ANA2019 Media Roundtable Transcript

A Review of Scientific Highlights

The 144th Annual Meeting of the American Neurological Association (ANA) was held October 13–15, 2019 at the Marriott St. Louis Grand, with a Pre-Meeting Symposium on October 12 on Brain-Computer Interfaces in Neurological Disease. More than 1,000 of the nation's top academic neurologists and neuroscientists, as well as students, trainees, and international professionals, convened to share three days of research at the forefront of neurology and neuroscience.

A "Highlights of the Meeting" roundtable was held for media at 11 a.m. Central on October 15, with option to call in. The roundtable featured the heads of major ANA2019 scientific sessions providing highlights from the research presented at those sessions:

- **David M. Holtzman, MD,** ANA President; Andrew B. and Gretchen P. Jones Professor and Chairman, Department of Neurology, Washington University School of Medicine in St. Louis. ***ANA2019 Symposium Chair: "Presidential Symposium: Dominantly Inherited and Late-Onset Alzheimer's Disease: Genetics, Biomarkers, Timecourse, and Treatments"***
- **Conrad (Chris) Weihl, MD, PhD,** Professor of Neurology, Washington University School of Medicine in St. Louis. ***ANA2019 Plenary Chair, "Optimizing Clinical Trial Design"***
- **Steven Small, MD, PhD,** Professor Emeritus of Neurology, University of California, Irvine; Dean, School of Behavioral and Brain Sciences, University of Texas at Dallas. ***ANA2019 Pre-Meeting Symposium Chair, "Brain-Computer Interfaces in Neurological Disease"***
- **Thomas Carmichael, MD, PhD,** Professor of Neurology, Geffen School of Medicine, University of California, Los Angeles. ***ANA2019 Plenary Chair, "Advances in Regenerative Medicine: Cellular Memory Systems in Brain Repair"***
- **Rachel Saunders-Pullman, MD, MPH,** Associate Professor of Neurology, Icahn School of Medicine at Mount Sinai. ***ANA2019 Plenary Chair, "Emerging Role of Microbiome in Neurological Disease"***
- **Robert Friedland, MD,** Mason C. and Mary D. Rudd Endowed Chair In Neurology, University of Louisville. ***ANA2019 Plenary Co-Chair, "Emerging Role of Microbiome in Neurological Disease"***

- **Argye Hillis, MD,** Professor of Neurology and Director, Cerebrovascular Division of Neurology, Johns Hopkins University. ***ANA2019 Plenary Co-Chair, "Language Disorders Across the Lifespan"***

The following is a transcript of the Media Roundtable. This transcript has been edited for length and clarity.

Denise Portner: My name is Denise Portner. I'm Senior Vice President at SteegeThomson Communications in Philadelphia, and it's my pleasure to welcome you to the ANA2019 media roundtable. We're speaking from the Marriott Grand in St. Louis during the ANA2019 annual meeting, and our goal this hour is to provide key takeaways from the science presented at the plenary sessions of the meeting. Because time is short and we have six presenters, we ask the journalists in the room and on the phone to please hold your questions until the end. Biographies of our speakers and other meeting news are available online at 2019.myana.org/press-kit.

Denise Portner: I'd like to start by introducing our outgoing ANA President, David Holtzman, of Washington University School of Medicine here in St. Louis, and he'll be speaking in a minute. Dr. Holtzman concludes his two-year term at the end of the meeting today. Our incoming ANA President, Justin McArthur of Johns Hopkins University, is here, as well as Dr. Elizabeth Ross of Weill Cornell Medical College, who has served as chair of the ANA's Scientific Program Advisory Committee for the past two years.

Denise Portner: I invite all of you to add them to your roll of contacts, as they are excellent sources for what's coming down the pike in neurology and neuroscience.

