Cyber Seminar Transcript

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Series: Mild TBI Diagnosis and Management Strategies

Session: Magnetoencephalography as a Potential Imaging Marker for Mild TBI and PTSD

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Dr. Ralph DePalma: It's a great pleasure today to have Dr. Mingxiong Huang, who is a career scientist and medical physicist at VA San Diego system, a professor in the University of California, San Diego, Department of Radiology, and co-director of the UCSD magnetoencephalography center. We've heard from him before, and we're looking forward to this update on his experience with mild TBI diagnosis management strategies using MEG. Mingxiong?

Dr. Mingxiong Huang: Thank you so much, Ralph, for the invitation, for the introduction. Let me see, you can, ok. Let me get started. So today's topic is about MEG, and MEG, magnetoencephalography, as a potential imaging marker for mild TBI and PTSD. It's really a great pleasure to have this opportunity to share some of the resources and research we have been doing in our laboratory at San Diego VA and UCSD. And today I'd like to try to cover three topics. The first one is about MEG slow wave and how do we use slow wave for detecting mild TBI. And the second topic is about MEG research using the functional connectivity on blast mild TBI. And our last topic, the third one, is MEG application in posttraumatic stress disorder, PTSD.

So we know the traumatic brain injury, TBI, is the leading cause of sustained impairments in our Veterans, active duty military personnel, and also civilian population. But mild TBI, you know, is often to be referred as invisible injury because detecting mild TBI has been quite challenging using conventional CT or MRI. As shown in the pie chart, with CT/MRI, we see this positive finding rate of sensitivity about 5 to 10%. And the reason of that because we believe, diffuse axonal injury, or DAI, or some other neurochemical damage or other leading factors in mild TBI, but the conventional CT/MRI, they are mainly sensitive to blood in the brain, so probably they are underestimating the existence of mild TBI. In the past, in the laboratory, from Dr. Jeff Lewine in our laboratory, we have used MEG slow-wave measurements or source imaging for mild TBI.

Before we talk about, you know, our human research using MEG for mild TBI, let's look at, review this new physiology of the 1-4 Hz slow wave and what did we learn from that. In the 70's, actually the three last publications from same laboratory by Gloor and Ball and Schaul, and they do animals, start in cat. Invasive animal study, they open the skull, placed electrical grid on the gray matter cortical neuron and some depth electrodes. They did two experiments. First one, and published the two papers, but introduced physical injury to the white matter tissue. When they do that, the electrode overlay, the gray matter neuron generated 1‑4 Hz delta wave. The conclusion is potentially the de-afferentation and the lack of afferent input through those gray matter neuron lead to this generation of delta wave. To confirm that, they used another approach. Instead of using the physical damage to the white matter tissue, they applied atropine to block or limit the cholinergic transmission. We know atropine is a very aggressive antagonist, acetylcholine neurotransmitter. By limiting the delivery of acetylcholine, the gray matter neuron also generate very similar delta wave 1-4 Hz. So from this three, animal research, we know that the delta wave generation can be due to de-afferentation in the gray matter. The cause can be due to physical damage to white matter tissue or can be some new chemical damage, for example, limitation or blockage of cholinergic systems.

In humans, in the resting-state MEG, we can measure those xxxx delta wave. And we believe there can be characteristic of neurological injury in the brain resulting from either physical damage to the white matter or some new chemical injuries. Here's the typical example of the MEG sensor wave from, shows 1-4 Hz delta wave. But we also know the delta wave generation in human is not limited to TBI. Patient with stroke, brain trauma, and epilepsy all potentially generate xxxx delta wave. But based upon structural imaging, when easily xxxx stroke and brain tumor, based upon the medical history we rule out epilepsy in this patient with ongoing symptoms, was injured by, say, car accident a few weeks with ongoing symptoms, we can link the slow-wave generation with the TBI by that wave.

Before we look at the abnormal in delta wave, we have to establish a healthy control now in the database. This study published in 2014, we used 41 healthy controls to establish a normative database for different frequency band. The top row shows the alpha band, which is 8-12 Hz, and second row is beta 18-30, third one is gamma band and 30 Hz to 80 Hz, and the one in the last row is a combination of delta plus theta. Delta is 1-4 Hz and theta is the 4-7 Hz. Now you have to look at the top one, alpha generator, and you can see the generation of alpha wave dominantly come from the back part of the head from the, in the regional cortex and this primary and secondary regional cortices and can also come from the, you know, cuneus, precuneus cortex. And also look at the two hots spot over here. Those are the sensorimotor areas in, you know, for the head.

So in the last 90 years, you know, since the first discovery of EEG signal by Hans Berger, placed the axial and back part of the head recording alpha wave, we know roughly what the generators are, you know. But now with MEG, we can see through the skull, localize those generators in millimeter accuracy.

And now let's look at the third row, which is the gamma band, and the gamma band is different from the alpha generator. You can see there's lots activity and energy from back part of the head. A lot of signal come from the prefrontal cortex. This technology we can establish our healthy control database, and in the delta band use that one, you know, for assessing something abnormal in patient with mild TBI. In this case, in this study we have a purpose, try to look at the sensitivity or positive detection rate, mild TBI, with MEG. Use of resting state recording, spontaneous recording with eyes closed, and there's three groups in our study. The first one had 36 mild TBI. Those are active duty military personnel or Veterans suffered blast mild TBI with ongoing post-concussion symptoms or PCS. The second group contains 48 more TBI injured by non-blast causes, could be motor vehicle accidents, sport, and fall, again with ongoing PCS. The average time window between the injury and the MEG exam is about seven months, so well past the acute phase and now in the chronic phase. And to establish a healthy control database as I showed previously, in this case we have 79 age-matched healthy control for the 1-4 Hz delta wave.

