Vanderbilt Audiology Journal Club: Vestibular Update - The Inion Potential

Recorded December 7, 2022

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- [Christy Huynh] Welcome back to the classroom, everyone. It is my delight to welcome back a wonderful esteemed group from the Vanderbilt University Medical Center. We have Dr. Gary Jacobson, Dr. Richard Roberts, and Dr. Daniel Romero. We're gonna hand it over to you now, Dr. Jacobson.

- All right, well, thank you very much. As always, I want to thank Continued for inviting us to present some of our research in the context of new developments in the assessment and management of vestibular function. Today, not to tip our hand, you know, too early, but the main topic today is going to be in evoked potential that actually may be originating from the vestibular cerebellum. So if this actually pans out to be what actually could be, it could be really a revolutionary change in clinical evoked potentials. And again, I want to thank Christy and Kimberly for all of your hard work. You make it look simple. When I think of continuing education activities, I think of this company.

You just simply, what is the lyrics? Simply the best. So I think we have some disclosures. And you see a lot of words in the disclosure slide. And the words actually, the sum of the words is we have no conflicts. So that's good. These days, that's really good. And we'll go through the learning objectives here. After this course, participants will be able to, you should be able to name the sonomotor responses that can be recorded from the head and neck in response to auditory and non-auditory stimuli. Second, we should be able to, or you should be able to describe how successful investigators have been, on average, recording the inion potential. Third learning outcome is you should be able to discuss the effects of gaze and head position supporting the likelihood of a vestibular cerebellar evoked potential.

And lastly, the last learning outcome, should be able to describe basic stimulus and recording parameters for the vestibular cerebellar evoked potential. So what I thought I would do is, since I'm the oldest one in the group, is to sort of create a historical

framework for the inion. It's actually called the inion response or inion potential. And this is a paper that was published in 1971. So that was its first appearance. And what we're going to find is that the early investigators felt that it was likely that this new evoked response originated from the vestibular end organ and specifically, the saccule. And this paper I'm going to review was published in 1971. The investigators were Townsend and Cody. So the story of the inion potential begins in the late 1960s and early 1970s.

And at that time, the campuses all over the United States were in turmoil over the Vietnam War. And we were attempting to develop EEG techniques to estimate audiometric thresholds. In particular, investigators were using long latency, cortically generated evoked responses for threshold estimation. However, those responses were dependent on subject state. And by that, I mean something as simple as fatigue could actually abolish the response. In the late 1960s, a different class of both potentials were described. And they were referred to as fast responses because their peak latencies were in the range of about 10 to 50, five, zero, milliseconds. Now, the MLR, the middle latency response is an example of a sensory evoked potential that was in the fast range.

And just remember, you know, it would still be a few years before the auditory brainstem response had been discovered. There were at least four evoked potentials that occurred in the zero to 50 millisecond time period. At least three of them were sound evoked muscle responses referred to as sonomotor or sound muscle responses. Like auditory sensory evoked potentials, they could be evoked with transient signals like clicks and tone bursts. The fourth response appeared, at least to me, to be the middle latency response. The three sonomotor responses included a sound evoked response recorded from the masseter muscle, and that was referred to as the acoustic jaw reflex. A response recorded from the postauricular muscle, and that's the muscle that if you contracted, you can wiggle your ears.

There are some people who can, some people who can't. And I fortunately or unfortunately can. And the last response was a response that you would record from the bump on the back of your head, which is called the occipital protuberance. And that evoked response was called the inion response. It would be later in the mid-1990s and mid-2000s before we would witness the discovery of the cVEMP and the oVEMP. The best stimuli for eliciting these evoked potentials often were identical to the evoked stimuli, evoking stimuli used to record the other sonomotor responses. And these were unfiltered clicks or low and mid frequency acoustical transients. And what differed between studies was where the active and non-inverting electrode were placed.

That variable determined which of these fast responses would be extracted from the electrical noise. The focus of our presentation will be the inion response that was identified in the late 1960s and then faded into obscurity until just a few years ago. So we're talking about evoked response and evoked response that was discovered almost 45 years ago and had a brief sort of coming out and then disappeared until the last couple of years. Cody and Bickford in 1969 demonstrated that the inion response was recordable from the occipital protuberance. And further, Tabor and colleagues, also in 1969, suggested the response could be used to assess vestibular function. Although it was reported that the response correlated poorly with the results of caloric testing.