First up is Dr. David Holtzman, our ANA President, and the Andrew B. and Gretchen P. Jones Professor and Chairman of the Department of Neurology at Washington University, St Louis. He was chair of the Presidential Symposium on "Dominantly Inherited and Late Onset Alzheimer's Disease: Genetics, Biomarkers, Time Course, and Treatments."

David Holtzman: Thanks very much, Denise. I'll try to, for each of the four speakers, make a point of what they said that is relatively new and will likely impact the field. The first speaker was Alison Goate, one of the leading geneticists who has studied Alzheimer's disease for many years. She identified the first causative gene that leads to dominantly inherited Alzheimer's disease. I think there were two main points that she really brought out. One is that all of the genes that lead to the relatively rare but important type of Alzheimer's disease, dominantly inherited Alzheimer's disease—which occurs usually clinically before the age of 50—are caused by mutations in genes that start the process of amyloid deposition in the brain earlier than it otherwise would normally occur. And that's borne out over many experiments over many years.

David Holtzman: The second major point is late onset Alzheimer's disease, which is more than 99% of the people we see as patients, which occurs after the age of 65, is also a highly genetic disease. And several of the new genetic findings of the last several years have really highlighted the role of the inflammatory cells in the brain, microglia, and several different gene alterations that have been discovered, such as TREM2 and CD33 and several others. These are, while they're not common mutations in these genes, they all are genes that are either exclusively expressed in the brain in microglial cells, or their products affect microglial cells. So I think that this is leading to a new potential target for therapy in the future, how to modify the microglial response in the brain.

David Holtzman: The second speaker was Gil Rabinovici. His work really highlighted the fact that what the field has discovered over the years is that the pathological process that underlines Alzheimer's disease begins about 20 years before the symptom onset, and Gil highlighted the many new technologies that have enabled us to determine that this pathology exists even before people are symptomatic. It includes amyloid imaging to detect the onset of amyloid deposition, tau imaging, which can see tau pathology, and some of the things Gil really highlighted is that when tau pathology starts, that very much coincides with when you can actually see the brain begin to degenerate and symptoms appear. I think that goes together very well with what a lot of other scientists have found, both in humans

and animal models, and really leads one to think that one could potentially target the molecule tau a little bit later in the course of the pathological progression, and hopefully get some ultimate treatment effects from doing that.

David Holtzman: The other speakers focused on dominantly inherited Alzheimer's disease as a potential model form of the disease to ultimately better understand and develop treatments. Yakeel Quiroz, who's originally from Colombia, was involved early on in characterizing patients with dominantly inherited Alzheimer's disease in Colombia who all have the same mutation that apparently originated in the 1400s from a person in Spain but now there's thousands of people in the country of Colombia that have this mutation. What she and her colleagues have found is that the course of the pathology of Alzheimer's disease in this population very much mimics what you see in late onset Alzheimer's disease, except that it occurs about 30 to 40 years prior to those that develop disease later. She illustrated—again with some of the biomarkers that are being used, amyloid imaging, tau imaging, spinal fluid studies, and blood studies—the whole time course by which this cascade occurs in the human brain.

David Holtzman: Finally, Randall Bateman, from Washington University, is leading not just an observational study of dominantly inherited Alzheimer's disease around the world, but the first secondary and soon-to-be primary prevention studies in that population of people with dominantly inherited disease. I think what was very exciting is that he and many other people around the world started a secondary prevention trial in which individuals who are identified, who have Alzheimer's pathology but they're still cognitively normal, were enrolled in a trial with several different treatments that started in 2012. In the next few months, the initial results of the first two treatments will be revealed.

David Holtzman: We don't know what those results will be, but it really highlights the fact that we knew that the pathology of this well before the symptoms, and so some of the failures that have occurred in the treatment of Alzheimer's disease over the last several years, in some ways, could have been predicted because they were targeting a molecule that had already been building up for many, many years.

So these studies, hopefully, we'll see what happens, are targeting the disease, at least the amyloid process, at a point when it's not yet fully developed and other processes leading to neurodegeneration have not yet occurred. We'll see if that ultimately has an effect.