This slide shows the main findings of our research, and we're trying to use MEG slow wave to look at the positive detection rate or sensitivity for mild TBI. The X axis, I'm sorry, the X axis shows the three groups, healthy control, blast mild TBI, and non-blast mild TBI. The Y axis shows, we xxxx cross wise maximum Z score as a measurement of the MEG slow wave. You can see the definition from our paper. The striking thing is the minimum overlap between this control group and the two TBI groups. If they pick up threshold, the solid line, none of the healthy control are above this threshold. With that kind of positive finding rate or sensitivity for the mild TBI group is 86.1%. For the non-blast mild TBI group, the positive detection rate is 83.3%. When combined, the blast and non-blast group together, we get the sensitivity approaching 85%. So it's much better than the combination of CT or MRI, structural MRI for mild TBI.

Because the sensitivity for this approach is very high, we can actually go look at individual subjects, look at their slow-wave generation. Here shows the 10 typical subjects, the slow-wave generation in the MNI, 132 atlas space. You can see the generation of the delta wave in the individual subjects is not homogenous. They can be, you know, in the multiple different areas, in the frontal area, in this case inferior frontal, superior frontal, temporal areas, and in this case occipital region. Thus, the nature of the mild TBI MI because we know the injury tend to generate, you know, different damages, different part of brain. And with MEG, we have sensitivity 85%, so we can look at the injury and the slow-wave generation in a single subject basis. And we also can look at the MEG slow-wave generation and how that correlates with symptom scores. In this case we see positive correlation between MEG slow-wave generation with personality change in this frontal area and trouble with concentration over here, effective lability, and again in frontal lobe, but the positive correlation between MEG slow wave and individual problem, this case in the right fusiform area, and positive correlation between MEG and depression in the singular cortex. So we can see this area show correlations between MEG slow-wave generation and PCS.

Another study we look at further the MEG slow wave with new psychological evaluation. In this case, we're looking at, you know, the D-KEFS, the Color-Word Interference inhibition scale. In this slide, anything shown in blue mean the xxxx correlation, and the stronger the slow-wave generation, the words or performance we can see is overwhelming in the frontal and potentially in the insular cortex, and generation slow wave not get correlated with the performance of common tasks. But we also see these few areas show positive correlation, in slow-wave generation in this case associated with better performance. So it's not just a one-side story.

And we also look at potential connection between MEG slow-wave generation and other MR technology, in this case diffusion tensor imaging. We know DTI is measuring the body motion, and we can use DTI to localize the location and also the orientation of white matter tracks shown over here. And patient with mild traumatic brain injury tend to show xxxx reduced fractional anisotropy, or FA values.

This example is a 17-year-old football player with three mild TBIs, with long list of symptoms. You can see there's headache, dizziness, fatigue, difficulties performing mental tasks, sleep problems, memory issue, and change in speech. There were multiple CT/MRIs that were all negative. We scanned the subject with both MEG and DTI. The MEG we see bilateral slow-wave generation. In the left hemisphere, we see posterior temporal lobe slow-wave generation from this group of cortical gray matter neurons. In the right hemisphere, we see actually three sub-clusters, if you look at the bottom. There's a bottom view to the view from middle direction. We see sub-clusters in the ventral, temporal, and the occipital areas generate xxxx slow wave. If the focus is this area of gray matter generate slow wave and then you look at the underlying white matter fiber track, get from DTI. See this box. We see huge reduction of FA signal compared with the other hemisphere. You see this is rest signal over here indicate there's track over there with reduced FA in this white matter track right underneath the area where we see MEG slow-wave generation. So that's a strong consistency because injury in the white matter fiber track might lead to de-afferentation and the generation of MEG slow wave in the xxxx white matter neuron just like animal starting cat from [inaudible 14:36] in their animal study in the '70's.

Now look at the other hemisphere. We have multiple slow-wave generation MEG, and look at this fiber track. In just one of the major fiber bundles, the inferior xxxx fasciculus, you see it in the cross here, the reduction at base quite obvious compared with this slide are thick and healthy-looking fiber. Here's, you know, the reduction of the FA is quite obvious. This is major fiber bundle, connect multiple gray matter areas together. Something wrong here. We're going to see de-afferentation and lead to the slow-wave generation in the gray matter neuron, gray matter MEG. So less consistency in this case, but overall, you know, we see about 25% of case in the MEG slow-wave generation and lead to, and the consistent with reduced FA in DTI, only 25%.

So the conclusion for the first part of my talk, with MEG slow-wave, going to measure the gray matter slow-wave generation due to the de-afferentation caused by potentially two factors; one of them is physical damage to the white matter axon. The second one, potentially some new chemical injuries, for example, limitation or blockage of, you know, cholinergic systems. With MEG, we see the very high sensitivity for detecting mild TBI approaching 85%. But only about 25% of the cases MEG slow-wave imaging are consistent with, in our case, reduced FA in white matter. In the literature it's very similar, you know, but in the literature people reported increased FA and decreased FA potentially related to [inaudible 16:26] but overall sensitivity using DTI for mild TBI is about 25% to 30% because there's huge overlap between the control group and the mild TBI group, unlike the MEG case we have sensitivity of 85% with a much smaller overlap.

