



Cover legend: This image shows vasopressin-releasing neurons of the supraoptic nucleus (magenta) expressing Fos (cyan) following activation by systemic sodium mediated in part by the ion channel Nax . These neurons maintain homeostasis in response to hypertonicity and hypernatremia. Nax expression on brain structures called sensory circumventricular organs is required for maintenance of body fluid balance, but whether the expression of this channel in vasopressin neurons plays a role in hypertonicity or hypernatremia homeostatic responses is unknown. Salgado-Mozo et al. used the depicted method and others to investigate this. See their manuscript on pages 8306–8316 for more information. Cover image: Sandra Salgado-Mozo.

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Judy Illes Division of Neurology, Department of Medicine, Neuroethics Canada, Vancouver, British Columbia, V6T 2B5, Canada

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REVIEW

Resting-State Functional MRI and PET Imaging as Noninvasive Tools to Study (Ab)Normal Neurodevelopment in Humans and Rodents

Charissa Millevert,^{1,2,5} Nicholas Vidas-Guscic,^{3,5} Liesbeth Vanherp,⁵ Elisabeth Jonckers,^{3,5} Marleen Verhoye,^{3,5} Steven Staelens,^{4,5} Daniele Bertoglio,^{3,4,5} and Sarah Weckhuysen^{1,2,5,6}

¹Applied & Translational Neurogenomics Group, Vlaams Instituut voor Biotechnologie (VIB) Center for Molecular Neurology, VIB, Antwerp 2610, Belgium ²Department of Neurology, University Hospital of Antwerp, Antwerp 2610, Belgium ³Bio-Imaging Lab, University of Antwerp, Antwerp 2610, Belgium ⁴Molecular Imaging Center Antwerp (MICA), University of Antwerp, Antwerp 2610, Belgium ⁵ μ NEURO Research Centre of Excellence, University of Antwerp, Antwerp 2610, Belgium ⁶Translational Neurosciences, Faculty of Medicine and Health Science, University of Antwerp, Antwerp 2610, Belgium

Neurodevelopmental disorders (NDDs) are a group of complex neurologic and psychiatric disorders. Functional and molecular imaging techniques, such as resting-state functional magnetic resonance imaging (rs-fMRI) and positron emission tomography (PET), can be used to measure network activity noninvasively and longitudinally during maturation in both humans and rodent models. Here, we review the current knowledge on rs-fMRI and PET biomarkers in the study of normal and abnormal neurodevelopment, including intellectual disability (ID; with/without epilepsy), autism spectrum disorder (ASD), and attention deficit hyperactivity disorder (ADHD), in humans and rodent models from birth until adulthood, and evaluate the cross-species translational value of the imaging biomarkers. To date, only a few isolated studies have used rs-fMRI or PET to study (abnormal) neurodevelopment in rodents during infancy, the critical period of neurodevelopment. Further work to explore the feasibility of performing functional imaging studies in infant rodent models is essential, as rs-fMRI and PET imaging in transgenic rodent models of NDDs are powerful techniques for studying disease pathogenesis, developing noninvasive pre-clinical imaging biomarkers of neurodevelopmental dysfunction, and evaluating treatment-response in disease-specific models.

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Articles

CELLULAR/MOLECULAR

Combinatory Actions of Co-transmitters in Dopaminergic Systems Modulate *Drosophila* Olfactory Memories

Daisuke Yamazaki, Yuko Maeyama, and Tetsuya Tabata

Institute of Quantitative Biosciences, The University of Tokyo, Tokyo, 113-0032, Japan

Dopamine neurons (DANs) are extensively studied in the context of associative learning, in both vertebrates and invertebrates. In the acquisition of male and female *Drosophila* olfactory memory, the PAM cluster of DANs provides the reward signal, and the PPL1 cluster of DANs sends the punishment signal to the Kenyon cells (KCs) of mushroom bodies, the center for memory formation. However, thermo-genetical activation of the PPL1 DANs after memory acquisition impaired aversive memory, and that of the PAM DANs impaired appetitive memory. We demonstrate that the knockdown of glutamate decarboxylase, which catalyzes glutamate conversion to GABA in PAM DANs, potentiated the appetitive memory. In addition, the knockdown of glutamate transporter in PPL1 DANs potentiated aversive memory, suggesting that GABA and glutamate co-transmitters act in an inhibitory manner in olfactory memory formation. We also found that, in γ KCs, the Rdl receptor for GABA and the mGluR DmGluRA mediate the inhibition. Although multiple-spaced training is required to form long-term aversive memory, a single cycle of training was sufficient to develop long-term memory when the glutamate transporter was knocked down, in even a single subset of PPL1 DANs. Our results suggest that the mGluR signaling pathway may set a threshold for memory acquisition to allow the organisms' behaviors to adapt to changing physiological conditions and environments.

