This Week in The Journal

Dopamine Transporter Is Rarely Endocytosed in Striatum

Ethan R. Block, Jacob Nuttle, Judith Joyce Balcita-Pedicino, John Caltagarone, Simon C. Watkins, et al.

(see pages 12845–12858)

The dopamine transporter (DAT) limits the spatial and temporal spread of dopaminergic signaling by taking up extracellular dopamine. This function is thought to be modulated by endogenous signaling pathways. For example, phosphorylation of DAT by protein kinase C (PKC) reduces dopamine uptake, whereas phosphorylation by extracellular signal-regulated kinase increases uptake. Although phosphorylation might alter uptake by changing the $V_{\text{max}}$ of the transporter, PKC-mediated phosphorylation has been proposed to reduce dopamine uptake primarily by promoting DAT endocytosis. It has further been proposed that sorting of endocytosed DAT to recycling endosomes underlies short-term reductions in uptake, whereas targeting the transporter for degradation in lysosomes underlies longer term modulation (Vaughan and Foster, 2013, Trends Pharmacol Sci 34:489).

To investigate these hypotheses and examine which endocytic pathways predominate under physiological conditions, Block et al. used knock-in mice expressing hemagglutinin-tagged DAT and examined DAT localization in acute brain slices and by electron microscopy. In the midbrain, most DAT (~75%) was associated with intracellular membranes, particularly within somata, where it was found primarily on nuclear, endoplasmic reticulum, and Golgi membranes. DAT was occasionally colocalized with markers of early, recycling, or intermediate/sorting endosomes in vesicular structures in the midbrain, but it never colocalized with markers of late endosomes or lysosomes.

Plasma membrane expression of DAT was higher in dopaminergic axons in the striatum than in the midbrain. Furthermore, DAT density was greater in axonal varicosities (putative presynaptic sites) than along intervening shafts, and most axonal DAT (~85%) was associated with the plasma membrane. Surprisingly, markers of early and recycling endosomes were rarely observed in dopaminergic axons, and DAT never colocalized with these markers. Moreover, markers of intermediate/sorting endosomes and lysosomes were never detected in dopaminergic axons. Finally, although amphetamine can induce DAT endocytosis in cultured neurons, amphetamine administration in vivo or in slices did not significantly change the subcellular distribution of DAT.

These results indicate that constitutive endocytosis rarely occurs in the axons of dopaminergic neurons, and when it does occur, internalized proteins are likely recycled to the plasma membrane rather than degraded in lysosomes. Thus, modulation of dopamine uptake must be regulated primarily by changes in DAT $V_{\text{max}}$ or lateral diffusion of DAT within the membrane.

Transcranial Direct Current Stimulation Enhances LTP

Joyce G. Rohan, Kim A. Carhuatanta, Shawn M. McInturf, Molly K. Milksavich, and Ryan Jankord

(see pages 12824–12832)

Transcranial direct current stimulation (tDCS) is increasingly being used to study and/or enhance human brain function. Anodal tDCS applied to different cortical regions has been reported to enhance sensory perception, motor learning, motor performance, working and episodic memory, and other cognitive functions. Importantly, these improvements often persist for several hours after stimulation. Although effects vary across studies and are often limited to select task elements and/or groups of participants, it is hoped that tDCS might ultimately be used to enhance recovery from injury, treat neuropsychiatric conditions, and improve cognitive performance.

How tDCS exerts its effects on brain function is poorly understood. Effects during the stimulation period are thought to be limited to changes in neuronal membrane potential, specifically depolarization in the case of anodal stimulation. Depending on its duration and intensity, however, anodal tDCS can also cause an increase in cortical excitability that persists for several hours after stimulation ends. This persistent effect requires activation of voltage-sensitive Na$^+$ channels, Ca$^{2+}$ channels, and NMDA receptors. It has therefore been suggested that tDCS enhances long-term potentiation (LTP; reviewed in Stagg and Nitsche, 2011, Neuroscientist 17:37).

Rohan et al. confirm this hypothesis. Rats were given anodal tDCS or sham treatment for 30 min, and brain slices were taken 0.5 or 24 h later. Anodal tDCS did not affect spontaneous activity or the size of field EPSPs (fEPSPs) evoked by electrical stimulation of Schaffer collaterals in the hippocampus. But theta-burst stimulation of Schaffer collaterals caused a greater increase in the slope and amplitude of subsequently evoked fEPSPs in tDCS-treated rats than in controls. This enhancement in LTP was still present 24 h after stimulation, and it was blocked by an NMDA receptor antagonist. tDCS also enhanced paired-pulse facilitation, but this effect neither persisted for 24 h nor required activation of NMDA receptors.

These data suggest that tDCS enhances LTP and affects presynaptic release probability at Schaffer collateral terminals in hippocampus. Perhaps the most important contribution of this study, however, is the demonstration that the effects of in vivo tDCS can be studied in slices taken 0.5–24 h after stimulation. This should simplify future investigations into the cellular mechanisms underlying the effects of tDCS.
Cover legend: Serotonin-releasing neurons in the *Drosophila* brain modulate a variety of behaviors. This image shows a fly brain with different types of these neurons expressing different fluorescent markers. Each neuron innervates selective parts of the *Drosophila* brain with elaborate arborization. For more information, see the article by Pooryasin and Fiala (pages 12792–12812).

This Week in The Journal

**Journal Club**

12609  The Contribution of Semantic Features to the White Matter Pathways of Tool Processing  
Jet M. J. Vonk

12612  The Neural Representation of Multiple Objects in the Primate Visual System  
Danique Jeurissen, Anne F. van Ham, and Matthew W. Self

**Articles**

**CELLULAR/MOLECULAR**

12703  Distinct Functions for Anterograde and Retrograde Sorting of SORLA in Amyloidogenic Processes in the Brain  
Sonya B. Dumanis, Tilman Burgert, Safak Caglayan, Annette Füchtbauer, Ernst-Martin Füchtbauer, Vanessa Schmidt, and Thomas E. Willnow

12714  Calcitonin Gene-Related Peptide Reduces Taste-Evoked ATP Secretion from Mouse Taste Buds  
Anthony Y. Huang and Sandy Y. Wu

12845  Brain Region-Specific Trafficking of the Dopamine Transporter  
Ethan R. Block, Jacob Nuttle, Judith Joyce Balcita-Pedicino, John Caltagarone, Simon C. Watkins, Susan R. Sesack, and Alexander Sorkin

