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Aberrant Electrical Activity in Neurodevelopment as an Etiology for Cognitive Disorders

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Pharmacological agents that block N-methyl-D-aspartate (NMDA) receptors and/or stimulate gamma-amino butyric acid (GABA) receptors are prominent among drugs that humans can be exposed to during both pre- and postnatal development. They include: recreational drugs such as alcohol, phencyclidine (PCP), and inhalants (e.g. toluene and alkylbenzenes); medical drugs such as anticonvulsants (e.g. felbamate) and some anesthetics (e.g. xenon); and drugs that are used both medically and recreationally (e.g. ketamine, nitrous oxide, and dextromethophan). Exposure of the developing brain to any of this diverse group of chemicals results in decreased electrical activity, and the potential consequences for the child are severe. For example, the leading non-genetic cause of mental retardation is fetal alcohol exposure, and there is support for the hypothesis that decreased NMDA receptor function during development is a cause of schizophrenia.

Despite indications that aberrant electrical activity-regulated development may cause cognitive deficits, a large gap in knowledge remains between these observations and successful intervention based on knowledge of the relevant cellular and molecular mechanisms. I will present two studies that help bridge this gap, and briefly discuss the clinical and cognitive significance of the results. First, to elucidate mechanisms that regulate activity-dependent synaptic remodeling in the developing mammalian visual system, we screened for genes whose expression in the lateral geniculate nucleus is regulated by spontaneously generated action potentials present prior to vision. These experiments indicated that the class I major histocompatibility complex, classically thought to mediate cell-cell interactions exclusively in immune function, plays an important role in neuronal signaling and electrical activity-regulated synaptic development. Second, we performed experiments that begin to tie together studies from different laboratories that separately demonstrate increased cell death and disrupted synaptic development due to decreased NMDA receptor function in the developing brain. Our

results raise the possibility that there is a causal relationship among NMDA receptor function, naturally occurring cell death, and synaptic pattern formation. A better understanding of this relationship should make a significant contribution to closing the gap between basic science and clinical applications that impact cognitive function.

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