Leveraging Insights and Approaches from Social and Affective Neuroscience to Promote Adaptive Aging: A Workshop

National Academies of Sciences, Engineering, and Medicine
Division of Behavioral and Social Sciences and Education
in collaboration with the
National Institute on Aging

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Table of Contents

Acronym Definitions

ACC	anterior cingulate cortex
ACEs	Adverse Childhood Experience Study
AD	Alzheimer's disease
AGeNeS-OT	Age-Related Genetic, Neurobiological, Sociobehavioral Model of Oxytocin
AIDS	acquired immunodeficiency syndrome
ALOE	Aging and Lifespan Optimization of Emotion
C. diff.	*Clostridium difficile*
COG-ED	Cognitive Effort Discounting
CRP	C-reactive protein
DISE	Daily Inventory of Stressful Events
DMC	Dual Mechanisms of Control
LBP	lipopolysaccharide-binding protein
LC	locus coeruleus
LLD	late-life depression
MARIGOLD	Mobile Affect Regulation Intervention with the Goal of Lowering Depression
MIDUS	Midline in the United States
MRI	magnetic resonance imaging
MTL	medial temporal lobe
N2	non-REM stage 2
NASEM	National Academies of Science, Engineering, and Medicine
NIA	National Institute on Aging
NPS	Neurological Pain Signature
PFC	prefrontal cortex
REM	rapid-eye movement
rtfMRI	real-time functional MRI
SWS	slow-wave sleep
TPJ	temporoparietal junction

Meeting Summary

Introduction

On November 18-19, 2019, the National Academies of Sciences, Engineering, and Medicine (NASEM), in collaboration with the National Institute on Aging (NIA), convened a workshop to identify gaps (1) in the understanding of age-related changes in social and emotional processes and (2) opportunities to leverage insights from the fields of social and affective science to support research on intervention development to promote healthy aging.

Workshop participants discussed evidence of social and emotional changes in aging in light of advances in psychological theory related to social and emotional processes, causal factors that shape life course social and emotional development (including the impact of early life adversity and cumulative disadvantage), and neurobiological and physiological changes associated with normal aging that are relevant to social and emotional functions. Because most emotions arise in social contexts, the social aspects of emotional development and social function were central to their discussions. Participants also focused on the development and impact of individual differences in social and affective phenotypes related to these functions, sometimes described as differences in affective style (e.g., reactivity, recovery, and resilience).

Social and affective neuroscience is the study of neural pathways that produce affect and emotion and modulate their effect on sociality and cognition, among many other psychological processes. For purposes of this meeting, affect is an evaluative neurobiological response to external and internal stimuli that manifests as psychological experience (i.e., positive or negative emotions). Emotions are more complex affective experiences involving cognitive appraisal or evaluation. Social and affective neuroscience also studies the psychological and neurobiological processes that support social behavior, social cognition, social interactions, and representations of the self and other in social contexts. Each component of these socioemotional, psychological, and neural pathways is critical to the healthy functioning of the individual. Evidence suggests that older adults experience improvements in socioemotional processing, even while experiencing a decline in cognitive abilities; although these effects are not universal and can vary significantly at the individual and subpopulation levels.

Understanding age-related differences in these processes and their neurobiological underpinnings may enable researchers to identify underlying processes that characterize normative aging and that may be mitigated or enhanced with direct and robust interventions to promote healthy, adaptive aging and improve quality of life for older adults.

Experts provided background in four broad areas:

- Basic issues in the social and affective neuroscience of aging

- Prefrontal executive function and affect
- Effect of social and prosocial behavior on the brain
- Socioemotional malleability and resilience

Meeting participants then engaged in facilitated discussions to identify gaps in existing research and new avenues for aging research, examine the paradox of social and emotional function, and evaluate the study of adaptive aging in a real-world context. These discussions led to the following suggestions:

- Establish a normative aging trajectory, to understand variability in age-related outcomes and to identify influential factors that mediate protective effects.
- Investigate mechanisms that mediate the benefits of social networks and self-regulation, to inform design of potential interventions.
- Dissect the individual social and emotional affective and cognitive functioning pathways and their integration and interaction during aging.
- Improve study design to include real-world context and to increase the generalizability of interventions and findings.

Research into the field of social and affective aging will expand current understanding of social and affective processing and normative aging. It will inform effective, generalizable, and real-world interventions to promote better socioemotional and cognitive functioning for older adults and to improve their quality of life. The meeting agenda and list of attendees are included as Appendices 1 and 2, respectively.

Basic Issues in the Social and Affective Neuroscience of Aging

What Do We Really Know About Aging and Emotion Regulation?

Derek Isaacowitz, Northeastern University

Despite negative health and social changes associated with aging, older adults report higher levels of positive affective experience than younger adults. This finding has led researchers to assume that older adults employ better emotion regulation, leading to higher levels of happiness, despite negative, age-related changes. Two theories/frameworks are most relevant to this assumption: Socioemotional Selectivity theory and the Process Model of Emotion Regulation.

Socioemotional Selectivity theory, developed by Laura Carstensen, hypothesizes that an individual's information-processing is rooted in motivation and time perception. An older person may perceive time as limited and thus might prioritize goals that generate positive affect. In support of this theory, studies have shown that, on average, older adults attend to and remember positively valenced more than negatively valenced material ("age-related positivity effects"); this may lead to a feeling of happiness when time horizons feel short.

The Process Model of Emotion Regulation, developed by James Gross, provides another relevant perspective and suggests that individuals employ five different groups of strategies for emotion regulation at varying timepoints: situation selection, situation modification, attentional deployment, cognitive change, and response modification. If older adults are different or better at emotion regulation, it might involve age differences in how these strategies are used.

To determine the best avenue to understand emotion regulation in older adults, Isaacowitz and colleagues sought to combine both approaches. When employed together, it is possible to consider whether older adults use and/or benefit more from more positive ways of implementing regulation strategies (known as tactics) within each of the emotion regulation strategies proposed by the Process Model of Emotion Regulation. Socioemotional selectivity theory suggests that older adults may rely more on positive tactics; examples of positive tactics include positive attentional deployment and positive reappraisal. Combining the models thus makes it possible to systematically test whether older adults are different and/or better at emotion regulation in terms of the tactics they rely on most.

A recent study published by Livingstone and Isaacowitz (2019) tested the five emotion regulation mechanisms in a laboratory setting. They found that young, middle-aged, and older adults reported similar trends in their use of positive tactics across the five emotion regulation strategies. No major age-related differences were found across the five strategy groups. That is, young, middle-aged, and older adults all showed fairly similar use of more vs. less positive tactics across the emotion regulation strategies; there was no evidence for substantial age differences in emotion regulation behavior in this laboratory study.

A second study assessed young, middle-aged, and older adults during their daily life, using a set of questions answered multiple times each day on the participants' smartphones over a period of 10 days. The questions asked whether participants attempted to alter their emotions, which strategies and tactics were used, and how they felt after they used the strategy or tactic. This study found that, although all age groups most frequently used positive strategies (i.e., tactics to increase positive emotion), the older adults employed such strategies the most. Thus, differences in use of tactics were of degree rather than of type. However, in terms of effectiveness, affect changes were similar across all age groups before and after use of all but two regulatory strategies (i.e., situation section and situation modification), which appeared to be more effective for younger than older adults. Overall, older adults still reported more positive affect throughout the study though.

Other researchers have also attempted to uncover age-related regulation differences, but most have reported similarities across age groups. These observations suggest that the use of emotion regulation strategies may be similar among all adult age groups, both in a laboratory setting and in daily life. Thus, the use of strategies themselves may not account for the positive affect differences observed in older adults. The higher rates of positive affect in older adults may be regulated by a separate underlying mechanism, such as age-related changes in situations, emotional reactivity, or judgment criteria for happiness.

Changes in Brain Affect Systems During Aging

Mara Mather, University of Southern California

Valence (i.e., degree of pleasantness; pleasant or unpleasant) and arousal (i.e., degree of intensity; high or low) are two key dimensions of affect. Most brain regions involved in emotion processing, including the amygdala, insula, and striatal regions, are activated in response to both positively and negatively valenced stimuli. However, one brain region, the ventromedial prefrontal cortex (PFC), is more associated with positive affect than negative affect. Understanding how the ventromedial PFC plays a specific role in valence has become a robust focus in the field of affective neuroscience.