12917  Kappa Opioid Receptor-Induced Aversion Requires p38 MAPK Activation in VTA Dopamine Neurons  

**DEVELOPMENT/PLASTICITY/REPAIR**

12693  Unmasking Proteolytic Activity for Adult Visual Cortex Plasticity by the Removal of Lynx1  
Noreen Bukhari, Poromendro N. Burman, Ayan Hussein, Michael P. Demars, Masato Sadahiro, Daniel M. Brady, Stella E. Tsirka, Scott J. Russo, and Hirofumi Morishita

12824 Modulating Hippocampal Plasticity with *In Vivo* Brain Stimulation
Joyce G. Rohan, Kim A. Carhuatanta, Shawn M. McInturf, Molly K. Miklasevich, and Ryan Jankord

12869 *Prox1* Regulates the Subtype-Specific Development of Caudal Ganglionic Eminence-Derived GABAergic Cortical Interneurons
Goichi Miyoshi, Allison Young, Timothy Petros, Theofanis Karayannis, Melissa McKenzie Chang, Alfonso Lavado, Tomohiko Iwano, Miho Nakajima, Hiroki Taniguchi, Z. Josh Huang, Nathaniel Heintz, Guillermo Oliver, Fumio Matsuzaki, Robert P. Machold, and Gord Fishell

SYSTEMS/CIRCUITS

12615 Representation of Muscle Synergies in the Primate Brain
Simon A. Overduin, Andrea d’Avella, Jinsook Roh, Jose M. Carmena, and Emilio Bizzi

12625 Age-Related Differences and Heritability of the Perisylvian Language Networks
Sanja Budisavljevic, Flavio Dell’Acqua, Frühling V. Rijswijk, Fergus Kane, Marco Picchioni, Philip McGuire, Timothea Toulopoulou, Anna Georgiades, Sridevi Kalidindi, Eugenia Kravariti, Robin M. Murray, Declan G. Murphy, Michael C. Craig, and Marco Catani

12635 Dynamic Changes from Depolarizing to Hyperpolarizing GABAergic Actions during Giant Depolarizing Potentials in the Neonatal Rat Hippocampus
Ilgam Khalilov, Marat Minlebaev, Marat Mukhtarov, and Roustem Khazipov

12659 A Simple Network Architecture Accounts for Diverse Reward Time Responses in Primary Visual Cortex
Marco A. Huertas, Marshall G. Hussain Shuler, and Harel Z. Shouval

12903 GnRH Neuron-Specific Ablation of Gq11 Results in Only Partial Inactivation of the Neuroendocrine-Reproductive Axis in Both Male and Female Mice: *In Vivo* Evidence for Kiss1r-Coupled Gq11-Independent GnRH Secretion
Andy V. Babwah, Victor M. Navarro, Maryse Ahow, Macarena Pampillo, Connor Nash, Mehri Fayazi, Michele Calder, Adrienne Elbert, Henryk F. Urbanski, Nina Wettschereck, Stefan Offermans, Rona S. Carroll, Moshmi Bhattacharya, Stuart A. Tobet, and Ursula B. Kaiser

BEHAVIORAL/COGNITIVE

12643 Characterization of Cortical Networks and Corticocortical Functional Connectivity Mediating Arbitrary Visuomotor Mapping
Andrea Brovelli, Daniel Chicharro, Jean-Michel Badier, Huifang Wang, and Viktor Jirsa

12673 3D Shape Perception in Posterior Cortical Atrophy: A Visual Neuroscience Perspective
Céline R. Gillebert, Jolien Schaeverbek, Christine Bastin, Veerle Neyens, Rose Bruffaerts, An-Sofie De Weer, Alexandra Seghers, Stefan Sunaert, Koen Van Laere, Jan Versijpt, Mathieu Vandenbulcke, Eric Salmon, James T. Todd, Guy A. Orban, and Rik Vandenberghe
Right Frontoinsular Cortex and Subcortical Activity to Infant Cry Is Associated with Maternal Mental State Talk
Alison E. Hipwell, Chaohui Guo, Mary L. Phillips, James E. Swain, and Eydie L. Moses-Kolko

Distinct Modulations in Sensorimotor Postmovement and Foreperiod β-Band Activities Related to Error Salience Processing and Sensorimotor Adaptation
Flavie Torrecillos, Julie Alayrangues, Bjørg Elisabeth Kilavik, and Nicole Malfait

Identified Serotonin-Releasing Neurons Induce Behavioral Quiescence and Suppress Mating in Drosophila
Atefeh Pooryasin and André Filali

Ventromedial Frontal Cortex Is Critical for Guiding Attention to Reward-Predictive Visual Features in Humans
Avinash R. Vaidya and Lesley K. Fellows

“Visual” Cortex of Congenitally Blind Adults Responds to Syntactic Movement
Connor Lane, Shipra Kanjlia, Akira Omaki, and Marina Bedny

Arginine Methyltransferase 1 in the Nucleus Accumbens Regulates Behavioral Effects of Cocaine
Yan Li (李燕), Ruiming Zhu (朱睿明), Wenjing Wang (汪文静), Dengqi Fu (付登琦), Jing Hou (侯静), Sen Ji (纪霖), Bo Chen (陈波), Zhengtao Hu (扈正桃), Xue Shao (邵雪), Xuri Yu (余旭日), Qian Zhao (赵倩), Baolai Zhang (张宝来), Changman Du (杜长蔓), Qian Bu (卜迁), Chunyan Hu (胡春燕), Yun Tang (唐芸), Lei Zhong (钟磊), Shengyong Yang (杨胜勇), Yinglan Zhao (赵瀛兰), and Xiaobo Cen (岑小波)

Spontaneous Activity Patterns in Primary Visual Cortex Predispose to Visual Hallucinations
Auréliane Pajani, Peter Kok, Sid Kouider, and Floris P. de Lange

A Neural Basis for Developmental Topographic Disorientation
Jiye G. Kim, Elissa M. Aminoff, Sabine Kastner, and Marlene Behrmann

Amyloid β Oligomers Disrupt Blood–CSF Barrier Integrity by Activating Matrix Metalloproteinases
Marjana Brkic, Sriram Balusu, Elien Van Wonterghem, Nina Gorlé, Iryna Benilova, Anna Kremer, Inge Van Hove, Lieve Moons, Bart De Strooper, Selma Kanazir, Claude Libert, and Roosmarijin E. Vandenbroucke

Impaired Cholinergic Excitation of Prefrontal Attention Circuitry in the TgCRND8 Model of Alzheimer’s Disease
Éliane Proulx, Paul Fraser, JoAnne McLaurin, and Evelyn K. Lambe