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Na_x Channel Is a Physiological [Na⁺] Detector in Oxytocin- and Vasopressin-Releasing Magnocellular Neurosecretory Cells of the Rat Supraoptic Nucleus

Sandra Salgado-Mozo,^{1,2} Zahra S. Thirouin,¹ Joshua C. Wyrosdic,¹ Ubaldo García-Hernández,² and Charles W. Bourque¹

¹Brain Repair and Integrative Neuroscience Program, Research Institute of McGill University Health Center, Montréal, Québec H3G1A4, Canada

²Department of Physiology, Biophysics and Neurosciences, Centre for Research and Advanced Studies, Instituto Politecnico Nacional, 07360 Mexico City, Mexico

The *Scn7A* gene encodes Na_x, an atypical noninactivating Na⁺ channel, whose expression in sensory circumventricular organs is essential to maintain homeostatic responses for body fluid balance. However, Na_x has also been detected in homeostatic effector neurons, such as vasopressin (VP)-releasing

magnocellular neurosecretory cells (MNC^{VP}) that secrete VP (antidiuretic hormone) into the bloodstream in response to hypertonicity and hypernatremia. Yet, the physiological relevance of Na_x expression in these effector cells remains unclear. Here, we show that rat MNC^{VP} in males and females is depolarized and excited in proportion with isosmotic increases in [Na⁺]. These responses were caused by an inward current resulting from a cell-autonomous increase in Na⁺ conductance. The Na⁺-evoked current was unaffected by blockers of other Na⁺-permeable ion channels but was significantly reduced by shRNA-mediated knockdown of *Scn7A* expression. Furthermore, reducing the density of Na_x channels selectively impaired the activation of MNC^{VP} by systemic hypernatremia without affecting their responsiveness to hypertonicity *in vivo*. These results identify Na_x as a physiological Na⁺ sensor, whose expression in MNC^{VP} contributes to the generation of homeostatic responses to hypernatremia.

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Loss of Depalmitoylation Disrupts Homeostatic Plasticity of AMPARs in a Mouse Model of Infantile Neuronal Ceroid Lipofuscinosis

Kevin P. Koster,¹ Eden Flores-Barrera,¹ Emilce Artur de la Villarmois,¹ Adriana Caballero,¹ Kuei Y. Tseng,¹ and Akira Yoshii^{1,2,3}

¹Department of Anatomy and Cell Biology, University of Illinois at Chicago, Chicago, Illinois 60612 ²Department of Pediatrics, University of Illinois at Chicago, Chicago, Illinois 60612 ³Department of Neurology, University of Illinois at Chicago, Chicago, Illinois 60612

Protein palmitoylation is the only reversible post-translational lipid modification. Palmitoylation is held in delicate balance by depalmitoylation to precisely regulate protein turnover. While over 20 palmitoylation enzymes are known, depalmitoylation is conducted by fewer enzymes. Of particular interest is the lack of the depalmitoylating enzyme palmitoyl-protein thioesterase 1 (PPT1) that causes the devastating pediatric neurodegenerative condition infantile neuronal ceroid lipofuscinosis (CLN1). While most of the research on Ppt1 function has centered on its role in the lysosome, recent findings demonstrated that many Ppt1 substrates are synaptic proteins, including the AMPA receptor (AMPA) subunit GluA1. Still, the impact of Ppt1-mediated depalmitoylation on synaptic transmission and plasticity remains elusive. Thus, the goal of the present study was to use the *Ppt1*^{−/−} mouse model (both sexes) to determine whether Ppt1 regulates AMPAR-mediated synaptic transmission and plasticity, which are crucial for the maintenance of homeostatic adaptations in cortical circuits. Here, we found that basal excitatory transmission in the *Ppt1*^{−/−} visual cortex is developmentally regulated and that chemogenetic silencing of the *Ppt1*^{−/−} visual cortex excessively enhanced the synaptic expression of GluA1. Furthermore, triggering homeostatic plasticity in *Ppt1*^{−/−} primary neurons caused an exaggerated incorporation of GluA1-containing, calcium-permeable AMPARs, which correlated with increased GluA1 palmitoylation. Finally, Ca²⁺ imaging in awake *Ppt1*^{−/−} mice showed visual cortical neurons favor a state of synchronous firing. Collectively, our results elucidate a crucial role for Ppt1 in AMPAR trafficking and show that impaired proteostasis of palmitoylated synaptic proteins drives maladaptive homeostatic plasticity and abnormal recruitment of cortical activity in CLN1.

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Protein 4.1N Plays a Cell Type-Specific Role in Hippocampal Glutamatergic Synapse Regulation

Anna N. Pushkin,¹ Yuni Kay,¹ and Bruce E. Herring^{1,2}

¹Neuroscience Graduate Program, University of Southern California, Los Angeles, California 90089 ²Department of Biological Sciences, Neurobiology Section, Dornsife College of Letters, Arts, and Sciences, University of Southern California, Los Angeles, California 90089

Many glutamatergic synapse proteins contain a 4.1N protein binding domain. However, a role for 4.1N in the regulation of glutamatergic neurotransmission has been controversial. Here, we observe significantly higher expression of protein 4.1N in granule neurons of the dentate gyrus (DG granule neurons) compared with other hippocampal regions. We discover that reducing 4.1N expression in rat DG granule neurons of either sex results in a significant reduction in glutamatergic synapse function that is caused by a decrease in the number of glutamatergic synapses. By contrast, we find reduction of 4.1N expression in hippocampal CA1 pyramidal neurons has no impact on basal glutamatergic neurotransmission. We also find 4.1N's C-terminal domain (CTD) to be non-essential to its role in the regulation of glutamatergic synapses of DG granule neurons. Instead, we show that 4.1N's four-point-one, ezrin, radixin, and moesin (FERM) domain is essential for supporting synaptic AMPA receptor (AMPA) function in these neurons. Altogether, this work demonstrates a novel, cell type-specific role for protein 4.1N in governing glutamatergic synapse function.

