



Cover legend: The somatosensory cortex is organized into distinct cortical layers. Layer II/III neurons extend collateral axon branches mainly in layers II/III and V. In this image, newly developed sparse (red) and bulk (green) labeling techniques were used to evaluate the branching patterns of single layer II/III neurons amongst the greater population of cortical projection neurons. Visualizing individual collateral branches is crucial for understanding the molecular mechanisms that drive their patterning in healthy and disease states. See the manuscript by Dorskind et al. (pages 7745–7765) for more information. Cover image: Joelle Dorskind.

7723 This Week in The Journal

Neuro and Beyond

- 7724 **Diversity in Neuroscience: How This Moment Is Different**
Joanne Berger-Sweeney

Journal Club

- 7727 **The ESCRT Pathway's Role in Prion Diseases and Beyond**
Hash Brown Taha

Research Articles

CELLULAR/MOLECULAR

- 7730 **Tonic Activation of NR2D-Containing NMDARs Exacerbates Dopaminergic Neuronal Loss in MPTP-Injected Parkinsonian Mice**
Ramesh Sharma, Chiranjivi Neupane, Thuy Linh Pham, Miae Lee, Sanghoon Lee, So Yeong Lee, Min-Ho Nam, Cuk-Seong Kim, and Jin Bong Park
- 7745 **Drebrin Regulates Collateral Axon Branching in Cortical Layer II/III Somatosensory Neurons**
Joelle M. Dorskind, Sriram Sudarsanam, Randal A. Hand, Jakub Ziak, Maame Amoah-Dankwah, Luis Guzman-Clavel, John Lee Soto-Vargas, and Alex L. Kolodkin

DEVELOPMENT/PLASTICITY/REPAIR

- 7766 **Structural and Functional Development of Inhibitory Connections from the Medial Nucleus of the Trapezoid Body to the Superior Paraolivary Nucleus**
Jongwon Lee, Amanda Clause, and Karl Kandler

SYSTEMS/CIRCUITS

- 7780 **High-Resolution Tractography Protocol to Investigate the Pathways between Human Mediodorsal Thalamic Nucleus and Prefrontal Cortex**
Liu Mengxing (刘梦醒), Garikoitz Lerma-Usabiaga, Francisco Clascá, and Pedro M. Paz-Alonso
- 7799 **Haploinsufficiency of *Shank3* in Mice Selectively Impairs Target Odor Recognition in Novel Background Odors**
Darya Ryndych, Alison Sebold, Alyssa Strassburg, Yan Li, Raddy L. Ramos, and Gonzalo H. Otazu

- 7812 **The Arousal-Related “Central Thalamus” Stimulation Site Simultaneously Innervates Multiple High-Level Frontal and Parietal Areas**
Paulo L. A. G. Morais, Pablo Rubio-Garrido, Ruthnaldo M. de Lima, Angélica Córdoba-Claros, Expedito S. de Nascimento Jr., Jeferson S. Cavalcante, and Francisco Clascá

BEHAVIORAL/COGNITIVE

- 7822 **Goal-Dependent Hippocampal Representations Facilitate Self-Control**
Micah G. Edelson and Todd A. Hare
- 7831 **How Grammar Conveys Meaning: Language-Specific Spatial Encoding Patterns and Cross-Language Commonality in Higher-Order Neural Space**
Jing Wang, Hui Lin, and Qing Cai
- 7842 **Temporal Dynamics of Brain Activity Predicting Sense of Agency over Muscle Movements**
John P. Veillette, Pedro Lopes, and Howard C. Nusbaum
- 7853 **Human Neuroimaging Reveals Differences in Activation and Connectivity between Real and Pantomimed Tool Use**
Juan Chen, Joseph U. Paciocco, Zhiqing Deng, and Jody C. Culham
- 7868 **Decoding Reach Direction in Early “Visual” Cortex of Congenitally Blind Individuals**
Łukasz Bola, Petra Vetter, Mohr Wenger, and Amir Amedi

NEUROBIOLOGY OF DISEASE

- 7879 **Dissociable Effects of Alzheimer’s Disease-Related Cognitive Dysfunction and Aging on Functional Brain Network Segregation**
Ziwei Zhang, Micaela Y. Chan, Liang Han, Claudia A. Carreno, Ezra Winter-Nelson, and Gagan S. Wig

Persons interested in becoming members of the Society for Neuroscience should contact the Membership Department at membership@sfn.org or 202-962-4911.