Mitochondrial Quality Control via the PGC1α-TFEB Signaling Pathway Is Compromised by Parkin Q311X Mutation But Independently Restored by Rapamycin
Almas Siddiqui, Dipa Bhaumik, Shankar J. Chinta, Anand Rane, Subramanian Rajagopalan, Christopher A. Lieu, Gordon J. Lithgow, and Julie K. Andersen
Intrinsic Functional Connectivity Patterns Predict Consciousness Level and Recovery Outcome in Acquired Brain Injury
Xuehai Wu, Qihong Zou, Jin Hu, Weijun Tang, Ying Mao, Liang Gao, Jianhong Zhu, Yi Jin, Xin Wu, Lu Lu, Yaojun Zhang, Yao Zhang, Zhengjia Dai, Jia-Hong Gao, Xuchu Weng, Liangfu Zhou, Georg Northoff, Joseph T. Giacino, Yong He, and Yihong Yang

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**Representation of Muscle Synergies in the Primate Brain**

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Evidence suggests that the CNS uses motor primitives to simplify movement control, but whether it actually stores primitives instead of computing solutions on the fly to satisfy task demands is a controversial and still-unanswered possibility. Also in contention is whether these primitives take the form of time-invariant muscle coactivations (“spatial” synergies) or time-varying muscle commands (“spatiotemporal” synergies). Here, we examined forelimb muscle patterns and motor cortical spiking data in rhesus macaques (Macaca mulatta) handling objects of variable shape and size. From these data, we extracted both spatiotemporal and spatial synergies using non-negative decomposition. Each spatiotemporal synergy represents a sequence of muscular or neural activations that appeared to recur frequently during the animals’ behavior. Key features of the spatiotemporal synergies (including their dimensionality, timing, and amplitude modulation) were independently observed in the muscular and neural data. In addition, both at the muscular and neural levels, these spatiotemporal synergies could be readily reconstructed as sequential activations of spatial synergies (a subset of those extracted independently from the task data), suggestive of a hierarchical relationship between the two levels of synergies. The possibility that motor cortex may execute even complex skill using spatiotemporal synergies has novel implications for the design of neuroprosthetic devices, which could gain computational efficiency by adopting the discrete and low-dimensional control that these primitives imply.

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**Age-Related Differences and Heritability of the Perisylvian Language Networks**

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Acquisition of language skills depends on the progressive maturation of specialized brain networks that are usually lateralized in adult population. However, how genetic and environmental factors relate to the age-related differences in lateralization of these language pathways is still not known. We recruited 101 healthy right-handed subjects aged 9–40 years to investigate age-related differences in the anatomy of perisylvian language pathways and 86 adult twins (52 monozygotic and 34 dizygotic) to understand how heritability factors influence language anatomy. Diffusion tractography was used to dissect and extract indirect volume measures from the three segments of the arcuate fasciculus connecting Wernicke’s to Broca’s region (i.e., long segment), Broca’s to Geschwind’s region (i.e., anterior segment), and Wernicke’s to Geschwind’s region (i.e., posterior segment). We found that the long and anterior arcuate segments are lateralized before adolescence and their lateralization remains stable throughout adolescence and early adulthood. Conversely, the posterior segment shows right lateralization in childhood but becomes progressively bilateral during adolescence, driven by a reduction in volume in the right hemisphere. Analysis of the twin sample showed that genetic and shared environmental factors influence the anatomy of those segments that satisfy task demands is a controversial and still-unanswered possibility. Also in contention is whether these primitives take the form of time-invariant muscle coactivations (“spatial” synergies) or time-varying muscle commands (“spatiotemporal” synergies). Here, we examined forelimb muscle patterns and motor cortical spiking data in rhesus macaques (Macaca mulatta) handling objects of variable shape and size. From these data, we extracted both spatiotemporal and spatial synergies using non-negative decomposition. Each spatiotemporal synergy represents a sequence of muscular or neural activations that appeared to recur frequently during the animals’ behavior. Key features of the spatiotemporal synergies (including their dimensionality, timing, and amplitude modulation) were independently observed in the muscular and neural data. In addition, both at the muscular and neural levels, these spatiotemporal synergies could be readily reconstructed as sequential activations of spatial synergies (a subset of those extracted independently from the task data), suggestive of a hierarchical relationship between the two levels of synergies. The possibility that motor cortex may execute even complex skill using spatiotemporal synergies has novel implications for the design of neuroprosthetic devices, which could gain computational efficiency by adopting the discrete and low-dimensional control that these primitives imply.

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**Dynamic Changes from Depolarizing to Hyperpolarizing GABAergic Actions during Giant Depolarizing Potentials in the Neonatal Rat Hippocampus**

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During development, GABA exerts depolarizing action on immature neurons and, acting in synergy with glutamate, drives giant depolarizing potentials (GDPs) in the hippocampal network. Yet, blockade of the GABA(A) receptors transforms GDPs to epileptiform discharges suggesting dual, both excitatory and inhibitory, actions of GABA in the immature hippocampal network. However, the nature of this dualism in early GABA actions is poorly understood. Here we characterized the dynamics of synaptic currents mediated by GABA(A) and glutamate receptors through an estimation of the changes in their conductance and driving forces in neonatal rat CA3
pyramidal cells during GDPs. We found that depolarizing GABAergic and glutamatergic currents act in synergy at the GDPs' onset. However, during the peak of the population discharge, the inward synaptic current was essentially mediated by glutamate receptors whereas GABA currents transiently switched their direction from depolarizing to hyperpolarizing as a result of neuronal depolarization above the GABA(A) reversal potential. Thus, the action of GABA on CA3 pyramidal cells dynamically changes during GDPs from excitatory at the GDPs' onset to inhibitory at the GDPs' peak. We propose that the dynamic changes in GABA actions occurring during GDPs enable GABAergic interneurons not only to initiate the discharge of pyramidal cells but also to control excitation in the recurrent CA3 network preventing epileptiform synchronization.