Valence has a different impact on younger versus older adults' attention and memory, with older adults favoring positive over negative stimuli relatively more than do younger adults. Research has found that this age-related positivity effect size increases when the experiment design does not include a goal-oriented task, which suggests an age-related *and* a goal-related effect. Mather used these observations as a foundation to study the impact of time-perspective manipulation and its subsequent influences on the positivity effect. Mather developed a study paradigm in which participants were divided into two imagined time perspective conditions: expansive (i.e., a life expectancy of 120 years in good health) and limited (i.e., a life expectancy of 6 remaining months in good health). Participants then completed tasks, and researchers recorded how their goals and behaviors changed.

Participants in both the expansive and limited conditions favored positive situations in an age-related manner, with older adults favoring positive stimuli (e.g., viewing a positively valenced image) more than younger adults. However, both younger and older participants in the limited condition favored positive stimuli significantly more than those in the expansive condition. Therefore, one's perception of time may have the power to shift goals, perhaps in a manner not consciously regulated by the individual, suggesting a role for implicit regulatory control of these behaviors.

Gross and colleagues published a model outlining distinctions between implicit and explicit emotion regulation. Explicit regulation is associated with the dorsolateral PFC and other regions involved in cognitive control, while the ventromedial PFC and anterior cingulate cortex (ACC) are associated with implicit control. Mather investigated implicit regulation through an emotion-induced blindness task, in which participants are rapidly shown an array of images and then shown the images again with one image rotated to the right or left. Regardless of an image's positive or negative valence, if the image had evoked a prior emotional response, young adults could not quickly identify the rotated picture (i.e., blindness), suggesting that their attention was captured by the emotional stimulus. Older adults displayed more blindness to positive figures than they did to negative images, suggesting that older adults respond more robustly to positive images. Prior to the task, older adults also displayed a functional connectivity between the amygdala and ventromedial PFC that was more associated with positivity, which suggests a fundamental

readiness for emotion regulation—a result that is consistent with the implicit regulation of emotions.

Cognitive resources are another key contributing factor to the positivity effect noted in older adults. The positivity effect seen in the control group disappeared when cognitive load was increased—such as when older adults were asked to read emotional tones and note when tone patterns changed within a set of images. To further investigate these interactions, Mather integrated these valence- and cognitive load–dependent factors within the emotion-induced blindness task previously described. Without cognitive load, older adults were more blind toward positive images (i.e., their attention was captured by these stimuli), while young adults displayed similar patterns of blindness for both positive and negative images. With increased cognitive load, the increased positivity blindness noted in older adults disappeared, and young adults displayed no effect. These observations suggest that, with cognitive load, older adults can improve task performance by not allocating increased attention to positively valenced images.

Similar to valence, arousal is a critical physiological response involved in affective neuroscience mechanisms. The locus coeruleus (LC) is a small nucleus within the brainstem that mediates arousal, through projections to a variety of brain regions; it also modulates brain function during states of arousal. Inputs to the LC are involved in gathering arousal information regarding behaviors such as sleep, stress response, and cognitive effort. Recently, researchers identified the LC as the first region in the brain to develop Alzheimer's disease (AD) pathology. These studies have found that abnormally phosphorylated tau proteins were found in the LC of a small subset of young children. By the age of 30, all participants displayed abnormal tau proteins in the LC, and a subset of these were identified as Stage 1 AD. These findings present AD as a continuum of pathology that varies by levels of tau pathology present and speed of progression. Mather hopes to study the impact of this abnormal tau protein phenotype within the bounds of the older adult brain's arousal system. Mather hypothesizes that older adults may intrinsically have high-tonic LC activity. Animal models with LC lesions are able to compensate by using the remaining active neurons to maintain levels of norepinephrine. This effect also may cause the age-related differences noted in humans, suggesting that the LC may be able to compensate for age-related phenotypes, although with less dynamic range during a state of arousal.

Challenges for future researchers include understanding how the LC and ventromedial PFC interact in aging, and how those interactions can be optimized. Affective processing is critical to many physiological pathways, and understanding how to optimize these processes will provide great benefits to older adults.

Prefrontal Executive Function and Affect

Brain Dynamics of Neurocognitive Developmental Change in Adolescence: Setting the Stage for Life Trajectories

Beatriz Luna, University of Pittsburgh

Aging is commonly studied in adults, but studies beginning in adolescence may inform the foundation for aging trajectories. Adolescence is characterized as the time when brain maturation processes shift from a stage of accumulation to specialization of functional processes determining life trajectories. Psychopathology typically emerges during this time period, suggesting that studies of this developmental stage may provide information on the initiation of variability in trajectories.

Luna developed The Driven Dual Systems Model, indicating that adolescence is a time when new access to adult-level executive function is driven by enhanced reward motivational processes. This unique balance of cognitive and motivation function, influencing behavior, may underlie the peak in sensation-seeking known to occur in adolescence. This model is supported by Luna's studies that have found evidence for adult-level engagement of prefrontal systems in adolescence during voluntary inhibitory control, in a task whereby subject have to suppress the reflexive tendency to look at a peripheral visual stimulus and adolescents have difficulty performing. Instead they found that adolescents did not engage the anterior cingulate cortex (ACC), a region that supports performance monitoring and engages cognitive control systems.

However, when a reward is contingent on inhibiting a response, adolescent performance improves to adult levels as reward systems are hyper-engaged in the ventral striatum in parallel to increased recruitment of executive inhibitory control systems. Indeed, adolescence dopaminergic systems are engaged at greater levels during a rewarded state. Luna and colleagues found that the ventral tegmental area, where dopamine is produced, is more highly connected to the ventra striatum, where reward is processed, providing further evidence for heightened reward-driven behaviors. More definitive evidence emerged from a recent study by Luna and Larsen. Informed by animal models, they used a molecular magnetic resonance imaging (mMRI) machine, which performs simultaneous MRI and positron emission tomography scans to more directly assess developmental changes in dopaminergic function. Measurements of tissue iron in the brain were also obtained because iron is a key component in dopamine synthesis and allows for non-invasive measures that inform striatal dopaminergic neurophysiology. Tissue iron in the striatum increases through adolescence, and this measure is closely associated with the concentration of a presynaptic dopamine marker.

Findings suggest that the amount of dopamine that an individual synthesizes is established in adolescence, but the density of dopamine receptors decreases with age. In adolescents, more dopamine correlates with better cognition, while increased brain-iron levels undermine cognition in adults. These studies support the Goldman-Rakic model, which

indicates that dopamine and cognition are associated in an inverted-u function where too little or too much undermines cognition. This specific balance may be critical in adolescent brain plasticity for specialization into adulthood, and decreases in dopaminergic processing may attenuate the influence of reward processing on behavior. In aging, striatal dopaminergic systems are further attenuated, affecting the influence of rewards on behavior especially if cognition is decreasing in its ready effectiveness.

Luna and colleagues have also found that during adolescence, brain functional processes show greater variability in their expression associated with variability in cognitive responses. This suggests that the brain may be actively exploring optimal engagement of whole brain systems for optimal behavioral function. Importantly, Luna and colleagues have proposed that adolescence is a time of critical period plasticity when prefrontal executive systems are actively specializing during a time of increased dopaminergic function, leading to specialization and stability in adulthood. Different brain system will become predominant in a Hebbian process of "use it or lose it" into adulthood. Subsequently, brain maturational factors including myelination and perineuronal nets solidify brain systems that will predominate in determining function-defining modes of operation through the lifespan, setting the stage for aging.

Connectivity has been studied to a great degree in the context of adolescence and aging, specifically in three areas: fronto-limbic regions associated with reward processing, fronto-amygdala regions associated with emotion, and fronto-hippocampal regions associated with memory.

The extant literature indicates that with aging, white matter fiber integrity between cognitive networks and basal ganglia remains unchanged, while fibers traveling from limbic systems show decreasing integrity. Connectivity between the amygdala and the ventromedial PFC is reduced, both structurally and functionally, with aging. In contrast, in adolescence fronto-striatal and fronto-amygdala connectivity is increased, suggesting increased predominance of affective systems on cognition. However, connectivity between the hippocampus and executive prefrontal systems increases into adulthood, engaging memory systems and enhancing how experience and context are integrated during puberty. In aging, these circuits are all decreased, affecting both the influence of affective and memory systems on cognitive control of behavior.