David Holtzman: He also described the fact that there's now other targets in the disease—tau, inflammation, et cetera—that also, hopefully in the future, will be attempted to be targeted in that population. I think it leaves us with some real hope that, by using this type of approach, maybe we'll be able to see some of the first results of a disease-modifying therapy.

Denise Portner: Yes, it is very encouraging. Thank you. Next we're going to hear from Dr. S. Thomas Carmichael, Professor and Chair of Neurology at the David Geffen School of Medicine at the University of California, Los Angeles. He chaired a Plenary entitled, “Advances in Regenerative Medicine: Cellular Memory Systems in Brain Repair.” Dr. Carmichael?

S. Thomas Carmichael: Good morning. Our session focused broadly on parallels between mechanisms of learning and memory in the brain, and those that mediate tissue repair and recovery after brain injury. We had four speakers that highlighted various parallel cellular and molecular elements in memory and tissue repair. The session led off with an overview and broad painting of the picture of learning and memory, and where we are with studies of molecular memory systems by Dr. Alcino Silva, a recognized leader in that field. He described a very recent effort in which he characterized an unexpected finding of an inflammatory system that actually is involved in brain neuron signaling, and has a major control point in how the brain forms memories. One of the interesting spinoffs of this is that it's also a receptor for the HIV virus, there's a really tractable pharmacology out there already that allows us to control and manipulate this system called a CCR5 receptor. Alcino has further found that this receptor system, which potentially limits learning and memory formation in its normal role, is induced with aging, and may underlie some of the cognitive dysfunction that we experience as we age.

S. Thomas Carmichael: Then, transitioning to my talk in collaboration with Dr. Silva, we explored CCR5 signaling in stroke recovery, and found that CCR5 is a really interesting target to enhance stroke recovery. It's induced uniquely by stroke, so it's in the right place in the right time. It's normally known to limit memory, and it can be blocked to enhance recovery in stroke, it's a parallel between learning and memory and recovery. The drug that's used to treat AIDS patients that blocks this receptor is also effective in mice in enhancing in recovery, and then a final element, there are humans with a naturally occurring mutation in this receptor, that of course are resistant to the AIDS virus. They also recover better in stroke, in an observational study that we did in Israel.

S. Thomas Carmichael: This has led to a clinical trial, a phase two trial, that we've now initiated at Yale, Burke, and UCLA to understand if pharmacological blockade of CCR5 enhances recovery in stroke. The third talk was Dr. Mark Tuszynski, a Professor in Neurosciences at UCSD, and he picked up this theme of looking at some of the molecular systems that are active in normal motor learning, and whether we can identify drugs that mimic those molecular systems, whether you might get a drug that turns on a motor learning molecular program; and he outlined a process by which you might determine that in the lab, and some drugs that might do that based on what might be called an in silico screen, using a bioinformatics database to mine some of the data in an earlier stage.

S. Thomas Carmichael: Dr. Tuszynski is now looking at drugs that turn on a motor learning transcriptome, and see if they do indeed enhance learning by themselves, a sort of learning drug. The final talk was from Dr. Nicole Calakos, who's done some really interesting work in habit learning, not the kind of learning that we've been talking about before where we learn information, but when we learn motor procedures or motor habits, which involve a different part of the brain called the basal ganglia. And her work has looked at how learning or overuse in a particular movement might produce what could be called a bad form of learning, a dystonia, or a tic, or an unwanted and unplanned motor movement. She's now really drilled down on that and found molecular systems that these movement-induced abnormalities—like writer's block might be an example of

that—the molecular systems that those turn on, and they represent the bad side of a molecular memory system, when they are active, and enhance the brain's abnormal movements. So that represents that platform.

Denise Portner: Thank you, Dr. Carmichael. Next we have Dr. Steven Small, Professor and Chair Emeritus of Neurology at the University of California, Irvine, and currently Dean of the School of Behavioral and Brain Sciences at the University of Texas at Dallas, and he chaired the Pre-Meeting Symposium on Brain-Computer Interfaces in Neurological Disease. Dr. Small?

