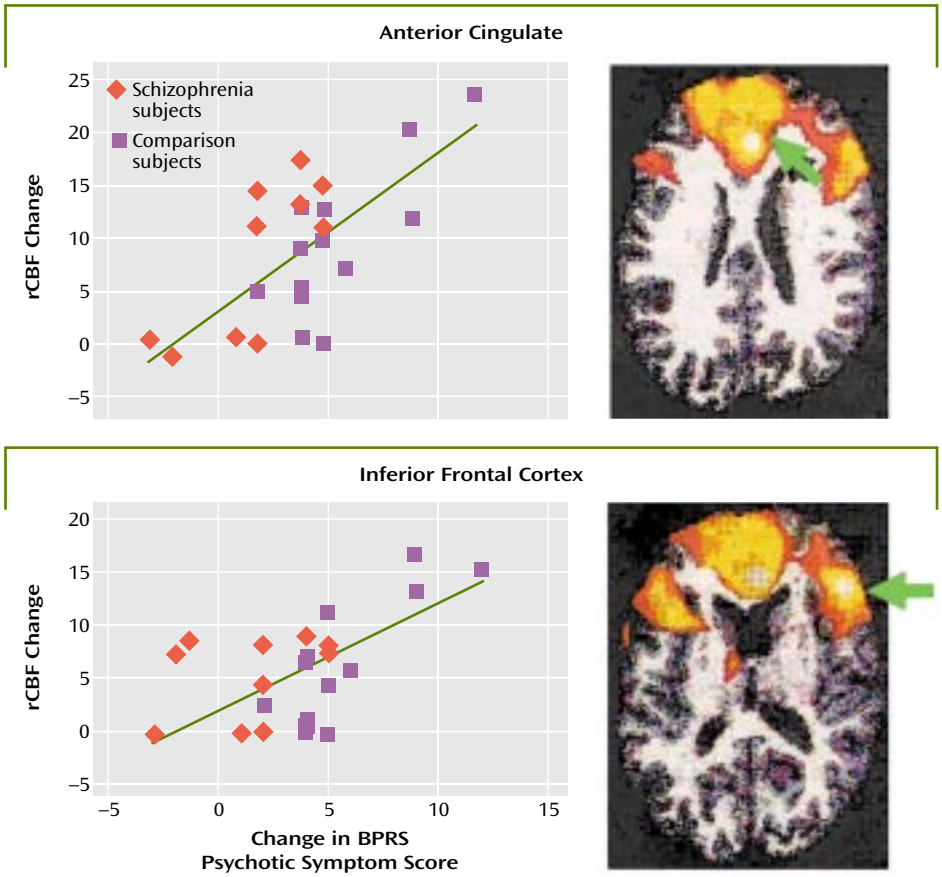
Schizophrenia, VIII



Pharmacologic Models

Ketamine is a commonly used anesthetic that has mild psychotomimetic properties in adults. It produces illusory experiences, mild dissociation of thought, and alterations in cognition, all for a period of 20–30 minutes after a single administration. Investigators have been interested in ketamine for its potential of being a model of schizophrenia, both for positive and negative symptoms. Ketamine produces mild psychotomimetic symptoms in persons with schizophrenia similar to those of healthy subjects and often exacerbates the volunteer's underlying psychotic symptoms. This phenomenon suggests an association with the biology of the illness. Pharmacologically, ketamine acts as an open channel, noncompetitive *N*-methyl-D-aspartate (NMDA) antagonist. It blocks ion flow through the NMDA-gated glutamate ionophore. These clinical observations are consistent with a hypothesis of glutamate receptor hypofunction in schizophrenia, an idea proposed by several investigators in the field. In order to explain the mechanism of action of ketamine in the human brain, we utilized functional brain imaging ($[^{15}O]H_2O$ positron emission tomography [PET]). One of the strengths of functional imaging is the ability to associate changes in symptoms (induced by task, environment, or drug) with regional alterations in neuronal activity. Psychotic symptoms in persons who received ketamine were assessed with the Brief Psychiatric Rating Scale. The response of healthy and schizophrenia volunteers to ketamine was a dose-sensitive increase in psychotic symptoms, similar in both groups except that the schizophrenia volunteers started from a higher psychosis baseline. PET scans acquired with $[^{15}O]$-labeled water, which provides regional cerebral blood flow (rCBF) measurements, were done during ketamine administration. The magnitude of change in psychotic symptoms correlated with the magnitude of increase in rCBF in the anterior cingulate ($r=0.69$, $df=21$, $p<0.01$) and the inferior frontal cortex ($r=0.66$, $df=20$, $p<0.01$). The imaging data suggest that these two areas of the brain play some role in the mediation of the psychotic symptoms produced by ketamine. These data provide information about which brain areas might be active in producing or mediating psychotic symptoms in humans.

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