

Epilepsy and Alzheimer's disease: Overlapping mechanisms and therapeutic opportunities?

A workshop convened by the Alzheimer's Association® with support from the Band Foundation

Since the early decades of studies of electroencephalography (EEG) (Letemendia et al. J Neurol Neurosurg Psychiat 1958), which detects electrical activity in the brain, scientists have known of the presence of seizures in people with Alzheimer's dementia. Even today, however, the links between Alzheimer's disease and epilepsy are not well understood. A growing number of studies have identified epileptiform activity — a sharp brain wave that could serve as a marker for an individual with epilepsy — as a potential factor in the progression of Alzheimer's. This link suggests novel avenues for deciphering the biological mechanisms of both disorders, as well as identifying novel diagnostic and treatment strategies.

Introduction

On September 25 and 26, 2017, the Alzheimer's Association convened a workshop assessing the current state of the field regarding epileptiform activity in Alzheimer's. Chaired by Drs. Lennart Mucke (Gladstone Institute and the University of California, San Francisco), Frances Jensen (University of Pennsylvania) and Steven White (University of Washington), this meeting gathered leading specialists from both the Alzheimer's and epilepsy research communities. It featured five main themes for discussion: (1) brain changes in disease and the associated measures of biological change, (2) cellular and network mechanisms, (3) protein handling and inflammation, (4) genetics, and (5) clinical translations. Lastly, a summary discussion session identified gaps in knowledge that need to be addressed — suggesting areas of future research and collaboration.

In convening this discussion, the Alzheimer's Association looked to build on the work undertaken since the 2008 meeting of the National Institute of Neurological Disorders and Stroke (NINDS) at the National Institutes of Health (NIH). The 2008 discussion opened the door to explore the relationships of hyperactivity in the brain network and Alzheimer's disease and spurred interest in the field. The mission of the current workshop is to come up with ways to push the field forward.

Dr. Mucke gave the opening presentation, an overview pointing to research indicating that subtle epileptiform activity is more common in people with Alzheimer's disease than previously realized. According to one study, more than 40 percent of individuals with Alzheimer's in their early sixties had epileptiform activity. Other studies have shown the presence of "silent" hippocampal seizures detected by EEG, primarily during sleep (Lam et al. Nat Med 2017; Horvath et al, J Alzheimer Dis 2017). Moreover, for people with Alzheimer's who experience this activity, their dementia tends to progress faster.

He added that the use of the anti-epileptic drug levetiracetam has been shown to reverse cognitive deficits in genetically engineered Alzheimer's-like mice (Sanchez et al. PNAS 2012) and in individuals living with mild cognitive impairment (MCI) due to Alzheimer's or amnesic MCI (Bakker et al. 2012 and 2015).

The overview session concluded with Dr. Andrew Cole of Harvard Medical School, who discussed novel, sensitive methods of detecting subtle epileptiform activity in the aging brain, especially during sleep. One technique involving foramen ovale electrodes, a new recording method, can detect abnormal electrical discharges and seizures that standard EEGs cannot (Sheth et al. Epilepsia 2014). Such procedures may be able to assess how subclinical epileptiform discharges — meaning no detectable signs or symptoms by physical exam or lab

test — in the brain affect the earliest brain changes in the Alzheimer's disease continuum, including abnormal beta-amyloid and tau production and accumulation.

Brain Changes in Alzheimer's and Epilepsy

Growing evidence suggests overlapping brain changes in Alzheimer's and epilepsy. Dr. Julie Schneider of Rush University, Dr. Delia Talos of the University of Pennsylvania, and Dr. Jensen described the brain changes seen in Alzheimer's — namely, tau tangles and amyloid plaques, which are hallmarks of Alzheimer's disease — and epilepsy. Further, both diseases involve the death of interneurons, a special type of nerve cell in the brain, in two different brain regions, which leads to the loss of rhythmic activity in nerve cell networks (Palop et al. 2007; Lam et al. 2017; Noebels JL et al. 2015). These interrelated brain changes may contribute to different disease progressions.

Dr. Schneider pointed out that about one-third of older individuals have sufficient levels of brain changes associated with Alzheimer's to fulfill the criteria for a pathologic diagnosis of Alzheimer's. Yet those with greater neural reserve — the capacity to tolerate age-related change — which might be related to education level, physical activity and other factors, may develop dementia symptoms at a later time in life than individuals with less neural reserve. Alzheimer's also tends to occur along with other brain changes, including cerebral vascular disease and Lewy body dementia (LBD).

