anterior cingulate and the raphe regions are specifically involved, but with less certainty. The separate methodological challenges associated with these two non-invase 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 nexus, 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.

References

1. Lui S, Zhou XJ, Sweeney J, Gong QY. Psychoradiology: The Frontier of Neuroimaging in Psychiatry. *Radiology*, In press. [Invited Review]
2. Gong QY, He Y (2015). Depression, Neuroimaging and Connectomics: A Selective Overview. *Biological Psychiatry*, 77 (3), 223–35. [Invited Review]
3. Gong Q, Lui S, & Sweeney JA (2015). A selective review of cerebral abnormalities in patients with frst-episode schizophrenia before and after treatment. *American Journal of Psychiatry*. online; Epub ahead of print [Invited Review]
4. Gong QY, Li L, Du M, Pettersson-Yeo W, Crossley N, Yang X, Li J, Huang X, & Mechelli A (2014). Quantitative prediction of individual psychopathology in trauma survivors using resting-state fMRI. *Neuropsychopharmacology,* 39(3), 681–687
5. Zhang J, Wang J, Wu Q, Kuang W, Huang X, He Y, & Gong Q (2011). Disrupted brain connectivity networks in drug-naive, first-episode major depressive disorder. *Biological Psychiatry*, 70(4), 334–42.
6. Lui S, Wu Q, Qiu L, Yang X, Kuang W, Chan RC, Huang X, Kemp GJ, Mechelli A, & Gong QY (2011). Resting-state functional connectivity in treatment-resistant depression. *American Journal of Psychiatry,* 168(6), 642–648.
7. Jia Z, Huang X, Wu Q, Zhang T, Lui S, Zhang J, Amatya N, Kuang W, Chan RC, Kemp GJ, Mechelli A, & Gong QY (2010). High-field magnetic resonance imaging of suicidality in patients with major depressive disorder. *American Journal of Psychiatry,* 167(11), 1381–1390.
8. Gong Q, Wu Q, Scarpazza C, Lui S, Jia Z, Marquand A, Huang X, McGuire P, & Mechelli A (2011). Prognostic prediction of therapeutic response in Depression using high-field MR imaging. *NeuroImage,* 55(4), 1497–503.
9. Liao Y, Huang X, Wu Q, Yang C, Kuang W, Du M, Lui S, Yue Q, Chan RCK, Kemp GJ, & Gong QY (2013). Is depression a disconnection syndrome? Meta-analysis of diffusion tensor imaging studies in patients with MDD. *Journal of Psychiatry & Neuroscience,* 38(1), 49–56
10. Lui S, Parkes LM, Huang X, Zou K, Chan RC, Yang H, Zou L, Li D, Tang H, Zhang T, Li X, Wei Y, Chen L, Sun X, Kemp GJ, & Gong Q (2009). Depressive disorders: focally altered cerebral perfusion measured with arterial spin-labeling MR imaging. *Radiology,* 251(2), 476–84.
11. Chen S, Wu X, Lui S, Wu Q, Yao Z, Li Q, Liang D, An D, Zhang X, Fang J, Huang X, Zhou D, & Gong QY (2012). Resting-state fMRI study of treatment-naive temporal lobe epilepsy patients with depressive symptoms. *NeuroImage,* 60(1), 299–304
12. Jia Z, Wang Y, Huang X, Kuang W, Wu Q, Lui S, Sweeney JA, & Gong QY (2014). Impaired frontothalamic circuitry in suicidal patients with depression revealed by diffusion tensor imaging at 3.0 T. *Journal of Psychiatry & Neuroscience,* 39(3), 170–177.
13. Qiu L, Lui S, Kuang W, Huang X, Li J, Zhang J, Chen H, Sweeney JA, & Gong QY (2014). Regional increases of cortical thickness in untreated, first-episode major depressive disorder. *Translational Psychiatry,* 4, e378.
14. Li F, Huang X, Tang W, Yang Y, Li B, Kemp GJ, Mechelli A, & Gong QY (2014). Multivariate pattern analysis of DTI reveals differential white matter in individuals with obsessive-compulsive disorder. *Human Brain Mapping,* 35(6), 2643–2651.

