Embargoed until Oct. 20, 10:30 a.m. CST
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Exploring the Role of Synapses and Neural Networks in Brain Health

Studies show how malfunctioning synapses may contribute to certain brain diseases

CHICAGO — Research released today demonstrates the importance of healthy neural networks for normal behavior and how malfunctioning synapses — the sites where neurons connect and communicate — may contribute to brain disorders. The findings were presented at Neuroscience 2015, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Today's new findings show that:

- Experiments in a mouse model of schizophrenia suggest that the breakdown of coordinated activity between groups of neurons may underlie psychosis (Jordan Hamm, abstract 282.02, see attached summary).
- Disrupted synaptic communication in rats follows accumulation of a lesser-known neurotoxic protein that might contribute to Alzheimer's disease pathology (Paula Pousinha, abstract 131.01, see attached summary).
- Lifelong memories may be stored in the structure of the perineuronal net, a mesh of stable proteins that encapsulates neurons (Sakhina Palida, abstract 391.04, see attached summary).
- Key support protein guides the formation of synapses at inhibitory neurons, which are necessary for normal social behavior in mice (Shawn Tan, abstract 572.15, see attached summary).

Other recent findings show that:

- Fingolimod, a drug already used for multiple sclerosis, improved performance on cognitive tests and preserved synaptic architecture in a mouse model of Huntington's disease, and further study will explore whether the drug might benefit Huntington's patients (Andrés Miguez, abstract 556.07, see attached summary).

"Synapses are the hubs of neuronal communication, and these findings demonstrate how even subtle disruptions at synapses lead to abnormal behaviors or disease states," said moderator Valina Dawson, PhD, director of the Neuroregeneration Program and co-director of the Stem Cell Program in the Institute for Cell Engineering at Johns Hopkins University. "The studies make strides toward understanding how synaptic health can improve brain health."

This research was supported by national funding agencies such as the National Institutes of Health, as well as private and philanthropic organizations. Find out more about synapses and neurological disorders at *BrainFacts.org*.

Related Neuroscience 2015 Presentations:

Presidential Special Lecture: The Molecular Logic of Neural Circuits: Implications for Autism and Schizophrenia
Sunday, Oct. 18, 5:15-6:25 p.m., Hall B1

Presidential Special Lecture: Immune Mechanisms of Synapse Loss in Health and Disease
Monday, Oct. 19, 5:15-6:25 p.m., Hall B1

Abstract 282.02 Summary

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Study Suggests Breakdown in Coordinated Neural Activity Underlies Psychosis

Researchers observe disorganized neural activity in a mouse model of schizophrenia

Using a mouse model of schizophrenia, researchers have identified what appear to be the neural underpinnings of the disordered perception and thought that typically accompany psychosis. The research was released today at Neuroscience 2015, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health. The finding is a key step toward developing targeted, effective treatments for psychotic disorders.

Schizophrenia is a disabling psychotic disorder that affects 1 to 2 percent of the population and is marked by perceptual distortions, hallucinations, and grossly disorganized thought. Psychosis is not limited to disease, however. "Psychotic states are somewhat common part of human experience, occurring as a consequence of drug use, anesthesia, or even sleep deprivation," said lead author Jordan Hamm, PhD, of Columbia University in New York. How the psychotic state arises in the brain is not well understood.

In the new study, researchers engineered transgenic mice to produce a calcium-sensitive protein in their brain cells. Then, they used calcium imaging — an indicator of neuronal firing — to watch the coordinated activity of about 120 neurons that comprise a small brain circuit in the primary visual cortex, an area disrupted in the schizophrenic brain. Mice were continuously treated for one week with ketamine, an anesthetic that produces psychotic-like changes in brain structure and behavior.

Hamm likens the coordinated activity of neurons in healthy mice to pixels on a television screen that form cohesive images by acting in concert. But after mice were treated with ketamine, "such patterns became disorganized, as though neurons were acting on their own rather than as a coherent group," Hamm said. "Imagine watching a television in which each pixel activates, but in which adjacent ones rarely cooperate together to form coherent, stable images."

Previous investigations of the brain activity underlying psychosis have mainly used brain imaging or have measured activity of individual neurons, which would miss the disruptions seen in the current study.

"Our findings support a novel model for linking disruptions in brain function to deviations in perception and thought seen in psychosis," Hamm said. In order to develop effective treatments, researchers must understand the precise alterations in brain activity underlying psychotic states, he added.

