CURE WEBINAR

Epilepsy's Impact on Memory and Cognition over Time

(Transcript)

Laura Lubbers:	00:05	Welcome everyone to today's webinar. My name is Laura Lubbers, and I am the Chief Scientific Officer at CURE, and I want to thank you all for joining us today. CURE is pleased to continue our leaders in epilepsy research webinar series, which consists of webinars that highlights some of the key research that's being done in epilepsy. Today's webinar, which is being sponsored by our friends at Sunovion will focus on cognitive deficits, and memory problems, a common issue among adults with chronic epilepsy.
Laura Lubbers:	00:34	And it will be presented by Dr. Bruce Hermann. CURE's mission is to find a cure for epilepsy by promoting, and funding patient-focused research. This year, we are celebrating 20 years of impact in the field of epilepsy research. CURE has been instrumental in advancing research in many areas including infantile spasms, post-traumatic epilepsy, Sudden Unexpected Death in Epilepsy or SUDEP, and genetics just to name a few areas.
Laura Lubbers:	01:03	Today's webinar is entitled Epilepsy's Impact on Memory and Cognition Over Time. And we'll discuss the course of cognitive, and memory aging in person with chronic epilepsy. In addition, factors that contribute to healthy cognitive, and brain aging will be addressed. Dr. Hermann is a professor in the department of neurology, and the director of the Charles Matthews neuropsychology section at the University of Wisconsin School of Medicine and Public Health in Madison, Wisconsin.
Laura Lubbers:	01:35	The focus of his research is the impact of epilepsy on brain structure, cognition, and psychiatric status, and the effects of chronic epilepsy on brain, and cognitive development, and aging. Before Dr. Hermann begins, I'd like to encourage everyone to ask questions. You may submit your questions anytime during the presentation by typing them into the questions tab of the GoToWebinar control panel, and clicking send. My colleague from CURE, Brandon Laughlin will read them aloud during the Q&A portion of the webinar.
Laura Lubbers:	02:06	We do want this webinar to be as interactive, and informative as possible. However, to respect everyone's privacy, we ask that you make your questions general, and not specific to a loved one's epilepsy. I also want to mention that today's webinar as well as all previous, and future webinars will be recorded, and are available on the CURE website. So, with that, I'll turn it over to you, Dr. Hermann.

Bruce Hermann:	02:31	Thanks Dr. Lubbers, and it's a pleasure, and honor to be here today, and to address this topic. It sounds like there's a lot of interest in this topic, and it's one that's near and dear to my heart of course. And what we'll do today is address these four points. Spend a little bit of time, I'm talking about making sense of memory, and cognitive complaints. It's a great concern in the general population these days, as well as people with epilepsy in particular. We'll talk, say a few words about cognitive changes that occur with normal aging, that's important to understand
Bruce Hermann:	03:07	Say just a few words about how we assess cognition, and then we'll move into some findings, looking at cognitive, and brain aging in individuals with epilepsy, primarily adults. But we'll say a few words about children if we have time, and we'll also talk a bit about maintaining cognitive health. Here we go. So, first of all, cognitive complaints are common in people with epilepsies. I mentioned they're common in people with epilepsy in the general population, and of cognitive complaints, subjective memory concerns are especially prominent.
Bruce Hermann:	03:43	And one study that was done in 1992, it's a bit dated now, but it was an excellent study, showed that there were more subjective memory problems compared to healthy controls. 54% in individuals with epilepsy compared to 23% of the control group. And self-reports of cognitive issues, and memory are complicated by depression, which has made this a somewhat difficult area relying just on subjective complaints.
Bruce Hermann:	04:10	I could use a little help here, Brandon. I don't see the advance button. There we go. So, we're going to first of all, spend a few minutes trying to make sense of memory complaints. There we go. So, we have a pretty busy neuropsychology service here in the department of neurology at the University of Wisconsin. We see approximately 2,000 different patients per year, and they come to us with a variety of conditions, a variety of concerns, a variety of disorders. And prominent are subjective complaints about cognition, and particularly memory.
Bruce Hermann:	04:55	And so, one thing we do is we spend a fair amount of time trying to figure out exactly what they mean by memory problems. So, can you give us some specific examples of what you mean, what you're concerned about? Either the patient themselves or a significant other who comes with them to the clinic. And the types of complaints that we get are very, very mixed, and here are a few examples. So, some folks will say, "Well, I have trouble. I'm always misplacing things about the house. I'm always looking for something."

