A Cognitive Neuroscience Trifecta

The article by Thakkar et al. in this issue (1) examines the brain functioning correlates of a very simple but highly important process: imitation. Using brain imaging and a simple task—observing versus imitating simple hand movements—the authors uncover brain dysfunctions in people with schizophrenia that may have major social cognitive relevance. Brain regions associated with imitation were underactivated during imitation and overactivated during observation. Thus, there is evidence of inefficient and nonspecific regional brain functioning. These findings are similar to reports over the past two decades in studies of neurocognitive functioning using much more complex procedures. There too, the findings suggested underactivation of important regions (as defined by the brain functioning of healthy individuals) during task performance and overactivation of regions that appear less relevant to the task immediately at hand.

As major social problems are commonly seen in people with schizophrenia, understanding their origin, both neurobiological and behavioral, is critically important. While study of the activation of the brain while observing versus imitating hand movements may seem too specific to be relevant, it actually targets a critical learning process with specific relevance to social functioning. Many higher-level social skills are learned through observation and imitation. From the beginning, infants learn many skills through imitation, starting with basic motor skills learned in the preverbal period.

Perhaps the most influential theory of social functioning was advanced by Bandura in 1971 (2). "Social learning theory" posits that a person's observation of another individual modeling behavioral acts will result in learning social functioning through imitation. Much of the research on social learning theory focused on the characteristics of the model and the observer's relationship to that model. The Thakkar et al. article presents critical data suggesting that the basic neurobiological processes of observation and imitation of others may be deficient in people with schizophrenia, with many higher levels affected in a bottom-to-top manner. As a result, these findings have the potential to have identified the first step in the cascade of poor social functioning in schizophrenia: the inability to learn through basic observational and imitative processes.

The Thakkar et al. piece is not the only excellent article on the neuroscience of social and neurocognition in this issue. In fact, this issue contains a trifecta of important studies in the cognitive and social neuroscience of schizophrenia. In a study of resting-state activity in the hippocampus, Tregellas et al. (3) also found evidence consistent with misallocation of brain activation in people with schizophrenia. Specifically, greater resting activity of the hippocampus (particularly the right side) was observed in people with schizophrenia compared with healthy subjects. Of specific interest was the finding that greater resting activity in people with schizophrenia was correlated with more severe negative symptoms as assessed by the Scale for Assessment of Negative Symptoms. Furthermore, greater resting activity was associated with poorer cognitive performance as measured by the composite scores on the MATRICS Consensus Cognitive Battery (MCCB), a comprehensive neurocognitive assessment battery. Thus, greater resting activity

appears not only to be a marker of the illness, but also to be associated with the two features of the illness that lead to the greatest functional morbidity.

Negative symptoms are clearly implicated in social deficits in schizophrenia, and cognitive impairments are associated with impairments in vocational and everyday functional skills. Thus, this finding, albeit in a small sample, has the potential to identify a common neurobiological substrate of the phenotypic factors that are the strongest candidates for determining the substantial wide-ranging disability seen in schizophrenia.

It is one thing to find what is broken on a neurobiological basis in schizophrenia and quite another to fix it. In fact, until the past 10 years, we were much further along in the process of finding than fixing neurobiological deficits. The review article in this issue by Keshavan et al. (4) highlights the striking progress made in the treatment of cognitive impairments through cognitive training in people with schizophrenia in the past 10 years. Much more than a review article, this is a synthesis of the results and a sophisticated attempt to highlight the neurobiological benefits of cognitive training. The developing understanding of the potential for cognitive training to promote neuroplastic change is in the forefront in this article and is presented quite clearly as the rationale for selection of cognitive training strategies.

Also considered, however, are a number of the practical concerns regarding making sure that patients benefit from the interventions. These include the apparent need in most intervention trials for patients to receive some sort of psychosocial intervention to optimize real-world functional outcomes and the concerns regarding other possibly mediating factors, such as motivation and emotional states.

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One additional critical strength of the Keshavan et al. article is the clear description and delineation of the strategic targets of the intervention. For the past 30 or more years, cognitive psychologists have differentiated between top-down (global cognitive skills such as executive functioning) and bottom-up (basic cognitive skills such as sensation and perception). The logic of each target for intervention is easy to understand: If you train a global cognitive process, such as teaching patients strategies for planning ahead, you intrinsically exercise many basic skills, such as enhancing their ability to pay attention. This is sometimes called the top-down approach, which contrasts with helping patients enhance their basic skills, such as learning to pay attention to sensory stimuli, as a prerequisite for learning global cognitive tasks. This is referred to as the bottom-up approach.

Where these three articles meet is at the juncture of top-down versus bottom-up. Thakkar et al. (1) present evidence that the highly specific imitation skills that may underlie complex social interactions are impaired and have a neurobiological basis. Tregellas et al. (3) demonstrate that resting-state activation of the hippocampus is differentially related to two of the most global indices of functioning collected in contemporary schizophrenia research—the MCCB and total score on a measure of negative symptoms. Thus, evidence is presented here that basic neurobiological abnormalities are associated with molecular indices of social interactions as well as complex cognitive and symptomatic factors. The evidence to date is insufficient to allow us to decide whether a cognitive training intervention aimed at basic imitation processes, such as those Thakkar et al. studied, would be more likely to normalize the impaired brain activation than an intervention aimed at global neurocognitive performance. What we do know is that these interventions exist and

that we can now reliably identify and measure the brain functioning correlates of these processes.

These three articles represent the state of the art in translational neuroscience. They also provide concrete directions for the development of interventions aimed at our true goal: normalization of the lives of people with schizophrenia.

References

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Dr. Harvey has worked as a consultant for Abbvie, Boeheringer Ingelheim, En Vivo Pharma, Forest Labs, Genentech, Roche, Sunovion, and Takeda Pharma and has contracted research with Genentech. Dr. Freedman has reviewed this editorial and found no evidence of influence from these relationships.