Genetic variant impairs communication within the brain

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For some time now it has been known that certain hereditary factors enhance the risk of schizophrenia or a manic-depressive disorder. However, just how this occurs had remained obscure. Researchers at the Zentralinstitut für Seelische Gesundheit in Mannheim, Heidelberg University and Bonn University are now able to answer this question, at least for one common genetic variant: this impairs the interoperation of certain regions of the brain. The study is to appear on 1st May in the prestigious scientific journal *Science*. It will also be suited to provide fresh stimuli for the search for cures.

The scientists examined test persons with whom a certain genetic trait had undergone a characteristic mutation. A year ago, a research team had demonstrated that this mutation was, amongst other things, associated with an enhanced risk of schizophrenia. In addition to this, people carrying this variant were more susceptible to a bipolar malady also known as a manic-depressive disorder. In the present case, however, our results were based on examinations of 115 healthy subjects.

"At this point, no-one had the slightest idea of what effect the genetic variant we had observed might have on the brain", declares Professor Dr. Andreas Meyer-Lindenberg. The director of the Zentralinstitut für Seelische Gesundheit was the initiator of the study. "We examined our test subjects in magnetic resonance tomographs, which reveal how the various areas of the brain interoperate".

Result: persons suffering from this high-risk genetic variant exhibited a

change in the communication between their dorsolateral prefrontal cortex (DLPFC) and other regions of their brains. The DLPFC plays an active role in the working memory and diverse "higher" cerebral functions. It comprises a right-hand and a left-hand fraction, and it was the communication between these two halves which had become impaired. In contrast to this, the link between the DLPFC and the hippocampus, a further region of the brain of importance for the memory, was improved. Both these noteworthy phenomena had already been shown to exist in patients suffering from schizophrenia.

Moreover, carriers of this high-risk gene also displayed an enhanced linkage between the amygdala and a number of other cerebral regions. The amygdala, also known as the "almond", plays an active role in the manner in which we cope with our emotions. "Which is why we have related this phenomenon to the bipolar impairment, which is, as we know, characterised by erratic mood swings", Professor Dr. Dr. Henrik Walter of Bonn University explains.

Over 100 years ago, the German psychiatrist Carl Wernicke had already suspected that schizophrenia might be attributable to impaired interoperation between different regions of the brain. The new study, employing an innovative combination of modern genetics and cerebral imaging, has confirmed this suspicion.

The mutated gene contains the building plan for a protein whose precise function is still not clear. Diverse study groups worldwide are currently engaged in finding answer to this question - amongst other reasons, because this could provide approaches to novel treatments. "It is impressive that using modern methods we are able to trace such subtle genetic effects in the living brain", says Professor Dr. Peter Kirsch, head of the Study Group for Cerebral Imaging in Mannheim. Carriers of this variant, incidentally, must not be worried that they are destined to suffer from schizophrenia or bipolar impairment. "This genetic variant plays

only a minor role in these disorders", says Dr. Christine Esslinger from the Zentralinstitut für Seelische Gesundheit reassuringly. Other factors must at all events become involved before a disorder such as this breaks out.

More information: Neural Mechanisms of a Genomewide Important Psychosis Variant. Christine Esslinger, Henrik Walter, Peter Kirsch, Susanne Erk, Knut Schnell, Claudia Arnold, Leila Haddad, Daniela Mier, Carola Opitz von Boberfeld, Kyeon Raab, StephanieH.Witt, Marcella Rietschel, Sven Cichon, Andreas Meyer-Lindenberg. *Science*, 1.5.2009

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