Cognition and the aging brain: Maintenance, reserve and compensation

Overview: Dr. Maria Natasha Rajah, McGill University

The advent of neuroimaging methods has contributed significantly to our understanding of how healthy aging impacts the brain and cognitive abilities, and has informed our models of cognitive aging. Functional neuroimaging findings have shown that the aging brain is not passive but shows considerable plasticity and may actively resist age-associated anatomical and physiological deterioration. One goal of ongoing research in the cognitive neuroscience of aging has been to better understand the neural basis of successful cognitive aging. Successful cognitive aging can be defined in relation to the person (the best this person can do), or in relation to the population (the best in the group). It has been hypothesized that how well an individual ages may be related to the concepts of brain maintenance, cognitive reserve and compensation. However, there remains a lack of clarity in how these concepts are defined in the field and how they relate to one another. This has led to researchers forming seemingly contradictory predictions for these concepts. For example, some researchers predict compensation in high-performing older adults (OA) because they are the ones supposedly benefitting from, and hence exhibiting, compensation. In contrast, other researchers predict it in low-performing OAs because they “need” compensatory mechanisms to offset cognitive decline. Yet, others have suggested that the term compensation should be reserved for specific cases where a positive correlation between activity and performance is observed only in OA, and not young adults. Clearly, greater consensus on how to define ‘compensation’ and other key terms in the field is needed to advance research in cognitive neuroscience of aging so that scientists can better communicate research findings using standardized definitions. This is the motivation for the proposed symposium. The organizer (Rajah) will present an overview of the rationale for the symposium and provide initial definitions for these concepts, focusing on the idea of cognitive reserve. The following presenters will provide a more detailed definition of each the concepts of brain maintenance (Nyberg) and compensation (Reuter-Lorenz, Cabeza) with supporting data. The symposium will conclude with a presentation providing a general framework for how the concepts of brain maintenance, compensation and reserve are linked and how to formally examine the validity and utility of these concepts (Rugg).
**Brain maintenance**

Neuroimaging studies of the aging brain provide support that a strong predictor of preserved memory and cognition in older age is brain maintenance, or relative lack of brain pathology. Evidence for brain maintenance comes from different levels of examination, but up to now relatively few studies used a longitudinal design. Examining factors that promote brain maintenance in aging is a critical task for the future, and may be combined with the use of new techniques for multimodal imaging.

**Compensation in the aging brain: Networks and representations**

Healthy aging is associated with significant anatomical and physiological brain decline. Fortunately, functional neuroimaging evidence suggests that the aging brain actively compensates for cognitive decline by reorganizing its functions. Whereas most fMRI studies of cognitive aging have investigated changes at the level of univariate activity, we focus on compensation at the level of networks and representations. At the network level, we reliably find age-related increases in prefrontal cortex (PFC) integration with the episodic memory network. In a graph theory study, we found that during episodic memory retrieval, the module (community of nodes) that included the medial temporal lobe showed greater integration with PFC and other regions for older compared to younger adults. Unfortunately, age-related increases in network integration are constrained by white-matter decline. We link functional connectivity (fMRI) to white-matter (DTI) using structural equation modeling. At the representational level, we have found evidence for compensatory mechanisms in the occipitio-temporal cortex.
(OTC). In this region, activation patterns for different visuo-semantic categories (e.g., faces vs. houses) are usually less differentiated for older adults (age-related dedifferentiation). Using representational similarity analyses (RSA) based on a deep convolutional neural network (DNN), we have found that older adults show sensory-related dedifferentiation in posterior OTC as well as semantic-related “hyperdifferentiation” in anterior OTC. In sum, compensatory changes in the aging brain can be found not only at the level of univariate activity (as usually reported), but also at the level of networks and representations.

Speaker #4: Dr. Michael D. Rugg
*University of Texas at Dallas*

**Age-related differences in the neural correlates of cognitive processing: From description to interpretation**
Age-related differences in task-related neural activity have been reported for more than two decades, but the interpretation of these differences is still under debate. Using data from my laboratory as examples, I will give an overview of the different classes of findings that have been described in this literature. I will discuss some of the methodological and conceptual barriers that have impeded our ability to interpret patterns of age-related differences in brain activity in terms of such concepts as maintenance, reserve, and compensation. I will conclude with a discussion of strategies for future research that could help establish the functional significance of these differences, and hence advance understanding of the different ways that aging might impact cognitive and neural function.

