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Research Reveals New Insights Into the Aging Brain

From genes to circuits: factors that influence cognitive decline

CHICAGO — Research released today provides valuable new insights into how the brain ages. From genes to proteins, from cells to circuits, subtle deficits can lead to declines in cognitive abilities. 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.

While Alzheimer's disease and other age-related brain disorders lead to major neural deficits, brain function also declines in healthy aging adults. Understanding both pathological and "normal" age-related brain changes will aid researchers in developing therapies and preventive measures against cognitive declines in the world's rapidly aging population.

Today's new findings show that:

- Bone marrow transplants from young mice improve age-related declines in brain structure and function in older mice (Melanie Das, abstract 370.03 see attached summary).
- In aged rats, a brain area that regulates emotion and decision-making demonstrates enhanced responses to unexpected reward (Rachel Samson, abstract 179.03, see attached summary).
- Measurements of electromagnetic activity in the human brain suggest that network connectivity changes with age and this influences cognitive performance (Matthias Treder, abstract 401.04, see attached summary).
- Newly identified genes in mice may underlie cognitive decline in both Alzheimer's disease-affected brains and normal aging brains (Catherine Kaczorowski, abstract 377.06, see attached summary).

"Today, the global population is aging at a rate unprecedented in history, and researchers are desperately working to find ways to minimize the impact of age-related declines in brain function," said moderator Carol Barnes, PhD, director of the Evelyn F. McKnight Institute at the University of Arizona and a leader in the field of aging research. "The research presented today takes major steps toward understanding the blood-born factors, genes, and circuits within the brain that influence cognition in aging and provides the foundation for future treatments and preventive measures aimed at protecting brain function late in life." Barnes is also an author of one of the presented studies (abstract 179.03).

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 information about the aging brain at *BrainFacts.org*.

Related Neuroscience 2015 Presentation:
Symposium: Identifying and Manipulating the Synapses, Cells, and Circuits of Memory Engrams: Implications for Memory and Memory Disorders
Sunday, Oct. 18, 8:30-11 a.m., S100A

Abstract 370.03 Summary

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Bone Marrow From Young Mice Rejuvenates Old Mice

Bone marrow transplant protects mouse brain, improves cognitive function

Bone marrow from young mice improves age-related declines in brain structure and function in older mice, according to research 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. Aged mice that received a bone-marrow transplant from young mice had less deterioration in brain structure and performed better on cognitive tests compared with mice that didn't receive the transplant. The new research supports the idea that young blood cells can protect the aging brain.

Cognitive decline is a normal part of aging, and severe cognitive impairment is the primary component of Alzheimer's disease, which is present in about 50 percent of the population over age 85 in the U.S. As humans live longer and the elderly make up a larger portion of the world population, it is crucial to find therapeutic options to delay or lessen age-associated cognitive dysfunction.

Previous research by other groups demonstrated that cognitive performance improved in aged mice when they received a transfusion of young blood. In those experiments, a young and an old mouse were temporarily surgically conjoined, allowing the mice to share a circulatory system. Scientists have identified some restorative factors in the blood — such as GDF11, a protein that stimulates the growth of neural stem cells in the aging brain — but how they work to protect cells in the brain remains unknown.

In the new study, the researchers extracted bone marrow from young mice, which contains hematopoietic cells — cells that have the capacity to become any type of blood cell and provide a continuous source of new blood cells throughout life. They transplanted the hematopoietic cells into aged mice, a treatment commonly used for leukemia patients. "While physical activity levels in mice drastically declined with age, old mice receiving young bone marrow were much more active than their age-matched counterparts," said lead author Melanie Das, PhD, of Cedars-Sinai Medical Center. Mice that received the transplant also performed better on a series of tests of spatial and working memory, and compared to control mice without the transplant, they had less brain shrinkage in the cortex and hippocampus, brain areas that normally thin with age.