Together, these results underscore that adolescence is a time of enhanced reward-driven behaviors within the context of adult-level cognitive control for the purpose of establishing lifespan trajectories. In aging, this mode of operation will set the stage for attenuation of many of these processes that result in varied aging trajectories. Challenges to the field of affective neuroscience include understanding brain mechanisms through in vivo imaging, but these concerns may be mitigated by machine-learning, computational, and big-data approaches. In addition, focus on studying and implementing interventions that improve trajectories in younger adults (i.e., targeted cognitive therapies, brain stimulation, or pharmacological approaches) may impact cognitive trajectories in aging.

Motivational and Affective Influences on Cognitive Aging

Todd Braver, Washington University, St. Louis

Researchers have heavily studied cognitive aging to understand why specific types of cognition show pervasive declines throughout life (i.e., fluid intelligence) while others increase and are stable at older ages (i.e., crystallized intelligence). To elucidate the mechanism behind these changes, researchers have focused on physiological changes observed with age. Brain volume decreases steadily in the lateral PFC and the hippocampus, while the primary visual cortex's volume remains stable. The abundance and density of dopamine receptors decline with age. Further, the de-differentiation of specific neural networks, including the dopaminergic pathway, may cause complex declines in cognition with age.

Conceptual frameworks developed over the past two decades have largely sought to explain the underlying mechanisms of cognition decline; one theoretical framework has focused on a shift in cognitive control. Braver developed the Dual Mechanisms of Control (DMC) framework, which postulates that cognitive aging reflects a dynamic shift from proactive to reactive control mechanisms in the older adult brain. Proactive control uses context and goal information (i.e., reward motivation) to "gate" PFC activity and filter out irrelevant stimuli, allowing the brain to focus on preparatory processes and attentional configuration toward the target event. In contrast, reactive control lacks a context/goal-dependent gating system, which allows the target event to induce transient reactivation of the PFC through episodic retrieval or conflict resolution. The DMC framework heavily relies on temporal dynamics (i.e., sustained vs. transient activity), inter- and intra-individual variation, and malleability (i.e., motivational, affective, and personality influences) that lead to the control mode responses.

Paxton and colleagues investigated temporal dynamics in brain activity and uncovered divergent profiles of sustained and transient activation, reflecting an age-dependent shift. Older adults showed less activation during cue-related activity, but dramatic increases in activation during probe-related activity, which suggests a reactive control strategy. In further support of the DMC theory, Braver found that older adults reported reduced proactive control in response to a cue. In response to a probe, they displayed increased reactive control, as compared to young adults. Braver conducted a follow-up study focusing on the malleability of control modes through training manipulation. Motivational manipulation resulted in an increase in cue-related activity and an overall change in behavioral performance in older adults, suggesting an intrinsic malleability. Young adults showed similar patterns of malleability but were consistently more proactive, while older adults responded reactively.

The DMC theory proposes complementary cost-benefit tradeoffs in control modes, which is supported in the literature. Proactive control is more effective but computationally costly and resource-demanding, which may cause the brain to be biased against this mode. Reactive control is efficient but more vulnerable to failure, because it requires strong

stimulus-specific cues and conflict-detection circuits. These observations led Braver to offer a motivational perspective on cognitive control that incorporates five features:

- Maintenance of cognitive goals is intrinsically costly.
- Goals are prioritized according to motivational (i.e., subjective) value.
- Incentive cues modulate goal representation and maintenance.
- Control is mediated via dopaminergic interactions in the PFC.
- Control engagement is construed as value-based decision-making.

Motivational selectivity is a common theme in many frameworks, specifically in regard to aging. It may be tightly connected with the dopaminergic, age-related effects observed in the PFC during aging. Other frameworks also incorporate cognitive neuroscience perspectives on motivational selectivity, such as Selective Engagement Theory by Hess, which postulates that cost/benefit ratios change with age, and the benefit threshold must be high to promote engagement. In their framework of Motivational Selectivity, Swirsky and Spaniol theorize that cognitive selectivity decreases with age, while motivational selectivity increases. In addition, the Affect-Integration-Motivation framework, crafted by Samanez-Larkin and Knutson, suggests that the frontostriatal circuits responsible for reward motivation are preserved during aging.

This led Braver and Westbrook to develop the Cognitive Effort Discounting (COG-ED) task, which allows a participant to frame cognitive effort decisions in economic terms (i.e., incentivizing participant effort toward different tasks). When shown tasks of varying cognitive load, older adults showed a steady decline in subjective value toward tasks of high effort, suggesting that motivational value is impacted by cognitive load. Incentive sensitivity mediated through the ventral striatum could predict individual variation in cost of cognitive effort (i.e., higher sensitivity of incentives when a low-effort cost was presented).

Future studies of motivational and affective influences on cognition should focus on understanding whether age-related cognitive control declines are malleable; the underlying cause of motivational selectivity in older adults; and whether the emotion paradox of aging can be resolved.

One potential research strategy would be to employ a multi-modal, multi-level analysis, including neuroimaging, laboratory task performance, and ecological momentary assessment (i.e., daily life observations).

The Role of Cerebrovascular Disease and Executive Functions in Affective and Cognitive Functioning in Aging

Faith Gunning, Cornell University

Four percent of older women and 3 percent of older men have a diagnosis of late-life depression (LLD), and LLD increases the risk of dementia, disability, and mortality. LLD represents the clinical expression of dysfunction in reward, salience, and cognitive control

networks. The current working model of LLD incorporates etiologic factors (e.g., vascular changes, genetics, repair responses, inflammation), predisposing factors (e.g., fronto-limbic abnormalities), and stress-related factors (e.g., inflammation, reactive oxygen species, dendritic remodeling) that feed into mechanisms mediating the expression of depression. The Vascular Depression hypothesis emerged from this model. Focusing on a subset of LLD related to vascular changes, this hypothesis posits that fronto-striatal dysfunction is caused by vascular lesions that disrupt the connection between the networks related to mood regulation and executive function, including negative impacts on cerebral blood flow and inflammatory responses. Individuals with vascular depression do not display normative depressive symptoms. Instead, they present with less sad mood and fewer negative thoughts, but poor initiation and more cognitive difficulties. They also do not respond to anti-depression drugs.

Studies by van Sloten linked the Vascular Depression hypothesis with models of white matter disease, which further informed the working model of LLD. In MRI studies, LLD was found to be associated with white matter hyperintensities, microbleeds, and cerebral microinfarcts. Moreover, LLD correlated with PFC hypoactivity and decreased structural connectivity, which may explain the poor executive function and lack of response to medication reported among these patients.

Apathy, which is characterized by a dramatic decrease in goal-directed behavior, is a highly prevalent comorbidity in patients with LLD; these patients display elevated cognitive impairment, increased resistance to treatment, and high risk for white matter disease and stroke. Researchers tested pharmacologic interventions for patients with LLD and those with LLD and apathy, but the interventions were not successful for either condition. This led researchers to attempt neuroscience-informed behavioral interventions to address the underlying pathophysiology, either by "rescuing" inefficient brain networks or by optimizing functions of the brain networks.

Engage-S is a personalized, reward-based psychotherapy tool that aims to improve engagement through exposure to social rewards. This tool would be readily available to community providers. Both animal and human functional MRI (fMRI) evidence suggests that exposure to social rewards provides a protective function, by recalibrating the brain's reward system. The goal of Engage-S is to recondition the reward system through repeated exposure to social interactions, in order to reduce depression and increase behavioral activation. This tool is still in preliminary testing stages, and currently no data are available.

Project EVO is an iPad-based video game that aims to mitigate cognitive control dysfunction. By incorporating gaming principles into a cognitive intervention, researchers hope to target a poorly functioning cognitive network and improve depressive outcomes. Because previous studies have reported that the cognitive cost of multitasking increases with age, Anguera and colleagues tested whether Project EVO improved older adults' multitasking abilities. After 6 months of using the computerized task training, older adults

reported a 10 percent increase in multitasking abilities, although there was no improvement in single-tasking abilities.

Anguera subsequently performed a randomized, controlled trial using participants with LLD, to evaluate the efficacy of Project EVO compared to standard psychotherapy for depression. After 4 weeks, participants' depressive symptoms improved similarly in both the experimental and standard therapy groups, but cognitive control improved only in the video game–based intervention group. Moreover, after 4 weeks of Project EVO, participants displayed demonstrative improvements in daily executive skills, functional connectivity, and mood control over standard therapy. These results suggest that Project EVO may provide an effective and accessible treatment platform that could improve upon standard psychotherapy interventions.

