Use of Neurotechnology in Normal Brain Aging and Alzheimer's Disease (AD) and AD-Related Dementias (ADRD)

NIA Virtual Workshop

Division of Neuroscience

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Acronym Definitions

AD   Alzheimer's disease

ADRD   Alzheimer's disease-related dementia

DN   Division of Neuroscience

DOT   diffuse optical tomography

ECG   electrocardiography

EEG   electroencephalography

FDA   U.S. Food and Drug Administration

fMRI   functional magnetic resonance imaging

FUS   focused ultrasound

GENUS   gamma entrainment using sensory stimuli

IDE   investigational device exemption

LED   light emitting diode

MCI   mild cognitive impairment

MRI   magnetic resonance imaging

NAPA   National Alzheimer's Project Act

NF   neurofeedback

NHP   non-human primate

NIA   National Institute on Aging

OSA   obstructive sleep apnea

PHG   parahippocampal gyrus

PreFx   pulse relaxation function

REM   rapid eye movement

RR   respiratory rate

SM   sleep movement

SWS   slow wave sleep

tDCS   transcranial direct current stimulation

TES   transcranial electrical stimulation

TLI   tailored lighting intervention

Executive Summary

To shape its national plan to address Alzheimer's disease, the NIA Division of Neuroscience held a virtual workshop on April 27, 2020. The purpose of the workshop was to identify opportunities for development or use of non-invasive devices that can (1) monitor neuronal function-based processes related to the aging brain and Alzheimer's disease (AD) and AD-related dementias (ADRD) and (2) be used as an intervention or therapeutic for age-related cognitive decline or AD/ADRD.

Industry professionals, academic researchers, and clinicians convened to share information and discuss the state-of-the art sensors and devices for in-home monitoring as well as their potential therapeutic use in brain aging and AD/ADRD. Three main recurring themes emerged for diagnosing or treating AD/ADRD: (1) predicting cognitive decline, (2) altering neural activity, and (3) using new technologies to collect high-fidelity bioinformatic data.

The first theme focused on predicting the onset of AD/ADRD in asymptomatic individuals. Olfactory brain regions show early signs of AD pathology, so a novel method has been developed to select at-risk individuals for AD/ADRD studies by using olfactory stimulation to test smell memory. Another predictor of AD/ADRD involves eye movements when viewing images. Because blood vasculature also changes with age, several novel devices use vasculature measures in the brain and eyes as predictors of cognitive decline.

The second theme involved the alteration of neural activity to improve cognition in individuals at risk for AD/ADRD. Researchers have demonstrated that light and sound may be used to synchronize neurons with each other, which may improve cognition. Furthermore, this neural synchrony can be visually translated to an individual in real time such that they may volitionally alter their brain activity. This technique, called neurofeedback, may provide therapeutic value in slowing cognitive decline. More direct ways to alter neural activation to improve cognition included direct electrical stimulation through the scalp and focused ultrasound to allow drugs to permeate the brain while increasing naturally occurring therapeutic neural responses. Light therapy and electrical stimulation have also been shown to improve sleep, resulting in cognitive benefits and reductions in AD-specific pathology. Optical techniques to activate neurons were also discussed. Finally, a digital memory book has been developed to assist caregivers and physicians to care for individuals with AD/ADRD and, ultimately, to improve neural integrity during the progression of the disease.

The third main theme revolved around new technologies to collect bioinformatic data from humans and new techniques to study AD pathology. Several companies are developing new flexible sensors that collect high-fidelity data with minimal power requirements, some of which are powered by the body itself. These sensors can be placed in a variety of locations to detect a host of data that may help in predicting, diagnosing, and tracking symptoms and sequelae associated with AD/ADRD. In commercialization is a mattress pad with sensors that can detect both movement and respiration with the goal of improving sleep quality of individuals with

sleep deficits by transitioning sleep studies from the laboratory to the home. Techniques to study AD pathologies included the expansion of neurons for high precision imaging.

Meeting Summary

Welcome and Opening Remarks
Eliezer Masliah, M.D., Director, Division of Neuroscience

The NIA Division of Neuroscience (DN) is focused on topics involving healthy brain aging and Alzheimer's disease (AD) and related dementias (ADRD), and neurotechnology is poised to facilitate diagnostic and therapeutic advances that address brain aging and AD/ADRD. The DN budget has quadrupled since 2016, and NIA aims to implement neurotechnological advances to further the goals of the National Alzheimer's Project Act (NAPA) that includes milestones to prevent and effectively treat AD/ADRD by 2025. The goals of this workshop were to provide updates on AD/ADRD-related research and help the DN guide research to achieve NAPA milestones. See Appendix A for workshop agenda and Appendix B for participants list.

Using Non-invasive Sensory Stimulation to Ameliorate Alzheimer's Disease Pathology and Symptoms
Li-Huei Tsai, Ph.D., Massachusetts Institute of Technology

Synchronized neural activity allows cells within and between brain regions to communicate, underlying all of cognition and behavior. These coordinated communication patterns occur at various frequencies (< 0.01 Hz to 600 Hz) and can be observed via local field potentials that vary little across mammals. Gamma oscillations (30 to 80 Hz) are of particular interest because they are associated with higher-order functions such as working memory, sensory processing, and spatial navigation, which gradually deteriorate in individuals with AD/ADRD. Indeed, gamma oscillations (at 40 Hz) are often attenuated in mice who exhibit AD pathology, with some analogous evidence found in humans. However, because AD/ADRD progresses over many years and because gamma attenuation can occur before the progression becomes measurably symptomatic, the precise stage in the disease at which gamma activity begins to diminish remains unclear. With a more precise understanding of this staging, clinicians may be able to exogenously enhance gamma to halt or slow disease progression.

To demonstrate this ability, Dr. Tsai and colleagues created the Gamma Entrainment Using Sensory Stimuli (GENUS) paradigm in which they exposed mice to lights flickering at 40 Hz, resulting in successful potentiation of 40 Hz gamma power in the mouse visual cortex. Through 1 hour of GENUS, beta amyloid peptides (signatures of AD) in the visual cortex were reduced by nearly 50 percent. Furthermore, GENUS resulted in potentiated gamma power in the hippocampus, somatosensory, and prefrontal cortex, and increased coherence within these regions. Repeated GENUS over a 3-week period also reduced amyloid plaque concentration in multiple brain regions including the visual, somatosensory, and prefrontal cortices and the hippocampus. In addition, GENUS reduced other AD pathology indicators, such as tau protein, in the hippocampus and visual and somatosensory cortices.

