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How is the brain modified by experience, deprivation and disease?

Our overarching interest is in the question of how experience and deprivation modify synaptic connections in the brain. Experience-dependent synaptic plasticity is the physical substrate of memory, sculpts connections during postnatal development to determine the capabilities and limitations of brain functions, is responsible for the reorganization of the brain after damage, and is vulnerable in numerous psychiatric and neurological diseases and contributes to their symptoms.

Historically, our major efforts to address this question have been focused on the visual cortex and hippocampus. The visual cortex is a site of robust experience-dependent synaptic plasticity, exemplified by the consequences of temporary monocular deprivation (MD) during childhood. MD sets in motion a stereotyped choreography of synaptic modification whereby the deprived-eye inputs to visual cortex rapidly lose strength and, with a delay, the open-eye inputs undergo a compensatory gain in strength. The behavioral consequence of this plasticity is severe visual impairment in the deprived eye. In humans, this condition is called amblyopia, responsible for loss of vision in over 1% of the world population. Thus, the visual cortex is an excellent preparation to connect the elementary molecular mechanisms of synaptic plasticity to their behavioral consequences. Further, insights into how synapses depress or potentiate have potential clinical applications for the treatment of amblyopia.

The hippocampus is a cortical structure that is critical to forms of learning and memory. The simple cellular architecture of the hippocampus also makes it amenable to electrophysiological investigations of synaptic plasticity that are much more difficult in other parts of the brain. In the early 1990?s we applied insights gained from a theoretical analysis of synaptic plasticity to establish a phenomenon called homosynaptic long-term depression (LTD). LTD is the functional inverse of long-term synaptic potentiation (LTP). Although LTD and

LTP are expressed at synapses throughout the brain, they are particularly robust at the Schaffer collateral synapses in the CA1 region of hippocampus. The hippocampus is therefore an excellent preparation to dissect the molecular basis of bidirectional synaptic plasticity. Insights gained here can not only be applied to synaptic modifications elsewhere in the brain, they are also relevant to understanding the basis of hippocampus-dependent memory storage and diseases of cognition.

In the course of studying LTD we made a discovery that has turned out to have major therapeutic significance for human developmental brain disorders that cause autism. One form of hippocampal LTD is triggered by activation of metabotropic glutamate receptor 5 (mGluR5) and requires immediate translation of mRNAs at synapses. In the course of studying this type of synaptic plasticity, we discovered that protein synthesis (and LTD) downstream of mGluR5 is exaggerated in the mouse model of fragile X (FX). Human FX is caused by the silencing of the FMR1 gene, and is the most common inherited form of intellectual disability and autism. Insight gained by the study of LTD suggested that exaggerated protein synthesis downstream of mGluR5 might be pathogenic, and contribute to many symptoms of the disease. Subsequent tests of the ?mGluR theory? have shown that inhibition of mGluR5 can correct multiple mutant phenotypes in animal models of fragile X ranging from mouse to fruit fly. Human clinical trials were initiated based on the strength of this science, and results to date indicate that treatments can be developed to substantially benefit this patient population. The mGluR theory has contributed to a major paradigm shift that genetic diseases of brain development, historically viewed as untreatable, may be ameliorated or corrected with appropriate therapy.

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Additional Publications

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