In addition to developing neuroscience-informed interventions, the identification of neuro-imaging biomarkers may help guide the treatment of mood disturbances in patients with LLD. Previous studies by Drysdale and colleagues have identified depression biotypes, each of which has unique functional connectivity phenotypes and depressive-symptom profiles (e.g., anhedonia, anxiety, insomnia). Biotypes 1 (characterized by increased anxiety, fatigue, and activity in the insula and ventrolateral PFC) and 3 (characterized by increased anhedonia, psychomotor retardation, and activity in various brain areas) preferentially respond to repetitive transcranial stimulation, which suggests that personalized treatment across these groups may be beneficial.

Challenges to this field include

- determining whether an MRI is a cost-effective method to guide interventions;
- treatment resistance in specific depression biotypes and subsets;
- limited accessibility of efficacious interventions; and
- engagement of affected individuals in interventions to promote adaptive aging.

How Social and Prosocial Behavior Affect the Brain

Neural and Psychological Mechanisms Linking Social Relationships to Health

James Coan, University of Virginia

Social relationships are intrinsically regulatory. Being social automatically influences a multitude of biological processes, such as cognitive and physical performance, emotion processing, pain, and development. Coan and colleagues focused on why and how sociality imparts these regulatory actions, using hand-holding tasks as a method for sociality.

Coan studied how social relationships may impact an individual's threat response, by recording brain activity from one participant while threatening to provide an electric shock to their counterpart, under three conditions: known partner hand-holding; stranger hand-holding; and no hand-holding. Threat-related activity in the dorsolateral PFC, hypothalamus, and posterior cingulate cortex was dramatically decreased when a participant was holding

hands with a known partner (romantic or otherwise), as compared to when the participant was alone.

The Neurological Pain Signature (NPS) is a tightly patterned expression network of regions in the brain that are associated with pain experience. Previous studies investigating the NPS have found that it is unaffected by placebo treatment, cognitive reappraisal, reward, and perceived control. However, the effect of physical touch had not yet been studied.

Coan posed two hypotheses to predict the impact of hand-holding on the NPS: (1) the effect is mediated through the PFC or (2) the effect is mediated through endogenous opioid activity. Studies exploring the first hypothesis have been unsuccessful, because the ventromedial PFC decreases in functional connectivity with other regions of the network when a person is alone, but once hand-holding is initiated, this effect disappears. The second hypothesis has not been substantiated in the literature: the hand-holding effect was present both with and without endogenous opioid activity. In a recent study, Lopez-Sola and colleagues investigated connectivity as a medium for the NPS-dependent hand-holding; participants reported increased pain relief during hand-holding and also displayed increased connectivity in the primary somatosensory cortex.

These studies suggest that the hand-holding effect is not mediated by self-regulatory mechanisms. This led researchers to infer that the hand-holding effect is induced by proximity to social resources, altering the perception of external demand and internal capability. To study this theory, Coan and colleagues employed a threat-based experimental design that involved holding hands with a friend, stranger, or no one—but in this study, both parties are threatened with electric shock at varying times. Researchers found that, when the threat was addressed to a hand-holding partner who was a friend, the subject's brain responded as if the threat was directed at themselves. The areas involved included the orbitofrontal cortex, lateral PFC, anterior insula, and putamen. Hand-holding with a stranger revealed similar correlations in brain activity.

These findings led Coan and colleagues to form the Social Baseline Theory, an ecological perspective that posits that social relationships economize physiological, cognitive, and emotional labor. Individuals adapt to their social environments, allowing the brain to expect access to predictable and efficacious social resources. Thus, social environments are perceived as resource-abundant niches in which individuals can reference their own capabilities against the accessibility of social resources, thereby creating a social baseline for each person. In the event that social baseline support is low (e.g., relationships are scarce, poor quality, or absent), the brain will mount a stress response to compensate for the lack of resources. With aging, these resources may become more critical, so the next steps in this field will be to understand how social forms of affect regulation are influenced.

Early Adversity and Mid-Life Physical, Cognitive, and Socio-Affective Health
Marc Schulz, Bryn Mawr College

Evidence supports the theory that adversity experienced in youth influences physical, cognitive, and socio-affective health throughout adulthood. According to the Adverse Childhood Experience Study (ACEs) by Felitti and colleagues (1998) and subsequent studies using the ACEs approach, these lasting effects can result in negative mental and physical health outcomes, including alcohol/substance abuse disorders, and can limit occupational success. While the field has applied multiple approaches and methods to analyze the potential impact of youth adversity, most research has been cross-sectional and relied on retrospective self-reports.

Schulz and colleagues are investigating the degree of overlap between retrospective and prospective reports of adversity, the predictive utility of retrospective and prospective reports in predicting adult health, and emotional processing pathways that may mediate childhood adversity–adult functioning links in two distinct cohorts followed since the 1940s: a sample of 268 individuals recruited as students from an elite university and 456 individuals recruited as young adolescents from poor, inner-city neighborhoods. The Harvard Study of Adult Development has followed these original participants closely for more than eight decades, and, more recently, has been studying 1,300 middle-aged children of these original participants. In this recent phase of the study, they have collected (1) a retrospective questionnaire data about childhood adversity and (2) extracted prospective data from study files on the presence/absence of adversity during the childhoods of the second-generation participants.

Schulz and colleagues compared data from the retrospective accounts to the prospective data at both the family and individual levels, in order to identify key differences between retrospective and prospective data. Confirmatory factor analyses found similar structure (e.g., factors) in the components of adversity at both the individual and family levels across the two perspectives. For most types of adversity (e.g., neglect, teasing or bullying at school, domestic violence, and physical or sexual abuse), the retrospective data yielded higher prevalence rates than did the prospective data, particularly with regard to maltreatment. The prospective data did capture similar prevalence rates in regard to school-based stressors, parental mental illness, divorce, and financial stress. These findings led the researchers to conclude that retrospective questionnaires generally capture more cases of adversity, whereas prospective files may selectively capture only the most serious or visible cases.

A recent study by Baldwin and colleagues found poor agreement between retrospective and prospective studies with regard to childhood maltreatment measures. The highest level of data consistency across both methods was found in reports of separation from parent; the lowest was related to emotional abuse. Schulz and colleagues also found generally poor levels of agreement between retrospective and prospective data. The highest levels of

agreement were for marital dissolution and parental death, where there was substantial agreement. Agreement for most types of maltreatment was poor.

Differing primary reporters (i.e., parent versus child), the passage of time (on average the participants were now about age 60), and the mutability of standards and norms (e.g., bullying as a construct was not commonly acknowledged in the 1940s and 1950s when these individuals were children) represent major challenges in these types of studies. Prospective data collection in the Harvard Study of Adult Development was not designed to assess childhood adversity; there were no direct systematic queries. Because of the nature of the study, the data are father-centric (information regarding the mothers are sparse) and there has been some attrition and missing data across five to six decades. Factors to consider about the quality of retrospective data include the motivation of participants, memory deficiencies or biases, and the difficulty of recalling family events in early childhood or beyond the knowledge of a child. While being cautious because of these challenges, researchers can use these retrospective and prospective assessments of adversity to examine their unique links with key adult outcomes. In preliminary analyses in the Harvard Study, retrospective analyses have stronger and more consistent associations with mid-adult health and wellbeing. For example, when examined together, recalled youth adversity has the expected negative links with perceived health and cognitive functioning in adulthood and positive association with anxiety and threat sensitivity. The prospective data only account for a small, but unique part of the variance in adult threat sensitivity, and interestingly this association is negative after controlling for the retrospective contribution.

Results from the Harvard Study of Adult Development and Baldwin and colleagues suggest that both retrospective and prospective accounts of adversity have limitations and that their agreement is often low. The consistently stronger links with adult outcomes found for retrospective data raise concerns about the role of common methods and the limitations of cross-sectional designs. The use of non-self-report data (e.g., biomarkers) for adult health outcomes is one important way to address some of these concerns. Further investigation is required to rigorously test links with retrospective and prospective data for possible confounding factors such as participant compliance, living conditions, and cohort-specific issues.

Longitudinal studies in this area are very rare and must be conducted to obtain more information on the overlap and merits of prospective and retrospective accounts. Future studies should focus on examining the impact of different types of adversity and integrating multiple levels of perspectives (e.g., individual vs. family level accounts of adversity); understanding the developmental timing effects on adversity outcomes; and dissecting the underlying epigenetic, neurodevelopmental, emotion, social, and cognitive mechanisms of the impact of adversity.