And here's the quote from the study in Douglas about DTI for mild TBI, except despite the continuous advancement in DTI and related diffusion techniques over the past 20 years, DTI techniques are sensitive for mild TBI at the group level only, and there's insufficient evidence that DTI plays a role at individual level. So likely there's limited sensitivity for using DTI and other diffuse MR technology for mild TBI.

And the question is, you know, are we limiting ourselves in the past 20 years just with the axonal injury model? That's the dominant model we have been looking at with DTI in the last 20 years, and to answer the question we need to use different measure.

So in this paper actually just published in Journal of Neurotrauma, we look at MEG with a measure of functional connectivity, or FC. In that paper, we actually reveal in other MEG research in the past but also 26 functional MR studies with mild TBI, the result actually is very interesting. Among the 26 papers, six showed increased functional connectivity, or FC, nine of them showed decreased FC, 15 of them showed increased in some area but decreased in other tracks and other regions. So it's kind of complicated. And among them, only four of them were studying blast mild TBI. The story for the MEG FC measure for mild TBI are also quite similar. People reported increased or decreased FC. Here's a list four publications. But since it's known so far before our publications and no people published the result using MEG for blast mild TBI, the question is, you know, whether there's decreased or increased FC in the blast mild TBI with MEG. That's the question we try to answer in this publication.

In this case, we have 26 blast mild TBI from active duty military personnel and Veterans and 22 healthy functional age-matched healthy controls, and we look at the MEG base resting state functional connectivity. All the TBIs are due to blast injury. We're looking at this case, and the three frequency bands. Top panel is beta band. Middle one is gamma. The lower part is low-frequency band. Anything showing in red is the mild TBI group, in that region showed stronger connectivity or functional connectivity than healthy controls. Shown in blue, there's a mild TBI group have reduced functional connectivity [inaudible 19:37] control.

Here we're looking at from region to global functional connectivity, basically from one specific region for the rest part of the brain. And for each focused event we're also looking at two typical MEG FC measure. The first one is the cross correlation with timeline. The second one is the popular phase-locking synchrony. One thing we can tell is highly consistency between the two different FC measures, and the patterns in many cases are identical. We see many, many areas [inaudible 20:11] means in those region we see increased functional connectivity in mild TBI over control. Also we see some blue, in those regions we see decreased FC. And those regions tend to be in the front, in the inferior frontal lobe, in some of the memory systems. In some cases occipital area shows the reduced FC and also another big area shows reduced FC. For the gamma band, there's only, you know, increased FC in the cerebellar. For the low frequency, which is 1-7 Hz, we see again dominant by increased FC from the inferior temporal lobe, in some of the memory area, basal ganglia, and the inferior and also dorsal prefrontal cortex.

So we see, you know, both increased and decreased FC. And then the question is how does, you know, increased/decreased FC correlate with neuropsychological evaluation? Now we look at one region, a bigger region in the vlPFC area, and see the FC how they correlate with neuropsychological exams. And the Y axis is FC measure, Fisher Z score, and the X axis is the neuropsychological evaluation. In this particular case, the MEG FC measure likely correlated with number-letter sequencing. Means the stronger the functional connectivity, the worse the performance. Also see, you know, another correlation between MEG FC measure and the verbal fluency, the letter fluency also show negative correlation. This too shows the increased FC is a bad thing because of the correlate negatively with performance of cognitive function. But with another measure, which is digital symbol coding, we see positive correlation. Basically MEG increased FC correlate with better performance.

So the story is rather complicated. Here's the conclusion from our study, and basically it was MEG measure in functional connectivity in blast mild TBI, and with MEG we show MEG actually functional connectivity measure is sensitive in detecting abnormal FC in mild TBI. We see high consistency between the two different FC matters, the cross correlation with the time lag and the phase-locking synchrony. Like the other measures, the other publications used fMRI, MEG or blast mild TBI group that shows decrease and also increase in functional connectivity over controls.

Why that's case, you know, in our paper we actually list at least three competing mechanisms, you know, list over here. The first one is the one we know for 20 years, you know, diffuse axonal injury, and with any damage in the white matter fiber track, that can predict a decreased FC. But also other competing mechanisms, for example, people reported GABA-disinhibition might lead to over-excitation in gray matter, then actually in some cases predict increase in the functional connectivity. The third mechanism, which is functional reorganization and compensatory mechanism, it also can predict increased FC.

So in real life, all these mechanisms and potentially more competing mechanism co-exist in the patient with mild TBI. And so we realized we need to be very careful trying to use, you know, the functional connectivity measure in the patient with mild TBI because there's multiple competing mechanisms, unlike the first topic when we talk about MEG slow wave and the xxxx is rather thin over there.

So for further reading, you're welcome to read those two papers which shows decreased, sorry, increased excitation and disinhibition after TBI can lead to higher likelihood of developing posttraumatic epilepsy. In many cases, epilepsy will increase the functional connectivity in specific tracks, and here's more, you know, a couple papers on that topic.

Now I would switch to the third topic on PTSD. We know PTSD is a leading issue in our active duty military personnel and our Veterans, and also PTSD can be triggered by national disaster, for example, the earthquake and tsunami in Japan in 2011. And PTSD can also trigger by man-made disaster. I personally experienced in 1989, the Tiananmen Square massacre. You know, the communist party of China sending, you know, the PRA, the People's Revolution Army, to Tiananmen Square using tanks and AK47 crush down peaceful protest by students and other citizens. I was lucky I was not there in Tiananmen Square that night, but two of my friends were killed during that massacre. After that massacre I actually experienced xxxx the typical symptoms PTSD. Awake a lot of the times and nightmare and was in severe depression for quite a few weeks. But my brain was able to adapt that kind of fear. I didn't develop full-scale PTSD.

