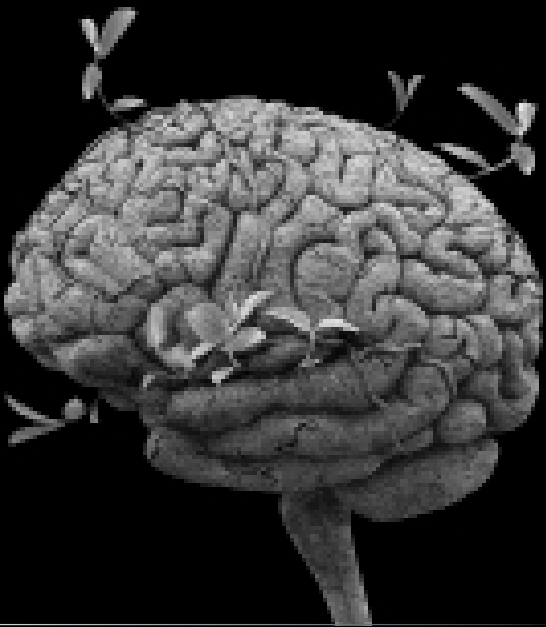
WAYNE STATE UNIVERSITY
Institute of Gerontology

Life-Span Plasticity of Brain and Behavior: A Cognitive Neuroscience Perspective



Margret M. and Paul B. Baltes Foundation International Conference

2011

The mission of the *Margret and Paul Baltes Foundation* is to advance research in developmental psychology and gerontology and to uphold its role in society. Drs. Margret and Paul Baltes were renowned German researchers and pioneers in many areas of modern gerontology. In addition to his illustrious research career, Paul Baltes made a unique contribution to promoting international scientific collaboration as the founding director of Germany's International Max Planck Research Network on Aging. His award-winning research and teaching focused on determining cognitive potential at various ages, the effects of cognitive training, reasons for functional loss, and the link between behavior, brain structure and society. Dr. Margret Baltes was a trail-blazing researcher in psychological gerontology who counted among her important contributions some of the first studies validating psychological methods for diagnosis of dementia.

Thursday, October 13, 2011

8:30 Welcome
Hilary H. Ratner
Vice-President for Research, Wayne State University

8:40 Opening remarks
Boris Baltes, M and P Baltes Foundation and
Department of Psychology, Wayne State University

9:00 Keynote presentation
Gerd Kempermann, Dresden,
Adult Hippocampal Neurogenesis: Activity-dependent Regulation and Functional Relevance

10:00 - 10:15 Coffee break

Session I:
Plasticity in the Context of Brain Maturation and Development

10:15 Silvia Bunge, University of California-Berkeley,
Brain Development and Plasticity Supporting High-Level Cognition

10:45 B.J. Casey, Cornell University Weill College of Medicine,
Nonlinear Neurobehavioral Changes During the Transition Into and Out of Adolescence

11:15 Noa Ofen, Wayne State University,
The Development of Memory Systems in the Brain

11:45 Brigitte Röder, University of Hamburg,
Perceptual and Cognitive Development and Plasticity

12:15 Moriah Thomason, Wayne State University,
Plasticity of Brain and Behavior in Infancy and Early Childhood

12:45 - 14:45 Lunch

14:45 ***Session II: Brain Aging and Constraints on Plasticity***

Lars Bäckman, Karolinska Institutet, Stockholm / Max Planck Institute for Human Development, Berlin,
Neurotransmitter Imaging, Functional Brain Sequelae of Cognitive Training.

15:15 Naftali Raz, Wayne State University,
Trajectories of Brain Aging, their Modifiers, and Cognitive Correlates.

15:45 Coffee Break

16:00 Denise C. Park, University of Texas at Dallas,
Constraints on Plasticity: Surprising Relationships between Neural Degradation and Cognitive Aging

16:30 Shu-Chen Li, Max Planck Institute for Human Development, Berlin,
Dopamine's Computational Roles in Regulating Processing Fluctuation and Plasticity

17:00 - 18:00 Moderated Discussion
Mod: Patricia Reuter-Lorenz, University of Michigan

Friday, October 14, 2011

Session III: Cognitive Plasticity and the Brain in Normal and Abnormal Development

9:00 Claudia Voelcker-Rehage, Jacobs University, Bremen,
Cognitive Plasticity in Older Adults: The Effect of Physical Activity on Brain Functioning

9:30 Bogdan Draganski, LREN, Département des Neurosciences Cliniques, CHUV, Université de Lausanne, Switzerland and Max Planck Institute for Cognitive Neuroscience, Leipzig, Germany,
Computational Anatomy and Structural Brain Plasticity - Where Are We Now and Where Do We Want to Go?