Bruce Hermann:	05:21	Others will say, "I can't think of words or names when I'm talking." Others will say, "My kids or my spouse tells me, I repeat myself. I told you that, you said that before." Others will say, "I read a page in a book, and I get to the bottom, and I don't know what I just read. I'm driving, and I can't remember where I'm going. I can't remember names after I'm introduced, and I go to another room, and forget why I went there." So, you can tell it's a wide diversity of symptoms.
Bruce Hermann:	05:52	Now, first of all, just a few words about memory, and then we'll start to categorize of these complaints. So, there are two different types of memory, two categories. We're going to be very specific in this presentation, so-called declarative and procedural. And declarative memory is a memory of facts, and events, and refers to those memories, which can be declared or discussed. It is in large part, focuses on someone's autobiographical history, and their day-to-day recall.
Bruce Hermann:	06:24	Procedural memory are things that refers to things that are involved in learning to do various activities, and there're various subtypes. And under declarative is what's called episodic memory, which is our day-to-day where you call, and this is moderated. Everything is moderated by a distributed system, but a particularly important note in that system is the hippocampus. Hippocampus is a structure deep in the temporal lobes, it's very involved in memory function, and it's important in epilepsy because this structure is often affected in very common forms of epilepsy such as temporal lobe epilepsy.
Bruce Hermann:	06:59	So, there's good reason neuroanatomically, and the rationale of particular seizure types to be concerned about memory. Now, if we go back, and for a second, talk about how does one make a memory, an episodic memory? Three things have to happen. First, there has to be registration of what you want to remember. So, if you're sitting listening to a talk such as this, one thing you need to do is actually pay attention. Sometimes people will sit, watch a TV show, listen to a lecture, and they're actually somewhere else in their head.
Bruce Hermann:	07:38	They might be worrying about something, thinking of things that they have to do, and the information is just not getting into their memory system, so to speak. Second, if things get into the memory structures such as the hippocampus, and the mesial temporal lobe system, then the brain has to do something that you really don't have control of. It consolidates or stores that information over time. Even though you may or may not want to remember it, the brain has this knack for keeping information around for a period of time, and that's critically important.

Bruce Hermann:	08:08	And third, if someone says, "Well, what was the talk about?" Then you need to pull it out of memory, assuming that you paid attention, that your brain consolidated it over time. So, can it be pulled out, and can it be retrieved? So, if we think about our complaints that some people may present with, registration or attention failures are captured by some of these symptoms. I read a page, and I have no idea what I just read. There really doesn't require any consolidation at all.
Bruce Hermann:	08:40	I have a conversation, and can't recall what was just said, in one ear and out the other, or I'm introduced to someone, and I can't recall their name, a common complaint. I go into a room, why am I not there? These are really not related to ongoing memory issues per se. These are more failures of input, and sustained attention, and concentration. An important distinction. They're very common complaints.
Bruce Hermann:	09:08	Retrieval failures tend to drive people a little nutty. They're embarrassing, they're annoying, and I think most folks can relate to these, words in speech. Can't think of a common word, you can talk about the word, but just can't pull it out when you want it in an effective fashion. Names of individuals, you might know who they are, where they live, who their spouse is, what they do for a living, just can't recall their name. Rapid recall of factual information, politicians, movie titles, street names and so on.
Bruce Hermann:	09:39	And generally, in retrieval problems, recall is facilitated by cueing. So, if you see a person, you can't think of their name, if I were to give you three names, you could probably pick that correct name out quite quickly and easily. So, that's another indication that's not forgotten, there's just some problems with access. And memory failures themselves, the type of difficulties that we really worry about where there's poor recall, and increase forgetting of things from day-to-day that they have clearly paid attention to, clearly salient in their lives, and cueing does not help bring back those memories.
Bruce Hermann:	10:20	And in the worst possible cases, every day is a new day where there's poor recall of what happened the day before. Thankfully, this does not happen too often, but these are the sorts of memory failures that we're worried about that are probably related to abnormalities in discrete regions of the brain, such as the hippocampus. Now, individuals may not only have epilepsy, they may have other medical comorbidities. We know from very large studies looking at comorbidity studies of epilepsy with other disorders that people with epilepsy actually

have a higher rate of other medical conditions compared to the general population.

Bruce Hermann: 11:00 So, in these conditions themselves, can affect aspects of cognition. So, for example, those individuals who have anxiety or mood disorders sometimes have a lot of difficulty paying attention. They're focused within their head. They're worrying, they're concerned, and have trouble adequately paying... their attention is somewhat divided. And so, their registration is low. Sleep disorders are very common. Sleep apnea is very common. That leads to increased fatigue during the day. And if you're very, very fatigued, you can't pay attention. And again, not processing well.

Bruce Hermann: 11:42 Individuals who have chronic pain may take medications for their chronic pain, and then sometimes the pain gets so great, you just have to pay attention to the pain. And again, it decreases your awareness to the world about you, and same with ADHD. So, these medical comorbidities could affect how well memory functions on a day-to-day basis. Retrieval problems such as names or word in a speech occurs with normal aging, you see this more in aging individuals. It occurs in other medical disorders such as multiple sclerosis, that's a white matter disease, and it also occurs in cerebrovascular disease.

Bruce Hermann: 12:17 So, these sorts of difficulties, retrieval problems are a bit more frequent in those conditions. And the true memory problems, consolidation and storage difficulties are commonly noted in epilepsy, in particular temporal lobe epilepsy, but in other epilepsies as well. And also, in other medical conditions that can affect areas in or around the hippocampus, and important structures are involved in memory consolidation, encephalitis, amnestic mild cognitive impairment, and focal strokes.

Bruce Hermann: 12:58 So, in summary, this part here, memory complaints are really quite common. And in a careful interview, one can get... this can be helpful in targeting the underlying issues. Is it registration consolidation or retrieval? An objective cognitive assessment will be helpful in characterizing the nature of the problem. That's what we do. We conduct neuropsychological evaluations and again, as I showed you, the comorbidities of epilepsy may play a role in the adequacy of cognition.

