

Brain Changes in Schizophrenia Respond to Non-Drug Therapy

By John Gever, Senior Editor, MedPage Today

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Reviewed by [Dori F. Zaleznik, MD](#); Associate Clinical Professor of Medicine, Harvard Medical School, Boston and

Dorothy Caputo, MA, RN, BC-ADM, CDE, Nurse Planner

A non-drug "cognitive enhancement therapy" stopped and even reversed the brain shrinkage that often accompanies schizophrenia, results of a randomized trial showed.

Patients with recent-onset schizophrenia who participated in two years of social-cognitive training and exercise sessions showed smaller losses in gray matter in some brain regions and greater increases in others, compared with a control group treated with conventional supportive therapy, reported Matcheri S. Keshavan, MD, of Beth Israel Deaconess Medical Center in Boston, and colleagues.

Cognitive enhancement therapy "can protect against gray matter loss and may even support gray matter growth in medial temporal areas of the brain in service of cognitive enhancement among patients with early course schizophrenia," Keshavan and colleagues wrote online in *Archives of General Psychiatry*.

The intervention included personalized computer-based neurocognitive training using such tools as the Orientation Remediation Module created by Yehuda Ben-Yishay, PhD, and PSSCogReHab software developed by Odie Bracy, PhD.

These sessions were conducted with pairs of patients, who also stayed together in group socialization and experiential learning sessions. Three or four patient pairs participated in these sessions, which included "both innovative cognitive exercises and psychoeducation that foster the development of social-cognitive abilities and effective social interaction," Keshavan and colleagues explained.

"Generalization to real-world settings is an explicit goal of cognitive enhancement therapy, and is promoted through weekly homework assignments and individual coaching sessions tailored to the unique needs of the patient," they wrote.

The goal, they indicated, was to help patients overcome the cognitive deficits that typically accompany schizophrenia, even in its early stages.

"Progressive loss of gray matter, frontal hypofunction, and decreased white matter integrity have been consistently observed in patients with schizophrenia," Keshavan and colleagues noted.

The resulting deficits do not respond to antipsychotic drugs, although cognitive therapy has been helpful in previous trials in improving performance in standardized tests.

But the current study is the first to demonstrate that these improvements correspond to physical changes in the brain.

Keshavan and colleagues randomized 53 symptomatically stable patients with schizophrenia or schizoaffective disorder and who showed pronounced cognitive deficits to receive cognitive enhancement therapy or a control program called enriched supportive therapy.

The latter is a talk-based approach in which patients are taught stress reduction and illness management techniques. It was provided in weekly individual sessions initially, followed by biweekly sessions.

Patients, who had a mean age of 26, were evaluated with about a dozen neurocognitive and social function tests and also underwent MRI scans at baseline and after two years of treatment to measure brain volume in different regions.

As they expected, the researchers found significant improvements in patients' cognitive and social abilities.

These were significantly correlated with changes in gray matter volume in regions including the left amygdala and the left parahippocampal and fusiform gyrus:

- Left amygdala: social cognition, $\beta=0.25$, $P=0.03$; neurocognition, $\beta=0.09$, $P=0.56$
- Left parahippocampal gyrus: social cognition, $\beta=0.24$, $P=0.03$; neurocognition, $\beta=0.41$, $P=0.004$
- Left fusiform gyrus: social cognition, $\beta=0.33$, $P=0.02$; neurocognition, $\beta=0.54$, $P=0.004$

Patients assigned to cognitive enhancement therapy had slight increases in mean volumes of those areas as well as in the left hippocampus, all of which are in the medial temporal lobe. Small increases were also seen in the right insula in the temporal lobe and the left anterior cingulate in the frontal lobe.

In contrast, patients in the control group had decreases in mean volume in all areas. For the four structures in the medial temporal lobe, the differences between groups were statistically significant.

So-called mediator analyses indicated that the neuroprotective effects offered by cognitive enhancement therapy were centered in the left-side amygdala and parahippocampal and fusiform gyrus.

These same regions have been identified as centers for social and cognitive functioning in the population at large.

Keshavan and colleagues concluded that the program "can have direct benefits to the brains of patients with schizophrenia."

But they also noted several limitations to the study. The relationship of the relatively modest changes they saw in brain volume to actual brain function is not fully known, and they suggested that future studies incorporate functional neuroimaging to confirm the suggestion seen in the current trial.

The researchers also pointed out that the therapy appeared to have little effect on other regions previously believed to mediate neurocognitive deficits in schizophrenia, such as the dorsolateral prefrontal cortex, anterior cingulate, and hippocampus.

They suggested that brain morphology may be an imperfect indicator of brain function, with strong correlations in some areas and situations but not others.

Keshavan and colleagues also said the lack of a healthy control group meant the study had no normative data on brain volumes in young adults over time. They noted that earlier studies had suggested that healthy young people had some loss of gray matter, although it appeared to occur in regions other than those seen in the current study.

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Study authors reported relationships with Abbott and GlaxoSmithKline. Two authors are co-owners of CET Training LLC, a company that designs cognitive enhancement therapies.

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