Major hurdles must be addressed before the strategy can be considered in humans. For example, bone marrow transplantation requires complete irradiation of the recipient's existing immune system — a risky procedure at any age, but particularly hard on elderly patients. "Another obstacle in using bone marrow transplantation in patients is the need for a continuous, expandable source of hematopoietic cells," Das added. Nevertheless, she said, "Our findings suggest that there may be a therapeutic potential for one day using young hematopoietic cells in staving off age-related cognitive decline," Das said.

Research was supported with funds from the Board of Governors Regenerative Medicine Institute at the Cedars-Sinai Medical Center.

Scientific Presentation: Monday, Oct. 19, 1-3:45 p.m., N462A

370.03, Hematopoietic cell rejuvenation delays age-related cognitive decline
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TECHNICAL ABSTRACT: Aging is the number one risk factor for neurodegenerative diseases and age-associated conditions are projected to represent over half the global disease burden by the year 2030. Thus, it is imperative to identify therapeutic strategies for age-associated deterioration in order to promote healthy aging in the elderly population. A series of aging studies using heterochronic parabiosis, in which an old and young mouse are surgically conjoined temporarily allowing them to share a circulatory system, demonstrated that tissue in aged mice is rejuvenated by young blood. The brains of old mice receiving young blood showed increased neurogenesis, cognitive function and synaptic connections. While some blood-borne factors have been identified that could contribute to these effects, cell-based mechanisms have yet to be identified. By transplanting young bone marrow into old mice we have developed a novel model to test whether rejuvenation of hematopoietic cells can delay aging in the nervous system. We found significant improvements in overall activity and lifespan in old mice receiving young bone marrow compared to age-matched controls. Further, old mice receiving young bone marrow showed drastic improvement in the Y-maze compared to old controls, suggesting a role for hematopoietic cells in modulating cognitive decline in old age. Old mice with young bone marrow also showed increased hippocampal volume and cortical thickness compared to old controls, both regions of the brain that normally atrophy in aging. Additionally, activated macrophages and inflammatory cytokines are reduced in number in the hippocampus and the presence of senescent cells is significantly reduced in old mice receiving bone marrow compared to old controls. This work indicates that young hematopoetic cells can directly contribute to the rejuvenation of the aging brain.

Abstract 179.03 Summary

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Risk-Taking Declines With Age, but Reward Responses Not Dampened in Older Rats

Aged rats show enhanced activity in brain area associated with emotion, decision-making

As we age, we tend to make less-risky choices when choosing between a certain outcome and an uncertain outcome, such as a guaranteed small reward and the uncertain chance of a larger reward. However, researchers at the University of Arizona found that while older rats were more risk-averse, they had enhanced — not reduced — activity in an area of the brain involved in emotion and decision-making. They speculate that the behavioral change might instead arise from compromised connections between this brain area and other areas. 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.

In the study, the researchers presented aged and young rats with a choice of two levers: pressing one lever guaranteed a small food reward, whereas pressing the other held an uncertain chance of winning a larger reward. Compared to young rats, the older rats more often chose the sure bet, demonstrating that the older rats were more risk-averse.

During the task, the researchers made electrophysiological recordings from individual neurons in the basolateral amygdala (BLA), a brain area associated with emotion and decision-making. They recorded from more than 10,000 neurons in 13 rats — a technologically daunting feat. In general, BLA neurons in aged rats fired at higher frequencies than did young rats' neurons. Unexpectedly, the researchers found that BLA neuron firing in aged rats was particularly heightened compared to young rats when they received a large reward. "This exaggerated effect on neuronal firing rates in old rats when they receive an unexpected large reward suggests preserved if not enhanced responsiveness to reward in the BLA," said lead author Rachel Samson, PhD. This was the first study to measure the impact of aging on BLA neuron activity during such a task.