15. Zhao YJ, Du MY, Huang XQ, Lui S, Chen ZQ, Liu J, Luo Y, Wang XL, Kemp GJ, & Gong QY (2014). Brain grey matter abnormalities in medication-free patients with major depressive disorder: a meta-analysis. *Psychological Medicine,* 44(14), 2927–2937
16. Qiu L, Huang X, Zhang J, Wang Y, Kuang W, Li J, Wang X, Wang L, Yang X, Lui S, Mechelli A, & Gong QY (2014). Characterization of major depressive disorder using a multiparametric classification approach based on high resolution structural images. *Journal of Psychiatry & Neuroscience,* 39(2), 78–86.
17. Du M, Liu J, Chen Z, Huang X, Li J, Kuang W, Yang Y, Zhang W, Zhou D, Bi F, Kendrick KM, & Gong QY (2014). Brain grey matter volume alterations in late-life depression. *Journal of Psychiatry & Neuroscience,* 39(6), 397–406.
18. Zhang H, Li L, Wu M, Chen Z, Hu X, Chen Y, Zhu H, Jia Z, & Gong Q (2015). Brain gray matter alterations in first episodes of depression: A meta-analysis of whole-brain studies. *Neuroscience and Biobehavioral Reviews*, 60:43–50. doi: 10.1016/j.neubiorev. 2015.10.011.
19. Chen Z, Zhang H, Jia Z, Zhong J, Huang X, Du M, Chen L, Kuang W, Sweeney JA, & Gong QY (2015). Magnetization transfer imaging of suicidal patients with major depressive disorder. *Scientific Reports,* 5, 9670. doi: 10.1038/srep09670.

Speaker 3: Anthony Grace, USA

Title: Imbalance between the amygdala and the hippocampus in down-modulating dopamine system responsivity in animal models of depression

Abstract

Dysregulation of the mesolimbic dopamine (DA) system has garnered increasing attention as a key component of major depressive disorder (MDD). It is thought to be particularly relevant to anhedonia, the reduced interest in pleasurable stimuli, which is considered to be a core symptom of MDD. We have shown that rats exposed to either Chronic Mild Stress (CMS) or Learned Helplessness, two stress-induced animal models of depression, resulted in stress-exposed animals showing a reduction in ventral tegmental area (VTA) DA neuron population activity, i.e. the number of DA neurons active and available to respond to environmentally salient rewarding stimuli. This suggests that in MDD, there is a reduced ability of the DA system to respond to rewarding stimuli, which could therefore represent the neural substrate of clinical anhedonia. Drawing from human neuroimaging research, we identified two candidate regions that were investigated in the present study. The infralimbic prefrontal cortex (ILPFC) is the rodent homologue of human Brodmann Area 25, a region that is established to be key to MDD pathophysiology and is under investigation as a target of deep brain stimulation for treatment resistant depression. We found that activation of the ILPFC or the habenula in normal rats potently suppressed VTA DA neuron population activity ($p<0.05$), albeit in different patterns. ILPFC activation primarily affected medial VTA DA neurons, whereas LHb activation inhibited more central and lateral VTA DA neurons. In rats that underwent CMS (which impacts primarily medial VTA DA neurons), only ILPFC inactivation restored VTA DA neuron population activity to normal levels, while LHb inactivation had no restorative effect on DA neuron population activity.

We have also examined the impact of the rapid acting antidepressant ketamine. In rats exposed to learned helplessness, the decrease in DA neuron activity was accompanied by long-term depression in the hippocampus-accumbens circuit that normally activates the dopamine system, suggesting that the lack of hippocampal drive fails to offset the ILPFC down-regulation. 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

Alan Frazer, Ph.D.; Flavia Carreño, Ph.D.; Gregory Collins, Ph.D.; Daniel Lodge, Ph.D.

Department of Pharmacology, University of Texas Health Science Center at San Antonio

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.[1] 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.[2] 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 $\alpha5$ subunit of the $GABA_A$ receptor with this subunit being localized primarily in the hippocampus.[3] 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.