Research was supported with funds from the National Institute of Mental Health, the Brain and Behavior Research Foundation, the Department of Defense, and the Defense Advanced Research Projects Agency.

Scientific Presentation: Monday, Oct. 19, 8-10:45 a.m., S102

282.02, Fragmented cortical microcircuit motifs in an NMDAR-hypofunction mouse model support an attractor hypothesis of psychotic states.
***J. P. HAMM**, D. PETERKA, R. YUSTE; Columbia University, New York, NY

TECHNICAL ABSTRACT: At the microcircuit level, layer 2/3 neocortical neurons cooperate in distributed synchrony, forming recurrent patterns of activity which are the likely building blocks of perceptions or thought. Psychotic brain states, such as those experienced in schizophrenia (SZ) or some neurological syndromes (e.g. anti-NMDA-receptor encephalitis), may involve a critical disruption in the stability and reliability of these network activity patterns (i.e., motifs). Such a disruption could theoretically explain abnormalities in perception and thought characteristic to psychosis. Past work has only supported this hypothesis computationally, or has probed patterned network dynamics indirectly with electrophysiology (EEG, LFPs). Here we used two-photon calcium imaging to measure the simultaneous activity of 60-110+ cortical neurons in awake mice. We virally expressed calcium indicators (GCaMP6s/f) in primary visual cortex, a region with known functional and anatomical abnormalities in SZ as well as direct functional relevance for understanding psychosis phenomenology (e.g. visual hallucinations). We imaged populations at rest (no visual stimuli) and during the presentation of full-field moving square wave gratings (6 orientations, 12 directions) of 100 % contrast and .08 cycles per degree. We quantified single cell responses and network-level activity before and one week after continuous delivery of ketamine (KET), an NMDA-receptor antagonist previously demonstrated to recreate perceptual and cognitive symptomology of SZ in healthy humans as well as electrophysiological and anatomical biomarkers of SZ in rodents. Chronic KET increased ongoing activity and decreased orientation selectivity at the single neuron level, consistent with known abnormalities in cortical inhibitory interneurons identified in SZ brains post-mortem as well as after chronic KET in rodents. When network activity was considered en masse, population-level activity patterns became largely disorganized after KET, exhibiting diminished regularity across both periodic "upstates" during rest and in visually evoked brain states. Pairwise correlations between cells showed a shift toward intermediate values across the network (i.e. away from uncorrelated and highly correlated values). These changes were not accompanied with an increase in functional dimensionality (or number of activity states), suggesting an overall disorganization of cortical activity. These results suggest a shallowing of the basins of dynamical attractors in cortical microcircuits which could explain or contribute to disordered perception and cognition fundamental to psychotic pathology.

Abstract 131.01 Summary

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Lesser-Known Protein Fragment May Contribute to Alzheimer's Disease

Amyloid-beta is likely not the only culprit in disease pathology

A protein fragment called amyloid-beta (Aβ) is widely recognized as a toxic species that contributes to Alzheimer's disease pathology. But now French researchers have demonstrated in rats that another protein fragment called AICD may also cause Alzheimer's-associated damage, according to findings released today at Neuroscience 2015, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

"Identification of additional culprits participating in Alzheimer's disease-related neurotoxicity and memory loss could provide crucial new insights into disease mechanism and help design innovative therapies," said lead author Paula Pousinha, PhD, of CNRS in Valbonne, France.

Alzheimer's disease is a fatal neurodegenerative disorder that robs people of their cognitive abilities, particularly the ability to form new memories. There is no cure, and even palliative therapies are sorely lacking. Alzheimer's disease affects an estimated 5 million Americans.

A major hypothesis about how brain damage occurs in Alzheimer's disease revolves around Aβ, a toxic protein fragment that accumulates outside neurons and forms so-called senile plaques thought to disrupt neuronal signaling. Aβ is formed when amyloid precursor protein (APP) is enzymatically cut into several pieces. Though the extracellular Aβ fragment has been the center of attention, another fragment called APP intracellular domain (AICD) remains inside cells, with unknown consequences. Like Aβ, there is evidence that AICD accumulates in the brain in mouse models of the disease and in Alzheimer's disease patients.