The researchers speculate that the age-related decline in risk-taking is not due to a deficit in the BLA. "The current data points to age-related changes in connectivity between structures involved in reward and decision-making as a probable cause for differences in risk attitudes in aged rats and older adults," Samson said. Another brain area critical to decision-making and heavily affected by aging is the nucleus accumbens (NA). The researchers hypothesize that connections between the BLA and the NA might be compromised with age, which could contribute to risk aversion. In future studies, they plan to address that possibility by simultaneously recording activity from neurons in the BLA and the NA.

Research was supported with funds from the McKnight Brain Research Foundation, the National Institute on Aging, and the Canadian Institutes for Health Research.

Scientific Presentation: Sunday, Oct. 18, 10-11 a.m., Hall A

179.03, Enhanced single unit firing to unexpected large rewards in aged amygdala neurons
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TECHNICAL ABSTRACT: With aging, changes in emotional regulation can lead to biases in decision making towards certain or safe options. In fact, we found that aged rats are more risk averse and will more readily select a small certain reward over a larger probabilistic one. The activity of neurons in the basolateral complex of the amygdala (BLA) was examined in young and aged rats during rest and while acquiring and performing a probabilistic decision making task. The greatest modulation in firing rate occurred following reward, with the largest change occurring after uncertain large rewards, a modest change in firing rate following small/certain rewards and no change when rewards were not delivered. When all neurons that fired at or above 0.1 Hz were analyzed, the variability and amplitude of change following rewards was much larger in old than in young rats. When neurons with a firing rate below 1Hz were excluded from analysis in both age groups, the young and aged rats did not differ in the amplitude of change of their firing rates in response to uncertain/large rewards. To better characterize how BLA neurons change their firing rate to uncertain rewards, BLA cells were separated into four categories: regular, irregular, irregular/bursty and bursty, based on their local variance, which is a measure of the variability between adjacent inter-spike intervals (ISI). Regular firing neurons accounted for only 1-2% of the 10,000 BLA neurons recorded, and had high firing rates at rest, which were reduced following reward delivery in aged rats. In contrast, irregular neurons accounted 20% of the BLA neural population, and showed the greatest increase in firing rate following large rewards, in both age groups. The vast majority of neurons (60%) had a local variance around 1.5 and an ISI distribution indicating that these cells alternated between irregular and burst firing modes. Following rewards, some of these cells displayed increases and others decreases in firing rates. This effect was consistent across age groups. Finally, bursty neurons accounted for the remaining 20% of the BLA population and only in aged rats did these cells show an increase in firing rate following uncertain/large reward delivery. Thus the change in firing rates of BLA neurons to unexpected rewards appears to be mediated by neurons from all categories, but aging appears to selectively impact low firing rate BLA neurons in a way that allows the aged network to be more responsive to rewards. This effect may contribute to the age-related increases in risk aversion found during probabilistic decision making tasks.

Abstract 401.04 Summary

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Network Connectivity Changes May Underlie Cognitive Decline in Aging

New measurements of brain's electromagnetic activity reveal altered connectivity

The cognitive decline that comes with aging is due to physiological changes in the brain, but scientists are still working to understand those changes. Researchers have now measured the brain's electromagnetic activity to show that connectivity between brain areas changes with age and this influences cognitive performance. 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.

Scientists had previously suspected that changes in brain network connectivity were to blame for age-related cognitive decline, but most studies of neural connectivity have used functional magnetic resonance imaging (fMRI), which measures blood flow as an indicator of brain activity. However, since blood flow also changes with age, fMRI can make it more difficult to separate age-related changes in blood flow from the true brain changes in aging. To more directly measure neural activity, University of Cambridge researchers used magnetoencephalography (MEG), a technique that does not rely on blood flow but rather detects the coordinated electromagnetic activity of groups of brain cells — a direct indicator of neural activity. "Using this particular type of MEG measurement, we can infer connectivity between two regions in the brain by looking at the information shared in their electrical activity" said lead author Matthias Treder, PhD.

