



Neuro(re)development of brain circuitry: linking cell biology to psychiatric discoveries

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A commentary on

Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis

by Cross-Disorder Group of the Psychiatric Genomics Consortium, Smoller JW, Craddock N, Kendler K, Lee PH, Neale BM, Nurnberger JJ, Ripke S, Santangelo S, Sullivan PF. *Lancet* (2013) 381(9875):1371–9. doi: 10.1016/S0140-6736(12)62129-1

Neurodevelopmental defects are thought to contribute to psychiatric disorders by disrupting the proper wiring of neural circuits. While these defects may underlie putative developmental disorders like schizophrenia, their contribution to others, like major depressive disorder, are less clear. Genome-wide association studies (GWAS) have identified many genes associated with individual disorders. However, given the diverse etiologies and ages of onset of common psychiatric disorders, one might expect individual gene variants to associate mainly with one or two disorders sharing common mechanisms (e.g., defects in synaptic transmission or disrupted axon connectivity). It was therefore surprising that the Cross-Disorder Group of the Psychiatric Genomics Consortium recently identified mutations in L-type calcium channels common to five psychiatric disorders (1), not all of which are thought to be neurodevelopmental in origin (autism spectrum disorder, attention deficit-hyperactivity disorder, bipolar disorder, major depressive disorder, and schizophrenia).

One possibility raised by these results is that a fundamental mechanism is used by the nervous system throughout early

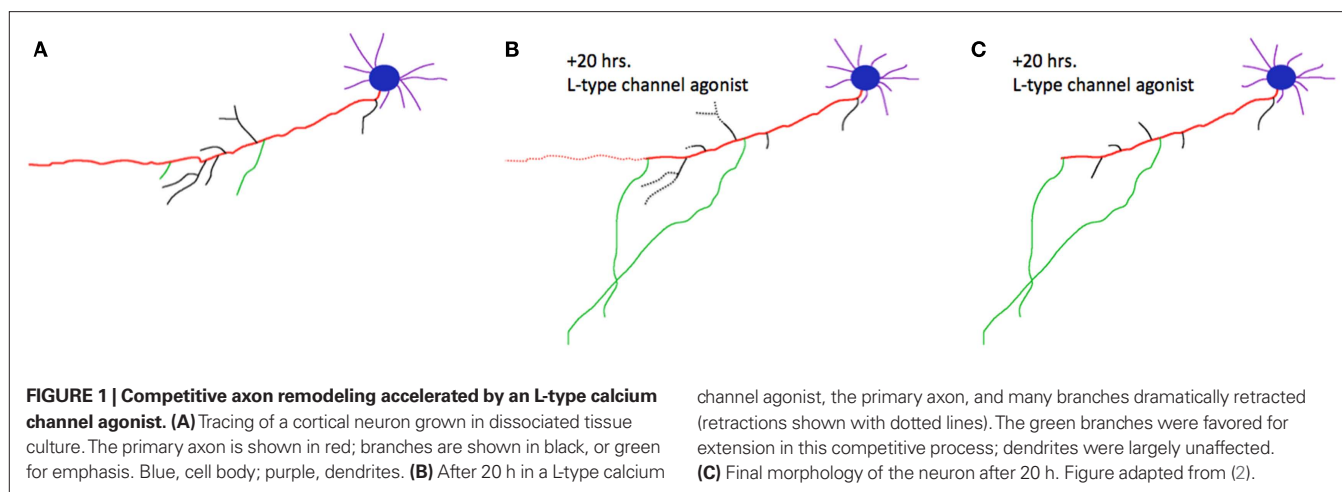
development and into adulthood, that, when disrupted, increases susceptibility to psychiatric disorders in general. If there were such a fundamental mechanism at work, what would it look like? First, it would of course have to operate through L-type channels. Second, it would have to be utilized broadly in the nervous system to account for the pleiotropic effects of these mutations. Third, it would have to operate both during neurodevelopment and in mature circuitry, since the Psychiatric Genomics Consortium (1) implicated these genes in disorders of varied neurodevelopmental contributions.

Basic research from the last decade has identified a common cell biological mechanism that meets these criteria and could potentially explain this source of shared risk for psychiatric disorders: competitive axon remodeling. During competitive axon remodeling, electrical activity drives a local depolarization that leads to L-type voltage gated calcium channel activation and calcium influx localized to a branch or small group of branches (2). These stimulated branches are favored for extension or further branching, and a competitive mechanism is engaged that causes pruning of unstimulated branches from the same axon (2–4). Blocking L-type calcium channels slows competitive axon remodeling, while stimulating these channels accelerates this process (2), fulfilling the first criterion of dependence on L-type channels. An example of this process is shown in **Figure 1**. This process has been identified in cortical neurons (2), hippocampal neurons (3), and peripheral neurons (4), meeting the second criterion of broad utilization. Finally, imaging of axon dynamics in the adult neocortex has demonstrated that mature axons

continue to dynamically extend and retract branches (5, 6). Although at a lower rate than in pre- and post-natal critical periods, this process still occurs at these later, post-developmental stages of life. In addition to the large-scale axon remodeling in development, the capacity for experience-dependent, competitive axon remodeling is preserved through adulthood in primates as well (7, 8). This shows that axon remodeling is not limited to developmental windows, but instead that neural circuits continue to “re-develop” with experience in adulthood.

Importantly, gene expression data from humans (Human Brain Transcriptome) suggest that the two L-type calcium channel-associated genes identified by the Psychiatric Genomics Consortium (CACNA1C and CACNB2) (1) are broadly expressed in the nervous system. Furthermore, expression of these genes is upregulated between embryonic weeks 13–19, when long-distance axonal tracts such as the corpus callosum are being established (9). Unlike some developmental genes, the expression of these two genes remains high through adulthood. This places these genes at the right times and in a sufficiently broad distribution of brain areas to influence competitive axon remodeling in each of these psychiatric disorders.

Continued axon remodeling throughout life provides a conceptual framework of neurodevelopment (and the slower neural re-development in adulthood) that could go awry during psychiatric illness. As with any proposed mechanism relating the molecular genetics with the observed clinical outcomes, empirical validation, or refutation is required. Validation could yield important alternative signaling pathways that influence competitive axon growth (10). In addition, this type of investigation is more likely



to elucidate the biological underpinnings of disease, which the National Institute of Mental Health recently endorsed in favor of symptom-based diagnosis used in the Diagnostic and Statistical Manual of Mental Health. Although it is not currently clear that a single common mechanism links L-type channel mutations to the associated disorders, pursuit of this kind of fundamental link is worthwhile for the conceptual advances and therapeutic targets that might be discovered if true.

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