

This Week in The Journal

● Cellular/Molecular

Macrophages Can Promote Regeneration . . .

Benoit Barrette, Marc-André Hébert, Mohammed Filali, Kathleen Lafortune, Nicolas Vallières, Geneviève Gowing, Jean-Pierre Julien, and Steve Lacroix
(see pages 9363–9376)

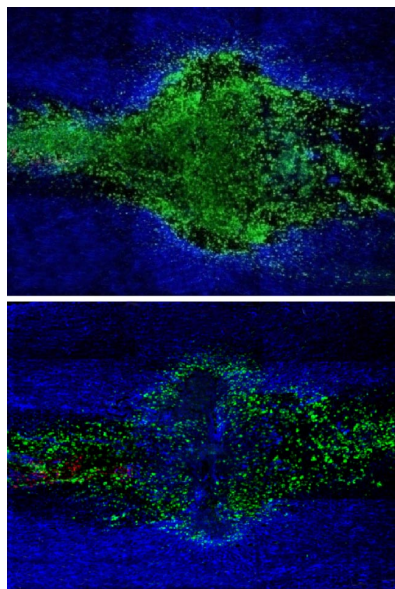
The role of macrophages in recovery from nerve injury is controversial. Some studies show that macrophages improve regeneration, but others show the opposite effect. This week, each side of the controversy gains support. After crushing a peripheral nerve in mice, Barrette et al. locally depleted myeloid white blood cells (both granulocytes and macrophages) that expressed a specific protein. This reduced axonal regeneration and functional recovery. Depletion of myeloid cells in peripheral nerve grafts, which normally permit some regeneration of spinal axons, rendered the grafts unable to support such growth. Additional experiments suggested that myeloid cells normally enhance regeneration by clearing myelin debris (which is likely to contain growth-inhibiting molecules), secreting growth-promoting neurotrophic factors (likely from granulocytes or a subset of macrophages), and stimulating the growth of new blood vessels, which axons often grow along as they regenerate.

▲ Development/Plasticity/Repair . . . *But Macrophages Can Also Hinder Regeneration*

Kevin P. Horn, Sarah A. Busch, Alicia L. Hawthorne, Nico van Rooijen, and Jerry Silver
(see pages 9330–9341)

In contrast to Barrette et al. (above), Horn et al. report that macrophages may hinder regeneration in the spinal cord of rats by promoting axonal retraction. CNS axons normally retract from a site of injury. To examine the role of macrophages in this process, Horn et al. specifically targeted phagocytic cells with toxin enclosed in liposomes. Depleting macrophages after a spinal cord crush did not affect the initial retraction of injured axons, but prevented later retraction that normally occurs after macrophages invade the spinal cord. In

vitro studies on dorsal root ganglion neurons revealed that when an activated macrophage contacts a dystrophic axon, the macrophage adheres to and tugs on the axon, pulling it from the substrate and causing retraction. Together, these two studies suggest that whether myeloid cells help or hinder axon regeneration may depend on what type of myeloid cells are present (i.e., what subtypes of macrophages and granulocytes) and where and how macrophages are activated (e.g., by peripheral or CNS cues).



Many macrophages (green) but few astrocytes (blue) were present at a lesion site 7 d after nerve crush (top). Treatment with toxic liposomes greatly reduced the number of macrophages, but astrocytes remained (bottom). See the article by Horn et al. for details.

■ Behavioral/Systems/Cognitive

Histone Deacetylase Inhibitors Eliminate Cocaine Sensitization

Pascal Romieu, Lionel Host, Serge Gobaille, Guy Sandner, Dominique Aunis, and Jean Zwiller
(see pages 9342–9348)

In the nucleus, DNA wraps around histone proteins, which pack the DNA and make it less accessible for transcription. Many transcriptional activators promote histone acetylation, which opens the chromatin structure and helps recruit transcription machinery to the newly accessible genes. Conversely, some gene repressors promote

deacetylation of histones. Because drug dependence is mediated partly by changes in gene expression, inhibitors of histone acetylation and deacetylation might prevent the development of drug dependence. Romieu et al. support this hypothesis by showing that administering histone deacetylase inhibitors shortly before giving rats access to cocaine reduced cocaine self-administration and decreased the number of times a rat poked its nose in a hole to receive a dose of cocaine. When control rats receive cocaine daily, their response to a dose increases over time. This increased responsiveness, called sensitization, is thought to promote dependence. Cocaine sensitization was prevented by histone deacetylase inhibitors, suggesting inhibitors may effectively reduce dependence.

◆ Neurobiology of Disease

K_{ATP} Expression Affects Seizure Susceptibility

Libor Velíšek, Jana Velíšková, Ondrej Chudomel, Ka-Lai Poon, Kimberly Robeson, Barbara Marshall, Archana Sharma, and Solomon L. Moshé

(see pages 9349–9362)

Hypoglycemic seizures occur in several diseases, particularly diabetes. In rats (and humans) seizures are induced by excess insulin, which stimulates glucose uptake throughout the body, reducing the amount available to neurons. The substantia nigra pars reticulata (SNR) has been implicated in seizure control: hyperpolarization of SNR neurons is anticonvulsant, whereas increased firing in SNR is proconvulsant. To further investigate the mechanism of hypoglycemic seizures, Velíšek et al. injected insulin into control rats that had fasted overnight. Fasting doubled the probability that insulin would induce a seizure and decreased the latency to seizure. But increased susceptibility in blood glucose levels did not explain the difference. Instead, the proconvulsant effect of fasting was associated with decreased expression of K_{ATP} channels specifically in the SNR. These channels normally open (causing hyperpolarization) only when ATP levels are low (e.g., during hypoglycemia). Decreased K_{ATP} expression prevents hyperpolarization of SNR neurons during hypoglycemia, and thus is proconvulsant.