Steven Small: Thank you very much. Brain-computer interfaces are a very exciting, new technology that is just beginning to emerge. A brain-computer interface is a computer-based system that acquires brain signals, analyzes them, and translates them into commands that are relayed to an output device to carry out a desired action. In principal, any type of brain signal could be used to control the BCI system.

Steven Small: BCI systems carry the potential to replace lost motor and sensory functions, direct control of prostheses, deliver artificial sensation, and other types of sensory and motor phenomena. BCI technology is maturing, and such devices have started to enter human clinical studies, although just a few at the moment. Before I discuss the speakers at our Symposium, I just want to talk about the take home messages from that Symposium, which were that there are different kinds of recording approaches, whether surface recording on the skull outside of the brain, or direct recording from inside the brain. There are systems that are open loop or closed loop, that is whether they need external intervention in order to work or whether they are completely self-contained, that all the feedback loops are within the computer. Some require external devices outside the body, and some are now being developed to be completely internal.

Steven Small: The fundamental issues raised by the speakers have to do with decoding and encoding. In order to understand what the brain is doing, one has to decode the signals in the brain, for example, the intention to move and what kind of movement was intended, and then to encode the right signals to produce the desired phenomena

in the person, whether sensory or motor. There are examples of BCI in commercialization right now, many of which are non-medical, such as gaming or driving, where you take brain signals and try to directly use them, say, to drive a car. They're used in medicine right now, for example, in epilepsy. It's well known that we can use responsive neuro stimulation, we can try to read from the brain when a seizure will occur, and then stimulate the brain to try to prevent that seizure from occurring, and a few others.

Steven Small: I would also like to say that regarding brain-computer interfaces, I'm showing a chart here that shows that work in BCI is growing dramatically, and from 1990 to 2010, the number of papers presented has gone from something like a dozen to almost 500 papers in a year. The speakers that we had in our Symposium were terrific scientists, starting with Karunesh Ganguly from the University of California, San Francisco, who is interested in stroke, particularly motor output in stroke, and much of his work has been of a fundamental nature, investigating animal models of stroke and trying to record signals from the area around the lesion in a stroke. Stroke causes focal damage to the brain, and the areas around those lesions have certain properties for recovery, and recording in these regions can infer information about the intention of the organism to move, even if the animal can't move. So understanding the intention to move, and being able to decode that signal and exactly what kind of movement it is, is very important in stroke.

Steven Small: Dr. Sheila Nirenberg, from the Weill Cornell Medical College at Cornell University, is interested in vision, particularly in blindness, and she presented an extraordinary novel technique using opto-genetics, where she's injecting viruses into the retina or near the retina that have genes encoding for light-sensitive cells that will produce signals based on light that comes in through the eyes. Her biggest challenge is to encode those signals in a way that the brain can understand what the visual image is. It's extremely novel, extremely exciting and different from the others.

Steven Small: Third, Dr. An Do, from the University of California, Irvine, is working in the area of spinal cord injury, and is recording from both outside of the brain, using EEG, and inside the brain, in terms of direct

recording, to try to decode intention to walk, and then to encode the motor commands for walking. He's building, along with his collaborators at CalTech and other institutions, a fully embedded closed loop system for that.

Steven Small: And last but not least is one of the pioneers in the field, Dr. Leigh Hochberg from the Massachusetts General Hospital and Brown University School of Engineering. Dr. Hochberg pioneered direct recording in the human brain, both for the purposes of ameliorating stroke and spinal cord injury, again, to decode the signals for movement, and then encode motor commands for movement that can be understood by a prosthesis. He's one of the few people that's actually done this in individual human trials, and is still trying to perfect this technology. He is also moving to a completely closed loop system in the future.

