In This Issue

Volume 79, Number 9, May 1, 2016

A brief summary of the articles appearing in this issue of *Biological Psychiatry*.

Review: Gamma Oscillation Models of Schizophrenia

Data from human studies have suggested that *N*-methyl-D-aspartate (NMDA) receptor deficits in parvalbumin-expressing (PV) inhibitory neurons may contribute to schizophrenia. This is thought to result in changes in the cortical network that manifest into positive and negative symptoms of the disease and are reflected in abnormal electroencephalography activity in schizophrenia patients. This hypothesis is being explored in several animal models of the disease, the results of which **Jadi *et al.*** (pages 716–726) review in this article. They also review the computational models of cortical dynamics that can potentially link the neurotransmission deficits to electroencephalogram abnormalities observed in the animal models, and ultimately schizophrenia patients.

Hippocampus, Cognition, and NMDA Receptors

Anti-NMDA receptor encephalitis is an autoimmune encephalitis that manifests with a characteristic neuropsychiatric syndrome and mainly affects young women, the majority of whom suffer from persistent memory impairment despite unremarkable routine clinical magnetic resonance imaging. Investigating a large cohort of recovering patients using advanced imaging analyses, **Finke *et al.*** (pages 727–734) identify structural damage of the hippocampus that includes selective atrophy of hippocampal subfields and impaired hippocampal microstructural integrity, which strongly correlated with memory performance, disease severity, and disease duration. These data demonstrate the importance of rapid diagnosis and immunotherapy to prevent long-term structural and cognitive deficits.

Recent discovery that hippocampal GluN receptors, which are involved in synaptic plasticity and memory, can rapidly traverse the synapse at the neuronal surface has raised the question of whether this surface trafficking sustains GluN receptor physiological functions. Using a multipronged approach, **Potier *et al.*** (pages 735–745) provide evidence that estradiol regulates NMDA receptor surface dynamics and is a necessary cellular mechanism for hippocampal synaptic plasticity and associative memory. These findings aid our understanding of GluN receptor signaling implicated in various neuropsychiatric and aging-related cognitive disorders.

Targeting NMDA Receptors to Treat Rett Syndrome

Using a circuit-based approach in wild-type and Rett syndrome mice, **Mierau *et al.*** (pages 746–754) show that NMDA receptor maturation is slower in PV interneurons than in pyramidal neurons. Loss of *Mecp2*, which causes Rett syndrome, accelerated the NMDA receptor subunit switch in PV cells while delaying it in pyramidal cells. Decreasing NMDA receptor GluN2A subunit expression prevented the NMDA receptor defect only in PV cells. Together, these findings indicate that PV-cell-based NMDA receptors may serve as a novel target for the development of new circuit-based therapies for Rett syndrome.

Recent findings have identified the NMDA receptor as a possible target for intervention in Rett syndrome, a neurodevelopmental disorder. **Patrizi *et al.*** (pages 755–764) performed a preclinical trial of low-dose ketamine, an NMDA antagonist, in a murine model of Rett syndrome. Daily exposure to ketamine reversed deficits in cortical neuronal activity and connectivity in conjunction with significant improvements in general health and survival in *Mecp2*-null mice. These data support a potential drug intervention strategy for Rett syndrome.

Ketamine: Network Effects and Stress Resilience

The brain circuits underlying the antidepressant effects of ketamine remain largely unknown. **Lv *et al.*** (pages 765–775) used resting-state functional magnetic resonance imaging to examine sustained network effects in monkeys after single-dose ketamine administration. Results show synergistic regulation of cortico-limbic-striatal circuits precisely opposing the altered brain activity observed in depressed patients. These findings suggest that local synaptic plasticity triggered by ketamine translates into prolonged network reconfiguration and provides mechanistic insight into developing circuit-targeted long-term therapeutics.

Enhancing stress resilience in at-risk individuals may be a way to prevent the development of negative consequences following stress exposure. Using social defeat, learned helplessness, and a chronic corticosterone model, **Brachman *et al.*** (pages 776–786) found that ketamine protected mice against stress-induced depressive-like behavior for at least 4 weeks following administration. These data suggest that ketamine may augment stress resilience and may help protect against stress-induced psychiatric disorders such as posttraumatic stress disorder.

ISSN: 0006-3223