Flickering light is not the only effective stimulus to reduce AD pathology; auditory waves may be tuned to gamma frequencies and used in GENUS. Like results found using visual stimuli, auditory GENUS resulted in gamma entrainment and reduced levels of amyloid in the auditory cortex and the hippocampus. Furthermore, combining both auditory and visual GENUS reduced AD pathology (amyloid) earlier than either did in isolation. Both visual and auditory GENUS paradigms also resulted in significantly improved spatial memory functioning in several mouse models, assessed using the Morris water maze.

The responses of neurons and microglia to gamma entrainment may underly GENUS' success in reducing amyloid symptomology and increasing spatial memory functioning. Entrainment results in less amyloid beta production from (1) neurons and (2) enlarged microglia. These enlarged microglia then clear amyloid beta from the surrounding environment. Changes in vasculature may also contribute to the success of GENUS: 1 week of auditory stimulation increased blood vessel diameter by up to 200 percent in the auditory cortex and hippocampus, and these changes in vasculature may increase the clearance of amyloid.

Dr. Tsai has recently transitioned GENUS from animal to human testing. Participants view a light bar and listen to audio that either independently or concurrently transmit 40 Hz visual and audio stimuli. EEG signals show that both visual and auditory stimulation, independently, increase gamma frequencies across large extents of the brain, with the strongest effect from concurrent stimulation. In addition, no adverse effects (e.g., headaches, altered vision/hearing, or seizures) were reported. Testing on individuals with mild AD is now under way.

Discussion

Dr. Tsai clarified that GENUS can be used to instantiate a wide range of neural frequencies outside of the gamma band. She also described several implications for future research:

- Individuals who participate in GENUS are instructed to stare at the LED panel for 1 hour, with researchers using an eye tracker to ensure alertness and attention. To make the trial more dynamic and interesting for the users, the research team is actively developing a procedure to couple the light panel with a tablet that plays videos.
- It is unclear whether the effects of unisensory stimulation are additive or synergistic, and future research may address this question. Regardless, the combination of auditory and visual stimulation results in the strongest response (i.e., greatest neural amplitude) and least amount of time to observe morphological changes of neuroanatomy.

Flipping the Switch: How to Use Light to Improve the Lives and Health of Persons with Alzheimer's Disease and Related Dementias

Mariana G. Figueiro, Ph.D., FIES, Lighting Research Center, Rensselaer Polytechnic Institute

Light is the most potent stimulus to synchronize the 24-hour mammalian circadian rhythm. For this reason, exposure to bright light at the wrong time of day (e.g., in the evening) can disrupt one's circadian phase and a host of downstream physiological processes that are entrained to that phase, such as sleep. It may therefore be possible to use bright light to shift the circadian phase of individuals with AD/ADRD who frequently endorse sleep disturbances. Furthermore, improved sleep will likely lead to improved cognition and mood. While exposure to light all day is ideal, researchers recommend that individuals with AD/ADRD (or at risk for AD/ADRD) receive at least 2 hours of bright light in the morning.

Studies that investigate the clinical significance of light therapy often yield mixed results because study parameters are not always optimized. To achieve clinically relevant results, light administration requires several qualities. First, the wavelengths administered should center around the short-wavelength (blue) spectrum (~450 nm), and the brightness of light should be sufficient to suppress melatonin by at least 30 percent (~350 lux at the eye). Second, light must be presented in a manner that allows transmission to the rear of the retina. This delivery may include light-emitting goggles, high-output lamps, and light tables. For circadian entrainment, daytime bright light (morning is recommended) and evening dim light is needed. Finally, light must be accurately measured. Measurement devices can include wearables, such as neck pendants, clothing pins, and wrist bands (however, wrist bands are not ideal because they can become covered).

Dr. Figueiro and colleagues designed a study that optimized these parameters in order to more rigorously assess the effect of light on sleep and AD/ADRD. The study assessed the benefits of a 14-week tailored lighting intervention (TLI) for individuals with AD/ADRD. Bright light exposure decreased sleep disturbances, agitated behavior, and depressive symptoms. With this success, the research team conducted a 6-month TLI, again showing that bright light exposure reduced sleep deficiency, agitation, and depressive symptoms. To assess the effect of light on specific amyloid pathology (i.e., amyloid and tau), the research team then conducted a similar experiment in the AD mouse model (5XFAD), comparing bright and dim light exposures (bright/dark vs. dim/dark living conditions). Bright light significantly reduced cortical levels of amyloid (AB42) compared to dim light. The team now plans to investigate the effects of flickering 40Hz light on the brain health of individuals with AD/ADRD.

Discussion

Dr. Figueiro clarified that bright blue light and light emitted in the 40 Hz gamma band likely act on different physiological systems. Bright light is helpful for circadian entrainment and sleep, whereas 40 Hz light modulates the neural physiology of a variety of brain regions, resulting in long-term positive effects. Dr. Figueiro envisions blue light exposure serving as a primary treatment for sleep deficits in individuals with AD/ADRD and 40 Hz exposure serving as a secondary treatment to augment bright light exposure therapy and improve cognition.

Dr. Figueiro also identified several areas for future research:

- Researchers are currently conducting fMRI studies to investigate the impact of high- and low-wavelength light on alertness and the extent to which different wavelengths alter brain functioning and morphology.
- Reductions of amyloid levels in mice may result from bright light–assisted sleep. The exact mechanism requires further study.

Taking the Pulse of Aging: Optical Measures of Arterial Stiffness as Early Predictors of Brain and Cognitive Decline

Monica Fabiani, Ph.D., University of Illinois at Urbana-Champaign

In older adults, arteries stiffen and the amount of blood that diffuses through blood vessels diminishes. Vascular dysfunction often results in a buildup/less clearing of amyloid peptides associated with cognitive decline and dementia, and is itself associated with diminished brain volume and function. Informed by the relationship between vascular health and cognition, Dr. Fabiani, Dr. Gratton, and colleagues developed a novel noninvasive procedure to measure arterial stiffness to determine an individual's susceptibility to cognitive decline.