Bruce Hermann: 13:35 Now, what's interesting is what makes things a little bit more complicated is the landscape of what's normal in terms of cognition changes with increasing chronological age. So, the world population is aging. It's hard to get away from discussions such as these, the aging, the world populations, the relevance

of Alzheimer's disease, and other neurodegenerative disorders is discussed everywhere these days. My own State of Wisconsin is clearly aging. So, you can see the State in 2005, and 2035, the blues represent aging of the various counties.

Bruce Hermann: 14:13 You can see there's just a sea change in the age distribution of the population from 2005 to 2035. Now, with the normal aging, some cognitive abilities remain stable or even improve over time, and some cognitive abilities decline with normal aging. And so, that makes it somewhat difficult sometimes for people to understand what's going on. So, cognitive changes, some abilities remain stable such as one's vocabulary, fund of information, and knowledge about the world. As you can see here, performances stay stable from adolescents out up to age 70 a little bit beyond.

Bruce Hermann: 14:59 So, they're very stable cognitive function. In fact, they call it crystallized intelligence. So, it's very stable over the decades. In contrast, some abilities change surprisingly early, and have a steady slow decline over the decades. And this, for example, is just how fast you can do something. People can still do it accurately, they can still do it appropriately, but just slower over the time. Rapid novel problem solving, thinking on your feet very quickly, solving problems in your head. The adequacy with which people can do that will slow over time, and they're not just quite as adept as they were when they're younger.

Bruce Hermann: 15:40 So, you can see this steady slow change it takes place. Again, if you look from 20 to 70, it's a relatively mild, but discernible decline. And what about memory? Well, memory shows the same pattern, and these graphs come from some of our major neuropsychological tests from the normative data. So, these are population-based controls, and memory itself also declines over the decades. So, that's a normal course of aging. Just one more picture of this. This is another demonstration from specific cognitive abilities.

Bruce Hermann: 16:19 And you can see that the abilities go down again from beginning surprisingly early from the twenties, involves speed of processing, working memory. Where in long-term memory, there's world knowledge or semantic information remains stable, and increases over the decade. So clearly, major changes and patterns of cognition over time. And not only that, there are some changes in brain structure that take place over the decades as well. So, there are some brain regions that reduce in volume with normal aging including the hippocampus shown here.

Bruce Hermann:	17:01	And this is very important in the memory function as we showed you before, and there are some brain regions where there are minimal changes. So, this represents repeated scans of individuals across different decades of life, and the patterns are really quite clear. So, normal cognition can be a moving target, so to speak. People may accurately report change or decline over time. Someone who says when they're 50 that my memory is changing compared to when they were 30 is probably absolutely correct.
Bruce Hermann:	17:38	The question is whether the change or decline is normal for age or whether it's an abnormal change for age. And that's a difficult question to answer, but it's something that's not that hard to with formal cognitive assessment because those are age-normalized tests. We'll say a few more words about that in a couple minutes. Now, just a few words about cognitive screening, and neuropsychological assessment, and then we'll take a look at some epilepsy research data.
Bruce Hermann:	18:10	From the cognitive assessment perspective, we are what I would say we are domain assessors. If someone comes to see us whether they be a child, a teenager, a young adult or somebody who's 75 or 80, they'll of course take different tests. But what we want to do is we want to be sure to assess the major cognitive domains, which are shown over here on the left. The major domains are intelligence, language, and some specific examples are given there, visual abilities, visual perceptual abilities.
Bruce Hermann:	18:49	Of course, memory, we want to look at verbal memory and visual memory. We look at learning and retention. We look at a big category called executive function, processing speed, sensorimotor function, and emotional status. But here, we're focusing on memory. And when we look at memory, and some of you I'm sure have undergone neuropsychological assessment. It can be assessed in a variety of ways. One common way is to present a wordlist to someone, examine or reads the word list.
Bruce Hermann:	19:23	The patient says back as many words as they can, and you do that several times to look at a learning curve. And then that stops, and examiner goes on to administer other tests for a period of time, and then they say, "Hey, what do you remember from that wordlist now?" And that's the memory component. How well are they able to consolidate, and recall newly acquired information over a delay interval? There's a lot of variability in the test. So, some of the wordlist go from three up to 16 words in length.

Bruce Hermann: 19:52 They vary in terms of how many times they get to hear the wordlist. There are other tasks where short prose passages are read, generally two or three long sentences, one to two presentations. Another big category of verbal memory are word pairs, and include both easy, and hard pairs. So, depending on the preference of the neuropsychologists, you might take one or more of these categories of tests. And again, what's of most interest is once the learning phase takes place is how well can the person retain what they learned over time.

Bruce Hermann: 20:35 Okay. So now, let's move to cognition and memory in epilepsy. Now, we've been talking in fairly broad terms about epilepsy up to this point, but there are many factors that can be involved in how well one can perform. There are several features of epilepsy that are fixed. That means they come with the person, they really can't be changed over time, and they're shown in the fixed box over there on the left, such as what's the underlying pathology that cause the person's epilepsy? What side of the brain does the epilepsy originate from if it's a focal epilepsy?