For current submission policies and manuscript preparation guidelines, authors should refer to our Information for Authors at <https://www.jneurosci.org/content/information-authors>.

Manuscripts should be submitted online at <https://jneurosci.msubmit.net>. Please contact the Central Office with any questions at jn@sfn.org or 202-962-4000.

Articles

CELLULAR/MOLECULAR

Tonic Activation of NR2D-Containing NMDARs Exacerbates Dopaminergic Neuronal Loss in MPTP-Injected Parkinsonian Mice

Ramesh Sharma,^{1,2,3} Chiranjivi Neupane,^{1,2,3} Thuy Linh Pham,^{1,2} Miae Lee,² Sanghoon Lee,³ So Yeong Lee,³ Min-Ho Nam,⁴ Cuk-Seong Kim,^{1,2} and Jin Bong Park³

¹Department of Biomedicine, Chungnam National University, Daejeon 35015, Republic of Korea ²Physiology, Chungnam National University, Daejeon 35015, Republic of Korea ³Laboratory of Veterinary Pharmacology, College of Veterinary Medicine and Research Institute for Veterinary Science, Seoul National University, Seoul 08852, Republic of Korea ⁴Brain Science Institute, Korea Institute of Science and Technology (KIST), Seoul 02792, Republic of Korea

NR2D subunit-containing NMDA receptors (NMDARs) gradually disappear during brain maturation but can be recruited by pathophysiological stimuli in the adult brain. Here, we report that 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) intoxication recruited NR2D subunit-containing NMDARs that generated an Mg^{2+} -resistant tonic NMDA current (I_{NMDA}) in dopaminergic (DA) neurons in the midbrain of mature male mice. MPTP selectively generated an Mg^{2+} -resistant tonic I_{NMDA} in DA neurons in the substantia nigra pars compacta (SNpc) and ventral tegmental area (VTA). Consistently, MPTP increased NR2D but not NR2B expression in the midbrain regions. Pharmacological or genetic NR2D interventions abolished the generation of Mg^{2+} -resistant tonic I_{NMDA} in SNpc DA neurons, and thus attenuated subsequent DA neuronal loss and gait deficits in MPTP-treated mice. These results show that extrasynaptic NR2D recruitment generates Mg^{2+} -resistant tonic I_{NMDA} and exacerbates DA neuronal loss, thus contributing to MPTP-induced Parkinsonism. The state-dependent NR2D recruitment could be a novel therapeutic target for mitigating cell type-specific neuronal death in neurodegenerative diseases.

The Journal of Neuroscience, November 15, 2023 • 43(46):7730–7744

Drebrin Regulates Collateral Axon Branching in Cortical Layer II/III Somatosensory Neurons

Joelle M. Dorskind,¹ Sriram Sudarsanam,¹ Randal A. Hand,¹ Jakub Ziak,¹ Maame Amoah-Dankwah,¹ Luis Guzman-Clavel,^{1,2} John Lee Soto-Vargas,^{1,3} and Alex L. Kolodkin¹

¹Solomon H. Snyder Department of Neuroscience, Johns Hopkins Kavli Neuroscience Discovery Institute, The Johns Hopkins University School of Medicine, Baltimore, Maryland 21205 ²Summer Internship Program (NeuroSIP), Solomon H. Snyder Department of Neuroscience, Johns Hopkins Kavli Neuroscience Discovery Institute, The Johns Hopkins University School of Medicine, Baltimore, Maryland 21200 ³Basic Science Institute-Summer Internship Program (BSI-SIP), Johns Hopkins Kavli Neuroscience Discovery Institute, The Johns Hopkins University School of Medicine, Baltimore, Maryland 21200