So what do we know about PTSD neurocircuitry? There's quite a few models. One involved actually is by xxxx and Chen, and their model actually predicted there would be hyperactivity in the amygdala, the emotion center, and hyperactivity in hippocampus. But that model also predicted there will be hypoactivity in vmPFC, the ventromedial prefrontal cortex. We know vmPFC is very important in the area that send down top modulation suppress the activity from amygdala and hippocampus. And patient with PTSD have hyposignal over here, predict there's less top-down modulation. That probably one of the reasons we see the hypersignal from amygdala and hippocampus.

And we learn actually quite a lot, you know, the function of the vmPFC area, the ventromedial prefrontal cortex, from this case, Phineas Gage, the railroad worker, you know, and happening actually , disaster happening over here. They tried to peddle gunpowder right over there, you know, for the railroad construction. Something terrible happening. The metal rod penetrated his skull and brain, generated massive damage to his vmPFC area. It's a miracle to survive with this damage, but left over profound deficit in his personality. Drastic change. Before the injury he was polite and nice gentleman. After injury to his vmPFC area, he become a monster basically. So we know the vmPFC is very important area sending down top-down modulation.

Also learned from another case. This case, the famous patient, H.M., the bilateral xxxx damage to his left and right hippocampus. There were a few hundred paper published in the single case. Originally led by, you know, Dr. Brenda Milner, excellent research from her laboratory in this case. We learned so much about xxxx damage to the hippocampus leading to profound memory deficit in the patient, H.M.

And also we learned from another doctor, which is not good one, Dr. Walter Freeman and his notorious lobotomy. His hypothesis is all this mental illness or psychiatric disorder is due to too much connections between thalamus and the frontal lobe. Somehow [inaudible 28:47] fiber and those patients would be mental illness free, but the convention lobotomy is very difficult to perform involving remove big piece of skull. So one day he come up with this pretty good idea, you know, and using an ice breaker and a hammer. So he used the ice breaker to push eyeball around. We know that the skull behind eye socket is very, very thin, and they used a hammer to chip ice breaker in and then [inaudible 29:19] this ice breaker violently to cut fiber. Very bad practice.

At the beginning, his ice breaker actually point in this direction. And his patient outcome is, many of the patients actually become, you know, very "numb" emotional [inaudible 29:40]. Try to improve his outcome he deviated and [inaudible 29:44] picture taken in later part of his career he pointed his ice breaker up for the break. And the consequences are even more devastating and many of those patients become crazier. Why that's the case? You can switch back to this slide. We know at the beginning of his career his ice breaker potentially damaged amygdala. As a result of that, you know, patient become numb and have no sense of fear. In later part of career, he might be damaging vmPFC. He might actually further reduce the top-down modulation and the outcome of the patient actually is even worse. And actually many, many patients die during the operation. He performed thousands of cases in the east coast and the west coast as time rolled by. And he made a top 10 list of the worst doctors in history of medicine. Not good list to be on.

So in our research, we try to see, you know, can we address some of the concerns with MEG. And the first xxxx we try to answer the question is MEG source imaging able to detect in the abnormal electromagnetic signal in PTSD neurocircuitry? If yes, at what frequency band because using fMRI in the past we cannot tell in what frequency band these with hyper- and hyposignal. With MEG, there's excellent, you know, in the temporal resolution in millisecond we convert into a nice frequency band we can look at alpha, beta, gamma, high gamma, and low-frequency band. So that more information provided by MEG. And also going to see the similarity between MEG and research and the other, and the fMRI or PET research.

So here's the protocol we have with MEG. Again, resting state MEG with eyes closed. We have 25 active duty military personnel and Veterans diagnosed with PTSD with CAPS score at least 41, so at least have the partial PTSD. We also have HMS and healthy controls, 30 of them. So MEG, looking at different xxxx again, and hypothesis is we're going to see this hyperactivity in amygdala and hippocampus and potentially hypoactivity in vmPFC, and we're going to hopefully see additional error light up.

Here's how we process the data. We, I'm going to talk on the detail with ICA and MaxFilter to remove the noise and artifacts, divide the epoch, entire recording into 2.5 seconds epoch, and within each epoch we run through different frequency and band-pass filter for alpha around 10 Hz, beta between 30 Hz, gamma 30-80 Hz, high gamma 80-150 Hz, and low frequency which is 1‑7 Hz. We performed MEG source imaging and convert everything into the MNI space and subvoxel rhythm transformation and look at the group differences between PTSD and the control and the voxel-wise approach xxxx family-wise error.

Here's the main findings we have in beta band. Anything shown in yellow is the PTSD group higher, hypersignal than controls. Anything shown in blue is PTSD have hyposignal or reduced activity compared with controls. You can see immediately, and these two white arrows point out to the bilateral hyperactivity from amygdala and the hyperactivity from the left hippocampus, exactly the matched prediction from the PTSD neurocircuitry model. And also we see the area in blue, this is vmPFC. We see reduced function in energy activity in PTSD and hypoactivity of vmPFC also predicted by existing PTSD neurocircuitry theory. In addition we see something else because we also see the hypersignal from bilateral over the frontal cortex. Also see profound hyposignal, the blue, from ventral and the dorsal PFC areas. I mentioned in the past the vmPFC send down top-down modulation to amygdala. The ventral and the dorsolateral prefrontal cortex, vlPFC and the dlPFC, also send down top-down modulation in an indirect way to amygdala. So you see those two areas also have hyposignal. In addition was xxxx signal from the precuneus and other region as well. This is a beta band which is 15-30 Hz.