Discussant: Dr. Maria Natasha Rajah
*McGill University*
Cognitive and neural plasticity in older age: Mechanisms of change in cognitive training interventions

Overview: Dr. Julia Karbach, University of Koblenz-Landau, Germany

The field of cognitive training research has been rapidly evolving over the last decade. Given that cognitive functions decline in older age, many studies have focused on older adults and aimed at designing interventions to compensate or delay age-related cognitive decline. Despite many encouraging findings, the evidence for the effectiveness of cognitive training is mixed and inconsistent findings have inspired a heated debate in the field. While most researchers agree that prolonged practice on a task results in significant performance improvements that also benefit performance on similar tasks (near transfer), the more controversial question is whether training on one ability also transfers to related but untrained cognitive abilities or even improves cognitive performance in everyday life (far transfer). A number of recent studies showed that even if training is successful at the group level, individual differences in training-related performance gains are usually very large. As a consequence, the field is slowly shifting from just testing whether or not training works to analyzing for whom it works in order to disentangle the mechanisms driving training-related changes in performance and brain activity. The symposium will highlight recent findings investigating these mechanisms in different cognitive domains and with different methodological approaches. The first talk (Susanne Jaeggi et al.) will be on effects of spacing and consolidation on working-memory training outcomes and on individual differences that might moderate the effectiveness of the intervention. The second presentation (Matthias Kliegel et al.) will zoom in on possible moderators of training and transfer effects by reporting data from a randomized controlled trial comparing strategy training and process-based training of prospective memory. The focus will be on behavioral and neural changes as well as everyday life correlates of those effects. In the third talk (Sandra Dörrenbächer et al.), the focus will be on neural effects of cognitive training. The study combined functional magnetic resonance imaging (fMRI) and region-of interest (ROI) analyses in order to track spatio-temporal interactions underlying changes in neural activity after executive control training. The final presentation (Chandramallika Basak et al.) will report results of a comprehensive meta-analysis on randomized controlled trials comparing training-related cognitive gains between healthy aging and adults with mild cognitive impairment as well as across three different types of cognitive training (trainings targeting specific single cognitive components, trainings targeting multiple cognitive components, or trainings engaging non-specific cognitive abilities). Paul Verhaeghen will discuss the four presentations.
Speaker #1: Dr. Susanne Jaeggi  
*University of California Irvine*

**Training working memory in older adults using tablet technology – The effects of spacing and consolidation**

The vast majority of our nation’s population will experience some cognitive decline as a function of age. Therefore, the development of effective interventions to mitigate age-related cognitive decline is of critical importance in that those interventions might not only impact older adults’ cognitive functioning, but ultimately, contribute to their health and quality of life. There is accumulating evidence that cognitive interventions targeting working memory are beneficial in that they show generalizing effects that go beyond specific training effects. Despite the promising results, more research is needed to make cognitive interventions more robust, and to uncover their underlying mechanisms. I will be discussing the results of a randomized controlled multi-site trial in which we focus on the interventions’ optimal scheduling (i.e., spacing of training sessions) in a population of healthy older adults. We find that older adults do benefit from training by showing improved performance in non-trained working memory tasks, and importantly, those benefits seem to last up to 6 months after training completion. However, the spacing of training does not seem to result in added benefits, if anything, participants seem to suffer from overnight forgetting as expressed in impaired training performance as a function of spacing, indicating deficits in consolidation. I will be discussing the implications of our findings for learning and plasticity in old age.

Speaker #2: Dr. Matthias Kliegel  
*University of Geneva, Switzerland*

**Prospective memory training in healthy aging: Moderators of strategy- and process-based training and transfer effects**

Prospective memory (PM) refers to the processes underlying the formation and realization of delayed intentions (e.g., taking medication in time). PM failures belong to the most frequent everyday memory problems and have been shown to be key predictors for loss of independence in old age. However, despite its importance for everyday functioning, studies targeting PM training in older adults are still scarce and little is known about pathways to improve PM in healthy older adults. In the present project (MemoryTrain, funded by ARC), an RCT was conducted comparing a strategy-based (n= 40; focusing on several compensatory strategies, including homework) and a process-based (n= 40; using a Virtual Week scenario where difficulty can be adapted) PM training arm with an active control group (n= 40; book reading club). Each condition involved four sessions/week for 6 weeks. Pre-Post assessments included both laboratory and everyday life PM tasks as well as key moderators such as cognitive control and working memory, motivation and metacognitive variables as well as markers of cognitive reserve. Data collection will be terminated by the end of 2017. Analyses will particularly target moderators of training and transfer effects comparing strategy training and process-based training in their effects and moderation pathways.