Proper cortical lamination is essential for cognition, learning, and memory. Within the somatosensory cortex, pyramidal excitatory neurons elaborate axon collateral branches in a laminar-specific manner that dictates synaptic partners and overall circuit organization. Here, we leverage both male and female mouse models, single-cell labeling and imaging approaches to identify intrinsic regulators of laminar-specific collateral, also termed interstitial, axon branching. We developed new approaches for the robust, sparse, labeling of Layer II/III pyramidal neurons to obtain single-cell quantitative assessment of axon branch morphologies. We combined these approaches with cell-autonomous loss-of-function (LOF) and overexpression (OE) manipulations in an *in vivo* candidate screen to identify regulators of cortical neuron axon branch lamination. We identify a role for the cytoskeletal binding protein drebrin (Dbn1) in regulating Layer II/III cortical projection neuron (CPN) collateral axon branching *in vitro*. LOF experiments show that Dbn1 is necessary to suppress the elongation of Layer II/III CPN collateral axon branches within Layer IV, where axon branching by Layer II/III CPNs is normally absent. Conversely, *Dbn1* OE produces excess short axonal protrusions reminiscent of nascent axon collaterals that fail to elongate. Structure-function analyses implicate Dbn1^{S142} phosphorylation and Dbn1 protein domains known to mediate F-actin bundling and microtubule (MT) coupling as necessary for collateral branch initiation upon *Dbn1* OE. Taken together, these results contribute to our understanding of the molecular mechanisms that regulate collateral axon branching in excitatory CPNs, a key process in the elaboration of neocortical circuit formation.

The Journal of Neuroscience, November 15, 2023 • 43(46):7745–7765

DEVELOPMENT/PLASTICITY/REPAIR

Structural and Functional Development of Inhibitory Connections from the Medial Nucleus of the Trapezoid Body to the Superior Paraolivary Nucleus

Jongwon Lee,¹ Amanda Clause,¹ and Karl Kandler^{1,2}

¹Department of Neurobiology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania 15261 ²Department of Bioengineering, University of Pittsburgh, Pittsburgh, Pennsylvania 15261

The medial nucleus of the trapezoid body (MNTB) in the auditory brainstem is the principal source of synaptic inhibition to several functionally distinct auditory nuclei. Prominent projections of individual MNTB neurons comprise the major binaural nuclei that are involved in the early processing stages of sound localization as well as the superior paraolivary nucleus (SPON), which contains monaural neurons that extract rapid changes in sound intensity to detect sound gaps and rhythmic oscillations that commonly occur in animal calls and human speech. While the processes that guide the development and refinement of MNTB axon collaterals to the binaural nuclei have become increasingly understood, little is known about the development of MNTB collaterals to the monaural SPON. In this study, we investigated the development of MNTB-SPON connections in mice of both sexes from shortly after birth to three weeks of age, which encompasses the time before and after hearing onset. Individual axon reconstructions and electrophysiological analysis of MNTB-SPON connectivity demonstrate a dramatic increase in the number of MNTB axonal boutons in the SPON before hearing onset. However, this proliferation was not accompanied by changes in the strength of MNTB-SPON connections or by changes in the structural or functional topographic precision. However, following hearing onset, the spread of single-axon boutons along the tonotopic axis increased, indicating an unexpected decrease in the tonotopic precision of the MNTB-SPON pathway. These results provide new insight into the development and organization of inhibition to SPON neurons and the regulation of developmental plasticity in diverging inhibitory pathways.

The Journal of Neuroscience, November 15, 2023 • 43(46):7766–7779

SYSTEMS/CIRCUITS

High-Resolution Tractography Protocol to Investigate the Pathways between Human Mediodorsal Thalamic Nucleus and Prefrontal Cortex

Liu Mengxing (刘梦醒),¹ Garikoitz Lerma-Usabiaga,^{1,2} Francisco Clascá,³ and Pedro M. Paz-Alonso^{1,2}

¹Basque Center on Cognition, Brain and Language, 20009 Donostia-San Sebastián, Spain ²Ikerbasque, Basque Foundation for Science, 48013 Bilbao, Spain ³Department of Anatomy and Neuroscience, School of Medicine, Autónoma de Madrid University, 28029 Madrid, Spain