And we also see something similar in the high-frequency gamma, which is top panel, and high gamma band. In the high gamma band we see, again, hyperactivity from the amygdala and the hippocampus, and we also see the hypoactivity from the vmPFC and the hypo also there in the gamma band in multiple slides. This is the high frequency. What about low frequency? Low frequency is shown over here. This is the alpha band, around 10 Hz, and this is the low frequency, 1-7 Hz. So the only two tiny areas show hypersignal showing below here, predominantly by this hypoactivity in alpha and low frequency from the frontal area, ventrolateral prefrontal cortex, and from the dlPFC area and also from the precuneal cortex. I'm sorry there's some background noise from the jet flowing over my head and we're in the airway in San Diego Navy base.

So there's profound reduction in the hyposignal in the alpha band, which actually makes a lot of sense because we know alpha signal is the signal, and with no central input, the brain is relaxing and generates this beautiful 10 Hz oscillation. And for PTSD, even though their eyes closed and is resting state, supposedly resting, the brain is busy. When the brain is busy, they have reduced alpha wave which shows up over here that might be able to explain, they have hard time fall asleep and other issues. So on the, in conclusion for study, what, before we conclude, you know, we also look at the potential PTSD symptom, how the PTSD symptoms correlate with MEG finding.

We find in the beta band we see positive correlation between MEG and source magnitude and the CAPS scores in the left amygdala area. Also in the beta band we see positive correlation between MEG in the left posterolateral OFC with the CAPS scores. We also see that correlation, and with vmPFC in beta and gamma band, and that correlation in precuneus and CAPS scores. But the interesting thing is we look at this area separately, each area, although we see both differences shown previously, but they still overlap between PTSD and healthy controls. So each individual area we cannot use that one as a biomarker for, you know, for diagnose PTSD. However, as a post hoc analysis after we published paper, we look at by combining all this area together, amygdala and OFC, vmPFC, and the precuneus area together, we generate a high-dimensional space with multiple measures, and by using the support vector machine, SVM, now we can actually classify PTSD but 93% accuracy, in healthy control we get 95% accuracy.

So in our opinion, the individual area might not be sufficient to provide the MEG marker for PTSD, but if you combine this area together, look at the signal and the circuitry and entire circuitry with multiple areas together, we probably can actually classify the PTSD from healthy controls where [inaudible 38:41] data try to validate the finding.

And how similar is our finding with other people's research? Here shows fMRI research from the laboratory from Yan and colleagues published in 2013, resting state fMRI because see, again, very nice, you know, hyperactivity from bilateral amygdala and hippocampus just like our MEG finding, and hypoactivity from the vlPFC and precuneus cortex very similar to our MEG findings. Of course fMRI can see something deeper. We also see hypoactivity from thalamus. MEG measures some activity would be quite challenging. So what makes the difference with the vmPFC. We see a big cluster of blue with our MEG finding, but that reduction of hypoactivity is missing in this fMRI research. So this has similarity but also differences between the fMRI and the MEG findings.

So in conclusion, in the MEG fMRI, I'm sorry, the MEG research for PTSD in the beta and gamma band our results show hyperactivity in the amygdala and the hippocampus. Our MEG research showed the signal maybe come from beta and gamma band. We also saw in this hypoactivity in vmPFC, dlPFC, precuneus, and some other areas. We xxxx some robust findings in the hyperactivity in the posterolateral OFC area, and our MEG finding actually highly correlated with PTSD CAPS scores, and also find, our MEG finding are highly consistent with other fMRI and PET research. But MEG will provide more information regarding the frequency of the electric magnetic signal and we're going to see some more areas showing abnormal signal with our MEG research in PTSD.

This slide shows actually the connection between the first topic and the last topic of my talk. The first topic we talked about MEG slow-wave generation in mild TBI, and the third topic we just finished, looking at the abnormal neurocircuitry in PTSD. So we know there's connection there because in the many research published if persisting mild TBI would potentiate the development of PTSD sometimes double the likelihood of PTSD development if the subject have persisting mild TBI. The question is why. In this pilot study we showed before, patient with mild TBI, comorbid mild TBI and PTSD, which this slide shows the abnormal slow wave. Remember when I talk about in first topic, the MEG slow-wave generation. We can see this generation MEG slow wave is not arbitrary. [Inaudible 41:50] we see the slow-wave generation potentially indicate there's injury by TBI in the vmPFC area and also shows, you know, very highly consistent this slow-wave generation in the dlPFC area. And this [inaudible 42:06] we know from our third topic, vmPFC and dlPFC are important areas sending down top-down modulation to suppress the activity in amygdala and hippocampus.

This slide shows mild TBI damage potentially measured by slow wave from vmPFC and dlPFC actually might be the key. So if there's injury in those areas showing this delta wave generation and xxxx reduce the top-down modulation potentially lead to the potentiation of PTSD.

But the last one I want to talk about which is the ongoing research and it's about the mechanism of the slow-wave generation, and for example, you know, what's the question? Is slow wave just a bad thing, and you get xxxx consequences of brain injury or are [inaudible 43:11] would be whether the slow wave is a signature of ongoing neuronal rearrangement and potentially healing process that happened in the said injury.

