

This Week in The Journal

Working-Memory Deficits in Parietal Cortex in Schizophrenia

Britta Hahn, Benjamin M. Robinson, Carly J. Leonard, Steven J. Luck, and James M. Gold

(see pages 8378–8387)

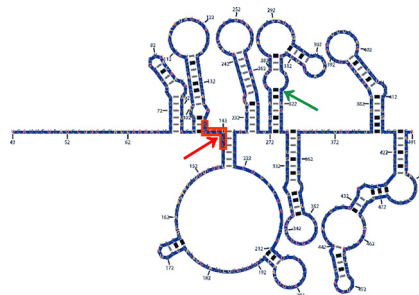
Hallucinations and delusions are the most widely recognized symptoms of schizophrenia, but deficits in basic cognitive functions might be more debilitating. Many of these deficits stem from impairments in working memory, the ability to maintain and transform mental representations of stimuli. Manipulation of items in working memory depends on activity in the prefrontal cortex (PFC) and numerous studies have demonstrated that prefrontal circuits are altered in schizophrenia. But other brain areas are also thought to participate in working memory. For example, activity in the posterior parietal cortex (PPC) is thought to help maintain mental representations. Therefore, deficits in PPC function might contribute to working-memory deficits in schizophrenia.

Hahn et al. tested this hypothesis by administering a change-detection task, which requires maintenance, but not manipulation of items in working memory. On each trial, participants viewed an array of 1–7 colored squares, then after a brief delay, they viewed a single one of these squares and reported whether it had changed color. Based on participants' performance, the authors calculated *K* value, a measure of the number of items stored in working memory. This value increases with the number of presented items until it peaks at working-memory capacity, after which it decreases, because participants can no longer maintain representations of all items. Although *K* values were smaller in schizophrenia patients than in controls, the inverted-U relationship between *K* value and set size was apparent in both groups.

The authors next used functional magnetic resonance imaging to identify regions in which activity varied linearly with *K* value. A cluster in PPC including superior and inferior parietal lobules and the

intraparietal sulcus showed significant differences in activation patterns between groups. Whereas activation significantly increased with *K* value in control participants, the slope was statistically indistinguishable from zero in schizophrenia patients. Notably, the slope was correlated with scores on a cognitive assessment in both groups, and differences in slope explained >40% of the differences in cognitive scores between groups.

These results suggest that impairment in PPC function contributes to working-memory deficits and, likely as a consequence, other cognitive deficits in schizophrenia patients. Therefore, future studies of cellular- and circuit-level mechanisms of schizophrenia should examine PPC as well as PFC.



Predicted structure of the rs3800373 minor allele mRNA, with miR-320a seed site (red arrow) and SNP (green arrow) indicated. See Linnstaedt et al. for details.

FKBP5 mRNA Structure Linked to Post-Traumatic Pain Risk

Sarah D. Linnstaedt, Kyle D. Riker, Cathleen A. Rueckeis, Katrina M. Kutchko, Lela Lackey, et al.

(see pages 8407–8420)

Interactions between environmental and genetic factors influence how people are affected by traumatic experiences. Genetic influences include single-nucleotide polymorphisms (SNPs) in genes that regulate stress responses. Many SNPs lie outside protein-coding regions of DNA, yet affect protein function by altering gene expression. For example, SNPs in promoter or enhancer regions can affect the binding of transcription factors or cofactors and thus disrupt transcriptional regulation.

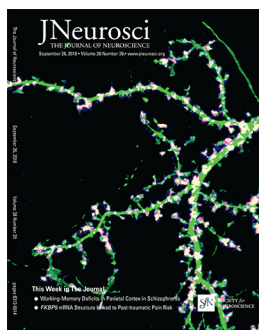
Recently, researchers discovered that SNPs in noncoding regions of mRNA can also affect protein expression. These SNPs, called ribosnitches, change mRNA secondary structure and thus alter mRNA splicing, transport, or degradation. Linnstaedt et al. report that this type of SNP influences the development of chronic pain after traumatic injury.