10:00 Coffee break

10:45 John Hannigan, Wayne State University,
Teratological Constraints on Plasticity

11:15 Yee Lee Shing, Max Planck Institute for Human Development and Humboldt University, Berlin,
The Development of Episodic Memory Across the Lifespan

11:45 Diane Chugani, Wayne State University,
Role of Serotonin in Synaptic Plasticity: Relevance to Treatment of Autism

12:15 - 13:45 Lunch

Session IV:
Aging and Modification of Brain and Behavior

14:00 Martin Lövdén, Karolinska Institutet,
Spatial Navigation Experience Shapes Adult Development of Brain Structure in Interaction with the Brain-Derived Neurotrophic Factor (BDNF) Gene

14:30 Scott D. Moffat, Wayne State University,
Cognitive and Neural Correlates of Cortisol Exposure in Human Aging

15:00 John Woodard, Wayne State University,
Using Functional Magnetic Resonance Imaging as a Biomarker of Cognitive Decline in Healthy Older Adults.

15:30 Coffee break

15:45 Cindy Lustig, University of Michigan,
Neuroimaging Application to Cognitive Training in Older Adults

16:15 - 17:30 Moderated Discussion.
Mod: Ulman Lindenberger, MPIB, Berlin

17:30 Closing remarks
Naftali Raz

Gerd Kempermann
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Adult Hippocampal Neurogenesis: Activity-dependent Regulation and Functional Relevance

Adult hippocampal neurogenesis lifelong produces low numbers of new granule cells that add to the mossy fiber connection between the dentate gyrus and CA3. The hypothesis is that new neurons are critical to the function of the dentate gyrus and several specific functions have been hypothesized. We follow the idea that the new neurons allow an activity-dependent optimization of the mossy fiber tract in order to cope with situations of novelty and complexity. The precursor cells that are stimulated by activity and training might build up a "neurogenic reserve" that allows flexible response to cognitive challenges in the course of life.

By now many studies have investigated the function of the hippocampus after adult neurogenesis had been suppressed or ablated. Gain-of-function experiments, in contrast, have been rare. Physical exercise and environmental enrichment both increase adult neurogenesis and are additive in their effect. However, despite similar end results they appear to have specific sub-effects on adult neurogenesis. Are these differences also found in behavioral tasks that assess neurogenesis-specific functions? We use a modification of the classic Morris water maze that allows the analysis of the strategies used by the mice to navigate to the hidden platform. Thereby we can ask how new neurons might increase cognitive flexibility during the acquisition and reversal period of the task. Are the results of the two gain-of-function paradigms complementary to the loss-of-function experiments? From the behavioral consequences of both positive and negative regulation of adult neurogenesis a first synthesis can be attempted of what the new neurons are good for.

One key consequence of the findings is that “regulation” by activity and “function” of the new neurons have to be regarded as connected.

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Brain Development and Plasticity Supporting High-Level Cognition

The capacity to reason with complex information and to solve novel problems, often referred to as fluid reasoning, is a central characteristic of human cognition. During childhood, the emerging capacity to reason supports learning across multiple domains. I will summarize briefly a series of neuroscientific studies involving young adults showing that a key component of fluid reasoning is the ability to jointly consider multiple relations between mental representations, or relational integration. I will then discuss the changes in brain structure and function that support reasoning development over childhood and adolescence. Finally, I will present evidence for improved reasoning ability after intensive training, both in children and in college students.