Social Brain Connectivity

Meghan Meyer, Dartmouth College

Historically, social brain connectivity has been studied during rest, in part, because the same brain regions associated with social cognition also actively communicate during rest. Resting-state scans have become the standard to understand social brain connectivity and the three distinct subsystems that act as the brain's default network of activity:

- *dorsomedial*: temporoparietal junction (TPJ), lateral temporal cortex, dorsomedial PFC, and temporal pole
- *core*: posterior cingulate cortex and anterior medial PFC
- *medial temporal lobe (MTL)*: retrosplenial cortex, ventromedial PFC, parahippocampal cortex, hippocampus proper, and posterior inferior parietal lobe

The dorsomedial, core, and MTL subsystems are correlated with social inference, reflection of self, and episodic memory, respectively. Each of these systems has displayed age-related declines in connectivity.

In a 2011 study, Sallet and colleagues sought to investigate whether sociality may impact brain structure and function. They assigned 23 macaques at birth to specific social networks of varying size and scanned their brains before and after living in these social networks for a year to analyze connectivity changes. They found that as the network size increased, the brain structure and resting-state functional connectivity in regions that are homologous to the human default network (except the MTL subsystem) also increased.

Previous studies of human aging have established a similar relationship between social networks and the degree of cognitive decline. In one study by Bennett and colleagues, social network size among older adults showed an attenuated relationship between neurofibrillary tangles and cognitive function. These findings are consistent with others suggesting that social networks buffer against cognitive decline in older ages.

In studying three subsystems of the brain's default network in the context of aging and connectivity, Meyer and colleagues found that the dorsomedial subsystem's connectivity decreases with age but increases proportionally as a function of larger social network size.

Each of these studies may highlight a possible site of intervention, to enhance or maintain social brain connectivity during aging. For example, the macaque study suggests that individuals must engage in social activities to experience the benefits of brain growth and increased connectivity. Meyer and colleagues recently crafted a working-memory task, in which participants received information about an increasing number of people. Default regions proportionally increased activity as social network size grew. Activity in the dorsolateral and medial PFC maximally increased when two people were included in the task, and then plateaued.

Together, these studies support the theory that the social brain is engaged by default at rest, and that social-brain connectivity at rest mediates the association between age and social network size. Going forward, social working-memory training may enhance social-brain connectivity and improve outcomes for older adults.

Prosociality and Aging

Ulrich Mayr, University of Oregon

One generally underappreciated, age-related difference is the overall increase in prosocial and decrease in anti-social behavior. For example, older adults are dramatically less likely to break the law than younger adults. From a theoretical perspective, these age-related trends provide an interesting challenge: Crime and other anti-social behaviors are often explained through a dual-systems account, such as in Gottfredson and Hirschi's General Theory of Crime. A patient, deliberative system (typically associated with self-control, working-memory, and PFC integrity) needs to keep an impatient, reward-driven system (often associated with neural reward areas) in check in order to promote prosocial and moral behavior and prevent selfish and socially inadequate behavior. However, the neurocognitive foundation of the deliberative, self-control system, namely PFC integrity and working memory are also known to decline with age. These trends should lead to an increase in anti-social behavior across the life span—the opposite of what is observed. Therefore, the simple dual-systems account does not appear to provide a sufficient explanation for the lifespan development of prosocial tendencies.

An alternative account is the value-based decision framework, which assumes that any behavior (prosocial or otherwise) is the result of a simple cost-benefit analysis. In this context, the economist Jim Adreoni has differentiated between two forms of altruistic behaviors. Impure altruistic actions are motivated by selfish motives, such as signaling wealth or good character. These types of motives can only be fulfilled through actions for which one is actually responsible. Pure altruistic motives, in contrast can be fulfilled by simply seeing someone in need better off, no matter whether one was actively involved in the good deed or not.

In several studies, Mayr and colleagues capitalized on this active/passive distinction for how impure and pure altruistic motives can be satisfied. They showed that even passively observing money going to a charity activates neural reward areas. Furthermore, the greater this activity (compared to the activity when the same amount of money goes to oneself) predicts how much money participants actually give away when they are responsible for giving, in a separate part of the study. These results support the value-based decision framework. They also suggest that pure altruistic motives are an important factor in prosocial behavior and can be measured through neural imaging.

In a cross-sectional study by Hubbard, Mayr, and colleagues, participants ages 20-70 completed a detailed assessment on financial status, real-world giving behavior, and political and religious attitudes, self-reported measures of prosocial tendencies (e.g.,

agreeableness, empathy, compassion), and the neural indicator of pure altruistic motives. In a factor analysis, prosocial disposition, giving choices, and neural utility gave rise to a robust general factor. Importantly, this "general benevolence" factor showed a strong, positive correlation with age, but also with separately assessed, real-world giving and volunteering behavior. These results indicate an age-related shift toward a genuine concern for the wellbeing of others. This motivational shift provides a potential explanation for the often replicated finding that older adults donate substantially more money to charity than young adults.

Future research needs to look at longitudinal trends and attempt to identify the drivers of the observed, motivational differences between young and old adults. Thus, ideal studies to move this field forward would include experiments with lifespan samples, as well as longitudinal neuroscience-based studies of prosociality precursors and trajectories, with the intent to inform subsequent interventions. To provide theoretical guidance in such attempts, Mayr and colleagues have recently proposed to expand the value-based decision framework to incorporate both distal factors (i.e., resources, constraints, or motivational orientations) and proximal factors (e.g., benefits and costs) to predict an individual's prosocial behavior. Understanding prosocial behavior is critical, because it not only benefits society as a whole, but also seems to make the individual actor happier and healthier.

Dynamic Systems Underlying Age-Related Deficits in Social Cognitive Function

Anne Krendl, Indiana University, Bloomington

Social relationships induce a protective effect on physical and mental health. The maintenance of these high-quality relationships is critical for maintaining the health of older adults. However, the social abilities that help older adults build quality relationships decline with age. These social abilities include theory of mind—the ability to accurately infer others' mental or emotional states—emotion recognition, deception detection, and prejudice inhibition. As compared to young adults, older adults typically express more prejudice toward other races and socially stigmatized groups (e.g., the homeless and individuals with substance abuse or mental health conditions). However, older adults with high executive functioning express less prejudice and engage in more inhibition in response to stigma than do older adults with low executive functioning.

Neural correlates of racial stereotyping and prejudice are well characterized in social neuroscience literature. To identify the mechanism underlying older adults' increase in racial prejudice, Krendl and colleagues studied how young and older adults responded to an implicit race-perception task. Older adults with high executive functioning experienced relatively less activity in the amygdala in response to an image of an African American, as compared to older adults with impaired executive ability. Older adults with high executive functioning also had higher levels of connectivity in the PFC, which may attenuate the negative bias.

Studies on age-related deficits of social cognition have two important limitations:

- Studies tend to focus on how specific brain regions respond to a stimulus, and less on how the brain regions involved interact.
- Aging has an impact on more than what is experienced during a task; task activation may be constrained by how brain regions interact at an individual's baseline.

Theory of mind is an important sociocognitive process that is critical for social relationships. During task performance and at rest, older adults typically have impaired theory of mind and decreased activation in the commonly associated regions (i.e., medial PFC and right TPJ). In a recent study by Hughes and colleagues, weakened connections between the right TPJ and temporal pole predicted older adults' theory of mind performance deficits, suggesting that the crosstalk between these two brain regions is important.

Aging is a dynamic process and understanding how aging impacts brain connectivity is critically important. Future studies in network neuroscience will provide unique insights into the effects of aging and cognition. Individual dysregulation differences between rest and task states may highlight points of intervention for increased adaptive aging.

Malleability and Resilience

Novel Brain-Interventional Approaches Towards Promotion of Social-Cognitive and Affective Aging

Natalie Ebner, University of Florida

Oxytocin is a neuropeptide that is synthesized within magnocellular neurons of the paraventricular and supraoptic nuclei of the hypothalamus and released through the posterior pituitary gland into the periphery as well as via projections directly into specific brain regions, such as the amygdala, hippocampus, and the striatum. Oxytocin functions at a variety of physiological and anatomical levels (e.g., cell, epigenetic, peripheral). The proposed benefits of oxytocin reported in the scientific literature include improved physical health (e.g., reduced fatigue, pain, inflammation), social cognition, and socioemotional functioning (e.g., affect, trust). However, oxytocin has not been robustly studied in terms of aging and how age-related alterations in the oxytocin system may inform mechanisms of functional change with age.