BEHAVIORAL/COGNITIVE

Characterization of Cortical Networks and Corticocortical Functional Connectivity Mediating Arbitrary Visuomotor Mapping

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Adaptive behaviors are built on the arbitrary linkage of sensory inputs to actions and goals. Although the sensorimotor and associative frontostriatal circuits are known to mediate arbitrary visuomotor mappings, the underlying corticocortical dynamics remain elusive. Here, we take a novel approach exploiting gamma-band neural activity to study the human cortical networks and corticocortical functional connectivity mediating arbitrary visuomotor mapping. Single-trial gamma-power time courses were estimated for all Brodmann areas by combing magnetoencephalographic and MRI data with spectral analysis and beam-forming techniques. Linear correlation and Granger causality analyses were performed to investigate functional connectivity between cortical regions. The performance of visuomotor associations was characterized by an increase in gamma-power and functional connectivity over the sensorimotor and frontoparietal network, in addition to medial prefrontal areas. The superior parietal area played a driving role in the network, exerting Granger causality on the dorsal premotor area. Premotor areas acted as relay from parietal to medial prefrontal cortices, which played a receiving role in the network. Link community analysis further revealed that visuomotor mappings reflect the coordination of multiple subnetworks with strong overlap over motor and frontoparietal areas. We put forward an associative account of the underlying cognitive processes and corticocortical functional connectivity. Overall, our approach and results provide novel perspectives toward a better understanding of how distributed brain activity coordinates adaptive behaviors.

SYSTEMS/CIRCUITS

A Simple Network Architecture Accounts for Diverse Reward Time Responses in Primary Visual Cortex

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Many actions performed by animals and humans depend on an ability to learn, estimate, and produce temporal intervals of behavioral relevance. Exemplifying such learning of cued expectancies is the observation of reward-timing activity in the primary visual cortex (V1) of rodents, wherein neural responses to visual cues come to predict the time of future reward as behaviorally experienced in the past. These reward-timing responses exhibit significant heterogeneity in at least three qualitatively distinct classes: sustained increase or sustained decrease in firing rate until the time of expected reward, and a class of cells that reach a peak in firing at the expected delay. We elaborate upon our existing model by including inhibitory and excitatory units while imposing simple connectivity rules to demonstrate what role these inhibitory elements and the simple architectures play in sculpting the response dynamics of the network. We find that simply adding inhibition is not sufficient for obtaining the different distinct response classes, and that a broad distribution of inhibitory projections is necessary for obtaining peak-type responses. Furthermore, although changes in connection strength that modulate the effects of inhibition onto excitatory units have a strong impact on the firing rate profile of these peaked responses, the network exhibits robustness in its overall ability to predict the expected time of reward. Finally, we demonstrate how the magnitude of expected reward can be encoded at the expected delay in the network and how peaked responses express this reward expectancy.
3D Shape Perception in Posterior Cortical Atrophy: A Visual Neuroscience Perspective

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Posterior cortical atrophy (PCA) is a rare focal neurodegenerative syndrome characterized by progressive visuo-perceptual and visuo-spatial deficits, most often due to atypical Alzheimer’s disease (AD). We applied insights from basic visual neuroscience to analyze 3D shape perception in humans affected by PCA. Thirteen PCA patients and 30 matched healthy controls participated, together with two patient control groups with diffuse Lewy body dementia (DLBD) and an amnestic-dominant phenotype of AD, respectively. The hierarchical study design consisted of 3D shape processing for 4 cues (shading, motion, texture, and binocular disparity) with corresponding 2D and elementary feature extraction control conditions. PCA and DLBD exhibited severe 3D shape-processing deficits and AD to a lesser degree. In PCA, deficient 3D shape-from-shading was associated with volume loss in the right posterior inferior temporal cortex. This region coincided with a region of functional activation during 3D shape-from-shading in healthy controls. In PCA patients who performed the same fMRI paradigm, response amplitude during 3D shape-from-shading was reduced in this region. Gray matter volume in this region also correlated with 3D shape-from-shading in AD. 3D shape-from-disparity in PCA was associated with volume loss slightly more anteriorly in posterior inferior temporal cortex as well as in ventral premotor cortex. The findings in right posterior inferior temporal cortex and right premotor cortex are consistent with neurophysiologically based models of the functional anatomy of 3D shape processing. However, in DLBD, 3D shape deficits rely on mechanisms distinct from inferior temporal structural integrity.

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Unmasking Proteolytic Activity for Adult Visual Cortex Plasticity by the Removal of Lynx1

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Experience-dependent cortical plasticity declines with age. At the molecular level, experience-dependent proteolytic activity of tissue plasminogen activator (tPA) becomes restricted in the adult brain if mice are raised in standard cages. Understanding the mechanism for the loss of permissive proteolytic activity is therefore a key link for improving function in adult brains. Using the mouse primary visual cortex (V1) as a model, we demonstrate that tPA activity in V1 can be unmasked following 4 d of monocular deprivation when the mice older than 2 months are raised in standard cages by the genetic removal of Lynx1, a negative regulator of adult plasticity. This was also associated with the reduction of stubby and thin spine density and enhancement of ocular dominance shift in adult V1 of Lynx1 knock-out (KO) mice. These structural and functional changes were tPA-dependent because genetic removal of tPA in Lynx1 KO mice can block the monocular deprivation-dependent reduction of dendritic spine density, whereas both genetic and adult specific inhibition of tPA activity can ablate the ocular dominance shift in Lynx1 KO mice. Our work demonstrates that the adult brain has an intrinsic potential for experience-dependent elevation of proteolytic activity to express juvenile-like structural and functional changes but is effectively limited by Lynx1 if mice are raised in standard cages. Insights into the Lynx1–tPA plasticity mechanism may provide novel therapeutic targets for adult brain disorders.

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**Distinct Functions for Anterograde and Retrograde Sorting of SORLA in Amyloidogenic Processes in the Brain**

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SORLA is a neuronal sorting receptor implicated both in sporadic and familial forms of AD. SORLA reduces the amyloidogenic burden by two mechanisms, either by rerouting internalized APP molecules from endosomes to the trans-Golgi network (TGN) to prevent proteolytic processing or by directing newly produced Aβ to lysosomes for catabolism. Studies in cell lines suggested that the interaction of SORLA with cytosolic adaptors retromer and GGA is required for receptor sorting to and from the TGN. However, the relevance of anterograde or retrograde trafficking for SORLA activity in vivo remained largely unexplored. Here, we generated mouse models expressing SORLA variants lacking binding sites for GGA or retromer to query this concept in the brain. Disruption of retromer binding resulted in a retrograde-sorting defect with accumulation of SORLA in endosomes and depletion from the TGN, and in an overall enhanced APP processing. In contrast, disruption of the GGA interaction did not impact APP processing but caused increased brain Aβ levels, a mechanism attributed to a defect in anterograde lysosomal targeting of Aβ. Our findings substantiated the significance of adaptor-mediated sorting for SORLA activities in vivo, and they uncovered that anterograde and retrograde sorting paths may serve discrete receptor functions in amyloidogenic processes.