The amount of blood that diffuses through the brain can be detected using pulse diffuse optical tomography (DOT), which uses infrared light detectors to measure the amount of oxy-hemoglobin and deoxy-hemoglobin in the arteries. Pulse-DOT essentially detects the pulsatory function of arteries, like a pulse oximeter used on a fingertip, using thousands of sensors around the head. Pulse-DOT has a spatial resolution of 10-20 mm and can penetrate approximately 30 mm from the sensor. By mathematically measuring the area under the curve between the peak systole and diastole, researchers can calculate a pulse relaxation function (PReFx), which serves as a measure of arterial elasticity; diminished PReFx values correspond with increased arterial stiffening.

Arterial inelasticity (arteriosclerosis), as measured with PReFx, has been shown to correspond with advanced aging, diminished cardiorespiratory fitness, reduced total gray and white matter in the brain, increased white matter signal abnormalities, and greater vascular dysfunction. Lower PreFx values are also correlated with neural network desegregation (a hallmark of aging) and, perhaps most importantly, multiple measures of cognitive decline, both locally and globally.

Pulse-DOT is a novel noninvasive procedure that is well positioned to detect the presence of predictors of age-related cognitive decline. The method can assess the overall health of the cerebrovascular system and could be used to tailor interventions targeting populations at risk for AD/ADRD.

Discussion

Dr. Fabiani identified several areas for future research:

- Dr. Fabiani is currently assessing the time needed for pulse-DOT to detect potential cognitive decline. Although reversal of cognitive decline is unlikely, pulse-DOT may allow clinicians to halt or slow decline.
- Research indicating positive correlations between exercise and arterial elasticity included "typical" research volunteers (i.e., athleticism was not overtly selected for). Therefore, many individuals can likely improve arterial elasticity through exercise. However, the optimal range of exercise (e.g., type, duration, and frequency) is currently unknown.

Biointegrating Sensing for Assessing Parameters Relevant in Aging and AD/ADRD

Shuai "Steve" Xu, M.D., M.Sc., Northwestern University

Wearable devices that continuously record biometric data from individuals, such as actigraphy watches and heart rate monitors, enable clinicians to better care for their patients while providing essential data for researchers. Although useful, current devices are limited in the type of data they can record and in their ability to *predict* biological processes. Dr. Xu's team has developed several devices that can record high-fidelity biometric data relevant to aging and AD/ADRD. Furthermore, these devices are flexible, like wearing a band-aid, which enhances their durability and thus increases patient adherence.

One such device is the ADAM sensor that is placed on the suprasternal notch (the visible dip in the center of the neck, between the clavicles). At this special location, the sensor can detect numerous physiological signals directly relevant to aging and AD/ADRD, such as respiration, heart rate, and body position and movement. Placement on this location requires comfortable, soft electronics for feasibility and patient comfort. Future iterations of the sensor will be targeted towards measurement of blood pressure, which has been associated with cognitive decline.

Dr. Xu's team has also developed algorithms to integrate physiological data from the ADAM sensor to derive more sophisticated measurements. Approximately 50 individuals with ADRD have difficulty swallowing. Algorithms have used the ADAM sensor to detect swallowing events and can even differentiate the swallowing of solid food, saliva, and water. The sensor may therefore be used in the development of therapeutic devices to improve swallowing. In addition, the ADAM sensor may be used to detect sleep disturbances, specifically breathing-related sleep disorders, and respiratory rate and effort.

Finally, it may be possible to use the ADAM sensor to measure aspects of complex behavior important for maintaining cognitive integrity, such as social activity. Older individuals disproportionately suffer from loneliness, which is a risk factor for cognitive decline. The ADAM sensor can measure acoustic waveforms, allowing it to detect socialization between two

individuals. Dr. Xu hopes to incorporate these data into future algorithms to identify at-risk individuals and determine when social interventions are needed. The ADAM sensor works like a microphone; however, it has a superior battery life (1 week of continuous recording on a single charge) and does not pick up speech (thereby avoiding privacy concerns).

Discussion
Dr. Xu clarified two aspects of ADAM's use:

- A single ADAM sensor cannot discriminate between two individuals talking to each other and an individual talking to themselves. For this reason, a pair of ADAM users (i.e., a sensor on each individual) is required to detect socialization.
- ADAM is currently 85 percent accurate at discriminating sleep from wake using electroencephalography (EEG) as the gold standard.

Optogenetics, Expansion Microscopy, and Other Tools for Mapping and Controlling the Aging Brain

Ed Boyden, Ph.D., Massachusetts Institute of Technology

AD/ADRD ultimately develops from deficits in brain functioning at the cellular level. Assessing the dynamics of brain functioning at the neural level can thus provide insight into global cognitive dysfunction. Three main activities, in particular, are required to understand the neural underpinnings of AD/ADRD, which include (1) mapping molecules, wiring, and neural connections, (2) controlling neural activity, and (3) observing neural activity involved in AD/ADRD. Dr. Boyden presented several methods to facilitate study at these three levels.

Dr. Boyden has helped develop the first method, which expands neurons to create cellular images with nanoscale resolution, by moving biomolecules away from each other. In this method, called expansion microscopy, researchers synthesize polymer chains of swellable materials into neural tissue. These chains permeate throughout the tissue, wrapping around and between biomolecules, both inside and outside cells. As the polymer expands, the biomolecules separate but retain their relative spatial positions (i.e., distortions are minimal). This expansion allows fluorescent dyed molecules to become individually discriminable and allows researchers to conduct nanoimaging studies using standard microscopes on expanded tissue.

The second method, optogenetics, enables researchers to control high speed neural electrical dynamics in vivo. With this technique, researchers genetically modify neurons using naturally occurring opsins (light-activated proteins) such that the neurons are either activated or inhibited when exposed to a specific wavelength of light. This technique is also extremely precise on both a temporal and spatial scale; a single action potential can be evoked in a single cell.