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Cover legend: Rendering of major structural components from a tomographic reconstruction of a mushroom-shaped spine. Surface membrane of spine is rendered as a yellow-brown shell. Large gold filaments match the size and shape of actin filaments.

The identity of the very fine green filaments is unknown, but they are likely to correspond to spectrin filaments. Two vesicles (purple) festooned with vesicle-associated proteins (green) mingle with the actin-like filaments in the interior of the spine.

Vertical filaments (red) and transmembrane structures (both azure) provide a backbone of interlocking scaffolding elements largely independent of other structures in the body of the spine. For more information, see the article by Chen et al. in this issue (pages 9321–9327).

i This Week in The Journal

Toolbox

- 9321 **Life Inside a Thin Section: Tomography**
Xiaobing Chen, Christine A. Winters, and Thomas S. Reese

Journal Club

- 9328 **Sources of Spatial and Feature-Based Attention in the Human Brain**
Marius V. Peelen and Ryan E. B. Mruzek

Brief Communications

- 9519 **Growth of White Matter in the Adolescent Brain: Role of Testosterone and Androgen Receptor**
Jennifer S. Perrin, Pierre-Yves Hervé, Gabriel Leonard, Michel Perron, G. Bruce Pike, Alain Pitiot, Louis Richer, Suzanne Veillette, Zdenka Pausova, and Tomáš Paus

Articles

CELLULAR/MOLECULAR

- 9363 **Requirement of Myeloid Cells for Axon Regeneration**
Benoit Barrette, Marc-André Hébert, Mohammed Filali, Kathleen Lafortune, Nicolas Vallières, Geneviève Gowing, Jean-Pierre Julien, and Steve Lacroix
- 9404 **A Dominant Role of GTRAP3-18 in Neuronal Glutathione Synthesis**
Masahiko Watabe, Koji Aoyama, and Toshio Nakaki
- 9440 **Fidelity of Complex Spike-Mediated Synaptic Transmission between Inhibitory Interneurons**
Michael T. Roberts, Kevin J. Bender, and Laurence O. Trussell
- 9536 **Amplification of Transducer Gain by Angiotensin II-Mediated Enhancement of Cortical Actin Density in Osmosensory Neurons**
Zizhen Zhang and Charles W. Bourque

DEVELOPMENT/PLASTICITY/REPAIR

- 9330 **Another Barrier to Regeneration in the CNS: Activated Macrophages Induce Extensive Retraction of Dystrophic Axons through Direct Physical Interactions**
Kevin P. Horn, Sarah A. Busch, Alicia L. Hawthorne, Nico van Rooijen, and Jerry Silver

- 9386 **Constraint-Induced Movement Therapy in the Adult Rat after Unilateral Corticospinal Tract Injury**
Irin C. Maier, Kaspar Baumann, Michaela Thallmair, Oliver Weinmann, Jeannette Scholl, and Martin E. Schwab
- 9504 **Molecular Specification and Patterning of Progenitor Cells in the Lateral and Medial Ganglionic Eminences**
Eric S. Tucker, Samantha Segall, Deepak Gopalakrishna, Yongqin Wu, Mike Vernon, Franck Polleux, and Anthony-Samuel LaMantia
- 9557 **Direct Cortical Inputs Erase Long-Term Potentiation at Schaffer Collateral Synapses**
Yukitoshi Izumi and Charles F. Zorumski

BEHAVIORAL/SYSTEMS/COGNITIVE

- 9342 **Histone Deacetylase Inhibitors Decrease Cocaine But Not Sucrose Self-Administration in Rats**
Pascal Romieu, Lionel Host, Serge Gobaille, Guy Sandner, Dominique Aunis, and Jean Zwiller
- 9377 **Octopamine Regulates Sleep in *Drosophila* through Protein Kinase A-Dependent Mechanisms**
Amanda Crocker and Amita Sehgal
- 9414 **Time Constants of h Current in Layer II Stellate Cells Differ along the Dorsal to Ventral Axis of Medial Entorhinal Cortex**
Lisa M. Giocomo and Michael E. Hasselmo
- 9426 **Goal Representations Dominate Superior Colliculus Activity during Extrafoveal Tracking**
Ziad M. Hafed and Richard J. Krauzlis
- 9486 **Reactive Oxygen Species Derived from NOX1/NADPH Oxidase Enhance Inflammatory Pain**
Masakazu Ibi, Kuniharu Matsuno, Dai Shiba, Masato Katsuyama, Kazumi Iwata, Tomoko Kakehi, Takayuki Nakagawa, Kazunori Sango, Yasuhito Shirai, Takahiko Yokoyama, Shuji Kaneko, Naoaki Saito, and Chihiro Yabe-Nishimura
- 9495 **Evaluating the Negative or Valuing the Positive? Neural Mechanisms Supporting Feedback-Based Learning across Development**
Anna C. K. van Duijvenvoorde, Kiki Zanolie, Serge A. R. B. Rombouts, Maartje E. J. Raijmakers, and Eveline A. Crone
- 9525 **Region and Sex Differences in Constituent Dopamine Neurons and Immunoreactivity for Intracellular Estrogen and Androgen Receptors in Mesocortical Projections in Rats**
Mary F. Kritzer and Lela M. Creutz
- 9545 **Emergence of Novel Representations in Primary Motor Cortex and Premotor Neurons during Associative Learning**
Neta Zach, Dorrit Inbar, Yael Grinvald, Hagai Bergman, and Eilon Vaadia
- 9564 **State-Dependent Presynaptic Inhibition Regulates Central Pattern Generator Feedback to Descending Inputs**
Dawn M. Blitz and Michael P. Nusbaum