Steven Small: The future of brain-computer interfaces is bright, very interesting, and extremely novel.

Denise Portner: Thank you so much, Dr. Small. Next we have Dr. Rachel Saunders-Pullman, Associate Professor of Neurology at the Icahn School of Medicine at Mount Sinai, and her co-chair Robert Friedland, the Mason C. and Mary D. Rudd Endowed Chair in Neurology at the University of Louisville, and their Plenary focused on the “Emerging Role of the Microbiome in Neurological Disease.”

Rachel Saunders-Pullman: So more systematic studies on the microbiome have really come to the fore in the last 10 years, especially in neurological disease. We're now understanding the microbiome is an integral player in the so-called brain axis between the central nervous system, the immune system, the gut, and the microbiome. These relationships are felt to be bidirectional, with neurologic disease affecting the microbiome, and the microbiome playing a role in modulating disease.

Rachel Saunders-Pullman: And so clinicians, researchers, and patients are really motivated to understand the complex nature of the microbiome, and its influence on even metabolism, immunity, inflammation, and whether there is a means there to intervene. And our speakers presented on the role

of the microbiome across a range of neurologic disease, and one of the overarching themes was that there was a lot of association studies, limited experimental observation, and a few human studies, but nonetheless there was some data presented suggesting tremendous promise.

Rachel Saunders-Pullman: As mentioned, my co-chair Dr. Friedland, is here also to answer questions. So first, a real pioneer in microbiome work, Dr. Susan Erdman, from MIT, spoke about the microbiome in a broader sense, and then focused particularly on the hormone oxytocin and the relationship with the microbiome and oxytocin in early development. She showed via demonstrating a multi-generational effect of microbiome on oxytocin in human behavior, and proposed the microbiome as a target that may be modifiable.

Rachel Saunders-Pullman: She described the next level of microbiome research in an ongoing, randomized clinical trial, of peripartum women with a microbial intervention or a placebo, and assessment of internal oxytocin levels, nurturing behaviors, and childhood outcomes. Our next speaker, Dr. Emmanuelle Waubant from UCSF reported some very interesting data supporting an association between the gut biome and multiple sclerosis, particularly pediatric onset MS, and her group and others demonstrated subtle differences in the gut microbiota between patients with MS and those without, and suggested a research route to better understand the role of the microbiome.

Rachel Saunders-Pullman: She emphasized absence and depletion of specific microbes and potential association with blood immune markers, and also potential associations with MS relapse. She did emphasize when there were times where associations were shown but causation could not be inferred.

Rachel Saunders-Pullman: Then Dr. Timothy Sampson, a microbiologist from Emory University, discussed the association between the microbiome and neurodegenerative disease, with particular focus on Parkinson's disease. There are multiple lines of evidence in Parkinson's suggesting the gut may play a role in age-related neurodegeneration, especially with Parkinson’s Disease.

Rachel Saunders-Pullman: He highlighted early involvement of the dorsal motor nucleus and the role of the vagus and reviewed some literature on vagotomy and Parkinson's. And he highlighted, as well, that the microbiome may have a role with synuclein progression.

Rachel Saunders-Pullman: And then finally, the Soriano Lectureship recipient, Dr. Louise McCullough of the University of Texas Health Science Center at Houston, discussed potential roles for gut microbiome to increase and influence stroke, and particularly potential effects on stroke recovery. She discussed the microbiome in aging and inflammation (inflammaging) and exciting preliminary animal models suggesting that pretreatment with specific probiotic organisms might improve stroke outcomes.

Rachel Saunders-Pullman: Overall, to emphasize, a tremendous potential to analyze gut microbiota and return a dysbiotic state to a healthy state.

Denise Portner: Thank you.

Robert Friedland: If I could add?

Denise Portner: Yes, absolutely.

Robert Friedland: Thank you, Rachel.

