Is cognitive impairment in schizophrenia ready for diagnostic prime time?

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The question of whether cognitive impairment should become one of the formal diagnostic criteria for schizophrenia reflects the wide acceptance that cognitive performance provides an important signal about the integrity of cortical function in schizophrenia. Further, the fact that cognitive impairment has a powerful relationship to functional disability suggests that the inclusion of a cognitive impairment criterion might focus clinical attention on disability reduction, the major therapeutic challenge of the illness (1). As noted by Richard Keefe, a cognition criterion might also serve to re-draw diagnostic boundaries, better establishing a "point of rarity" between schizophrenia and bipolar disorder. Such a redefinition could result in more homogeneous clinical phenotypes, possibly facilitating both genetic and treatment research. However, there are practical, statistical, and theoretical issues to consider before taking such a dramatic step.

In order for a cognitive impairment criterion to serve the purpose of clinical heterogeneity reduction, it would need to be mandatory: a patient could not get the diagnosis of schizophrenia without meeting this criterion. Therefore, validated assessment approaches designed to provide the data needed to make a yes or no decision about the presence of cognitive impairment would have to be available, and would need to be applicable across clinical settings, countries, and cultures. No such assessment tool exists, and given the work that would be involved in developing one, it is reasonable to assume that such a tool will not become available in the foreseeable future. Thus, in practical terms, it seems nearly certain that the height of the instrument development hurdle will effectively eliminate the possibility of a cognitive impairment criterion being introduced into any international diagnostic classification system in the near term.

The question remains, however, whether a cognitive criterion would help establish a useful "point of rarity" among ill patients. What is the evidence that cognitive impairment is sensitive and specific when comparing patients with DSM-IV schizophrenia to healthy controls? Consider the data on the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) published by Wilk et al (2), which included 575 schizophrenia patients who were compared to the RBANS healthy control standardization sample. The patient mean standard score of 70 fell two full standard deviations (SD) below normal, a degree of impairment that exceeds the expectations established by several meta-analyses (3,4). In this unusually impaired group, if one uses a cut-off score of 85 (1 SD below normal) to define impairment, this would correctly identify 80% of patients as impaired, but would falsely diagnose 16% of controls as having schizophrenia (using the cognition criterion alone). Using a 2 SD cut score, the false positive diagnosis rate drops to 2%, but the true positive rate drops to 50% – fully half the patients fail to meet the criterion. The risk of false positives in this context is relatively unimportant: a healthy person has no other symptoms of schizophrenia, so a false positive on the cognitive criterion is of no practical consequence. The false negative problem, however, has important implications: relative to healthy controls, the 1 SD cut-off misses 20% of patients, whereas the 2 SD cut-off misses 50%. One could argue that these are not "false negatives", but represent patients with a form of illness that does not include marked cognitive impairment – they do not have the newly defined form of schizophrenia. Thus, the use of a cognitive impairment criterion results in a dramatic redrawing of diagnostic boundaries, one that might require the reclassification of 20-50% of patients with DSM-IV schizophrenia depending on the cut-off employed.

The problem becomes even more pronounced in the separation of bipolar patients from schizophrenia patients. For ease of argument, assume bipolar patients are "half" as impaired as patients with schizophrenia (there is RBANS data documenting that this is a reasonable estimate, see 5). The use of a 1 SD cut-off would result in the diagnosis of a very sizeable portion of bipolar patients as having schizophrenia, while the use of a 2 SD cut-off would still capture a significant minority of bipolar patients, with the cost of a false negative rate of 50% for DSM-IV schizophrenia patients. In short, rather than defining clear points of rarity, the use of a cognition criterion would significantly redraw the diagnostic map.

Given these concerns, what would be gained with a cognition criterion? One argument is that it would highlight cognitive impairments as a treatment target for clinicians and encourage drug development. While the cognition criterion

could foster increased clinical awareness, it cannot alter clinical care for the foreseeable future, given lack of any available treatments. Further, there is substantial industry interest in the development of cognitive enhancers, as the market for such compounds is enormous: nearly every patient with schizophrenia. Might the cognition criterion result in more homogeneous clinical phenotypes, thereby enhancing research on biological pathways and genetic risk factors for schizophrenia? This is a potential benefit that could be investigated in existing data sets where cognitive measures have been obtained along with other biological measures or treatments. The question would be whether the "schizophrenia" signal is enhanced when samples are limited to subjects demonstrating different degrees of cognitive impairment. Such supportive evidence would be needed in order to justify the effort required to overcome the measurement hurdles and implementation challenges of adding a cognitive impairment criterion to the DSM.

References

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