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Patterns of normal brain activity may predispose individuals to different symptoms of psychosis

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A new study released today offers a potential predictive technique to anticipate how individuals might behave during a psychotic episode. The study, in the June 18 issue of *The Journal of Neuroscience*, related the brain activity of healthy participants to how they behaved after exposure to ketamine (a psychosis-inducing drug that mimics schizophrenia symptoms). The findings help explain why schizophrenia symptoms vary greatly from person to person and may ultimately help personalize diagnosis and intervention.

"In schizophrenia, why might one individual suffer predominantly from biz arre and unpleasant perceptions, while another is haunted by frightening beliefs that he is being persecuted, and yet another is mainly troubled by difficulties in ordering his thoughts and motivating himself?" asked Paul Fletcher, MD, at the University of Cambridge, the senior researcher who led the study.

Fletcher and colleagues hypothesize that these different symptoms have distinct biological underpinnings, each of which may disrupt normal cognitive processes. The researchers reason that individual differences in normal cognitive functioning — that is, each person's unique patterns of brain activity — might indicate which processes are most at risk of being compromised by drug-induced psychosis or schizophrenia.

Schizophrenia symptoms include "negative" ones that involve the loss of

normal behaviors, including social withdrawal and reductions in speech, and "positive" ones that involve the gain of abnormal ones (or the excess of normal behaviors) such as hallucinations, delusions, and disordered thought. However, schizophrenia symptoms vary unpredictably from person to person.

Ketamine, known by the street name "Special K," is an often-abused analgesic that induces both positive and negative symptoms. Like schizophrenia, the effects of ketamine are variable and unpredictable. Ketamine works by blocking receptors for the neurotransmitter glutamate, which are also implicated in schizophrenia.

Using functional magnetic resonance imaging (fMRI), the researchers profiled 15 people exposed to either ketamine or placebo while they did a variety of cognitive tasks. The researchers then evaluated participants' behaviors using several accepted psychiatric scales. One month later, participants returned to repeat the testing in the opposite drug condition, so each participant was imaged and observed after exposure to both placebo and ketamine.

The researchers found that increased brain activity during some tasks in the placebo condition predicted behaviors in the ketamine condition. The brain's temporal lobe is important in speech, hearing, and memory, and the frontal lobe in "executive" functions — planning, decision-making, and correcting and troubleshooting errors. Participants who showed more frontal and temporal brain activity while imagining the sounds of voices in the placebo condition were more likely to experience strange perceptions in the ketamine condition. Others who showed increased activity in these brain regions while trying to complete simple sentences were more likely to have disordered thoughts when exposed to ketamine.

In contrast to these positive symptoms, participants who showed

increased frontal response to an attentional task in the placebo condition showed increased vulnerability to negative symptoms in the ketamine condition. Similarly, participants who showed increased response in frontal, thalamic, and caudate regions — brain areas linked together in a circuit that is important in executive and motor functions, and which is impaired in many neuropsychiatric diseases — also tended to show negative symptoms in the ketamine condition.

"These researchers have certainly taken a great step forward for our understanding of schizophrenia," said Graham Williams, DPhil, at Yale University, an expert unaffiliated with the study. "At last, we have a tangible, biological approach to unraveling the complex and mystifying symptoms displayed by patients with schizophrenia," Williams said.

The study authors note that the brain profiles associated with ketamine-induced symptoms do not imply increased disease risk in the healthy volunteers, but offer insight into how disease and drug use can cause different effects in different people.

"Our findings may provide a vulnerability marker to predict psychotic symptoms induced by drugs or disease," said study author Fletcher. "This perhaps raises the prospect of early intervention strategies targeted toward schizophrenia patients' individual patterns of symptom vulnerability," he said.

Source: Society for Neuroscience