Neural Processes of Affective Change in Aging

August 2-3, 2018

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Contents

Acronyms

2-AG	2-Arachidonoylglycerol
AD	Alzheimer's disease
BLA	basolateral amygdala
CFC	contextual fear conditioning
DG	dentrate gyrus
EBR	eyeblink startle reflex
EMG	electromyography
FTD	frontotemporal dementia
fMRI	functional MRI
HPA	hypothalamic-pituitary-adrenal
LC	locus coeruleus
MIDUS	Midlife in the United States study
MRI	magnetic resonance imaging
MTL	medial temporal lobe
NE	norepinephrine
NFE	novelty facilitated extinction
NMDA	*N*-methyl-D-aspartate
PET	positron emission tomography
PFC	prefrontal cortex
PPA	Parahippocampal Place Area
REM	rapid eye movement
VMPFC	ventromedial PFC
VTA	ventral tegmental area

Introduction

Affective neuroscience research is conducted at different levels of analysis with varied approaches. There is a need to foster collaboration in the affective neuroscience field among basic, animal, behavioral, and population-level researchers. On August 2-3, 2018, the National Institute on Aging Divisions of Behavioral and Social Research and Neuroscience convened an expert workshop in Bethesda, Maryland, to discuss developments in affective neuroscience research as it relates to aging, enhance collaboration opportunities, and advance knowledge within the field.

The aim of the workshop was to generate insights that can inform new causal hypotheses to explain aging-related changes in human affect. Experts from both within and outside the aging field addressed (1) the foundations and historical context of affective neuroscience of aging related to the experience, perception, and regulation of emotion and (2) emerging theories and approaches in affective neuroscience related to neural networks in affective neuroscience, neuromodulatory influences on affective processes and motivated behavior, neural circuitry for associative learning and affective regulation, and alignment of studies in animals and humans to accelerate research on emotional function in aging. The workshop highlighted questions and knowledge gaps related to these issues and included discussion of the complex relationships between experimental constructs, animal models, human neurophysiology, and behavioral plasticity. The goal of these discussions was to expand theories and approaches in aging. The full agenda is provided in Appendix A, and the participants list is provided in Appendix B.

Age-Related Changes in Emotion and Emotion Regulation

Kevin Ochsner, Columbia University

There have been many hypotheses to explain why, in cross-sectional studies, older adults tend to report more positive affect than younger adults. In recent years imaging data have shown increased prefrontal cortex (PFC) activity in older adults when viewing stimuli with emotional valence,[1] which suggests that executive function may play a key role in age-related affective changes and could implicate cognitive emotion regulation strategies known to depend on PFC, such as reappraisal.[2] Reappraisal involves reinterpreting an emotionally charged stimulus in ways that alter the affective response. However, the hypothesis that older adults experience more positive affect because of increased executive control in PFC seems to contradict the well-known structural degradation of PFC over time, along with the concomitant normative cognitive decline associated with aging. Investigators have attempted to resolve the apparent paradox by differentiating two forms of reappraisal for negative stimuli: (1) minimizing reappraisal, during which the intensity of both negative valence and arousal is down-modulated, and (2) positive reappraisal, during which the negative valence *itself* is re-cast to become more positive. The former is likely more effortful and more reliant on cognitive control

[1] K. Nashiro, et al., "Age differences in brain activity during emotion processing: reflections of age-related decline or increased emotion regulation," *Gerontology* 58, 156-163 (2012).

[2] K.N. Ochsner, et al., "Functional imaging studies of emotion regulation: a synthetic review and evolving model of the cognitive control of emotion," *Ann. N. Y. Acad. Sci.* 1251(1) (2012).

processes, whereas the latter is more likely to align with older adults' known tendencies to choose to look at and better remember positive stimuli.

As such, investigators hypothesized that positive reappraisal on its own may explain why older adults tend to experience more positive affect. Brain imaging data from behavioral trials comparing older and younger adults showed that older adults were less effective than younger adults at diminishing negative affect, but were more effective at generating positive affect, even when exposed to negative stimuli and not instructed by investigators to do so. Further studies have shown that older adults choose to reappraise more frequently than younger adults, but both young and older individuals distribute their choices equally between minimizing reappraisal and positive reappraisal strategies. Expanding on previous work,[3] Dore and colleagues are using the multivariate Picture-Induced Negative Emotion Signature[4]—a pattern of brain activity in regions such as the left amygdala, right insula, and posterior cingulate cortex that activates in response to photographs with negative emotional valence—to test whether brain data can predict age-related differences in regulation choices. Results again suggest that older adults choose to regulate their emotions more often. Additional behavioral experiments have found evidence that making categorical judgements of emotional stimuli leads to a boundary effect, wherein perceptions of emotion shift when going from continuous to categorial judgements. This category boundary effect was also linked to shifts in amygdala and insular brain activity according to *conscious* emotional categorizations, revealing another link between executive function and affective states.[5] Future research will utilize at-home experiments to investigate categorization thresholds with greater ecological validity.

Emotional Aging: Expecting Differences, Finding Some Similarity

Derek Isaacowitz, Northeastern University

Older adults report more positive and less negative affect than younger adults.[6] Socioemotional selectivity theory suggests that motivational shifts lead older adults to attend more to, and better remember, positive as opposed to negative stimuli. Isaacowitz and colleagues have focused on emotion regulation strategies earlier in the process model than reappraisal, such as situation selection and attentional deployment. They used stationary eye tracking tasks to test the attentional hypothesis in two parts: (1) Do older and younger adults attend differently to the same valenced stimuli? and (2) If so, is this linked to differences in self-reported emotion experience between older and younger adults? Findings showed fairly robust attentional preferences for positive and away from negative stimuli in older adults compared to younger

[3] B.P. Doré, et al., "Neural predictors of decisions to cognitively control emotion," *J. Neurosci.* 37(10), 2580-2588 (2017).
[4] L.J. Chang, et al., "A sensitive and specific neural signature for picture-induced negative affect," *PLoS Biol.* 13(6), e1002180 (2015).
[5] A.B. Satpute, et al., "Emotions in 'black and white' or shades of gray? How we think about emotion shapes our perception and neural representation of emotion," *Psychol. Sci.* 27(11), 1428-1442 (2016).
[6] D.K. Mroczek and C.M. Kolarz, "The effect of age on positive and negative affect: a developmental perspective on happiness," *J. Pers. Soc. Psychol.* 75, 1333-1349 (1998).

adults. However, these preferences to attend to positive stimuli were not consistently linked to self-reports of positive affect, suggesting they may not always serve as emotion regulation strategies.[7]

Isaacowitz and colleagues also considered the possibility that stronger positive affect in older adults may result from older adults' intentional reduction in exposure to negative stimuli (a form of situation selection), rather than to more positive attention. This hypothesis has been tested by creating affective environments containing negative, neutral, and positive stimuli, and allowing older and younger adults to select their emotional exposures. Findings to date consistently show no age differences in situation selection.[8] In a forthcoming study of aging and emotion regulation tasks led by Kimberly Livingstone,[9] adults of different ages completed a series of five tasks representing each strategy type specified by the process model: situation selection, situation modification, attentional deployment, cognitive change, and response modulation. For example, for situation modification, participants watched videos of increasingly intense valence (both positive and negative videos were used) and were told that they could press the space bar on a keyboard as often as they liked to skip 10 seconds ahead. Researchers were interested in how often differing age groups would choose to skip content for both positive and negative videos, at different valence intensities. Preliminary Bayesian analyses for preferences (effectiveness data are not yet available) suggest few to no meaningful age differences across the emotion regulation tasks.