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DEVELOPMENT/PLASTICITY/REPAIR

The Role of Protocadherin γ in Adult Sensory Neurons and Skin Reinnervation

Rebecca M. Long,¹ Honyi Ong,¹ Wendy Xueyi Wang,^{2,3} Prashanth Komirishetty,¹ Aparna Areti,¹ Ambika Chandrasekhar,¹ Matt Larouche,¹ Julie L. Lefebvre,^{2,3} and Douglas W. Zochodne¹

¹Division of Neurology, Department of Medicine and the Neuroscience and Mental Health Institute, University of Alberta, Edmonton, Alberta T6G 2G3, Canada ²Program for Neuroscience and Mental Health, Hospital for Sick Children, Toronto, Ontario M5G 1X8, Canada ³Department of Molecular Genetics, University of Toronto, Toronto, Ontario M5R 0A3, Canada

The clustered protocadherins (cPcdhs) play a critical role in the patterning of several CNS axon and dendritic arbors, through regulation of homophilic self and neighboring interactions. While not explored, primary peripheral sensory afferents that innervate the epidermis may require similar constraints to convey spatial signals with appropriate fidelity. Here, we show that members of the γ -Pcdh (Pcdh γ) family are expressed in both adult sensory neuron axons and in neighboring keratinocytes that have close interactions during skin reinnervation. Adult mice of both sexes were studied. Pcdh γ knock-down either through small interfering RNA (siRNA) transduction or AAV-Cre recombinase transfection of adult mouse primary sensory neurons from floxed Pcdh γ mice was associated with a remarkable rise in neurite outgrowth and branching. Rises in outgrowth were abrogated by Rac1 inhibition. Moreover, AAV-Cre knock-down in Pcdh γ floxed neurons generated a rise in neurite self-intersections, and a robust rise in neighbor intersections or tiling, suggesting a role in sensory axon repulsion. Interestingly, preconditioned (3-d axotomy) neurons with enhanced growth had temporary declines in Pcdh γ and lessened outgrowth from Pcdh γ siRNA. *In vivo*, mice with local hindpaw skin Pcdh γ knock-down by siRNA had accelerated reinnervation by new epidermal axons with greater terminal branching and reduced intra-axonal spacing. Pcdh γ knock-down also had reciprocal impacts on keratinocyte density and nuclear size. Taken together, this work provides evidence for a role of Pcdh γ in attenuating outgrowth of sensory axons and their interactions, with implications in how new reinnervating axons following injury fare amid skin keratinocytes that also express Pcdh γ .

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SYSTEMS/CIRCUITS

Nfia Is Critical for AII Amacrine Cell Production: Selective Bipolar Cell Dependencies and Diminished ERG

Patrick W. Keeley,¹ Stephanie Trod,¹ Bruno N. Gamboa,¹ Pete J. Coffey,¹ and Benjamin E. Reese^{1,2}

¹Neuroscience Research Institute, University of California, Santa Barbara, California 93106-5060 ²Department of Psychological and Brain Sciences, University of California, Santa Barbara, California 93106-5060

The nuclear factor one (NFI) transcription factor genes *Nfia*, *Nfib*, and *Nfix* are all enriched in late-stage retinal progenitor cells, and their loss has been shown to retain these progenitors at the expense of later-generated retinal cell types. Whether they play any role in the specification of those later-generated fates is unknown, but the expression of one of these, *Nfia*, in a specific amacrine cell type may intimate such a role. Here, *Nfia* conditional knockout (*Nfia*-CKO) mice (both sexes) were assessed, finding a massive and largely selective absence of AII amacrine cells. There was, however, a partial reduction in type 2 cone bipolar cells (CBCs), being richly interconnected to AII cells. Counts of dying cells showed a significant increase in *Nfia*-CKO retinas at postnatal day (P)7, after AII cell numbers were already reduced but in advance of the loss of type 2 CBCs detected by P10. Those results suggest a role for *Nfia* in the specification of the AII amacrine cell fate and a dependency of the type 2 CBCs on them. Delaying the conditional loss of *Nfia* to the first postnatal week did not alter AII cell number nor differentiation, further suggesting that its role in AII cells is solely associated with their production. The physiological consequences of their loss were assessed using the ERG, finding the oscillatory potentials to be profoundly diminished. A slight reduction in the b-wave was also detected, attributed to an altered distribution of the terminals of rod bipolar cells, implicating a role of the AII amacrine cells in constraining their stratification.