Dr. Boyden and his collaborators have also developed the third method, which uses a robot to direct the evolution of proteins in order to produce fluorescent indicators with specific features

of interest. In one example of this procedure, they developed fluorescent indicators that fluoresce during action potentials, which allows researchers to monitor the activity of discrete neurons in a living animal. Additionally, optogenetics may be performed at the same time, allowing simultaneous neural stimulation/inhibition and recording.

Expansion microscopy, optogenetics, and fluorescent recording will hopefully be useful tools to study how brain circuits change in aging and how they may be repaired. For instance, expansion microscopy may be used to identify clusters of proteins that serve as biomarkers of age-related cognitive decline.

Discussion

Dr. Boyden noted the opportunity to expand future research to human subjects. To date, all research using optogenetics has been conducted in animals, including nonhuman primates, and researchers have successfully used optogenetics to induce memories and sensory inputs using rodents. Several companies want to conduct optogenetic studies in humans.

Sleep Movements and Respiratory Coupling in Mild Cognitive Impairment

Marie Hayes, Ph.D., Activas Diagnostics and the University of Maine
Ali Abedi, Ph.D., Activas Diagnostics and the University of Maine

Individuals with mild cognitive impairments (MCI) often report difficulty sleeping. Coupling of high frequency sleep movements (SM) and respiratory rate (RR) may serve as a biomarker for sleep loss and weakening of coupling integrity may be used to identify individuals with preclinical MCI. To establish the utility of SM-RR coupling as a diagnostic measurement, Drs. Hayes and Ali developed a mattress pad that uses 32 pressure sensors to detect both respiration and movement during sleep.

In their study, Drs. Hayes and Abedi used the mattress to record SM and RR of aging community participants with MCI and normal cognition over two nights. MCI was associated with poor sleep (e.g., decreased sleep duration and increased wake bout time) and neurocognitive deficits. Dr. Abedi then used the mattress pad data to design an algorithm to predict which participants had MCI. Researchers used 60 percent of the participant data to train the algorithm and the remaining 40 percent to test the algorithm. Using only SM-RR coupling data, the algorithm identified MCI individuals with 95 percent accuracy (using a neural network-based approach). The mattress pad is being commercialized.

Transcranial Electrical Synchronization to Improve Deep Sleep and Memory in Normal Aging and Mild Cognitive Impairment

Don Tucker, Ph.D., Brain Electrophysiology Lab (BEL) Company

Memory decline in aging may be partially due to the loss of deep sleep (slow wave sleep [SWS]). The amount of SWS per night continuously declines until the age of 30, at which point some individuals plateau, whereas others continue to decline. Slow wave activity can benefit cognition in (at least) two discrete ways: (1) SWS is positively correlated with hippocampal activity and deficient SWS results in diminished memory retention, and (2) the increased circulation of cerebrospinal fluid during SWS clears out AD pathology—such as amyloid beta and tau—that surround neurons. The loss of sleep, which is a common result of the aging process, therefore reduces the amount of time for clearance of amyloid peptides and tau proteins from the brain during SWS, resulting in memory impairment.

It may be possible to artificially induce SWS using transcranial electrical stimulation (TES). Specifically, TES can forcibly synchronize neuronal activity in limbic regions that naturally act as the neural generators of SWS; namely, the parahippocampal gyrus (PHG) and caudal orbitofrontal cortex (areas that also often show AD-related pathology). Inducing neural synchrony in PHG has been shown to directly improve memory consolidation, which add to the cognitive benefits already induced by cerebrospinal fluid–mediated metabolic clearance during SWS. As a proof of concept, Dr. Tucker increased the length of SWS in 11 young adults using TES. Neural synchrony may therefore serve as a potential therapy to maintain SWS during the aging process and forestall cognitive impairments associated with dementia.

Discussion

Dr. Tucker described an enhancement to be explored in future research. To date, Dr. Tucker's team has administered TES using a headband that can also record neural activity between periods of stimulation. The headband applies a stimulus of 0.5 Hz at 0.5 mV for 5 minutes then records for 1 minute. The team selected a frequency of 0.5 Hz to synchronize canonical endogenous slow wave brain activity without introducing overt stimulation. Future iterations of the device may include adhesive electrodes to increase comfort and diminish movement artifacts.

EEG-Guided Training to Improve Working Memory in Patients with Cognitive Symptoms

Fiza Singh, M.D., University of California, San Diego

Virtually all aspects of cognitive functioning, including problem solving, planning, and forming long-term memories, require working memory. Working memory is particularly important because it is a fluid and flexible form of limited capacity memory where information can be manipulated. Working memory depends, at least in part, on the dorsolateral prefrontal cortex; its engagement causes local neural circuits within this region to activate in a coordinated manner, producing gamma oscillations that can be visually displayed using EEG recording.

When individuals have their own electrical activation visually presented to them, they can then alter their own gamma oscillations, in a process called neurofeedback (NF). Dr. Singh reviewed the potential applicability of NF to shaping cognitive health.

Previous studies have used NF to allow healthy individuals to navigate virtual environments using solely their own brain function, which is monitored through scalp sensors and transmitted to a computer running the virtual environment. NF has also enabled patients with schizophrenia to volitionally influence gamma oscillations in their prefrontal cortices. This NF training resulted in improvements on several cognitive domains. Therefore, Dr. Singh and colleagues are developing a randomized placebo-controlled NF gamma oscillation treatment study for adults with MCI and at risk for developing AD/ADRD to improve cognitive outcomes.

Discussion
Dr. Singh described two directions for future research:

- Participants in Dr. Singh's NF development studies can select their NF modality from a collection of videogames or movies that provide gamma-dependent feedback. Future studies may include auditory neural feedback.
- Studies may also investigate the role of theta-gamma coupling in MCI.

Exploring Retinal Blood Flow Dynamics for Clues in Assessment of Brain Health
Abhishek Rege, Ph.D., Vasoptic Medical, Inc.

The retina is an extension of the brain, and shares anatomical and physiological similarities. For this reason, the eye can serve as a window into the brain and allow clinicians to make inferences about neural health. Dr. Rege and colleagues have developed an instrument (XyCAM RI) that images dynamic blood flow in the retina, and have used it to research differences between the retinal vascular status of healthy control participants and individuals with MCI. While the differences were significantly suggestive even with a small number of subjects, the research team plans to enroll 30 individuals as healthy controls and 30 individuals with MCI to robustly verify these findings.