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**Calcitonin Gene-Related Peptide Reduces Taste-Evoked ATP Secretion from Mouse Taste Buds**

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Immunoelectron microscopy revealed that peripheral afferent nerve fibers innervating taste buds contain calcitonin gene-related peptide (CGRP), which may be as an efferent transmitter released from peripheral axon terminals. In this report, we determined the targets of CGRP within taste buds and studied what effect CGRP exerts on taste bud function. We isolated mouse taste buds and taste cells, conducted functional imaging using Fura-2, and used cellular biosensors to monitor taste-evoked transmitter release. The findings showed that a subset of Presynaptic (Type III) taste cells (53%) responded to 0.1 μM CGRP with an increase in intracellular Ca2+. In contrast, Receptor (Type II) taste cells rarely (4%) responded to 0.1 μM CGRP. Using pharmacological tools, the actions of CGRP were probed and elucidated by the CGRP receptor antagonist CGRP8-37. We demonstrated that this effect of CGRP was dependent on phospholipase C activation and was prevented by the inhibitor U73122. Moreover, applying CGRP caused taste buds to secrete serotonin (5-HT), a Presynaptic (Type III) cell transmitter, but not ATP, a Receptor (Type II) cell transmitter. Further, our previous studies showed that 5-HT released from Presynaptic (Type III) cells provides negative paracrine feedback onto Receptor (Type II) cells by activating 5-HT1A receptors, and reducing ATP secretion. Our data showed that CGRP-evoked 5-HT release reduced taste-evoked ATP secretion. The findings are consistent with a role for CGRP as an inhibitory transmitter that shapes peripheral taste signals via serotoninergic signaling during processing gustatory information in taste buds.

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**Right Frontoinsular Cortex and Subcortical Activity to Infant Cry Is Associated with Maternal Mental State Talk**

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The study objective was to examine neural correlates of a specific component of human caregiving: maternal mental state talk, reflecting a mother’s proclivity to attribute mental states and intentionality to her infant. Using a potent, ecologically relevant stimulus of infant cry during fMRI, we tested hypotheses that postpartum neural response to the cry of “own” versus a standard “other” infant in the right frontoinsular cortex (RFIC) and subcortical limbic network would be associated with independent observations of maternal mental state talk. The sample comprised 76 urban-living, low socioeconomic mothers (82% African American) and their 4-month-old infants.

Before the fMRI scan, mothers were filmed in face-to-face interaction with their infant, and maternal behaviors were coded by trained researchers unaware of all other information about the participants. The results showed higher functional activity in the RFIC to own versus other infant cry at the group level. In addition, RFIC and bilateral subcortical neural activity (e.g., thalamus, amygdala, hippocampus, putamen) was associated positively with maternal mental state talk but not with more global aspects of...
observed caregiving. These findings hold when accounting for perceptual and contextual covariates, such as maternal felt distress, urge to help, depression severity, and recognition of own infant cry. Our results highlight the need to focus on specific components of caregiving to advance understanding of the maternal brain. Future work will examine the predictive utility of this neural marker for mother–child function.

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DEVELOPMENT/PLASTICITY/REPAIR


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Docosahexaenoic acid (DHA) is an ω-3 polyunsaturated fatty acid that is essential in brain development and has structural and signaling roles. Acute DHA administration is neuroprotective and promotes functional recovery in animal models of adult spinal cord injury (SCI). However, the mechanisms underlying this recovery have not been fully characterized. Here we investigated the effects of an acute intravenous bolus of DHA delivered after SCI and characterized DHA-induced neuroplasticity within the adult injured spinal cord. We found robust sprouting of uninjured corticospinal and serotonergic fibers in a rat cervical hemisection SCI model. A mouse pyramidotomy model was used to confirm that this robust sprouting was not species or injury model specific. Furthermore, we demonstrated that corticospinal fibers sprouting to the denervated side of the cord following pyramidotomy contact V2a interneurons. We also demonstrated increased serotonin fibers and synaptophysin in direct contact with motor neurons. DHA also increased synaptophysin in rat cortical cell cultures. A reduction in phosphatase and tensin homolog (PTEN) has been shown to be involved in axonal regeneration and synaptic plasticity. We showed that DHA significantly upregulates miR-21 and downregulates PTEN in corticospinal neurons. Downregulation of PTEN and upregulation of phosphorylated AKT by DHA were also seen in primary cortical neuron cultures and were accompanied by increased neurite outgrowth. In summary, acute DHA induces anatomical and synaptic plasticity in adult injured spinal cord. This study shows that DHA has therapeutic potential in cervical SCI and provides evidence that DHA could exert its beneficial effects in SCI via enhancement of neuroplasticity.

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BEHAVIORAL/COGNITIVE

Distinct Modulations in Sensorimotor Postmovement and Foreperiod β-Band Activities Related to Error Salience Processing and Sensorimotor Adaptation

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In a recent study, Tan et al. (2014a,b) showed that the increase in β-power typically observed after a movement above sensorimotor regions (β-rebound) is attenuated when movement-execution errors are induced by visual perturbations. Moreover, akin to sensorimotor adaptation, the effect depended on the context in which the errors are experienced. Thus the β-rebound attenuation might relate to neural processes involved in trial-to-trial adaptive mechanisms. In two EEG experiments with human participants, along with the β-rebound, we examine β-activity during the preparation of reaches immediately following perturbed movements. In the first experiment, we show that both foreperiod and postmovement β-activities are parametrically modulated by the sizes of kinematic errors produced by unpredictable mechanical perturbations (force field) independent of their on-line corrections. In the second experiment, we contrast two types of reach errors: movement-execution errors that trigger trial-to-trial adaptive mechanisms and goal errors that do not elicit sensorimotor adaptation. Movement-execution errors were induced by mechanical or visual perturbations, whereas goal errors were caused by unexpected displacements of the target at movement initiation. Interestingly, foreperiod and postmovement β-activities exhibit contrasting patterns, pointing to important functional differences of their underlying neuronal activity. While both types of reach errors attenuate the postmovement β-rebound, only the kinematic errors that trigger trial-to-trial motor-command updates influenced β-activity during the foreperiod. These findings suggest that the error-related modulation of the β-rebound may reflect salience processing, independent of sensorimotor adaptation. In contrast, modulations in the foreperiod β-power might relate to the motor-command adjustments activated after movement-execution errors are experienced.