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Dynamic Changes in Local Activity and Network Interactions among the Anterior Cingulate, Amygdala, and Cerebellum during Associative Learning

Hunter E. Halverson,^{1,2,4} Jangjin Kim,³ and John H. Freeman^{2,4}

¹Department of Psychiatry, University of Iowa, Iowa City, Iowa 52242 ²Department of Psychological and Brain Sciences, University of Iowa, Iowa City, Iowa 52242 ³Department of Psychology, Kyungpook National University, Daegu 41566, South Korea ⁴Iowa Neuroscience Institute, University of Iowa, Iowa City, Iowa, 52242

Communication between the cerebellum and forebrain structures is necessary for motor learning and has been implicated in a variety of cognitive functions. The exact nature of cerebellar–forebrain interactions supporting behavior and cognition is not known. We examined how local and network activity support learning by simultaneously recording neural activity in the cerebellum, amygdala, and anterior cingulate cortex while male and female rats were trained in trace eyeblink conditioning. Initially, the cerebellum and forebrain signal the contingency between external stimuli through increases in theta power and synchrony. Neuronal activity driving expression of the learned response was observed in the cerebellum and became evident in the anterior cingulate and amygdala as learning progressed. Aligning neural activity to the training stimuli or learned response provided a way to differentiate between learning-related activity driven by different mechanisms. Stimulus and response-related increases in theta power and coherence were observed across all three areas throughout learning. However, increases in slow gamma power and coherence were only observed when oscillations were aligned to the cerebellum-driven learned response. Percentage of learned responses, learning-related local activity, and slow gamma communication from cerebellum to forebrain all progressively increased during training. The relatively fast frequency of slow gamma provides an ideal mechanism for the cerebellum to communicate learned temporal information to the forebrain. This cerebellar response-aligned slow gamma then provides enrichment of behavior-specific temporal information to local neuronal activity in the forebrain. These dynamic network interactions likely support a wide range of behaviors and cognitive tasks that require coordination between the forebrain and cerebellum.

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Angular Head Velocity Cells within Brainstem Nuclei Projecting to the Head Direction Circuit

Jalina A. Graham, Julie R. Dumont, Shawn S. Winter, Joel E. Brown, Patrick A. LaChance, Carly C. Amon, Kara B. Farnes, Ashlyn J. Morris, Nicholas A. Streltsov, and Jeffrey S. Taube

Department of Psychological Brain Sciences, Dartmouth College, Dartmouth, New Hampshire 03755

The sense of orientation of an animal is derived from the head direction (HD) system found in several limbic structures and depends on an intact vestibular labyrinth. However, how the vestibular system influences the generation and updating of the HD signal remains poorly understood. Anatomical and lesion studies point toward three key brainstem nuclei as key components for generating the HD signal—nucleus prepositus hypoglossi, supragenual nucleus, and dorsal paragigantocellularis reticular nuclei. Collectively, these nuclei are situated between the vestibular nuclei and the dorsal tegmental and lateral mammillary nuclei, which are thought to serve as the origin of the HD signal. To determine the types of information these brain areas convey to the HD network, we recorded neurons from these regions while female rats actively foraged in a cylindrical enclosure or were restrained and rotated passively. During foraging, a large subset of cells in all three nuclei exhibited activity that correlated with the angular head velocity (AHV) of the rat. Two fundamental types of AHV cells were observed; (1) symmetrical AHV cells increased or decreased their firing with increases in AHV regardless of the direction of rotation, and (2) asymmetrical AHV cells responded differentially to clockwise and counterclockwise head rotations. When rats were passively rotated, some AHV cells remained sensitive to AHV, whereas firing was attenuated in other cells. In addition, a large number of AHV cells were modulated by linear head velocity. These results indicate the types of information conveyed from the vestibular nuclei that are responsible for generating the HD signal.

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BEHAVIORAL/COGNITIVE

Cognitive Aging and the Primate Basal Forebrain Revisited: Disproportionate GABAergic Vulnerability Revealed

Cristina Bañuelos,¹ Joshua R. Kittleson,¹ Katherine H. LaNasa,¹ Christina S. Galiano,¹ Stephanie M. Roth,¹ Evelyn J. Perez,¹ Jeffrey M. Long,¹ Mary T. Roberts,² Sania Fong,^{1,2} and Peter R. Rapp¹

¹Laboratory of Behavioral Neuroscience, National Institute on Aging, Baltimore, Maryland 21224 ²California National Primate Research Center, University of California, Davis, California 95616

Basal forebrain (BF) projections to the hippocampus and cortex are anatomically positioned to influence a broad range of cognitive capacities that are known to decline in normal aging, including executive function and memory. Although a long history of research on neurocognitive aging has focused on the role of the cholinergic basal forebrain system, intermingled GABAergic cells are numerically as prominent and well positioned to regulate the activity of their cortical projection targets, including the hippocampus and prefrontal cortex. The effects of aging on noncholinergic BF neurons in primates, however, are largely unknown. In this study, we conducted quantitative morphometric analyses in brains from young adult (6 females, 2 males) and aged (11 females, 5 males) rhesus monkeys (*Macaca mulatta*) that displayed significant impairment on standard tests that require the prefrontal cortex and hippocampus. Cholinergic (ChAT⁺) and GABAergic (GAD67⁺) neurons were quantified through the full rostrocaudal extent of the BF. Total BF immunopositive neuron number (ChAT⁺ plus GAD67⁺) was significantly lower in aged monkeys compared with young, largely because of fewer GAD67⁺ cells. Additionally, GAD67⁺ neuron volume was greater selectively in aged monkeys without cognitive impairment compared with young monkeys. These findings indicate that the GABAergic component of the primate BF is disproportionately vulnerable to aging, implying a loss of inhibitory drive to cortical circuitry. Moreover, adaptive reorganization of the GABAergic circuitry may contribute to successful neurocognitive outcomes.