XyCAM RI's operation creates several benefits for patients and practitioners. The instrument operates by imaging the motion of red blood cells in the vasculature; the speed of red blood cell movement causes blurring in speckle images obtained under laser illumination, which the instrument translates into a signal measure that corresponds to blood flow velocity. This method provides dynamic blood flow videos instead of static images, does not require pupil dilation, does not require dye, uses mild illumination intensity, and is easy to employ in a clinical setting. Furthermore, XyCAM RI is also under investigation as a potential screening mechanism for diabetic retinopathy.

Discussion

Dr. Rege clarified that the XyCAM RI unit can image with a 25-degree field of view on a 1200-pixel diameter sensor, which can resolve a vessel with diameter as small as 30microns. He also noted that future work will assess vascular dementia in AD/ADRD by evaluating morphological changes to blood vessels and changes to blood flow.

The Eyes Have It: Advances of Eye Tracking for the Assessment of Cognition in Aging and Neurodegenerative Disease
Nick Bott, Psy.D., Neurotrack Technologies, Inc., and Stanford University

Dr. Bott reviewed specific eye tracking tasks that can be effectively conducted on smart devices to facilitate assessment of cognitive function. Eye movements can provide insight into the cognitive abilities of healthy individuals compared to individuals on the trajectory of pathological cognitive decline. Some relevant eye tracking variables include novelty preference, proportion of eye fixations, proportion of time spent on an item, number of transitions into and out of a specific region, duration of the first gaze, and number of fixations in the first gaze. Until recently, eye tracking was possible only in research settings but, because of modern computing power and camera technology, smartphones and tablets may be used to collect these data. Researchers and large technology companies (e.g., Apple, Inc.) are beginning to leverage wearables, tablets, and smart phones to develop ecological biomarkers to discriminate healthy individuals from individuals with cognitive impairment.

Eye tracking software may facilitate the prediction or diagnosis of AD/ADRD and has shown to differentiate AD/ADRD and healthy controls during attention tasks (saccade and anti-saccade tasks). Eye tracking is also used to predict the course of cognitive impairment over several years. In many of these cases, data from devices with embedded cameras are comparable to data from commercial eye trackers, which facilitates study of community populations.

Discussion

Dr. Bott described two implications for future research:

- Eye tracking is a useful standalone measure, but incorporating data from multiple sensors offers added value. Future studies will incorporate additional devices to collect multimodal data for richer composites of cognitive symptomology.
- The portability of smart devices may solve a persistent challenge to ensuring that the community environment supports accurate, clinically useful data collection. One of the most significant factors that shapes the clinical usefulness of a diagnostic task is ensuring that participants pay close attention to the task, which may be verified with eye tracking.

OLFACT™: Screening Test for Dementia Based Upon the Sense of Smell
Lloyd Hastings, Ph.D., Osmic Enterprises, Inc.

Recruiting participants for AD/ADRD clinical trials is challenging because at-risk individuals often must be studied before disease onset, but biomarker testing to identify these individuals is expensive, invasive, and not always reliable. Because AD/ADRD is difficult to predict, only approximately 10 percent of individuals recruited into studies develop clinically significant cognitive impairment. However, the olfactory system may be used to solve the problem of participant recruitment.

The olfactory system is one of the earliest brain regions that develops AD pathology, and deficits in the sense of smell are some of the earliest symptoms associated with AD/ADRD. For this reason, Dr. Hastings and his team developed Olfactory Function Assessment by Computerized Testing (OLFACT). This test uses a machine (olfactometer) that administers smells to a study participant, who must then identify and remember the smell for later recall. OLFACT is less stressful for participants than cognitive batteries, takes 10-15 minutes to administer, does not require specialized training, and uses centralized cloud storage to streamline multi-site testing.

Using olfactometry data from a cohort of 600 participants, researchers created a model demonstrating that individuals who perform in the lowest 10th percentile are nearly four times more likely to develop dementia 10 years after the baseline test. Although not a diagnostic tool, OLFACT is an affordable method that is quick to administer and may supplement current AD/ADRD predictors, such as biomarkers, to increase the likelihood of recruiting asymptomatic individuals who will develop AD/ADRD into clinical research studies.

Discussion
Dr. Hastings clarified that OLFACT lacks the specificity to differentiate among types of dementia. Its utility lies in the ability to increase the likelihood of recruiting individuals who are likely to develop dementia, especially when combined with other predictive tests such as eye tracking and retinal imaging.

He also described a new way to harness the test in future research. Initial evidence suggests that individuals infected with SARS-CoV-2 report anosia and other olfactory deficits. OLFACT may therefore serve as a useful instrument in screening for COVID-19, and Dr. Hastings is currently in discussion with other researchers to begin this line of work.

Transcranial Direct Current Stimulation Across the Dementia Spectrum
Ben Hampstead, Ph.D., University of Michigan

Dr. Hampstead led a team to advance the application of transcranial direct current stimulation (tDCS) to improve cognitive performance in those with Alzheimer's disease and related dementias (ADRD). The tDCS procedure involves running an electrical current through the

brain; current is applied through an anode and returns via a cathode. The spatial precision of tDCS can be further improved by splitting the electrical current among multiple electrodes that surround a single electrode; an approach known as "high definition" tDCS. This procedure has been successfully tested by targeting the motor cortex and eliciting a motor evoked potential. In addition to eliciting a motor response, tDCS may also improve performance on cognitive tasks.

Although tDCS can improve cognitive performance, its effectiveness can vary widely, partly because cognitive processing regions are widespread (whereas motor processing regions are anatomically circumscribed). Furthermore, individual differences in the size/shape of the brain increases variability in the foci and amount of electricity delivered. Dr. Hampstead provided evidence that the standard dosing approach (e.g., 2mA applied at the scalp) results in ~250-350% variability in electrical current delivered to the targeted brain area, even in "healthy" older adults. Brain pathology likely also increases variability among individuals since lesioned, atrophied, or disease-burdened brain tissue may possess a different impedance than healthy tissue and can unpredictably redirect electrical current, causing off-target modulation. The optimal length and frequency of stimulation is also unknown and likely variable; approximately half of tDCS protocols arbitrarily stimulate for 20 minutes at 2mA. Thus, Dr. Hampstead argued that far more information is needed about dose-response relationships.