These results raise several issues for the broader field of affective aging. Journals tend to reject papers that do not feature significant age-related differences because a lack of age differences does not equate to age similarity. However, tools such as Bayesian analysis and two one-sided test (TOST) can help to quantify confidence that null effects are meaningful, though these methods may require large samples. Null age effects using these more nuanced analyses should be publishable and should inform theories of aging. Evidence now suggests that there may be substantial similarities in emotion regulation strategies across ages. Thus, socioemotional theories of aging should account for contextual, task-based, and other factors that may help to predict and explain not only when age groups are different in emotional processes, but also when they are similar.

Discussion

Dr. Isaacowitz explained that his research team has modified many stimulus factors in both the affective environment and in eye tracking studies of attention in search of potential moderators, but thus far have not identified any clear patterns. However, because the strongest positivity effects in studies of attention have been found in the most highly

[7] D.M. Isaacowitz and F. Blanchard-Fields, "Linking process and outcome in the study of emotion and aging," *Perspect. Psychol. Sci.* 7(1), 3-17 (2012).

[8] M. Sands, et al., "Characterizing age-related positivity effects in situation selection," *Int. J. Behav. Dev.* 42(4), 396-404 (2018).

[9] K.M. Livingstone and D.M. Isaacowitz. "Age differences and similarities in spontaneous use of emotion regulation tactics across five laboratory tasks." *J. Exp. Psychol. Gen.* (in press).

constructed experimental situations, further eye tracking trials are currently being conducted in participants' homes to more directly investigate possible contextual factors.

Emotional Valence and Arousal in the Aging Brain

Mara Mather, University of Southern California

Structural volume of the PFC, which is associated with emotional regulation, declines with age. Yet, older adults show improved emotional regulation compared with younger adults. While investigating this paradox, researchers found that working memory resources appear related to positivity bias in older adults, such that older adults' bias for remembering relatively more positive than negative items and events than younger adults do disappears under a greater working memory load.[10] Previous hypotheses have suggested that older adults choose to prioritize emotional goals because of their perception of limited remaining time in their life. New research shows that, compared with younger adults, older adults experience very rapid attentional distraction (within 200 milliseconds of stimulus onset) in response to positive stimuli, suggesting a pre-conscious mechanism.[11] Surprisingly, even this positivity effect in early attention disappeared under working memory load. Thus, older adults' inclination to preferentially process positive stimuli is seen at early stages of attention yet depends on cognitive capacity at that moment. In addition, this bias may be tied to increased resting-state functional connectivity between PFC and the amygdala.[12]

Attention and memory are also influenced by arousal, which enhances processing of salient stimuli. The locus coeruleus (LC) modulates brain activity according to momentary changes in arousal. It is hypothesized that noradrenergic neurons project from the LC, releasing norepinephrine (NE) at varicosities with NMDA (*N*-methyl-D-aspartate) receptors. Excitatory glutamate spills over from nearby synapses, binding to NMDA receptors, interacting with NE, and creating local hotspots of activity.[13] Researchers investigated age differences by targeting the Parahippocampal Place Area (PPA) using high- and low-salience images of buildings and pairing them with fear-conditioned tones to test the influence of arousal on PPA processing.[14] Younger adults' frontoparietal network showed greater increases in connectivity with the LC under arousal than those of older adults. The younger group also showed an interaction effect in PPA activity between arousal and salience processing while the older group did not. These age differences suggest that arousal induces excitatory and inhibitory effects through different

[10] Mather, M., & Knight, M. "Goal-directed memory: The role of cognitive control in older adults' emotional memory." *Psychol. Aging.* 20(4), 554-570 (2005).
[11] B.L. Kennedy, R. Huang, M. Mather. "Age differences in emotion-induced blindness: Positivity effects in early attention." Manuscript under review.
[12] M. Sakaki, et al., "Amygdala functional connectivity with medial prefrontal cortex at rest predicts the positivity effect in older adults' memory," *J. Cogn. Neurosci.* 25(8), 1206-24 (2013).
[13] M. Mather, et al., "Norepinephrine ignites local hotspots of neuronal excitation: how arousal amplifies selectivity in perception and memory," *Behav. Brain Sci.* 39:e200 (2016).
[14] T.H. Lee, et al., "Arousal increases neural gain via the locus coeruleus-noradrenaline system in younger adults but not in older adults," *Nat. Hum. Behav.* 2, 356-366 (2018).

mechanisms: the former by direct LC interactions with specific cortical areas, and the latter by broad-scale attention networks that become less effective in later life.

Panel Discussion

Moderated by Lis Nielsen, National Institute on Aging

Meeting participants highlighted several challenges to, and questions to consider when, designing and interpreting aging studies:

- How might heterogeneity in emotional function vary in systematic ways between older and younger subjects? For example, because older adults are prescribed more medications, the resulting diversity of pharmaceutical regimens may cause greater heterogeneity in older cohorts than in younger cohorts.
- More data are needed on test-retest reliability for key methods in the fields of social, cognitive, and affective neuroscience. Such additional data could help investigators to determine which methods are suitable for longitudinal studies.
- How might differing cultural preferences for arousal or valence of stimuli map onto aging differences across contexts?
- How might period effects influence the phenomenon of positivity bias? Are there feasible ways to investigate those possibilities?

In relation to period effects (i.e., differences in generational experiences such as the Great Recession) and other potential experimental confounds, discussants highlighted the risks of relying on cross-sectional studies comparing younger and older populations. Cross-sectional data alone cannot capture phenomena such as period effects, so longitudinal data are needed to explore such possibilities.

Another major challenge for the design and interpretation of affective aging studies is the need to control for sex differences. Investigating mood and emotion regulation necessarily implicates some of the brain's most sexually dimorphic circuits. And although these sex differences are not always significant, they change over the life course (e.g., puberty, menopause, old age). For example, the PFC and dorsolateral brain regions develop differently in men and women. Studies need to be designed to address sex differences or there will be the risk that they have missed important, yet hidden, interaction effects.

Participants also discussed the challenges of using animal models to probe underlying neural circuitry and to model aging-related affective changes in humans. For example, human trials that study high-level cognitive factors (e.g., a subject's awareness of their own time horizons, which is hypothesized to be an important driver of the positivity effect) can design experiments to manipulate these factors. The difficulty of modeling such high-level constructs in animals limits the utility of these models for studying some of the major questions addressed by the field. For example, although investigators can study reward circuitry in both mice and humans, the activity of reward circuits in humans may be affected by conscious processing of high-level concepts (e.g., whether an individual feels they are leading "a meaningful life") that may have no analogue in mice. Thus, animal models cannot easily be applied to investigate or test

hypotheses that refer to high-level psychological constructs, which may nevertheless play an important role in human aging.