Research indicates that epileptic activity may have a role in promoting the onset of the Alzheimer's-related brain changes and may also accelerate the timeline for an individual to develop symptoms of Alzheimer's. Such findings stress the need for longitudinal studies — repeated observations of individuals over extended periods of time — of epileptiform activity in the brains of older people at risk of dementia.

Cellular and Network Mechanisms

Understanding the biological underpinnings common to Alzheimer's and epilepsy is essential to the development of tools to better detect and diagnose these diseases and treat them. Discussion led by Dr. Jorge Palop of the Gladstone Institutes and the University of California, San Francisco, and Dr. Istvan Mody of UCLA described processes that appear to affect the function of interneurons in both disorders. Several studies have examined the protein mechanisms underlying the epilepsy/dementia connection. Such studies found that: (1) decreased levels of calbindin — a calcium-regulating protein linked to epilepsy — occur in the brain of people with Alzheimer's and in Alzheimer's-like mice (Palop et al. PNAS 2003); and (2) tau may promote both cognitive decline and epileptogenesis — a gradual process by which a normal brain develops epilepsy (Maeda et al EMBO Rep 2016; Tai et al Brain 2016).

Functioning of certain interneurons appears to be compromised in some epilepsy and in Alzheimer's. These impairments may be due to the loss of a protein called Nav1.1. Nav1.1 has been shown to promote cognition by enhancing the health of the interneurons, preserving their normal rhythmic activity (meaning these nerve cells operate at a normal pace or rhythm) in the brain. Using molecular tools, researchers are able to activate the Nav1.1 protein activity in Alzheimer's-like mice. This activation restores the normal cell function, reduces the beta-amyloid accumulation and improves cognitive function. (Verret et al. Cell 2012; Martinez-Losa et al. in press; Frederiksen et al. Europ Journal of Neurosci 2017, Tsai study). This treatment has also been shown to prevent hyperexcitability in the rodents' nerve cell network, thus reducing epileptiform activity. Such work suggests the need for targeted interneuron therapies that can treat both epilepsy and Alzheimer's.

Brain function is mediated through a series of electrical currents. Dr. Inna Slutsky of Tel Aviv University noted that the machinery of the brain's electrical circuits is dynamically regulated throughout the nerve cell's lifespan. Nerve cell circuits in the brain can become unstable as the brain ages, leading to over-activity, epileptiform events such as spikes (short but sharp changes in brain wave activity) and seizures (longer changes in brain wave activity), among other events that impact how the nerve cells communicate with one another. Such instability may represent a "silent signature" of mild cognitive impairment and early Alzheimer's dementia (Palop et al. 2007; Verret et al 2012). Therapies that preserve activities of the electrical system of the brain will need to be designed to avoid impairing communication between nerve cells.

Dr. Marc Aurel Busche of Harvard Medical School continued the discussion of nerve cell networks. He described research showing that in Alzheimer's-like mice there can be over-activation of the nerve cells, which leads to both the loss of nerve cell function and the development of amyloid plaques. Dr. Erik Roberson of the University of Alabama-Birmingham highlighted ongoing work to understand the role of tau in geriatric epilepsy and Alzheimer's. One study observed that over-activation of the nerve cells of Alzheimer's-like mice could be prevented by reducing the levels of tau (Hall et al. J Neurosci 2015). There is also an abnormal rhythm of the nerve cells, which may relate to epileptiform discharges (Busche et al. Science 2008).

The hippocampus is a specific region of the brain known to be impacted in the early stages of Alzheimer's. Dr. John Disterhoft of Northwestern University suggested that aging has different effects on the nerve cells in the hippocampus and in particular nerve cells in specific parts of the hippocampus that are vital for memory formation. In aging Alzheimer's-like mice, researchers are able to measure the interaction between the nerve cells in these two regions of the hippocampus, and they have observed a decrease in their communication (Simkin and Disterhoft, 2016). These different forms of nerve cell dysfunction, which require separate treatments to ameliorate, may work together to promote memory deficits and epileptiform activity in Alzheimer's dementia.

