion of cognitive characteristics in the diagnostic criteria of schizophrenia could be interpreted in several ways. Firstly, they may have considered cognitive impairment as a gateway criterion for the diagnosis of the disorder. One potential problem with this approach, however, is that it would result in the reclassification of substantial numbers (depending on the severity of impairment incorporated in the definition) of schizophrenia patients who would no longer meet diagnostic criteria for the disorder. Conversely, it is also possible that Keefe and Fenton1 only considered adding cognitive impairment as a criterion within section A of DSM-V. This change would not necessarily influence the diagnosis of patients with cognitive impairment. However, for those patients who were cognitively intact, it would be more difficult to satisfy criteria for the disorder (eg, if 3 clinical symptoms were required as compared with the current 2). This approach would still lead to a reclassification of some, but not all, patients with schizophrenia who were not cognitively impaired.

Alternative Approaches for Inclusion of Cognitive Impairment in Schizophrenia

To our knowledge, the psychosis working group for DSM-V is not advocating the inclusion of cognition as part of the diagnostic criteria for schizophrenia. However, there may be several alternative ways to include cognitive impairment in the diagnostic classification of schizophrenia. One approach would involve the use of cognitive impairment as a specifier, rather than an inclusion criterion. This is similar to the current practice used in obsessive-compulsive disorder of further classifying the syndrome using insight as a specifier. Moreover, within such a system, cognitive impairment could be further defined as “moderate” (1 SD impairment in at least 2 domains) or “severe” (2 SD impairments in at least 2 domains). This approach would increase attention to, and awareness of, cognitive deficits in schizophrenia without causing diagnostic shifts.

A second alternative would involve adoption of a dimensional approach to clinical classification. While replacing the categorical classification system with a dimensional approach represents one possibility to refining the current diagnostic system, such a radical option is unlikely to be accepted at this stage. However, a more feasible change is one in which the classification system is based on a hybrid model of categorical and dimensional approaches. In both alternatives, cognitive impairment would be represented as one of the dimensions within the system. In a hybrid system, a patient meeting diagnostic criteria for schizophrenia would be further defined according to the severity of their symptoms within different dimensions (such as positive and negative symptoms and cognitive impairment). Akin to using cognitive impairment as a specifier, this approach would prevent diagnostic shifts based on cognitive impairments.

We contend that, at this stage, DSM-V should certainly include cognitive impairment in the diagnostic classification of schizophrenia but through means that would not exclude cases based on their relatively preserved cognitive abilities. We suggest that incorporating cognitive impairment either as a specifier or as a dimension within a hybrid classification system would provide the most appropriate means of satisfying this agenda. Additionally, in line with Keefe and Fenton,1 the state independent nature of the cognitive deficits should be emphasized, and the severity of the impairment should be clearly defined.

Looking to the future, the addition of cognitive impairment as an inclusion criterion for schizophrenia should not be considered until such time as there is consistent evidence for a specific impairment that can differentiate between the major psychoses. At present, it is unlikely that cognitive impairment can help to differentiate schizophrenia from mood disorders based on current diagnostic boundaries. This does not necessarily mean that we should consider major psychoses, including affective psychoses and schizophrenia as a unitary concept. The potential utility of cognitive testing as a tool to better understand heterogeneous entities within the major psychoses and schizophrenia should be tested rigorously. While historically there has been some suggestion that poor
functioning schizophrenia cases should be differentiated from patients with better prognoses (ie, type 1 and 2 schizophrenia).\textsuperscript{40,50} these subtypes have been thought to lack validity and stability.\textsuperscript{50} More recently, it has been proposed that there exists a “deficit” schizophrenia subtype, which appears to be a more reliable diagnosis.\textsuperscript{51} Indeed, “deficit” schizophrenia patients are more cognitively impaired (approximately 0.5 ES) as compared with their nondeficit counterparts.\textsuperscript{52} However, a 0.5 SD difference in cognitive ability still indicates a significant overlap in the cognitive performance of both groups and limits its utility in distinguishing between subtypes. Also, this category does not adequately represent schizophrenia patients with poor prognoses because only 15%-20% of all cases would be classified into this category.\textsuperscript{50} Future neurobiological and clinical research, as well as developments in genetics, could lead to a more effective subtyping of schizophrenia and mood disorders. In that case, the inclusion of specific cognitive criteria may be helpful in distinguishing between subtypes of these disorders. Alternatively, cognitive deficits could prove to be a common dimension of all major psychoses that differ only in relative severity.

Finally, we suggest that cognitive impairment should also be considered as a specifier of BD and psychotic depression. There is already sufficient evidence supporting the stability and persistence of cognitive deficits in euthymic patients with BD, and currently available literature points toward consistent cognitive impairment in late-onset depression.\textsuperscript{53} Inclusion of a cognitive specifier or dimension, at least as a research norm, could lead to increased attention to cognitive deficits in mood disorders, which in turn may help to differentiate between syndromes within the mood disorders spectrum.

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