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Impaired Cholinergic Excitation of Prefrontal Attention Circuitry in the TgCRND8 Model of Alzheimer’s Disease

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Attention deficits in Alzheimer’s disease can exacerbate its other cognitive symptoms, yet relevant disruptions of key prefrontal circuitry are not well understood. Here, in the TgCRND8 mouse model of this neurological disorder, we demonstrate and characterize a disruption of cholinergic excitation in the major corticothalamic layer of the prefrontal cortex, in which modulation by acetylcholine is essential for optimal attentional function. Using electrophysiology with concurrent multiphoton imaging, we show that layer 6 pyramidal cells are unable to sustain cholinergic excitation to the same extent as their nontransgenic littermate controls, as a result of the excessive activation of calcium-activated hyperpolarizing conductances. We report that cholinergic excitation can be improved in TgCRND8 cortex by pharmacological blockade of SK channels, suggesting a novel target for the treatment of cognitive dysfunction in Alzheimer’s disease.

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BEHAVIORAL/COGNITIVE

Identified Serotonin-Releasing Neurons Induce Behavioral Quiescence and Suppress Mating in Drosophila

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Animals show different levels of activity that are reflected in sensory responsiveness and endogenously generated behaviors. Biogenic amines have been determined to be causal factors for these states of arousal. It is well established that, in Drosophila, dopamine and octopamine promote increased arousal. However, little is known about factors that regulate arousal negatively and induce states of quiescence. Moreover, it remains unclear whether global, diffuse modulatory systems comprehensively affect brain activity determine general states of arousal. Alternatively, individual aminergic neurons might selectively modulate the animals’ activity in a distinct behavioral context. Here, we show that artificially activating large populations of serotonin-releasing neurons induces behavioral quiescence and inhibits feeding and mating. We systematically narrowed down a role of serotonin in inhibiting endogenously generated locomotor activity to neurons located in the posterior medial protocerebrum. We identified neurons of this cell cluster that suppress mating, but not feeding behavior. These results suggest that
serotonin does not uniformly act as global, negative modulator of general arousal. Rather, distinct serotoninergic neurons can act as inhibitory modulators of specific behaviors.

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Ventromedial Frontal Cortex Is Critical for Guiding Attention to Reward-Predictive Visual Features in Humans

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Adaptively interacting with our environment requires extracting information that will allow us to successfully predict reward. This can be a challenge, particularly when there are many candidate cues, and when rewards are probabilistic. Recent work has demonstrated that visual attention is allocated to stimulus features that have been associated with reward on previous trials. The ventromedial frontal lobe (VMF) has been implicated in learning in dynamic environments of this kind, but the mechanism by which this region influences this process is not clear. Here, we hypothesized that the VMF plays a critical role in guiding attention to reward-predictive stimulus features based on feedback. We tested the effects of VMF damage in human subjects on a visual search task in which subjects were primed to attend to task-irrelevant colors associated with different levels of reward, incidental to the search task. Consistent with previous work, we found that distractors had a greater influence on reaction time when they appeared in colors associated with high reward in the previous trial compared with colors associated with low reward in healthy control subjects and patients with prefrontal damage sparing the VMF. However, this reward modulation of attentional priming was absent in patients with VMF damage. Thus, an intact VMF is necessary for directing attention based on experience with cue–reward associations. We suggest that this region plays a role in selecting reward-predictive cues to facilitate future learning.

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Modulating Hippocampal Plasticity with In Vivo Brain Stimulation

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Investigations into the use of transcranial direct current stimulation (tDCS) in relieving symptoms of neurological disorders and enhancing cognitive or motor performance have exhibited promising results. However, the mechanisms by which tDCS effects brain function remain under scrutiny. We have demonstrated that in vivo tDCS in rats produced a lasting effect on hippocampal synaptic plasticity, as measured using extracellular recordings. Ex vivo preparations of hippocampal slices from rats that have been subjected to tDCS of 0.10 or 0.25 mA for 30 min followed by 30 min of recovery time displayed a robust twofold enhancement in long-term potentiation (LTP) induction accompanied by a 30% increase in paired-pulse facilitation (PPF). The magnitude of the LTP effect was greater with 0.25 mA compared with 0.10 mA stimulations, suggesting a dose-dependent relationship between tDCS intensity and its effect on synaptic plasticity. To test the persistence of these observed effects, animals were stimulated in vivo for 30 min at 0.25 mA and then allowed to return to their home cage for 24 h. Observation of the enhanced LTP induction, but not the enhanced PPF, continued 24 h after completion of 0.25 mA of tDCS. Addition of the NMDA blocker AP-5 abolished LTP in both control and stimulated rats but maintained the PPF enhancement in stimulated rats. The observation of enhanced LTP and PPF after tDCS demonstrates that non-invasive electrical stimulation is capable of modifying synaptic plasticity.

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NEUROBIOLOGY OF DISEASE

Mitochondrial Quality Control via the PGC1α-TFEB Signaling Pathway Is Compromised by Parkin Q311X Mutation But Independently Restored by Rapamycin

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Following its activation by PINK1, parkin is recruited to depolarized mitochondria where it ubiquitinates outer mitochondrial membrane proteins, initiating lysosomal-mediated degradation of these organelles. Mutations in the gene encoding parkin, PARK2, result in both familial and sporadic forms of Parkinson’s disease (PD) in conjunction with reductions in removal of damaged mitochondria. In contrast to what has been reported for other PARK2 mutations, expression of the Q311X mutation in vivo in mice appears to involve a downstream step in the autophagic pathway at the level of lysosomal function. This coincides with increased PARIS expression and reduced expression of a reciprocal signaling pathway involving the master mitochondrial regulator peroxisome proliferator-activated receptor-gamma coactivator (PGC1α) and the lysosomal regulator transcription factor EB (TFEB). Treatment with rapamycin was found to independently restore PGC1α-TFEB signaling in a manner not requiring parkin activity and to abrogate impairment of mitochondrial quality control and neurodegenerative features associated with this in vivo model. Losses in PGC1α-TFEB
signaling in cultured rat DAergic cells expressing the Q311X mutation associated with reduced mitochondrial function and cell viability were found to be PARIS-dependent and to be independently restored by rapamycin in a manner requiring TFEB. Studies in human iPSC-derived neurons demonstrate that TFEB induction can restore mitochondrial function and cell viability in a mitochondrially compromised human cell model. Based on these data, we propose that the parkin Q311X mutation impacts on mitochondrial quality control via PARIS-mediated regulation of PGC1α-TFEB signaling and that this can be independently restored via upregulation of TFEB function.