The answer to any of them will not make difference using MEG slow wave but as a potential biomarker for localized said injury and potentially make big difference. We try to design a therapy, and if the first case is true, basically if the slow wave is merely consequences of that injury and [inaudible 43:42] we design the treatment to try to cancel this out because xxxx go the other way. On the other hand, if the slow wave signature of ongoing repairment of healing process, the treatment would try to facilitate or increase delta wave through the treatment. Eventually when finish the entire course of treatment, bring the slow wave down. So they're different strategies.

So we tend to believe, you know, with more evidence, kind of believe actually the slow-wave generation is not a mere xxxx consequences, actually might indicate some healing process happening in the brain in the said injury. And there's quite a few actually in articles I published over here. Last three of them shows actually in a sleep study by change in the delta wave sleep you can change the consequences of TBI recovery, and during the delta wave sleep the brain actually woke the metabolic clearance process. The brain actually kicks in and cleans up these toxic chemical, for example, the beta-amyloid. And so, you know, at least during the delta wave sleep the slow wave is a good thing associated with metabolic clearance, clean out beta-amyloid and other toxic chemicals. Too much toxic chemical like beta-amyloid actually disrupt the non-REM sleep and stations three and four we see this delta wave pop up, so there's mapped connection between the delta wave generation and the healing process at the xxxx in sleep studies.

Now we try to collect more evidence to see whether we can use that, by facilitating or increase the delta wave in the treatment, we can actually speed up that process. You know, of course, the ultimate goal is try to bring down in the slow wave at end of treatment. But during each treatment might be, you know, facilitating this, that the delta wave generation might be a good thing.

So I would like to thank my collaborator and also want to thank the VA for the many years of strong support for research and also funding agency from DoD, from National Football League, from Brain Trauma Foundation, and [inaudible 45:56], my long-time collaborator, Dr. Roland Lee, Dr. Sharon Nichols, Dr. Deborah Harrington on the TBI work, and my long-term collaborator, Dr. Dewleen Baker, of VA San Diego for PTSD research and also involved mild TBI. And there's other resources you can look at, you know, checking the video and the interview or, you know, national public, National Public Radio interview, and [inaudible 46:22] and the publication from our laboratory, link over here. If any questions, you know, and the comment, please let me know. And thank you so much and I'd like to also thank xxxx for organizing this seminar.

And then I want to, hopefully you can just check those boxes for the polling questions. You can check more than one box, whether you're interested in mild TBI and PTSD diagnosis or treatment, or doing any animal research or human research, or your role is providing support in social working or PTSD/mild TBI. I like to thank you all so much for your attention. I think next one would be the question section. I'd love to answer some questions from you.

Heidi: Excellent. Well, thank you so very much. We do have the poll question up, so for our attendees, please just select as many responses as applies to you. And it looks like we've got the majority of votes in, so I'll go ahead and close this and share the results real quick before we get into the Q&A. So it looks like 54% of respondents would like to, or are interested in diagnosing TBI and PTSD, 62% in treating it, 8% animal research regarding TBI and PTSD, half of our respondents also selected human research, and 23% social work or other support TBI and PTSD. So thank you to those respondents, and I'm going to turn it back to your screen while we do the Q&A, so just click show my screen one more time please.

Dr. Mingxiong Huang: Alright.

Heidi: And we do have lots of great questions that have already come in. If anybody wants to submit a question, just use the question section of the GoToWebinar control panel on the right-hand side of your screen. Click the plus sign next to the word questions. That will expand the dialogue box and you can submit your question or comment there. And actually, Mingxiong, can you go back to your contact info slide. We'll just leave that up. I think it's the very last one. Just click on it one more time.

Dr. Mingxiong Huang: Oh, the contacts. This one?

Heidi: Yes. Just wanted to get your, I'm sorry, the one with your email on it. There we go. Perfect. Ok, so the first question came in pretty close to the beginning. How did you go about testing the healthy control data prior to adding the study? That is, did you get consent from the healthy control? Please describe the process you went through since my colleague is doing normal control using EMG.

Dr. Mingxiong Huang: Oh, yeah, for the healthy control, you know, both healthy control and also mild TBI patients signed a consent form approved by the VA. And the MEG research was considered to be minimum risk because MEG is totally noninvasive and imaging, functional imaging technology. There's no radiation come from the MEG scanning, so we can perform the measurement many times, and only requirements is the subject cannot have too many metal objects in their body. The metal object will generate potentially large artifact, would contaminate the energy signal. So, but other than that, MEG is totally noninvasive, risk free to the subjects, so we have no issue getting the consent and getting xxxx approval for healthy control subjects.

Heidi: Thank you. The next question. I might pronounce this word wrong, so I apologize. Is there a difference in sagittal sections of the frontal cortex between the different symptoms?

Dr. Mingxiong Huang: So we use both sagittal and also the axial views, and I just try to highlight different subjects xxxx for the abnormal slow-wave generation. And it's just for convenience. Sometimes we use axial views, sometimes we use sagittal views, sometimes we use both, and in some cases we use three views, axial, sagittal, and coronal. That's for, you know, for demonstration purpose. And depend upon the location of the foci, we're going to choose which view to use. In some cases we also use the, you know, the FreeSurfer way. FreeSurfer is a free package, you know, mgh. You can inflate the brain like a balloon so you can see all the sulcus and gyri at the same time. Sometimes we also see the brain, the MEG abnormal slow wave on top of the inflated brain surface so you can see this one, it's one view. So those views are just to select, to highlight the location of the injury. And depending on the injury we might pick up, you know, axial or sagittal view.