Previous work suggested that SNP rs3800373 in *FKBP5*—a gene that regulates levels of inflammatory mediators and glucocorticoids—influenced the risk of developing chronic pain after motor-vehicle collisions. Linnstaedt et al. now report that rs3800373 genotype interacts with stress to enhance pain risk. Specifically, in people who possessed at least one copy of the minor allele of rs3800373, the amount of distress reported immediately after an accident was correlated with the severity of chronic pain reported 6 weeks later. In addition, *FKBP5* mRNA levels were positively correlated with cortisol and glucocorticoid-receptor mRNA levels in these patients during their initial treatment.

Analysis of *FKBP5* using various bioinformatics tools indicated that rs3800373 likely influences base-pairing in *FKBP5* mRNA. Notably, the minor allele appears to promote formation of a stem-loop structure in a region where microRNA miR-320a binds. Consistent with this, *in vitro* assays showed that miR-320a binding to *FKBP5* mRNA was lower for the minor allele than for the major allele, even though rs3800373 is distant from the miR-320a binding site. Furthermore, whereas *FKBP5* mRNA and miR-320a levels were inversely correlated in people with the major rs3800373 allele, the levels were unrelated in people with minor alleles.

Together with previous work, these results suggest that by changing mRNA secondary structure, the minor allele of rs3800373 impairs binding of miR-320a, which normally represses *FKBP5* expression. This might disrupt regulation of the stress response or increase expression of inflammatory mediators. Future work should further elucidate the molecular mechanisms linking this allele to chronic pain risk.

This Week in The Journal was written by Teresa Esch, Ph.D.



Cover legend: This image shows dendrites from a rat hippocampal neuron in culture. Overexpressing neuroligin-1 in the neuron led to the production of elaborate dendritic spines, in which ADGRB1/BAI1 (blue) and neuroligin-1 (red) are strongly co-localized. Loss of neuroligin-1 results in loss of BAI1 at spines, and overexpression of neuroligin-1 requires BAI1 to drive dendritic spine development. For more information, see the article by Tu et al. (pages 8388 – 8406).

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S-Nitrosylation of Divalent Metal Transporter 1 Enhances Iron Uptake to Mediate Loss of Dopaminergic Neurons and Motoric Deficit

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Elevated iron deposition has been reported in Parkinson's disease (PD). However, the route of iron uptake leading to high deposition in the substantia nigra is unresolved. Here, we show a mechanism in enhanced Fe²⁺ uptake via S-nitrosylation of divalent metal transporter 1 (DMT1). While DMT1 could be S-nitrosylated by exogenous nitric oxide donors, in human PD brains, endogenously S-nitrosylated DMT1 was detected in postmortem substantia nigra. Patch-clamp electrophysiological recordings and iron uptake assays confirmed increased Mn²⁺ or Fe²⁺ uptake through S-nitrosylated DMT1. We identified two major S-nitrosylation sites, C23 and C540, by mass spectrometry, and DMT1 C23A or C540A substitutions abolished nitric oxide (NO)-mediated DMT1 current increase. To evaluate *in vivo* significance, lipopolysaccharide (LPS) was stereotactically injected into the substantia nigra of female and male mice to induce inflammation and production of NO. The intranigral LPS injection resulted in corresponding increase in Fe²⁺ deposition, JNK activation, dopaminergic neuronal loss and deficit in motoric activity, and these were rescued by the NO synthase inhibitor L-NAME or by the DMT1-selective blocker ebselen. Lentiviral knockdown of DMT1 abolished LPS-induced dopaminergic neuron loss.

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The Adhesion-GPCR BAI1 Promotes Excitatory Synaptogenesis by Coordinating Bidirectional Trans-synaptic Signaling

