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The social life of neurons: synaptic communication deficits as a common denominator of autism, schizophrenia and other cognitive disorders

Detlef H. Heck¹ and Lu Lu^{1,2}

¹Department of Anatomy and Neurobiology, University of Tennessee Health Science Center, Memphis, TN38016, USA

²Jiangsu Key Laboratory of Neuroregeneration, Nantong University, Nantong 226001, China

Autism and autism spectrum disorders such as Angelman syndrome, affect the ability to successfully integrate and participate in social interactions or to understand social exchanges between others. Ongoing interdisciplinary research aims to identify genetic, molecular and neurophysiological causes of autistic phenotypes. Multiple lines of evidence from different disciplines are intersecting at the synapse, the site of chemical communication between neurons and also believed to be the key site of learning in the brain. The human brain contains an estimated 10^{11} neurons, each of which communicates with thousands of other neurons via synaptic connections (1, 2). The estimated number of synapses in the entire human brain is an astronomical 10^{14} (1). The neuronal networks formed by this large number of massively interconnected neurons generate complex spatiotemporal patterns of neuronal activity that require coordinated activity across large populations of neurons using both short- and long-range synaptic connections. On an even larger scale, the mammalian brain is composed of many structurally diverse networks, including the neocortex, thalamus, basal ganglia etc. Healthy brains are characterized by the continuous generation of behavior-related spatiotemporal activity patterns that propagate across multiple brain areas. These patterns, which include synchronous events as well as oscillatory activity at frequencies between ~0.1 and 200 Hz, are believed to be causally linked to higher cognition, including memory formation and retrieval (3). Consistent with this view are findings of abnormalities in large-scale brain activity patterns in patients with cognitive disorders including autism (4). It seems likely that even comparatively minor deficits in the development or maintenance of millions of synaptic connections may have cumulatively large effects on the coordination of spatiotemporal activity patterns associated with cognitive processes. With hundreds of genes involved in the formation of the postsynaptic density in humans, synaptic abnormalities may be a common denominator for many heritable cognitive disorders including autism and schizophrenia (5). Besides network dynamics, deficient synaptic transmission may also be responsible for deficits in the release of neuromodulatory transmitters such as dopamine, that have been associated with autism and schizophrenia (6). The findings by Kaphzan and colleagues reported in this issue (7) provide exciting new evidence for synaptic communication deficits as a common theme in cognitive disorders by showing a direct link between schizophrenia and Angelman syndrome (AS, an autism spectrum disorder) at the level of synaptic plasticity and learning. Kaphzan et al. show that neuregulin-ErbB4 (NRG1-ErbB4) signaling is abnormal in a *Ube3a*-deficient mouse model

Corresponding author: Detlef H. Heck, Ph.D., Dept. Anatomy and Neurobiology, University of Tennessee Health Science Center, 855 Monroe Ave., Memphis, TN 38163, Phone: (+1) 901 448 1678, Fax: (+1) 901 448 7193, dheck@uthsc.edu.

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of Angelman syndrome, resulting in deficits in hippocampal synaptic plasticity and contextual fear memory. The NRG1-ErbB4 pathway has long been implicated in schizophrenia, but thus far schizophrenia and Angelman syndrome have not been considered related in any way. In their report, however, Kaphzan et al. point out several shared clinical and neurophysiological abnormalities, that led them to investigate the role of *ErbB* in *Ube3a*-deficient mice. Most cases of AS in humans are caused by the loss of expression of the maternally imprinted *UBE3A* gene. In the brain expression of the maternal *UBE3A* allele is highest in the cerebellum and hippocampus, hence the focus on synaptic plasticity in the hippocampal region.

Kaphzan and colleagues convincingly establish the link between the two diseases at the neurophysiological and behavioral level in the mouse model. We looked for corroborative data that would connect these two diseases also at the gene level using a systems genetic methods and the BXD family of mice, one of the most widely used genetic reference populations. We carried out a genomic correlation analysis to identify potential interactions of *ErbB4* transcripts with any of the other ~43,000 transcripts using a massive data set (8) available online at GeneNetwork.org. This genetic analysis revealed a significant ($P = 0.00033$) negative correlation between the expression of the *Ube3a* and *ErbB4* transcripts in healthy mice (Fig. 1). Both transcripts are highly variable in expression and this variation can be traced back to their cognate genes, a finding that excludes a major common regulator as a potential mechanism behind the negative correlation. Interestingly, the expression of a number of genes that have been associated with schizophrenia (e.g. *Ate1*), autism (e.g. *Mbd5*) or both (e.g. *Cln3*) show highly significant ($p < 0.0001$) negative correlations with *ErbB4* and positive correlations with *Ube3a*. The competitive or cooperative mechanisms behind these correlations and its biological impact on protein and neuronal function remain to be determined.

Kaphzan and colleague have shown that one gene associated with synaptic transmission and plasticity (*ErbB4*) can be involved in two seemingly unrelated brain disorders. The same turns out to be true for *SHANK3*, which encodes a scaffold protein in the post-synaptic density of excitatory synapses, and is among the genes most strongly associated with autism. A recent case report by Gauthier and colleagues revealed that two de novo mutations in *SHANK3* were associated with Schizophrenia (9), suggesting that *SHANK3* deficits represent a common denominator at least for schizophrenia and autism. Whether *SHANK3* is also involved in AS is currently unknown.

New studies on the biological relevance of sleep have revealed a mechanism that could further complicate synaptic communication deficits and network dysfunction in autism and other cognitive disorders. A large proportion of patients with psychiatric brain disorders often also have abnormal sleep patterns. Recent studies suggest that a crucial function of sleep is to allow for a renormalization of synaptic strength which seems to continually increase during the wakeful state (10). This renormalization is essential for the ability of neuronal networks to normally communicate and store new information, i.e. to learn. Thus, lack of sleep may result in increased synaptic excitability and decreased plasticity, and this would impair all brain functions from simple motor to complex cognitive tasks.

The approach by Kaphzan and colleagues is very promising. It is likely that, as with *ERBB4* and *SHANK3*, other synaptic proteins that are currently strongly associated with one particular mental disorder or spectrum of disorders, will be found to have a role in a broad range of disorders and might provide unexpected new targets for pharmacological or genetic interventions.

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Figure 1.

Pearson correlation analysis of mRNA expression levels for the ErbB4 (X axis) and the Ube3a gene (Y axis) in 67 BxD recombinant inbred mouse strains. Dots represent results for individual strains. The line represents a linear least-square fit.