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Articles

CELLULAR/MOLECULAR

Brain Region-Specific Trafficking of the Dopamine Transporter

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The dopamine (DA) transporter (DAT) controls dopaminergic neurotransmission by removing extracellular DA. Although DA reuptake is proposed to be regulated by DAT traffic to and from the cell surface, the membrane trafficking system involved in the endocytic cycling of DAT in the intact mammalian brain has not been characterized. Hence, we performed immunolabeling and quantitative analysis of the subcellular and regional distribution of DAT using the transgenic knock-in mouse expressing hemagglutinin (HA) epitope-tagged DAT (HA-DAT) and by using a combination of electron microscopy and a novel method for immunofluorescence labeling of HA-DAT in acute sagittal brain slices. Both approaches demonstrated that, in midbrain somatodendritic regions, HA-DAT was present in the plasma membrane, endoplasmic reticulum, and Golgi complex, with a small fraction in early and recycling endosomes and an even smaller fraction in late endosomes and lysosomes. In the striatum and in axonal tracts between the midbrain and striatum, HA-DAT was detected predominantly in the plasma membrane, and quantitative analysis revealed increased DAT density in striatal compared with midbrain plasma membranes. Endosomes were strikingly rare and lysosomes were absent in striatal axons, in which there was little intracellular HA-DAT. Acute administration of amphetamine in vivo (60 min) or to slices ex vivo (10–60 min) did not result in detectable changes in DAT distribution. Altogether, these data provide evidence for regional differences in DAT plasma membrane targeting and retention and suggest a surprisingly low level of endocytic trafficking of DAT in the striatum along with limited DAT endocytic activity in somatodendritic areas.

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BEHAVIORAL/COGNITIVE

“Visual” Cortex of Congenitally Blind Adults Responds to Syntactic Movement

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Human cortex is comprised of specialized networks that support functions, such as visual motion perception and language processing. How do genes and experience contribute to this specialization? Studies of plasticity offer unique insights into this question. In congenitally blind individuals, “visual” cortex responds to auditory and tactile stimuli. Remarkably, recent evidence suggests that occipital areas participate in language processing. We asked whether in blindness, occipital cortices: (1) develop domain-specific responses to language and (2) respond to a highly specialized aspect of language—syntactic movement. Nineteen congenitally blind and 18 sighted participants took part in two fMRI experiments. We report that in congenitally blind individuals, but not in sighted controls, “visual” cortex is more active during sentence comprehension than during a sequence memory task with nonwords, or a symbolic math task. This suggests that areas of occipital cortex become selective for language, relative to other similar higher-cognitive tasks. Crucially, we find that these occipital areas respond more to sentences with syntactic movement but do not respond to the difficulty of math equations. We conclude that regions within the visual cortex of blind adults are involved in syntactic processing. Our findings suggest that the cognitive function of human cortical areas is largely determined by input during development.

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GABAergic Cortical Interneurons

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Neurogliaform (RELN+/+) and bipolar (VIP+) GABAergic interneurons of the mammalian cerebral cortex provide critical inhibition locally within the superficial layers. While these subtypes are known to originate from the embryonic caudal ganglionic eminence (CGE), the specific genetic programs that direct their positioning, maturation, and integration into the cortical network have not been elucidated. Here, we report that in mouse expression of the transcription factor Prox1 is selectively maintained in postmitotic CGE-derived cortical interneuron precursors and that loss of Prox1 impairs the integration of these cells into superficial layers. Moreover, Prox1 differentially regulates the postnatal maturation of each specific subtype originating from the CGE (RELN+, Calb2+/+, and VIP). Interestingly, Prox1 promotes the maturation of CGE-derived interneuron subtypes through intrinsic differentiation programs that operate in tandem with extrinsically driven neuronal activity-dependent pathways. Thus, Prox1 represents the first identified transcription factor specifically required for the embryonic and postnatal acquisition of CGE-derived cortical interneuron properties.

Arginine Methyltransferase 1 in the Nucleus Accumbens Regulates Behavioral Effects of Cocaine

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Recent evidence suggests that histone modifications play a role in the behavioral effects of cocaine in rodent models. Histone arginine is known to be methylated by protein arginine N-methyltransferases (PRMTs). Evidence shows that PRMT1 contributes to >90% of cellular PRMT activity, which regulates histone H4 arginine 3 asymmetric dimethylation (H4R3me2a). Though histone arginine methylation represents a chemical modification that is relatively stable compared with other histone alterations, it is less well studied in the setting of addiction. Here, we demonstrate that repeated noncontingent cocaine injections increase PRMT1 activity in the nucleus accumbens (NAc) of C57BL/6 mice. We, subsequently, identify a selective inhibitor of PRMT1, SKLB-639, and show that systemic injections of the drug decrease cocaine-induced conditioned place preference to levels observed with genetic knockdown of PRMT1. NAc-specific downregulation of PRMT1 leads to hypomethylation of H4R3me2a, and hypoacetylation of histone H3 lysine 9 and 14. We also found that H4R3me2a is upregulated in NAc after repeated cocaine administration, and that H4R3me2a upregulation in turn controls the expression of Cdk5 and CaMKII. Additionally, the suppression of PRMT1 in NAc with lentiviral-short hairpin PMRT1 decreases levels of CaMKII and Cdk5 in the cocaine-treated group, demonstrating that PRMT1 affects the ability of cocaine to induce CaMKII and Cdk5 in NAc. Notably, increased H4R3me2a by repeated cocaine injections is relatively long-lived, as increased expression was observed for up to 7 days after the last cocaine injection. These results show the role of PRMT1 in the behavioral effects of cocaine.

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DEVELOPMENT/PLASTICITY/REPAIR

Prox1 Regulates the Subtype-Specific Development of Caudal Ganglionic Eminence-Derived GABAergic Cortical Interneurons

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While these subtypes are known to originate from the embryonic caudal ganglionic eminence (CGE), the specific genetic programs that direct their positioning, maturation, and integration into the cortical network have not been elucidated. Here, we report that in mouse expression of the transcription factor Prox1 is selectively maintained in postmitotic CGE-derived cortical interneuron precursors and that loss of Prox1 impairs the integration of these cells into superficial layers. Moreover, Prox1 differentially regulates the postnatal maturation of each specific subtype originating from the CGE (RELN+, Calb2+/+, and VIP). Interestingly, Prox1 promotes the maturation of CGE-derived interneuron subtypes through intrinsic differentiation programs that operate in tandem with extrinsically driven neuronal activity-dependent pathways. Thus, Prox1 represents the first identified transcription factor specifically required for the embryonic and postnatal acquisition of CGE-derived cortical interneuron properties.