Animal research suggests that certain measurements of the oxytocin system appear to be stable during aging such as total oxytocin cell counts within the paraventricular nucleus. However, animal models of aging also display increased oxytocin levels in cerebrospinal fluid, decreased concentration of oxytocin in the septum and hippocampus, and reduced oxytocin receptor gene (OXTR) binding in the caudate putamen, olfactory tubercle, and ventromedial hypothalamic nucleus. Together, these findings implicate oxytocin as a possible mechanism for age-related behavior changes.

Ebner and colleagues proposed the Age-Related Genetic, Neurobiological, Sociobehavioral Model of Oxytocin (AGeNeS-OT) Model, which postulates that oxytocin is associated with a

variety of genetic and epigenetic, neurobiological, and sociobehavioral effects during aging, and each of these systems provides crosstalk to the others. Thus, the AGeNeS-OT model can be used to inform basic research and interventions for older adults. One major challenge to many brain interventions is drug delivery, specifically through the blood–brain barrier, but Born and colleagues found that intranasal administration of synthetic oxytocin circumvents those challenges and can target central functions, possibly via trigeminal or olfactory nerve pathways. Shahrestani and colleagues report that intranasal oxytocin interventions enhance facial emotion identification, as one crucial socioemotional capacity, but these effects have not been applied to an aging population yet.

Recent studies by Ebner's team found that, after self-administering intranasal oxytocin, older male adults displayed a specific increase in socioemotional abilities (i.e., attention toward one's own feelings) and increased connectivity between the amygdala and the medial PFC; these effects were not observed in older female adults. At baseline, older men had the lowest endogenous plasma oxytocin levels, suggesting that this population may be specifically responsive to an oxytocin intervention and may explain why older males displayed the largest improvement in socioemotional abilities; prior to the intervention, this population had the greatest deficit of socioemotional abilities, and providing oxytocin may improve socioemotional processes that were dampened at lower oxytocin concentrations.

A clinical trial (NCT01823146) is currently under way to study the effects of a 4-week, intranasal oxytocin intervention in adults ages 55-95. Each participant undergoes four baseline visits to obtain initial cognitive, socioemotional, and physiological information, which is reassessed when the intervention ends. Preliminary data reveal an increase in regional gray matter volume in the amygdala, hippocampus, and putamen after receiving oxytocin treatment, which is consistent with animal model studies. The oxytocin-induced putamen enlargement was associated with improved processing speed. Thus far, the trial has found no side effects of intranasal oxytocin treatment. This intervention shows promise for promoting and improving socioemotional abilities in older adults.

Neurofeedback is another research area that may provide an avenue for intervention in older adults, specifically through real-time functional MRI (rtfMRI) to train and promote cognition and emotional processing. Neurofeedback is a type of physiological feedback that presents neural activity to a participant performing a task during an MRI scan to facilitate real-time self-regulation. Previous studies have found that rtfMRI-guided neurofeedback training resulted in improved control over target brain regions. However, this technique has not yet been applied in the context of aging, and behavioral benefits of this technique are less clear. Other researchers have proposed models focusing the rtfMRI neuroregulatory intervention within the dorsal ACC, which typically shows reduced activation during aging, to overcome age-related attention deficits and improve processing. Preliminary data from Ebner's ongoing Flexible Brain Study (NCT03872414) have shown that neurofeedback methods are successful in young and certain older participants, but these results are not universal across the cohort.

The field must include more novel tools, such as rtfMRI-guided neurofeedback and pharmacological interventions (i.e., oxytocin administration), to further promote healthy and adaptive aging. Challenges to these studies include the lack of established standards (e.g., dosage, frequency, training scheme, tasks used, analysis protocols), especially in sociocognitive or affective research. Another challenge is the high demand that these studies place on participants, leading to potential recruitment and compliance concerns. Researchers must continue to seek new mechanisms and techniques to improve outcomes for older adults. They also must consider inter-individual differences in response to treatment and ensure that these interventions can have a translational impact.

The Gut Microbiome, Behavior, and Aging

Janice Kiecolt-Glaser, The Ohio State University

The human microbiome includes more than 1,000 diverse microbial species, whose collective genomes are 150 times larger than the human genome. Microbiota are the body's denizens: they absorb and digest nutrients supplied by their host, synthesize vitamins and neurotransmitters, and regulate immune, endocrine, and neuronal functions. A healthy microbiome is diverse in both richness (i.e., the number of species present) and evenness (i.e., abundance across all species). However, this diversity has been shown to decrease with age. This imbalance, also known as dysbiosis, is associated with immunosenescence, chronic inflammation, frailty, and chronic diseases.

The microbiome regulates many pathways in the brain, through a network called the bidirectional microbiota-gut-brain axis. Stress and negative emotional responses can influence the microbial composition and habitat of the gut and lead to dysbiosis, as shown in mouse models, where stress was associated with declines in the richness and diversity of the microbiota. Gut dysbiosis also can disrupt tight junctions in the gut epithelia and induce a more porous intestinal barrier, highlighting the need for maintaining gut–brain access.

Leakiness of the gut is associated with stress and a decrease in microbiota diversity. Leakiness involves the mucosal layers of the gut increasing in permeability, to the degree that bacterial products can enter circulation and mount an inflammatory response. Kiecolt-Glaser and colleagues studied the impact of hostile behavior on gut leakiness, by having couples discuss a disagreement. Interestingly, the quality of the couple's interaction was strongly related to physiology; the more negative behaviors experienced during the conflict correlated with increased production of lipopolysaccharide-binding protein (LBP), a common biomarker for endotoxemia (i.e., gut leakiness). Further, those individuals with high levels of LBP correlated with dramatically increased levels of C-reactive protein (CRP), a measure of inflammation.

Clostridium difficile (*C. diff.*) is a common gut bacterium that, during dysbiosis, can cause damaging infections in humans and animals. While 90 percent of hospital-related *C. diff.* infections are cured, approximately 20 percent of infections recur, even after antibody treatment. Fecal microbiota transplants can mitigate the infection, but specific microbiota

populations have been shown to cause unwanted effects in the recipient of the transplant. For example, a fecal transplant from a donor can cause the recipient to gain weight.

Stress and depression induce poor health behaviors, such as unhealthy eating habits, sedentary behavior, smoking, alcohol abuse, and poor sleep quality. Specific to diet, high caloric intake, sugary foods, and low vegetable intake are all associated with depression; the converse is also seen (i.e., healthy diets associated with reduced depressive symptoms). A healthy diet is the best method for maintaining the microbiome. Studies have found the Mediterranean diet to reduce inflammation and reduce risk for depression, cardiovascular disease, type 2 diabetes, and total mortality. Overall, these observations solidify the links among the microbiome, behavior, and overall health.

Research in this field must focus on age-related changes in gastrointestinal physiology, to elucidate how these changes affect digestion, absorption, microbiota composition, and function of the microbiome. Further, it is not clear whether chronological aging is the primary indicator, or whether health status, medication use, and other lifestyle factors may be playing a larger role. Further understanding of the relationship between the gut microbiota and age-related neurological changes may provide a basis for the development of interventions to improve cognitive functioning and promote healthy behaviors.

The Role of Positive Emotion Regulation for Adaptive Aging

Judith T. Moskowitz, Northwestern University

Many skills, behaviors, and practices have been studied for their capacity to maintain positive affect in the midst of stress. In order to identify methods for stress reduction, Moskowitz previously studied caregivers who provided care to a partner with acquired immunodeficiency syndrome (AIDS) or who recently experienced the death of a partner due to AIDS. Participants were interviewed on a weekly basis about negative feelings and outcomes in response to the stress. While the caregivers reported negative experiences regarding the situation, many participants questioned why the researchers were not also asking about positive events that had occurred during the week. Subsequent interviews included questions about meaningful positive events, and 99 percent of the responses contained positive updates (i.e., partner made dinner). Noticing positive events is one of the practices employed to increase positive affect; others include emotional literacy, mindfulness, positive reappraisal, and focus on strengths. Most importantly, interventions using these practices must be studied in a real-life setting, in order to impart positive emotional control on a daily basis and promote higher overall levels of wellbeing.