Animal studies have established that the mediodorsal nucleus (MD) of the thalamus is heavily and reciprocally connected with all areas of the prefrontal cortex (PFC). In humans, however, these connections are difficult to investigate. High-resolution imaging protocols capable of reliably tracing the axonal tracts linking the human MD with each of the PFC areas may thus be key to advance our understanding of the variation, development, and plastic changes of these important circuits, in health and disease. Here, we tested in adult female and male humans the reliability of a new reconstruction protocol based on *in vivo* diffusion MRI to trace, measure, and characterize the fiber tracts interconnecting the MD with 39 human PFC areas per hemisphere. Our protocol comprised the following three components: (1) defining regions of interest; (2) preprocessing diffusion data; and, (3) modeling white matter tracts and tractometry. This analysis revealed largely separate PFC territories of reciprocal MD–PFC tracts bearing striking resemblance with the topographic layout observed in macaque connection-tracing studies. We then examined whether our protocol could reliably reconstruct each of these MD–PFC tracts and their profiles across test and retest sessions. Results revealed that this protocol was able to trace and measure, in both left and right hemispheres, the trajectories of these 39 area-specific axon bundles with good-to-excellent test-retest reproducibility. This protocol, which has been made publicly available, may be relevant for cognitive neuroscience and clinical studies of normal and abnormal PFC function, development, and plasticity.

The Journal of Neuroscience, November 15, 2023 • 43(46):7780–7798

Haploinsufficiency of *Shank3* in Mice Selectively Impairs Target Odor Recognition in Novel Background Odors

Darya Ryndych, Alison Sebold, Alyssa Strassburg, Yan Li, Raddy L. Ramos, and Gonzalo H. Otazu

Department of Biomedical Sciences, New York Institute of Technology College of Osteopathic Medicine, Old Westbury, New York 11568

Individuals with mutations in a single copy of the *SHANK3* gene present with social interaction deficits. Although social behavior in mice depends on olfaction, mice with mutations in a single copy of the *Shank3* gene do not have olfactory deficits in simple odor identification tasks (Drapeau et al., 2018). Here, we tested olfaction in mice with mutations in a single copy of the *Shank3* gene (Peça et al., 2011) using a complex odor task and imaging in awake mice. Average glomerular responses in the olfactory bulb of *Shank3B*^{+/-} were correlated with WT mice. However, there was increased trial-to-trial variability in the odor responses for *Shank3B*^{+/-} mice. Simulations demonstrated that this increased variability could affect odor detection in novel environments. To test whether performance was affected by the increased variability, we tested target odor recognition in the presence of novel background odors using a recently developed task (Li et al., 2023). Head-fixed mice were trained to detect target odors in the presence of known background odors. Performance was tested using catch trials where the known background odors were replaced by novel background odors. We compared the performance of eight *Shank3B*^{+/-} mice (five males, three females) on this task with six WT mice (three males, three females). Performance for known background odors and learning rates were similar between *Shank3B*^{+/-} and WT mice. However, when tested with novel background odors, the performance of *Shank3B*^{+/-} mice dropped to almost chance levels. Thus, haploinsufficiency of the *Shank3* gene causes a specific deficit in odor detection in novel environments. Our results are discussed in the context of other *Shank3* mouse models and have implications for understanding olfactory function in neurodevelopmental disorders.

The Journal of Neuroscience, November 15, 2023 • 43(46):7799–7811

The Arousal-Related “Central Thalamus” Stimulation Site Simultaneously Innervates Multiple High-Level Frontal and Parietal Areas

Paulo L. A. G. Morais,^{1,2} Pablo Rubio-Garrido,² Ruthnaldo M. de Lima,¹ Angélica Córdoba-Claros,² Expedito S. de Nascimento Jr.,¹ Jeferson S. Cavalcante,¹ and Francisco Clascá²

¹Federal University of Rio Grande do Norte, RN CEP 59078-900, Natal, Brazil ²Universidad Autónoma de Madrid, 28029 Madrid, Spain