Another challenge of applying animal models is the scarcity of existing knowledge on aging-related changes in the relevant animals (e.g., differences in "freezing" behavior between younger and older mice). Conducting further studies to investigate such differences could facilitate the use of animal models to test hypotheses of aging in humans. Participants raised the possibility that such studies may already have been conducted, but that null results led them to remain unpublished.

The Fundamentals of Emotion: Allostasis, Interoception and Categorization Within a Predicting Brain

Lisa Feldman Barrett, Northeastern University

Although it is permanently enclosed in the skull, the brain must learn about and make sense of the world outside. This so-called reverse-inference problem describes many brain processes. Starting with initial conditions, the brain makes predictions about incoming inputs—by constructing concepts, matching to categories, and modifying categories (learning) to predict better next time.[15] For example, the brain can create concepts to help organize its memory of past experiences and can use those concepts to make immediate predictions about its real-time environment, priming the neural circuitry to fit its predictions.[16] There is good evidence that multiple brain systems work by constructing predictions. When incoming sensory information does not match expectations, the brain generates a prediction error signal. The amygdala is one structure that can serve this role. Prediction errors help the brain improve its future predictions (i.e., errors help the brain learn). Investigators have found that all exteroceptive brain operations work predictively and are now discovering that interoceptive brain operations work in much the same way.

Evidence suggests that the limbic system, which cascades out to motor and sensory systems, contains the most powerful predicting regions.[17] Mapping of brain systems that include all limbic cortices reveals that they coincide with the default mode network and salience network, both of which are crucial for coordinating neural signals across the entire brain.[18] These networks also include regions that have been referred to as the primary interoceptive cortex (i.e., mid-to-posterior insular cortex), which is responsible for detecting sensory changes within the body. Most of these changes are experienced low-dimensionally as affect, valence, arousal,

[15] L.F. Barrett, "The theory of constructed emotion: an active inference account of interoception and categorization," *Soc. Cogn. Affect. Neurosci.* 12(1), 1-23 (2017).
[16] H. Barbas, "General cortical and special prefrontal connections: principles from structure to function," *Ann. Rev. Neurosci.* 38, 269-289 (2015).
[17] L.F. Barrett and W.K. Simmons, "Interoceptive predictions in the brain," *Nat. Rev. Neurosci.* 16, 419-429 (2015).
[18] I.R. Kleckner, et al., "Evidence for a large-scale brain system supporting allostasis and interoception in humans," *Nat. Hum. Behav.* (2017).

and other similarly blunt sensations. Moreover, these limbic regions not only detect but also predictively modulate interoceptive change.

This view of the brain helps to explain why allostasis, interoception, and categorization are closely linked with emotion. Because this view constitutes a general theory of brain functioning, it could prove to be a fruitful guide to investigating affective changes in aging as well.

Behavioral, Physiological, and Imaging Studies of Arousal, Valence, and Salience Processing

Brad Dickerson, Massachusetts General Hospital

Functional neuroanatomy studies of arousal, valence, and salience processing in healthy adults and in older adults with frontotemporal dementia (FTD) have revealed potential brain-based biomarkers for conditions such as Alzheimer's disease (AD) and dementia with Lewy Bodies. Within a single brain network (e.g., the salience network), resting state and task state data provide complementary information that can reveal underlying functional processes and thereby suggest potential pathways to explain aging-related malfunction in memory, cognition, and affect. To explore affective factors such as arousal and salience, investigators have used functional connectivity magnetic resonance imaging (MRI) to test the hypothesis that three extensive brain networks derived from three amygdala subregion "hubs" (provisionally named the perception, affiliation, and aversion networks) relate to social network size in healthy adults.[19]

Imaging data show that connectivity strength of the perception and affiliation (but not the aversion) networks to the amygdala is positively related to social network size. Investigators developed a Social Impairment Rating Scale, which was intended to link measures of social behavior (e.g., socioemotional detachment, lack of response to social cues) to measures of atrophy in the perception, affiliation, and aversion networks.[20] Investigators administered the rating scale to 20 subjects who had frontotemporal lobal degeneration, along with their caregivers, and measured cortical thicknesses and subcortical volumes. Atrophy in the perceptual network was linked to lack of eye contact and a diminished sensitivity to social cues such as facial expressions; atrophy in the affiliation network was linked to coldness and diminished empathy; and atrophy in the aversion network was linked to increased trust and gullibility (effects that were also related to diminishment in the salience network).

Research has also indicated that FTD patients show autonomic markers (e.g., low cardiac vagal tone) that have been linked to low agreeableness (as measured by a collateral-completed

[19] K.C. Bickart, et al., "Intrinsic amygdala-cortical functional connectivity predicts social network size in humans," *J. Neurosci.* 32(42), 14729-14741 (2012).

[20] K.C. Bickart, et al., "Atrophy in distinct corticolimbic networks in frontotemporal dementia relates to social impairments measured using the Social Impairment Rating Scale," *J. Neurol. Neurosurg. Psychiatry* 85, 438-448 (2014).

personality inventory) and that could contribute to emotional blunting.[21] In addition, persons with AD show amygdala atrophy, which may enable investigators to use positron emission tomography (PET) imaging to diagnose AD.[22] More research is needed to account for residual variance, but it is possible that many aspects of normal aging, including affective changes, are the result of subclinical neurodegenerative pathology.

Findings from the Neuroscience Project in the Midlife in the U.S. (MIDUS) Study

Stacey Schaefer, University of Wisconsin-Madison

The longitudinal Midlife in the United States (MIDUS) study investigates how emotion, genetics, behavior, experience, social environment, personality, and other psychological factors influence Americans' health and well-being as they age. MIDUS's neuroscience project combines psychophysiological measures such as corrugator electromyography (EMG) and eyeblink startle reflex (EBR) with functional MRI (fMRI) data to study connections between aging and the time course of emotional responses (i.e., affective chronometry). EMG and EBR data from the MIDUS core sample indicated that older adults responded more positively than younger adults to neutral stimuli but showed reduced affective recovery from negative stimuli.[23] However, attempts to reproduce these results in the more recent MIDUS refresher sample revealed no age relationships or differences. It is possible that period effects (e.g., due to the Great Recession) or age differences between the core and refresher samples—at the time of data collection, the MIDUS Main sample was approximately 6 years older, on average, than the refresher sample—could help to explain the difference in findings. Task-based fMRI data, collected as participants viewed negatively valenced images, followed by a black screen, followed by a neutral face probe to measure lingering emotional response, suggest that aging is associated with decreased reliance on executive processes and lateral PFC function during negative affective processing, and greater reliance on the ventromedial PFC.[24] Spillover valence effects have also been linked to aging: in contrast to younger adults, older adults show a heightened negative valence response to emotionally neutral stimuli if immediately preceded by an emotionally negative stimulus, an effect that fMRI data suggest is bilaterally mediated by the amygdala.[25]

More recently, investigators have found that individual differences in affective chronometry measures predict mortality risk. Researchers combined temporal facial EMG and EBR measures

