## Cell Adhesion Molecules: Druggable Targets for Modulating the Connectome and Brain Disorders?

The human brain develops and modulates more than a trillion connections in ways that depend fundamentally on ligand recognition mediated by cell adhesion molecules (CAMs). These cell surface proteins display single transmembrane, GPI-anchored and other configurations (Li *et al*, 2009). Products of at least 500 human CAM genes transduce information about ligands expressed by neighboring cells and extracellular matrix, altering cellular signaling and morphology. Understanding the CAM language for establishing and shaping brain connections is key to understanding the connectome.

Common variants in CAM genes have been associated with many human brain and neuropsychiatric disease phenotypes, largely based on modest contributions of multiple genomic variations within each of these genes. Such genetic architecture is unsatisfying for efforts to establish statistically ironclad associations, but is consistent with the likely importance of and selective pressure on the roles that CAMs play. Addiction, abilities to quit smoking, schizophrenia, autism, ADHD, RLS/Willis Ekbom syndrome, cerebral cortical volume and memory provide a sampling of phenotypes associated with variation in CAM genes (Schormair *et al*, 2008; Uhl *et al*, 2008). Decoding the language of CAMs is thus also essential to understanding many brain disorders and phenotypes.

Tests of a growing number of mouse models of altered CAM expression support many of their associations with human disorders and phenotypes. Altered expression of individual CAMs can provide relatively selective effects (Ishiguro *et al*, 2006). More devastating phenotypes can follow simultaneous deletion of several related CAMs (Uetani *et al*, 2006), supporting functional redundancies provided by multimember CAM families. The overall constellation of phenotypes from mice with altered expression of single CAM genes supports the idea that many CAM 'antagonists' (or 'agonists') might modulate brain connections and activities with modest overall toxicities/side effects and favorable therapeutic indices.

An example: CDH13 and PTPRD are CAMs that share human associations with addiction, haplotypes that influence levels of human brain expression and expression in addiction-related neuronal circuits (Uhl *et al*, 2008). Humans with selected CDH13 and PTPRD haplotypes and mice with reduced expression display altered dose–response relationships for psychostimulant reward (JD and GRU, submitted). Heterozygote knockouts that approximate the level-of-expression differences identified in humans display few systemic pathologies.

Should we thus think about CDH13, PTPRD, and other CAMs as potentially druggable targets for modulating brain phenotypes, establish robust screening assays, test libraries of small-molecule ligands for *in vitro* effects, and test for *in vivo* effects of lead and more optimized structures? Availability of good crystal structures for CDH13 (Ciatto *et al*, 2010) and a number of CAMs could aid this effort. Information about naturally occurring membrane bound, matrix, and soluble CAM ligands will help. Small molecules that recognize members of several of these CAM subfamilies, often identified based on their potential antitumor properties, can provide valuable starting points. Disease association and mouse model data can provide targets and estimates of potential toxicities. Data for the detailed pattern of CAM expression in brain, and in other organs, can also help us to estimate the specificity of possible CAM ligands. Studies in conditional knockout mice will help to define the contributions of developmental *vs* adult CAM expression to disease phenotypes. Improving currently spotty understanding of the intracellular signaling consequences of CAM–ligand interactions will aid CAM targeting.

Our answer is thus yes. CAMs may be among the most promising and understudied druggable targets for modulating the connectome and influencing brain disorders.

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## Circuits in Sync: Decoding Theta Communication in Fear and Safety

Theta-frequency (4–12 Hz) oscillations were first isolated and came of age as an important concept in neurophysiology in the dorsal hippocampus

(dHPC). Extensive work on hippocampal theta oscillations has demonstrated how theta is generated via the interplay of precisely timed inputs. It has led to the notion of inhibition as a theta pacemaker, and clarified the role theta has in organizing cell activity and other oscillations. During behavior, hippocampal theta has been implicated in creating windows for Hebbian plasticity, as well as organizing neural coding for memory formation and spatial navigation. This review focuses on theta oscillations in fear and anxiety, a topic of recently increased interest.

Initial efforts at characterizing the role of theta in fear began with an examination of theta oscillations in the amygdala and related structures. For example, pyramidal cells of the basolateral amygdala (BLA) show a prominent theta oscillation and have a combination of ionic conductances that allow cells to intrinsically resonate at the theta frequency (Pape and Driesang, 1998). Furthermore, the amygdala shows increased theta activity and synchrony with the hippocampus during presentation of fear-conditioned stimuli (Seidenbecher *et al*, 2003). Similarly, hippocampal recordings have shown that in the ventral (vHPC) but not dorsal hippocampus, theta increases with innate anxiety (Adhikari *et al*, 2011), indicating that theta modulates anxiety in the vHPC separately from spatial navigation in the dHPC.

Recent studies focusing on theta in circuit-level communication during fear and safety suggest that it may open temporary windows of communication between areas. Simultaneous recordings show increased theta-range synchrony between the BLA and hippocampus during presentations of fear-conditioned stimuli and in sleep after fear conditioning, possibly aiding memory consolidation (Seidenbecher *et al*, 2003; Popa *et al*, 2010). Similarly, recordings in the vHPC and prefrontal cortex (mPFC) demonstrate increased theta-frequency synchrony between the two regions during anxiety. Moreover, mPFC neurons become more phase-locked to vHPC theta input with elevated anxiety (Adhikari *et al*, 2011), indicating that vHPC sends information about anxiety to the mPFC.

Interestingly, as fear subsides during extinction of conditioned fear, BLA–mPFC theta synchrony increases (Lesting *et al*, 2011), indicating that prefrontal inputs to the amygdala use theta as a mechanism for communicating safety. Indeed, neural firing in the BLA becomes entrained to incoming mPFC theta only when animals are presented with conditioned stimuli that are recognized as safe or when animals are in the relative safety of the periphery in the otherwise aversive open field (EL and JAG, unpublished observations). Thus, mPFC–BLA synchrony increases and cellular networks in the BLA are entrained to theta input from the mPFC when animals actively recognize safety, likely driving local inhibitory networks that decrease fear.

Recent evidence shows that interneurons in the BLA can be organized by hippocampal theta (Bienvenu *et al*, 2012), opening the possibility that the same could be true for prefrontal inputs. Therefore, entrainment of BLA cell assemblies by mPFC theta input could organize local inhibitory circuits of the BLA to provide an effective mechanism for the mPFC to signal safety.

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# Toward Identification of Neural Markers of Suicide Risk in Adolescents

Suicide remains a leading cause of adolescent morbidity and mortality. Despite identification of risk factors and protective factors for suicidal behavior, we have limited understanding of the mechanisms underlying risk for suicide attempt. Adolescence is a time of high risk for suicidal behavior, as well as a time that intervention and treatment may have the greatest impact because of structural brain changes and significant psychosocial development during this period. Functional magnetic resonance imaging (fMRI) studies have promise to yield markers of risk for suicidal behavior in adolescents because they can help identify neurobiological underpinnings of pathophysiologic mechanisms that are not observable at the behavioral level, and can also provide targets for future neurobiological interventions. Markers of risk for suicidal behavior are beginning to be elucidated, but as yet have not been applied to the clinical management of adolescents at risk for suicide.