these potential mechanisms is an important future goal given the prevalence of sleep disruption in society and the connection between REMs disturbance and cognitive decline in aging and Alzheimer's disease.

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Abel T, Havekes R, Saletin JM, Walker MP (2013). Sleep, plasticity and memory from molecules to whole-brain networks. *Curr Biol* **23**: R774–R788.

Boyce R, Glasgow SD, Williams S, Adamantidis A (2016). Causal evidence for the role of REM sleep theta rhythm in contextual memory consolidation. *Science* **352**: 812–816.

Grosmark AD, Mizuseki K, Pastalkova E, Diba K, Buzsaki G (2012). REM sleep reorganizes hippocampal excitability. *Neuron* **75**: 1001–1007.

Hengen KB, Torrado Pacheco A, McGregor JN, Van Hooser SD, Turrigiano GG (2016). Neuronal firing rate homeostasis is inhibited by sleep and promoted by wake. *Cell* **165**: 180–191.

Malvache A, Reichinnek S, Villette V, Haimerl C, Cossart R (2016). Awake hippocampal reactivations project onto orthogonal neuronal assemblies. *Science* **353**: 1280–1283.

Rasch B, Born J (2013). About sleep's role in memory. *Physiol Rev* **93**: 681–766.

Siegel JM (2001). The REM sleep-memory consolidation hypothesis. *Science* **294**: 1058–1063.

Tononi G, Cirelli C (2014). Sleep and the price of plasticity: from synaptic and cellular homeostasis to memory consolidation and integration. *Neuron* **81**: 12–34.

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The Neuroimmune Basis of Excessive Alcohol Consumption

The interplay between brain, behavior, and immune responses in the etiology and progression of alcohol abuse is a paradigm-shifting direction in addiction research that has transformed therapeutic outlook for alcohol use disorders (AUDs). Alcohol is thought to increase neuroimmune-related gene and protein expression through (i) gut-derived microbial products that activate innate immune cells, causing systemic induction of proinflammatory cytokines that are transported from blood to brain, as well as (ii) direct actions in the brain, where cross talk among neurons, glia, and other cells contributes to the release and signaling of immune molecules with inflammatory and neuromodulatory properties (Crews and Vetreno, 2016).

Interest in the alcohol-neuroimmune field was fueled by gene expression studies showing strong representation of immune- and inflammatory-related genes in brains from human alcoholics and rodents exposed to chronic alcohol (Liu *et al*, 2006; Robinson *et al*, 2014). Deletion of chemokines and other immune genes reduced alcohol drinking in mice and provided corroborating behavioral validation for several immune mediators that were predicted by the genomic studies (Blednov *et al*, 2012; Robinson *et al*, 2014). In contrast, immune activation by lipopolysaccharide (LPS) produced prolonged increases in alcohol consumption in mice, and treatment with either LPS or chronic intermittent alcohol produced overlapping changes in mouse brain transcriptomes (Robinson *et al*, 2014). The LPS-induced escalation in drinking may be related to persistent activation of immune genes in the brain that are also induced by chronic alcohol exposure.

It has been hypothesized that positive feedback cycles of proinflammatory peripheral-central immune signaling promote excessive alcohol drinking. In support of this, alcohol craving and consumption were positively correlated with elevated plasma levels of inflammatory cytokines in human alcoholics (Leclercq *et al*, 2014). Centrally, expression of innate immune molecules (eg, HMGB1, TLRs, and RAGE) increased in the brains of alcoholics and alcohol-exposed rodent models, and immune marker expression in humans was correlated with total lifetime alcohol consumption and age of drinking onset (Crews and Vetreno, 2016). Neuroimmune signaling has also been associated with synaptic remodeling and epigenetic changes induced by intermittent alcohol exposure in adolescent brain (Montesinos *et al*, 2016), where persistent synaptic and molecular changes during development may increase susceptibility to AUDs.

Investigating the genomics and pharmacology of neuroimmune pathways in chronic alcohol consumption is currently a goal for NIAAA, underscoring the impact of this area on research initiatives. Another priority is the use of novel computational resources that connect gene networks with potential therapeutic compounds. If alcohol causes genetic changes and neuroadaptations in immune pathways that are conserved across species (including humans), then cross-species brain genomic datasets and computational approaches could be used to link alcohol-related patterns in gene coexpression with investigational or FDA-approved drugs that can normalize the networks and reduce drinking. The 'gene network to pharmacotherapy' approach, together with behavioral validation of identified targets in animal models and alcoholics, aims to link specific neuroimmune pathways to addiction vulnerability and fast-track treatment strategies for AUDs. The accumulating evidence for alcohol-neuroimmune signaling, together with emerging computational tools, is forging a revolutionary course for addiction research with renewed impetus and expectation for positive therapeutic outcome.

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Blednov YA, Ponomarev I, Geil C, Bergeson S, Koob GF, Harris RA (2012). Neuroimmune regulation of alcohol consumption: behavioral validation of genes obtained from genomic studies. *Addict Biol* **17**: 108–120.

Crews FT, Vetreno RP (2016). Mechanisms of neuroimmune gene induction in alcoholism. *Psychopharmacology (Berl)* **233**: 1543–1557.