Speaker #3: Dr. Sandra Dörrenbächer  
*Saarland University, Germany*

**Compensation in brain-activity dynamics after executive-control training in older adults: on the underlying spatio-temporal interactions**
Executive control is neurally subserved by the interplay of transient and sustained brain activity across fronto-parietal and fronto-striatal networks. Older adults show an altered dynamic recruitment of brain activity. Recent evidence suggests that practice in executive control may enable older adults to redistribute their brain activity across cortical and subcortical networks, which in turn can help them compensate for performance impairments. However, changes have only been analyzed in spatial, but not temporal aspects of brain activity. Here, we examined training-related changes in old age by applying a hybrid functional magnetic resonance imaging design that tracks the spatio-temporal interactions of brain activity. Fifty healthy older adults were assigned to an executive-control training group or an active-control group and their pre/post-activity-change maps were compared against those of 25 untrained younger controls. After training, older adults showed the same performance as untrained young adults. More importantly, as compared to the active-control group, executive-control training promoted a fine-tuning of transient activity in fronto-parietal circuits, which was related to performance improvement; but an overall reduction of sustained activity in fronto-striatal circuits. The post-training neural pattern was different from untrained younger adults, suggesting neural compensation. The results emphasize the importance of spatio-temporal interactions in training-induced neural changes in older adults.

Speaker #4: Dr. Chandramallika Basak
*University of Texas at Dallas*

**Comparing cognitive benefits from single-component and multi-component cognitive training modules: A meta-analysis of randomized controlled trials in healthy aging and mild cognitive impairments**

Although cognitive training is touted to be beneficial during the long pre-clinical phase of Alzheimer’s disease (AD) that includes healthy aging and mild cognitive impairment (MCI), past meta-analyses on cognitive training have typically focused either on healthy aging or MCI. Moreover, no meta-analysis so far has compared the extent of transfer between different training modules during this long pre-clinical phase of AD. The main goals of the current comprehensive meta-analysis on randomized controlled trials therefore were to compare the training-related cognitive gains a) between healthy aging and adults with mild cognitive impairment (MCI), and b) compare the extent of transfer from two different cognitive training modules, one that targets a specific single cognitive component (e.g., executive functions) and another that targets multiple cognitive components, either sequentially or simultaneously. Results from 200 training studies using multi-level modeling showed that, in general, cognitive training moderately benefited cognition in older adults when compared to controls (net gain effect size, Hedge’s g=.30), with no significant difference between healthy aging and MCI on overall cognition. Simultaneous multi-component training resulted in broadest far transfer. For single component training, the most effective approach for far transfer was training on executive functions/working memory. Additional moderator analyses showed that total hours of training, hours/week, gender distribution, and publication quality did not influence the overall cognitive net gain effect size.

Discussant: Dr. Paul Verhaeghen
*Georgia Institute of Technology*
New insights on the role of strategies in cognitive aging

Overview: Dr. Dayna. R. Touron, University of North Carolina at Greensboro

Although some cognitive decline with healthy aging appears inevitable, much research demonstrates that a substantial portion of the observed cognitive performance deficits in older adults is due to age-related changes in strategy repertoire, distribution, execution, and selection. Although mnemonic strategies were traditionally the focus of this research, a strategic contribution to cognitive aging has been demonstrated for diverse cognitive domains beyond memory, such as problem solving, skill acquisition, and judgment and decision making. Naturally, this vast research has also yielded inconsistent findings, calling for continued precision of theories on cognitive strategy variations with aging. As a further challenge, strategy trainings often fail to yield transfer effects. Featuring talks by researchers from the USA, Germany, and Italy, the current symposium will therefore focus on new insights on the role of strategies in cognitive aging (across the domains of memory, attention, and event segmentation) that help resolve the aforementioned inconsistencies and challenges. First, Dayna R. Touron (University of North Carolina at Greensboro, USA) will give an overview of basic findings as well as challenges and new directions. The first two research talks will then report novel insights on aging and traditional mnemonic strategies. First, Beatrice G. Kuhlmann (University of Mannheim, Germany) will demonstrate the moderating role of task conditions for age-related strategy deficiencies in episodic memory. Her data demonstrate that test-format expectations (recognition versus recall) during study substantially magnify age-related differences in episodic memory, mediated via age-related differences in encoding strategy production and utilization when attempting to prepare for recall. Next, Elena Cavallini (University of Pavia, Italy) will present a novel concept for cognitive strategy training, specifically aimed at facilitating strategy transfer. On the example of mnemonic training, she will demonstrate how and for whom transfer to novel (laboratory and everyday) tasks can be supported in the training. In turn, Heather Bailey (Kansas State University, USA) will explore the contribution of cognitive strategies to age-related differences in a new domain, event segmentation, which then tie back to age-related differences in memory for events. Finally, Alan Castel (University of California, Los Angeles, USA) will demonstrate an increasingly selective attention focus in older learners and discuss how prior knowledge and metacognitive insights can enable more effective attention allocation in older adults.
Speaker #1: Dr. Beatrice G. Kuhlmann  
University of Mannheim, Germany