[21] C.G. Guo, et al, "Dominant hemisphere lateralization of cortical parasympathetic control as revealed by frontotemporal dementia," *PNAS* 113(17), E2430-E2439 (2016).
[22] S.P. Poulin, et al., "Amygdala atrophy is prominent in early Alzheimer's disease and relates to symptom severity," *Psychiatry Res. Neuroimaging* 194(1), 7-13 (2011).
[23] C.M. van Reekum, et al., "Aging is associated with positive responding to neutral information but reduced recovery from negative information," *Soc. Cogn. Affect. Neurosci.* 6(2), 177-185 (2011).
[24] C.M. van Reekum, et al., "Aging is associated with a prefrontal lateral-medial shift during picture-induced negative affect," *Soc. Cogn. Affect. Neurosci.* 13(2), 156-163 (2018).
[25] D.W. Grupe, et al., "Behavioral and neural indices of affective coloring for neutral social stimuli," *Soc. Cogn. Affect. Neurosci.* 13(3), 310-320 (2018).

in response to negative stimuli with 10-year follow up mortality data. They discovered that individuals with initial high-magnitude emotional responses yet quick recovery showed significantly lower 10-year follow-up mortality than individuals with blunted initial emotional responses that gradually increased after stimulus offset. The implications of these differences for health and wellbeing are currently being investigated.

Discussion

Dr. Schaefer noted that sex differences were controlled for and do not appear to drive any of the observed effects. Dr. Drew, noting that animal model results show that trauma exposure can sensitize startle responses for extended time periods, asked whether data on trauma exposure have been collected. Dr. Schaefer explained that MIDUS contains many stress-related measures, and that although they have not been analyzed in connection with mortality, doing so could be fruitful.

Fetal Origins of the Impact of SeXX on Emotion and Memory Circuitries

Jill Goldstein, Massachusetts General Hospital

Memory, stress regulation, and emotion regulation are crucial components of healthy aging, and brain regions that regulate emotion and relate to memory are highly sexually dimorphic both in terms of function and development. Indeed, sex differences in chronic mood and memory disorders are pervasive. Investigators believe that developmental factors during gestation and early life (e.g., maternal hypertension, malnutrition, hypoxia) may cause dysfunction in the brain's so-called arousal regions (e.g., the medial PFC, periaqueductal grey, and anterior cingulate cortex), which connect to the central autonomic network and overlap with memory circuits.

The timing of these influences can have prodigious effects on prenatal brain development, including during periods when sex-specific neuroanatomy and physiology are being formed. Prenatal maternal stressors lead to a maternal immune response and dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, which can cause changes in fetal brain organization that result in sexually dimorphic neural circuitry and hormonal pathway dysfunction. Adverse maternal exposures during first trimester can result in some sex effects on offspring brain development, given the direct effect of genes on sexual brain differentiation prior to gonad differentiation. However, the primary driver of sexual differentiation is gonadal hormone regulation of brain development initiated during second trimester when the testes begin to secrete testosterone. Testosterone masculinizes the male brain and has direct and indirect effects through aromatization into estradiol. Estradiol and androgens have a major impact at every stage of neuronal growth and development. Maternal adverse exposures during this period of gestation can have greater effects on sex differences in fetal brain development given the potential disruption of the gonadal hormone regulation of brain development.

Although disruptions in the healthy sexual differentiation of the brain do not necessarily lead to adverse behavioral differences between the sexes, they could set the stage for the development of disorders such as major depression and cardiovascular disease, as well as memory decline later in life. For example, ongoing population-level neuroscience studies following a cohort from prenatal development through age 55 demonstrated the impact of abnormal maternal prenatal immune dysregulation on offspring memory circuitry structure and function in women post menopause, but not in the men of similar age.

Panel Discussion

Moderated by Kevin Ochsner, Columbia University

Participants discussed the comparative merits of cross-sectional and longitudinal cohorts in aging studies. They agreed that both types of cohorts are crucial because they provide different information that can help to test hypotheses. Longitudinal data may allow more explanatory variance to be captured. However, it remains a serious challenge to validate multivariate constructs such as emotional wellbeing and emotion regulation and to build them into longitudinal studies. Multiple measures of behavior and of brain function are used to reflect age-related differences (e.g., sociality, self-report, lab tasks, open-ended analyses of resting state connectivity). It is unclear which types of measures will succeed in capturing age-related change. In general, age differences are difficult to observe, which suggests there may be greater value in examining individual differences. Existing efforts to integrate such constructs in studies such as MIDUS, which uses a diary protocol to capture fluctuations in daily affect, do so at great financial expense. Such methods also significantly increase participant burden. Alternatively, passive data collection methods may help to solve these problems in future research. For example, monitoring smartphones, tracking social media accounts, or distributing actigraphy devices could help investigators collect data continuously or repeatedly without significantly raising participant burden.

However, these techniques do not address fundamental measurement validity problems. Most existing research paradigms study participants in highly controlled experimental environments. In such cases, the effects these environments have on the phenomena being studied are not known in advance. Thus, investigators are unaware of how their data are affected by unnatural experimental environments: thus, researchers must aim to enhance ecological validity and generalizability to real-world settings. In the real world, each behavior or emotional state is contingent on the prior moment, and experiments are often explicitly designed to break that contingency.

It is critical when investigating brain connectivity and function to maintain awareness of "degeneracy," which occurs when different brain structures perform similar functions under certain conditions. Related to sex differences in affect, among the conditions that can influence this phenomenon are hormonal variations in the body, which undergo significant changes across the menstrual cycle and therefore must be accounted for when analyzing brain activity. For example, menstrual cycling influences emotional reactivity, which is linked to at-rest connectivity in the salience and default mode networks. Several discussants emphasized the

distinction between degeneracy and redundancy. The latter refers to distinct strings of genetic information that produce identical phenotypic effects, such that dysfunction in one string does not produce a noticeable phenotypic change. These two unrelated concepts are sometimes confused.

Motivation and Effort Discounting in the Context of Aging and Dopamine

David Zald, Vanderbilt University

Animal research using amphetamines has shown that effort discounting—the inverse relationship between the perceived value of a reward and the amount of effort required to obtain it—and general motivation are modulated by the brain's dopamine system.[26] It is also known that in humans dopamine system features (such as the number of neurons in the substantia nigra, as well as the number of D2 receptors and dopamine transporters) decline with age. Investigators seeking possible connections between aging and dopamine decline, motivation, and effort discounting in humans used the Effort Expenditure for Reward Task (EEfRT),[27] which quantifies effort in terms of the number of finger presses with the dominant index finger and the non-dominant pinky and administered amphetamine or placebo to experimental and control groups, respectively.[28]

Although multiple aspects of the brain's dopamine system diminish with age, which suggests that older age would be associated with greater effort discounting, no linear age effect on discount rate was found, and effort expenditure was not significantly correlated with D2 receptor levels in aged subjects. Indeed in an initial study, older adults were more likely than younger adults to pursue high-effort rewards, with middle-aged subjects willing to expend the most effort. fMRI results in the same subjects showed a relationship between discounting functions and subjective value representation, which did not change with age. In considering these results, it must be noted that not all aspects of the dopamine decline with age. For instance, middle-aged adults, despite having fewer dopamine cells and transporters, show *higher* striatal dopamine release as measured with PET in response to amphetamine than younger adults. This result is consistent with the finding that willingness to expend effort remains static as subjects age. Investigators have proposed that dopamine synthesis and release may compensate for other declines in the dopamine system and may vary across brain regions.[29]