These observations led Moskowitz and colleagues to establish studies with a day-to-day component. One such study was the Aging and Lifespan Optimization of Emotion (ALOE) Study, which is ongoing and seeks to investigate positive emotional reactivity and aging outside of a laboratory setting. Another such study is the Mobile Affect Regulation Intervention with the Goal of Lowering Depression (MARIGOLD) Study, an online, self-guided survey that participants completed weekly at home to report on their emotions. The

in-home survey participants' responses were compared to a control group who reported their daily emotions to researchers without the online intervention. Participants receiving the intervention were further divided into subgroups—receiving the intervention either by itself or with resource enhancements, such as facilitator contact, online discussion board access, and/or virtual badges for participation. Participants were assessed at baseline, post-intervention, and at a 1-month and 3-month follow-up. Researchers adapted the Daily Inventory of Stressful Events (DISE) from the Midlife in the United States (MIDUS) Study to record a participant's daily emotions and stressful experiences. From baseline to the 3-month follow-up, participants showed greater increases in daily positive emotions, as compared to the control group. Participants displayed reduced emotional reactivity to stress over time, relative to the control group, suggesting a better ability to decrease negative emotion and maintain or increase positive emotion in response to stressful situations. Further, a reduction in depression was recorded in the MARIGOLD participants. No age-related effects were observed in terms of either positive or negative emotion reactivity.

These interventional studies highlight older adults' ability to reappraise situations in favor of positive experiences. Incorporating more imaging components and biomarker analyses into these studies would add robustness and effectiveness to such interventions and could promote adaptive aging through improved affective processing.

Sleep's Role in Age-Related Changes in Emotion and Cognition

Rebecca Spencer, University of Massachusetts, Amherst

The Two-Process Model of Sleep Regulation is characterized by the intertwining of the circadian alerting signal and homeostatic sleep pressure, which collectively drive sleep and sleep timing. The circadian altering signal promotes alertness in an individual after waking up, which steadily declines throughout the day. Homeostatic sleep pressure, like a thermostat, will be low when you wake up but accumulate across the day. This homeostat will increase sleep propensity when sleep pressure is high (it has been awhile since sleep or sleep has been insufficient). Sleep is optimized when the circadian altering signal is at its lowest and homeostatic sleep pressure is highest.

Older adults circadian clock is phase advanced: they tend to go to bed early. They also experience a dampened circadian rhythm. Older adults take more naps than younger adults, causing the homeostatic sleep drive and its recovery periods to become shallow. As a result, aging changes the timing of the sleep process, which can impair social, mental, and emotional functioning.

Sleep architecture, or the proportions of time spent in specific sleep stages, also changes with aging. Older adults experience less sleep overall and specifically less rapid-eye movement (REM) sleep, less slow-wave sleep (SWS), and more non-REM stage 2 (N2) sleep. Each of these sleep stages performs a unique function: SWS is associated with memory

consolidation and glymphatic function, REM is associated with emotion processing, and N2 is associated with motor learning.

Jones and colleagues studied the intersection of sleep and emotional memory during aging, by presenting images to provoke positive or negative emotion and asking participants to rate each image in terms of valence and arousal. After a period of sleep or wakefulness, participants were asked to recall which images they rated previously. Young adults showed a sleep benefit (better memory following sleep than an equivalent period of wake) for negative items but not positive items. Conversely, older adults had a sleep benefit for positive but not negative items. These benefits to memory were associated with SWS for both groups. Changes in valence paralleled the changes in memory. Young adults show a protection of valence for negative items following sleep while older adults showed a protection of emotional valence for positive (and not negative items) following sleep. This protection of valence for both groups was associated with time spent in REM sleep late in the night (i.e., REM3%).

These age-related changes may be explained by mechanisms present during SWS sleep; memories are replayed during this stage. Rodent model studies by Colgin and colleagues (2016) found a higher correlation between hippocampal firing during task-learning if the task was followed by rest compared to the control condition (i.e., no rest). MRI studies during sleep in humans illustrate that the hippocampus is active during sleep, specifically the parahippocampal gyrus. Together, these studies and observations suggest that a memory replay in the hippocampus during SWS sleep, in conjunction with synchronous cortical firing (in the form of sleep spindles and slow oscillations) integrate memories to form a more stable memory in the cortex. These mechanisms are age-dependent, because aging is associated with reduced SWS sleep, impaired relay ability, and reduced volume and integrity in the hippocampus and amygdala.

Age-related changes in sleep and circadian rhythms can impair socioemotional functioning. Brain function can be dramatically altered by poor sleep, including reduced memory restructuring, reduced hippocampal replay, and reduced PFC function and connectivity. Previous studies have sought to develop interventions to target and improve sleep. Findings indicated that cognitive behavioral therapy and activities such as taking daily walks can improve sleep. However, effect sizes for these studies are small. Such research could be improved upon, to identify and support robust interventions to promote better sleep throughout the lifespan.

Group Discussion 1: New Avenues for Aging Research

Facilitator: Beatriz Luna, University of Pittsburgh

Perception of Older Adults

In assessing where the field of affective and social neuroscience may proceed, it is important to revisit the scope and goals of the meeting: lifespans are lengthening, and leveraging research on social and affective function in aging may inform how to ensure the best possible trajectories and promote improved quality of life for older adults. Negative

stereotypes about older adults are important to remember because they exist and can be difficult to counter within aging populations and society as a whole, leading to adverse impacts on health and behavior. Such negative perceptions about aging can limit the ability of researchers (especially those less familiar with aging research) and others to both recognize and promote the strengths of older populations (i.e., greater life experience and increased prosocial behavior). Whereas, on average, cognitive ability declines with age, not all older individuals develop cognitive impairment, and variations in cognitive ability are apparent at all ages. Study designs also must be cognizant of how these confounding factors (i.e., negative perceptions of aging) may influence well-established age-related differences, such as working memory decline.

Normative and Abnormal Aging

The field of social and affective neuroscience and aging would greatly benefit from defining normal and abnormal aging processes and patterns. Establishing a trajectory of normal aging in social and affective domains will inform researchers on age-related variability among older adults, highlighting specific concerns, developmental areas of interest, and normal types of decline or improvement. In addition, such a trajectory may elucidate key factors or behaviors that impart protective effects, such as resilience and adaptability. In addition, studies of aging and psychiatric disorders typically focus on patient outcomes, but they could greatly benefit from establishing a baseline for normal functioning (possibly through an extension of the Baby Brain and Cognitive Development or Adolescent Brain and Cognitive Development studies to include older age groups). Increased incidence of depression and other age-related phenotypes may be linked to specific exposures or capacities present earlier in life, and tracking that development would be beneficial. Disadvantaged groups may experience health disparities that affect the trajectory of aging; these individuals may age at a faster rate and experience declines earlier in life. Determining the social context and affective processes that account for such disparities, as well as how disadvantage impacts normal aging, will aid in developing strategies to improve the quality of life for the entire aging population.

Social Connections

Social connections are critical for maintaining positive health at any life stage, and uncovering the mechanisms mediating these benefits will inform future intervention strategies. Social isolation is known to increase with age because of many factors, including mobility limitations, declining health, loss of social network members or social roles, and increasing numbers of older adults living alone, and is associated with a variety of negative health outcomes. For example, having a social network with ample resources is associated with suppression of AD progression. Social networks form a baseline of cognitive and emotional resources to which an individual becomes acclimated, and they can provide a protective effect in response to stressors and other negatively valenced situations. A common misconception about aging is that older adults experience fewer stressors because they may be retired and settled. However, for many older adults, retirement is stressful: it entails moving from a state of known and dependable patterns to a state of unknowns and changes in social resources, which can cause negative outcomes such as depression,

isolation, and perceived lack of purpose. Understanding methods for mitigating these stressors for older adults would substantially improve quality of life and could produce interventions to promote a healthier trajectory.

Self-Regulation

Studies such as those presented by Isaacowitz showed a lack of age-related differences in emotion regulation. However, differences may be present in other forms of regulation. For example, self-regulation implicitly functions to select situations the individual views as lower-cost and cognitively favorable, in lieu of turning to a social resource. The difference between social regulation and self-regulation may uncover specific age-related differences that highlight possible mechanisms of the positivity bias seen in older adults. Including additional tasks to evaluate self-regulation alongside other forms of regulation will highlight, measure, and improve the understanding of age-related regulation.