Ready … Set … Test! Examining older adults’ adaptation to the expected memory-test format  
Age-related memory differences are more pronounced on recall than on recognition tests. Three experiments examined whether older adults are aware of recall’s particular difficulty and adapt strategies accordingly. Young (17-30 years) and older (59-87 years) participants either expected a recognition or a recall test while encoding word lists. Whereas young adults had adequate test-difficulty expectations already after reading format descriptions, older adults needed practice with the format. Recall-expecting young adults consistently outperformed their recognition-expecting peers on both test formats. Recall patterns indicated that recall-expecting young adults engaged more inter-item relational processing, both of adjacent unrelated study items (E2) and of distant semantically-related items (E3). For older adults, recall-expectancy effects were mixed: There was consistently no effect on recognition (E1-3) but improved recall of unrelated (E2) but not of semantically-related (E3) words. Recall patterns suggested that recall-expecting older adults did not engage more relational processing of adjacent items in E2 but unsuccessfully tried to use semantic clustering in E3. Thus, there are qualitative differences in how young and older adults prepare for recall and whether older adults can successfully prepare for recall depends on the study material. Thereby, observed age-group differences in memory can be substantially magnified under recall expectancies.

Speaker #2: Dr. Elena Cavallini  
University of Pavia, Italy

A learner-oriented approach for improving older adults’ memory and transfer, based on strategy adaptation  
Training older adults to use mnemonic strategies typically improves their memory performance on the trained tasks. However, standard strategy training rarely produces transfer to tasks that are not practiced during training. Given the general failure of mnemonic training programs to achieve transfer, we developed a novel intervention based on a learner-oriented approach. During the training, older adults are treated as active partners in attempting to achieve generalization of strategic behavior. We explicitly engage older adults in a discussion about how their newly acquired strategies (interactive imagery and sentence generation) could potentially be adapted for use in different task environments. Thus, we promote transfer in the training program itself by giving them a procedure to be followed for every new task based on task analysis and strategy adaptation.

Speaker #3: Dr. Heather Bailey  
Kansas State University

The role of knowledge in age-related differences in the segmentation and memory of everyday activities  
Everyday we encounter a continuous stream of activity, and one way that our perceptual systems deal with such activity is by segmenting the activity into discrete, meaningful events. Segmentation is one type of encoding strategy that helps people organize dynamic activity in memory, and previous work has shown that individuals who segment more normatively are better able to remember the activity. Segmentation ability, however, declines with age, presumably due to changes in working memory. Although working memory and episodic memory often to decline with age, semantic knowledge remains intact. Thus,
recent work from our lab has evaluated whether older adults are able to use their intact semantic knowledge to more effectively segment and remember novel everyday activities. Results indicate that activating prior knowledge improves segmentation ability for both young and older adults; however, this manipulation did not benefit memory to the same extent. Age-related changes in segmentation and memory will be discussed as well as implications for future memory interventions.