In the study, the researchers performed MEG on 520 adults, aged 18 to 88, in the resting state — that is, when subjects were not engaged in a particular task. During a separate session, the researchers presented subjects with a series of cognitive tests designed to measure variables such as fluid intelligence and multitasking ability. Using sophisticated statistical techniques, the researchers related the connectivity measurements to changes in cognitive ability in the aging brain. "Here, we show for the first time that age-related networks of electromagnetic neural activity are important to maintain cognitive function in old age," Treder said.

The researchers next plan to investigate how brain network activity gives rise to cognitive performance and how demographic factors such as education level influence brain network activity. Eventually, the researchers hope to identify mental or physical exercise interventions that might optimize network activity and cognitive performance.

Research was supported with funds from the Biotechnology and Biological Sciences Research Council.

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

401.04, Life-span changes in resting state networks using magnetoencephalography: a PLS regression analysis
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TECHNICAL ABSTRACT: Healthy ageing has been associated with decreased specialization in brain function. Such characterization has focused largely on describing age-dependent differences in the connectivity between intrinsically coupled brain areas of the resting brain, i.e. resting state networks. The majority of findings, however, are based on functional magnetic resonance imaging (fMRI), which estimates neural connectivity indirectly through temporally correlated changes in blood oxygenation levels. Thus, previous assessment of the ageing effects on network connectivity could be sensitive to differences in vascular function. In the current study we characterized age-dependent resting state networks using magnetoencephalography (MEG), which provides a more direct measure of neural activity with greater temporal resolution. To this end, we investigated resting state MEG scans of 520 subjects (aged 18-88) from the Cambridge Center for Ageing and Cognition (www.cam-can.org, Cam-CAN) cohort. We used minimum-norm estimates (MNE) to calculate time dependent activity at 6000 locations on the cortical surface, which were subsequently morphed onto a common average brain. For the connectivity analysis in six standard frequency bands we first performed a regression-based orthogonalization of the complex wavelet time series to counteract field spread. Then, we calculated the envelopes of the time series and we determined the envelope correlation matrix. The vectorized correlation matrices were used as predictors of age and cognitive variables in a partial least squares (PLS) regression model. We found that changes in network structure in alpha and beta bands predicted the age of participants, with cross-validated r-values of 0.5 and 0.3, respectively. These results indicate that the observed cognitive decline in ageing is linked to the factors we identified in the electrophysiological signature of the resting state network as it changes across the lifespan.

Abstract 377.06 Summary

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Common Genes May Contribute to Alzheimer's Disease, Normal Aging

Study in genetically diverse mice reveals gene candidates

Cognitive deficits are a defining feature of Alzheimer's disease, but similar failings can occur as part of the normal aging process. Research in mice now suggests that brain changes in Alzheimer's and normal aging might share common genetic roots. By identifying those roots, scientists hope they might one day be able to identify, monitor, and treat people at high risk for Alzheimer's disease and cognitive decline, even before symptoms arise. 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.

Most studies in mice focus on a single genetic strain of animals that are not representative of other mouse strains, much less the human population. To get a picture of what genes might be involved in age- and Alzheimer's-related memory decline, the researchers studied a large "family" made up of 15 genetically diverse strains of mice. They gave middle-aged mice a standard memory test. When they compared the memory test results across the population of mouse strains to differences in the genetic sequence of these strains, the scientists identified a region on chromosome 4 with high genetic sequence variability across the mouse population — that is, the genes located in this region differed in sequence from one strain to another — and these sequence differences likely influenced the animals' memory capabilities.

Honing in on the region, a particular gene stood out as a candidate that might influence age-related memory. The gene, called heterochromatin protein 1 binding protein 3 (*Hp1bp3*), codes for the protein HP1BP3, which was associated with memory. Mice that lose functional HP1BP3 protein have severe memory deficits, and in aged mice, the protein accumulates in the hippocampus, a brain area critical to memory. Other research shows that the HP1BP3 protein is elevated in brains of Alzheimer's disease mouse models. Together, the results suggest that this gene plays an important role in memory, but that too much of its protein product may be a bad thing.