Robert Friedland: I found that talking about the microbiota usually needs some introduction. It's a very complex community, one of the most complex bacterial communities in the world, 800 to 1000 different organisms all living in the same place, inside our bodies, one to two kilograms of living bacteria. They're necessary, and this is shown by the observation that cows can't digest grass and termites can't digest wood, it's their bacteria that do all the metabolic work for them. And because it's so important for us to tolerate them, and it's necessary for them to help us tolerate them, so we have a bi-directional relationship in which we have evolved a capacity to tolerate them, they have evolved the capacity to make sure that we tolerate them.

Robert Friedland: Because of that, the immune system is very strongly affected by these organisms. There's an immunological component of many of these diseases, of course MS and stroke and Alzheimer's, Parkinson's, and other things important for neurologists. It has been said that the gut bacteria, which include organisms in the mouth, nose, and intestines, and elsewhere, constitute our largest environmental exposure.

Robert Friedland: So when we have diseases like Alzheimer's, Parkinson's, and many others that have a strong genetic component, but also interact with some environmental factor, it's likely that this environmental factor could be residing in the microbiota.

Robert Friedland: And finally the other desirable point about this, which was raised by several of the speakers today, is that it's relatively easy to alter the contents of the microbiome and to change the metabolic and other products that they're producing. So with probiotics, prebiotics, antibiotics, and transplants, and just with diet in a period as little as two weeks, we can all change what bacteria are living in us. We can help perhaps affect the health of our patients by making these alterations.

Denise Portner: Thank you, Dr. Friedland and Dr. Saunders-Pullman, very much. Our next presenter is Dr. Argye Hillis, Professor of Neurology and Director of the Cerebrovascular Division of Neurology at Johns Hopkins University, and she co-chaired a Plenary on “Language Disorders Across the Lifespan.”

Argye Hillis: Thank you very much. So our session was examining the disorders of language, the early stages of reading through adulthood when people have strokes that can affect language, and then through aging when people can develop a progressive or degenerative disease that affects primarily language.

Argye Hillis: That last neurodegenerative disease or condition is called primary progressive aphasia, a relatively recently described clinical syndrome, first described by Dr. Marsel Mesulam in 1982. He was our first speaker, he's a professor of neurology at Northwestern, and he's one of the founding fathers of behavioral neurology. He

described the clinical syndrome, and then more recent advances showing that there are, in fact, three different types of primary progressive aphasia. Three different clinical syndromes that are caused by different neurological diseases, underlying diseases.

Argye Hillis: The first type that he talked about was non-fluent or agrammatic variant primary progressive aphasia. It's a condition where people have difficulty speaking, but understand words and can recall what was said to them, but they have difficulty articulating. It's generally due to atrophy in the frontal parts of the brain, particularly the posterior and anterior frontal cortex. It is most commonly due to one of the tauopathies, so frontotemporal dementia, frontotemporal lobar degeneration that's caused by tau; it can also be caused by other very closely related tauopathies, like progressive supranuclear palsy and corticobasal degeneration.

Argye Hillis: The next one is called logopenic primary progressive aphasia, meaning "too few words." They have difficulty with naming and also have difficulty with sentence repetition, but relatively intact word comprehension. He showed some data that very closely associated with atrophy in the left temporoparietal junction, which is an area very important for short term memory, and that's one reason we have difficulty with sentence repetition.

Argye Hillis: And then semantic variant primary progressive aphasia's a condition that affects word meanings. People with this condition have trouble understanding words, eventually even have trouble understanding objects, and the condition is generally due to a different type of frontotemporal lobe degeneration caused by TDP-43.

Argye Hillis: He talked about the fact that these conditions affect networks of the brain, we like to think now of the dorsal stream of processing language in the brain being primarily a parietal to frontal stream of processing where it's important if it's used to convert meanings of words to articulation, to production. It's very much affected in the agrammatic variant and logopenic variant, whereas the ventral stream of language is primarily a temporal lobe network that is involved in or has degenerated in semantic variant primary progressive aphasia.

