

bonding. Building up on the seminal work by Jaak Panksepp and colleagues, recent genetic studies suggest that different neurochemicals including dopamine, oxytocin, and particularly opioid peptides regulate different aspects of sociability (Pearce *et al*, 2017). Human positron emission tomography (PET) studies have highlighted that the endogenous opioid system, best known for its role in pain and reward, supports also social bonding in humans. Prosocial behavior, such as social laughter, triggers endogenous opioid release in thalamus and insular cortex concurrently with increased calmness and amusement (Manninen *et al*, 2017). Such group-level opioid release via contagious laughter, rather than time-consuming dyadic bonding, may have allowed humans to significantly extend their social sphere. Yet conversely, also social rejections or losses may trigger similar endogenous opioid activation as social bonding (Hsu *et al*, 2013), paralleling the contribution of the opioid system to processing of purely sensory pleasure and pain in humans. Thus, the opioid system seems to modulate both motivation towards social contacts and support, and away from solitude.

Capacity for vicarious experience is a key feature of human sociability: feeling others' pain in our own mind may create a strong urge to help others in distress. Fusion imaging work combining PET with functional magnetic resonance imaging shows that the more opioid receptors humans have in their brain, the more strongly their frontocortical areas respond to seeing others' distress (Karjalainen *et al*, 2017). Similarly, placebo analgesia (modulated by the opioid system) also reduces empathy-related brain responses towards others' distress (Rutgen *et al*, 2015). Accordingly, the physical and vicarious pain might share the same neuromolecular basis, and opioidergic neurotransmission may facilitate more complex prosocial motivation than just social bonding.

Molecular imaging studies have also established that individual differences in endogenous opioid system function explains individual differences in

sociability. In particular, opioid receptor availability in the frontal cortex—a region involved in variety of socio-emotional processes—predicts both the security of romantic attachment bonds (Nummenmaa *et al*, 2015) as well as the tendency for prosocial expressions such as laughter in social settings (Manninen *et al*, 2017). Genetic as well as experience-dependent plasticity of the endogenous opioid system might thus constitute an important precursor for trait-like differences in social behavior, including prosociality and helping behavior.

All in all, these results extend pharmacological work in non-human primates showing that opioid agonists decrease and antagonists increase social grooming (analogous prosocial behavior to human social laughter), suggesting a shared opioidergic bonding mechanism across humans and other primates. Furthermore, the recent data show that in humans the opioid system has evolved to serve not only reproductive or maternal dyadic bonding, but also large-scale affiliative bonding and altruistic behaviour such as helping triggered by seeing others—even unfamiliar individuals—in distress.

Most humans strive for social contacts throughout their lifespan, and lack of social contacts has significant negative consequences for both psychological and somatic health. Accordingly, properly functioning endogenous opioid system could be an important precursor for psychological resiliency and well-being in general. This may explain why disruption of the endogenous opioid system by, for example, heroin abuse may lead to antisocial behavior. However, the specific role of the opioid system in different types of social relationships (such as romantic versus affiliative) needs to be resolved in future studies.

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Hsu DT, Sanford BJ, Meyers KK, Love TM, Hazlett KE, Wang H *et al* (2013). Response of the mu-opioid system to social rejection and acceptance. *Mol Psychiatry* **18**: 1211–1217.

Karjalainen T, Karlsson HK, Lahnakoski JM, Glerean E, Nuutila P, Jaaskelainen IP *et al* (2017). Dissociable roles of cerebral mu-opioid and type 2 dopamine receptors in vicarious pain: a combined PET-fMRI study. *Cereb Cortex* 1–10.

Manninen S, Tuominen L, Dunbar RIM, Karjalainen T, Hirvonen J, Arponen E *et al* (2017). Social laughter triggers endogenous opioid release in humans. *J Neurosci* **37**: 6125–6131.

Nummenmaa L, Manninen S, Tuominen L, Hirvonen J, Kallioikoski KK, Nuutila P *et al* (2015). Adult attachment style is associated with cerebral  $\mu$ -opioid receptor availability in humans. *Hum Brain Mapp* **36**: 3621–3628.

Pearce E, Wlodarski R, Machin A, Dunbar RIM (2017). Variation in the  $\beta$ -endorphin, oxytocin, and dopamine receptor genes is associated with different dimensions of human sociality. *Proc Natl Acad Sci USA* **114**: 5300–5305.

Rutgen M, Seidel EM, Silani G, Rieccansky I, Hummer A, Windischberger C *et al* (2015). Placebo analgesia and its opioidergic regulation suggest that empathy for pain is grounded in self pain. *Proc Natl Acad Sci USA* **112**: 5638–5646.

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## Modulating Amygdala–Hippocampal Network Communication: A Potential Therapy for Neuropsychiatric Disorders

Contextual processing imbues appropriate salience to our experiences and facilitates flexible behavioral adaptation. Dysfunction in contextualizing information increases the risk of inappropriate responses to environmental conditions and has been implicated in a broad range of psychopathologies, including post-traumatic stress disorder, schizophrenia, and substance abuse disorders (Maren *et al*, 2013).