Speaker #4: Dr. Alan Castel (replacing Dr. Patrick Lemaire)

University of California, Los Angeles

Selective memory as a memory strategy in older age
We are often in situations in which we are overwhelmed with information. This places challenges on attention and can influence what is later remembered. In response to these cognitive challenges, older adults may use a metacognitive strategy to selectively focus on important information, in order to remember this high-value information in the future. The ability to selectively remember high-value information may come at a cost of remember less, especially so in terms of lower-value information. I will present a theoretical framework that illustrates how the strategic allocation of attention can be used effectively when people have metacognitive insights that their memory capacity is limited. Older adults may also use prior knowledge and established schemas to incorporate new information with what is already in memory, making decisions about what to remember on a “need-to-know” basis. Older adults may choose to focus on high-need and high-yield information (that has a strong likelihood of future use), in order to maximize rewards and avoid potential losses. I will discuss some findings regarding how “lifelong students of memory” (older adults) find effective ways to remember what is of most importance, forget what is not needed, and how this judicious use of memory can lead to efficient memory in light of the memory impairments that might accompany older age.
Prosocial tendencies across the adult life span: Cognitive, motivational, and neural factors

Overview: Dr. Ulrich Mayr, University of Oregon

Prosocial behavior positively affects the individual as well as society as a whole. Results from prior investigations of demographic trends in prosocial behavior and altruism indicate that prosocial behaviors often increases with age, particularly in the realm of monetary donations. As aging individuals represent a disproportionate source of monetary contributions to the public good, it is important to better understand the relationship between aging and tendencies for prosocial behavior and determine the underlying motivational, cognitive, and neural processes. This symposium encompasses a set of papers that approach the common theme using both social-cognitive and neuroscientific perspectives. Ulrich Mayr will present an overview on aging and prosocial tendencies and discuss potential cognitive and motivational factors. He will also include research results on the presence of an age-modulated, higher-order General Benevolence factor, informed by neural, behavioral, and psychological measures. Ryan Best will present behavioral and affective data on charitable giving in non-monetary domains, where older adults do not hold a resource advantage compared to younger adults. Results are related to the General Benevolence conception and theories of age-related shifts in motivation across adulthood. Julia Spaniol will present a series of studies investigating the mechanisms and boundary conditions of the age-related increase in altruism using the intertemporal choice paradigm. When choosing between immediate and delayed gains, losses, and charitable contributions, choice patterns show greater altruism in older adults compared to older adults. However, this age difference is reduced when decisions are made under acute stress. Pär Bjälkebring will present data on the socioemotional aspects of prosocial behavior. Reporting an age-related positivity bias in charitable giving, older adults are found to draw more positive affect, and hence benefit more, from monetary donations compared to younger adults. Lastly, Natalie Ebner will present a series of studies showing the affective and social-cognitive effects of intranasal oxytocin administration in aging.
Decisions between self-interested vs. altruistic outcomes across adulthood
How do older adults make decisions that contrast self-interest with altruistic outcomes? Recent research by Mayr and colleagues utilizing data collected from multiple measurement domains (neural, behavioral, and psychological) has provided evidence for positive relation of age and a general benevolence dimension, a latent factor representing genuine altruism. However, these findings were limited to monetary giving, and the results may be due to older adults generally valuing money less than younger adults. We present an experiment where online participants are asked to make decisions and rate their attitudes towards hypothetical charitable-giving transactions in three non-monetary domains in which older adults generally experience losses (physical energy, remaining life time) or stability (social support) compared to younger adults. We tested the general benevolence model with these domains and found evidence for a domain-specific benevolence dimension. The domain-specific benevolence is positively associated with age in some domains (physical energy) but not others (life time, social support). These findings suggest that age differences in charitable giving may reflect differences in the marginal utility of money as opposed to an age-related increase in altruistic concern for the greater societal good.

Greater emotional gain from giving in older adults: Age-related positivity bias in prosocial behaviors
We investigated age-related positivity bias in prosocial behaviors in three studies. In Study 1, participants (n = 353, age range 20–74 years) were asked to rate their affect toward a person in need and how much money they would be willing to donate to help this person. We found that older adults were more motivated by positive affect and less motivated by negative affect compared to younger adults. In Study 2, participants (n
108, age range 19–89) used a diary to list prosocial behaviors they performed every day for a week and rated their daily affect toward these behaviors. We found that older adults had more positive affect toward their daily prosocial behaviors. In study 3 we followed up on these participants to rate their affect toward a specific donation made. We found that the level of positive emotional reaction from monetary donations was higher in older participants. Overall, we found support for an age-related positivity bias in charitable giving. We concluded that older adults draw more positive affect from both the planning and outcome of prosocial behavior and hence seem to benefit more from engaging in prosocial behavior compared to their younger counterparts.