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Nonlinear Neurobehavioral Changes During the Transition Into and Out of Adolescence

Adolescence is a developmental period characterized by suboptimal decisions and actions. The traditional explanation of adolescent behavior has been suggested to be due to the protracted development of the prefrontal

cortex. Yet, this explanation fails to account for differences between children and adolescents, only adolescents relative to adults. We provide a model that takes into consideration the development of the prefrontal cortex together with subcortical limbic regions (e.g., nucleus accumbens & amygdala) involved in desire and emotionality to account for the nonlinear changes in behavior observed during adolescence, relative to childhood and adulthood. A biologically plausible conceptualization of the neural mechanisms underlying these nonlinear changes in behavior, as a heightened responsiveness to social cues while impulse control is still relatively immature during this period will be presented. Recent human imaging and animal studies will be described that provide a biological basis for this view, suggesting differential development of limbic systems relative to top-down control systems during adolescence relative to childhood and adulthood (imbalance model). This developmental pattern may be exacerbated in those adolescents with genetic or environmentally based predispositions that increase their risk for suboptimal regulation of behavior.

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The Development of Memory Systems in the Brain

Neuroimaging evidence implicates the involvement of regions in the prefrontal cortex (PFC), parietal cortex, and medial temporal lobes (MTL) in declarative memory processes in adults. There is limited evidence, however, as for the development of declarative memory systems in the brain. I will present data from a series of studies examining functional brain development of systems supporting memory encoding and retrieval. In all studies, memory accuracy increased with age. These age-related increases in memory accuracy were particularly robust for memory

that was rich in details, as assessed both by subjective and objective measures of memory quality. In all studies, brain activations associated with memory were found in MTL and PFC across all participants. Activations associated with encoding and retrieval of memories that were rich in contextual details increased with age in specific PFC, but not in MTL, regions. Memory-related activations in lateral parietal cortex during encoding and retrieval also increased with age. These results suggest that regions in the PFC and parietal cortex that are important for declarative memory processes have protracted developmental trajectory. Developmental effects in MTL regions are subtle and appear for more demanding memory tasks or memorization of more complex materials.

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Perceptual and Cognitive Development and Plasticity

Neural plasticity is related to compensatory plasticity and sensory recovery after visual deprivation in humans. The visual deprivation approach in humans allows investigating major principles of developmental plasticity. Electrophysiological and brainimaging studies in congenitally blind humans have provided evidence for a reorganization of both cortical regions associated with the intact modalities (intramodal plasticity), multisensory regions and brain areas predominantly associated with the deprived modality (intermodal plasticity). These changes have commonly been interpreted to contribute to compensatory performance improvements observed in this population. While a comparison of compensatory plasticity in congenitally and late blind adults reveals differences between developmental and adult plasticity, the investigation of people who had been totally blind for the first few months of their life (e.g. due to dense bilateral congenital cataracts) before their eyesight was restored

provides an opportunity to investigate critical periods for the recovery of both visual and multisensory functions. Results of recent studies suggest that these patients show impairments both in more complex visual tasks and no or limited multisensory capacities. These data suggest critical or sensitive periods for the development of more complex visual and multisensory functions requiring the binding of multiple features. It will be speculated how crossmodal compensatory plasticity in totally blind adults and functional recovery after sensory restoration might be linked.

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Spatial and Temporal Plasticity of Human Brain Networks in Development

Massive refinements in synaptic connections within and between neural circuits are believed to underlie significant gains in cognitive and affective ability observed in children across development. My work stems from an interest in determining how function across multiple, distributed brain networks impacts the individual developmental trajectories of children. How does the maturation of wide-scale brain neural networks coincide with the development of cognitive abilities in children? How does development proceed in a characteristically different fashion in children with early emotional psychopathology? How are these brain systems altered as the brain chemistry of children differs? In this talk, I will present novel methods for detecting and characterizing large-scale human brain networks. I will review cases where application of resting-state fMRI has already provided new insights into how human brain networks develop, mature, and get disrupted in psychiatric and neurological disorders. I will contrast resting-state fMRI with more conventional task-activation fMRI studies

and discuss how it is being paired to other imaging technologies. What I will cover in this talk will demonstrate the power of a distributed system-level understanding of brain function across the human lifespan, and will provide the first evidence of test-retest reliability in resting-state fMRI studies of children/young adolescents ages 9-15.