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Excitatory synapses are specialized cell–cell contacts located on actin-rich dendritic spines that mediate information flow and storage in the brain. The postsynaptic adhesion-G protein-coupled receptor (A-GPCR) BAI1 is a critical regulator of excitatory synaptogenesis, which functions in part by recruiting the Par3-Tiam1 polarity complex to spines, inducing local Rac1 GTPase activation and actin cytoskeletal remodeling. However, a detailed mechanistic understanding of how BAI1 controls synapse and spine development remains elusive. Here, we confirm that BAI1 is required *in vivo* for hippocampal spine development, and we identify three distinct signaling mechanisms mediating BAI1's prosynaptogenic functions. Using *in utero* electroporation to sparsely knock down BAI1 expression in hippocampal pyramidal neurons, we show that BAI1 cell-autonomously promotes spinogenesis in the developing mouse brain. BAI1 appears to function as a receptor at synapses, as its extracellular N-terminal segment is required for both its prosynaptogenic and prosynaptogenic functions. Moreover, BAI1 activation with a *Stachel*-derived peptide, which mimics a tethered agonist motif found in A-GPCRs, drives synaptic Rac1 activation and subsequent spine and synapse development. We also reveal, for the first time, a trans-synaptic function for BAI1, demonstrating in a mixed-culture assay that BAI1 induces the clustering of presynaptic vesicular glutamate transporter 1 (vGlut1) in contacting axons, indicative of presynaptic differentiation. Finally, we show that BAI1 forms a receptor complex with the synaptogenic cell-adhesion molecule Neuroligin-1 (NRLN1) and mediates NRLN1-dependent spine growth and synapse development. Together, these findings establish BAI1 as an essential postsynaptic A-GPCR that regulates excitatory synaptogenesis by coordinating bidirectional trans-synaptic signaling in cooperation with NRLN1.

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Transneuronal Downregulation of the Premotor Cholinergic System After Corticospinal Tract Loss

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Injury to the supraspinal motor systems, especially the corticospinal tract, leads to movement impairments. In addition to direct disruption of descending motor pathways, spinal motor circuits that are distant to and not directly damaged by the lesion undergo remodeling that contributes significantly to the impairments. Knowing which spinal circuits are remodeled and the underlying mechanisms are critical for understanding the functional changes in the motor pathway and for developing repair strategies. Here, we target spinal premotor cholinergic interneurons (IN) that directly modulate motoneuron excitability via their cholinergic C-bouton terminals. Using a model of unilateral medullary corticospinal tract lesion in male rats, we found transneuronal downregulation of the premotor cholinergic pathway. Phagocytic microglial cells were upregulated in parallel with cholinergic pathway downregulation and both were blocked by minocycline, a microglia activation inhibitor. Additionally, we found a transient increase in interneuronal complement protein C1q expression that preceded cell loss. 3D reconstructions showed ongoing phagocytosis of C1q-expressing cholinergic INs by microglia 3 d after injury, which was complete by 10 d after injury. Unilateral motor cortex inactivation using the GABA_A receptor agonist muscimol replicated the changes detected at 3 d after lesion, indicating activity dependence. The neuronal loss after the lesion was rescued by increasing spinal activity using cathodal *trans*-spinal direct current stimulation. Our finding of activity-dependent modulation of cholinergic premotor INs after CST injury provides the mechanistic insight that maintaining activity, possibly during a critical period, helps to protect distant motor circuits from further damage and, as a result, may improve motor functional recovery and rehabilitation.

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Protein Tyrosine Phosphatase Receptor Type J (PTPRJ) Regulates Retinal Axonal Projections by Inhibiting Eph and Abl Kinases in Mice

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Eph receptors play pivotal roles in the axon guidance of retinal ganglion cells (RGCs) at the optic chiasm and the establishment of the topographic retinocollicular map. We previously demonstrated that protein tyrosine phosphatase receptor type O (PTPRO) is specifically involved in the control of retinotectal projections in chicks through the dephosphorylation of EphA and EphB receptors. We subsequently revealed that all the mouse R3 subfamily members (PTPRB, PTPRH, PTPRJ, and PTPRO) of the receptor protein tyrosine phosphatase (RPTP) family inhibited Eph receptors as their substrates in cultured mammalian cells. We herein investigated the functional roles of R3 RPTPs in the projection of mouse retinal axon of both sexes. *Ptpro* and *PtpRJ* were expressed in mouse RGCs; however, *PtpRJ* expression levels were markedly higher than those of *Ptpro*. Consistent with their expression levels, Eph receptor activity was significantly enhanced in *PtpRJ*-knock-out (*PtpRJ*-KO) retinas. In *PtpRJ*-KO and *PtpRJ/Ptpro*-double-KO (DKO) mice, the number of retinal axons that projected ipsilaterally or to the contralateral eye was significantly increased. Furthermore, retinal axons in *PtpRJ*-KO and DKO mice formed anteriorly shifted ectopic terminal zones in the superior colliculus (SC). We found that c-Abl (Abelson tyrosine kinase) was downstream of ephrin–Eph signaling for the repulsion of retinal axons at the optic chiasm and in the SC. c-Abl was identified as a novel substrate for PTPRJ and PTPRO, and the phosphorylation of c-Abl was upregulated in *PtpRJ*-KO and DKO retinas. Thus, PTPRJ regulates retinocollicular projections in mice by controlling the activity of Eph and c-Abl kinases.