The final speaker of this session, Dr. Yadong Huang of the Gladstone Institutes and the University of California, San Francisco, reported a study using mouse models with APOE-e4, a gene linked to higher Alzheimer's disease risk. These mice developed decreased numbers of a specific type of nerve cell called GABAergic interneurons, which led in turn to deficits in the brain known as memory replay. Memory replay helps animals consolidate spatial memory. However, studies have shown that by removing APOE-e4 they could prevent the loss of these nerve cells and restore electrical activity linked to memory replay (Knoferle et al, J Neurosci 2014, and Gillespie Neuron paper). These findings suggest connections of the underlying biology of genes that increase risk for both diseases by promoting epileptiform activity and cognitive decline.

Protein Handling and Inflammation

The brain functions through a series of chemical reactions that tells the brain cells to function in specific ways. Understanding the links of these chemical reactions, their downstream biological consequence and how these may be linked to disease are essential to unlocking the mysteries of these diseases and developing novel therapy approaches to treat them. There was a robust discussion of how epilepsy and Alzheimer's may be connected by an amyloid-linked enzyme called mechanistic target of rapamycin (mTOR) and to brain inflammation. Different forms of epilepsy involve toxic beta-amyloid and tau depositions, heightened activity of the mTOR and other pathologic features that also occur in Alzheimer's disease (Tai et al. Brain 2016). These

epilepsies, moreover, increase one's risk for cognitive decline. In fact, many people with Alzheimer's and epilepsy experience seizures at an early stage of disease, suggesting a potential role for epilepsy in the onset and progression of Alzheimer's. Such findings suggest a "bi-directional relationship" between epilepsy and Alzheimer's, as well as therapies that can target biomarkers common to both diseases.

Dr. Michael Wong of Washington University in St. Louis described how over activation of mTOR leads to the development of tumors on multiple organs and also involves neurological symptoms such as severe epilepsy. This severe epilepsy is referred to as tuberous sclerosis complex (TSC). In mice models of TSC, mTOR activity initiates the proliferation of a type of brain cell called glial cells and leads to abnormal brain swelling. Early treatment of TSC with rapamycin, however, prevents glial cell proliferation and brain swelling (Zeng et al. *Ann Neurol* 2008). It also prevents epileptic seizures and prolongs the survival of these animals. In addition, Dr. Wong pointed out that mTOR dysfunction in Alzheimer's can lead to the controlled removal of unwanted molecules and accumulation of both beta-amyloid and tau. Studies have found that treatment with rapamycin and similar compounds can induce the cell's clearance or trash removal mechanisms and lead to lower amyloid and tau levels in Alzheimer's-like models (Taumutola et al. *Expert Rev Neurother* 2017). Such efforts identify mTOR as a possible therapeutic target for both Alzheimer's and epilepsy.

The immune system has been implicated in contributing to both epilepsy and Alzheimer's. Dr. Bruce Lamb of Indiana University and Dr. Annamaria Vezzani of the Mario Negri Institute for Pharmacological Research in Milan, Italy, focused on the roles of inflammation in Alzheimer's and epilepsy. Dr. Lamb discussed the possible function of a protein called triggering receptor expressed on myeloid cells 2 (TREM2) in the increased inflammation seen in Alzheimer's (Jay et al. 2015; 2017). Traditionally, TREM2 was thought to be important for regulating inflammation and stimulating the removal of damaged nerve cells. Dr. Lamb's research, however, has found that TREM2 in the brain is expressed on the surface of immune cells that are found near toxic beta-amyloid accumulation in the brain. On the other hand, TREM2 deficiency also appears to promote tau related brain changes and tau-related cell death of the nerve cells (Bemiller et al. submitted 2017). These multiple effects from a single protein in Alzheimer's suggest that TREM2's role in the disease may be stage dependent. Future research efforts will need to clarify how TREM2 is involved in Alzheimer's and how dementia-related innate immune system pathways may be linked to epilepsy.

Dr. Vezzani highlighted how the immune system activates nerve cells to produce neuroinflammation in epilepsy (Roseti et al. *Neurobiol Dis* 2015). This process involves two special types of protein that appear to generate seizures in animal models (Vezzani et al. *Nature Rev Neurol* 2011; Vezzani et al. *Brain Behav IMM* 2011). Moreover, anti-inflammatory treatments targeting these processes have significantly reduced seizure recurrence and delayed seizure onset in rodent models. Such therapies could prove successful in human clinical trials, and they might show promise in treating Alzheimer's-related inflammation.