To determine how AICD affects neurons, the researchers used a virus to increase production of AICD in the adult rat brain. They made electrophysiological recordings from individual pairs of neurons in the hippocampus, a brain area crucial to memory and affected early in Alzheimer's disease. The recordings showed that the neurons that contain more AICD failed to integrate incoming signals, Pousinha said, and they displayed impaired long-term potentiation, a main biological mechanism associated with memory formation at a cellular level. The defects could be rescued with pharmacological treatments that normalized activity of receptors found in synapses.

"Our results provide entirely novel evidence that increased *in vivo* production of AICD alone is enough to perturb synapse function in hippocampal neurons," Pousinha said. "These data suggest that, in addition to Aβ, AICD could also participate in the disruption of synaptic communication during the progression of Alzheimer's disease."

Research was supported with funds from ATIP/AVENIR program (CNRS), Fondation pour la Recherche Médicale, and French Fondation pour la Coopération Scientifique – Plan Alzheimer.

Scientific Presentation: Sunday, Oct. 18, 8-9 a.m., Hall A

131.01, Increased APP intracellular domain (AICD) production perturbs synaptic signal integration via increased NMDAR function
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TECHNICAL ABSTRACT: Alzheimer's disease (AD) is a neurodegenerative disease that begins as mild short-term memory deficits and culminates in total loss of cognition and executive functions. The main culprit of the disease, resulting from Amyloid-Precursor Protein (APP) processing, has been thought to be amyloid-b peptide (Ab). However, despite the genetic and cell biological evidence that supports the amyloid cascade hypothesis, it is becoming clear that AD etiology is complex and that Ab alone is unable to account for all aspects of AD [Pimplikar et al. J Neurosci.30: 14946. 2010]. Gamma-secretase not only liberates Ab, but also its C-terminal intracellular counterpart called APP intracellular domain (AICD) [Passer. et al. JAlzheimers Dis.2: 289-301. 2000], which is known to also accumulate in AD patient's brain [Ghosal et al. PNAS.106:18367. 2009], but surprisingly little is known about its functions in the hippocampus. To address this crucial issue, we increased AICD production in vivo in adult CA1 pyramidal neurons, mimicking the human pathological condition. Different ex-vivo electrophysiological and pharmacological approaches, including double- patch of neighbor neurons were used. We clearly demonstrate that in vivo AICD production increases synaptic NMDA receptor currents. This causes a frequency-dependent disruption of synaptic signal integration, leading to impaired long-term potentiation, which we were able to rescue by different pharmacological approaches. Our results provide convincing and entirely novel evidence that increased in vivo production of AICD is enough, per se, to cause synaptic dysfunction in CA1 hippocampal neurons.

Abstract 391.04 Summary

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Lifelong Memories May Be Stored in Structure Encapsulating Neurons

Research shows perineuronal net is made of stable proteins and would be ideal for encoding information

Scientists have long wondered how the human brain encodes memories that can last a lifetime. It turns out that the perineuronal net — a stable protein coating that encapsulates neurons — may have the capability to store long-term memories in its structure, according to an animal study released today at Neuroscience 2015, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

"Similar to the way that messages can be carved into stone for long-term preservation, we believe that the perineuronal net provides for stable encoding of information in the brain," said lead author Sakina Palida of the University of California, San Diego.

In order to understand memory encoding, researchers have mostly focused on synapses, the sites at which neurons connect and communicate with each other. But synaptic proteins only have a lifetime of a few weeks, so they would need to be faithfully recopied hundreds to thousands of times to store lifelong memories — an unlikely scenario. Instead, "We believe that the changes made in the brain to encode and store a memory must be as stable as the memory itself," Palida said.

The research team identified a viable candidate for such long-term storage in the perineuronal net, a stable extracellular structure made of protein and carbohydrates that wraps around neurons during brain development and then exhibits little to no turnover. The researchers developed a method to fluorescently label perineuronal net proteins in transgenic mice so that they could watch dynamic, activity-dependent structural changes in live brain cells. The imaging experiments revealed new details about the neuronal coating. For one thing, they showed that the perineuronal net encapsulates neurons throughout the entire brain, rather than in selected areas as was previously thought. They also showed how the nets change over time. "Perineuronal nets are eroded only when a synapse is strengthened, forming a hole at the growing synapse," Palida said. The researchers hypothesize that these synapse-associated holes somehow encode lifelong memories.

"Our results thus far suggest that the perineuronal net is a stable structure and an ideal substrate for encoding and storing memories in the brain over time," Palida said.