Bruce Hermann: 21:19 What lobe of the brain does it come from, does it originate from? What's the agent onset of the pathology and the seizures? What gender, and what's the overall intellectual capacity of the person? Now, on the right side of the slide are some factors that change over time, so-called remediable or dynamic factors, and these can be specifically, the number of medications. In addition, even though not having seizures, if someone were to do an EEG, it'd be possible to see that there are EEG abnormalities that are taking place that come and go, that can affect cognition.

Bruce Hermann: 21:59 Mood certainly affects how well now people can learn, and retain information over time. Of course, motivation, quality of sleep, and we talked about that a minute ago, and how a recent was the last seizure to the cognitive assessment. And third at the bottom, the course of the disease. How complicated is the epilepsy? Do they have a history of status epilepticus? How many generalized seizures have they had in their lifetime? Have they had head injuries associated with the seizures?

Bruce Hermann: 22:27 So, these are all things that are taken into consideration that can have an effect on a person's performance. Limited specifically to epilepsy, not counting for the moment, the additional comorbid conditions. Now, we have this belief that the various types of epilepsy are especially associated with risks of a specific cognitive function. So, for example, temporal lobe epilepsy tends to affect the hippocampus, the mesial temporal

lobe. And so, we expect there to be particular problems with anterograde memory, forgetfulness.

Bruce Hermann: 23:02 If someone has focal epilepsy, then we would expect by virtue of brain behavior relationships, they would have more difficulty with executive functions. In the pediatric population, those who have backs or rolandic epilepsy might be more likely to have language problems. Those with absence epilepsy, attention difficulties, and so on. So, when someone comes in, they have a particular type of epilepsy, there's some attention directed towards these specific expected areas of difficulty.

Bruce Hermann: 23:32 Now, concern about the cognitive course in the context of chronic epilepsy is very longstanding. The first investigator to look at this issue was J. Tylor Fox in 1924. And in those days in the UK if you had epilepsy, it is possible that you would be placed in an epilepsy colony. And there, they had children, and adults, and Fox looked at cognition in children with epilepsy, five to 16, tested them one year later, gave the test of the time, and reported some deterioration that was quite marked in 8%, and it varied with their seizure frequency.

Bruce Hermann: 24:13 So, the point of this is that in 1924 is the first empirical study of worry about cognition, and its course in people with established epilepsy. This has gone on again over the decades. This comes from Lennox and Lennox in 1960, and what you can see as he looked at the course of cognition, this is the rate of mental handicap, and he looked at those who had absence epilepsy or petit mal, and what you can see is whether you had under a thousand or over a thousand seizures, it didn't really affect your intelligence.

Bruce Hermann: 24:50 On the other hand, when he counted the number of generalized tonic-clonic seizures that patients had, then there was an increase in impact on intelligence. So, Lennox counted seizures, and broke them out by seizure syndrome, and others have done the same over time. Now, my colleagues and I have just completed a review, and I just want to show you a couple of things. What you really want to have in a study like this is you want to have people with epilepsy, and a control group, healthy people who do not have seizures so you can control variety of factors including chronological age differences over time.

Bruce Hermann: 25:37 And there have been in the literature 20 controlled studies, 11 in children, nine in adults over the years. And the number of patients that have been investigated is actually pretty modest if you compare this to the general age aging literature. This is not a lot of studies, it's not a lot of participants. There's a

tremendous amount of variability over time, a tremendous amount of variability between these studies. And there are more studies without controls. It's more problematic literature than the 14 pediatric, 16 adult studies and again, a modest number of patients.

Bruce Hermann: 26:19 So, this is a vastly understudied area of investigation. In general, the conclusions from reviews are that a subset of individuals have a more rocky course going forward in terms of cognition. And we'll look at some evidence in just a second. So again, with certain seizure types, we expect to see certain cognitive deficits. And we've been carrying out in the past, we carried out a controlled prospective study of persons who had temporal lobe epilepsy who were seen here at the University of Wisconsin, came here for their care.

Bruce Hermann: 26:56 And so, if we look at, this is their neuropsychological profile, and the solid line is where controls perform. Let's say this is average or normal control performance, downgoing bars represent performance is poor compared to controls, upgoing bars would mean better performance. So, these are our memory tests right here. And as you would expect, those individuals with temporal lobe epilepsy are having more memory problems. They're all downgoing bars.

Bruce Hermann: 27:23 However, if you look at the other cognitive abilities, and do a very thorough assessment, what you see is other areas go down as well. Now, these sorts of studies, and you see these in multiple epilepsy syndromes. We call these average cognitive profiles, and they've done this with measures of depression, with quality of life, and so on. You look at them, you say, "Oh my gosh, this is terrible." Although you do have these memory problems, there's broader cognitive dysfunction, and so on.

Bruce Hermann: 27:54 And at some level, it paints a really problematic picture of epilepsy. But seeing patients come through the clinic, there are some who have temporal lobe epilepsy, longstanding in nature that don't show this pattern. This is an average profile. So, the question is, is are there groups of patients that cluster within... have similar cognitive profiles? So, are there some who are relatively unscathed, some who are more effective, and so on? The answer is absolutely yes, and it's informative, and it paints a different picture of the cognitive consequences of epilepsy.