The *Hp1bp3* gene could influence cognitive decline through its regulation of many other genes. "The HP1BP3 protein is known to help control the structure of folded DNA, called chromatin, and can regulate the extent to which certain genes are expressed," said senior author Catherine Kaczorowski, PhD, of University of Tennessee Health Sciences Center. The researchers identified a gene that may be regulated by HP1BP3, called *Wdfy3*, which helps clear misfolded proteins from cells. The buildup of misfolded proteins can lead to cell dysfunction and is thought to contribute to Alzheimer's pathology.

In collaboration with the Translational Genetics Research Institute in Phoenix, they also investigated *Wdfy3* sequence variation in a diverse human population, some of whom had Alzheimer's disease. They identified specific mutations in Wdfy3 that were associated with the pathological markers for Alzheimer's disease. They also found differences in the levels of WDFY3 protein were linked to cognitive decline in normal aging mice. "We believe that these genes likely play a role in both normal aging and disease," Kaczorowski said.

"The identification of genetic differences, including gene mutations, that influence a person's likelihood of developing Alzheimer's or cognitive deficits will not only contribute to understanding pathways involved in disease progression, but also help to develop new ways to identify at-risk patients and enable more effective treatments," Kaczorowski said.

Research was supported with funds from the National Institute on Aging and the American Federation for Aging Research.

Scientific Presentation: Monday, Oct. 19, 1-4:15 p.m., N228

377.06, Systems genetics of 'normal' aging identifies novel candidates misregulated in Alzheimer's disease
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TECHNICAL ABSTRACT: 'Normal' age-associated cognitive decline is generally less severe than that seen in pathological dementias such as Alzheimer's disease (AD), and occurs in the absence of gross neuropathological changes. However, we recently identified several candidates that are known to confer risk for AD (*Trem2 & Inpp5d*) as significantly associated with memory status in a 'normal' aging murine genetic reference group (BXD panel). This led to the hypothesis that common

mechanisms underlie both ‘normal’ aging and AD-related memory deficits. Using standard contextual fear conditioning, we obtained an average memory index for each of 15 aging BXD strains tested (age=14±0.7mo). Memory index varied across the population (range=0-61.4% freezing during memory test) and genetic interval mapping identified an area on chromosome 4 that suggestively modulates memory function during aging. Heterochromatin protein 1 binding protein 3 (*Hp1bp3*) was identified as a top candidate responsible for aging- and AD-related memory decline given that: 1) age-matched BXD hippocampal transcript data identified *Hp1bp3* as *cis*-regulated, 2) HP1BP3 protein is enriched in the hippocampus of aging impaired mice, 3) disruption of *Hp1bp3* in *Hp1bp3*$^{-/-}$ mice disrupts hippocampus-dependent working memory function as measured on the T-maze test of spontaneous alternation [WT=91 ± 4%, KO= 49 ± 7%, t(12)=5.095, p<.001)], 4) *HP1BP3* transcript is enriched in the hippocampus of human AD patients as compared to age-matched non-demented controls, and 5) *Hp1bp3* is known to directly interact with amyloid precursor protein (APP), a well-known gene product harboring causal mutations linked to overproduction of Aβ and AD. Our systems genetics approach allowed for the identification of expression QTLs (eQTLs) that mapped to the *Hp1bp3* locus. One such eQTL was *Wdfy3*, an autophagy protein found to be enriched in impaired murine hippocampal proteome and human AD hippocampal transcriptome. Utilization of existing GWAS data confirmed *WDFY3* is nominally significantly associated with late-onset AD across a diverse human population. As dysfunction in autophagic processes has been linked to memory decline in both aging and AD, we provide a functional link between *Hp1bp3*, its downstream effector *Wdyfy3*, and memory deficits in both conditions. These genes and additional candidates identified via our systems genetics approach will be combined with multi-layered omics data in order to create network models that better predict and understand the common mechanisms underlying memory decline in both ‘normal’ aging and AD.