[26] J.D. Salamone, et al., "Effort-related functions of nucleus accumbens dopamine and associated forebrain circuits," *Psychopharmacology* 191(3), 461-482 (2007).
[27] M.T. Treadway, et al., "Worth the 'EEfRT'? The effort expenditure for rewards task as an objective measure of motivation and anhedonia," *PLoS One* 4(8), e6598 (2009).
[28] M.C. Wardle, et al., "Amping up effort: effects of *d*-amphetamine on human effort-based decision-making," *J. Neurosci.* 31(46), 16597-16602 (2011).
[29] T.M. Karrer, et al., "Reduced dopamine receptors and transporters but not synthesis capacity in normal aging adults: a meta-analysis," *Neurobiol. Aging* 57, 36-46 (2017).

Discussion

Imaging data intended to measure features of the dopamine system, such as receptors and transporters can be influenced by a number of features, including unstimulated levels of extracellular dopamine. This can create interpretational problems. However, these measures are still considered a reliable indicator of transporter and receptor levels because the impact of dopamine levels on specific PET measures are relatively modest. This remains true even as transporter or receptor levels diminish, potentially altering the proportion of dopamine transporters or receptors to extracellular dopamine.

Experiments on dopamine and motivation behavior in rodents have discovered that previous exposure to a specific reward can influence motivation (i.e., a rodent that recognizes a low-value reward will be less likely to expend effort). However, investigators in human trials have not studied these sorts of learning effects on dopamine and have used money to allow precise and consistent quantification of rewards.

Consequences of Early Life Trauma on Healthy Aging: Sleep Factors

Donald Wilson, New York University School of Medicine

Sleep plays an important role in cognition, memory, and emotion regulation, and early life events program sleep patterns across the life course. Research indicates that sleep may provide a pathway connecting early life trauma to later life memory and emotion regulation problems. Several rodent experiments have demonstrated early life influences on sleep in later life. For example, fetal alcohol exposure is associated with severe sleep fragmentation and reduced non-rapid eye movement (non-REM) sleep. In addition, inducing physical abuse of rat pups by their mothers (by depriving them of bedding material—a model of scarcity adversity) led the pups to display impulsivity, social anxiety, depressive behavior, and dramatic changes in amygdala function by adolescence. This same early life trauma also resulted in deleterious sleep patterns (e.g., reduced non-REM sleep) as the pups aged. REM sleep was unaffected.

In addition to general sleep structure, investigators have also studied how sleep spindles are affected by early life traumas. In humans, sleep spindles are densest during non-REM sleep and are associated with memory consolidation and emotional regulation. In rat models, early trauma not only predicts negative cognitive and emotional outcomes, but also is linked to life-long sleep spindle decrease. The mechanism underlying the effective brain pathway appears to involve somatostatin-expressing GABAergic neuron functionality.[30] Electroencephalogram data from fetal alcohol–exposed rats reveal that their brains have impaired differentiation of waking and sleeping activity patterns. However, researchers have used optogenetics to activate somatostatin-expressing GABAergic neurons in the basal forebrain to increase time spent in slow-wave sleep, thereby improving sleep consolidation. Ongoing research is exploring brain mechanisms and interventions in more detail, and how early life events can lead to variation in aging outcomes.

[30] M. Xu, et al., "Basal forebrain circuit for sleep-wake control," *Nat. Neurosci.* 18, 1641-1647 (2015).

Discussion

In humans, several methods are available to help improve sleep. Cognitive behavioral therapy can dramatically improve sleep hygiene, and pharmaceutical sleep-aids can also be effective. Sleep apnea is a significant and widespread problem. Many people who spend a full 8 hours asleep each night still receive inadequate rest because of sleep fragmentation. Several ongoing intervention efforts for sleep apnea aim specifically to improve sleep consolidation. Sleep impairment in normal aging could contribute to a myriad of cognitive and emotional negative outcomes.

Endocannabinoid Modulation of Affect, Stress Responsivity, and Cognition

Sachin Patel, Vanderbilt University Medical Center

2-Arachidonoylglycerol (2-AG) is an endocannabinoid (a lipid neuromodulator) that is associated with healthy regulation of emotion and stress. Higher levels of 2-AG signaling are linked to lower stress susceptibility. Experiments in animal models show that deficiency or interference in 2-AG signaling increases anxiety,[31] impairs fear extinction,[32] and worsens the adverse consequences of stress. Conversely, augmenting 2-AG with pharmaceuticals reduces anxiety and promotes an adaptive short-term stress response.[33] Among the circuit mechanisms believed to underlie these effects are amygdala-PFC connections, which include amygdala projections to PFC and feedback circuits that project back to the amygdala. When basolateral amygdala (BLA) projections to PFC are excited, animal anxiety increases. However, the presence of 2-AG activates cannabinoid receptor type 1, which inhibits glutamate release and reduces amygdala-PFC signal transmission, thereby reducing anxiety.

Laboratory experiments have shown that stress-induced anxiety is associated with BLA-PFC circuit-specific and cell-specific endocannabinoid signaling collapse. Cannabinoids normally dampen incoming signals to the amygdala, which modulates stress-responsivity. However, after stress exposure, bilateral BLA-PFC connections hyperactivate. This can become exacerbated by local endocannabinoid depletion in PFC feedback projections to the BLA, causing mimicry of a continuous stress signal. Investigators have shown that the enzyme cyclooxygenase-2 (COX-2) metabolizes 2-AG in vivo, promoting anxiety-like behavior. Understanding these mechanisms could lead to new interventions that promote adaptive stress-responsivity and reduce anxiety.[34]

[31] B.C. Shonesy, et al., "Genetic disruption of 2-Arachidonoylglycerol synthesis reveals a key role for endocannabinoid signaling in anxiety modulation," *Cell Rep.* 9(5), 1644-1653 (2014).
[32] V.S. Cavener, et al., "Inhibition of diacylglycerol lipase impairs fear extinction in mice," *Front. Neurosci.* 12, 479 (2018).
[33] G. Bedse, et al., "Functional redundancy between canonical endocannabinoid signaling systems in the modulation of anxiety," *Biol. Psychiatry* 82(7), 488-499 (2017).
[34] A.J. Morgan, et al., "Detection of Cyclooxygenase-2-derived oxygenation products of the endogenous cannabinoid 2-Arachidonoylglycerol in mouse brain," *ACS Chem. Neurosci.* 9(7), 1552-1559 (2018).

Discussion
Investigators do not yet know how long 2-AG collapse lasts. However, they have performed trials in which they stressed laboratory rats and found that individual differences in 2-AG signaling deficiencies predicted a heightened stress response. Age differences have not yet been explored systematically.