Heidi: Thank you. The next question, can you talk more about why you think increased functional connectivity sometimes predicted better neuropsychological test performance and at other times worse performance?

Dr. Mingxiong Huang: That's a very good question. So, you know, in my slide we see there's, we show there's three potential competing mechanisms associated with functional connectivity. And for increased functional connectivity, xxxx due to, you know, functional reorganization or compensatory mechanism. Basically the brain tries to compensate for the loss of function by recruiting alternative pathway. So if that's the case, if where we see increased functional connectivity in some of the alternative pathway that was recruited after the injury and we can predict, in this case the recruitment of this alternative pathway will likely predict better outcome. So in that case we see positive correlation, and the increase I see will predict better cognitive performance. But there's another, there's one other mechanism for increased FC potentially will be these GABAergic disinhibition. The injury to the GABA-interneuron might actually produce over-excitation. In some cases, might lead to posttraumatic epilepsy, but many cases even though it's not epilepsy but there still be in a lot of firing due to the lack of GABAergic inhibition. So in that case the increased FC, because this firing might be a bad thing. You know, so that's the reason we think using functional connectivity, typically with the increased functional connectivity, we have been taking into consideration multiple competing mechanisms. It's not always a good thing or always a bad thing, and depend upon the nature of injury, of ultimate mechanism of recovery. And so that's why using FC potentially as a biomarker for mild TBI has been quite challenging. In one of my slides the fMRI research there showed increased, decreased and sometimes same study some area showed increased FC, some area show decreased FC or similar situation showed in our study and other MEG functional connectivity research, in this mild TBI patient populations. So be very careful using FC, you know, as a tool for measure something abnormal in mild TBI population.

Heidi: Thank you. The next question, for MEG, is ink used in tattoos a safety concern?

Dr. Mingxiong Huang: It's not a safety concern and depends upon the location of tattoo. If a tattoo is too high, say, on the face area, anything above shoulder, but in some cases might produce a large artifact and the channel becomes very noisy and will not cause any risk to the subject. MEG is totally a passive monitoring device like EEG and will measure the magnetic signal from neuron. It's very passive. The sensor is very sensitive, using what's called a SQUID sensor, the superconducting quantum interference device, and needs to be cooled down into the liquid helium temperature, 4-5 degree xxxx. The image sensor totally noninvasive, so the tattoo would not generate any risk to the subject but potentially contaminate the recording. And we have to do, in some cases, using hardware and software that cancels out those artifacts, but in many cases, artifact too strong. We just cannot use the data.

Heidi: Thank you. You emphasized that MEG was useful at the individual case level for diagnosing conditions. Is MEG widely available in VA hospitals? How expensive is it to add to a research protocol? Do you recall the cost per person?

Dr. Mingxiong Huang: Good question. You know, there's about 30-plus xxxx MEG systems in the US, many in the major city area. And there's many in the East Coast and there's three or four in the West Coast, many of them in the middle part of the country, and also in southern part [inaudible 56:37] in Texas. There's not, you know, in the VA, MEG system inside the VA, but there's, many VA systems have access to the MEG system and people in the university. The system we have is sitting in the UCSD campus which is only, you know, 1.5 miles away from the San Diego VA Medical Center. The MEGs have been used routinely in clinical diagnosis, patient with epilepsy, and also for functional localization, and for pre-surgical mapping if the patient with brain tumor. It's new area with MEG for mild TBI and PTSD. The cost for research scan in xxxx center is quite similar, about $500 to $550 per hour. But for clinical diagnosis, the price is much higher. For example, for making a diagnosis patient with epilepsy the insurance company, based upon the CPT code, paid us in neighborhood, for Medicare, you know, $2,200, insurance company up to $5,000, $6,000 dollars per clinical case. So that's a different price for clinical diagnosis versus research.

Heidi: Thank you. Can some of the white matter change relate to cortical gray matter damage as a secondary retrograde change?

Dr. Mingxiong Huang: The white matter damage in our study, we believe, might lead to the slower generation, and that's why, you know, in about 25% of the cases when we see damage in white matter tissue we measured with DTI we see reduced FA, and the 25% to 30% of cases we also see, you know, of course the generation of MEG delta wave from the gray matter neuron. But the other cases, you know, we see slower generation in the cortical gray matter neuron, but we don't see underlying abnormal signal from the DTI. So the reason of that potentially there's additional mechanism. I mentioned in another source for slow-wave generation can be, you know, chemical damage with a limitation or blockage of acetylcholine in the cholinergic pathway that might also lead to slow-wave generation after TBI. But because it's not physical damage in those cases with abnormal, you know, chemical injury, and the sensitivity using a DTI or other structural image technology to see something abnormal will be small. And we believe, you know, why the MEG we see about 85% sensitivity or DTI white matter measure shows about 25% to 30% in sensitivity is because MEG we measure both the consequences of physical damage for the white matter axon as well as additional neurochemical injury. For example, limitation or blockage of cholinergic systems.

Heidi: Thank you. Just a few more questions. I know we're at the top of the hour. Are you able to say on?

Dr. Mingxiong Huang: Yes.

Heidi: Ok. Excellent! Thank you so much. For attendees, if any of you do need to leave at the top of the hour, as I said, once you exit the session, please wait just a second and fill out the feedback survey when it comes onto your screen. Ok, the next question, have you analyzed MEG on Veterans with multiple brain injuries and PTSD? If so, are there differences from those with single injuries?

