

# The glutamate hypothesis of schizophrenia

Since the 1960s, biopsychologists have known that schizophrenia is associated with dysregulation of dopamine activity. The main reason for believing this is because drugs that reduce dopamine neurotransmission reduce schizophrenia symptoms in the majority of patients and because administering drugs that increase dopamine activity can induce schizophrenia-like symptoms in clinically normal people and animals.

The glutamate hypothesis is an extension of the dopamine hypothesis. It acknowledges the role of dopamine but suggests that dopamine dysregulation is caused, in turn, by abnormalities in brain systems that use glutamate as their primary neurotransmitter.

In many parts of the brain, glutamate has the effect of regulating dopamine activity. When glutamate activity increases, dopamine activity decreases, so glutamate has an inhibitory effect on dopamine activity. Where it comes to schizophrenia, what was assumed to be the result of excessive dopamine might actually be the result of too little glutamate activity.

There are a number of reasons for believing that schizophrenia is caused by abnormal glutamate activity. First, there are the effects of administering PCP, ketamine and similar drugs. These drugs block activity of the NMDA glutamate receptors. Taken in sufficient doses, they cause psychological changes that mimic the positive, negative and cognitive symptoms of schizophrenia (Javitt & Zukin, 1991). Second, if schizophrenia patients are given PCP or ketamine the result is a marked increase in their symptoms that lasts for some time (Malhotra et al, 1997). Third, post-mortem studies comparing brain tissue of schizophrenia patients with controls have found structural differences in areas related to glutamate including (1) reduced volume of parts of the dorsolateral prefrontal cortex, (2) reduced dendritic branching and (3) reduced volume of glutamate receptors in the schizophrenia patients (Hu et al, 2014).

Post-mortem brain tissue studies like these have the advantage over other methods that they are the only way of observing abnormalities at the level of molecules and cells. Brain imaging techniques are improving but can get nowhere near the same level of detail. Studies with non-human animals have the problem that, whilst there are substantial similarities between humans and animal models (e.g. the same genes, proteins and cell types are found in mice) there are also significant differences (e.g. in molecules, architecture and connectivity). Consequently, even if something that *looks like* schizophrenia can be recreated in an animal model we can't assume it is exactly the same disorder as in humans.

However, there are also limitations to post-mortem studies. The people from whom schizophrenia tissue samples are taken typically die several decades after the onset of the disease. It is therefore difficult to tell whether the changes observed in schizophrenia patients are caused by the disease or by some other factor, such as ageing, substance use (e.g. nicotine) or the long-term effects of antipsychotic medication.