That alone suggested to the investigators that the response either was vestibular and generated by the otolith system, or the response was not dependent at all on the function of the vestibular system. The authors assembled illustrative case reports that they hoped would help determine the neuroanatomic origins of the inion potential. Now who are these two gentlemen? This gentleman is Dr. Mike Metz. And Mike Metz taught at Cal State Fullerton in the early 1970s when I was an undergraduate student, and he actually got me interested in audiology. So since he was a co-author on that paper, I

thought I would just throw that in as maybe a little bit of interest. So through the 1960s, no one had studied the inion response in pathological conditions.

And Townsend and Cody in 1971 suggested a link existed between the inion potential and the saccule. However, there was no published work exploring that hypothesis. Accordingly and as shown here, the purpose of the investigation was to identify the end-organ receptor for the inion response when it was evoked by acoustical stimuli. So what were methods that were used in the original papers to record this response, this inion response? What's shown in this slide are characteristic examples of recording parameters for the inion response. An active electrode was usually placed at the occipital protuberance. The reference electrode was placed at the tip of the nose and the ground electrode was placed at the mid-frontal location. Approximately where Fpz is located.

Stimuli were usually mid-frequency burst, presented at a rate of about two per second and at a high intensity. One interesting wrinkle in their paradigm was the use of three pounds of traction to increase the muscle tonus of those of the cervical musculature that actually attaches to the occipital protuberance. The investigator's intention was for the high intensity tone burst to interrupt the ongoing muscle activity, much like occurs for the cVEMP. And this device and referred to as a Mnemotron, was the first of the signal averaging computers. At that moment in time, the signal averaging computer didn't exist. There were actually some aiding computers that existed. So this is actually the first of the signal averagers that made it possible for researchers and clinicians to extract from the EEG and EMG stimulus synchronized changes in the EMG and EEG that became evoked potentials.

This table adapted from Cody and Bickford shows the mean peak latency of the inion response, it was about 14 milliseconds and there were no ear effects. The first negative peak of the response was referred to as the A wave, and it occurred in normals at

about 10 to 15 milliseconds post-stimulus onset. The second negative peak was referred to as B wave. It occurred later in range of 25 to 31 milliseconds. And occasionally, according to the investigators, there was a C wave and a D wave, but that varied from subject to subject. Stimulus intensity had be well above the subject's threshold for that inion response to appear. And flexing the neck increased the amplitude of the response. And this is actually your first look at the inion response.

And if we look at the bottom right tracing here, there's a couple of things I just wanna draw your attention to. First thing is a negativity, a negative deflection actually is a positive. So a negative deflection, a downward deflection is actually a positive polarity waveform and an upward deflection is a negative polarity waveform. So what we're looking at here is negative at about 14 milliseconds. That's what the investigators would've referred to as the A wave. And this wave form here, the second negative deflection is about 29 milliseconds, and they would've referred to this as the B wave. Why do some people represent negativity as an upward deflection? It's just an artifact of the way neurophysiologist represent electrical potentials of the brain.

This is a table adapted from the original article just showing that lower frequencies and mid frequencies are associated with a higher percentage of presence when they're evoked. Now these are a couple of many case reports that help clinicians understand the origins of the inion response. The subject was a 59-year-old male with normal hearing and bilaterally absent caloric responses and absent rotational responses. Caloric responses were absent due to streptomycin therapies. Inion responses were present bilaterally. It's known that the effect of streptomycin is to destroy the sensory epithelium, but selective to the semicircular canals. 90% of the hair cells were destroyed. Sensory cells of the utricle and saccule were spared. And these findings suggested that the inion response originated from the utricle or saccule.

This second example was a 36-year-old male with a normal right ear and endolymphatic hydrops affecting the left ear. Caloric testing elicited a normal response from each ear, and average inion response was evoked with 1,000 hertz tone burst at about 110 dB SPL, presented to the normal ear. And no inion response was observed on stimulation of the ear with endolymphatic hydrops. The response shows a bilaterally normal caloric test and an absent inion response in the ear with endolymphatic hydrops. So what is shown here in this slide is a summary of the results from the Townsend and Cody paper. Both vestibular neuritis and vestibular nerve sections abolishes the response. And that finding suggested that the inion response is vestibular and not an auditory evoked potential.