Young but not older adults decreased their investment after breach in trust (but not lottery) trials. Older adults in the oxytocin condition increased while those in the placebo condition decreased their investment after breach in trust (but not lottery) trials. Our data suggest reduced sensitivity to deception cues and a trust-enhancing effect of oxytocin in aging. Integration of cognitive, socio-affective, and neurobiological profiles underlying age-related vulnerabilities in trust-related decisions will inform prevention of victimizations in aging.

Speaker #4: Dr. Natalie C. Ebner
University of Florida

Uncovering age-related vulnerabilities in trust-related decision making
Older adults are confronted with consequential decisions, which often require trusting others. A rapidly aging population, combined with age-related changes in decision making, render fraud targeting older adults a growing public-health concern. Addressing online fraud, Study 1 recorded browsing activity over 21 days during which phishing attacks were simulated. Older women were the most vulnerable group to these attacks. There was a discrepancy, particularly among older adults, between self-reported susceptibility awareness and behavior. Further, higher susceptibility was associated with lower memory and positive affect particularly in old-old adults. In Study 2, young and older adults self-administered intranasal oxytocin or placebo before investing in partners (trust) and computer lotteries. After half of the trials, participants were informed that only 50% of their investments bore returns.
Risk and Protective Factors for Cognitive Decline: New Insights from Longitudinal Studies

Overview: Dr. Anja Soldan, Johns Hopkins University

This symposium will present new findings from longitudinal cohort studies that have followed middle-aged and older cognitively normal individuals over time in order to identify potential risk and protective factors for future cognitive decline and impairment. The risk factors that will be examined in this symposium include brain amyloid and tau aggregations (the two hallmarks of Alzheimer’s disease), neurodegeneration (as measured by atrophy on MRI), genetic variants, depressive symptoms, and cardiovascular risk factors, including obesity, hypertension, and cholesterol levels. Potential protective factors that will be discussed include proxy measures of cognitive reserve, such as years of education, literacy, and vocabulary knowledge, and self-reported engagement in social, cognitive, and physical activities.

The symposium will begin with a discussion of seminal findings from the Harvard Aging Brain Study (N=247, mean baseline age=74, mean follow up=4 years). This presentation will focus on the role of amyloid and tau, as measured by PET imaging, as well as the role of brain atrophy in determining future cognitive trajectories in multiple cognitive domains among individuals with normal cognition.

The second presentation will discuss initial findings from the Preclinical Alzheimer’s Disease Consortium, a collaboration of 5 longitudinal studies that have collected cognitive, biomarker, and lifestyle data among individuals who were cognitively normal when first enrolled (WRAP, ACS, BIOCARD, AIBL and BLSA). Following a brief overview of the Consortium, the presentation will focus on the association between cerebrospinal fluid markers of amyloid, tau, and neurodegeneration (N=585, mean baseline age = 59, mean follow-up =7 years) and future rates of cognitive decline using the recently proposed amyloid/tau/neurodegeneration (ATN) classification system.

The third talk will present findings from the Baltimore Longitudinal Study of Aging (N=622, mean baseline age = 71, mean follow-up = 4 years). The focus here will be on the association between cardiovascular and genetic risk factors, education, sex, and depressive symptoms and rates of brain atrophy among individuals who remain cognitively normal over time and those who develop cognitive impairment. Lastly, the symposium will turn to a discussion of potential protective factors, as examined in the BIOCARD study (N=189, mean baseline age = 57, mean follow-up = 12 years). This presentation centers on the degree to which self-reported engagement in lifestyle activities is associated with current cognitive performance, prior longitudinal cognitive trajectories, and baseline levels of cognitive reserve, as measured by years of education, literacy, and vocabulary.
Cognitive decline in preclinical Alzheimer’s Disease

Work across multiple research groups has shown that clinically normal (CN) individuals with abnormal levels of beta-amyloid (Aβ+) show cognitive decline and risk of progression to Alzheimer’s disease (AD) dementia compared to Aβ- CN. To further categorize CN individuals along the AD trajectory, preclinical staging criteria have been proposed to combine Aβ status with neurodegeneration (ND) markers. In this framework, Aβ-/ND- are considered Stage 0, Aβ+/ND- are Stage 1, and Aβ+/ND+ are Stage 2. In a study of 247 older CN, we have shown that Stage 2 (Aβ+/ND+) shows cognitive decline over time compared to all other groups. The ability to measure the other pathological hallmark of AD, the aggregation of Tau, has recently become available and integrated into studies of CN. In addition to higher levels of Tau in the Aβ+ CN compared to Aβ- CN, we have shown that elevated Tau in the medial temporal lobe and inferior temporal cortex is predictive of memory decline among the Aβ+ CN group. Overall, studies investigating the pathophysiological processes of AD have found elevated risk of future decline in Aβ+ CN, providing an opportunity to test whether disease-modifying treatments applied during the preclinical stage of AD will prevent clinical symptoms.