Argye Hillis: I gave the next talk, and I spoke about the treatment of language disorders, recent advances and treatment of both primary progressive aphasia and post-stroke aphasia. So I talked about some recent behavioral therapies that have been shown to be effective in randomized clinical trials, primarily using something called speech entrainment, where you speak with the person in reading, discourse, and so on, and it generalizes to improving conversation. This has been used by Julius Fridriksson and colleagues, and also in post-stroke aphasia more recently by my home at University of Texas in primary progressive aphasia.

Argye Hillis: Very impressively, her trial showed improvements in language. It lasted for up to a year in people who have a progressive language problem. And I talked about some ways that we can augment language therapies using a transcranial direct current stimulation, or a transcranial magnetic stimulation, which actually changed the neural plasticity in the brain, so it can help un-damage parts of the brain, take over for the damaged parts of the brain. In the case of transcranial direct current stimulation, it's a non-invasive, non-painful stimulation over the skull that changes the threshold of activation of neurons in the area that is stimulated.

Argye Hillis: I showed some evidence from post-stroke aphasia; there was a relatively large randomized trial, double-blind, sham-control trial, showing that, although everybody made some improvements, the patients who received transcranial direct current stimulation with the same computer-delivered language therapy made 70% greater gains in language than the people who received sham.

Argye Hillis: Also, I reviewed a randomized crossover trial in primary progressive aphasia by Kyrana Tsapkini and colleagues in my lab, showing that giving transcranial direct current stimulation plus language therapy had greater effects than sham plus the same language therapy in the same individuals at different times in a randomized order of administration. There was maintenance of gains even on untrained items, naming things that they hadn't seen in therapy, even at two months, again in that progressive condition.

Argye Hillis: I also reviewed some evidence that transcranial direct current stimulation seems to have resulted in changes in connectivity of the networks, so strengthening connectivity or correlations of activation between the stimulated area and other parts of the cortex, and that it may be more effective in particular gene carriers. Animal studies have suggested that transcranial direct current stimulation works by a mechanism that it uses, brain drive, neurotrophic factor of BDNF, and individuals who have the most common, normal Val/Val of BDNF gene showed greater response to TDCS than individuals who had at least one MET allele of the BDNF gene.

Argye Hillis: Then our next speaker was Maria Luisa Gorno-Tempini, professor of neurology at UCSF, who talked about both primary progressive aphasia and developmental dyslexia and their relationship. She has some very interesting data showing that developmental dyslexia learning disability is much more common in people who have logopenic variant primary progressive aphasia than other types of primary progressive aphasia or the general population.

Argye Hillis: She hypothesized, and provided some evidence consistent with the hypothesis, that people, that developmental dyslexia may cause a vulnerability to logopenic variant primary progressive aphasia. So there are some pathological changes in the brain in some people with developmental dyslexia, and that may make them present with, if they're going to have Alzheimer's disease because they have [inaudible 00:36:18] variant or they have other vulnerabilities to Alzheimer's disease, they show it earlier in life, in their 50s instead of their 70s or 80s, but it also affects things, left temporoparietal area of the brain, instead of bilateral hippocampi, which we see more typically in Alzheimer's disease.

Argye Hillis: She showed that people with developmental dyslexia tend to have problems with phonological processing, and that's the same with people with logopenic variant primary progressive aphasia. And finally, Jason Yeatman spoke about developmental dyslexia and how that can be seen as an impairment in neural networks in the brain, and that behavioral treatment of dyslexia, at least if it's intensive enough, can actually change the connectivity in the brain and restore some of the more normal networks of the brain.

Denise Portner: Wonderful. Thank you, Dr. Hillis. And finally, we have Dr. Conrad Weihl, professor of neurology at Washington University School of Medicine here in St. Louis, and he is going to chair the "Optimizing Clinical Trial Design" Plenary that is to follow this session.