Genes in Alzheimer's and Epilepsy

Specific genes have been implicated in Alzheimer's and in epilepsy, respectively. Dr. John Hardy of University College London, Dr. Jeff Noebels of Baylor University, and Dr. Daniel Felsky of Columbia University focused on the connections between a person's genes and Alzheimer's disease and epilepsy. Many of the genes implicated to increase an individual's risk of Alzheimer's, which include specific forms of genes as TREM 2 and APOE-e4, are present in immune cells found in the brain and respond to the presence of beta-amyloid at the membranes

of these cells. (Guerreiro et al. JAMA Neurol 2013). Such findings suggest that these risk genes may be involved in plaque-related membrane damage and that changes in these genes may be acting to compromise their damage-controlling function. Genetic research also suggests that beta-amyloid promotes the tau-related brain changes and brain cell death seen in Alzheimer's.

Dr. Noebels noted a change in scientific opinion regarding the presence of seizures in people with Alzheimer's. Early opinion did not agree that seizures occurred in Alzheimer's due to insensitive measures and the inability to detect the "silent" seizures that often occur deep in the brain of individuals with Alzheimer's. Despite better knowledge of these links, discovering genes related to both Alzheimer's and epilepsy has been difficult. The number of genetic mutations linked to sporadic Alzheimer's disease is still relatively small. Expanding the number of the gene pool will be necessary to identify those that affect risk for both diseases.

Dr. Felsky then described a novel technology that may hasten the discovery of genes that link Alzheimer's and epilepsy. He presented research that analyzed how cooperation between specific genes may promote the brain changes in Alzheimer's and epilepsy (Mostafavi et al. under review). This study used a sequencing procedure that employs sophisticated computer modeling to identify two gene candidates that cooperate to achieve over-activation of the nerve cells and epileptiform seizures in Alzheimer's.

Clinical Translations: Diagnostics and Therapy

Measurements of biological changes — biomarkers — of the brain during disease progression will provide important information for better detecting, diagnosing and ultimately treating these diseases. Dr. Talos and Dr. Jensen provided context for how the brain changes of epilepsy may overlap with Alzheimer's disease. Different forms of epilepsy involve toxic beta-amyloid and tau depositions, heightened activity of the amyloid-linked enzyme known as mTOR, and other pathologic features that also occur in Alzheimer's disease (Tai et al. Brain 2016). These epilepsies, moreover, increase one's risk for cognitive decline. In fact, many people with Alzheimer's and epilepsy experience seizures at an early stage of disease, suggesting a potential role for epilepsy in the onset and progression of Alzheimer's. Such findings suggest a "bi-directional relationship" between epilepsy and Alzheimer's, as well as potential for therapies that can target common biomarkers of both diseases. Future research, however, will be needed to clarify how biomarkers in Alzheimer's and epilepsy are similar and how they may differ.

Dr. Brian Litt of the University of Pennsylvania addressed the importance of technology that can accurately measure epileptiform activity in the brain and do this over a longer period of time than is possible with traditional EEGs. Data mined from these techniques will give a better understanding of how epileptiform activity affects larger brain networks and how it may interact with Alzheimer's disease processes. To improve electrophysiological monitoring techniques, bioengineers are now seeking the assistance of specialists outside the medical community, including software engineers. Dr. Litt also stressed the importance of sharing research in this field through a common data ecosystem.

Dr. Greg Holmes of the University of Vermont assessed how subclinical epileptiform activity affects cognitive health. He pointed to research finding that epileptic activity (specifically the activity that can be measured by EEG) affected human memory, thinking and reasoning depending on where they occurred in the brain. Discharges in the left hemisphere were associated with errors in verbal tasks, while discharges in the right hemisphere were associated with nonverbal test impairments (Aarts et al. 1984). In general, Dr. Holmes argued that epileptiform spikes need to be accurately detected and monitored, especially in the young, as they appear to be associated with detrimental cognitive effects within the developing brain.