In human and nonhuman primates, deep brain stimulation applied at or near the internal medullary lamina of the thalamus [a region referred to as “central thalamus,” (CT)], but not at nearby thalamic sites, elicits major changes in the level of consciousness, even in some minimally conscious brain-damaged patients. The mechanisms behind these effects remain mysterious, as the connections of CT had not been specifically mapped in primates. In marmoset monkeys (*Callithrix jacchus*) of both sexes, we labeled the axons originating from each of the various CT neuronal populations and analyzed their arborization patterns in the cerebral cortex and striatum. We report that, together, these CT populations innervate an array of high-level frontal, posterior parietal, and cingulate cortical areas. Some populations simultaneously target the frontal, parietal, and cingulate cortices, while others predominantly target the dorsal striatum. Our data indicate that CT stimulation can simultaneously engage a heterogeneous set of projection systems that, together, target the key nodes of the attention, executive control, and working-memory networks of the brain. Increased functional connectivity in these networks has been previously described as a signature of consciousness.

The Journal of Neuroscience, November 15, 2023 • 43(46):7812–7821

BEHAVIORAL/COGNITIVE

Goal-Dependent Hippocampal Representations Facilitate Self-Control

Micah G. Edelson and Todd A. Hare

Zurich Center for Neuroeconomics, Department of Economics, University of Zurich, Zürich, 8006, Switzerland

Hippocampal activity linking past experiences and simulations of the future with current goals can play an important role in decision-making. The representation of information within the hippocampus may be especially critical in situations where one needs to overcome past rewarding experiences and exert self-control. Self-control success or failure may depend on how information is represented in the hippocampus and how effectively the representation process can be modified to achieve a specific goal. We test this hypothesis using representational similarity analyses of human (female/male) neuroimaging data during a dietary self-control task in which individuals must overcome taste temptations to choose healthy foods. We find that self-control is indeed associated with the way individuals represent taste information (valence) in the hippocampus and how taste representations there adapt to align with different goals/contexts. Importantly, individuals who were able to shift their hippocampal representations to a larger degree to align with the current motivation were better able to exert self-control when facing a dietary challenge. These results suggest an alternative or complementary neurobiological pathway leading to self-control success and indicate the need to update the classical view of self-control to continue to advance our understanding of its behavioral and neural underpinnings.

The Journal of Neuroscience, November 15, 2023 • 43(46):7822–7830

How Grammar Conveys Meaning: Language-Specific Spatial Encoding Patterns and Cross-Language Commonality in Higher-Order Neural Space

Jing Wang,^{1,2,4} Hui Lin,³ and Qing Cai^{1,2,4,5}

¹Key Laboratory of Brain Functional Genomics (MOE & STCSM), Affiliated Mental Health Center (ECNU), Institute of Brain and Education Innovation, School of Psychology and Cognitive Science, East China Normal University, Shanghai 20062, China ²Shanghai Changning Mental Health Center, Shanghai 200335, China ³Shanghai Key Laboratory of Artificial Intelligence in Learning and Cognitive Science, LAIX Inc., Shanghai 200090, China

⁴Shanghai Center for Brain Science and Brain-Inspired Technology, East China Normal University, Shanghai 200062, China ⁵New York University-ECNU Institute of Brain and Cognitive Science, New York University, Shanghai 200062, China

Languages come in different forms but have shared meanings to convey. Some meanings are expressed by sentence structure and morphologic inflections rather than content words, such as indicating time frame using tense. This fMRI study investigates whether there is cross-language common representation of grammatical meanings that can be identified from neural signatures in the bilingual human brain. Based on the representations in intersentence neural similarity space, identifying grammatical construction of a sentence in one language by models trained on the other language resulted in reliable accuracy. By contrast, cross-language identification of grammatical construction by spatially matched activation patterns was only marginally accurate. Brain locations representing grammatical meaning in the two languages were interleaved in common regions bilaterally. The locations of voxels representing grammatical features in the second language were more varied across individuals than voxels representing the first language. These findings suggest grammatical meaning is represented by language-specific activation patterns, which is different from lexical semantics. Commonality of grammatical meaning is neurally reflected only in the interstimulus similarity space.