Bruce Hermann: 28:35 So, first of all, we did this, and it's called cluster analysis, and we could find a group of 47. So, here's average performance for the controls, and here's a group of patients with temporal lobe epilepsy, and here are the cognitive domains. And as you can

see, they're very close to the control performance, we call them Cluster 1, almost half of the patient group. So, they look very unaffected, to tell you the truth. Cluster 2, which is about 25% of the sample showed what we'd expect to see in this population.

Bruce Hermann: 29:16 The biggest problem was memory. They were down in some other cognitive abilities, but pretty close to Cluster 1, and other cognitive domains, relatively memory impaired group. The third group, about 28% were more globally affected in terms of their cognitions. They were affected in memory, executive function, and speed. So, the point being that there are different groups of people who have similar cognitive profiles you can identify with almost half of individuals with chronic epilepsy, relatively unaffected.

Bruce Hermann: 29:52 Now, the question is, is whether these profiles are associated with other markers to give them some validity. Now, if you just look at the demographic, and epilepsy characteristics, as you go from least to most affected, people get a little bit older in Cluster 3. They have a longer duration of epilepsy, 27 years compared to 17 years here. A little bit more in the way of anticonvulsant medications, but it's primarily age and duration.

Bruce Hermann: 30:23 The other thing that's interesting is that there are different patterns of brain abnormality. So, take images, we took images of these folks, did some post-processing to derive volumes of brain tissue, total cerebral tissue, total cerebral gray, white, cerebral spinal fluid, and their hippocampal volumes. In Cluster 1, the most intact group again, here is average performance, performance of the controls. And the biggest finding was a decrease in their hippocampal volume, which makes sense in terms of the temporal lobe epilepsy.

Bruce Hermann: 31:01 Cluster 2, which was more adversely affected in terms of cognition. They had more memory problems, and they have greater atrophy in hippocampus, a little bit more abnormality diffusely represented. And the third group was our most affected group, and they showed the most abnormality, more atrophy in terms of total tissue, white matter, hippocampus, and they had more CSF. So, there are biological markers of these cognitive profiles, which is meaningful.

Bruce Hermann: 31:30 Now, what's really, I think important is that they differ in terms of their cognitive trajectory. So, we brought folks back four years later, and retested them with the same test battery, and zero shows the performance compared to controls. And the thing that's very clear is that Cluster 3, the most impaired group

pre at baseline showed the more problematic cognitive course in language, immediate and delayed memory, just how fast they could do things.

Bruce Hermann: 32:03 So, the prospect of cognitive trajectories are tied up with how impaired they are at baseline, and it speaks to A group to worry about. So, there definitely is A group to worry about. They are the minority, a very 25% or 26%, so it is a minority of the group of individuals. They have temporal lobe epilepsy. The rest of the group has modest changes that really aren't problematic or clinically significant. And the changes, well, if you actually look at the scores, here are the patients, here are the controls, here's composite memory score.

Bruce Hermann: 32:43 You can see from time one to time two, four years later they go down just a little bit while the controls pick up a few points. That's a practice effect. So, not a huge sea change, but you can see the difference. And here's a speed-based measure. Higher scores mean you're a little bit slower. You can see the epilepsy group gets a little bit slower from time one to time two. In general, the controls are quicker, and they stay the same from time one to time two. So, there is a subgroup that does show some problematic change over time.

Bruce Hermann: 33:10 And the best predictor of a problematic change over time was the presence of baseline abnormalities in brain imaging where we could quantify this baseline IQs. Those who had lower IQs were a little bit more at risk for adverse changes. Those who have higher IQs have what's called more reserved. Lower duration, a longer duration predicted some of these problematic changes, and the remaining variables including onset age, epilepsy medications, and seizure frequency really weren't powerful predictors.

Bruce Hermann: 33:43 So, it's possible to identify a group at risk, find their predictors, and to really hone in on these groups. Now, these folks were in their mid-40s on average. In fact, when they came back at time two, they were about 44 or 45 years old. So, still very young, and the question is what's going to happen over the ensuing decades? What does the cognitive aging process look like going forward? And that's a very difficult question to ask because we just don't have these population-based controls where you can study this aging process over time.

Bruce Hermann: 34:14 And there is one cohort that is a very special cohort that is located in all places, Turku, Finland. And I'll say a few words about this cohort, and this is actually a project that CURE is a sponsoring. And this is a cohort of individuals that Professor

Sillanpaa got together when he was early in his career. He was a child neurologist, had an MD, and he was working on a PhD. And he decided to gather a population-based cohort of children with epilepsy under age 16 in that general region.

Bruce Hermann: 34:50 And he also obtained population-based controls, and he studied this group, got his PhD in 1973, and he has followed this cohort over the decades. And he's kept in touch with them, studied them episodically, and it's been a gold mine of information about population-based characteristics of individuals with childhood onset epilepsy, and they're course over life. And they were age 4.7 years when they entered the study. And at present, they're 57 years old, and Matti aged, so have we, and his cohort has gotten older, and has a lifetime of neurological health, social education, vocational, and epilepsy history.

Bruce Hermann: 35:39 So, it's just an unbelievable resource. And with professor Sillanpaa, and investigators here, we proposed a collaboration of aging, and epilepsy specialist here at UW and Turku for those patients to go back to the University of Turku to be seen and assessed. And they went back, and took some cognitive testing. They had a brain MRI, they had some advanced imaging, including glucose, and amyloid PET scanning. They had an EEG, clinical interview, and DTI, and some other measures.