Leclercq S, De Saeger C, Delzenne N, de Timary P, Starkel P (2014). Role of inflammatory pathways, blood mononuclear cells, and gut-derived bacterial products in alcohol dependence. *Biol Psychiatry* **76**: 725–733.

Liu J, Lewohl JM, Harris RA, Iyer VR, Dodd PR, Randall PK *et al* (2006). Patterns of gene expression in the frontal cortex discriminate alcoholic from nonalcoholic individuals. *Neuropsychopharmacology* **31**: 1574–1582.

Montesinos J, Pascual M, Rodriguez-Arias M, Minarro J, Guerri C (2016). Involvement of TLR4 in the long-term epigenetic changes, rewarding and anxiety effects induced by intermittent ethanol treatment in adolescence. *Brain Behav Immun* **53**: 159–171.

Robinson G, Most D, Ferguson LB, Mayfield J, Harris RA, Blednov YA (2014). Neuroimmune pathways in alcohol consumption: evidence from behavioral and genetic studies in rodents and humans. *Int Rev Neurobiol* **118**: 13–39.

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Oxytocin-Augmented Psychotherapy: Beware of Context

The hypothalamic peptide oxytocin modulates a wide range of social and cognitive functions in humans and nonhuman primates. As a result, much effort is currently being devoted to developing oxytocin into an adjunct treatment for mental illness, with a particular focus on anxiety, autism, and schizophrenia spectrum disorders.

In the field of imaging neuroscience, one of the most consistent findings with oxytocin is an inhibition of human amygdala responses to fearful facial expressions following exogenous administration of a single nasal dose—an effect recently replicated in macaques (Liu *et al*, 2015). An oxytocin-induced modulation of neural activity in the amygdala and other regions is in line with observations that intranasal administration yields increased cerebrospinal fluid concentrations of the peptide in humans (Striepens *et al*, 2013) as well as macaques (Freeman *et al*, 2016), although much controversy still exists regarding the exact route of brain penetration.

We recently reported that oxytocin may facilitate fear extinction by down-regulating the amygdala and concomitantly upregulating medial prefrontal cortex activity in healthy volunteers (Eckstein *et al*, 2015), implicating the peptide as a potential adjunct treatment during extinction-based psychotherapy to reduce fear renewal. Interestingly, in a follow-up imaging study, oxytocin produced the opposite effect by promoting fear-conditioned responses (Eckstein *et al*, 2016). Thus, depending on the timing of administration, i.e., prior to versus after conditioning, the peptide can enhance the acquisition or extinction of fear, leading to contrary behavioral outcomes. Another intriguing example in this vein is a social economics experiment, in which volunteers could donate money for a charity project located in the Kongo delta. Subjects treated with placebo devoted more money to saving the rainforest rather than supporting the indigenous population living in that reserve. Under oxytocin treatment, participants showed the opposite behavioral pattern, suggesting that administration of the peptide can transiently alter altruistic attitudes and reward values, thereby shaping decisions towards social priorities (Marsh *et al*, 2015). These results are in accord with current concepts that the contextual framing of an experimental scenario interacts with oxytocin and determines its effects in a top-down regulatory manner (Quattrocki and Friston, 2014). The latter is substantiated by our observation that oxytocin increased the hedonic pleasure associated with social touch when heterosexual male volunteers were made believe that a female experimenter performed the touch as opposed to a male (Scheele *et al*, 2014).

Contextual framing not only matters to 'message makers' in journalism, advertising, or politics—it is also of crucial relevance to psychotherapy, especially when interventions are trialled with oxytocin. Converging evidence from a series of imaging experiments carried out in our laboratory suggests that nasal oxytocin evokes a shift in the neural activity away from the amygdala to the anterior insula, pregenual anterior cingulate cortex, and precuneus—areas that orchestrate the conscious monitoring of what happens in and around us. Current attempts to translate oxytocin neuroscience to psychotherapy thus face the crucial caveat that therapeutic context should be strictly controlled to avoid the risk of unfavorable outcomes.

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Eckstein M, Becker B, Scheele D, Scholz C, Preckel K, Schlaepfer TE *et al* (2015). Oxytocin facilitates the extinction of conditioned fear in humans. *Biol Psychiatry* **78**: 194–202.

Eckstein M, Scheele D, Patin A, Preckel K, Becker B, Walther A *et al* (2016). Oxytocin facilitates Pavlovian fear learning in males. *Neuropsychopharmacology* **41**: 932–939.

Freeman SM, Samineni S, Allen PC, Stockinger D, Bales KL, Hwa GG *et al* (2016). Plasma and CSF oxytocin levels after intranasal and intravenous oxytocin in awake macaques. *Psychoneuroendocrinology* **66**: 185–194.

Liu N, Hadj-Bouziane F, Jones KB, Turchi JN, Averbeck BB, Ungerleider LG (2015). Oxytocin modulates fMRI responses to facial expression in macaques. *Proc Natl Acad Sci USA* **112**: E3123–E3130.

Marsh N, Scheele D, Gerhardt H, Strang S, Enax L, Weber B *et al* (2015). The neuropeptide oxytocin induces a social altruism bias. *J Neurosci* **35**: 15696–15701.

Quattrocki E, Friston K (2014). Autism, oxytocin and interoception. *Neurosci Biobehav Rev* **47**: 410–430.