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Dopamine and Cognition: Aging-Related and General Influences

There are marked age-related losses of both pre- and post-synaptic markers of dopaminergic neurotransmission. Earlier work indicated that such losses are powerful mediators of age-related cognitive deficits (e.g., executive functions, speed, working and episodic memory). I will review current work on this theme focusing on (a) the relationship between dopamine (DA) and BOLD activity during working memory; (b) pharmacological simulation of cognitive aging by means of a DA antagonist; (c) release of DA during cognitive performance; (d) the links among different dopaminergic pathways; and (e) the role of DA in cognitive plasticity.

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The Course of Structural Brain Aging and its Modification by Vascular and Genetic Risk Factors

In vivo neuroimaging studies of healthy adults reveal differential shrinkage of the brain parenchyma and expansion of the ventricular system, with the tertiary

association (prefrontal and parietal) cortices, the neostriatum, and the cerebellum showing the greatest rate of shrinkage, and white matter evidencing a highly nonlinear life-span trajectory of volume change. The mechanisms of these changes are unclear but they undoubtedly reflect multiple physiological and pathological processes that increase and decrease brain volume. Such influences include apoptosis, demyelination, gliosis, and de novo neuro- and myelogenesis. In addition, vascular risk, exemplified by essential hypertension exacerbates regional brain shrinkage and proliferation of white matter damage in spite of relatively successful control by medication. Genetic variants that affect availability of key neurotransmitters and enzymes that control vascular and inflammatory processes also contribute to individual variability in brain aging. The shape of the resultant trajectory of change may be representative of a quasi-periodic function and it remains unclear what would be the optimal time window in which brain aging can be faithfully observed. Charting individual trajectories of age-related change is a challenging task but understanding of trailing-leading relationships between neural and cognitive variables may hold the key to expansion of the human health span.

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Constraints on Plasticity: Surprising Relationships between Neural Degradation and Cognitive Aging

The question addressed here is one posed by the Scaffolding Theory of Aging and Cognition (Park & Reuter-Lorenz, 2009). How do different measures of neural degradation affect cognitive aging? Is age-related cognitive decline mediated subtantially by amyloid deposition, white matter lesions, and hippocampal volume? Does increased frontal activation occur in

relation to these neural insults as the scaffolding model predicts? We have collected multiple measures of age-related degradation on a large, healthy life-span sample including measures of amyloid deposition, white matter hyperintensities, hippocampal and frontal volume. We present evidence outlining the relationship of these measures to functional brain activity and to cognition, addressing what factors most affect neural activity and cognitive function.

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Aging Neuronal Gain Control: Dopamine's Computational Roles in Regulating Processing Fluctuation and Plasticity

Mechanisms of neuronal gain control affect the stimulus-response transfer function of cortical neurons to regulate the signal-to-noise ratio of information transmission. Neuromodulation as well as other aspects of neural dynamics, such as synaptic noise, neuronal synchronization, and shunting inhibition, are different modes of neuronal gain control that may interact. By reviewing and reporting empirical evidence and formal theories, this presentation focuses on neuromodulation as one of the underlying mechanisms of Welford's (1958) neural noise hypothesis and Baltes' (1987) developmental reserve concept of aging. Modeling age-related decline in dopamine modulation by stochastically attenuating the gain control of neural networks results in greater random processing fluctuation, slower learning and more limited plasticity. These model-based predictions can, in part, be supported by recent results showing effects of dopamine relevant genes on processing fluctuation, learning, and memory plasticity.

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Cognitive Plasticity in Older Adults:
The Effect of Physical Activity on Brain Functioning

The importance of physical activity for improvement and preservation of cognitive abilities in old age has repeatedly been examined. It is unclear, however, whether different dimensions of fitness, i.e. physical and motor fitness are differentially associated with cognitive performance and brain activation patterns. Furthermore, studies that investigate the effects of different types of interventions and longer-term effects are missing. Besides this, it is well known that genetic predispositions might influence cognitive performance, particularly in older adults. Thus, we (1) analyzed the relationship between older adults' motor and physical fitness and their performance in cognitive functioning. (2) We performed a 12-month intervention study to investigate the effects of cardiovascular and coordination training (control group: relaxation and stretching) on cognition in older adults. (3) We analyzed the effect of COMT polymorphism on the relationship between fitness and cognition. Results revealed (1) that not only physical fitness, but also motor fitness showed a strong association with cognitive functioning. Functional brain imaging data revealed that physical and motor fitness were differentially related to cognitive processes. (2) Twelve months of cardiovascular or coordination training improved executive functioning but with differential effects on speed and accuracy. In parallel, neurophysiological results also revealed different changes (increases and reductions) in brain activity for both interventions in frontal, parietal, and sensorimotor cortical areas. And (3) hierarchical regression analyses revealed a positive influence of motor and physical fitness and of the interaction between motor/physical

