Cognitive deficits in schizophrenia: short-term and long-term

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Richard Keefe provides a compelling case for inclusion of cognitive impairment in the diagnostic criteria for schizophrenia. From both a clinical and pathophysiological perspective, there is little doubt that cognitive deficits are a core component of the disease (1). From a nosological perspective (2), we agree that inclusion of a cognitive criterion may improve both diagnostic validity and clinical utility relative to current standards. However, we also suggest that such improvements must be balanced with an awareness of long-term consequences of such a shift.

Perhaps the most persuasive argument for inclusion is the well-replicated finding of strong correlation of cognitive abilities with functional outcomes (3). Of greatest diagnostic significance is the fact that this relationship holds true not only concurrently, but also longitudinally. For example, in a study of first-episode patients at the Zucker Hillside Hospital, global cognitive ability was the only baseline variable that was able to predict both social/vocational functioning *and* symptom remission over the subsequent five years (4). Only a small percentage (14%) of patients successfully attained a two-year period of recovery in both domains, and global cognitive performance was by far the strongest predictor ($p<0.0001$). Even in the prodromal phase, before the onset of frank psychosis, cognitive deficits significantly predict subsequent diagnosis (5). In defining diagnostic validity, Goodwin and Guze stated that "diagnosis is prognosis" (6); applied to schizophrenia, Robins and Guze declared that "good prognosis schizophrenia is not mild schizophrenia, but a different illness" (7). Assuming this model of schizophrenia is correct, a cognitive impairment requirement would enhance the diagnostic validity of the construct.

As a matter of clinical utility, placement of cognitive deficit in DSM-V would begin a much-needed process of clinical education and updating of standard psychiatric evaluation practices. The significant relationship between cognitive deficits in schizophrenia and public sector costs (8) contributes strong economic incentives towards development of treatments for cognitive deficits. In the US, governmental agencies such as the Food and Drug Administration and the National Institute of Mental Health have thrown their support behind the development of novel pharmaceutical approaches targeting cognitive enhancement as a primary endpoint (9,10). In response to this, industry is developing a range of putatively nootropic molecules, based on a wide variety of mechanisms (11). Thus, in the not-too-distant future, clinicians will need formal mechanisms by which to designate patients for such treatment, and to monitor its progress.

For several reasons, however, the immediate impact of adding a cognitive criterion may be limited, unless it initiates a more comprehensive re-evaluation of diagnostic, clinical, and research practices. First, given the strong linkage between cognitive deficits and functional impairment, it is probable that the current "B" criterion in DSM-IV captures much of the territory to be identified by the proposed cognitive impairment criterion. Second, while the cognitive deficits in schizophrenia are profound (1-2 SD below normal), the cognitive differences between schizophrenia and affective disorders are subtle (0.5 SD) and state-related, thus making it unlikely that the "point of rarity" between the two classes of illness will be substantially enhanced.

Moreover, the often insidious progress of cognitive decline, which can begin long before the manifest symptomatology, complicates the proposed diagnosis of "significant decline from premorbid levels". As noted by Keefe, it is possible for deficits to begin in early childhood (~0.5 SD) and slowly progress through the prodromal period in adolescence (an additional ~0.5 SD), with an additional precipitous decline (also ~0.5 SD) around the onset of psychosis. We have observed this modal progression in two independent studies. In a follow-back study of school records obtained from first episode schizophrenia patients, a one grade-level deficit was observed at the beginning of primary school, incrementally increasing to a two grade-level deficit by high school (12). Separately, we found that patients prodromal for schizophrenia-spectrum psychosis displayed cognitive impairments of about 1 SD on average, about half of which appeared to represent decline from earlier levels (5).

Taken together, the evidence above (and that reviewed by Keefe) suggests that cognitive deficits in schizophrenia represent a dimensional phenomenon rather than an absolute threshold. Such a conception is also consistent with recent genetic findings, which strongly point to a polygenic model in which multiple genes of small effect individually contribute to illness susceptibility via multiple pathophysiological processes (13). For example, recent evidence suggests that a variant in DTNBP1 (dysbindin), which slightly elevates risk for schizophrenia, is also associated with severity of negative symptoms and generalized cognitive deficits (14-16). At the same time, variants in DISC1 are associated with persecutory delusions and specific deficits in working memory (17,18).

Therefore, we would suggest that Keefe's proposal be considered in the context of recent suggestions for a dimensional approach to diagnostic systems (19) and clinical practice (20). Development of a brief assessment of degree of cognitive impairment suitable for clinical application, with appropriate adjustments for age, socio-economic status, and prior history, should be a priority for further research. A dimensional approach may also mitigate any

medico-legal and ethical complications which could ensue from a criterion-based categorization of cognitive impairment. In a categorical system, a diagnostic finding of "cognitive impairment" could be misinterpreted by courts or other legal entities, possibly leading to confusion with issues of competence or a paradoxical denial of certain educational or vocational opportunities. Overall, we feel that Keefe's proposal is likely to lead to improved diagnosis, prognosis, and treatment even in the context of current diagnostic standards. In the longer term, current research may lead to more fundamental changes in our diagnostic system, but the potential for unintended consequences must be clearly recognized.

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