NEUROBIOLOGY OF DISEASE

- 9349 **Metabolic Environment in Substantia Nigra Reticulata Is Critical for the Expression and Control of Hypoglycemia-Induced Seizures**
Libor Velíšek, Jana Velíšková, Ondřej Chudomel, Ka-Lai Poon, Kimberly Robeson, Barbara Marshall, Archana Sharma, and Solomon L. Moshé

- 9451 **Systemic Inflammation Alters the Kinetics of Cerebrovascular Tight Junction Disruption after Experimental Stroke in Mice**
Barry W. McColl, Nancy J. Rothwell, and Stuart M. Allan
- 9463 **Ischemia Enhances Activation by Ca²⁺ and Redox Modification of Ryanodine Receptor Channels from Rat Brain Cortex**
Ricardo Bull, José Pablo Finkelstein, Jorge Gálvez, Gina Sánchez, Paulina Donoso, María Isabel Behrens, and Cecilia Hidalgo
- 9473 **Inhibitors of Cytochrome c Release with Therapeutic Potential for Huntington's Disease**
Xin Wang, Shan Zhu, Zhijuan Pei, Martin Drozda, Irina G. Stavrovskaya, Steven J. Del Signore, Kerry Cormier, Ethan M. Shimony, Hongyan Wang, Robert J. Ferrante, Bruce S. Kristal, and Robert M. Friedlander
- 9575 **Behavioral Recovery in MPTP-Treated Monkeys: Neurochemical Mechanisms Studied by Intrastratial Microdialysis**
Sabrina Boulet, Stéphanie Mounayar, Annie Poupard, Anne Bertrand, Caroline Jan, Mathias Pessiglione, Etienne C. Hirsch, Claude Feuerstein, Chantal François, Jean Féger, Marc Savasta, and Léon Tremblay
- 9585 **Decreased Striatal Dopamine Release Underlies Increased Expression of Long-Term Synaptic Potentiation at Corticostriatal Synapses 24 h after 3-Nitropropionic-Acid-Induced Chemical Hypoxia**
Garnik Akopian, Cynthia Crawford, M. Flint Beal, Maurand Cappelletti, Michael W. Jakowec, Giselle M. Petzinger, Ling Zheng, Stacey L. Gheorghie, Carmela M. Reichel, Robert Chow, and John P. Walsh

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Growth of White Matter in the Adolescent Brain: Role of Testosterone and Androgen Receptor

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The growth of white matter during human adolescence shows a striking sexual dimorphism; the volume of white matter increases with age slightly in girls and steeply in boys. Here, we provide evidence supporting the role of androgen receptor (AR) in mediating the effect of testosterone on white matter. In a large sample of typically developing adolescents ($n = 408$, 204 males), we used magnetic resonance imaging and acquired T1-weighted and magnetization transfer ratio (MTR) images. We also measured plasma levels of testosterone and genotyped a functional polymorphism in the AR gene, namely the number of CAG repeats in exon 1 believed to be inversely proportional to the AR transcriptional activity. We found that the testosterone-related increase of white-matter volume was stronger in male adolescents with the lower versus higher number of CAG repeats in the AR gene, with testosterone explaining, respectively, 26 and 8% of variance in the volume. The MTR results suggest that this growth is not related to myelination; the MTR decreased with age in male adolescents. We speculate that testosterone affects axonal caliber rather than the thickness of the myelin sheath.

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Articles

CELLULAR/MOLECULAR

Requirement of Myeloid Cells for Axon Regeneration

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The role of CD11b⁺ myeloid cells in axonal regeneration was assessed using axonal injury models and CD11b-TK^{mt-30} mice expressing a mutated HSV-1 thymidine kinase (TK) gene regulated by the myeloid-specific CD11b promoter. Continuous delivery of ganciclovir at a sciatic nerve lesion site greatly decreased the number of granulocytes/inflammatory monocytes and macrophages in the distal stump of CD11b-TK^{mt-30} mice. Axonal regeneration and locomotor function recovery were severely compromised in ganciclovir-treated CD11b-TK^{mt-30} mice. This was caused by an unsuitable growth environment rather than an altered regeneration capacity of neurons. In absence of CD11b⁺ cells, the clearance of inhibitory myelin debris was prevented, neurotrophin synthesis was abolished, and blood vessel formation/maintenance was severely compromised in the sciatic nerve distal stump. Spinal cord-injured axons also failed to regenerate through peripheral nerve grafts in the absence of CD11b⁺ cells. Therefore, myeloid cells support axonal regeneration and functional recovery by creating a growth-permissive milieu for injured axons.

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A Dominant Role of GTRAP3-18 in Neuronal Glutathione Synthesis

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Glutathione is an essential reductant which protects cells and is reduced in neurodegenerative disorders such as Parkinson's and Alzheimer's diseases. Neurons rely mainly on extracellular cysteine for glutathione synthesis and a cysteine transporter termed excitatory amino acid carrier 1 (EAAC1). However, the mechanisms underlying neuronal cysteine uptake have remained elusive. Herein, we show glutamate transport-associated protein for EAAC1 (GTRAP3-18) to interact with EAAC1 at the plasma membrane and thereby regulate neuronal glutathione levels. Glutathione increased in the mouse brain as well as in primary cultured neurons, when the GTRAP3-18 protein level was decreased by genetic manipulations, whereas glutathione decreased when GTRAP3-18 was increased. Furthermore, glutathione contents that had been increased, by a translocator and activator of EAAC1, were suppressed by increased cell surface GTRAP3-18 protein. Our results demonstrate GTRAP3-18 to dominantly and negatively determine the intracellular glutathione contents in neurons.