fitness and COMT genotype on executive functioning. This relationship was particularly strong for the val/val carriers. Our data suggest that besides cardiovascular training also other types of physical activity improve cognition of older adults. The mechanisms, however, that underlie the performance changes seem to differ depending on the intervention and might be related to genetic polymorphisms.

Bogdan Draganski
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Computational Anatomy and Structural Brain Plasticity - Where Are We Now and Where Do We Want to Go?

In my talk, I will put emphasis on the necessity for a paradigm shift for studying structural brain plasticity and effects of ageing using computational anatomy. I will present recently developed quantitative magnetic resonance imaging techniques capturing in vivo tissue properties of the brain to further touch on novel methods for image processing and analysis allowing for accurate data handling and straightforward interpretation. Additionally, there will be a brief excursus in exploring anatomical connectivity features of the brain based on diffusion-weighted imaging.

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Experiential, Genetic and Epigenetic Effects on Human Neurocognitive Development

For several years we have employed psychophysics,

electrophysiological (ERP) and magnetic resonance imaging (MRI) techniques to study the development and plasticity of the human brain. We have studied deaf and blind individuals, people who learned their first or second spoken or signed language at different ages, and children of different ages and of different cognitive capabilities. Over the course of this research we have observed that different brain systems and related functions display markedly different degrees or 'profiles' of neuroplasticity. Some systems appear quite strongly determined and are not altered even when experience has been very different. Other systems are highly modifiable by experience and are dependent on experience but only during particular time periods ("sensitive periods"). There are several different sensitive periods, even within a domain of processing. A third 'plasticity profile' is demonstrated by those neural systems that remain capable of change by experience throughout life. We have also observed the two sides of plasticity in several domains of processing: i.e. systems that are most modifiable (i.e. display more neuroplasticity) display both more enhancements in the deaf and blind and greater vulnerability in those with or at risk for developmental disorders. Guided by these findings, we are conducting a program of research on the effects of different types of training on brain development and cognition in typically developing children of different ages. In one series of studies we are targeting the most changeable and vulnerable systems in 3-5 year old preschoolers (at-risk for school failure for reasons of poverty) whom we study before and after 8 weeks during which the children receive attention training and their parents receive training in parenting and attention skills once a week. Standardized measures of cognition and ERP measures of attention and language document large and significant effects of these different types of inputs on neurocognitive function. Genetic and Gene × Environment (training) interactions are also evident in these data. These studies will contribute to a basic understand-

ing of the nature and mechanisms of human brain plasticity. In addition, they can contribute information of practical significance in the design and implementation of educational programs.

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Teratological Constraints on Plasticity

Prenatal exposure to drugs of abuse or environmental toxicants can profoundly affect neurocognitive function. A common feature of such teratogenic outcome appears to be altered behavioral and neural plasticity in response to postnatal environmental stimuli or events. The neurobehavioral teratology of Fetal Alcohol Spectrum Disorder (FASD) in children, adolescents and young adults, and the effects of perinatal alcohol exposure in animal models, illustrates the potential value of a multi-dimensional developmental perspective on plasticity. Such a perspective can aid our understanding of the variability in the behavioral expression of FASDs, neural mechanisms, and response to environment-based interventions. The life-long consequences of impaired neuronal plasticity after prenatal insult are not often specifically considered in a life-span development context, despite a general, implicit appreciation for an increased risk for the emergence of “secondary disabilities” as exposed children grow. Prenatal alcohol exposure appears to constrain neurobehavioral plasticity as evidenced by 1) impaired learning, memory and other specific cognitive functions; 2) altered neural and behavioral responses to pharmacological challenges; 3) limited neurochemical and/or neuroanatomical plasticity; 4) shifts in timing and depth of maturational transitions; and 5) differential responses to environmental enrichment. Nevertheless, sufficient neurocognitive plasticity appears to remain after

risk-level prenatal alcohol exposure to support positive responses to targeted treatments by exposed animals and, we hypothesize, children as well. Altered neurobehavioral plasticity implies myriad possible mechanisms, including epigenetic modification, and suggests specific age-appropriate strategies for intervention with people of all ages with FASD.