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The Causal Role of Temporoparietal Junction in Mediating Self–Other Merge during Mentalizing

Fanru Sun (孙凡茹),¹ Tianshu Yang (杨天舒),^{2,3,4} Ning Liu (刘宁),^{2,3} and Xiaohong Wan (万小红)¹

¹State Key Laboratory of Cognitive Neuroscience and Learning and IDG/McGovern Institute for Brain Research, Beijing Normal University, Beijing 100875, People's Republic of China ²State Key Laboratory of Brain and Cognitive Science, Institute of Biophysics, Chinese Academy of Sciences, Beijing 100101, People's Republic of China ³College of Life Sciences, University of Chinese Academy of Sciences, Beijing, 100049, China ⁴Department of Radiology, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai 200025, People's Republic of China

Mentalizing is a core faculty of human social behaviors that involves inferring the cognitive states of others. This process necessitates adopting an allocentric perspective and suppressing one's egocentric perspective, referred to as self–other distinction (SOD). Meanwhile, individuals may project their own cognitive states onto others in prosocial behaviors, a process known as self–other merge (SOM). It remains unclear how the two opposing processes coexist during mentalizing. We here combined functional magnetic resonance imaging (fMRI) and repetitive transcranial magnetic stimulation (rTMS) techniques with intranasal oxytocin (OT^{int}) as a probe to examine the SOM effect in healthy male human participants, during which they attributed the cognitive states of decision confidence to an anonymous partner. Our results showed that OT^{int} facilitated SOM via the left temporoparietal junction (ITPJ), but did not affect neural representations of internal information about others' confidence in the dorsomedial prefrontal cortex, which might be dedicated to SOD, although the two brain regions, importantly, have been suggested to be involved in mentalizing. Further, the SOM effect induced by OT^{int} was fully mediated by the ITPJ

activities and became weakened when the ITPJ activities were suppressed by rTMS. These findings suggest that the ITPJ might play a vital role in mediating SOM during mentalizing.

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Cognitive Reappraisal and Expressive Suppression Evoke Distinct Neural Connections during Interpersonal Emotion Regulation

Zixin Liu,¹ Kelong Lu,³ Ning Hao,¹ and Yanmei Wang^{1,2}

¹Shanghai Key Laboratory of Mental Health and Psychological Crisis Intervention, School of Psychology and Cognitive Science, East China Normal University, Shanghai, 200062, China ²Shanghai Changning Mental Health Center, Shanghai, 200335, China ³School of Mental Health, Wenzhou Medical University, Wenzhou, Zhejiang, 325035, China

Interpersonal emotion regulation is the dynamic process where the regulator aims to change the target's emotional state, which is presumed to engage three neural systems: cognitive control (i.e., dorsal and ventral lateral PFC, etc.), empathy/social cognition (i.e., dorsal premotor regions, temporal-parietal junction, etc.), and affective response (i.e., insula, amygdala, etc.). This study aimed to identify the underlying neural correlate (especially the interpersonal one), of interpersonal emotion regulation based on two typical strategies (cognitive appraisal, expressive suppression). Thirty-four female dyads (friends) were randomly assigned into two strategy groups, with one assigned as the target and the other as the regulator to downregulate the target's negative emotions using two strategies. A functional near-infrared spectroscopy system was used to simultaneously measure participants' neural activity. Results showed that these two strategies could successfully downregulate the targets' negative emotions. Both strategies evoked intrapersonal and interpersonal neural couplings between the cognitive control, social cognition, and mirror neuron systems (e.g., PFC, temporal-parietal junction, premotor cortex, etc.), whereas cognitive reappraisal (vs expressive suppression) evoked a broader pattern. Further, cognitive reappraisal involved increased interpersonal brain synchronization between the prefrontal and temporal areas at the sharing stage, whereas expressive suppression evoked increased interpersonal brain synchronization associated with the PFC at the regulation stage. These findings indicate that intrapersonal and interpersonal neural couplings associated with regions within the abovementioned systems, possibly involving mental processes, such as cognitive control, mentalizing, and observing, underlie interpersonal emotion regulation based on cognitive reappraisal or expressive suppression.

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Different Faces of Medial Beta-Band Activity Reflect Distinct Visuomotor Feedback Signals

Antoine Schwey,¹ Demian Battaglia,^{2,3} Jyotika Bahuguna,^{3,4} and Nicole Malfait¹

¹Institut de Neurosciences de la Timone, Unité Mixte de Recherche 7289, Centre National de la Recherche Scientifique, Aix-Marseille Université, 13005 Marseille, France ²Institut de Neurosciences des Systèmes, Unité Mixte de Recherche 7289, Institut National de la Santé et de la Recherche Médicale, Aix-Marseille Université, 13005 Marseille, France ³Institut d'Etudes Avancées de l'Université de Strasbourg, Université de Strasbourg, 67084 Strasbourg, France ⁴Department of Psychology, Carnegie Mellon University, Pittsburgh, Pennsylvania 15213