Group Discussion 2: Paradox of Social and Emotional Function

Facilitator: Natalie Ebner, University of Florida

Heterogeneity of Older Adults

Many researchers within the field of social and affective neuroscience have investigated and heavily debated the possibility of an age-related paradox between social, emotional, and cognitive processes. Social and emotional functioning improve during aging, while cognitive function declines. At an aggregate level, this paradox appears to be accurate. On average, older adults experience cognitive declines and show improvements in social and emotional processing. However, the field must transition from these aggregate studies toward individual-level studies in order to probe sub-population and individual differences in affective and cognitive functions in aging. Older adults are not a uniform population with similar cognitive abilities, experiences, and motivations. Instead, they display a wide spectrum of cognitive and socioemotional abilities, as well as disabilities, which suggests that this paradox may not be accurate for all older adults. Therefore, research questions could be reframed to investigate how cognitive abilities may predict changes in affective processing and how these mechanisms can be altered to improve affect outcomes. Including targeted sampling of a specific group of older adults, such as those with limited mobility or hearing, will provide additional information to understand the vast variability in aging processes.

Integrated Processing Systems

Not all researchers are convinced that the abovementioned paradox accurately depicts age-related processing changes. Social, emotional, and cognitive functioning mechanisms should be studied as an integrated processing system rather than in isolation. The paradox does not include the possibility of interplay between the three processing streams (social, emotional, and cognitive) and how these interactions may adapt or decline in aging. It is highly probable that affective processing interacts with cognitive functioning indirectly throughout the lifespan, but these interactions are understudied. The main challenges to determining the validity of this paradox are that the mechanisms of action for each pathway

are not well-established, and they are not well understood as an integrated regulatory system. Improving the understanding of these processes at a granular level would improve researchers' ability to understand the individual impact and trajectory of each pathway, as well as how these pathways integrate and change with age.

Group Discussion 3: Adaptive Aging in a Real-World Context

Facilitator: James Coan, University of Virginia

Real World Context and Generalizability

A major issue within the field of social and affective neuroscience is the pervasive lack of real-world context. Most research takes place within a laboratory setting, in which participants do not naturally interact with other people; thus, these experiments cannot map efficiently onto real-world behaviors. Many studies highlight the importance of environment, and their outcomes will be more applicable and translatable if they study older adults in a natural and comfortable setting. Sleep, adaptive function, relationship behavior, and health behavior (i.e., diet and exercise) would benefit from real-world research to inform mechanisms of environmental design, social regulation, implicit regulation, and explicit self-regulation. It should be noted that laboratory or clinical studies still hold significance in the field, because the clinic is a normative environment for some older adults.

Many developed interventions are not generalizable to the general population because of specific study limitations and the lack of real-world context. Study designs can be improved through better understanding of how researchers seek to generalize and how well laboratory studies can be generalized (e.g., diversity of subjects, situations).

Studies may be generalized to older adults as a homogeneous group, but older adults are in varying degrees of physical and cognitive health. One may be running marathons, while another of the same age is in a nursing home, and therefore understanding the heterogeneity of older adults is pertinent to creating representative cohorts of participants. In addition to the need for individual-level studies, environment-level interventions may uncover other types of age-related effects (e.g., feelings of social isolation) and maximize an ecological type of change.

Study Design Improvements

The challenges of real-world context and generalizability, as well as accessibility and scalability of interventions, must be met in order to produce advancements in the field. Interventions may be successful in the laboratory without improving the lives of older adults, even if the intervention is properly studied and implemented. Improvements are needed regarding study design and methods, to account for real-world and real-time measurements and generalizability. Strategies such as quasi-experimental studies, field research, and situational sampling may mitigate issues of accessibility, scaling, and effectiveness to produce more accurate findings of daily activities and behaviors, which will help inform better interventions.

In addition, interventions must be robustly validated at each level of the translational spectrum (i.e., from basic laboratory science to randomized, controlled trials) with novel methodologies that add generalizability. Incorporating implementation and dissemination experts at the translational levels of intervention and study design would also address concerns and highlight possible sites of improvement, facilitating the smoother implementation of interventions.

If we hope to tailor interventions that meet the greatest needs, future research should include subpopulations of older adults, such as those in nursing homes and those in disadvantaged groups, both before and after retirement. Doing so will improve the breadth and quality of information available.

Appendix 1: Agenda

Leveraging Insights and Approaches from Social and Affective Neuroscience to Promote Adaptive Aging: A Workshop

The National Academies of Science, Engineering, and Medicine
The Keck Center, 500 5th Street NW, Room 106

November 18-19, 2019

Day One: November 18, 2019

9:00 am **Welcome and Academies Introduction**
Adrienne Stith Butler, NAS, BBCSS

Overview of Workshop
Mara Mather, University of Southern California

Sponsor's Welcome
Lisbeth Nielsen and Luci Roberts, NIA

9:30 am **Basic Issues in the Social and Affective Neuroscience of Aging**

Speakers:
- Derek Isaacowitz, Northeastern University
- Mara Mather, University of Southern California

10:30 am **Prefrontal Executive Function and Affect**

Speakers:
- Beatriz Luna, University of Pittsburgh
- Todd Braver, University of Washington in St. Louis
- Faith Gunning, Cornell University

12:00 pm **Lunch**

1:15 pm **How Social and Prosocial Behavior Affect the Brain**

Speakers:
- James Coan, University of Virginia
- Marc Schulz, Bryn Mawr College
- Meghan Meyer, Dartmouth College
- Ulrich Mayr, University of Oregon

3:15 pm **Break**

3:30 pm **How Social and Prosocial Behavior Affect the Brain, Continued**

Speaker:
- Anne Krendl, Indiana University, Bloomington

4:00 pm **Malleability and Resilience**

Speaker:
- Natalie Ebner, University of Florida

4:30 pm **Adjourn Day One**

Day 2: November 19, 2019

9:00 am **Welcome**
Mara Mather, University of Southern California

9:15 am **Malleability and Resilience, Continued**

Speakers:
- Janice Kiecolt-Glaser, The Ohio State University
- Judith T. Moskowitz, Northwestern University
- Rebecca Spencer, University of Massachusetts

10:45 am **Break**

11:00 am **Group Discussion 1: New Avenues for Aging Research**
Beatriz Luna, University of Pittsburgh (Facilitator)

11:45 am **Lunch**

12:45 pm **Group Discussion 2: Paradox of Social and Emotional Function**
Natalie Ebner, University of Florida (Facilitator)

1:30 pm **Group Discussion 3: Adaptive Aging in Real World Context**
James Coan, University of Virginia (Facilitator)

2:15 pm **Closing Comments**
Mara Mather, University of Southern California

2:30 pm **Adjourn Day Two**

Appendix 2: Attendees

Leveraging Insights and Approaches from Social and Affective Neuroscience to Promote Adaptive Aging: A Workshop

The National Academies of Science, Engineering, and Medicine
The Keck Center, 500 5th Street NW, Room 106

November 18-19, 2019

Speakers
Todd Braver, Washington University, St. Louis
*James Coan, University of Virginia
*Natalie Ebner, University of Florida
Faith Gunning, Cornell University
*Derek Isaacowitz, Northeastern University
Janice Kiecolt-Glaser, The Ohio State University
Anne Krendl, Indiana University, Bloomington
*Beatriz Luna, University of Pittsburgh
*Mara Mather, Workshop Steering Committee Chair, University of Southern California
Ulrich Mayr, University of Oregon
Judith Moskowitz, Northwestern University
Meghan Meyer, Dartmouth College
*Marc Schulz, Bryn Mawr College
Rebecca Spencer, University of Massachusetts

National Institute on Aging
Audie Atienza, Senior Program Officer, Division of Behavioral and Social Research (DBSR)
Melissa Gerald, Program Director, DBSR
Lisbeth Nielsen, Chief, Individual Behavioral Processes Branch, DBSR
Luci Roberts, Program Officer, Division of Neuroscience
Luke Stoeckel, Program Director, Mechanistic and Translational Decision Science, DBSR
Bethany Stokes, Rose Li & Associates (contractor)

National Academies, Board of Behavioral, Cognitive, and Sensory Science
Adrienne Stith Butler, Associate Board Director
Julie Shuck, Study Director
Jacquie Cole Miles, Senior Program Assistant

** Workshop Steering Committee Members*