Denise Portner: So Dr. Weihl, predict what we're going to hear. [laughter]

Conrad Weihl: I'll probably talk initially about what the concept of the Symposium was about. The idea of optimizing clinical trials. Myself, I'm a translational neuroscientist, I'm a basic scientist because it's become very clear to me that as we start to translate therapies, we're still behind the game in how we're understanding how to design the clinical trial so that we can effectively see an outcome.

Conrad Weihl: It's even more frustrating to see drugs that we know hit their pharmacologic target but don't have the desired efficacy and wondering, is that because the drug doesn't work or is that because we just don't understand the actual history, we don't understand patient population, we don't understand what's important to patients, or we don't understand how to diversify our patient population in the clinical trial? So each of those four points is being addressed in the Optimizing Clinical Trial Design session.

Conrad Weihl: Initially we're going to have a talk by Merit Cudkowicz from Mass General Hospital, she's going to talk about how we can be more innovative in the way we design clinical trials, like creating platform trials that can use a single placebo with multiple different interventions and adapt that as we start to get information so that we can really start honoring patients' time, and also designing more streamlined trials.

Conrad Weihl: The second talk will be by Nick Johnson at Virginia Commonwealth University. Nick is going to talk about the importance of understanding what's important to a patient, meaning, are we actually designing therapies that are addressing the burdens that a patient might have that is meaningful to them, and them being able to take that, create a metric of it, validate it, and then validate that in the actual history as well as in an interventional trial and being able to take this presumed questionnaire rather than a physical

exam to the FDA and say, this is really making a difference to this patient.

Conrad Weihl: Our third talk will be from a doctor of physical therapy at Nationwide Children's Hospital, Lindsay Alfano, and she will be talking about creating novel outcome measures that we might not be thinking of when we actually see patients with certain diseases. In particular, one example is in a disease called spinal muscular atrophy which we do actually have a new therapy for, but one question is, how soon does that disease start to manifest in patients? Can we actually design outcome measures that we can actually see the disease begin prior to us as clinicians even seeing the disease begin?

Conrad Weihl: By using different metrics such as she uses a Kinect system, which is a video game system, to actually monitor a baby as it just lays on its back and moves. Can we use that to start quantifying differences and changes? The other's using this for patients with Duchenne muscular dystrophy, and looking at upper extremity measures rather than looking at how far they walk, looking at how much can they use, and what's called their reachable work space, which is really what's important for many of these patients as they get older and non-ambulatory.

Conrad Weihl: And then our fourth talk is from Allison Willis Wright at University of Pennsylvania, and she's really going to start to talk about how, even at the time of enrolling patients in clinical trials, how we need to start thinking about diversifying that population. Because if we create a clinical trial based around a population of patients, we want to make sure that that patient population is diverse, contained, a representation of the general population so that whenever these interventions do go into commercialization, that they are reflective of what the population looks like.

Conrad Weihl: I'll be excited if there's other things that we hear about, but that's the general idea.

Denise Portner: That's great. Thank you everybody for your time and participating in our media round table. If you have any remaining questions, or

want to speak with anybody afterward, please contact me or Katie Pflaumer, and we look forward to working with you throughout the year. Thank you.

About the American Neurological Association (ANA)

From advances in stroke and dementia to movement disorders and epilepsy, the American Neurological Association has been at the vanguard of research since 1875 as the premier professional society of academic neurologists and neuroscientists devoted to understanding and treating diseases of the nervous system. Its monthly *Annals of Neurology* is among the world's most prestigious medical journals, and the ANA's *Annals of Clinical and Translational Neurology* is an online-only, open access journal providing rapid dissemination of high-quality, peer-reviewed research related to all areas of neurology. The acclaimed ANA Annual Meeting draws faculty and trainees from the top academic departments across the U.S. and abroad for groundbreaking research, networking, and career development. For more information, visit www.myana.org or follow @TheNewANA1 on Twitter, @AmericanNeurologicalAssociation on Facebook, or @ananeurology on Instagram.