In several recent studies, Dr. Hampstead's team has used MRI-based computational modeling to ensure a comparable amount of electrical current reaches the targeted brain region across participants. This revolutionary approach will enhance our understanding of dose-response relationships and of the "true" neuromodulatory potential for tDCS. In healthy individuals, this tDCS procedure has been shown to successfully modulate fMRI activation in the region of interest and increase memory as a result. The team is conducting the procedure in older adults across the AD spectrum (e.g., MCI and ADRD) as well as with other forms of dementia (e.g., frontotemporal dementia). Preliminary results suggest promising evidence of neural activation results. This and future work will determine the efficacy of tDCS as a therapy for ADRD patients in addition to optimizing the amount, duration, and frequency of tDCS currents to achieve clinically meaningful results.

Discussion
Dr. Hampstead clarified that he is investigating using near infrared spectroscopy and EEG to assess the neurophysiological effects of tDCS because not every patient is fMRI compatible.

Ultrasound-Mediated Treatment of Alzheimer's Disease
Elisa Konofagou, Ph.D., Columbia University

The blood–brain barrier impedes the ability of potential AD/ADRD therapeutics to reach all areas of the brain, including regions such as the hippocampus that are critical for cognitive processing. However, research in mice has shown that, when injected into the bloodstream, microbubbles can be agitated using focused ultrasound (FUS). This agitation causes the capillaries in the brain to expand and contract, loosening the blood–brain barrier junctions and

allowing normally blocked therapeutics to pass through and access neurons and glial cells. The capillaries loosen enough to allow drug permeation; no lasting damage occurs.

Dr. Konofagou's research attempts to leverage the fact that FUS increases microglial activation at the site of capillary "sonication." In the AD mouse model, FUS induced microglial response in the hippocampus that decreased the amount of AD pathology (tau proteins). Furthermore, the performance of FUS-sonicated mice in the Morris water maze improved, indicating memory improvements. Short-term memory enhancement was also positively correlated with the degree to which the blood–brain barrier loosened.

Although FUS in non-human primates (NHPs) requires a change in frequency to penetrate the animals' thicker skulls, sonication still evokes a regional microglial response with no resultant gross pathology and results in the appearance of progenitor cells, indicative of neural growth. FUS can also improve speed and accuracy of cognitive tasks in NHPs.

Dr. Konofagou and colleagues are applying these learnings to design an FUS system for humans in a clinical setting. They will be able to monitor the location of the brain where sonication events occur, and they plan to recruit six individuals with MCI or early AD to measure amyloid pathology before and after FUS.

Discussion
Dr. Konofagou clarified the safety of the procedure. The FDA has approved the microbubbles, and an IRB has approved the FUS procedure in humans. Although microglia are activated by the procedure, no apparent damage to the capillaries has been observed, even in NHPs that received 60 sonications.

She also described the potential expansion of the research for human subjects. Repeated sessions of FUS combined with pharmacological administration have resulted in neuron restoration in Parkinson's patients. Testing in patients with dementia has yet to occur.

Self-Powered Wearables for Vigilant Health Monitoring
Veena Misra, Ph.D., North Carolina State University

Passive physiological data collection is poised to provide useful health data to both patients and their doctors, enabling identification of various pathological risk factors, including those associated with AD/ADRD. However, wearable devices to collect such data must comfortable, wireless, and self-powered. Dr. Misra directs the Advanced Self-powered Systems of Advanced Sensors and Technologies (ASSIST) center, which focuses on engineering such devices.

ASSIST develops flexible sensors that are both low powered and autonomous, fueled by renewable energy such as body heat; a single 40 cm^2 sensor can produce and store an average of 1,200 μW of energy in a single day. Sensors can also record a combination of sound, light, motion, chemicals, and electricity produced by the body or the surrounding environment, including bioinformatics such as heart activity, motor movement, emotional state (galvanic skin response), blood pressure, skin temperature, exposure to air pollutants (which may exacerbate

AD pathology), sun exposure, speech, and metabolic changes (from concentration of chemicals and pH level of sweat). Because some measurements require biochemical information from sweat, and not everyone sweats enough for data collection, ASSIST has created hydrogels that alter the osmotic gradient on the skin to pull sweat from the skin and into the sensor.

ASSIST monitors neural activity using small near-infrared spectrometry sensors that can discriminate among deep sleep, light sleep, and waking events. ASSIST is also developing a free floating, wireless, 2.5 x 2.5 x 1.5 mm implantable optical and electrical stimulation device for future implantation into AD/ADRD patients that will allow neurosurgeons to activate brain regions in conscious patients. ASSIST has also developed several form factors to enable recording by a variety of these sensors, including vests, wrist bands, and chest patches.

Discussion
Dr. Misra described limits on and potential future directions of data collection:

- Measurements such as electrocardiography (ECG) rely on 500 Hz recording for high fidelity, which require more power than an autonomous sensor can produce. The ASSIST sensors can record 80-100 Hz, which is sufficient for discerning heart rate (R to R peaks). Other kinds of data, such as EEG, are not possible to record because the frequency and processor intensities are too great.
- Future sensors may benefit from the addition of solar cells to harvest light energy, and some may be applied to the foot, using heat and friction to measure gait.

Digital Memory Book
Neo Mohsenvand, B.Sc., Massachusetts Institute of Technology

Caregivers for individuals with AD/ADRD often experience depression, stress, fatigue, weight gain, and insomnia. One method for caregivers to both cope with these difficulties and to improve the wellbeing of the individual with AD/ADRD is to create memory books filled with annotated photos from that individual's life. This process, however, can be time consuming, especially given the statistic that the average American will own more than 50,000 photos and videos by the year 2025. For this reason, Mr. Mohsenvand and colleagues have developed a digital memory book that automates the collation of photos and uses facial recognition to allow caregivers to tag and annotate those photos in a streamlined manner. The platform uses the annotated pictures to generate a personal knowledge graph of the AD/ADRD patient and to map out relationships between the user and associated individuals, objects, and locations. The platform detects whether information is missing and, if so, prompts caregivers to provide it.