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Fidelity of Complex Spike-Mediated Synaptic Transmission between Inhibitory Interneurons

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Complex spikes are high-frequency bursts of Na⁺ spikes, often riding on a slower Ca²⁺-dependent waveform. Although complex spikes may propagate into axons, given their unusual shape it is not clear how reliably these bursts reach nerve terminals, whether their spikes are efficiently transmitted as a cluster of postsynaptic responses, or what function is served by such a concentrated postsynaptic signal. We examined these questions by recording from synaptically coupled pairs of cartwheel cells, neurons which fire complex spikes and form an inhibitory network in the dorsal cochlear nucleus. Complex spikes in the presynaptic soma were reliably propagated to nerve terminals and elicited powerful, temporally precise postsynaptic responses. Single presynaptic neurons could prevent their postsynaptic partner from firing complex but not simple spikes, dramatically reducing dendritic Ca²⁺ signals in the postsynaptic neuron. We suggest that rapid transmission of complex spikes may control the susceptibility of neighboring neurons to Ca²⁺-dependent plasticity.

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Amplification of Transducer Gain by Angiotensin II-Mediated Enhancement of Cortical Actin Density in Osmosensory Neurons

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Osmosensory neurons transduce osmotic signals into a neural spike code that commands behavioral and endocrine responses that mediate body fluid homeostasis. Although changes in osmoregulatory reflex gain are known to occur under physiological and pathological conditions, the basis for this modulation is unknown. Here, we show that angiotensin II amplifies osmosensory transduction by enhancing the proportional relationship between osmolality, receptor potential, and action potential firing in rat supraoptic nucleus neurons. This effect is mediated by a phospholipase C- and protein kinase C-dependent increase in cellular mechanosensitivity that is associated with a rapid increase in cortical actin filament density. Preventing this increase with cytochalasin D eliminated the enhancement of mechanosensitivity, whereas enhancing actin filament density with jaspalakinolide potentiated mechanosensitivity and occluded the effects of angiotensin II. These results indicate that a receptor-mediated increase in cortical actin density can enhance osmosensitivity in acutely isolated supraoptic neurons.

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DEVELOPMENT/PLASTICITY/REPAIR

Another Barrier to Regeneration in the CNS: Activated Macrophages Induce Extensive Retraction of Dystrophic Axons through Direct Physical Interactions

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Injured axons of the adult CNS undergo lengthy retraction from the initial site of axotomy after spinal cord injury. Macrophage infiltration correlates spatiotemporally with this deleterious phenomenon, but the direct involvement of these inflammatory cells has not been demonstrated. In the present study, we examined the role of macrophages in axonal retraction within the dorsal columns after spinal cord injury *in vivo* and found that retraction occurred between days 2 and 28 after lesion and that the ends of injured axons were associated with ED-1⁺ cells. Clodronate liposome-mediated depletion of infiltrating macrophages resulted in a significant reduction in axonal retraction; however, we saw no evidence of regeneration. We used time-lapse imaging of adult dorsal root ganglion neurons in an *in vitro* model of the glial scar to examine macrophage–axon interactions and observed that adhesive contacts and considerable physical interplay between macrophages and dystrophic axons led to extensive axonal retraction. The induction of retraction was dependent on both the growth state of the axon and the activation state of the macrophage. Only dystrophic adult axons were susceptible to macrophage “attack.” Unlike intrinsically active cell line macrophages, both primary macrophages and microglia required activation to induce axonal retraction. Contact with astrocytes had no deleterious effect on adult dystrophic axons, suggesting that the induction of extensive retraction was specific to phagocytic cells. Our data are the first to indicate a direct role of activated macrophages in axonal retraction by physical cell–cell interactions with injured axons.

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Constraint-Induced Movement Therapy in the Adult Rat after Unilateral Corticospinal Tract Injury

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Smaller spinal cord injuries often allow some degree of spontaneous behavioral improvements because of structural rearrangements within different descending fiber tracts or intraspinal circuits. In this study, we investigate whether rehabilitative training of the forelimb (forced limb use) influences behavioral recovery and plastic events after injury to a defined spinal tract, the corticospinal tract (CST). Female adult Lewis rats received a unilateral CST injury at the brainstem level. Use of the contralateral impaired forelimb was either restricted, by a cast, or forced, by casting the unimpaired forelimb immediately after injury for either 1 or 3 weeks. Forced use of the impaired forelimb was followed by full behavioral recovery on the irregular horizontal ladder, whereas animals that could not use their affected side remained impaired. BDA (biotinylated dextran amine) labeling of the intact CST showed lesion-induced growth across the midline where CST collaterals increased their innervation density and extended fibers toward the ventral and the dorsal horn in response to forced limb use. Gene chip analysis of the denervated ventral horn revealed changes in particular for growth factors, adhesion and guidance molecules, as well as components of synapse formation suggesting an important role for these factors in activity-dependent intraspinal reorganization after unilateral CST injury.

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Molecular Specification and Patterning of Progenitor Cells in the Lateral and Medial Ganglionic Eminences

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We characterized intrinsic and extrinsic specification of progenitors in the lateral and medial ganglionic eminences (LGE and MGE). We identified seven genes whose expression is enriched or restricted in either the LGE [biregional cell adhesion molecule-related/downregulated by oncogenes binding protein (*Boc*), Frizzled homolog 8 (*Fzd8*), *Ankrd43* (ankyrin repeat domain-containing protein 43), and *Ikaros* family zinc finger 1] or MGE [Map3k12 binding inhibitory protein 1 (*Mbip*); zinc-finger, SWIM domain containing 5 (*Zswim5*); and *Adams5* [a disintegrin-like and metallopeptidase (repolysin type) with thrombospondin type 1 motif, 5]]. *Boc*, *Fzd8*, *Mbip*, and *Zswim5* are apparently expressed in LGE or MGE progenitors, whereas the remaining three are seen in the postmitotic mantle zone. Relative expression levels are altered and regional distinctions are lost for each gene in LGE or MGE cells propagated as neurospheres, indicating that these newly identified molecular characteristics of LGE or MGE progenitors depend on forebrain signals not available in the neurosphere assay. Analyses of *Pax6*^{Sey/Sey}, *Shh*^{-/-}, and *Gli3*^{Xtj/Xtj} mutants suggests that LGE and MGE progenitor identity does not rely exclusively on previously established forebrain-intrinsic patterning mechanisms. Among a limited number of additional potential patterning mechanisms, we found that extrinsic signals from the frontonasal mesenchyme are essential for Shh- and Fgf8-dependent regulation of LGE and MGE genes. Thus, extrinsic and intrinsic forebrain patterning mechanisms cooperate to establish LGE and MGE progenitor identity, and presumably their capacities to generate distinct classes of neuronal progeny.