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The gonadotropin-releasing hormone (GnRH) is the master regulator of fertility and kisspeptin (KP) is a potent trigger of GnRH secretion from GnRH neurons. KP signals via Gαq11-coupled receptor, and mice bearing a global deletion of Kiss1r or a Kiss1r neuron-specific deletion of Kiss1r would diminish but not completely block KP-triggered GnRH secretion and activation of the neuroendocrine-reproductive axis in both male and female mice. In Vivo Evidence for Kiss1r-Independent GnRH Secretion

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The endogenous dynorphin-α opioid receptor (KOR) system encodes the dysphoric component of the stress response and controls the risk of depression-like and addiction behaviors; however, the molecular and neural circuit mechanisms are not understood. In this study, we report that KOR activation of p38 MAPK in ventral tegmental (VTA) dopaminergic neurons was required for conditioned place aversion (CPA) in mice. Conditional genetic deletion of floxed KOR or floxed p38α MAPK by Cre recombinase expression in dopaminergic neurons blocked place aversion to the KOR agonist U50,488. Selective viral rescue by wild-type KOR expression in dopaminergic neuron somatic excitability through a p38 MAPK effect on GIRK deactivation kinetics rather than by presynaptically inhibiting dopamine release.

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Articles

CELLULAR/MOLECULAR

Kappa Opioid Receptor-Induced Aversion Requires p38 MAPK Activation in VTA Dopamine Neurons

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The endogenous dynorphin-α opioid receptor (KOR) system encodes the dysphoric component of the stress response and controls the risk of depression-like and addiction behaviors; however, the molecular and neural circuit mechanisms are not understood. In this study, we report that KOR activation of p38α MAPK in ventral tegmental (VTA) dopaminergic neurons was required for conditioned place aversion (CPA) in mice. Conditional genetic deletion of floxed KOR or floxed p38α MAPK by Cre recombinase expression in dopaminergic neurons blocked place aversion to the KOR agonist U50,488. Selective viral rescue by wild-type KOR expression in dopaminergic neurons of KOR−/− mice restored U50,488-CPA, whereas expression of a mutated form of KOR that could not initiate p38α MAPK activation did not. Surprisingly, while p38α MAPK inactivation blocked U50,488-CPA, p38α MAPK was not required for KOR inhibition of evoked dopamine release measured by fast scan cyclic voltammetry in the nucleus accumbens. In contrast, KOR activation acutely inhibited VTA dopaminergic neuron firing, and repeated exposure attenuated the opioid response. This adaptation to repeated exposure was blocked by conditional deletion of p38α MAPK, which also blocked KOR-induced tyrosine phosphorylation of the inwardly rectifying potassium channel (GIRK) subunit Kir3.1 in VTA dopaminergic neurons. Consistent with the reduced response, GIRK phosphorylation at this amino terminal tyrosine residue (Y12) enhances channel deactivation. Thus, contrary to prevailing expectations, these results suggest that α opioid-induced aversion requires regulation of VTA dopaminergic neuron somatic excitability through a p38α MAPK effect on GIRK deactivation kinetics rather than by presynaptically inhibiting dopamine release.

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Intrinsic Functional Connectivity Patterns Predict Consciousness Level and Recovery Outcome in Acquired Brain Injury

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For accurate diagnosis and prognostic prediction of acquired brain injury (ABI), it is crucial to understand the neurobiological mechanisms underlying loss of consciousness. However, there is no consensus on which regions and networks act as biomarkers for consciousness level and recovery outcome in ABI. Using resting-state fMRI, we assessed intrinsic functional connectivity strength (FCS) of whole-brain networks in a large sample of 99 ABI patients with varying degrees of consciousness loss (including fully preserved consciousness state, minimally conscious state, unresponsive wakefulness syndrome/vegetative state, and coma) and 34 healthy control subjects. Consciousness level was assessed using the Glasgow Coma Scale and Coma Recovery Scale-Revised on the day of fMRI scanning; recovery outcome was assessed using the Glasgow Outcome Scale 3 months after the fMRI scanning. One-way ANOVA of FCS, Spearman correlation analyses between FCS and the consciousness level and recovery outcome, and FCS-based multivariate pattern analysis were performed. We found decreased FCS with loss of consciousness primarily distributed in the posterior cingulate cortex/precuneus (PCC/PCU), medial prefrontal cortex, and lateral parietal cortex. The FCS values of these regions were significantly correlated with consciousness level and recovery outcome. Multivariate support vector machine discrimination analysis revealed that the FCS patterns predicted whether patients with unresponsive wakefulness syndrome/vegetative state and coma would regain consciousness with an accuracy of 81.25%, and the most discriminative region was the PCC/PCU. These findings suggest that intrinsic functional connectivity patterns of the human posteroomedial cortex could serve as a potential indicator for consciousness level and recovery outcome in individuals with ABI.

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BEHAVIORAL/COGNITIVE

Spontaneous Activity Patterns in Primary Visual Cortex Predispose to Visual Hallucinations

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According to theoretical frameworks casting perception as inference, vision results from the integration of bottom-up visual input with top-down expectations. Under conditions of strongly degraded sensory input, this may occasionally result in false perceptions in the absence of a sensory signal, also termed “hallucinations.” Here, we investigated whether spontaneous prestimulus activity patterns in sensory circuits, which may embody a participant’s prior expectations, predispose the observer toward false perceptions. Specifically, we used fMRI to investigate whether the representational content of prestimulus activity in early visual cortex is linked to subsequent perception during a challenging detection task. Human participants were asked to detect oriented gratings of a particular orientation that were embedded in noise. We found two characteristics of prestimulus activity that predisposed participants to hallucinations: overall lower prestimulus activity and a bias in the prestimulus activity patterns toward the to-be-detected (expected) grating. These results suggest that perceptual hallucinations may be due to an imprecise and biased state of sensory circuits preceding sensory evidence collection.

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A Neural Basis for Developmental Topographic Disorientation

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Developmental topographic disorientation (DTD) is a life-long condition in which affected individuals are severely impaired in navigating around their environment. Individuals with DTD have no apparent structural brain damage on conventional imaging and the neural mechanisms underlying DTD are currently unknown. Using functional and diffusion tensor imaging, we present a comprehensive neuroimaging study of an individual, J.N., with well defined DTD. J.N. has intact scene-selective responses in the parahippocampal place area (PPA), transverse occipital sulcus, and retrosplenial cortex (RSC), key regions associated with scene perception and navigation. However, detailed fMRI studies probing selective tuning properties of these regions, as well as functional connectivity, suggest that J.N.’s RSC has an atypical response profile and an atypical functional coupling to PPA compared with human controls. This deviant functional profile of RSC is not due to compromised structural connectivity. This comprehensive examination suggests that the RSC may play a key role in navigation-related processing and that an alteration of the RSC’s functional properties may serve as the neural basis for DTD.

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