The inion response could be recorded with an acoustical stimulus even from deaf patients. And this suggested that the inion response also was vestibular. Administration of curare, which is a paralyzing agent, almost completely abolished the response. And this evidence suggested the response was myogenic in origin. It was possible to record the response in a patient with no semicircular canal function due to streptomycin toxicity. And this finding suggests that the inion response probably is saccular or utricular in origin. And lastly, it was possible to record the response from a patient with endolymphatic hydrops but who had normal caloric responses. And this finding suggested that the inion response originated in the utricle or saccule as a source and probably the saccule, primarily because endolymphatic hydrops affects the saccule more often in a higher level of severity than the utricle.

And with that, if you wanted to do a little bit of sleuthing and read the original articles, this would be a good set of articles for you to read to develop some background. What I was very surprised about was the lack of detail in the description of how these waveforms were recorded. And what we're going to hear about in the next two speakers are the results of contemporary research, including work done in our lab, looking in detail at these inion responses. So at this point, I'm going to turn things over

to Richard Roberts, who is my esteemed colleague. And he will discuss a more contemporary publication describing the inion potential.

- Thanks, Gary. The obvious connection to Gary's paper is that the inion response was also recorded in this paper by Todd et al. However, the inion response was just one of many they recorded in trying to better understand if there is a way to measure a vestibular cerebellar response with air conducted stimuli. There's a lot to unpack in this paper and my goal is to cover the main points. The interested reader would do well to review this work possibly a few times because there's so much covered. The main purpose of this investigation was to simultaneously record several vestibular evoked potentials to determine if there really is a cerebellar and specifically, vestibular cerebellar contribution. So that was the main goal or purpose.

And it's well established that cervical VEMP amplitude increases with sternocleidomastoid muscle contraction. We all are aware of that. That's why it's important, for sure, in research applications and potentially in clinical applications to monitor SCM EMG activity during acquisition of cVEMP responses. There's a certain myogenic or muscle contribution to that response. It's also well established that ocular VEMP amplitude gets larger as you avert the eyes from straight ahead to upward gaze. Like the sternocleidomastoid muscle in the cVEMP, this is an effect of extraocular muscle contraction, specifically the inferior oblique of the eye, contralateral to the stimulated ear. Being completely honest here, my understanding has always been that directing the eyes of the patient upwards, not only increases contraction of the muscle, but decreases the distance between the muscle and the recording electrode, and that's what helps generate a larger amplitude oVEMP response.

However, there's at least some evidence from Todd et al 2012 that the larger amplitude may relate to a cerebellar influence on the otolith ocular reflex, which is measurable with the oVEMP. Further, Angelaki has shown that gaze modifies. So looking upward or

downward modifies otolith organ-driven the vestibulo-ocular reflex, VOR gain. So think utricle and saccule. The connections are present to support the cerebellar influence. Todd et al 2012 suggested the cerebellum exerts an inhibitory effect on the extraocular muscles to keep them directed straight ahead. To avert the eyes upward requires a release or decrease in the magnitude of cerebellar inhibition so the extraocular muscles can contract more. And in effect of that greater contraction, which is related to the decreased cerebellar inhibition, can be measured as a larger oVEMP response.

This leads to the assumptions that are underpinning the study that I'm gonna talk about. If recorded responses are modulated by eye positions like the oVEMP, there's more likely to be some cerebellar contribution, and so those vestibular related potentials would be more likely to be neurogenic or sensory. On the other hand, if recorded responses are modulated by head position, recall that neck muscles move the head, then the vestibular potential is more likely to be muscular or myogenic. As we look at the methods, there were 11 youngish subjects in the study. And yes, I see the age range goes up to 53, but I'm 53 so I think I can still pull off youngish, but maybe not for too much longer.

All subjects denied vestibular hearing impairment and all had bilaterally present cVEMPs, cervical VEMPs. Stimuli were 500 hertz tone pips presented around 130 decibels peak sound pressure level. The investigators recorded from electrode locations all over the scalp, so 64 channel EEG, but also under the eyes, so infraocular electrodes and onto the neck muscles, the splenius muscles. Some electrode sites were considered more closely, and we're gonna get into that. This figure is just to remind us all the location of the splenius muscles. These electrode sites are referred to as the CB electrode sites for this current investigation. There are certainly more details on methods in the paper, but here are some additional key points, I think, we need to cover. There were three gaze position tasks that were considered with the head kept neutral for each to decrease the potential for neck muscle influence.