Research was supported with funds from the National Institute of Neurological Disorders and Stroke, the National Institute of General Medical Sciences, and the National Institute on Aging.

Scientific Presentation: Monday, Oct. 19, 4-5 p.m., Hall A

391.04, Visualizing structure and activity-dependent changes in the perineuronal net, a putative substrate for very long-term memory
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TECHNICAL ABSTRACT: Long-term memories can be encoded and maintained in the brain for up to a lifetime, however the molecular mechanisms responsible for such long-lasting information storage are not yet understood. While the majority of synaptic proteins undergo rapid synthesis and degradation, we believe that the molecular changes made to encode a highly stable memory must be equally stable and not as susceptible to metabolic turnover. We propose that very long-term memories are maintained in the pattern and size of holes formed in the perineuronal net (PNN), the highly stable extracellular structure that coats neurons in the brain. The PNN is essential for normal brain function and memory, restricts synapse formation in mature animals, and is locally eroded by enhanced protease secretion and activity at synapses when they strengthen. Here we characterize the structure of the PNN by examining the localization of individual carbohydrate and protein components around mature synapses in cultured neurons and whole brain slices. We additionally demonstrate that the PNN appears around neurons throughout the brain and is not restricted to parvalbumin-positive inhibitory neurons labeled with a traditional PNN marker, Wisteria floribunda agglutinin. Finally, we describe a new method for genetically encoding fluorescent reporters into the PNN, and use this method to track activity-dependent structural changes of PNN in live neurons over time. Our data demonstrate that the PNN, an extracellular structure that is stably altered at mature synapses, is an ideal candidate for long-term memory storage.

Abstract 572.15 Summary

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Mouse Study Reveals Importance of Inhibitory Neuron Development in Navigating Social Hierarchies

Brain-derived neurotrophic factor plays pivotal role

Navigating social hierarchies is among the most complex behaviors that mammals undertake, and researchers are working to understand the underlying brain activity behind it. New research shows that a specific protein plays a critical role in the development of inhibitory neurons required for normal social behavior in mice. The findings were released today at Neuroscience 2015, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Humans — and rodents — are very social animals. Our every interaction with other humans follows rules according to a social hierarchy, and failure to navigate that hierarchy can have far-reaching consequences. Social behavior is mediated by circuits made up of excitatory neurons, which ramp up activity, and inhibitory neurons, which quiet it. Excitatory and inhibitory neurons act in a coordinated and balanced fashion. Previous studies have shown that when that balance is disrupted in mice, so is the formation of social hierarchies among the animals.

Researchers in Singapore hypothesized that establishing the excitatory-inhibitory balance might depend on brain-derived neurotrophic factor (BDNF), a protein that is essential for guiding inhibitory neurons to form functional connections with other cells. Scientists engineered transgenic mice that lacked the receptor for BDNF, called tropomyosin receptor kinase B (TrkB), in a large population of inhibitory neurons found in the cortex. "TrkB knockout mice displayed intact sensory, motor, and cognitive abilities and were otherwise normal," lead author Shawn Tan said. "However, when we carried out behavioral tests for social dominance in group-housed males, we found that TrkB knockout mice were more dominant than wild-type mice."

The researchers' preliminary data suggests that the social hierarchy is less stable in groups of TrkB knockout mice. Normally, some mice play more dominant roles, while others are subservient, and peer-induced injuries are uncommon once social hierarchies are stabilized. Compared with control mice, TrkB knockout mice gave one another more injuries to the back and genitals, indicating that the hierarchy was disrupted. The researchers also found that the balance between excitation and inhibition in the prefrontal cortex (PFC), a key region of the brain that regulates social behavior, was altered in the TrkB knockout mice. "The findings shine new light on the biological factors molding our social relationships," Tan said.

Research was supported with funds from the Singapore Ministry of Education Academic Research Fund and the Duke-NUS Signature Research Program Block Grant.

