anterior cingulate and the raphe regions are specifically involved, but with less certainty. The separate methodological challenges associated with these two non-invasive imaging modalities will be discussed.

**Speaker 2: Qiyong Gong, China**

**Title:** High-field magnetic resonance imaging studies of major depressive disorder: a circuit-based analysis

**Abstract**

Major depressive disorder (MDD) is characterized by persistent, pervasive feelings of sadness, guilt, and worthlessness and often results in an increased risk of suicide. Imaging evidences suggest that MDD is a kind of disconnection syndrome, however, the related brain circuitry and networks remain poorly understood.

Magnetic resonance (MR) imaging allows noninvasive investigation of the circuits and brain networks in vivo. MR diffusion tensor tractography, for example, can track the fiber bundles and permits the assessment of the structural connectivity of the brain. In addition, the fast development of functional MR imaging (fMRI) opens a new window to explore how different parts of the brain functionally connect, interact and coordinate with each other. In particular, the functional connectivity MR imaging (fcMRI) enables the functional connectivity between the brain regions to be effectively investigated.

Using high-field MR imaging, researches on MDD has generally focused on two major clinical issues, i.e., suicidality and refractoriness. Studies using diffusion tensor imaging have revealed microstructural abnormalities of the frontal-striatal circuits passing through the anterior limb of the internal capsule associated with suicidality among MDD patients. With respect to refractoriness of the MDD, study has revealed differences in functional connectivity related to treatment responsiveness, with the non refractory group showing a decrease mainly in the limbic-striatal-pallidal-thalamic circuits, and the refractory group showing a decrease mainly in thalamo-cortical circuits.

In addition to the investigation of brain circuitry, brain connectome study of MDD using the high-field MR imaging is also promising. Given that MDD is a ‘disorders’ encompassing multiple, heterogeneous, behavioral phenotypic features, MDD is increasingly understood as a disorder of distributed effects of aberrant interaction in the brain, i.e. a network-based disorder. Several core brain networks have been identified using intrinsic physiological coupling in resting-state fMRI data, such as default mode network (DMN), salience network (SN) and central executive network (CEN). Depression is characterized by both stimulus-induced heightened activity and a failure to normally down-regulate activity broadly within the DMN. Study suggests that brain regions in DMN, SN and CEN are linked together through the dorsal nucleus, and this help explain how symptoms of MDD arise in distinct networks—decreased ability to focus on cognitive tasks, rumination, excessive self-focus, increased vigilance, and emotional, visceral, and autonomic dysregulation—could occur concurrently and behave synergistically. In addition, the combination of resting-state fMRI and graph-based network analysis allows revealing the topological organization of whole-brain functional networks, such as small-world properties and network modularity, and study has revealed disrupted topological organization of intrinsic functional brain networks during rest in MDD patients.

In summary, the alterations of the brain circuitry and connectome in MDD can be investigated using the high-field MR imaging. In conjunction with the advanced imaging analysis, MR imaging of these circuit-based abnormalities not only provides unique insight into the underlying psychopathologies, but also is potentially of translation value in assisting early detection, therapeutic intervention and prognostic prediction of the patients with MDD.

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A single dose of ketamine restores hippocampal-accumbens drive, normalizes dopamine neuron firing, and reverses behavioral despair in the forced swim test.

These data suggest that the ILPFC and LHb regulate different subpopulations of DA neurons within the mesolimbic system. This appears to have important relevance to understanding the DA system deficits observed in the CMS model of MDD, as this striking pattern of differential regulation appears to explain the unique restorative capacity of ILPFC inactivation in reversing the abnormal DA system hypoactivity observed in this widely used model. Furthermore, these data highlight the importance of the ILPFC as a critical node in depressive circuitry and a potential link between affective and motivational systems in the rodent brain.

Speaker 4: Alan Frazer, USA
Title: Brain Circuits Involved in the Antidepressant-Like Effects of Ketamine

Abstract
There is great interest in studying ketamine given the rapid and sustained behavioral improvement it causes in patients with treatment resistant depression. Much research has focused on the molecular mechanisms of action of ketamine and there is evidence that NMDA receptor antagonism is a necessary component of its activity. Further, such receptors on GABAergic interneurons in the hippocampus are likely to be a primary target for NMDA receptor antagonists. However, there is a lack of understanding with regard to the contribution of specific brain circuits involved in either its rapid and/or sustained antidepressant-like effects. We used different approaches to examine the role of the ventral hippocampus (vHipp)-medial prefrontal cortex (mPFC) pathway in ketamine’s sustained antidepressant-like response in rats, as measured by the use of the forced swim test (FST). These included (1) inactivating pharmacologically the vHipp to mPFC pathway with lidocaine; (2) determining if activation of the pathway using DREADDs would mimic the effect of ketamine in the FST; and (3) activating the pathway using optogenetics to see if this reproduced the effects of ketamine or inactivating it optogenetically to determine if this prevented the effect of ketamine. All three approaches gave results from which it could be concluded that the vHipp to mPFC pathway is both necessary and sufficient for ketamine’s antidepressant-like effect. Activation or inhibition of other pathways neither reproduced ketamine’s effect nor blocked it. Because of this, we hypothesized that another way to mimic the antidepressant-like effect of ketamine would be to block or reduce GABAergic transmission in the hippocampus. L-655,708 is a negative allosteric modulator of GABA\(_A\) receptors and as such, would be expected to block GABAergic activity. In addition, it exhibits selectivity for the \(\alpha\) subunit of the GABA\(_A\) receptor with this subunit being localized primarily in the hippocampus. Systemic administration of this drug produced a sustained (7 days) antidepressant-like effect in the FST. To examine possible rewarding effects of ketamine that could contribute to its abuse potential, self-administration experiments were carried out. Ketamine was self-administered by rats. However, L-655,708 was not. It should be possible, then, to develop novel antidepressants that recapitulate the beneficial effects of ketamine without having abuse-liability.