Given the essential role of contextual processing in adaptive behavior and its derangement in neuropsychiatric disorders, recent research has focused on

how the brain processes contextual information. Translational research in both rodents and humans has honed in contextual processing from a psychological perspective to its core brain circuitry—the amygdala–hippocampal circuit, which appears to be conserved across species (Milad and Quirk, 2012). Structural and functional alterations of this circuit have been observed in patients with neuropsychiatric disease, and are associated with a negative emotional memory bias and a broader fear generalization gradient (Gerritsen *et al*, 2012). Translating from ‘circuit neuroscience’ to ‘circuit neurotherapy’ requires understanding of the oscillatory mechanisms controlling amygdala–hippocampal interactions during the processing of salient information. In our recent study (Zheng *et al*, 2017) using direct human intracranial recordings, we demonstrated unidirectional influence from the amygdala to the hippocampus during contextual fear processing. In addition, we showed that such modulation is mediated through coherent theta and alpha frequency oscillations between these two core brain structures.

Neuropsychiatric disorders are primarily treated with pharmacological means, targeting large swaths of brain tissue. To capture the underlying mechanistic process, a circuit-level perspective might provide a deeper understanding of neuropsychiatric disorders and improved interventions with greater efficacy and fewer side effects. A potential clinical application of our study is the modulation of oscillatory phase couplings between the amygdala and the hippocampus. Phase alignment or coupling between brain regions provides a temporal window for coordinated inter-regional information transfer and communication. Information transfer errors may occur due to over-coupling or under-coupling between brain structures, including failures in terminating irrelevant communication or extracting meaningful signals. These alterations in communication dynamics have been proposed to underlie neuropsychiatric disorders (Voytek and Knight, 2015). To ‘break’ such pathological couplings, amygdala–hippocampal network

interactions could be altered with stimulation-based therapy to induce temporal phase synchronization (eg, enhanced phase alignment with phase resetting) or desynchronization (eg, reduced phase alignment with neural noises) between the two brain structures. This provides a theoretical framework for circuit-specific and stimulation-based intervention approaches, such as deep brain stimulation, transcranial alternating current stimulation (tACS), and transcranial magnetic stimulation. Furthermore, greater specificity can also be achieved by taking individual oscillatory variation into account. For example, using tACS parameters specific to individuals’ dominant theta frequency improves short-term memory capacity (Vosskuhl *et al*, 2015). Our study also showed that instead of conforming to the conventional definition of theta (4–7 Hz)/alpha (8–12 Hz) frequency rhythms, amygdala–hippocampal dynamics are contingent upon subject-specific low frequency oscillations (Zheng *et al*, 2017). Identifying such individualized electrophysiological features in patients with psychiatric disorders could enable stimulation parameters to be tailored for subject-preferred neuronal firing frequencies, leading to personalized therapeutic interventions.

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Gerritsen L, Rijpkema M, van Oostrom I, Buitelaar J, Franke B, Fernandez G *et al* (2012). Amygdala to hippocampal volume ratio is associated with negative memory bias in healthy subjects. *Psychol Med* **42**: 335–343.

Maren S, Phan KL, Liberzon I (2013). The contextual brain: implications for fear conditioning, extinction

and psychopathology. *Nat Rev Neurosci* **14**: 417–428.

Milad MR, Quirk GJ (2012). Fear extinction as a model for translational neuroscience: ten years of progress. *Annu Rev Psychol* **63**: 129–151.

Vosskuhl J, Huster RJ, Herrmann CS (2015). Increase in short-term memory capacity induced by down-regulating individual theta frequency via transcranial alternating current stimulation. *Front Hum Neurosci* **9**: 257.

Voytek B, Knight RT (2015). Dynamic network communication as a unifying neural basis for cognition, development, aging, and disease. *Biol Psychiatry* **77**: 1089–1097.

Zheng J, Anderson KL, Leal SL, Shestuyuk A, Gulsen G, Mnatsakanyan L *et al* (2017). Amygdala–hippocampal dynamics during salient information processing. *Nat Commun* **8**: 14413.

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## Modeling Non-Syndromic Autism with Human-Induced Pluripotent Stem Cells

Genetically, autism can broadly be segregated into syndromic and non-syndromic forms. Accounting for a small percentage of total ASD cases, syndromic ASD includes incidences of the disease with known genetic cause and unique clinical presentation, while non-syndromic ASD with unknown genetic etiology accounts for the remaining majority of ASD cases (Sztainberg and Zoghbi, 2016). The genetic underpinnings of non-syndromic ASD likely involve small effects of many genes and/or rare *de novo* mutations in a susceptible genetic background (de la Torre-Ubieta *et al*, 2016). Unfortunately, non-syndromic ASD is difficult to model precisely because of this genetic heterogeneity. The use of human-induced pluripotent stem cells (hiPSCs) offers an opportunity to uncover some of the molecular mechanisms behind non-syndromic ASD. hiPSCs possess the same genetic make-up of the individual they were derived from. Thus, hiPSCs derived from individuals with non-syndromic ASD can accurately recapitulate the heterogeneous genetics found in this form of the disease.

Recently, our laboratory and collaborators utilized hiPSCs to model non-