Dystrobrevin Clusters BK Channels
Bojun Chen, Ping Liu, Haiying Zhan, and Zhao-Wen Wang

The dystrophin-associated protein complex (DAPC), which forms at neuromuscular junctions and CNS synapses, stabilizes membranes, acts as a scaffold for signaling molecules, clusters neurotransmitter receptors, and contributes to calcium homeostasis. Mutations in DAPC proteins cause muscle degeneration—often accompanied by mental retardation—in muscular dystrophies. Chen et al. have identified a novel role for one component of the DAPC, dystrobrevin: clustering of the calcium- and voltage-activated potassium channel BK near calcium channels in synaptic terminals and muscles. In Caenorhabditis elegans, dystrobrevin colocalized with the BK channel SLO-1 in muscle and motor neuron terminals, and null mutations in dystrobrevin prevented normal clustering of SLO-1. BK channels help repolarize membranes, limiting calcium influx, and null mutations in either SLO-1 or dystrobrevin appeared to impair this function, thus increasing neurotransmitter release and the frequency of muscle calcium transients. Expression of mouse dystrobrevin rescued SLO-1 clustering in neurons, suggesting that dystrobrevin plays a similar role in mammalian neurons.

Behavioral/Systems/Cognitive
Prefrontal Cortex Connections Are Reduced in Psychopaths
Julian C. Motzkin, Joseph P. Newman, Kent A. Kiehl, and Michael Koenigs

Psychopathy is a neurodevelopmental disorder characterized by a combination of emotional components (e.g., superficial charm, manipulativeness, callousness, and lack of remorse) and antisocial components (e.g., impulsivity, irresponsible, and aggressive). Structural abnormalities in multiple cortical and limbic regions have been proposed to underlie psychopathy, but the ventromedial prefrontal cortex (vmPFC) appears to be especially important. Damage to this area often causes previously normal people to develop psychopathic traits, as famously demonstrated by the case of Phineas Gage. To further elucidate brain abnormalities in psychopaths, Motzkin et al. performed diffusion tensor imaging and functional magnetic resonance imaging on psychopathic and nonpsychopathic criminals. Psychopathy was associated with decreased integrity of the white matter tract connecting vmPFC to the temporal lobe, and with lower levels of correlated activity (thought to reflect functional connectivity) between vmPFC and the amygdala and precuneus/posterior cingulate cortex. These connections have been linked to emotional regulation and self-reflection, respectively.

Neurobiology of Disease
Human HCN2 Mutation Is Linked to Epilepsy
Jacopo C. DiFrancesco, Andrea Barbuti, Raffaella Milanesi, Stefania Coco, Annalisa Bucchi, et al.

Hyperpolarization-activated cyclic nucleotide-gated (HCN) channels underlie $I_{Na}$, a mixed cation current carried by Na$^+$ and K$^+$. HCN channels are expressed in many neurons, where they regulate rhythmic firing, dendritic integration, and excitability. Because HCN channels open—leading to current influx—as cells become hyperpolarized and close upon depolarization, they help stabilize resting membrane potentials. Furthermore, because they are partially open at resting membrane potentials—thus reducing membrane resistance—they dampen the effects of other currents, reducing neuronal excitability. Although knock-out of HCN channels causes seizures in mice, no Hcn mutations have been definitively linked to human epilepsy until now. DiFrancesco et al. identified a homozygous single-nucleotide mutation in the channel-gating region of Hcn2 in a single epilepsy patient. Expressing normal and mutated Hcn2 in cultured rat cortical neurons revealed that the mutation shifted the activation threshold to more negative potentials, making the channel largely nonfunctional at physiological voltages and thus increasing neuronal excitability.