Lessons from MATRICS

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In 2002, Hyman and Fenton\(^1\) observed that it may be unrealistic for a drug to be effective for all the manifestations of a complex disorder such as schizophrenia. They recommended that drug development focus on components of these disorders that may be more proximate to the pathophysiology. This approach led to National Institute of Mental Health’s (NIMH) support of the MATRICS (Management and Treatment Research to Improve Cognition in Schizophrenia) initiative that developed tools to support the development of drugs that targeted impaired cognition in schizophrenia. The products from this initiative have had a substantial influence on the pharmaceutical industry, which has made a substantial investment in drug development for this indication. A more modest process\(^2\) focused on negative symptoms as a target.

The first results from these trials have been a bit confusing. One trial of an alpha 7 nicotinic agonist focused on cognition and found an effect on negative symptoms.\(^3\) Another study of a neuro-protective peptide\(^4\) failed to find an effect on measures of cognition but may have detected a signal on a measure of functional capacity. These results are both preliminary and unreplicated, but they serve as a reminder that this is a very new therapeutic area and it is unclear how a pharmacological agent will lead to an improvement in functioning. To be clear, the cross-sectional associations between cognitive impairment and negative symptoms and impaired functioning in schizophrenia have been shown in a number of individual studies and meta-analyses. However, it is unclear how improvement in these domains can lead to improved functioning. It is important to realize that the tools developed for these trials may be perfectly adequate and this will become clear when the right drug engages the right molecular target. Given the relationships between composite scores on the MATRICS Consensus Cognitive Battery (MCCB) and scores on functional capacity measures such as the UCSD Performance-based Skills Assessment (UPSA),\(^5\) it is likely that a strong effect on cognition will be associated with an effect on an individual’s ability to carry out functionally meaningful tasks. However, rather than waiting for that drug, this may be a good time to review experiences from these trials and speculate about things that might obscure a signal.

The current trial designs\(^6,7\) assume that an effective cognition enhancing drug or an agent for negative symptoms will result in improvement on a drug compared with a baseline without any additional interventions. The responses of schizophrenia patients to \(D\)-amphetamine\(^8\) can be used as support for this design because oral administration leads to improvement on cognitive measures and negative symptoms particularly diminished expressiveness. However, it is unclear if the short-term activation from \(D\)-amphetamine leads to improved functioning or to sustained improvement in cognition or negative symptoms when it is administered chronically. It is also conceivable that a drug may improve an individual’s ability to engage neural networks that have functioned suboptimally, but only when the individual has been trained to use this newly improved resource. For example, if a patient has had impaired working memory for decades, that individual may have developed processes over the years for compensating for this deficit by using less efficient strategies using other neural processes. In order to detect an effect of a drug, it would be necessary to retrain the person to use the more efficient processes. This would support a trial design that includes both cognitive training and a drug. The study could include cognitive training as a condition in a 2 × 2 or similar design to determine if the cognitive training is a necessary component or all study subjects could be administered cognitive training.

It is also important to consider whether studies are being conducted on subjects who are most likely to show an effect. Large industry studies as well as those from academic groups such as the NIMH TURNS (Treatment Units for Research on Neurocognition in Schizophrenia) are enrolling patients who are similar to those who have participated in other large trials. These individuals tend to be in their 40s and to have had more...
than 20 years of treatment for schizophrenia. These trials also tend to have subjects who are largely unemployed and unmarried. These patients also show substantial cognitive impairment; usually well over 2 SDs below the mean on their MCCB composite scores. Although this is a relatively convenient sample to recruit, these may not be the individuals who are most likely to show improvements in these indications. Conceivably, the best responses may occur early in the illness when subjects are actively involved in school or work. It is also unclear if these agents will be effective throughout the range of severity. Drugs to improve cognition or negative symptoms may be more effective in individuals with relatively mild impairment compared with those who tend to enter current clinical studies.

There are a number of approaches that may be helpful to move the field forward. First, we should remain skeptical as to whether or not we are measuring the right thing. The important therapeutic goal is to improve functioning, and there may be a number of paths for doing this that are more effective than improving the MCCB composite score or a composite negative symptom score. It may be useful to identify individuals who are able to improve their functioning from a variety of treatments and use this to develop new hypotheses and define the most important targets that are proximal to neural systems. For cognition, the best targets may be attention, processing speed, or even measures of neural plasticity (which can be derived from an individual’s response to training). The NIMH Research Domain Criteria (RDoC) initiative⁹ which will focus on linking genes to circuits to behaviors is likely to succeed when there are better descriptions as to how alterations in the functioning of neural circuits are translated into human behavior and subjective experience. Careful interviewing of subjects in research trials using qualitative research methods may reveal drug effects that are unexpected. A large number of clinical trials in schizophrenia are currently underway that are addressing several new molecular targets. We are likely to learn the most from these trials if we have an open mind as to how these drugs will affect patients.

References