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Scans Link 2 Key Pieces of Schizophrenia Puzzle

Using functional brain imaging, National Institute of Mental Health scientists for the first time have linked two key, but until now unconnected, brain abnormalities in schizophrenia. They have shown that the less patients' frontal lobes activate during a working memory task, the more the chemical messenger dopamine, thought to underlie the delusions and hallucinations of schizophrenia, rises abnormally in the striatum, a relay station deep in the brain. Together with other evidence, this suggests that the excess dopamine activity that antipsychotic drugs quell may be driven by a defect in the prefrontal cortex, the brain's executive control center. Andreas Meyer-Lindenberg, M.D., Karen Berman, M.D., and colleagues report on their PET (positron emission tomography) study, published online January 28, 2002, in *Nature Neuroscience*.

The most disabling form of mental illness, schizophrenia affects one percent of the adult population, typically in young adulthood, with hallucinations, delusions, social withdrawal, flattened emotions and loss of social and personal care skills. Although the cause of the disorder remains a mystery, studies that shed light on the role of dopamine in schizophrenia hold promise for advancing understanding and, ultimately, improving treatments.

The researchers used two different types of radioactive tracers in the same scanning sessions with 6 patients and 6 healthy controls to simultaneously monitor two different types of brain activity. A radioactive form of oxygen revealed where blood flowed, and hence what parts of the brain were active during the experimental task. A radioactively-tagged chemical precursor of dopamine indicated activity of this chemical messenger. The PET scanner employs an array of radiation detectors to get a fix on the destinations of the tracers, producing color-coded, quantitative images of the activity being measured.

The scans were taken while subjects performed an abstract reasoning / working memory task that activates the prefrontal cortex. As in previous studies, the patients showed reduced prefrontal activation and performed poorly on the task, suggesting disturbed functioning of that part of the brain. Also consistent with previous findings, patients' striatal dopamine activity was abnormally elevated. In patients, but not in controls, the researchers observed a tight coupling and highly significant inverse correlation between these two abnormalities, suggesting that they share a "common pathophysiological mechanism."

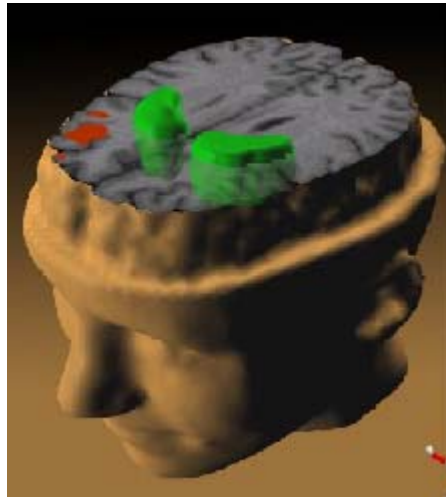
The striking linkage is likely traceable to a primary dysfunction of the prefrontal cortex, argue the investigators, who cite basic science findings that dopamine activity in the striatum is under the control of the prefrontal area. Stimulating or inhibiting this area affects firing of striatal neurons and dopamine release. A recent study in rats found that neurons that project from

the prefrontal cortex to the striatum are inhibitory in effect, suggesting an anatomical mechanism by which reduced prefrontal activity might take the brakes off striatal dopamine release. Using magnetic resonance spectroscopy, colleagues in the NIMH Clinical Brain Disorders Branch have discovered a similar correlation between decreased NAA (N-Acetyl Aspartate), an indicator of the health of cells, in the prefrontal cortex, and excess dopamine release in response to amphetamine.

"These results provide a long-sought insight into the roots of dopamine dysregulation in schizophrenia," said Berman. "They suggest a possible treatment strategy that targets prefrontal cortex dysfunction, not just excess dopamine."

Also participating in the research were: Daniel Weinberger, M.D., Philip Kohn, Giuseppe Esposito, M.D., NIMH; Robert Miletich, M.D., Ph.D., Mario Quarantelli, M.D., National Institute on Neurological Disorders and Stroke; Richard Carson, Ph.D., NIH Clinical Center.

While patients performed a working memory task, the less the prefrontal cortex (red) activated, the more dopamine increased in the striatum (green).



Source: Andreas Meyer-Lindenberg, M.D., Ph.D., NIMH Clinical Brain Disorders Branch