Amyloid/Tau/Neurodegeneration (ATN) profiles among cognitively normal individuals and their cognitive outcomes

This study compared the rate of cognitive decline among eight groups of cognitively normal individuals divided on the basis of their cerebrospinal fluid (CSF) biomarker profiles. Three CSF biomarkers associated with Alzheimer’s disease (AD) were examined: amyloid, phosphorylated tau (a marker of neurofibrillary tangle pathology), and total tau (a marker of neurodegeneration). The analysis included 800 middle-aged and older participants (mean baseline age 59.5 years, mean follow-up 7.1 years), from four different cohort studies of preclinical AD. Cognitive performance was measured using a previously validated factor score reflecting global cognitive performance across multiple cognitive domains. Within each cohort, participants’ baseline levels of the CSF biomarkers were first dichotomized as normal vs. abnormal; participants were then classified into one of 8 distinct amyloid/tau/neurodegeneration (A/T/N) groups. The greatest cognitive decline was evident among the group with abnormal levels of all three biomarkers (A+/T+/N+, N=69, slope=-0.31, p=0.021). The rate of decline for the group with abnormal levels of amyloid and neurodegeneration only was similar, but did not reach significance, likely reflecting the small sample size (A+/T-/N+, N=19, slope=-0.26, p=0.2). Our results demonstrate that cognitively normal individuals with abnormal CSF biomarkers of amyloid, tau, and neurodegeneration are at greatest risk of cognitive decline.

Predictors of neurodegeneration in cognitively healthy and subsequently impaired older adults

Background: Known risk factors of dementia may accelerate neurodegeneration among persons vulnerable to having subsequent impairment (SI) among nondemented, community-dwelling older adults.
adults. Methods: There were 622 cognitively healthy and 78 SI Baltimore Longitudinal Study of Aging participants with dementia risk factors and brain volumes from 1994 onward. Linear mixed effects models were used to examine associations of dementia risk factors with annual rates of regional volumetric change, and evaluate effect modification of sex and SI on these associations. A stepwise backward approach was used to select predictors of neurodegeneration. Only acquired scans while participants were cognitively healthy were included in the analysis. Results: Age, sex, low educational level, ApoE4 allele, hypertension, obesity, and low HDL cholesterol were predictors of neurodegeneration. Sex and SI modified the association of predictors with accelerated annual rates of decline in regional brain volumes. Men experienced greater volumetric loss than women. Predictors of neurodegeneration had a larger effect on annual declines in brain volumes among SI, compared to cognitively healthy. Conclusions: SI brains could be more vulnerable to the presence of predictors of neurodegeneration than the cognitively healthy brains, suggesting that cross-sectional samples of nondemented individuals could be heterogeneous.

Speaker #4: Dr. Corinne Pettigrew
*Johns Hopkins University*

**Relationship between self-reported lifestyle activities and longitudinal cognitive change**
We examined the relationship between current engagement in various lifestyle activities and both current cognitive performance and prior longitudinal cognitive trajectories, and whether these relationships were independent of levels of cognitive reserve (CR). Participants (n=189) were cognitively normal at baseline and have been prospectively followed with annual assessments as members of the BIOCARD study (M=12y); 27 participants developed MCI over time. Self-reported engagement in physical, cognitive, and social activities was measured by the CHAMPS questionnaire. Cognitive performance and CR were both measured by composite scores. Cross-sectionally, better cognitive performance was associated with higher engagement in cognitive activities among all subjects. Longitudinally, the relationships between current activity engagement and prior cognitive trajectories differed by diagnosis. Among MCI subjects, higher engagement in physical and cognitive activities, and higher total engagement, was associated with less decline in prior cognitive performance (p < .05), and some of these effects were independent of baseline CR. Among cognitively normal subjects, lifestyle activities were not associated with prior cognitive trajectories. Greater engagement in lifestyle activities may modify the rate of cognitive decline among those who develop symptoms of MCI, independent of CR. Prospective longitudinal evaluations are needed to confirm these findings.