Ruprecht-Karls-Universität Heidelberg
Medizinische Fakultät Mannheim
Dissertations-Kurzfassung

Brain networks in pharmacological fMRI of NMDA antagonists

Autor: Robert Becker
Institut / Klinik: Zentralinstitut für Seelische Gesundheit Mannheim (ZI)
Doktorvater: Prof. Dr. A. Sartorius

In recent years network methods have gained great popularity in the analysis of resting state data obtained by functional magnetic resonance imaging (fMRI). Network alterations have been found to be induced by various psychiatric disorders as well as drug induced states. Depression, being one of the most prevalent psychiatric disorders, is of special interest for psychiatric research. Brain networks have been found to be affected by depression in many clinical studies examining a variety of patient cohorts (different ages, types of depression, treatment status).
Ketamine, an N-methyl-d-aspartate (NMDA) receptor antagonist, was found to act antidepressantly at sub anaesthetic doses. In contrast to conventional antidepressants (e.g. selective serotonin reuptake inhibitors), ketamine acts very quickly (within hours) and reliably even in treatment resistant patients. However ketamine also induces dissociative effects, often percieved as aversive.
Since this discovery was made, other NMDA receptor antagonists are examined as potential glutamatergic antidepressants sharing ketamine's antidepressant action but not its dissociative effects. Two candidate drugs were investigated here: Lanicemine (AZD7665), a low trapping NMDA channel blocker, and traxoprodil, a non-competitive antagonist targeting the NR2B subgroup of the receptor.
One objective of this work was the translation of network methods mostly developed for human studies to preclinical fMRI and the demonstration of their translational potential in a study comparing effects of ketamine across species. Network alterations were supposed to be similar in humans and rats.
As expected, we found largely congruent effects. In both species ketamine induced a more segregated network structure as well as large-scale connectivity alterations. These results show the direct translatability of network methods across species and therefore underline their potential for preclinical neuroscientific research.
Furthermore the network effects of traxoprodil and lanicemine were investigated in another fMRI study in rats. Based on to the effects of ketamine found in previous studies we expected increased connectivity in the hippocampal-prefrontal (Hc-PFC) network as well as reduced network integration. For traxoprodil results were expected to be generally similar to those found for ketamine. Due to its similar mechanism of action we expected similar but less pronounced results for lanicemine compared to ketamine. Nevertheless, deviating results between different NMDA antagonists might help explaining the mechanisms underlying their effects.
Like ketamine, traxoprodil induced an increase in Hc-PFC coupling, however its effect was less pronounced. Lanicemine hardly had any significant effect on this subnetwork. The extent to which Hc-PFC coupling was induced by the three drugs corresponds well to their antidepressant efficacy in clinical trials, which suggests a central role of Hc-PFC coupling in the action of glutamatergic antidepressants.