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Increased Synthesis of Chondroitin Sulfate Proteoglycan Promotes Adult Hippocampal Neurogenesis in Response to Enriched Environment

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Chondroitin sulfate proteoglycan (CSPG) is a candidate regulator of embryonic neurogenesis. The aim of this study was to specify the functional significance of CSPG in adult hippocampal neurogenesis using male mice. Here, we showed that neural stem cells and neuronal progenitors in the dentate gyrus were covered in part by CSPG. Pharmacological depletion of CSPG in the dentate gyrus reduced the densities of neuronal progenitors and newborn granule cells. 3D reconstruction of newborn granule cells showed that their maturation was inhibited by CSPG digestion. The novel object recognition test revealed that CSPG digestion caused cognitive memory impairment. Western blot analysis showed that expression of β -catenin in the dentate gyrus was decreased by CSPG digestion. The amount of CSPG in the dentate gyrus was increased by enriched environment (EE) and was decreased by forced swim stress. In addition, EE accelerated the recovery of CSPG expression in the dentate gyrus from the pharmacological depletion and promoted the restoration of granule cell production. Conversely, the densities of newborn granule cells were also decreased in mice that lacked chondroitin sulfate *N*-acetylgalactosaminyltransferase 1 (CSGALNacT1), a key enzyme for CSPG synthesis (T1KO mice). The capacity of EE to promote granule cell production and improve cognitive memory was impaired in T1KO mice. These findings indicate that CSPG is involved in the regulation of adult hippocampal neurogenesis

and suggest that increased synthesis of CSPG by CSGalNacT1 may mediate promotion of granule cell production and improvement of cognitive memory in response to EE.

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SYSTEMS/CIRCUITS

Interneuron Simplification and Loss of Structural Plasticity As Markers of Aging-Related Functional Decline

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Changes in excitatory neuron and synapse structure have been recognized as a potential physical source of age-related cognitive decline. Despite the importance of inhibition to brain plasticity, little is known regarding aging-associated changes to inhibitory neurons. Here we test for age-related cellular and circuit changes to inhibitory neurons of mouse visual cortex. We find no substantial difference in inhibitory neuron number, inhibitory neuronal subtypes, or synapse numbers within the cerebral cortex of aged mice compared with younger adults. However, when comparing cortical interneuron morphological parameters, we find differences in complexity, suggesting that arbors are simplified in aged mice. *In vivo* two-photon microscopy has previously shown that in contrast to pyramidal neurons, inhibitory interneurons retain a capacity for dendritic remodeling in the adult. We find that this capacity diminishes with age and is accompanied by a shift in dynamics from balanced branch additions and retractions to progressive prevalence of retractions, culminating in a dendritic arbor that is both simpler and more stable. Recording of visually evoked potentials shows that aging-related interneuron dendritic arbor simplification and reduced dynamics go hand in hand with loss of induced stimulus-selective response potentiation (SRP), a paradigm for adult visual cortical plasticity. Chronic treatment with the antidepressant fluoxetine reversed deficits in interneuron structural dynamics and restored SRP in aged animals. Our results support a structural basis for age-related impairments in sensory perception, and suggest that declines in inhibitory neuron structural plasticity during aging contribute to reduced functional plasticity.