The circuit-specificity of 2-AG action highlights an important difference between endogenous and exogenous cannabinoids. Regulating endogenous cannabinoid systems maintains spatial and temporal specificity, whereas ingesting exogenous cannabinoids (e.g., by smoking cannabis plants) activates all cannabinoid receptors indiscriminately. In addition to lacking spatial and temporal specificity, this ultimately downregulates endogenous cannabinoid tone.

Panel Discussion

Moderated by Mara Mather, University of Southern California

Explaining human behavior in terms of brain activity becomes especially challenging with age-related brain changes. For example, neuromodulatory systems can influence arousal differently in an aging brain compared with a younger brain: NE neurons in the LC diminish with age, but NE levels do not. Results of animal trials show that damaging LC neurons cause remaining NE neurons to develop more axons and produce more NE, perhaps to compensate for the damage. Various neuromodulatory systems, many of which tend to deteriorate with age, influence arousal and sleep/wake cycling. Such deterioration can lead to under-arousal, or, conversely, may lead to compensatory effects—such as those in the LC—that can lead to over-arousal.[35] These effects have important implications for interpreting aging studies, designing experimental controls, and extrapolating animal models to humans, not least because of the ambiguity of constructs such as arousal (discussed further below). Furthermore, it is a general interpretive challenge that differing brain pathways can lead to similar behavioral outcomes, which highlights the need to collect multimodal data to test specific causal hypotheses.

Animal studies allow invasive and precise spatial and temporal measures that are not possible in human trials. These methodological limitations pose many challenges. Investigators too often assume a homology between animal and human neural circuitry. For example, human dopaminergic systems contain more extensive projections to cortical areas than in rodents. In certain cases, erroneous interpretations of underlying brain activity muddle the distinction between tonic and phasic neurotransmitter release. Some such problems may be solved by designing experiments to isolate brain laterality (much like controlling for sex differences), which may help to discover overlooked neural mechanisms.

[35] M. Mather, How arousal-related neurotransmitter systems compensate for age-related decline. In A. Thomas and A. Gutchess (Eds.), *Handbook of Cognitive Aging: A Life Course Perspective* (Cambridge: Cambridge University Press, in press.

Conceptual ambiguities also need to be addressed. For instance, discussions during this workshop shifted from distinguishing concepts such as valence, arousal, salience, and attention, toward making finer distinctions between different forms of arousal. There is a risk that these different conceptual levels can become combined, or that higher-level concepts such as arousal are left insufficiently differentiated, creating interpretive ambiguity. At an even higher level, experimenters and subjects may associate different connotations with a single concept (e.g., arousal often has sexual connotations). Harmonizing terms and concepts across researchers, laboratories, and institutions is important to facilitate experimental validity as well as collaboration. For example, the most commonly mentioned brain circuit has been PFC-amygdala connectivity. However, it remains unclear whether the pathways being described across various experiments and datasets are the same or distinct sub-circuits. Indeed, the PFC-amygdala circuit is itself a subcomponent of a larger circuit, and brain imaging methods are often insufficiently granulated to determine where various sub-circuits diverge.

Another conceptual problem is the ingrained assumption that the younger brain is the ideal, and that all brain changes with age are to be interpreted as dysfunction. In connection with the changing survival and computational problems the brain must solve across the life course, some age-related brain changes may in fact be highly adaptive.

Cognitive Neurostimulation: Intrinsic Neuromodulation and Implications for Learning

R. Alison Adcock, Duke University

Motivation is not merely a response state to external stimuli: it is regulated by internal mental representations. Investigators have used fMRI to monitor subjects' ability to self-motivate by willfully activating midbrain activity while receiving neurofeedback. Subjects learned to elevate and sustain ventral tegmental area (VTA) activity by producing and generalizing motivational states, even without receiving rewards or reward cues. During feedback training, investigators observed heightened connectivity between the VTA and the striatum (areas crucial for learning from feedback). VTA connectivity with the hippocampus, which is involved in long-term memory, began during training and continued afterward.[36] These results suggest that dopamine networks adapt during neurofeedback training to anticipate rewards.

Investigators also explored how internal representations are modified by surprises under different conditions. They embedded surprising stimuli within memory encoding paradigms, one in which subjects sought a monetary reward and the other in which they sought to avoid a punishing shock.[37] In response to surprises, reward group subjects showed activity in the hippocampus proper, whereas punishment group subjects showed activity in the overlying medial temporal lobe (MTL) cortex, especially parahippocampal cortex. Only the reward group

[36] J.J. MacInnes, et al., "Cognitive neurostimulation: learning to volitionally sustain ventral tegmental area activation," *Neuron* 89(6), 1331-1342 (2016).

[37] V.P. Murty and R.A. Adcock, "Enriched encoding: reward motivation organizes cortical networks for hippocampal detection of unexpected events," *Cereb. Cortex* 24(8), 2160-2168 (2014).

created a hippocampal selectivity for the incentivized items. Thus, different motivational states recruit different neuromodulatory systems and MTL encoding substrates, leading to long-term memory representations that are distinct in form and context.

These findings suggest that the brain is designed to store memories in a form that will support future behaviors that match behaviors from the time a memory was encoded. Motivational state is hypothesized to be an important variable in determining brain state during memory encoding. Motivational control of flexible behavior leads to relational memory representation through activity in the VTA and hippocampus, whereas simpler reactive behavior leads to salient, but sparse memory representation through activity in the amygdala and cortical MTL.[38] These results contradict the view that motivation to learn depends mainly upon valence and arousal.

Mechanism of Threat Control

Elizabeth Phelps, Harvard University

The ability to learn about threats is crucial to survival. However, when mechanisms for threat learning are misapplied, they can cause anxiety and acute threat disorders. Existing treatments for anxiety disorders, such as cognitive behavioral therapy and pharmaceuticals, tend to be less effective in older populations. Fear extinction is an alternative therapy. Animal trials have shown that the ventromedial PFC (vmPFC) is necessary for the learning and retrieval of extinction.[39] Aging and stress, both of which are associated with diminished prefrontal inhibition of the amygdala, may be linked to impaired extinction learning.[40] As an alternative to amygdala inhibition via vmPFC, investigators have sought to intervene by influencing memory reconsolidation (when memories are retrieved, updated, and re-stored).[41] Investigators have shown that threat-conditioned memories can be altered during this process to become non-threatening. These reconsolidation findings have not always been replicated, and there are difficulties in translating this to the clinic.