Growing clinical data further implicates a link between Alzheimer's and epilepsy. Research has found similar racial disparities in both Alzheimer's and epilepsy risk. African Americans have a significantly higher risk for both diseases, which may be attributable to a gene profile that differs from whites and other lifestyle/environmental contributors such as cardiovascular and metabolic health (Mayeda et al. *Alzheimers Dement* 2016; Faught et al. *Neurology* 2012). Aging may also present a similar risk factor in Alzheimer's and epilepsy, as the risk for both disorders increases significantly after age 65 (Hauser et al. *Epilepsia* 1993; Rocca et al. *Alzheimers Dement* 2011). On the other hand, epilepsy-related hyperexcitability may be more prominent in people who develop Alzheimer's at an earlier age. Data shows that neuronal hyperexcitability is more prominent in autosomal-dominant Alzheimer's (which often begins in one's 40s and is also known as familial Alzheimer's) and younger-onset Alzheimer's disease (beginning before the age of 65) than in the more common sporadic form that typically progresses after age 65. More research will need to clarify the complex role of aging in Alzheimer's and epilepsy.

Lastly, Dr. Michaela Gallagher of Johns Hopkins University discussed the possibilities of using antiepileptic drugs in Alzheimer's therapy. She pointed to research showing elevated nerve cell activity in two different brain regions during amnesic mild cognitive impairment (aMCI), often considered an early stage of Alzheimer's (Yassa et al., 2010; 2011). Future therapies for treating Alzheimer's in its early stages, such as aMCI, could use antiepileptic compounds that target nerve cell over-activity along with other treatments aimed at reducing beta-amyloid and tau levels. The drug Levetiracetam has already shown promise as a potential antiepileptic component in Alzheimer's therapy.

Future Directions

The primary aims of this discussion are to highlight work to date and the field's current understanding of the linkage between Alzheimer's and epilepsy; to identify gaps in our knowledge; and to develop a roadmap for future research directions. Dr. Lennart Mucke led a concluding discussion that focused on key unanswered questions in the field. There is a clear need to better understand how multiple mechanisms promote the brain's network dysfunction, including epileptiform activity as a component, and how the larger nature of network dysfunction may contribute to disease-related brain changes. Epileptiform activity is one manifestation, or "branch," but the role of other branches, such as over-active brain cells and how their link to specific task-related performance, should also be explored in human and animal studies. Such knowledge will help clarify whether epileptiform discharges are specifically related to Alzheimer's progression or whether other aspects of network dysfunction are involved.

The complexity of brain network dysfunction will require the development of devices that can better monitor subtle changes. Short-term, daytime EEG exams have proven inadequate at capturing certain types of epileptiform activity related to memory and cognition. Often these abnormal events in brain activity occur during sleep or deep in the temporal lobe. Devices will need to monitor activity over longer periods of time, at multiple sites in the brain, and in a minimally invasive manner. Improvements in monitoring technology will clarify how aberrant electrical activity over time leads to disease progression.

Dr. Cole and others suggested the need to find more sensitive methods of capturing variability of cognitive function in Alzheimer's dementia. Individuals living with Alzheimer's can have significant variation in their functional performance and this may be due, in part, to recurring epileptiform activity. Other areas of future research should focus on identifying how specific factors related to Alzheimer's affect network dysfunction; this may give rise to better

understanding of network dysfunction in epilepsy. These factors include newly discovered Alzheimer's and epilepsy related risk genes, inflammatory actors such as microglia, and neurodegeneration-linked proteins such as tau and beta-amyloid. For example, what role does tau play in epileptogenesis?

Researchers will also need to adopt a variety of approaches for identifying potential treatments. Are there therapies that can be beneficial for both Alzheimer's and epilepsy? If so, what are the proper dosages, and at what stage of disease(s) may these therapies be most helpful? The anti-epileptic drug levetiracetam has shown promise in Alzheimer's studies, but determining the proper dosage level is vital, as the drug is toxic at higher doses. These trials are on-going now. Should investigators reexamine therapeutic options that have barely failed in earlier trials? Should they look for compounds that do not necessarily target the root of Alzheimer's or epilepsy but may affect the symptoms for an individual? While effective treatment is needed now, imperfect therapies that affect a person's symptoms and improve quality of life or arrest disease progression in part are better than the current state of treatment.

Finally, there was uniform agreement on the need of making data on epilepsy and Alzheimer's more widely available to researchers. The Alzheimer's Disease Neuroimaging Initiative (ADNI), for example, is already dedicated to sharing its data on Alzheimer's biomarkers. Yet, many brain banks place barriers to the access of clinical study results. Increased data sharing could help assist the progress of research on epilepsy, Alzheimer's disease, and many other neurological disorders.

Representatives from the National Institutes of Health, the Alzheimer's Association, and several epilepsy funding organizations participated in these discussions to inform their activity and future investment.