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Auditory Predictive Coding across Awareness States under Anesthesia: An Intracranial Electrophysiology Study

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The systems-level mechanisms underlying loss of consciousness (LOC) under anesthesia remain unclear. General anesthetics suppress sensory responses within higher-order cortex and feedback connections, both critical elements of predictive coding hypotheses of conscious perception. Responses to auditory novelty may offer promise as biomarkers for consciousness. This study examined anesthesia-induced changes in auditory novelty responses over short (local deviant [LD]) and long (global deviant [GD]) time scales, envisioned to engage preattentive and conscious levels of processing, respectively. Electroencephalographic recordings were obtained in human neurosurgical patients (3 male, 3 female) from four hierarchical processing levels: core auditory cortex, non-core auditory cortex, auditory-related, and PFC. Stimuli were vowel patterns incorporating deviants within and across stimuli (LD and GD). Subjects were presented with stimuli while awake, and during sedation (responsive) and following LOC (unresponsive) under propofol anesthesia. LD and GD effects were assayed as the averaged evoked potential and high gamma (70–150 Hz) activity. In the awake state, LD and GD effects were present in all recorded regions, with averaged evoked potential effects more broadly distributed than high gamma activity. Under sedation, LD effects were preserved in all regions, except PFC. LOC was accompanied by loss of LD effects outside of auditory cortex. By contrast, GD effects were markedly suppressed under sedation in all regions and were absent following LOC. Thus, although the presence of GD effects is indicative of being awake, its absence is not indicative of LOC. Loss of LD effects in higher-order cortical areas may constitute an alternative biomarker of LOC.

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BEHAVIORAL/COGNITIVE

Coherent Activity between the Prelimbic and Auditory Cortex in the Slow-Gamma Band Underlies Fear Discrimination

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The medial prefrontal cortex and the basolateral amygdala (BLA) are essential for discriminating between harmful and safe stimuli. The primary auditory cortex (Te1) sends projections to both sites, but whether and how it interacts with these areas during fear discrimination are poorly understood. Here we show that in male rats that can

differentiate between a new tone and a threatening one, the selective optogenetic inhibition of Te1 axon terminals into the prelimbic (PL) cortex shifted discrimination to fear generalization. Meanwhile, no effects were detected when Te1 terminals were inhibited in the BLA. Using a combination of local field potential and multiunit recordings, we show that in animals that discriminate successfully between a new tone and a harmful one, the activity of the Te1 and the PL cortex becomes immediately and tightly synchronized in the slow-gamma range (40–70 Hz) at the onset of the new tone. This enhanced synchronization was not present in other frequency ranges, such as the theta range. Critically, the level of gamma synchrony predicted the behavioral choice (i.e., no freezing or freezing) of the animals. Moreover, in the same rats, gamma synchrony was absent before the fear-learning trial and when animals should discriminate between an olfactory stimulus and the auditory harmful one. Thus, our findings reveal that the Te1 and the PL cortex dynamically establish a functional connection during auditory fear-discrimination processes, and that this corticocortical oscillatory mechanism drives the behavioral choice of the animals.

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Posterior Parietal Cortex Dysfunction Is Central to Working Memory Storage and Broad Cognitive Deficits in Schizophrenia

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PFC dysfunction is widely believed to underlie working memory (WM) deficits in people with schizophrenia (PSZ), but few studies have focused on measures of WM storage devoid of manipulation. Research in neurotypical individuals has shown that storage capacity is more closely related to posterior parietal cortex (PPC) than PFC, suggesting that reductions in WM storage capacity in schizophrenia that are associated with broad cognitive deficits may be related to neural activity in PPC. In the present human neuroimaging study, 37 PSZ and 37 matched healthy control subjects of either sex completed a change detection task with varying set sizes while undergoing fMRI. The task was designed to emphasize WM storage with minimal top-down control demands. Whole-brain analysis identified areas in which BOLD activity covaried with the number of items maintained in WM (K), as derived from task performance at a given set size. Across groups, K values independent of set size predicted BOLD activity in PPC, including superior and inferior parietal lobules and intraparietal sulcus, and middle occipital gyrus. Whole-brain interaction analysis found significantly less K -dependent signal modulation in PSZ than healthy control subjects in left PPC, a phenomenon that could not be explained by a narrower K value range. The slope between K and PPC activation statistically accounted for 43.4% of the between-group differences in broad cognitive function. These results indicate that PPC dysfunction is central to WM storage deficits in PSZ and may play a key role in the broad cognitive deficits associated with schizophrenia.