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Direct Cortical Inputs Erase Long-Term Potentiation at Schaffer Collateral Synapses

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Long-term potentiation (LTP), a synaptic mechanism thought to underlie memory formation, has been studied extensively at hippocampal Schaffer collateral (SC) synapses. The SC pathway transmits information to area CA1 that originates in entorhinal cortex and is processed by the dentate gyrus and area CA3. CA1 also receives direct excitatory input from entorhinal cortex via the perforant path (PP), but the role of this cortical input is less certain. Here, we report that low-frequency stimulation of PP inputs to CA1 has no lasting effect on basal SC transmission, but effectively depotentiates SC synapses that have undergone LTP in a manner that can be reversed by subsequent high-frequency stimulation of SC inputs. This depotentiation does not require NMDA receptors, group I metabotropic glutamate receptors, or L-type calcium channels, but involves adenosine acting at A₁ receptors. Given the limited storage capacity of the hippocampus, these observations provide a mechanism by which input from cortex can help to reset synaptic transmission in the hippocampus and facilitate additional information processing.

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Histone Deacetylase Inhibitors Decrease Cocaine But Not Sucrose Self-Administration in Rats

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Regulation of gene expression is known to contribute to the long-term adaptations taking place in response to drugs of abuse. Recent studies highlighted the regulation of gene transcription in neurons by chromatin remodeling, a process in which posttranslational modifications of histones play a major role. To test the involvement of epigenetic regulation on drug-reinforcing properties, we submitted rats to the cocaine operant self-administration paradigm. Using the fixed ratio 1 schedule, we found that the histone deacetylase (HDAC) inhibitors trichostatin A and phenylbutyrate dose-dependently reduced cocaine self-administration. Under the progressive ratio schedule, both trichostatin A and depudecin significantly reduced the breaking point, indicating that HDAC inhibition attenuated the motivation of rats for cocaine. Conversely, HDAC inhibition did not decrease self-administration for the natural reinforcer sucrose. This observation was correlated with measurements of HDAC activity in the frontal cortex, which was inhibited in response to cocaine, but not to sucrose self-administration. Control experiments showed that the decrease in the motivation for the drug was not attributable to a general motivational dysfunction because trichostatin A had no adverse effect on locomotion during the habituation session or on cocaine-induced hyperlocomotion. It was not attributable to anhedonia because the inhibitor had no effect on the sucrose preference test. In contrast, trichostatin A completely blocked the cocaine-induced behavioral sensitization. Together, the data show that epigenetic regulation of gene transcription in adult brain is able to influence a motivated behavior and suggest that HDAC inhibition may counteract the neural sensitization leading to drug dependence.

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Octopamine Regulates Sleep in *Drosophila* through Protein Kinase A-Dependent Mechanisms

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Sleep is a fundamental process, but its regulation and function are still not well understood. The *Drosophila* model for sleep provides a powerful system to address the genetic and molecular mechanisms underlying sleep and wakefulness. Here we show that a *Drosophila* biogenic amine, octopamine, is a potent wake-promoting signal. Mutations in the octopamine biosynthesis pathway produced a phenotype of increased sleep, which was restored to wild-type levels by pharmacological treatment with octopamine. Moreover, electrical silencing of octopamine-producing cells decreased wakefulness, whereas excitation of these neurons promoted wakefulness. Because protein kinase A (PKA) is a putative target of octopamine signaling and is also implicated in *Drosophila* sleep, we investigated its role in the effects of octopamine on sleep. We found that decreased PKA activity in neurons rendered flies insensitive to the wake-promoting effects of octopamine. However, this effect of PKA was not exerted in the mushroom bodies, a site previously associated with PKA action on sleep. These studies identify a novel pathway that regulates sleep in *Drosophila*.

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Time Constants of h Current in Layer II Stellate Cells Differ along the Dorsal to Ventral Axis of Medial Entorhinal Cortex

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Chronic recordings in the medial entorhinal cortex of behaving rats have found grid cells, neurons that fire when the rat is in a hexagonal array of locations. Grid cells recorded at different dorsal–ventral anatomical positions show systematic changes in size and spacing of firing fields. To test possible mechanisms underlying these differences, we analyzed properties of the hyperpolarization-activated cation current I_h in voltage-clamp recordings from stellate cells in entorhinal slices from different dorsal–ventral locations. The time constant of h current was significantly different between dorsal and ventral neurons. The time constant of h current correlated with membrane potential oscillation frequency and the time constant of the sag potential in the same neurons. Differences in h current could underlie differences in membrane potential oscillation properties and contribute to grid cell periodicity along the dorsal–ventral axis of medial entorhinal cortex.

