bromodomain inhibitors that display interesting effects. However, these are still early days and additional studies are still needed.

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REM Sleep on It!

Upon discovery, rapid-eye-movement sleep (REMs) was met with curiosity regarding its function due to its association with dreaming and the seemingly paradoxical occurrence of 'wake-like' eye and brain activity during sleeping behavior. Six decades later, a substantial body of evidence linking REMs to memory formation has been described (Rasch and Born, 2013). In humans, increased REM amounts have been reported following procedural memory tasks, as well as declarative memory tasks incorporating complex or emotionally relevant material. Furthermore, depriving REMs after learning of such tasks produced memory deficits. Similar findings have been described in rodents using tasks such as the Morris water maze and active or passive avoidance (Abel *et al*, 2013).

Despite the cumulative body of evidence, the debate surrounding the role of REMs in memory formation has persisted for some time (Rasch and Born, 2013; Siegel, 2001). This has been due to the difficulty in experimentally isolating REMs, which occurs in multiple episodes of varying (seconds to minutes) duration throughout sleep interposed by periods of non-REMs (NREMs). Thus, traditional pharmacological techniques are not temporally precise enough to selectively target REMs. Additionally, as REMs is an integral component of mammalian sleep, selective REM deprivation inevitably results in physiological changes, such as increased metabolic hormone levels, making interpretation of data obtained difficult. Correlative approaches avoid these issues but cannot prove a direct relationship (Rasch and Born, 2013).

To overcome these caveats, we took advantage of the temporally precise control of specific neural circuits enabled by the use of optogenetic techniques. Our approach was to target a population of GABAergic neurons within the medial septum of mice (MS^{GABA}) implicated in memory formation, yet not associated with the regulation of sleep itself. We therefore optogenetically silenced MS^{GABA} neurons specifically during REMs in the period immediately following learning of either a spatial novel object place recognition test ($n = 6$ mice) or standard fear conditioning paradigm ($n = 8$ mice). Critically, the occurrence of REMs during MS^{GABA} silencing was undisturbed as hallmark features of REMs—defined in the context of our experiments as a combination of sustained behavioral quiescence, muscle atonia, and absence of NREMs—and restful wakefulness-associated slow (1–4 Hz) EEG oscillatory activity—were indifferent from unsilenced control mice (Boyce *et al*, 2016). The following day mice in the test group demonstrated impaired spatial and fear-conditioned contextual memory. REMs was a critical factor as optical silencing of MS^{GABA} neurons for similar durations non-specifically during NREMs and wakefulness had no effect on cognition, although this result does not preclude involvement of NREMs in memory formation as well. Indeed, the non-specific MS^{GABA} inhibition occurring during NREMs did not influence the NREMs-associated neural activity patterns implicated in memory formation, including hippocampal sharp-wave ripples and neocortical spindles (Rasch and Born, 2013; Boyce *et al*, 2016).

Our study directly demonstrated for the first time that the activity of a specific population of neurons (MS^{GABA}) selectively during REMs is required for normal memory formation. However, a precise mechanistic understanding of how REMs helps consolidate spatial and contextual memories requires further work. The ~7 Hz theta EEG rhythm that occurs in rodents during REMs has been implicated in the processing of spatial information at the neuronal level (Rasch and Born, 2013). Therefore, considering we found that a significant decrease in theta power accompanied MS^{GABA} silencing selectively during REMs following learning in the test group (Boyce *et al*, 2016), it is possible that our experiments disrupted normal physiological processing of spatial information at the level of individual place cells, or perhaps that of more structured neuronal assemblies (Malvache *et al*, 2016). It is also possible that our optogenetic manipulation perturbed neural homeostasis during REMs (Grosmark *et al*, 2012; Tononi and Cirelli, 2014; but see Hengen *et al*, 2016). Fully investigating

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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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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