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Cognitive Training in Schizophrenia: Golden Age or Wild West?

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Six years ago, at the first Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) meeting, a neuroscientist questioned whether attention dysfunction was malleable in schizophrenia, despite a recent report that patients were 5 times more likely to work when cognitive remediation was combined with supported employment (1). The idea that impaired neural systems could demonstrate learning-induced plasticity was not part of the biological research lexicon at that point in time. Experimental neuroscientists were rightfully skeptical of a broad array of cognitive remediation interventions that were often studied under non-blinded and variously controlled conditions. Perplexing, also, was the homogeneity of effect sizes, despite widely varying treatment approaches, outcome measures, and length of intervention.

Golden Age or Wild West?

Six years later, the field is at a tipping point. The systems neuroscience of learning-induced plasticity is a mature and sophisticated area of inquiry. Concomitantly, trials of cognitive enhancing medications in schizophrenia have been disappointing, and investigators increasingly recognize that medications will need to be combined with cognitive enrichment strategies to drive meaningful clinical improvement. Studies of computerized cognitive training in schizophrenia show consistent patterns of increased prefrontal cortical activation as compared with various control conditions; the increased activation correlates with improvements in the trained cognitive domain, and in one instance, with transfer to an untrained meta-cognitive task and with better functioning at 6-month follow-up (2).

Why, then, is the story not over? Why, when it comes to understanding how to optimize functionally meaningful and enduring cognitive improvement in schizophrenia, does it seem as if we have entered the Wild West rather than the Golden Age? How does one make sense of the plethora of computerized and noncomputerized behavioral training approaches described in the literature? Do we have any evidence whatsoever on the critical neural mechanisms that drive functionally meaningful change?

Not surprisingly, the answers to these questions are complex, as highlighted by the report of Penadés *et al.* (3) in this issue. Put simply, the field is poised between two opposing perspectives: one that more broadly focuses on treatment development versus a targeted focus on plasticity in defined neural systems (Table).

In the study by Penadés *et al.* (3), which belongs to the broad cognitive remediation legacy, 15 individuals with schizophrenia engaged in cognitive remediation therapy (CRT), meeting with a

trained coach for 40 sessions of pencil-and-paper exercises in cognitive flexibility, working memory, and planning. After CRT, they demonstrated a reduction in overactivation of the central executive neural network independent component (CEN) as well as increased white matter integrity in the genu of the corpus callosum, compared with patients who met with a therapist for 40 sessions to discuss how to cope with symptoms and identify warning signs of relapse. Penadés *et al.* (3) have driven the final nail into the coffin on the idea that the brain in schizophrenia is not malleable! The question is malleable in response to what? Which neurobehavioral mechanisms are driving that malleability? And what exactly does it represent in terms of both short-term and long-term significance?

Malleable in Response to What?

We do not know from the report by Penadés *et al.* (3) whether the participants were blind to group allocation. We do not know whether the therapists in the control condition had the same training/enthusiasm/expectations for a positive outcome as did the CRT coaches, and we do not know whether the assessment personnel were blind to group assignment. Not only are all three factors a potential source of bias in the outcome data, they may actually represent critical mechanisms of neurobehavioral change. Almost half a century ago, Wagner (4) investigated brief attention and abstraction training in schizophrenia and found that the experimenter was a positive social reinforcer who clearly “enhanced the motivational condition of the subjects” and contributed to their improved cognitive performance. More recent research has established unequivocally that motivational factors and beliefs substantially affect people’s ability to recruit cognitive and neural resources to sustain learning over time (5).

Thus, in the study by Penadés *et al.* (3), as in many previous published reports, we cannot separate out the effects of nonspecific cognitive enhancing factors, such as therapist enthusiasm, participant motivation and expectations, and general cognitive and socioaffective stimulation, from the effects of a specific neurobehavioral training strategy in a defined neural system (in this case, strategy coaching for executive functions and working memory). Such nonspecific cognitive enhancement is by no means a bad thing, and in clinical settings one would want to harness it as intentionally as possible, but in an experimental design, it confounds our ability to isolate and identify the precise mechanisms that drive critical responses in neural systems of interest. In this light, it is sobering to consider the highly rigorous double-blind study by Dickinson *et al.* (6) comparing a cognitive remediation program for schizophrenia based on problem-solving educational software plus therapist coaching versus game-based software plus coaching. This study tightly controlled for the effects of nonspecific cognitive enhancing factors such as participant expectation and therapist motivation and contact and found no significant group differences on neurocognitive or functional outcome measures,