However, several methods have been shown to modulate prefrontal inhibitory mechanisms and thereby to improve threat control. For example, subjects who are given control over a stressor (e.g., moving a joystick allows you to escape a shock on some trials) show enhanced persistent threat control.[42] Internal locus of control (i.e., the belief that one's actions and attitudes can

[38] V.P. Murty and R.A. Adcock, "Distinct medial temporal lobe network states as neural contexts for motivated memory formation," in The Hippocampus from Cells to Systems: Structure, Connectivity, and Functional Contributions to Memory and Flexible Cognition (eds. D.E. Hannula and M.C. Duff), 467-501 (2017).
[39] M.R. Milad, et al., "Electrical stimulation of medial prefrontal cortex reduces conditioned fear in a temporally specific manner," *Behav. Neurosci.* 118(2), 389-394 (2004).
[40] E.A. Phelps, et al., "Extinction learning in humans: role of the amygdala and vmPFC," *Neuron* 43(6), 897-905 (2004).
[41] D. Schiller, et al., "Preventing the return of fear in humans using reconsolidation update mechanisms," *Nature* 463, 49-53 (2010).
[42] C.A. Hartley, et al., "Stressor controllability modulates fear extinction in humans," *Neurobiol. Learn. Mem.* 113, 149-156 (2014).

control external life events) also predicts better avoidance learning. Through the method of novelty facilitated extinction (NFE), in which an original fear-conditioned stimulus is replaced with a novel stimulus, learned extinction can be facilitated.[43] However, further research is needed to identify the underlying mechanisms of NFE.

Finding the Engram: Activation of Dentate Gyrus Memory Traces Rescues Age-Related Cognitive Decline

Christine Ann Denny, Columbia University

Engrams are physical instantiations of memories within the brain. In recent years, investigators have made substantial progress in identifying engrams.[44] Hippocampal expression of the *Arc* immediate early gene—particularly in the dentate gyrus (DG)—has been implicated in learning and in memory formation. *Arc* has the unusual ability to package its own genetic material and send it to other cells with a technique commonly used by viruses.[45] Investigators created a line of transgenic mice containing a cell tagging mechanism that permanently labels cells expressing *Arc* during a specified learning task.[46] Cross-referencing cell ensembles tagged during learning with the cell ensemble that expresses *Arc* during recall of that memory allows the overlapping cell population (the engram) to be identified. This method can pinpoint engrams for specific learning and memory tasks across the entire brain at single-cell resolution.

Experimental results using this technique in mice have shown that individual task-based memories can be manipulated by activating or inhibiting cells for specific engrams.[47] This has broad implications for treating learning and memory-related diseases, including those associated with aging. In conditions such as AD, lost memories may be retrievable by activating their corresponding engrams. Animal models have also demonstrated that optogenetic stimulation of engrams in the DG can reduce interference between memories and improve pattern separation in aged mice with chronic stimulation leading to enduring improvement.

Future human full brain maps with single-cell resolution would allow engrams to be identified for individual memories, enabling learning and memory function to be modified and improved across a broad range of conditions. In addition, maladaptive memories, such as those associated with learned fear and anxiety, could be therapeutically inhibited.

[43] J.E. Dunsmoor, et al., "Novelty-facilitated extinction: providing a novel outcome in place of an expected threat diminishes recovery of defensive responses," *Biol. Psychiatry* 78(3), 203-209 (2015).
[44] S. Tonegawa, et al., "Memory engram cells have come of age," *Neuron* 87(5), 918-931 (2015).
[45] E.D. Pastuzyn, et al., "The neuronal gene *Arc* encodes a repurposed retrotransposon gag protein that mediates intercellular RNA transfer," *Cell* 172(1-2), 275-288 (2018).
[46] C.A. Denny, et al., "Hippocampal memory traces are differentially modulated by experience, time, and adult neurogenesis," *Neuron* 83(1), 189-201 (2014).
[47] J.N. Perusini, et al., "Optogenetic stimulation of dentate gyrus engrams restores memory in Alzheimer's disease mice," *Hippocampus* 27(10), 1110-1122 (2017).

Changing the Valence of a Hippocampal Memory

Michael Drew, University of Texas at Austin

Hippocampal regions, especially the DG, encode and recall memories. Contextual fear conditioning (CFC) experiments in mice have shown that a single shock experience, modeling episodic memory formation, can induce lifelong fear of the context in which it took place. Hippocampal neurons record multimodal information about the environment, but the DG contains highly differentiated contextual information, which is crucial for pattern separation, and therefore also for encoding specific aspects of each memory, including emotional valence.[48] This suggests that manipulations of the DG could cause existing memories to acquire new valence, which could have significant implications for solving age-related problems of memory and affect.

Silencing the entire DG impairs CFC acquisition but not recall,[49] yet research on engrams indicated that engram cell activity in the DG was both necessary and sufficient for CFC recall.[50] To address the paradox, investigators conducted computer simulations using a hippocampal simulation program called the Bayesian Context Fear Learning Algorithm.[51] The simulations reproduced the paradoxical results but indicated that the DG is not *required* for recall. Rather, results suggest that neural activity in the DG contributes to both acquisition and recall through an interference process. Specifically, DG activity disrupts a pattern-completion process in hippocampal region CA3.

Context fear extinction has also been investigated in relation to DG activity. Because extinction is a learning process rather than an unlearning or a forgetting process, investigators expected the DG to be involved. Contrary to the prevailing conception of extinction as a process modulated by upstream suppression of fear, perhaps from the PFC, experiment results suggest that the hippocampus generates distinct memory representations for fear and extinction. Investigators hypothesize that competition between these representations may control fear extinction and relapse. Age-related changes in DG function may therefore affect fear extinction effectiveness.

Discussion

Although fear extinction is only one mode of valence change in a memory, the suspected mechanism underlying this effect could be indicating that every time a new memory is encoded by the hippocampus, valence is an indelible feature of that encoded memory. If so, that would

[48] T.J. McHugh, et al., "Dentate gyrus NMDA receptors mediate rapid pattern separation in the hippocampal network," *Science* 317(5834), 94-99 (2007).
[49] B.E. Bernier, et al., "Dentate gyrus contributes to retrieval as well as encoding: evidence from context fear conditioning, recall, and extinction," *J. Neurosci.* 3029-16 (2017).
[50] C.A. Denny, et al., "Hippocampal memory traces are differentially modulated by experience, time, and adult neurogenesis," *Neuron* 83(1), 189-201 (2014).
[51] F.B. Krasne, "A Bayesian context fear learning algorithm/automaton," *Front. Behav. Neurosci.* 3029-16 (2017).

suggest that altering the valence of any memory always involves creating a fresh memory, as opposed to re-writing an existing one.

Panel Discussion

Moderated by Brad Dickerson, Massachusetts General Hospital

Affective neuroscience research tends to focus on arousal and valence, but it is crucial that motivation is included. For example, incentive salience now appears to be a key factor in affective processes, which was unknown until the scope of inquiry was broadened to investigate motivation as an independent and complex causal variable. And yet, as with arousal and valence, it will be necessary to differentiate the construct of motivation conceptually into valid subcomponents to generate valid interpretations. The need for more precise concepts extends to measurements, because blunt behavioral measures can conceal functional details.

Similarly, prevailing interpretations of aging-related changes in affect can lead investigators to ignore realistic possible explanations for such changes. For example, interpreting the positivity effect as primarily due to the avoidance of negative stimuli led researchers to focus on some potential mechanisms over others.

Participants discussed the multivariate trajectories across the lifespan that could be interacting to produce certain affective changes, including changes in life goal formation, information intake, skill mastery, identity development, and habit development. Alternatively, it is possible that individual differences in affective style—perhaps related to behavioral factors such as exercise habits or to specific mental signatures—might manifest across the life course. Probing this possibility will require longitudinal data.