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Goal Representations Dominate Superior Colliculus Activity during Extrafoveal Tracking

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The primate superior colliculus (SC) has long been known to be involved in saccade generation. However, SC neurons also exhibit fixation-related and smooth-pursuit-related activity. A parsimonious explanation for these seemingly disparate findings is that the SC contains a map of behaviorally relevant goal locations, rather than just a motor map for saccades and fixation. This explanation predicts that SC activity should reflect the behavioral goal, even when the behavioral response is not fixation or saccades, and even if the goal does not correspond to a visual stimulus. We tested this prediction by using a tracking task that dissociates the stimulus and goal locations. In this task, monkeys tracked the invisible midpoint between two peripheral bars, such that the visual stimuli were peripheral but the goal was foveal/parafoveal. We recorded from SC neurons representing peripheral locations associated with the stimulus or central locations associated with the goal. Most neurons with peripheral

response fields did not respond differently during tracking than during passive viewing of the stimulus under fixation; most neurons with central response fields responded more during tracking than during fixation, despite the lack of a visual stimulus. Moreover, the spatial distribution of activity during tracking was larger than that during fixation or tracking of a foveal stimulus, suggesting that the greater spatial uncertainty about the invisible goal corresponded to more widespread SC activity. These results demonstrate the flexibility with which activity across the SC represents the location, as well as the spatial precision, of behaviorally relevant goals for multiple eye movements.

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Reactive Oxygen Species Derived from NOX1/NADPH Oxidase Enhance Inflammatory Pain

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The involvement of reactive oxygen species (ROS) in an augmented sensitivity to painful stimuli (hyperalgesia) during inflammation has been suggested, yet how and where ROS affect the pain signaling remain unknown. Here we report a novel role for the superoxide-generating NADPH oxidase in the development of hyperalgesia. In mice lacking *Nox1* (*Nox1*^{-/-}), a catalytic subunit of NADPH oxidase, thermal and mechanical hyperalgesia was significantly attenuated, whereas no change in nociceptive responses to heat or mechanical stimuli was observed. In dorsal root ganglia (DRG) neurons of *Nox1*^{+/-}, pretreatment with chemical mediators bradykinin, serotonin, or phorbol 12-myristate 13-acetate (PMA) augmented the capsaicin-induced calcium increase, whereas this increase was significantly attenuated in DRG neurons of *Nox1*^{-/-}. Concomitantly, PMA-induced translocation of PKC ϵ was markedly perturbed in *Nox1*^{-/-} or *Nox1*^{+/-} DRG neurons treated with ROS-scavenging agents. In cells transfected with tagged PKC ϵ , hydrogen peroxide induced translocation and a reduction in free sulfhydryls of full-length PKC ϵ but not of the deletion mutant lacking the C1A domain. These findings indicate that NOX1/NADPH oxidase accelerates the translocation of PKC ϵ in DRG neurons, thereby enhancing the TRPV1 activity and the sensitivity to painful stimuli.

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Evaluating the Negative or Valuing the Positive? Neural Mechanisms Supporting Feedback-Based Learning across Development

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How children learn from positive and negative performance feedback lies at the foundation of successful learning and is therefore of great importance for educational practice. In this study, we used functional magnetic resonance imaging (fMRI) to examine the neural developmental changes related to feedback-based learning when performing a rule search and application task. Behavioral results from three age groups (8–9, 11–13, and 18–25 years of age) demonstrated that, compared with adults, 8- to 9-year-old children performed disproportionately more inaccurately after receiving negative feedback relative to positive feedback. Additionally, imaging data pointed toward a qualitative difference in how children and adults use performance feedback. That is, dorsolateral prefrontal cortex and superior parietal cortex were more active after negative feedback for adults, but after positive feedback for children (8–9 years of age). For 11- to 13-year-olds, these regions did not show differential feedback sensitivity, suggesting that the transition occurs around this age. Pre-supplementary motor area/anterior cingulate cortex, in contrast, was more active after negative feedback in both 11- to 13-year-olds and adults, but not 8- to 9-year-olds. Together, the current data show that cognitive control areas are differentially engaged during feedback-based learning across development. Adults engage these regions after signals of response adjustment (i.e., negative feedback). Young children engage these regions after signals of response continuation (i.e., positive feedback). The neural activation patterns found in 11- to 13-year-olds indicate a transition around this age toward an increased influence of negative feedback on performance adjustment. This is the first developmental fMRI study to compare qualitative changes in brain activation during feedback learning across distinct stages of development.

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Region and Sex Differences in Constituent Dopamine Neurons and Immunoreactivity for Intracellular Estrogen and Androgen Receptors in Mesocortical Projections in Rats

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Many cortical and prefrontal functions show sex differences in their development, adult capacity, and dysfunction in disorders like schizophrenia. Correlations between circulating gonadal hormones and certain prefrontal functions have also been identified in humans and experimental animal models. Although multiple mechanisms may be involved, such hormone sensitivities/sex differences could be related to gonadal steroid actions on another regulator of cortical/prefrontal cortical function, the mesocortical dopamine system. Thus, although it is well known that perturbations in prefrontal dopamine signaling induce behavioral deficits, it is also known that several endpoints of these afferents are sensitive to gonadal steroids and/or are sexually dimorphic. This study explored possible substrates for this in two ways: by comparing the distributions of immunoreactivity for intracellular estrogen (α and β) and androgen receptors among retrogradely labeled dopaminergic and nondopaminergic mesocortical neurons projecting to prefrontal, premotor, and primary motor cortices, areas in which male rat dopamine axons are differentially hormone-sensitive; and by comparing anatomical data in males and females. These analyses revealed region-, cell-, and sex-specific specializations in receptor localization that paralleled established patterns of mesocortical hormone sensitivity, including the androgen sensitivity of dopamine axons and dopamine-dependent functions in prefrontal cortex. It was also found that the proportions of dopamine neurons making up mesocortical projections were $\sim 30\%$ in males, whereas in females, significantly more constituent cells were dopaminergic. Together, these features may be part of the neurobiology giving mesocortical afferents their hormone sensitivities and/or sex differences in physiology, function, and dysfunction in disease.

