

Memory Allocation

Memories are thought to be represented in the brain as enduring physical changes in ensembles of neurons, the ‘engram’. How are neurons chosen (or allocated) to become part of the engram? Is this process random? Evidence suggests it is not. We (Han *et al*, 2009) and others (Zhou *et al*, 2009) examined how fear/threat memories are encoded in the brain. In this paradigm, rodents learn to associate a tone with a shock and this association critically depends on the lateral amygdala (LA) (Repa *et al*, 2001). Manipulating levels of the transcription factor CREB in LA neurons influenced the likelihood of a neuron becoming part of a fear/threat memory engram. To determine ‘engram membership’ we quantified expression of the activity-regulated gene *arc* after encoding and/or retrieval. When CREB was virally overexpressed in random LA neurons, those infected neurons were more likely to be allocated to the engram than their non-infected neighbors. Conversely, when CREB function was virally suppressed, infected neurons were excluded from the engram (Han *et al*, 2009). These findings suggested that neurons with relatively higher CREB are more likely to ‘capture’ the memory. Definitive evidence for this emerged from subsequent experiments: genetic ablation or suppression of the CREB overexpressing cells (and not an equivalently sized random population of LA neurons) was sufficient to erase the memory (Han *et al*, 2009; Zhou *et al*, 2009).

CREB is involved in many biological processes. Which process is responsible for the increased likelihood of allocation? One candidate is neuronal excitability. Overexpression of CREB increases a neuron’s intrinsic excitability (Dong *et al*, 2006; Zhou *et al*, 2009). Might changes in neuronal excitability allow LA neurons with high CREB function to win the neuronal competition and become allocated to the engram? To test this, we manipulated excitability in LA neurons by targeting K^+ channels

and using genetic mediators of excitability (DREADDs, optogenetics). Remarkably, we found that increasing neuronal excitability via different methods mimicked the effects of CREB overexpression: Fear/threat memories were funnelled into these more excitable neurons. Conversely, blocking CREB-induced increases in neuronal excitability (by co-expressing Kir2.1, an inwardly rectifying K^+ channel, which reduces neuronal excitability) prevented their preferential allocation (Yiu *et al*, 2014). Our finding that neurons are recruited to an engram based on neuronal excitability was predicted by a recent biophysical modeling study (Kim *et al*, 2013).

Why allocate? Recalling a particular event might conjure up memories of closely related episodes. This phenomenon may reflect some underlying structure of the way in which our memories are organized, with memories that are related either in content or in time encoded by overlapping ensembles of neurons. Within this associative network, fluctuations in CREB/excitability determine whether memories are linked or, alternately, segregated. Is it possible to alter the structure or function of this fundamental associative network by hijacking the allocation process? For example, manipulating CREB levels in different neuronal ensembles might artificially link otherwise unrelated memories or, conversely, uncouple memories that would normally be allocated to overlapping populations of neurons. Understanding the rules of allocation might provide insights into a range of psychiatric conditions that are characterized by inappropriate associations such as schizophrenia. We wonder, therefore, to what extent different psychopathologies can be thought of as disorders of mis-allocation.

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Oxytocin, Social Cognition and Psychiatry

Oxytocin (OT) has an ancient role in modulating sensing and responding to social stimuli, from nematodes to man. OT regulates not only mammalian labor and nursing, but also maternal behavior. There is increasing evidence that OT influences human parenting and mediates the impact of parenting

on infant socio-emotional development (Rilling and Young, 2014). Preclinical studies suggest that OT increases the salience and rewarding value of social stimuli. OT acts in the rodent amygdala to enhance the salience of social olfactory cues, thereby facilitating social recognition, in the striatum to mediate social reward and in the hippocampus to enhance signal to noise neurotransmission. These fundamental processes likely contribute to more complex OT-mediated behaviors, including social bonding.

The effects of OT on social information processing in rodents make it an enticing pharmacological target for enhancing social cognition. However, two issues introduce skepticism for translating the compelling preclinical observations into effective pharmacotherapies to improve social functioning in psychiatric disorders, including autism and schizophrenia: (1) rodents use olfaction as the primary social perception modality, while primates rely more on visual and auditory social perception; (2) little is known regarding the pharmacokinetics of current OT administration methods or the impact of chronic OT treatment. Recent studies from our laboratory address these issues.

A common polymorphism in the human OT receptor (OXTR) gene predicts face recognition skills in families with a child with autism. This effect was present in all family members in two independent populations, yet there was no evidence of an association with autism diagnosis (Skuse *et al*, 2014). This study supports a role for the OT system in human visual social information processing analogous to its role in olfactory processing in rodents.

Nonhuman primates are useful for exploring the mechanisms of intranasal OT (IN-OT) administration. We showed that OT administered nasally by a pediatric nebulizer modestly elevates OT in the cerebrospinal fluid of anesthetized macaques (Modi *et al*, 2014). Importantly, intranasal OT also robustly elevated plasma OT for an extended period of time. Thus IN-OT may increase brain OT signaling, but

peripheral mechanisms should be considered.

Comparative studies of brain OXTR distribution in primates reveal the potential mechanisms by which OT modulates social information processing (Freeman *et al*, 2014a, b). In all primate species examined, OXTRs are concentrated in cholinergic regions involved in visual and auditory processing, including the nucleus basalis of Meynert, which coordinates neural activity in the amygdala and cortex, thereby modulating attention to visual cues.

IN-OT may enhance some aspects of social cognition through the mechanisms described above, but the efficacy may be limited by brain penetration. Stimulating endogenous central OT release pharmacologically is a viable alternative for increasing OT neural signaling. Melanocortin receptor agonists stimulate OT release from hypothalamic slices, potentiate OT release in the ventral striatum, and enhance OT-dependent behavior in prairie voles (unpublished data). Neonatal melanocortin receptor activation acutely activates OT neurons, and daily treatment for the first week of life enhances adult social bonding in prairie voles (Barrett *et al*, 2014). Thus, the OT system remains an attractive target for clinically enhancing social cognition, and alternative pharmacological strategies for enhancing OT neurotransmission should be explored.

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LJY has applied for a patent (US20120108510—Methods of improving behavioral therapies) for combining melanocortin agonists with behavioral therapies to enhance social cognition in psychiatric disorders.

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FKBP5 Allele-Specific Epigenetic Modification in Gene by Environment Interaction

The likelihood to develop stress-related psychiatric disorders in response to childhood trauma exposure may be moderated by the individual's genetic predisposition (Manuck and McCaffery, 2014). One of the genetic variants reported to alter the risk for psychiatric disorders following childhood trauma is a functional variant in *FKBP5*, a gene encoding a co-chaperone of the glucocorticoid receptor (GR). *FKBP5* is strongly induced following stress exposure via binding of activated GR to a number of intronic and promoter GR response elements (GREs). The protein itself then binds to the GR complex, reduces the affinity of GR to cortisol and decreases translocation of the GR to the nucleus, providing an ultrashort negative feedback for GR activation on the genomic and protein level (Zannas and Binder, 2014). We