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The Development of Episodic Memory Across the Lifespan

In this talk, I will present the two-component framework of episodic memory across the lifespan. In this framework, we hypothesized that (a) children's difficulties in episodic memory primarily originate from low levels of strategic operations, and reflect the protracted development of the prefrontal cortex; (b) deficits in episodic memory performance among older adults originate from impairments in both strategic and associative components, reflecting senescent changes in the prefrontal cortex and medio-temporal lobes. I will present three lines of work from our group that examine the validity of the two-component framework. First, the plasticity of episodic memory is greater in children than in older adults. With training, children show greater improvements and higher levels of asymptotic performance than older adults even when they initially perform at the same or lower levels. Second, compared to children, older adults have considerably greater difficulties in rejecting rearranged associative information. Individual difference in false alarm rate of associative recognition is uniquely related to the dentate gyrus volume of the hippocampus. Third, age-related decline in memory monitoring, in interaction with binding deficits, contribute to age differences in false memory for highly familiar events. I will discuss

the extent to which these findings support the two-component framework, and present ideas for future research that aims to elucidate mechanisms of lifespan differences in episodic memory.

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Role of Serotonin in Synaptic Plasticity: Relevance to Treatment of Autism

Changes in serotonin receptor density, serotonergic innervation and serotonin synthesis with age suggest that serotonin plays an important role in brain development. Indeed, there is a body of evidence indicating that serotonin regulates several aspects of brain development, including regulation of cell division, differentiation, neurite outgrowth and synaptogenesis. These effects have been observed on serotonergic neurons as well as in the tissues innervated by serotonergic terminals. There are several different mechanisms by which serotonin influences brain development. These include regulation of trophic factors and direct regulation of activity dependent plasticity. Although there is evidence for the potential involvement of several neurotransmitters in autism, the most consistent findings involve abnormalities in serotonin. Differences in serotonin synthesis between autistic and non-autistic children have been detected using functional imaging techniques. In non-autistic children, developmental changes in serotonin synthesis capacity were demonstrated using ±[11C]methyl-L-tryptophan (AMT) and positron emission tomography (PET). Non-autistic subjects undergo a period of high brain serotonin synthesis capacity during childhood followed by a decline at around age 6 years, but this developmental process is disrupted in autistic children, who did not show such age-dependent changes. The understanding of the role of serotonin in brain development together with knowledge of altered brain serotonin synthesis in autism suggests

therapeutic windows for treatment with serotonergic agents.

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Spatial Navigation Experience Shapes Adult Brain Development in Interaction with the Brain-Derived Neurotrophic Factor (BDNF) Gene.

Brain-behavior interactions are at the core of adult cognitive development, but these interactions, and the individual differences in how these interactions play out, are poorly understood. To inform this issue, I will report a series of intervention studies in which healthy younger and older men perform a spatial navigation task every other day over four months. Individuals in navigation training display navigation-related gains in performance and stable hippocampal volumes that are maintained four months after termination of training. Control groups display volume decrements consistent with longitudinal estimates of age-related decline. Cortical thickness of the medial parietal lobe display navigation-related increases in younger adults. Younger navigators also display increases in hippocampal N-acetylaspartate (NAA) as measured with magnetic resonance spectroscopy. Unlike measures of brain volume, changes in NAA are sensitive to metabolic and functional aspects of neural and glia tissue and are unlikely to reflect changes in microvasculature. Training-induced changes in NAA were absent in carriers of the Met substitution in the Brain-Derived Neurotrophic Factor (BDNF) gene, which is known to reduce activity-dependent secretion of BDNF. Among BDNF Val homozygotes, increases in NAA were strongly related to the degree of practice-related improvement in navigation performance, and normalized to pretraining levels four months after the last training session. I conclude that changes in demands on spatial

navigation can alter cortical thickness, hippocampal volume, and hippocampal NAA concentrations, confirming epidemiological studies suggesting that mental experience may have direct effects on neural integrity. BDNF genotype moderates some of these plastic changes, in line with the contention that gene-environment interactions shape the ontogeny of complex phenotypes.

