

Cognition as an Outcome Measure for Clinical Trials in Bipolar Disorder: What Can We Take from MATRICS?

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While there is a growing interest in the cognitive deficits that are present in patients with bipolar disorder and their relationship with functional disability, few studies have prioritized cognition as a primary outcome measure in clinical trials of bipolar disorder. As this appears to be a logical next step in optimizing the quality of life in patients with bipolar illness, it will be important to come to some consensus regarding the best method for assessing these impairments. Therefore, this ACNP workgroup was assembled in an effort to evaluate whether the MATRICS Consensus Cognitive Battery (MCCB), a battery of tests chosen by an expert panel to tap the primary domains impaired in patients with schizophrenia, might be applicable to bipolar disorder when cognitive enhancement trials are being considered. Although there are multiple advantages to utilizing the MCCB in studies of patients with bipolar disorder, particularly with regard to the psychometric quality of the MCCB tests, there are also potential disadvantages that need to be addressed.

The introductory remarks of this session reviewed briefly the convergent literature suggesting that patients with bipolar disorder have a similar neurocognitive profile across several domains of function when compared qualitatively to patients with schizophrenia; however, the deficits are generally less severe. Further, there are several critical features of the illness that influence neurocognitive functioning that differ from those noted in schizophrenia. The episodic nature of bipolar disorder requires that methodological designs control for a uniform mood state across subjects and clinical course bears directly on cognitive functioning including bipolar subtype, history of psychosis, number of prior episodes, age at onset, and duration of illness (Martinez-Aran 2004; Robinson and Ferrier, 2006). Finally, an important consideration in designing clinical trials is the frequency of neurocognitive impairment in patients with bipolar disorder and the relative cognitive heterogeneity that exists in comparison to the more uniform presentation seen in schizophrenia. Specifically, early data suggest that approximately 30% of bipolar patients do *not* present with significant cognitive impairment during euthymia (Martino et al. 2008); therefore, it may be critical to identify, at baseline, the subgroup of bipolar patients who will optimally benefit from cognitive enhancement strategies, a stipulation that is not routine in clinical trials in schizophrenia.

With these methodological issues in mind, the participants in the workgroup addressed several potential pros and cons of using the MCCB as a primary outcome measure for clinical trials of cognition in bipolar patients. The high points of the discussion were focused around several questions:

1. As the MCCB was designed specifically for use in schizophrenia trials, are the MCCB subtests sensitive enough to capture the more subtle deficits noted in BPD?

There are no published data to directly address this question; however, unpublished MCCB data from 46 euthymic bipolar patients, 52 stable schizophrenia patients, and 61 matched healthy controls from The Zucker Hillside Hospital were presented during this session to emphasize several points.

- Overall, consistent with prior work, the profiles of the patient groups were quite comparable, with bipolar subjects' performance falling intermediate to that of the schizophrenia patients and the healthy controls. Areas of possible weakness in the battery were evidenced by non-significant differences between bipolars and healthy controls in the domains of Reasoning/Problem-solving and Social Cognition.

2. What tests if any should supplement the MCCB to adequately capture deficits common to patients with bipolar disorder?

Numerous studies indicate executive functioning deficits in euthymic bipolar patients on some (Bora et al. 2008), but not all, executive tasks and the MCCB includes few executive functioning measures (NAB Mazes) on which there are limited or no published data in bipolar disorder.

- It was suggested that rather than replacing the NAB Mazes subtest, it might be prudent to incorporate some of the widely used “frontal” measures that tap into different aspects of executive functioning so as not to limit the assessment to reasoning skills. Specifically, set-shifting tasks (Trails B, WCST) and response-inhibition measures (Stroop) have shown to be sensitive to impairment in bipolar disorder.

Although social cognition research in bipolar disorder is in its relative infancy, several studies have demonstrated theory of mind deficits in euthymic patients.

- While the MSCEIT from the MCCB did not differentiate bipolars from healthy subjects, prior work indicates that more difficult social cognition measures may need to be implemented in bipolar studies (Hinting task, Eyes task).

There were significant verbal learning deficits as measured by the MCCB in the bipolar sample that was presented; however, they were much less severe than what has been described in the meta-analytic literature (Bora et al. 2008).

- The MCCB’s use of the HVLT may limit the battery’s ability to tap this domain adequately in bipolar disorder. Prior studies have generally used the more challenging CVLT and have reported effect sizes nearly double those seen in this dataset using the HVLT.

3. Are there neuroscience/affectively-based data to support supplementing the MCCB with more novel tasks in bipolar patients that might be more specific to the pathophysiology of the illness?

- This discussion focused largely on affective bias measures such as the affective go-no-go and the emotional Stroop. Although the group agreed that these tasks lend themselves well to imaging studies and appear to be sensitive to activity in brain regions that are responsible for affect regulation, it remains unclear as to whether the deficits reported in bipolar patients are present during euthymia or if they are state-dependent. Moreover, once controlling for general cognitive deficits such as those measured by the MCCB, the additional information obtained from these types of tasks may be limited. More work is needed in this area to answer this question adequately but these measures may serve as a useful supplement to the MCCB and provide additional information related to the pathophysiology of the disorder.

In summary, in considering the utility of the MCCB for clinical trials of cognition in bipolar disorder, it should be acknowledged that beyond the extensive process undertaken to devise this battery, there are several additional advantages associated with incorporating the MCCB into a battery for bipolar disorder: 1) given the expected widespread use in large-scale trials of patients with schizophrenia, adoption of MCCB in bipolar disorder would greatly facilitate the ability to compare cognitive functioning between schizophrenia and bipolar disorder; 2) the MCCB has commercial translations for six languages (German, Spanish-Spain, Spanish-Latin America, Chinese, Russian, and Hindi), with several other commercial translations underway, making this battery useful for international collaborations (<http://www.matrics.ucla.edu/matrics-ct/home.html>); and 3) The ongoing development of neuroscience-based and preclinical batteries that will parallel or complement the existing MCCB, suggests that future translational work will be made easier by inclusion of the MATRICS subtests in current data collections.

The final consensus of the workgroup was that while the MCCB may provide an ideal starting point in designing a battery to be used in bipolar patients for cognitive trials, supplemental measures should be considered with illness-specific factors in mind.