Bruce Hermann: 36:20 So, it's a very unique study, one of its kind coming back for evaluations so long after the onset of their epilepsy. And several collaborators on the Finland side, Professor Rinne runs a PET center, Matti, and Mira Karrasch was the neuropsychologist who conducted the neuropsychological evaluations. And the results are really quite interesting. So, here we have and these are learning trials. So, the participants are read 15 words in 15 seconds. There're five trials, and you can see people get better over time, and here are the controls, and they do exactly what you would expect to see.

Bruce Hermann: 37:04 They pick up a few words at first, and learn significantly over trials. Here are the epilepsy patients as a group, but when you break them into those whose epilepsy remitted, they had childhood onset epilepsy, and at some point in their life, it stopped and they went off of medications versus those who have active epilepsy. Still having seizures in their 50s, and/or on medications, but well controlled epilepsy, a huge difference. Those who had remitted epilepsy look very close to the controls.

Bruce Hermann: 37:35 In fact, they're not statistically significantly different across the trials or in their delayed recall. Whereas, those who had active

epilepsy did more poorly on the memory tasks, and other measures as well. So, the epilepsy remission was a major factor, and in fact, the majority of his uncomplicated cases with childhood epilepsy did remit. Now, the other interesting thing, which we hypothesized, but didn't know if we'd find it, was whether there was evidence of accelerated brain aging doing what's called an amyloid scan.

Bruce Hermann: 38:19 And so, amyloids are plaques, and they can now be imaged. And with the Turku group folks underwent their PET scans, and we found an increased incidence of amyloid deposition. It was not associated with cognition, but it's a worrisome finding, and it was especially increased in a subset of patients who had the genetic predisposition, the ApoE4 gene. So, we are now bringing all these folks back five years later to repeat the scans, and repeat the testing to see what this aging process looks like.

Bruce Hermann: 39:01 Does this progress or does it stop? We really don't know when this was laid down to be perfectly honest. And is a presence of baseline amyloid associated with problematic changes in cognition going forward? So, I think this is a one of a kind study. We're very excited to have the support, and the project design going at present. So, the question always is, well fine, but what can be done about all this? What can you do to help cognitive and brain aging? And in the epilepsy world, there's not a lot of information.

Bruce Hermann: 39:45 There's some, but not a lot. In the general aging literature, and especially in the preclinical Alzheimer's disease world. In Alzheimer's disease, there aren't many compounds that are that effective in retarding or helping the disease. And so, research is focused on folks who are at risk really earlier in their life. And there are also large population-based studies looking at midlife risk factors, and how they age cognitively, and how their brain ages. And it's clear that there are several factors associated with good or band cognitive aging.

Bruce Hermann: 40:22 Education and occupation are associated. Alcohol and nicotine consumption are associated. Stress to the degree to which one has cognitive leisure activities. They're physically active, they are obese, or not obese, and have a healthful diet, and degree to which they are burdened by other health diseases. And we know from the CDC surveillance studies that people with chronic epilepsy carry a lot of risk factors for abnormal cognitive aging in midlife. So, for example, there's fewer marriages in social networks can be more limited.

Bruce Hermann: 41:01 They are more physical, and mentally unhealthy days, and more living alone. So, it's really these factors, which become quite important, and this just shows that their self-reported health status is reduced compared to controls. But now, there's so much interest in this that if you Google this, if you Google healthy cognitive, and brain aging, and then put an NIA for National Institute of Aging, or put in CDC for Centers for Disease Control, or NINDS, or AARP, or IOM, that will take you to pages that will tell you about ways to maintain and improve cognitive health over the years.

Bruce Hermann: 41:49 And it's really, it's not surprising, and most of this is cross-sectional research. There are some prospective studies going on now, but physical activity is good. Helpful diet is important. Taking care of medical comorbidity is important. You see people all the time who have sleep apnea, and can't use their sleep pump for one reason or another, who have diabetes, and don't maintain their diets, and so on. So, it's crucial to pay attention not only to your epilepsy, but to other health conditions, and follow the recommendations.

Bruce Hermann: 42:19 Being physically active, using your mind in various activities, being interested and mentally active, and being around people, and socializing. Those are all quite important activities. Again, the major points in all of these websites, and really just go to those websites, and look them up. They're very good. Take care of your health, eat healthy foods, be physically active, keep your mind active, stay connected, everything your mother told you when you were little.

Bruce Hermann: 42:56 I'll say just a few words about children, and then open it up for questions. One interesting thing, and this is true, I think in both the adult population, the PF population is the comorbidities, and cognitive difficulties included have always been thought to be associated with the course of the disorder that things get worse, and worse as we've shown. Most people, their course is not complicated, it is true for a subset. But in the pediatric world, it has become crystal clear that actually, problems can be evident even at the very onset of the disorder, even before medications are prescribed.

Bruce Hermann: 43:35 Let me just give you a couple examples. A wonderful Dutch study published in... I don't see the year, there sorry. It looked at 51 children with newly diagnosed uncomplicated epilepsy. They did not have a lesion. They were in mainstream education, normal schools. They were seeing outpatient, and they had what is now called epilepsy only. And there are 48 sex matched

controls, and they tested the kids within 48 hours of the diagnosis before they were given any medications.