Beta-band (13–35 Hz) modulations following reward, task outcome feedback, and error have been described in cognitive and/or motor adaptation tasks. Observations from different studies are, however, difficult to conciliate. Among the studies that used cognitive response selection tasks, several reported an increase in beta-band activity following reward, whereas others observed increased beta power after negative feedback. Moreover, in motor adaptation tasks, an attenuation of the postmovement beta rebound follows a movement execution error induced by visual or mechanical perturbations. Given that kinematic error typically leads to negative task–outcome feedback (e.g., target missed), one may wonder how contradictory modulations, beta power decrease with movement error versus beta power increase with negative feedback, may coexist. We designed a motor adaptation task in which female and male participants experience varied feedbacks—binary success/failure feedback, kinematic error, and sensory-prediction error—and demonstrate that beta-band modulations in opposite directions coexist at different spatial locations, time windows, and frequency ranges. First, high beta power in the medial frontal cortex showed opposite modulations well separated in time when compared in success and failure trials; that is, power was higher in success trials just after the binary success feedback, whereas it was lower in the postmovement period compared with failure trials. Second, although medial frontal high-beta activity was sensitive to task outcome, low-beta power in the medial parietal cortex was strongly attenuated following movement execution error but was not affected by either the outcome of the task or sensory-prediction error. These findings suggest that medial beta activity in different spatio-temporal-spectral configurations play a multifaceted role in encoding qualitatively distinct feedback signals.

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Bursting with Potential: How Sensorimotor Beta Bursts Develop from Infancy to Adulthood

Holly Rayson,^{1,2,5} Maciej J. Szul,^{1,2} Perla El-Khoueiry,^{1,2} Ranjan Debnath,³ Marine Gautier-Martins,^{1,2} Pier F. Ferrari,^{1,2} Nathan Fox,⁴ and James J. Bonaiuto^{1,2}

¹Institut des Sciences, Cognitives Marc Jeannerod, Centre National de la Recherche Scientifique Unité Mixte de Recherche 5229, Bron, 69500, France ²Université de Lyon, Université Claude Bernard Lyon 1, Lyon, 69100, France ³Center for Psychiatry and Psychotherapy, Justus-Liebig University, Giessen, 35394, Germany ⁴University of Maryland, College Park, Maryland, 20742 ⁵Inovarian, Paris, France

Beta activity is thought to play a critical role in sensorimotor processes. However, little is known about how activity in this frequency band develops. Here, we investigated the developmental trajectory of sensorimotor beta activity from infancy to adulthood. We recorded EEG from 9-month-old, 12-month-old, and adult humans (male and female) while they observed and executed grasping movements. We analyzed “beta burst” activity using a novel method that combines time-frequency decomposition and principal component analysis. We then examined the changes in burst rate and waveform motifs along the selected principal components. Our results reveal systematic changes in beta activity during action execution across development. We found a decrease in beta burst rate during movement execution in all age groups, with the greatest decrease observed in adults. Additionally, we identified three principal components that defined waveform motifs that systematically changed throughout the trial. We found that bursts with waveform shapes closer to the median waveform were not rate-modulated, whereas those with waveform shapes further from the median were differentially rate-modulated. Interestingly, the decrease in the rate of certain burst motifs occurred earlier during movement and was more lateralized in adults than in infants, suggesting that the rate modulation of specific types of beta bursts becomes increasingly refined with age.

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Distinct Neural Components of Visually Guided Grasping during Planning and Execution

Lina K. Klein,¹ Guido Maiello,² Kevin Stubbs,³ Daria Proklova,³ Juan Chen,^{4,5} Vivian C. Paulun,^{6,7} Jody C. Culham,³ and Roland W. Fleming^{1,8}

¹Department of Experimental Psychology, Justus Liebig University Giessen, 35390 Giessen, Germany ²School of Psychology, University of Southampton, Southampton SO17 1PS, United Kingdom ³Department of Psychology, University of Western Ontario, London, Ontario N6A 5C2, Canada ⁴Center for the Study of Applied Psychology, Guangdong Key Laboratory of Mental Health and Cognitive Science, and the School of Psychology, South China Normal University, Guangzhou, 510631, China ⁵Key Laboratory of Brain, Cognition and Education Sciences, South China Normal University, Guangzhou 510631, China ⁶McGovern Institute for Brain Research, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139 ⁷Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139 ⁸Center for Mind, Brain and Behavior, University of Marburg and Justus Liebig University Giessen, Giessen, Germany, 35390

Selecting suitable grasps on three-dimensional objects is a challenging visuomotor computation, which involves combining information about an object (e.g., its shape, size, and mass) with information about the actor’s body (e.g., the optimal grasp aperture and hand posture for comfortable manipulation). Here, we used functional magnetic resonance imaging to investigate brain networks associated with these distinct aspects during grasp planning and execution. Human participants of either sex viewed and then executed preselected grasps on L-shaped objects made of wood and/or brass. By leveraging a computational approach that accurately predicts human grasp locations, we selected grasp points that disentangled the role of multiple grasp-relevant factors, that is, grasp axis, grasp size, and object mass. Representational Similarity Analysis revealed that grasp axis was encoded along dorsal-stream regions during grasp planning. Grasp size was first encoded in ventral stream areas during grasp planning then in premotor regions during grasp execution. Object mass was encoded in ventral stream and (pre)motor regions only during grasp execution. Premotor regions further encoded visual predictions of grasp comfort, whereas the ventral stream encoded grasp comfort during execution, suggesting its involvement in haptic evaluation. These shifts in neural representations thus capture the sensorimotor transformations that allow humans to grasp objects.