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Contextual-Dependent Attention Effect on Crowded Orientation Signals in Human Visual Cortex

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A target becomes hard to identify with nearby visual stimuli. This phenomenon, known as crowding, places a fundamental limit on conscious perception and object recognition. To understand the neural representation of crowded stimuli, we used fMRI and a forward encoding model to reconstruct the target-specific feature from multivoxel activation patterns evoked by orientation patches. Orientation-selective response profiles were constructed in V1–V4 for a target embedded in different contexts. Subjects of both sexes either directed their attention over all the orientation patches or selectively to the target. In the context with a weak crowding effect, attending to the target enhanced the orientation selectivity of the response profile; such effect increased along the visual pathway. In the context with a strong crowding effect, attending to the target enhanced the orientation selectivity of the response profile in the earlier visual area, but not in V4. The increase and decrease of orientation selectivity along the visual hierarchy demonstrate a contextual-dependent attention effect on crowded orientation signals: in the context with a weak crowding effect, selective attention gradually resolves the target from nearby distractors along the hierarchy; in the context with a strong crowding effect, while selective attention maintains the target feature in the earlier visual area, its effect decreases in the downstream area. Our findings reveal how the human visual system represents the target-specific feature at multiple stages under the limit of attention selection in a cluttered scene.

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Feedback-Based Learning in Aging: Contributions and Trajectories of Change in Striatal and Hippocampal Systems

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The striatum supports learning from immediate feedback by coding prediction errors (PEs), whereas the hippocampus (HC) plays a parallel role in learning from delayed feedback. Both regions show evidence of decline in human aging, but behavioral research suggests greater decline in HC versus striatal functions. The present study included male and female humans and used fMRI to examine younger and older adults' brain activation patterns during a learning task with choice feedback presented immediately or after a brief delay. Participants then completed a surprise memory task that tested their recognition of trial-unique feedback stimuli, followed by assessments of postlearning cue preference, outcome probability awareness, and willingness to pay. The study yielded three main findings. First, behavioral measures

indicated similar rates of learning in younger and older adults across conditions, but postlearning measures indicated impairment in older adults' ability to subsequently apply learning to discriminate between cues. Second, PE signals in the striatum were greater for immediate versus delayed feedback in both age groups, but PE signals in the HC were greater for delayed versus immediate feedback only in younger adults. Third, unlike younger adults, older adults failed to exhibit enhanced episodic memory for outcome stimuli in the delayed-feedback condition. Together, these findings indicate that HC circuits supporting learning and memory decline more than striatal circuits in healthy aging, which suggests that declines in HC learning signals may be an important predictor of deficits in learning-dependent economic decisions among older adults.

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A Neuronal Ensemble in the Rostral Agranular Insula Tracks Cocaine-Induced Devaluation of Natural Reward and Predicts Cocaine Seeking

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In substance use disorders, negative affect associated with drug withdrawal can elicit strong drug craving and promote relapse. One brain region implicated in those processes is the rostral agranular insular cortex (RAIC), although precisely how this region encodes negative affect associated with drug seeking is unknown. Here, a preclinical model was used where RAIC activity was examined in male Sprague Dawley rats during intraoral infusions of a sweet (saccharin) paired with impending but delayed access to cocaine self-administration, and for comparative purposes, during the sweet predicting saline self-administration or injection of lithium chloride (LiCl), or during intraoral infusions of a bitter taste (quinine). Consistent with previous work, cocaine-paired saccharin, LiCl-paired saccharin, and quinine all elicited aversive taste reactivity. However, the aversive taste reactivity elicited by the cocaine-paired tastant was qualitatively different from that evoked by the other two agents. Furthermore, differences in taste reactivity were reflected in RAIC cell firing, where distinct shifts in neural signaling were observed specifically after cocaine but not LiCl conditioning. Notably, low motivation for cocaine (indicated by low loading and slower latencies to lever press) was correlated with this shift in RAIC signaling, but aversive (gaping) responses were not. Collectively, these findings indicate that cocaine-paired tastants elicit unique aspects of aversive behaviors that differ from traditional conditioned taste aversion (LiCl) or quinine and that the RAIC plays a role in modulating drug-seeking behaviors driven by drug-induced dysphoria (craving), but not negative affect per se.