Roundtable Discussion

Derek Isaacowitz, Northeastern University

Meeting participants provided summary thoughts and suggested research directions that might help to advance the field of affective neuroscience in aging:

Conceptual Framework and Terminology

- Encourage exploratory research that challenges prevailing conceptions in the field.
- Develop suitably precise terminology to ensure meaningful experimental constructs, and harmonize terminology across investigators, laboratories, and institutions.
- Define “emotion” broadly to include constructs such as motivation, value, arousal, etc. ”Affect” encompasses a broad range of phenomena, which must be differentiated by using precise—but not restrictive—terminology.
- Identify the common and unifying motives that underlie affective phenomena, and how they can be measured. Drawing links between short-term reactive adaptation and long-term performance might yield valuable new insights.

- Update and improve constructs such as healthy aging and unhealthy aging; avoid the mental disease model and consider what constitutes adaptable, flexible functioning. In addition, develop animal models that map onto constructs such as "thriving."
- Interpret phenomena being studied as *systems* to stimulate questioning of overly simple explanations of underlying neural mechanisms. Pursue explanations that account for the brain's flexibility and adaptability.
- Propose more useful terminology to represent the construct of arousal, which can refer to many distinct concepts, such as activation, agitation, and engagement.
- When aligning behavior with neural circuits, be specific, both in terms of circuits and vocabulary.

Study Design and Methods

- Design experiments to control for sex differences when feasible and relevant.
- Subject common methodologies to test-retest reliability trials.
- Publish and disseminate null results that show no age differences.
- Design translational studies to align human imaging data with animal models to probe neural circuitry in detail (e.g., PFC-amygdala connections plus behavioral phenotyping).
- Use animal models to map high-dimensional brain activities and corresponding behaviors onto low dimensional psychological constructs. In addition, simulate hypothetical animal experiments using software models of neural circuitry to spur formation of new hypotheses.
- Improve sample population diversity.
- Develop ways to model clinical results in animal trials and basic neuroscience labs. In addition, align mouse and human datasets to map specific engrams in the human brain.
- Develop approaches to examine the effects of context on affective phenomena.

Research Topics

- Explore how demographics and psychological variables change with aging and investigate individual differences. Study designs often focus on individual differences at a specific time (e.g., during young adulthood) or on changes over time between groups. However, in aging studies the focus shifts toward individual differences in trajectories over time. Thus, longitudinal data, which require significant resources, are needed to supplement animal models.
- Take age-related similarities in affective phenomena seriously, as opposed to focusing exclusively on age-related differences. Similarities in patterns of affect across the lifespan often outweigh differences.
- Explore how neuromodulatory systems adapt to maintain function and compensate for deterioration of brain regions over the lifespan.
- Study how investigators can reliably interpret age-related changes. The degeneration or failure of a system is not always merely the loss of ability. Sometimes, it is the result of hyperactivity (i.e., "noise" being added to a system).
- Explore pathway differences between age-related cognitive and affective changes.

- Investigate whether the positivity effect may result from an interplay of conscious and unconscious factors that can be probed using working memory load.
- Leverage the ability for animal models to
    - Study aging trajectories via chronic manipulation of an animal's lifespan.
    - Obviate the need to map high-level concepts (e.g., arousal) onto brain activity.

Appendix A: Agenda

August 2, 2018

9:30 am	Opening Remarks *Luci Roberts and Lis Nielsen, National Institute on Aging*
9:50 am	Age-Related Changes in Emotion and Emotion Regulation *Kevin Ochsner, Columbia University New York, Morningside*
10:15 am	Emotional Aging: Expecting Differences, Finding Some Similarity *Derek M. Isaacowitz, Northeastern University*
10:40 am	The Two Major Dimensions of Emotion: Valence and Arousal; How Their Impact on Attention Changes with Age *Mara Mather, University of Southern California*
11:05 am	Panel Discussion *Lis Nielsen, National Institute on Aging*
11:35 am	The Fundamentals of Emotion: Allostasis, Interoception, and Categorization Within a Predicting Brain *Lisa Feldman Barrett, Northeastern University*
12:00 pm	Behavioral, Psychological, and Imaging Studies of Arousal, Valence, and Salience Processing *Bard C. Dickerson, Massachusetts General Hospital*
12:25 pm	Lunch
1:30 pm	Findings from the Neuroscience Project in the Midlife in the U.S. (MIDUS) Study *Stacey Schaefer, University of Wisconsin—Madison*
1:55 pm	Maintaining Emotional Stability in the Face of Negative Life Experiences *Jill M. Goldstein, Massachusetts General Hospital*
2:20 pm	Panel Discussion *Kevin Ochsner, Columbia University New York, Morningside*
3:10 pm	Break
3:25 pm	Motivation and Effort Discounting in the Context of Aging and Dopamine *David H. Zald, Vanderbilt University*
3:50 pm	Potential Consequences of Early Life Events on Normal Cognitive and Emotional Aging, with Special Emphasis on Gabaergic Circuitry and Sleep Disruption as a Mediator of These Effects *Donald A. Wilson, New York University School of Medicine*

4:15 pm	Preclinical Studies Examining the Role of the Endogenous Cannabinoid 2-Arachidonoylglycerol (2-AG) in the regulation of Affective Behaviors and Stress-Response Physiology *Patel Sachin, Vanderbilt University Medical Center*
4:40	Panel Discussion *Mara Mather, University of Southern California*

August 3, 2018

9 am	Cognitive Neurostimulation: Regulation of Intrinsic Neuromodulation and Implications for Learning *R. Alison Adcock, Duke University*
9:25 am	Mechanisms of Threat Control *Elizabeth A. Phelps, Harvard University*
9:50 am	Utilizing and Activity-Dependent Tagging System to Localize and Manipulate Engrams During Aging *Christine A. Denny, Columbia University Health Sciences*
10:30 am	How the Hippocampus Changes the Emotional Valence of a Memory *Michael R. Drew, University of Texas—Austin*
10:55	Panel Discussion *Moderator: Brad Dickerson, Massachusetts General Hospital*
11:55	Roundtable Discussion *Moderator: Derek Isaacowitz, Northeastern University*
12:20 pm	Closing Remarks and Adjourn

Appendix B: Participants List

National Institute on Aging

Lis Nielson, Chief, Individual Behavioral Processes Branch, Division of Behavioral and Social Research
Luci Roberts, Program Officer, Division of Neuroscience
Matthew Sutterer, Health Specialist, Division of Neuroscience

Invited Speakers

Rachel Alison Adcock, Duke University
Lisa Feldman Barrett, Northeastern University
Christine Ann Denny, Columbia University
Michael R. Drew, University of Texas, Austin
Jill M. Goldstein, Massachusetts General Hospital
Derek M. Isaacowitz, Northeastern University
Mara Mather, University of Southern California
Kevin N. Ochsner, Columbia University
Sachin Patel, Vanderbilt University Medical Center
Elizabeth Anya Phelps, New York University
Stacey Schaefer, University of Wisconsin-Madison
Donald A. Wilson, New York University School of Medicine
David H. Zald, Vanderbilt University