Scientific Presentation: Tuesday, Oct. 20, 3-4 p.m., Hall A

572.15, Loss of brain-derived neurotrophic factor (BDNF) signalling in cortico-limbic interneurons contributes to synaptic imbalance and abnormal social behaviour in mice
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TECHNICAL ABSTRACT: The execution of complex behavior is dependent on the establishment of a tight balance between inhibition and excitation in cortico-limbic circuits of the mammalian brain. Developmental disruptions to either component have been implicated in neuropsychiatric disorders. BDNF is an important trophic factor for the developmental maturation of inhibitory neurons and their synaptic transmission. Due to the lack of genetic knockout mouse models, behavioral consequences of impaired BDNF signaling in cortico-limbic inhibitory neurons have not been elucidated. Therefore, we generated conditional knockout mice in which tropomyosin receptor kinase B (TrkB), the cognate receptor for BDNF, is ablated from a subset of cortico-limbic interneurons. Although their motor coordination and movement were not impaired, these mice exhibited abnormal social behavior. Furthermore, electrophysiological analysis revealed an imbalance between excitatory and inhibitory neurotransmission within layer V local microcircuit of the prelimbic area in these mice. Taken together our results suggest a critical role of cortico-limbic interneuron BDNF-TrkB signaling in complex social behavior. Disruptions to this pathway may underlie some of the abnormal behavior present in neuropsychiatric disorders.

Speaker 556.07 Summary

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Multiple Sclerosis Drug Improves Brain Health, Behavior in Mouse Model of Huntington's Disease

Nanosymposium: Huntington's Disease Mechanisms II

Tuesday, Oct. 20, 1–4:15 p.m., Room N462A

Our research indicates that the drug Fingolimod, currently used to treat multiple sclerosis patients, could provide cognitive benefits in Huntington's disease.

Cognitive deficits, such as impaired concentration, reasoning, learning and memory, have been described in a number of brain disorders, including Huntington's disease. This inherited disease is caused by a mutation in the gene that codifies the protein huntingtin, provoking uncontrolled movements, as well as psychiatric and cognitive disturbances. Huntington's disease is a progressive neurodegenerative disorder usually manifested in early to middle adulthood and estimated to affect between 5 and 7 subjects out of 100000 in western countries. Up to date, medications cannot prevent the severe physical and mental decline experienced by patients, whose life expectancy is barely 15-20 years after the first symptoms begin. Remarkably, cognitive problems appear 10-15 years before the onset of motor dysfunction, and are one of the most distressing aspects of the disease for sufferers and their families. Bearing this in mind, our aim was to test the therapeutic potential of Fingolimod to improve cognitive function in Huntington's disease.

In order to reliably address the utility of Fingolimod chronic treatment in a preclinical model, the drug was administered to mice with Huntington's disease during 3 months, starting at pre-symptomatic stages. We combined behavioral, histological and biochemical analysis to assess Fingolimod effects on long-term memory and structural synaptic plasticity. Importantly, we found that Huntington's disease mice treated with Fingolimod performed better on memory tests, including spatial and object recognition tasks. These behavioral observations correlated with remarkable effects of the drug at the cellular level within the mouse hippocampus, a brain region that plays a crucial role in the acquisition, storage and retrieval of information. In particular, Fingolimod attenuated neuroinflammation and helped neurons preserve their dendritic spines, which are small protrusions that establish synaptic connections with other neurons, contributing to learning and memory function.

We associate these therapeutic effects of Fingolimod mainly to its action on BDNF (brain derived neurotrophic factor) signaling pathway, a key player in the modulation of synaptic plasticity, learning and memory. Notably, previous work from our research group, in both patients and animals with Huntington's disease, linked cognitive and synaptic deficits to an imbalance in levels of the BDNF receptors. Now we show that restoring BDNF receptors balance with Fingolimod is a promising strategy for treating cognitive impairment in this devastating disorder.

Given the safety profile of the compound, and the fact that it can also rescue motor deficits in Huntington's disease mice, our study suggests that Fingolimod may be an effective drug to treat Huntington's disease patients. Therefore, the next step of this research is to delve deeper into the underlying mechanisms of action of the drug and to carry out clinical trials in the mid-term.

In light of our findings, Fingolimod could potentially improve learning and memory in people who have other neurological disorders affecting the hippocampus, such as Alzheimer's disease. Furthermore, our results point to a possible contribution of the drug to the enhancement of cognitive function in multiple sclerosis patients, an issue that is currently under investigation.

Research was supported with funds from IDIBAPS Postdoctoral Fellowship-BIOTRACK supported by the European Community's Seventh Framework Program, Spanish Ministry of Economy and Competitiveness (MINECO), ISCIII-Subdirección General de Evaluación and European Regional Development Fund (RETICS and CIBERNED), and the CHDI Foundation (USA).