The Journal of Neuroscience, November 15, 2023 • 43(46):7831–7841

Temporal Dynamics of Brain Activity Predicting Sense of Agency over Muscle Movements

John P. Veillette,¹ Pedro Lopes,² and Howard C. Nusbaum¹

¹Department of Psychology, University of Chicago, Chicago, Illinois 60637 ²Department of Computer Science, University of Chicago, Chicago, Illinois 60637

Our muscles are the primary means through which we affect the external world, and the sense of agency (SoA) over the action through those muscles is fundamental to our self-awareness. However, SoA research to date has focused almost exclusively on agency over action outcomes rather than over the musculature itself, as it was believed that SoA over the musculature could not be manipulated directly. Drawing on methods from human–computer interaction and adaptive experimentation, we use human-in-the-loop Bayesian optimization to tune the timing of electrical muscle stimulation so as to robustly elicit a SoA over electrically actuated muscle movements in male and female human subjects. We use time-resolved decoding of subjects' EEG to estimate the time course of neural activity which predicts reported agency on a trial-by-trial basis. Like paradigms which assess SoA over action consequences, we found that the late (post-conscious) neural activity predicts SoA. Unlike typical paradigms, however, we also find patterns of early (sensorimotor) activity with distinct temporal dynamics predicts agency over muscle movements, suggesting that the “neural correlates of agency” may depend on the level of abstraction (i.e., direct sensorimotor feedback versus downstream consequences) most relevant to a given agency judgment. Moreover, fractal analysis of the EEG suggests that SoA-contingent dynamics of neural activity may modulate the sensitivity of the motor system to external input.

The Journal of Neuroscience, November 15, 2023 • 43(46):7842–7852

Human Neuroimaging Reveals Differences in Activation and Connectivity between Real and Pantomimed Tool Use

Juan Chen,^{1,2} Joseph U. Paciocco,³ Zhiqing Deng,¹ and Jody C. Culham^{3,4}

¹Center 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, Guangdong 510631, China ²Key Laboratory of Brain, Cognition and Education Sciences, South China Normal University, Ministry of Education, Guangzhou, Guangdong 510631, China ³Neuroscience Program, University of Western Ontario, London, Ontario N6A 5B7, Canada ⁴Department of Psychology, University of Western Ontario, London, Ontario N6A 5B7, Canada

Because the sophistication of tool use is vastly enhanced in humans compared with other species, a rich understanding of its neural substrates requires neuroscientific experiments in humans. Although functional magnetic resonance imaging (fMRI) has enabled many studies of tool-related neural processing, surprisingly few studies have examined real tool use. Rather, because of the many constraints of fMRI, past research has typically used proxies such as pantomiming despite neuropsychological dissociations between pantomimed and real tool use. We compared univariate activation levels, multivariate activation patterns, and functional connectivity when participants used real tools (a plastic knife or fork) to act on a target object (scoring or poking a piece of putty) or pantomimed the same actions with similar movements and timing. During the Execute phase, we found higher activation for real versus pantomimed tool use in sensorimotor regions and the anterior supramarginal gyrus, and higher activation for pantomimed than real tool use in classic tool-selective areas. Although no regions showed significant differences in activation magnitude during the Plan phase, activation patterns differed between real versus pantomimed tool use and motor cortex showed differential functional connectivity. These results reflect important differences between real tool use, a closed-loop process constrained by real consequences, and pantomimed tool use, a symbolic gesture that requires conceptual knowledge of tools but with limited consequences. These results highlight the feasibility and added value of employing natural tool use tasks in functional imaging, inform neuropsychological dissociations, and advance our theoretical understanding of the neural substrates of natural tool use.