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NEUROBIOLOGY OF DISEASE

A Functional riboSNitch in the 3' Untranslated Region of *FKBP5* Alters MicroRNA-320a Binding Efficiency and Mediates Vulnerability to Chronic Post-Traumatic Pain

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Previous studies have shown that common variants of the gene coding for FK506-binding protein 51 (*FKBP5*), a critical regulator of glucocorticoid sensitivity, affect vulnerability to stress-related disorders. In a previous report, *FKBP5* rs1360780 was identified as a functional variant because of its effect on gene methylation. Here we report evidence for a novel functional *FKBP5* allele, rs3800373. This study assessed the association between rs3800373 and post-traumatic chronic pain in 1607 women and men from two ethnically diverse human cohorts. The molecular mechanism through which rs3800373 affects adverse outcomes was established via *in silico*, *in vivo*, and *in vitro* analyses. The rs3800373 minor allele predicted worse adverse outcomes after trauma exposure, such that individuals with the minor (risk) allele developed more severe post-traumatic chronic musculoskeletal pain. Among these individuals, peritraumatic circulating *FKBP5* expression levels increased as cortisol and glucocorticoid receptor (*NR3C1*) mRNA levels increased, consistent with increased glucocorticoid resistance. Bioinformatic, *in vitro*, and mutational analyses indicate that the rs3800373 minor allele reduces the binding of a stress- and pain-associated microRNA, miR-320a, to *FKBP5* via altering the *FKBP5* mRNA 3' UTR secondary structure (i.e., is a riboSNitch). This results in relatively greater *FKBP5* translation, unchecked by miR-320a. Overall, these results identify an important gene–miRNA interaction influencing chronic pain risk in vulnerable individuals and suggest that exogenous methods to achieve targeted reduction in poststress *FKBP5* mRNA expression may constitute useful therapeutic strategies.

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A Brain–Heart Biomarker for Epileptogenesis

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Postinjury epilepsy is an potentially preventable sequela in as many as 20% of patients with brain insults. For these cases biomarkers of epileptogenesis are critical to facilitate identification of patients at high-risk of developing epilepsy and to introduce effective anti-epileptogenic interventions. Here, we demonstrate that delayed brain–heart coincidences serve as a reliable biomarker. In a murine model of post-infection acquired epilepsy, we used long-term simultaneous measurements of the brain activity via electroencephalography and autonomic cardiac activity via electrocardiography, in male mice, to quantitatively track brain–heart interactions during epileptogenesis. We find that abnormal cortical discharges precede abnormal fluctuations in the cardiac rhythm at the resolution of single beat-to-beat intervals. The delayed brain–heart coincidence is detectable as early as the onset of chronic measurements, 2–14 weeks before the first seizure, only in animals that become epileptic, and increases during epileptogenesis. Therefore, delayed brain–heart coincidence serves as a biomarker of epileptogenesis and could be used for phenotyping, diagnostic, and therapeutic purposes.

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TRPM2 Exacerbates Central Nervous System Inflammation in Experimental Autoimmune Encephalomyelitis by Increasing Production of CXCL2 Chemokines

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Multiple sclerosis (MS) is a chronic inflammatory disorder of the CNS characterized by demyelination and axonal injury. Current therapies that mainly target lymphocytes do not fully meet clinical need due to the risk of severe side effects and lack of efficacy against progressive MS. Evidence suggests that MS is associated with CNS inflammation, although the underlying molecular mechanism is poorly understood. Transient receptor potential melastatin 2 (TRPM2), a Ca^{2+} -permeable nonselective cation channel, is expressed at high levels in the brain and by immune cells, including monocyte lineage cells. Here, we show that TRPM2 plays a pathological role in experimental autoimmune encephalomyelitis (EAE), an animal model of MS. Knockout (KO) or pharmacological inhibition of TRPM2 inhibited progression of EAE and TRPM2-KO mice showed lower activation of Iba1-immunopositive monocyte lineage cells and neutrophil infiltration of the CNS than WT mice. Moreover, CXCL2 production in TRPM2-KO mice was significantly reduced at day 14, although the severity of EAE was the same as that in WT mice at that time point. In addition, we used BM chimeric mice to show that TRPM2 expressed by CNS-infiltrating macrophages contributes to progression of EAE. Because CXCL2 induces migration of neutrophils, these results indicate that reduced expression of CXCL2 in the CNS suppresses neutrophil infiltration and slows progression of EAE in TRPM2-KO mice. Together, the results suggest that TRPM2 plays an important role in progression of EAE pathology and shed light on its putative role as a therapeutic target for MS.

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