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Table. Schematic Outline of Two Opposing Perspectives that Inform the Approach to Cognitive Training Studies in Schizophrenia

Broad Cognitive Remediation Perspective	Targeted Cognitive Training Perspective
Emerges from 2 decades of psychology treatment research, with a focus on neuropsychological rehabilitation	Emerges from 2 decades of systems neuroscience research, with a focus on training-induced neuroplasticity in defined neural systems
Dominated by a treatment development paradigm	Dominated by an experimental medicine paradigm
Multiple active ingredients often embedded together in real-world settings in an effort to maximize behavioral change	Critical drivers of behavioral change are isolated to identify underlying pathophysiology as well as mechanisms of response to intervention

allowing us to conclude that the specific features of this problem-solving cognitive training method were not efficacious.

Which Neurobehavioral Mechanisms are Driving the Malleability?

Not surprisingly, the CRT subjects who practiced strategies to improve cognitive flexibility, planning, working memory, and verbal and spatial memory showed better performance on tests of cognitive flexibility and verbal and spatial memory.

What is more interesting is where the CRT subjects did not improve: on tests of working memory, despite receiving multiple exercises in working memory. The CRT group also did not improve on processing speed or on the N-back working memory task used during the imaging sessions, which makes it difficult to interpret imaging changes with respect to cognitive findings. Certainly CRT requires repeated engagement of prefrontal problem-solving and planning operations, and behavioral improvement in these operations appears to correlate with reduced overactivation in the CEN component teased apart from the tensorial independent component analysis. Again, these results are not surprising, given that Edwards *et al.* (7) demonstrated that just one session of strategy training on a cognitive control task had a significant effect in people with schizophrenia, normalizing prefrontal cortical activation dynamics.

Only a small portion of what is undoubtedly a rich and interesting imaging data set is shown in this article, and the reader must infer details of the group-by-time activation findings as well as key information about structure-function correlations. Furthermore, although the data are not shown, the authors inform us that there was a negative relationship between increased functional anisotropy in the corpus callosum and decreased CEN overactivation after CRT, and they propose that the increase in white matter integrity was associated with normalization of the functional activation pattern during the working memory task. As of yet, there are no known normal or expected structure-function relationships in these networks and anatomical structures, and given the lack of behavioral improvement in working memory task performance, this conclusion may be premature. Nonetheless, these are intriguing preliminary results that raise important questions for future studies.

What is the Long-Term Significance of the Malleability?

The proximal effects of CRT raise critical issues not only about mechanistic specificity but also about durability and generalization of change. The ultimate goal of any treatment is to generate long-lasting and meaningful gains in real-world functioning. Will more white matter in the genu of the corpus callosum do the trick? Or better performance on card-sorting tasks? At this point in time, we simply do not know. Given the striking executive dysfunction that characterizes schizophrenia,

it is reasonable to predict that cognitive remediation methods such as the CRT that focus on prefrontal planning and problem-solving capacities will have widespread and enduring benefits. We have argued elsewhere that, counterintuitively, the most robust and durable neurobehavioral gains in schizophrenia will occur when cognitive training targets early perceptual processing and working memory operations across well-defined distributed neural systems (8).

Popov *et al.* (9) have contrasted elements of these two approaches and shown very different behavioral and neural system effects. Although the long-term and real-world implications of these findings are not yet known, there are tantalizing hints from the aging literature. In a multisite, randomized, single-masked clinical trial of more than 2000 older adults, subjects who received 10 hours of computerized training in perceptual speed of processing showed significantly improved cognition, lower rates of depression, and lower medical expenditures at 1 and 5 years, plus greater self-rated health outcomes at 5 years, than those who received 10 sessions of therapist coaching in reasoning strategies or in memory strategies [e.g., (10)]. Taken together, emerging data suggest that strategy-coaching cognitive remediation approaches and perceptual learning/speed of processing cognitive training methods may harness quite different brain mechanisms, may be beneficial in different ways to different classes of individuals and may have very different long-term effects on neurocognitive functions and real-world outcomes. The challenge now is to design carefully controlled longitudinal studies that can investigate these questions fully and determine the optimal approach to driving personalized, functionally meaningful, and enduring malleability in the brains of people with schizophrenia and other neuropsychiatric illnesses. Only then will the West be won!

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