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Prospection of Potential Actions during Visual Working Memory Starts Early, Is Flexible, and Predicts Behavior

Rose Nasrawi,¹ Sage E. P. Boettcher,² and Freek van Ede¹

¹Institute for Brain and Behavior Amsterdam, Department of Experimental and Applied Psychology, Vrije Universiteit Amsterdam, Amsterdam 1081 BT, The Netherlands ²Department of Experimental Psychology, University of Oxford, Oxford OX2 6GG, United Kingdom

For visual working memory to serve upcoming behavior, it is crucial that we prepare for the potential use of working-memory contents ahead of time. Recent studies have demonstrated how the prospection and planning for an upcoming manual action starts early after visual encoding, and occurs alongside visual retention. Here, we address whether such “output planning” in visual working memory flexibly adapts to different visual-motor mappings, and occurs even when an upcoming action will only potentially become relevant for behavior. Human participants (female and male) performed a visual-motor working memory task in which they remembered one or two colored oriented bars for later (potential) use. We linked, and counterbalanced, the tilt of the visual items to specific manual responses. This allowed us to track planning of upcoming behavior through contralateral attenuation of β band activity, a canonical motor-cortical EEG signature of manual-action planning. The results revealed how action encoding and subsequent planning alongside visual working memory (1) reflect anticipated task demands rather than specific visual-motor mappings, (2) occur even for actions that will only potentially become relevant for behavior, and (3) are associated with faster performance for the encoded item, at the expense of performance to other working-memory content. This reveals how the potential prospective use of visual working memory content is flexibly planned early on, with consequences for the speed of memory-guided behavior.

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Fast Feedback Responses to Categorical Sensorimotor Errors That Do Not Indicate Error Magnitude Are Optimized Based on Short- and Long-Term Memory

Michael R. McGarity-Shiple, ¹ Simona Markovik Jantz, ¹ Roland S. Johansson, ³ Daniel M. Wolpert, ^{4,5} and J. Randall Flanagan ^{1,2}

¹Centre for Neuroscience Studies, Queen's University, Kingston, Ontario K7L 3N6, Canada ²Department of Psychology, Queen's University, Kingston, Ontario K7L 3N6, Canada ³Physiology Section, Department of Integrative Medical Biology, Umeå University, SE-901 87 Umeå, Sweden ⁴Department of Neuroscience, Columbia University, New York, New York, 10027 ⁵Zuckerman Mind Brain Behavior Institute, Columbia University, New York, New York 10027

Skilled motor performance depends critically on rapid corrective responses that act to preserve the goal of the movement in the face of perturbations. Although it is well established that the gain of corrective responses elicited while reaching toward objects adapts to different contexts, little is known about the adaptability of corrective responses supporting the manipulation of objects after they are grasped. Here, we investigated the adaptability of the corrective response elicited when an object being lifted is heavier than expected and fails to lift off when predicted. This response involves a monotonic increase in vertical load force triggered, within ~90 ms, by the absence of expected sensory feedback signaling lift off and terminated when actual lift off occurs. Critically, because the actual weight of the object cannot be directly sensed at the moment the object fails to lift off, any adaptation of the corrective response would have to be based on memory from previous lifts. We show that when humans, including men and women, repeatedly lift an object that on occasional catch trials increases from a baseline weight to a fixed heavier weight, they scale the gain of the response (i.e., the rate of force increase) to the heavier weight within two to three catch trials. We also show that the gain of the response scales, on the first catch trial, with the baseline weight of the object. Thus, the gain of the lifting response can be adapted by both short- and long-term experience. Finally, we demonstrate that this adaptation preserves the efficacy of the response across contexts.

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Establishing the Roles of the Dorsal and Ventral Striatum in Humor Comprehension and Appreciation with fMRI

Margaret Prenger, ^{1,2,3} Madeline Gilchrist, ^{2,3} Kathryn Van Hedger, ^{1,2,4} Ken N. Seergobin, ² Adrian M. Owen, ^{1,2,5} and Penny A. MacDonald ^{1,2,4}

¹BrainsCAN, University of Western Ontario, London, Ontario N6A 3K7, Canada ²Western Institute for Neuroscience, University of Western Ontario, London, Ontario N6A 3K7, Canada ³Department of Neuroscience, University of Western Ontario, London, Ontario N6A 3K7, Canada ⁴Clinical Neurological Sciences, Schulich School of Medicine & Dentistry, University of Western Ontario, London, Ontario N6A 3K7, Canada ⁵Departments of Physiology & Pharmacology and Psychology, University of Western Ontario, London, Ontario N6A 3K7, Canada

Humor comprehension (i.e., getting a joke) and humor appreciation (i.e., enjoying a joke) are distinct, cognitively complex processes. Functional magnetic resonance imaging (fMRI) investigations have identified several key cortical regions but have overlooked subcortical structures that have theoretical importance in humor processing. The dorsal striatum (DS) contributes to working memory, ambiguity processing, and cognitive flexibility, cognitive functions that are required to accurately recognize humorous stimuli. The ventral striatum (VS) is critical in reward processing and enjoyment. We hypothesized that the DS and VS play important roles in humor comprehension and appreciation, respectively. We investigated the engagement of these regions in these distinct processes using fMRI. Twenty-six healthy young male and female human adults completed two humor-elicitation tasks during a 3 tesla fMRI scan consisting of a traditional behavior-based joke task and a naturalistic audiovisual sitcom paradigm (i.e., *Seinfeld* viewing task). Across both humor-elicitation methods, whole-brain analyses revealed cortical activation in the inferior frontal gyrus, the middle frontal gyrus, and the middle temporal gyrus for humor comprehension, and the temporal cortex for humor appreciation. Additionally, with region of interest analyses, we specifically examined whether DS and VS activation correlated with these processes. Across both tasks, we demonstrated that humor comprehension implicates both the DS and the VS, whereas humor appreciation only engages the VS. These results establish the role of the DS in humor comprehension, which has been previously overlooked, and emphasize the role of the VS in humor processing more generally.