The Journal of Neuroscience, November 15, 2023 • 43(46):7853–7867

Decoding Reach Direction in Early “Visual” Cortex of Congenitally Blind Individuals

Łukasz Bola,¹ Petra Vetter,² Mohr Wenger,³ and Amir Amedi^{3,4}

¹Institute of Psychology, Polish Academy of Sciences, Warsaw, 00-378, Poland ²Visual & Cognitive Neuroscience Lab, Department of Psychology, University of Fribourg, Fribourg, 1700, Switzerland ³Department of Medical Neurobiology, Faculty of Medicine, Hebrew University Jerusalem, Jerusalem, Israel, 91120 ⁴Baruch Ivcher Institute for Brain, Cognition & Technology, Baruch Ivcher School of Psychology, Reichman University, Interdisciplinary Center Herzliya, Herzliya, Israel, 461010

Motor actions, such as reaching or grasping, can be decoded from fMRI activity of early visual cortex (EVC) in sighted humans. This effect can depend on vision or visual imagery, or alternatively, could be driven by mechanisms independent of visual experience. Here, we show that the actions of reaching in different directions can be reliably decoded from fMRI activity of EVC in congenitally blind humans (both sexes). Thus, neither visual experience nor visual imagery is necessary for EVC to represent action-related information. We also demonstrate that, within EVC of blind humans, the accuracy of reach direction decoding is highest in areas typically representing foveal vision and gradually decreases in areas typically representing peripheral vision. We propose that this might indicate the existence of a predictive, hard-wired mechanism of aligning action and visual spaces. This mechanism might send action-related information primarily to the high-resolution foveal visual areas, which are critical for guiding and online correction of motor actions. Finally, we show that, beyond EVC, the decoding of reach direction in blind humans is most accurate in dorsal stream areas known to be critical for visuo-spatial and visuo-motor integration in the sighted. Thus, these areas can develop space and action representations even in the lifelong absence of vision. Overall, our findings in

congenitally blind humans match previous research on the action system in the sighted, and suggest that the development of action representations in the human brain might be largely independent of visual experience.

The Journal of Neuroscience, November 15, 2023 • 43(46):7868–7878

NEUROBIOLOGY OF DISEASE

Dissociable Effects of Alzheimer's Disease-Related Cognitive Dysfunction and Aging on Functional Brain Network Segregation

Ziwei Zhang,¹ Micaela Y. Chan,¹ Liang Han,¹ Claudia A. Carreno,¹ Ezra Winter-Nelson,¹ and Gagan S. Wig^{1,2}, for the Alzheimer's Disease Neuroimaging Initiative (ADNI)

¹Center for Vital Longevity and School of Behavioral and Brain Sciences, University of Texas at Dallas, Dallas, Texas 75235 ²Department of Psychiatry, University of Texas Southwestern Medical Center, Dallas, Texas 75390

Alzheimer's disease (AD) is associated with changes in large-scale functional brain network organization. Individuals with AD exhibit less segregated resting-state brain networks compared with individuals without dementia. However, declines in brain network segregation are also evident as adult individuals grow older. Determining whether these observations reflect unique or overlapping alterations on the functional connectome of the brain is essential for understanding the impact of AD on network organization and incorporating measures of functional brain network organization toward AD characterization. Relationships between AD dementia severity and participant's age on resting-state brain system segregation were examined in 326 cognitively healthy and 275 cognitively impaired human individuals recruited through the Alzheimer's Disease Neuroimaging Initiative (ADNI) ($N = 601$; age range, 55–96 years; 320 females). Greater dementia severity and increasing age were independently associated with lower brain system segregation. Further, dementia versus age relationships with brain network organization varied according to the processing roles of brain systems and types of network interactions. Aging was associated with alterations to association systems, primarily among within-system relationships. Conversely, dementia severity was associated with alterations that included both association systems and sensory-motor systems and was most prominent among cross-system interactions. Dementia-related network alterations were evident regardless of the presence of cortical amyloid burden, revealing that the measures of functional network organization are unique from this marker of AD-related pathology. Collectively, these observations demonstrate the specific and widespread alterations in the topological organization of large-scale brain networks that accompany AD and highlight functionally dissociable brain network vulnerabilities associated with AD-related cognitive dysfunction versus aging.

The Journal of Neuroscience, November 15, 2023 • 43(46):7879–7892