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Emergence of Novel Representations in Primary Motor Cortex and Premotor Neurons during Associative Learning

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Neurons in the motor areas of cortex play a key role in associating sensory instructions with movements. However, their ability to acquire and maintain representations of novel stimulus features, especially when these features are behaviorally relevant, remains unknown. We investigated neuronal changes in these areas during and after associative learning, by training monkeys on a novel reaching task that required associating target colors with movement directions. Before and after learning, the monkeys performed a well known center-out task. We found that during learning, up to 48% of the neurons developed learning-related responses, differentiating between the associative task and the center-out task, although movement kinematics were the same. After learning, on returning to the center-out task in which color was irrelevant, many of these neurons maintained their response to the associative task; they displayed novel sensitivity to the color of the target that was relevant during learning. These neuronal responses prevailed in both the primary motor cortex and the ventral and dorsal premotor cortices, without degrading the information that the neurons firing carried about movement direction. Our results show that motor cortical neurons can rapidly develop and maintain sensitivities to novel arbitrary sensory features such as color, when such features are behaviorally relevant.

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State-Dependent Presynaptic Inhibition Regulates Central Pattern Generator Feedback to Descending Inputs

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Central pattern generators (CPGs) provide feedback to their projection neuron inputs. However, it is unknown whether this feedback is regulated and how that might shape CPG output. We are studying feedback from the pyloric CPG to identified projection neurons that regulate the gastric mill CPG, in the crab stomatogastric nervous system. Both CPGs are located in the stomatogastric ganglion (STG) and are influenced by projection neurons originating in the paired commissural ganglia (CoGs). Two extrinsic inputs [ventral cardiac neurons (VCNs) and postoesophageal commissure (POC) neurons] trigger distinct gastric mill rhythms despite acting via the same projection neurons [modulatory commissural neuron 1 (MCN1); commissural projection neuron 2 (CPN2)]. These projection neurons receive feedback inhibition from the pyloric CPG interneuron anterior burster (AB), resulting in their exhibiting pyloric-timed activity during the retraction phase of the VCN- and POC-triggered gastric mill rhythms. However, during the gastric mill protraction phase, MCN1/CPN2 exhibit pyloric-timed activity during the POC-triggered rhythm but fire tonically during the VCN-triggered rhythm. Here, we show that the latter, tonic activity pattern results from the elimination of AB inhibition of MCN1/CPN2, despite persistent AB actions within the STG and AB action potentials still propagating into each CoG. This loss of pyloric-timed AB input likely results from presynaptic inhibition of AB in each CoG because, when a secondary rhythmic AB burst initiation zone in the CoG is activated, the associated action potentials are selectively suppressed during the VCN protraction phase. Thus, rhythmic CPG feedback can be locally regulated, in a state-dependent manner, enabling the same projection neurons to drive multiple motor patterns from the same neuronal circuit.

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Metabolic Environment in Substantia Nigra Reticulata Is Critical for the Expression and Control of Hypoglycemia-Induced Seizures

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Seizures represent a common and serious complication of hypoglycemia. Here we studied mechanisms of control of hypoglycemic seizures induced by insulin injection in fasted and nonfasted rats. We demonstrate that fasting predisposes rats to more rapid and consistent development of hypoglycemic seizures. However, the fasting-induced decrease in baseline blood glucose concentration cannot account for the earlier onset of seizures in fasted versus nonfasted rats. Data obtained with *c-Fos* immunohistochemistry and [¹⁴C]2-deoxyglucose uptake implicate a prominent involvement of the substantia nigra reticulata (SNR) among other structures in the hypoglycemic seizure control. This is supported by data showing that fasting decreases the SNR expression of K_{ATP} channels, which link metabolism with activity, and is further confirmed with microinfusions of K_{ATP} channel agonist and antagonist. Data obtained with whole-cell and perforated patch recordings from SNR neurons in slices *in vitro* demonstrate that both presynaptic and postsynaptic K_{ATP} channels participate in the failure of the SNR to control hypoglycemic seizures. The results suggest that fasting and insulin-induced hypoglycemia can lead to impairment in the function of the SNR, leading thus to hypoglycemic seizures.

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Systemic Inflammation Alters the Kinetics of Cerebrovascular Tight Junction Disruption after Experimental Stroke in Mice

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Systemic inflammatory events, such as infection, increase the risk of stroke and are associated with worse outcome, but the mediators of this clinically important effect are unknown. Our aim here was to elucidate mechanisms contributing to the detrimental effects of systemic inflammation on mild ischemic brain injury in mice. Systemic inflammation was induced in mice by peripheral interleukin-1 β (IL-1 β) challenge and focal cerebral ischemia by transient middle cerebral artery occlusion (MCAo). Systemic inflammation caused an alteration in the kinetics of blood–brain barrier (BBB) disruption through conversion of a transient to a sustained disruption of the tight junction protein, claudin-5, and also markedly exacerbated disruption to the cerebrovascular basal lamina protein, collagen-IV. These alterations were associated with a systemic inflammation-induced increase in neurovascular gelatinolytic activity that was mediated by a fivefold increase in neutrophil-derived matrix metalloproteinase-9 (MMP-9) in the brains of IL-1 β -challenged mice after MCAo. Specific inhibition of MMP-9 abrogated the effects of systemic inflammation on the sustained but not the acute disruption of claudin-5, which was associated with phosphorylation of cerebrovascular myosin light chain. MMP-9 inhibition also attenuated the deleterious impact of systemic inflammation on brain damage, edema, neurological deficit, and incidence of hemorrhagic transformation. These data indicate that a transformation from transient to sustained BBB disruption caused by enhanced neutrophil-derived neurovascular MMP-9 activity is a critical mechanism underlying the exacerbation of ischemic brain injury by systemic inflammation. These mechanisms may contribute to the poor clinical outcome in stroke patients presenting with antecedent infection.