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Cognitive and Neural Correlates of Long-Term Cortisol Exposure in Human Aging

Individual differences in cognitive function, brain volumes and rates of change therein, are marked in human aging. A number of hypotheses have been offered to explain individual differences in cognitive changes throughout adulthood. There is considerable evidence from animal research that chronic exposure to high levels of adrenal corticosteroids causes atrophy of the hippocampus and contributes to age-related declines in memory. In humans, some evidence suggests that similar adverse effects may accompany excess cortisol (C) exposure. In this longitudinal study, we assayed over 8000 24-hour urine samples from over 2000 individuals in the Baltimore Longitudinal Study of Aging and investigated associations between history of C exposure and a number of cognitive and neural outcomes. Across the lifespan, C levels followed a U-shaped function with higher levels of C in the 20's and 30's, the nadir in mid-life followed by an increase in C levels into older age. There were marked individual differences in both average levels of C and in rates of change in C levels within individuals. A primary finding from the study was that higher C levels were associated with an increase in the rate of decline in verbal memory. This finding was robust with respect to controlling for the influence of possible confounding variables. This and other findings

from the study will be discussed in the context of a C as a significant modifier of cognitive and neural changes in human aging.

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Using Functional Magnetic Resonance Imaging as a Biomarker of Cognitive Decline in Healthy Older Adults

Alzheimer's disease (AD) neuropathology begins decades before the onset of observable symptoms. Initiating interventions after symptom onset may be too late to make a meaningful impact on disease course. Therefore, efforts to identify effective biomarkers for preclinical prediction of AD have intensified. Critical questions in the field include: 1) what biomarkers are most effective for predicting future cognitive decline, considering cost, ease of implementation, and invasiveness; 2) are combinations of biomarkers more effective than individual predictors; and 3) what information can biomarkers provide about the neuropathological and cognitive processes associated with AD progression? Structural and functional magnetic resonance imaging (MRI) techniques have shown promise for identifying cognitively intact older adults at risk for future cognitive decline. Structural MRI (sMRI) can reveal progressive pathological changes in neuroanatomical structures targeted by AD, while functional MRI (fMRI) may provide a window into early changes in brain function resulting from the biochemical cascade associated with AD. Task-activated fMRI studies have been successful in predicting cognitive decline in healthy older adults using test-retest intervals between 18 months and five years. fMRI assessing resting state connectivity, which does not rely on the ability to perform a task, has potential for revealing age- and disease-related changes in basic functional brain networks, such as the "Default

Mode Network" (DMN). DMN disruption is often seen in cognitive aging, and disease states, such as AD and mild cognitive impairment (MCI). Our group recently reported reduced regional functional connectivity in MCI patients compared with high-risk and control elders. Reduced resting state hippocampal-posterior cingulate functional connectivity may be associated with cognitive decline in MCI, while elevated functional connectivity in persons at-risk for AD may reflect early, preclinical compensatory changes. In summary, both sMRI and fMRI show promise for preclinical prediction of AD, are widely available, minimally invasive, and can be cost-effective.

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When Seniors Know Better than Scientists: Individual Differences in Memory Training and Transfer

Cognitive training programs for older adults often aim to improve a particular ability or set of abilities. However, it is important to remember that the individuals participating in those programs will differ in their abilities and preferences at baseline, and that this may influence how they engage with the training program. We analyzed data from a repetition-lag memory training procedure both from the perspective of which encoding task they were assigned by the experimenter and the type of encoding (deep vs. shallow) participants reported using in a debriefing questionnaire. Although deep encoding processes benefitted both training-task performance and transfer-task performance regardless of whether they were experimenter-designated or participant-chosen, participant-chosen strategies often had a larger impact on transfer-task performance. This was especially the case for participants in a experimenter-designated condition originally designed to suppress deep processing, suggesting that this "resistance training" may have had particularly

beneficial effects. The results suggest that allowing older adults to choose the processes they engage at training may help improve the transfer of training benefits to other tasks and to everyday life.