The brain circuits responsible for sustained, efficacious antidepressant effects by ketamine

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Mood disorders like major depressive disorder are likely accompanied by distributed system-level disturbances in brain circuitry. Converging evidence has demonstrated that a single subanesthetic dose of ketamine, a non-competitive N-methyl-D-aspartic acid (NMDA) receptor antagonist, produces a rapid-acting and long-lasting antidepressant response attributable to synaptic plasticity. By comparing the brain connectome of anesthetized monkeys 18 hours after ketamine and saline administration using resting-state fMRI technique and graph theoretical analysis, the relevant brain circuits that underlie the long-term, efficacious action of ketamine were uncovered. Ketamine intake induced persistent global reconfiguration of small-world properties, accompanied by large-scale downregulation of functional connectivity, most prominently in the orbital prefrontal cortex, subgenual and posterior cingulate cortices, and nucleus accumbens. Intriguingly, intrinsic connectivity with the medial prefrontal areas in the reward circuits was selectively downregulated. Global and regional regulations of the brain networks precisely opposed the maladaptive alterations in the depressed brain. These findings demonstrated that local synaptic plasticity triggered by blockade of NMDA receptors was capable of translating into prolonged network reconfiguration in the distributed cortico-limbic-striatal circuit, providing mechanistic insight into developing specific loci or circuit-targeted, long-term therapeutics.

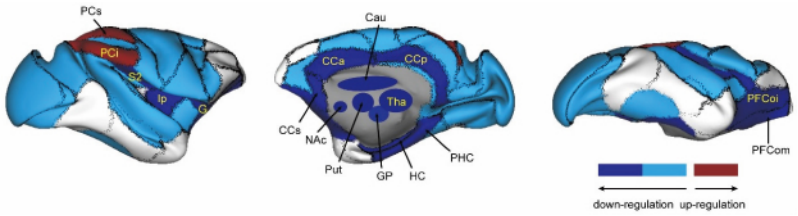

Figure Overall illustration of affected macaque brain regions, shown by lateral (left), medial (middle) and ventral (right) views on the right hemisphere. The most prominent up-and down-regulated brain regions modulated by ketamine are labelled.