

Neural circuits

Psilocybin shapes neural plasticity in selective brain networks

Although progress has been made in understanding how fast-acting antidepressants (such as ketamine) and psychedelics (such as psilocybin) work, the cellular and circuit mechanisms remain incompletely understood. In this paper, Jiang et al. show that a single dose of psilocybin differentially rewires specific brain network inputs to mouse dorsal medial frontal cortex.

The dorsal medial frontal cortex is strongly implicated in the effects of fast-acting antidepressants. Individuals with major depressive disorder have fewer dendritic spines on excitatory neurons, and in mice, increased spine density on frontal neurons in the dorsal medial frontal cortex is one of the effects of fast-acting antidepressants. In addition, of the two main subtypes of excitatory pyramidal neurons in frontal cortex (pyramidal tract (PT) and intratelencephalic (IT) neurons), the PT subtype is required for the long-term effects of psilocybin. To better understand the neural mechanisms that underlie the plasticity-promoting effects of this psychedelic drug, the authors set out to determine how psilocybin-induced structural plasticity maps onto specific neural pathways in the brain.

Using an engineered rabies virus for monosynaptic tracing, the authors investigated connectivity changes in presynaptic inputs to PT and IT neurons following a single dose of

psilocybin (or vehicle for the controls). They measured the fraction of presynaptic input before and after treatment, and from this inferred which brain areas and/or networks might be involved. Compared to vehicle, psilocybin increased presynaptic input fraction to PT cells from brain areas such as primary somatosensory cortex and retrosplenial cortex (RSP) that represent projections belonging to the visual–auditory and sensorimotor networks and medial network (the mouse equivalent of the default mode network), and decreased this fraction to PT cells from areas including the ventromedial prefrontal cortex and medial thalamic nuclei. By contrast, for the IT subtype, increases to the input fraction were found in projections located in the lateral aspect of the neocortex and ventromedial prefrontal cortex and there was a decreased input fraction from the sensorimotor network – overall indicating that psilocybin changes the organization of synaptic input to PT and IT subtypes in a cell-type- and network-specific manner.

Next, the authors investigated the mechanisms that drive this network plasticity. Using FOS expression as a proxy for neuronal activation, the authors found that brain regions with increases in psilocybin-induced FOS expression were associated with an increased input fraction to frontal PT neurons, whereas

increased FOS expression was associated with a loss of inputs to the IT subtype. The changes in FOS expression indicated a role for neuronal activation in the structural plasticity induced by psilocybin. The authors chose to focus on RSP as it has dense reciprocal connections with the dorsal medial frontal cortex and is a key region involved in the effects of psychedelics. Psilocybin administration induced a selective increase in spiking activity in these RSP projection neurons, and chemogenetic silencing of these neurons prevented the connectivity change induced by psilocybin administration.

“psilocybin changes the organization of synaptic input to PT and IT subtypes in a cell-type- and network-specific manner”

Together, these findings indicate that a single dose of psilocybin induces specific reorganization of large-scale brain networks in an activity-dependent manner, which might relate to its rapid antidepressant action.

Sian Lewis

Original article: Jiang, Q. et al. Psilocybin triggers an activity-dependent rewiring of large-scale cortical networks. *Cell* <https://doi.org/10.1016/j.cell.2025.11.009> (2025)