Dr. Mingxiong Huang: Great question. So we have looked at the data. We're in the middle collecting more information trying to study the relationship between multiple TBI and the slow-wave generation. And the study has not been finished, but you know, I can tell based upon the data we have, people with multiple TBI, the pattern of slow-wave generation tend to be more diffuse. You know, in case of just one single injury we tend to see maybe one or two foci with slow-wave generation, but people with multiple injury you can see there's many more areas show the slow-wave generation. One of the case, you know, the 17 years, in the football player I show in my presentation, this patient had three mild TBI. You can see slow generation can be from deeper hemisphere. One of them is left posterior temporal, another one is multiple area in the right hemisphere, the ventral, temporal, and occipital areas. So potentially people with multiple mild TBIs, the damage tend to be more diffuse.

How does one potentiate PTSD is another interesting question, and in my presentation I show there's four cases with comorbid mild TBI and PTSD. In those four cases, and with the common signature basically slow-wave generation in the vmPFC and the dlPFC regions. Those two regions I mentioned can send down top-down modulation to amygdala and the neurocircuitry. So we believe in multiple mild TBI, the likelihood to injure vmPFC and dlPFC is higher. So potentially in those people with multiple TBIs might become more vulnerable for developing PTSD, so the more TBI with multiple injuries, multiple, you know, mild TBI, might actually potentiate with even higher likelihood of developing PTSD.

Heidi: Thank you. Were all PTS subjects without a history of TBI?

Dr. Mingxiong Huang: In the third study we have 26 PTSD and 22 healthy controls. None of them, none of the 26 PTSD patients had mild TBI. So those cases, you know, we choose the ones with PTSD only, at least that don't have ongoing symptoms and don't have, they don't meet the criteria for mild TBI diagnosis. Basically the three criteria is by the VA, basically loss of consciousness less than 30 minutes, and the posttraumatic amnesia less than 24 hours, if there's any, you know, and the GCS score, the GCS score will be from 13-15. So none of the subjects in the PTSD group in our study meet this criteria, so we believe the 26 PTSD subjects did not have mild TBI.

Heidi: Thank you. We just have two questions left. Does inflammatory cells contribute to the slow-wave signal?

Dr. Mingxiong Huang: Yes. So the, of course, the inflammatory process might trigger xxxx in multiple neurotransmitters, so [inaudible 1:04:51] mechanism how that would affect the slow-wave generation is not quite clear. But there are studies shows, you know, people with inflammatory mechanism and [inaudible 1:05:03] generate, you know, the slow wave. So I think the answer is yes. In one of the, my last slide shows, you know, where the slow wave by themselves is a pure, you know, bad consequences of head injury or potentially either use the one, you know, for potentially as a signature of ongoing repairments in our neural reorganization or potentially healing process. And so in that case you can think about the slow wave just like a fever. Fever not always a bad thing. Fever indicates something is wrong with the body, but a fever might indicate the body trying to do some repairment. So, you know, we think the slow wave can play role like a fever. Might indicate there's ongoing brain reorganization or repairment of healing process happening on the site of injury. So that actually might open the door for potential treatment. If you can think by facilitating the slow wave on site of injury you can potentially speed up the healing process. Eventually you bring down the slow-wave generation, the inflammatory mechanism, and end the treatment. So to improve that, we always want to see reduction of slow wave, but during the treatment you might want to actually, it's not cancels out the delta wave, you might want to actually facilitate or increase the slow wave to speed up the healing process.

Heidi: Thank you. And the final question, is there any overall difference between blast mTBI and mTBI due to impact or acceleration?

Dr. Mingxiong Huang: Another great question. In our research, we were not able to see a clear-cut difference between blast mild TBI and non-blast causes due to motor vehicle accident and a sport injury and fall. The reason would be, it's very difficult have, in blast mild TBI only cause damage by the primary shock wave because always secondary and xxxx injuries, you know, follow the primary shock. In the secondary and the higher order injuries, the nature of the injury pretty much similar to the non-blast injury, and we, in our data [inaudible 1:07:38] some cases we see difference, but overall the difference actually is quite small. So far we have not seen a clear signature just related to the blast injury. So you know, for the paper we published and the data we have so far with the MEG findings, looks, you know, we cannot tell if there's a clear difference between blast mild TBI and non-blast mild TBI because there's other, and process follow the blast wave that's very similar to the non-blast nature of the injury.

Heidi: Thank you! Well, that is the end of the Q&A, but I do want to give you and Dr. DePalma an opportunity to make any concluding comments you'd like. Ralph, did you want to kick things off?

Dr. Ralph DePalma: Well, I would like to compliment Dr. Huang on, Mingxiong, on really an excellent and nuanced detailed presentation, and we're looking forward to hearing more from him in the future. Thank you very much!

Dr. Mingxiong Huang: Thank you, Ralph, so much for the invitation and for allowing me this opportunity to give this presentation and support and many, many years by the VA as research funding. So I really appreciate the strong support from VA for mild TBI and PTSD research. If anybody have any questions, you're welcome to send me email at mxhuang@ucsd.edu, and thank you all so much, and thank Marty[sp?] for organizing this web seminar.

Heidi: Thank you! It was my pleasure, and I appreciate you coming on and lending your expertise to the field. And of course, thank you to Dr. DePalma for organizing this and all of our TBI Cyberseminars. We do have several more coming up, so please keep an eye on your emails and sign up for those. And with that, I am going to close out the session now. So everybody please take just a moment and fill out the feedback survey that will populate on your screen. So thank you, once again, everyone, and have a great rest of the day.

[ END OF AUDIO ]