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Ischemia Enhances Activation by Ca²⁺ and Redox Modification of Ryanodine Receptor Channels from Rat Brain Cortex

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Cerebral ischemia stimulates Ca²⁺ influx and thus increases neuronal intracellular free [Ca²⁺]. Using a rat model of cerebral ischemia without recirculation, we tested whether ischemia enhances the activation by Ca²⁺ of ryanodine receptor (RyR) channels, a requisite feature of RyR-mediated Ca²⁺-induced Ca²⁺ release (CICR). To this aim, we evaluated how single RyR channels from endoplasmic reticulum vesicles, fused into planar lipid bilayers, responded to cytoplasmic [Ca²⁺] changes. Endoplasmic reticulum vesicles were isolated from the cortex of rat brains incubated without blood flow for 5 min at 37°C (ischemic) or at 4°C (control). Ischemic brains displayed increased oxidative intracellular conditions, as evidenced by a lower ratio (~130:1) of reduced/oxidized glutathione than controls (~200:1). Single RyR channels from ischemic or control brains displayed the same three responses to Ca²⁺ reported previously, characterized by low, moderate, or high maximal activity. Relative to controls, RyR channels from ischemic brains displayed with increased frequency the high activity response and with lower frequency the low activity response. Both control and ischemic cortical vesicles contained the RyR2 and RyR3 isoforms in a 3:1 proportion, with undetectable amounts of RyR1. Ischemia reduced [³H]ryanodine binding and total RyR protein content by 35%, and increased at least twofold endogenous RyR2 S-nitrosylation and S-glutathionylation without affecting the corresponding RyR3

endogenous levels. *In vitro* RyR S-glutathionylation but not S-nitrosylation favored the emergence of high activity channels. We propose that ischemia, by enhancing RyR2 S-glutathionylation, allows RyR2 to sustain CICR; the resulting amplification of Ca²⁺ entry signals may contribute to cortical neuronal death.
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Inhibitors of Cytochrome *c* Release with Therapeutic Potential for Huntington's Disease

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Release of mitochondrial cytochrome *c* resulting in downstream activation of cell death pathways has been suggested to play a role in neurologic diseases featuring cell death. However, the specific biologic importance of cytochrome *c* release has not been demonstrated in Huntington's disease (HD). To evaluate the role of cytochrome *c* release, we screened a drug library to identify new inhibitors of cytochrome *c* release from mitochondria. Drugs effective at the level of purified mitochondria were evaluated in a cellular model of HD. As proof of principle, one drug was chosen for in depth evaluation *in vitro* and a transgenic mouse model of HD. Our findings demonstrate the utility of mitochondrial screening to identify inhibitors of cell death and provide further support for the important functional role of cytochrome *c* release in HD. Given that many of these compounds have been approved by the Food and Drug Administration for clinical usage and cross the blood–brain barrier, these drugs may lead to trials in patients.

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Behavioral Recovery in MPTP-Treated Monkeys: Neurochemical Mechanisms Studied by Intrastratial Microdialysis

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Parkinson's disease (PD) patients express motor symptoms only after 60–80% striatal dopamine (DA) depletion. The presymptomatic phase of the disease may be sustained by biochemical modifications within the striatum. We used an appropriate specific 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) monkey model (Mounayar et al., 2007) to study the compensatory mechanisms operating in recovery from PD motor symptoms. We assessed the levels of DA and its metabolites (DOPAC, homovanillic acid), GABA, glutamate (Glu), serotonin (5-HT) and its metabolite (5HIAA) by repeated intracerebral microdialysis in awake animals before exposure to MPTP during full expression of the motor symptoms induced by MPTP and after recovery from these symptoms. Measurements were obtained from two functionally and anatomically different striatal areas: the associative-limbic territory and sensorimotor territory. Animals with motor symptoms displayed an extremely large decrease in levels of DA and its metabolites and an increase in Glu and GABA levels, as reported by other studies. However, we show here for the first time that serotonin levels increased in these animals. We found that increases in DA levels in the sensorimotor and/or associative-limbic territory and high levels of 5-HT and of its metabolite, 5HIAA, were associated with recovery from motor symptoms in this model. Determining whether similar changes in DA and 5-HT levels are involved in the compensatory mechanisms delaying the appearance of motor symptoms in the early stages of PD might make it possible to develop new treatment strategies for the disease.

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Decreased Striatal Dopamine Release Underlies Increased Expression of Long-Term Synaptic Potentiation at Corticostriatal Synapses 24 h after 3-Nitropropionic-Acid-Induced Chemical Hypoxia

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The striatum is particularly sensitive to the irreversible inhibitor of succinate dehydrogenase 3-nitropropionic acid (3-NP). In the present study, we examined early changes in behavior and dopamine and glutamate synaptic physiology created by a single systemic injection of 3-NP in Fischer 344 rats. Hindlimb dystonia was seen 2 h after 3-NP injections, and rats performed poorly on balance beam and rotarod motor tests 24 h later. Systemic 3-NP increased NMDA receptor-dependent long-term potentiation (LTP) at corticostriatal synapses over the same time period. The 3-NP-induced corticostriatal LTP was not attributable to increased NMDA receptor number or function, because 3-NP did not change MK-801 [(+)-5-methyl-10,11-dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5,10-imine] binding or NMDA/AMPA receptor current ratios. The LTP seen 24 h after 3-NP was D₁ receptor dependent and reversed by exogenous addition of dopamine or a D₂ receptor agonist to brain slices. HPLC and fast-scan cyclic voltammetry revealed a decrease in dopamine content and release in rats injected 24 h earlier with 3-NP, and much like the enhanced LTP, dopamine changes were reversed by 48 h. Tyrosine hydroxylase expression was not changed, and there was no evidence of striatal cell loss at 24–48 h after 3-NP exposure. Sprague Dawley rats showed similar physiological responses to systemic 3-NP, albeit with reduced sensitivity. Thus, 3-NP causes significant changes in motor behavior marked by parallel changes in striatal dopamine release and corticostriatal synaptic plasticity.

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