Bruce Hermann: 44:04 They took cognitive tests, behavioral measures, teachers and parents were interviewed, and their school career was looked into. And again, at onset before medications were given, there were more behavioral problems than the kids compared to controls. Again, shown here more attention problems, a little bit slower reaction time, a little bit slower learning, a little bit more difficulty with academic skills at the onset.

Bruce Hermann: 44:30 So, the story, and this has now been found in the adult population as well, that the time to pay attention to these comorbidities is at the time of diagnosis. It's critically important, and these kids at diagnosis prior to their epilepsy diagnosis, and first recognized seizure, had struggled with schooling. So, there's something happening neurodevelopmentally that was taking place even before the first seizure. And that's something that we found here the last 15 years or so.

Bruce Hermann: 44:59 We've been studying a large cohort of children with new onset epilepsy. Here are our results. You can see downgoing bars, and the various cognitive abilities, very similar to the Dutch cohort. But over time prospectively, this is at baseline two years later, and then five years following baseline. They're parallel lines, there is not decline. The children with epilepsy are offset a little bit. These are raw scores, not IQ scores.

Bruce Hermann: 45:31 They're offset a little bit at the time of diagnosis compared to controls, and they grow, and their cognition develops at the same rate, same incline over the five-year period with no decline over time. So, to an offset that proceeds going forward, and you can see this on other measures as well. This is a measure of executive function. Again, exactly the same thing.

Bruce Hermann: 46:00 So, in children with uncomplicated epilepsies, absence, juvenile myoclonic epilepsy, rolandic epilepsy, we just don't see deterioration, which is quite favorable. And the same with academic achievement, if I can orient it to this. Here are kids who have reading problems. It's a subset of kids. Some children with epilepsy have totally normal reading compared to the controls, does not worsen over time. It's pretty stable. Same for spelling.

Bruce Hermann: 46:31 Math gets a little bouncy, and a little bit worse over here. But largely, what you see at baseline is what you see over the years. So, let me stop there. I've talked a lot and I'm happy to answer a few questions. Everything I've shown you has been the result of

a huge collaborative team both here at the University of Wisconsin, as well as collaborators across the country, and of course our Finland collaborators. So, thanks for your attention, and happy to address a few questions in the time remaining.

Laura Lubbers: 47:05 Thank you Dr. Hermann. We'll now begin the Q&A portion as he indicated. Again, if you have questions, please submit them to the questions tab of the GoToWebinar control panel, and click send, and Brandon will read them aloud. I think there're probably already some questions there. Is that correct Brandon?

Brandon L.: 47:20 Oh yes. We received a great number of questions. I'll go ahead and ask a few that I have that were very popular questions in the time we have remaining. The first question, Dr. Hermann, is obviously, you've discussed memory problems and cognitive issues that do occur. How did researchers differentiate between the issues caused by antiepileptic drugs, and those that are caused by seizures?

Bruce Hermann: 47:52 Well, within the epileptic drugs, the best are the controlled clinical trials, right? And there's quite a bit of research about that, right? So, patients come in, they're randomized to drug A or drug B, they're tested before they're given those medications. And there are studies that have done this with healthy controls where they've taken no medications, and come into the study, and take some baseline testing, then are randomized to a drug treatment trial, and no treatment control trial.

Bruce Hermann: 48:22 And you can figure out the specific effects of particular drugs in that fashion. And they've also done this with patients with epilepsy, where they're randomized to one arm or another, and you can look at the effects of an add-on medication or a new medication. There are now, there are some very large studies where they've taken people at diagnosis, and randomize them into a one arm or the other. And it could be such as the childhood absence study, which was a major national study in the US that even compare the effects of seizure control as well as cognition.

Bruce Hermann: 49:04 If there's marginal or no differences in their ability to control the seizures, then really clearly the more preferred compound would be the one that has fewer cognitive complications. So, quite a big literature that addresses that through the years, and it's been worked out pretty carefully, and I can send CURE some references for that that might be useful to everyone.

Laura Lubbers:	49:30	Terrific.
Brandon L.:	49:30	Great. Thank you. Next question. Also, along the same lines there as antiepileptic drugs, is there research done when drugs come into the market on which medications, like Keppra that may have more of an impact on memory and cognition?
Bruce Hermann:	49:53	Yes. I mean, nowadays it's worked out pretty carefully. So, we have a good sense of the cognitive complications with some of these medications. It becomes clearer over time for sure, but cognition is now integrated in many of these drug development clinical trials and so on. Again, don't forget because what happens in my career, talk about cognition or talk about behavioral issues. Generally, the first question has to do with medications, and there's no question that it can have an effect. But these problems are present right at the get go even before any medications are given.
Bruce Hermann:	50:40	Can the medications exacerbate the cognitive difficulty? Sure, they can, but they are countering the effects of the seizures themselves, which have their own adverse effects. So, this research looking at new onset drug naive patients is just incredibly important. And again, there are subsets, some individuals at onset have no difficulties, and have a very uncomplicated course, whereas others from a cognitive perspective have difficulties early on, and were struggling with some issues even before the diagnosis of epilepsy, which no one fully understands, but everybody has observed that.
Brandon L.:	51:22	Great. And then a follow-up question to those questions is, is there an advantage to adults actually having genetic testing done to determine their type of epilepsy, and could that have an impact on knowing the cognitive issues, and the memory issues that may arise?
Bruce Hermann:	51:46	No. I mean, I think in the cognitive aging world, and especially in the Alzheimer's disease world, there are a couple of genes. I mean, it's a complicated business. I work with a preclinical AAD group here, and there's a lot of interest in genetics, and the primary gene has been the ApoE4 gene. I mean, there are genes for early onset dementia, but that's not what people are worried about. They're worried more about must having a family.
Bruce Hermann:	52:14	They're worried more about the course over the decades, and as they get older. And there are a couple of genes, but it's very poly genetic as they say, and you can have the gene, and not have Alzheimer's disease. You can not have the gene and have