The digital memory book employs an intuitive user interface designed to be accessed by individuals with AD/ADRD. Images are always paired with descriptive information, and individuals with AD/ADRD can view the events of an entire year in one page. The digital memory book is also interactive; individuals with AD/ADRD can review and rehearse memories through games that incorporate images, videos, and audio. The results of these games inform

caregiver and clinician understanding of the time course of memory loss, and researchers are employing memory analytics from these games to assess memory loss over time.

The ultimate goal is to exploit the digital memory book to identify what parts of an individual's memories have been lost and to predict which memories are most vulnerable. Machine learning can then be employed to focus content on vulnerable memories to help prevent their decay.

Discussion
Mr. Mohsenvand described several potential future studies related to the digital memory book:

- The book was recently developed, so its ability to predict, halt, or reverse MCI is unknown. Mr. Mohsenvand's goal is to conduct a longitudinal study that includes daily cognitive tests to assess the clinical relevance of the platform.
- Future studies may also incorporate peripheral physiological measures, such as electrodermal activity and heart rate, to indicate nonconscious recognition.

An Introduction to Regulatory Considerations for Neurodiagnostic and Non-Invasive Stimulation Devices

Jay Gupta, M.S.E., Center for Devices and Radiological Health/U.S. Food & Drug Administration

The FDA Office of Health Technology 5 (OHT5) receives Investigational Device Exemption (IDE) applications that involve neurological and physical medical devices.

The term "device" means an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, that is "intended for the use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease… or intended to affect the structure of any function of the body… and which does not achieve any of its primary intended purposes through chemical action… and which is not dependent upon being metabolized for the achievement of its primary intended purposes."[1]

Potential IDE applicants are encouraged to request an Informational Meeting with FDA before submitting a Pre-Submission (Pre-Sub) and then a formal IDE application. Although voluntary, Informational Meetings and Pre-Subs can help to set the applicant's expectations and are free of charge. All such interactions with FDA are confidential. Informational Meetings are used to share information with FDA without the expectation of feedback. Pre-Subs are intended to facilitate more in-depth reviews of study design (not data) with written feedback provided within 70 days of submission and may be accompanied by a meeting to clarify the feedback.[2]

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[1] See U.S. Food and Drug Administration website, "How to Determine if Your Product is a Medical Device."
[2] See FDA Guidance, "Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program."

IDEs are needed when a device study is a significant risk, which means that the device is "intended as an implant, is purported or represented to be for a use in supporting or sustaining human life, is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health, or otherwise presents potential serious risk for the health, safety, or welfare of a subject."[3] The necessity of an IDE is determined by both the device itself and its use within the context of the study. Review of IDE applications are completed within 30 days of receipt by FDA, which can result in approval, approval with conditions, or disapproval of the IDE. The FDA may also communicate study design considerations of future considerations not related to the safety of the proposed study.

Discussion
Applicants are responsible for making the initial risk determination and presenting it to their local IRB. The IRB should review the determination and modify if necessary. FDA is the final arbiter as to whether a device study is significant risk and makes the determination when an IDE is submitted to FDA or if requested by the applicant or IRB through a Study Risk Determination.[2,4]

Discussion

Is multisensory stimulation more effective than visual stimulus alone for brainwave entrainment?

Unisensory stimuli may be ideal for targeting specific brain regions (e.g., only the visual system or only the auditory system). Administering unisensory stimuli may also be the best approach in NF studies because participant attention would not be divided between two stimulus types. However, multisensory stimulation typically maximizes the number of synchronized brain regions. In both mice and humans, multisensory stimulation results in both wider propagation of entrainment and increased total signal amplitude, and may have longer-lasting benefits, than unisensory stimulation. Further, multisensory stimulation may increase overall cardiovascular blood flow because auditory and visual areas are perfused by different arteries, and may therefore be beneficial for aging individuals with stiffening arteries. Although cognition relies on a broad network of brain regions, segregation of neural activity within this network often corresponds with superior cognitive performance. Whether a broad spectrum of neural entrainment through multisensory stimulation is better for cognition than targeting specific brain regions with unisensory stimulation remains an open question, and thus requires further study.

Can EEG and sleep monitoring be used as specific neurological markers for AD/ADRD diagnosis and treatment?

Discussants agreed that sleep can be a predictor of cognitive decline, particularly because it plays an important role in metabolic functioning and memory consolidation. Furthermore, sleep

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[3] See Code of Federal Regulations Title 21.
[4] See FDA Information Sheet Guidance, "Significant Risk and Nonsignificant Risk Medical Device Studies."

measures are objective and therefore reliable. Biological and environmental sensors are improving and may be able to capture data about sleep patterns and context (e.g., light and sound of sleep environment) to inform research into sleep as a biomarker. Longitudinal studies utilizing these sensors will be necessary because an established model of the correspondence between the progression of memory impairment and sleep dysfunction does not exist.

One discussant noted that sleep studies may need to transition from the laboratory to the home. Most individuals with sleep complaints are reluctant to participate in laboratory sleep studies, which can be time consuming and expensive. Deploying innovative sleep sensors in the home setting would address these issues and would enable collection of quality bioinformatics in the comfort of the patient's home, and at a fraction of the cost.

What are barriers for using eye tracking or olfaction as an early sign of AD/ADRD?

The main barrier for olfactory studies is that an external device is needed to produce odors, forcing patients to travel to a laboratory and complicating community proliferation. Eye tracking can be conducted on a smart device virtually anywhere but must surmount concerns of health care providers who may be skeptical of novel screening methods. Thus, effective communication between clinicians and the scientists who develop new screening methods will be necessary to prevent the exclusion of potentially useful interventions from the health care system.

In addition, health care providers may be less familiar and therefore less comfortable with data that are "passively" collected over extended periods of time, particularly compared to discrete "active" tests that are conducted in the clinic. Developers and researchers involved in passive bioinformatic data collection must position new technology in a way that can demonstrate the benefit of both active and passive data to increase health care provider buy-in. The current challenge in diagnosing AD/ADRD is not the development of effective technologies, but the adoption of those technologies by clinicians.

How to bridge the gap of understanding among engineers, neuroscientists, clinicians, and caregivers?

