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## Unable to cope with uncertainty: the gateway to psychosis?

Imagine being plunged into a world in which events did not always have the same consequences, and with rules that changed without your knowledge. How would you adapt? Uncertainty as a factor in decision making is a fundamental issue in general psychology. Our world turns out to be more or less predictable, and our brain has to adapt to this uncertainty to make the best possible choices in any situation. This is the subject that attracted Fabien Vinckier and Raphaël Gaillard, researchers at St Anne's Hospital, Inserm and Paris Descartes University, in collaboration with Mathias Pessiglione, an Inserm researcher at the Brain and Spinal Cord Institute at Pitié-Salpêtrière Hospital, AP-HP, and Paul Fletcher, from the University of Cambridge in Great Britain. This study, which has been published in *Molecular Psychiatry*, reveals that our ability to adapt our decisions to the uncertainty inherent in any choice may be disrupted in the early stages of psychosis.

Participants were invited to play a computer game during which they had to decide whether to bet on symbols. The rules were not always applied, and were reversed from time to time (a symbol that always won money started to lose it, and vice versa). When subjected to these conditions, participants, in order to adapt their choices, had to be able to simultaneously detect changes in the rules of play and times of stability. It was possible to show, with the help of mathematical models, that to be most effective, participants use their confidence in the rules of play to make their choices.

In order to reproduce the conditions for the early stages of psychosis, participants were intravenously administered either a placebo or a very low dose of ketamine. Ketamine is an anaesthetic that is used daily in high doses in operating theatres, and which, at low doses, causes symptoms strongly resembling the early stages of a psychotic episode. Continuous measurement of the participants' behaviour and brain activity using functional magnetic resonance imaging (fMRI) made it possible to identify the effects of ketamine.

Using this model, the researchers demonstrated that ketamine affects the ability of participants to distinguish times when the rules of play are stable, and optimise their behaviour accordingly.

Thus, they did not come to a point where they systematically bet on the winning symbol (i.e. betting 100% of the time, even though the symbol only actually won 80% of the time), as if a persistent doubt unsettled them. This impairment is correlated with a disturbance in the fronto-parietal brain network.

*“This study characterises the key role of adaptation to uncertainty in decision-making, and its disruption in the early stages of psychosis. It should enable a better understanding of the onset of psychotic illness, and guide therapeutic innovation,”* explains Raphaël Gaillard, Professor of Psychiatry at Paris Descartes University, and Head of the Department of Mental Health and Therapeutics at St Anne’s Hospital.

This study reveals, in a pharmacological model of psychosis, the disruption of a person’s ability to finely adapt his/her behaviour to the uncertain nature of the environment. The brain bases for this impairment have been identified (a fronto-parietal network), and can be linked to the molecular pathway on which ketamine acts, and which is currently the focus of a search for new treatments for schizophrenia.

These findings are a continuation of a publication that appeared in the journal Science (Whitson, Science, 2008) on the onset of apparently psychotic phenomena (superstitions, conspiracy theories) in people who are subjected to strong uncertainty. Some psychotic symptoms, such as the emergence of delusions, could be a type of inappropriate response to the inability to construct and maintain a stable representation of the world

#### **Source**

Confidence and psychosis: a neuro-computational account of contingency learning disruption by NMDA blockade

Vinckier F \*, Gaillard R\*, Palminteri S, Rigoux L, Salvador A, Fornito A, Adapa R, Krebs MO, Pessiglione M, Fletcher PC

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