Alzheimer's disease. So, it's probably what's probably most important in midlife is probably to get after all the treatable factors, and my general opinion, and the research on that, we have folks here doing exercise research.

Bruce Hermann: 52:45 And in at-risk patients for Alzheimer's disease, and the exercise has positive effects on brain structure. It has positive effects on laying down of the plaques. It has positive effects on cognition going forward. So, I've seen a diet study using the mind diet where white matter volumes increase over time. So, I think if you look at the websites for the various organizations I mentioned, I think that's very important to take a look at. And it's extremely important area of research for epilepsy. It's just critical going forward.

Laura Lubbers: 53:35 Brandon, any other questions?

Brandon L.: 53:40 Sorry. Actually, one of the questions dealt with, you mentioned Alzheimer's question. Is there any research being done that shows that epilepsy patients are more or less likely to develop Alzheimer's?

Bruce Hermann: 53:54 Well, this is a very hot topic right now, and there's a lot of interest in this, and there's been some... if we address it from the standpoint of comorbidity studies, is there a higher incidence between epilepsy seizures, and Alzheimer's disease? There is a higher incidence, but that's driven in part by people who have Alzheimer's disease, and then develop seizures as part of that disease. The really complicated question is, and not that that's not complicated, but the question that people with chronic epilepsy have is what's my cognitive course?

Bruce Hermann: 54:34 And we just don't know too much about it because our literature cuts off about age 50. We need some large population-based studies that follow people into their older years. And that, we just don't have. We need that, and that would include imaging, and cognition, and life health history. I think that's why the Finland data are so important. They've collected all sorts of health activity, personal information on these patients at midlife. And one question would be is there anything in midlife that predicts the amyloid deposition in people in their 50s?

Bruce Hermann: 55:14 And if something can be found there, then that would have huge implications in terms of what to do, and have some... just certainly generate testable hypotheses anyway in terms of are there things we can do to reduce that risk. And, that question is, I mean, what's the risk of Alzheimer's disease? It's everywhere,

you pick up the paper, listen to the news, and it drives a lot of interest in cognition.

Brandon L.: 55:41 Great. One more question, and before we run out of time, does epilepsy actually affect long-term memory or search term memory one more than the other? Sorry.

Bruce Hermann: 55:56 Yeah. I think the one thing we didn't talk about is if you think about it, the seizures, I mean I've always been impressed for example, by moms who will say, "We studied for the test last night, yesterday afternoon, and Johnny knew everything, and you got cold, and you're forwards, backwards, and had it all down, and had a seizure the night, or a seizure in the evening. And then the next morning, just didn't recall any of the information.

Bruce Hermann: 56:29 They weren't postictal, but it's erased what they had learned. And in epilepsy, the seizures, I mean memory is a process. Consolidation takes place over time, over a long time period. And if something disrupts that process, then that won't be remembered. And episodic seizures, and probably even the spikes, if people have some clinical seizures, and they're not aware of, these things are taking place, and are affecting the laying down of new memories.

Bruce Hermann: 56:59 So, it could be that if a patient and spouse say, "Well, don't you remember that trip we took four years ago?" They may not recall that because the consolidation process had been affected by seizures, spikes, or clinical seizures. And the subclinical seizures are really a problem because you're not sure when those things occur. You see them in the monitoring units all the time. So, long-term memory can be affected, and it is an object of study at present.

Brandon L.: 57:27 Okay. Thank you.

Laura Lubbers: 57:32 Okay.

Brandon L.: 57:34 Laura, I'll turn it back to you.

Laura Lubbers: 57:36 Thank you. Thank you, Brandon, and thank you, Dr. Hermann. That was a terrific presentation. We also want to thank our sponsors Sunovion for sponsoring today's webinar. And I'd also like to thank the audience for being so engaged, and asking some great questions. It's clearly an area that needs... it has a lot of questions around it, and needs continued study. If you do have any questions about this topic or CURE's research

programs, please visit our website cure-, www.cureepilepsy.org, or you can reach us via email at info@cureepilepsy.org. and I want to thank you all again for joining us, and please do join us for our next webinar, which we'll address the issues of anxiety and depression in people with epilepsy. This webinar will be presented by Dr. Andres Kanner from the University of Miami, and will take place on Tuesday, August 14th at 1:00 PM Eastern Time. So again, thank you all, and enjoy your day.

Bruce Hermann: 58:35 Thank you.