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Second-generation antipsychotic drug-induced functional connectivity alterations and network modifications in rodent resting-state imaging

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Identifying quantifiable biomarkers in neuroimaging has become a major focus both in humans and translational models. The potential of linking resting-state brain phenotypes to drug efficacy is to facilitate the development of innovative drugs in the early stage. The number of new medicines in the treatment of schizophrenia and psychosis has been diminutive in the previous years, in spite of the need of new therapeutics to cope with negative symptoms and cognitive impairments. Thus, resting-state functional magnetic resonance imaging has increasingly been applied in the pharmacological research to study drug-induced alterations of functional connectivity within brain networks. However, there are only few studies on antipsychotic drug-induced alterations of resting-state functional connectivity in rodents. Quantitative comparisons of drug-induced network alterations are missing. Therefore, this study employed receptor binding affinities to relate the antipsychotics' molecular mechanism of action to brain network modifications.

Resting-state magnetic resonance images were acquired upon single-shot administration of three second-generation antipsychotics (amisulpride, risperidone and olanzapine) in Sprague-Dawley rats, in order to compare the drug-induced functional connectivity patterns and to identify a resting-state correlate of drug efficacy. Functional connectivity correlation coefficients between anatomically defined regions of interest and between independent components were not significantly changed upon drug administration, nor was the network constructed from these regions affected, irrespective of the dose of the antipsychotics. The reasons for the absence of significant drug effects may be due to small sample sizes and constraints of the methodology.

In the second step, the relationship between binding affinities to dopamine and serotonin receptors and drug-induced functional connectivity alterations of the prefrontal cortex and striatum were examined. A linear relationship between receptor binding affinities and functional connectivity measures was discovered only for the mid-dose of antipsychotics. Stronger affinity to serotonin 2A, 2C and 1A receptors and decreased affinity to dopamine 3 receptors was associated with increased prefrontal-striatal correlation coefficients. Moreover, stronger affinity to dopamine 3 receptors was associated with lower degree and lower local clustering of the striatum. On the contrary, higher affinity to serotonin 1A, 2A and 2C receptors was associated with higher degree, local clustering, and betweenness centrality of the striatum. Interestingly, no significant relationships were observed for dopamine 2 receptors, and for the low- and high-dose groups.

The results of this work indicate that drug-induced functional connectivity patterns may be linked with the drugs' mechanism of action on the molecular level. The findings illustrate the potential of investigating the relationship between molecular mechanisms and network-level effects. The association between strong anti-serotonergic affinity of antipsychotics with high fronto-striatal connectivity and local network modifications, such as increases in degree, local clustering and betweenness centrality, represents a potential brain phenotype that could be validated by including a higher number of antipsychotics in such investigations or by focusing on drug-induced network modifications in humans.