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NEUROBIOLOGY OF DISEASE

Spinal-Specific Super Enhancer in Neuropathic Pain

Yang Tao, Qi-Hui Wang, Xiao-Tong Li, Ya Liu, Run-Hang Sun, Heng-Jun Xu, Ming Zhang, Si-Yuan Li, Li Yang, Hong-Jun Wang, Ling-Yun Hao, Jun-Li Cao, and Zhiqiang Pan

Jiangsu Province Key Laboratory of Anesthesiology, Jiangsu Province Key Laboratory of Anesthesia and Analgesia Application Technology, NMPA Key Laboratory for Research and Evaluation of Narcotic and Psychotropic Drugs, Xuzhou Medical University, Xuzhou 221004, China

Dysfunctional gene expression in nociceptive pathways plays a critical role in the development and maintenance of neuropathic pain. Super enhancers (SEs), composed of a large cluster of transcriptional enhancers, are emerging as new players in the regulation of gene expression. However, whether SEs participate

in nociceptive responses remains unknown. Here, we report a spinal-specific SE (SS-SE) that regulates chronic constriction injury (CCI)-induced neuropathic pain by driving *Ntmt1* and *Prrx2* transcription in dorsal horn neurons. Peripheral nerve injury significantly enhanced the activity of SS-SE and increased the expression of NTMT1 and PRRX2 in the dorsal horn of male mice in a bromodomain-containing protein 4 (BRD4)-dependent manner. Both intrathecal administration of a pharmacological BRD4 inhibitor JQ1 and CRISPR-Cas9-mediated SE deletion abolished the increased NTMT1 and PRRX2 in CCI mice and attenuated their nociceptive hypersensitivities. Furthermore, knocking down *Ntmt1* or *Prrx2* with siRNA suppressed the injury-induced elevation of phosphorylated extracellular-signal-regulated kinase (p-ERK) and glial fibrillary acidic protein (GFAP) expression in the dorsal horn and alleviated neuropathic pain behaviors. Mimicking the increase in spinal *Ntmt1* or *Prrx2* in naive mice increased p-ERK and GFAP expression and led to the genesis of neuropathic pain-like behavior. These results redefine our understanding of the regulation of pain-related genes and demonstrate that BRD4-driven increases in SS-SE activity is responsible for the genesis of neuropathic pain through the governance of NTMT1 and PRRX2 expression in dorsal horn neurons. Our findings highlight the therapeutic potential of BRD4 inhibitors for the treatment of neuropathic pain.

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Complex Synaptic and Intrinsic Interactions Disrupt Input/Output Functions in the Hippocampus of *Scn1b* Knock-Out Mice

Jessica Hotard Chancey, Alisha A. Ahmed, Fernando Isaac Guillén, Vighnesh Ghatpande, and MacKenzie A. Howard

Departments of Neurology and Neuroscience, Center for Learning and Memory, Dell Medical School, University of Texas at Austin, Austin, Texas 78712

Pathogenic variants in *SCN1B* have been linked to severe developmental epileptic encephalopathies including Dravet syndrome. *Scn1b* knock-out (KO) mice model *SCN1B* loss-of-function (LOF) disorders, demonstrating seizures, developmental delays, and early death. *SCN1B* encodes the protein $\beta 1$, an ion channel auxiliary subunit that also has roles in cell adhesion, neurite outgrowth, and gene expression. The goal of this project is to better understand of how loss of *Scn1b* alters information processing in the brain, resulting in seizures and associated cognitive dysfunction. Using slice electrophysiology in the CA1 region of the hippocampus from male and female *Scn1b* KO mice and wild-type (WT) littermates, we found that processing of physiologically relevant patterned Schaffer collateral (SC) stimulation produces larger, prolonged depolarizations and increased spiking in KO neurons compared with WTs. KO neurons exhibit enhanced intrinsic excitability, firing more action potentials with current injection. Interestingly, SC stimulation produces smaller, more facilitating excitatory and IPSCs in KO pyramidal neurons, but larger postsynaptic potentials (PSPs) with the same stimulation. We also found reduced intrinsic firing of parvalbumin (PV)-expressing interneurons and disrupted recruitment of both parvalbumin-expressing and somatostatin (SST)-expressing interneurons in response to patterned synaptic stimulation. Neuronal information processing relies on the interplay between synaptic properties, intrinsic properties that amplify or suppress incoming synaptic signals, and firing properties that produce cellular output. We found changes at each of these levels in *Scn1b* KO pyramidal neurons, resulting in fundamentally altered cellular information processing in the hippocampus that likely contributes to the complex phenotypes of *SCN1B*-linked epileptic encephalopathies.

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