Workshops that convene professionals with different areas of expertise (e.g., academic researchers, bioengineers, and clinicians) serve to elucidate the current landscape of AD/ADRD research and treatment. Engineers often attend workshops and academic conferences to identify the tools that researchers and clinicians are missing and then fill those gaps with new technology. One discussant emphasized that caregivers are often excluded from this conversation despite their critical role in improving compliance with equipment use and treatment.

Cultivating a shared learning environment for engineers, neuroscientists, and clinicians—particularly during early training—will support integration of these fields. One discussant works in an environment where first-year bioengineering and neuroscience students attend classes

and work collaboratively in neuroengineering training. As a result, these students gain a different perspective on how to approach science than do students from other institutions. Multiple discussants added that they share common spaces with researchers from other related fields, which promotes fruitful interactions.

Engineers and product developers must consider how new technology will be presented to clinicians and researchers to maximize the likelihood of adoption. Working with scientists and regulatory bodies early in product development is necessary for creating, funding, and implementing the product.

Data sharing

Researchers have an obligation to share data collected through publicly funded research, but they encounter difficulties formatting, storing, and deidentifying those data. Researchers employ data formats dependent on proprietary data collection tools, but common data sharing formats are rarely enforced. Funding agencies may need to establish common formats and enforce their inclusion in accessible common databases, which will require funding to develop and maintain.

Protecting patient privacy is also a major hurdle for coalescing data into a central repository. Data mining experts have demonstrated the ability to reconstruct personal information from deidentified data using deep learning algorithms. Database security is therefore a top priority for researchers, and protecting sensitive personal information would be an excellent topic for a future workshop.

Discussants also noted the necessity to involve caregivers and data scientists in this effort.

Taken together, the workshop accomplished its goal in a zoom meeting format. It covered a broad range of topics, including neuronal circuit connectivity, multi-sensory systems, cardiovascular systems, multimodal approaches, and AD heterogenicity. The exciting sensors and devices are highly applicable to the aging and AD/ADRD populations and offer the opportunity for precision medicine at the individual level. Finally, the gaps and barriers in development of devices are recognized and identified.

Appendix A: Agenda

Use of Neurotechnology in Normal Brain Aging and Alzheimer's Disease (AD) and AD-Related Dementias(ADRD)

April 27, 2020
11:00 a.m. – 5:30 p.m. EDT

Agenda

11:00 a.m.   **Welcome & Introductions**
Laurie Ryan
Chief, Clinical Interventions and Diagnostics Branch

Eliezer Masliah
Director, Division of Neuroscience

Yuan Luo, Kristina McLinden, Coryse St. Hillarie-Clarke, Program Directors
Molly Wagster Chief, Behavioral & Systems Neuroscience Branch

11:10 a.m.   Using Non-invasive Sensory Stimulation to Ameliorate Alzheimer's disease Pathology and Symptoms
Li-Huei Tsai, Massachusetts Institute of Technology

11:30 a.m.   Flipping the Switch: How to use Light to Improve the Lives and Health of Persons with AD/ADRD
Mariana Figueiro, Rensselaer Polytechnic Institute

11:50 a.m.   Optical Measures of Arterial Stiffness as Early Predictors of Brain and Cognitive Decline
Monica Fabiani, University of Illinois at Urbana-Champaign

12:10 p.m.   Bio-Integrated Sensing for Assessing Parameters Relevant in Aging and AD/ADRD
Steve Xu, Northwestern University

12:30 p.m.   Optogenetics, Expansion Microscopy, and Other Tools for Mapping and Controlling the Aging Brain
Ed Boyden, Massachusetts Institute of Technology

12:50 p.m.   **BREAK**

1:00 p.m.	Sleep Movements and Respiratory Coupling is Impaired in Mild Cognitive Impairment: A Home-based Clinical Diagnostic Tool *Marie Hayes, Activas Diagnostics and the University of Maine*
1:20 p.m.	Transcranial Electrical Synchronization to Improve Deep Sleep and Memory in Normal Aging and Mild Cognitive Impairment *Don Tucker, Brain Electrophysiology Lab (BEL) Company*
1:40 p.m.	EEG-Guided Training to Improve Working Memory for Patients with Cognitive Symptoms *Fiza Singh, University of California, San Diego*
2:00 p.m.	Exploring Retinal Blood Flow Dynamics for Clues in Assessment of Brain Health *Abhishek Rege, Vasoptic Medical, Inc.*
2:20 p.m.	The Eyes Have It: Advances in Eye Tracking for the Assessment of Cognition in Aging and Neurodegenerative Disease *Nick Bott, Neurotrack Technologies, Inc., and Stanford University*
2:40 p.m.	OLFACT™: Screening Test for Dementia Based Upon the Sense of Smell *Lloyd Hastings, Osmic Enterprises, Inc.*
3:00 p.m.	**BREAK**
3:10 p.m.	Transcranial Direct Current Stimulation Across the Dementia Spectrum *Ben Hampstead, University of Michigan*
3:30 p.m.	Ultrasound-Mediated Treatment of Alzheimer's disease *Elisa Konofagou, Columbia University*
3:50 p.m.	Self-Powered Wearables for Vigilant Health Monitoring *Veena Misra, North Carolina State University*
4:10 p.m.	Digital Memory Book *Neo Mohsenvand, Massachusetts Institute of Technology*
4:30 p.m.	An Introduction to Regulatory Considerations for Neurodiagnostic and Non-Invasive Stimulation Devices *Jay Gupta, Center for Devices and Radiological Health/ U.S. Food & Drug Administration*

4:50 p.m.   **Discussion & Next Steps**

Chairs

1. Is multisensory stimulation more effective than visual stimulus alone for brainwave entrainment?

2. Can EEG and sleep monitoring be specific neuro markers for AD diagnosis and treatment?

Molly Wagster
Yuan Luo

3. What are barriers for using eye tracking as an early sign of AD/ADRD?

Questions/
Topicsfor
discussion

4. How to bridge the gap of understanding among engineers, neuroscientists, and clinicians?

5. Data sharing

Appendix B: Participants List

Use of Neurotechnology in Normal Brain Aging and Alzheimer's Disease (AD) and AD-Related Dementias (ADRD)

Participant List

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