Reviewer’s report

Title: Morphological correlates to cognitive dysfunction in schizophrenia as studied with Bayesian regression

Version: 1 Date: 9 December 2005

Reviewer: Martha Shenton

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Summary: The investigators applied two statistical methods to evaluate the correlation between morphological abnormalities on MRI scans and neuropsychological test performance in 71 patients diagnosed with schizophrenia, schizoaffective disorder, or psychosis not otherwise specified, compared with 65 controls. The main finding was enlarged ventricles, a common finding in schizophrenia. In addition, findings revealed smaller volume in the cerebellar vermis, and larger volume in the caudate and putamen in schizophrenia. The latter is also a common finding though it may be related to neuroleptic medications. Additionally, neurological test scores showed that verbal learning, recall of recently learned, vigilance, slower visuo-motor speed, impairments in executive functioning, and less efficient working memory characterized patients compared with controls. Moreover, impaired performance was correlated with larger ventricles and, more specifically, putamen and caudate were correlated with verbal learning problems, corpus callosum was correlated with verbal memory, and cerebellar vermis was correlated with several other measures in the patient group. The investigators concluded that the use of advanced statistical methods shows a correlation between morphological abnormalities and neuropsychological performance, although they noted that a larger sample is needed for validation.

Strengths of the Study: The investigators have access to an interesting subject population derived from the Human Brain Informatics (acronym HUBIN), established at the Karolinska Institute in Stockholm, Sweden. The concept of using advanced statistical methods to investigate and elucidate combinations of risk factors in schizophrenia, derived from an extensive database, is an important area of inquiry.

Some Areas Needing Further Attention: The main problem with this study is that the investigators have applied two statistical methods to a population of patients and controls with no a priori hypotheses. This lack of a priori hypotheses suggests that a validation sample is critical to include. Had the investigators had a small set of predetermined hypotheses, this would be less critical to validate.

Other problems include: (1) the issue of gender differences between groups has not been adequately addressed; (2) a discussion of the number of variables (i.e., 37 but another n=200 for the brain) has not been adequately reviewed with respect to the power needed to detect associations in pairs of data. (3) The word "change" for brain morphology is not appropriate, as brains over time are not being evaluated. A better word would be "morphological abnormalities" rather than "morphological changes". Similarly, the word "reduction" in reference to volume is misleading, as there is no indication of reduction per se. (4) Further information regarding the selection of the two statistical methods for data mining, including a further rationale, is needed. Specifically, because there are many data mining tools, why did the investigators select these two? (5) The results are very hard to follow. For example, why list all of the variations of neuropsychological tests that show differences? That is, is there one measure among the WCST that is most informative? Also the acronyms used are not defined in the table. Finally, the figures are quite confusing and the display chosen does not at all elucidate the findings but instead obfuscates them. A different approach to
showing the main findings of the study is needed. (6) When all is said and done, what does this 
study add to what we know about brain morphology abnormalities and their association with 
cognitive function in schizophrenia? What is the added value of this study? This needs to be clearly 
stated as it is not at all clear what new information is provided in this study. In fact in the discussion 
section, the investigators begin with findings from this study compared to other findings using this 
data set. Additionally, the discussion section is confusing as it is not clear what the point is of stating 
that volume is but one measure of abnormality in schizophrenia. (7) A native English speaker should 
go over the manuscript, as there are some odd uses of language.