They were zero degrees horizontal, straight ahead, eyes up 20 degrees, and eyes down 20 degrees. Recall the assumption is that eye position changes should modulate sensory responses with less myogenic interference. The investigators also had head position conditions of head up and head down plus or minus 20 degrees but with the eyes kept in a neutral position to determine effects of neck muscle modulation on the responses. Again, the assumption is that changes in responses with change in neck muscle contraction would suggest a myogenic response. Electrodes were at all these locations shown, but there were specific interest in the infraocular sites, which are labeled IO1 and IO2 and are shown in red here. This should measure the oVEMP response. Sites PO7 and PO8, circled in green, referred to parietal-occipital locations, which are just above the cerebellar hemispheres.

We will see there may be some support that this is a good recording location for a vestibular cerebellar potential. Site CB1 and CB2 marked in blue represent locations on the splenius, and this represents really a cVEMP-like response. Location Iz, you see right here in purple, marks the location of the inion. And so we can record the inion response like Gary was talking about previously from that electrode. As we move on to the results, a very interesting overall result was observed, looking at the grand means of the averaged evoked EEG activity. There's a marked lateralization of response activity at the posterior occipital electrode sites, which as you recall, are just above the cerebellar hemispheres. If we consider latencies of 10 and 17 milliseconds post-stimulus.

Right ear stimulation, which you see on the right panels, right ear stimulation led to greatest activity in the left posterior area, PO7, while left ear stimulation, shown kind of in these middle panels, created greatest activity in the right posterior occipital area, PO8. Both the head and the eyes are in a neutral position and what you're looking at right here, which should have led to minimal neck muscle contribution and maximum

cerebellar extraocular muscle inhibition. Just like Jacobson described, we can see multiple evoked potentials recorded from various electrode sites in response to the same stimulus. And the waveforms are shown here. You're looking at grand mean waveform data here. Waveforms on the left side of the figure represent responses ipsilateral to the stimulated ear while waveforms on the right side represent responses contralateral to the stimulated ear.

There are a few noteworthy results. First, we see the oVEMP response from the infraocular electrodes up in this region, and that's along with an opposite polarity response in the posterior occipital region, still occurring at the same latencies. And we even see a response in the CB electrodes, again, at the same latencies. Overall, waves seem more prominent for recordings contralateral to the stimulated ear and that was irregardless of if it was right ear stimulation or left ear stimulation. So the amplitudes are larger over on this side. There's also an inion response recorded. So you see this down in this area from the Iz electrode. Let's look a little closer at some of the waveforms, but also the amplitude data related to the eye gaze and head position conditions.

I've combined a few of the figures here to try and make things a little easier to see. Gaze effects on amplitude are in the left panels over on this side. So A, that area. And head position effects are in the right panels. This B side. If we review the infraocular electrodes, so that would be the top row, the top wave forms right here, we see that there was a significant effect of gaze with gaze up having the largest response. So here are the gaze conditions, and this little insert panel shows that we get the smallest amplitude at both N10 and P17 with gaze down, and then it increases some in gaze neutral, and then we get the largest amplitude with gaze up.

And we also see, if we look across the head position, the head position really did not impact the response that we're seeing in the infraocular electrodes, this oVEMP

response. So that was what would be expected. Considering the posterior occipital site, so this is the second set of waveforms we have, there's also a significant effect of gaze that you see but with largest amplitude really in neutral gaze. That's where we've got the largest amplitude for both of the waveforms. There is a head position by waveform interaction also with neutral head position enhancing the N17 wave more than the P10 wave. However, one might suggest the results look fairly similar for head position, head position on the right side, and gaze position on the left.

If you look overall, we just see that gaze down or the head down position does have a little bit more of an effect on N17. If we go down one more, then these are the responses from our CB electrodes or the splenius muscle sites. And there really is no effective gaze there. There is a head position by wave interaction that is even more obvious in this panel with the highest magnitude P17 in the head down position. And in 10, that would be this response, the lower response, the triangles really looks more like the posterior occipital electrode responses, amplitude responses for both gaze and head position with the neutral head position, giving you the largest response. It's also particularly noteworthy that the CB task effects are almost identical to those recorded from Iz and shown in the bottom panels as the inion response.

The inion amplitude is depicted in the panels off to the side with the filled squares. Those are our inion amplitude responses. There is minimal effective gaze on the inion response, but there's a pretty clear effective head position on the inion amplitude that's similar to the P17, so this response from P17 in the CB waveform. If we look across all responses, you can see a bit of an effect even in the waveforms with the light gray traces, which are a little bit more challenging to see. There seems to be more gaze effects, so more cerebellar inhibition on 10 millisecond responses, so the earlier waveform, and more head position effects, so neck muscle effects on the 17 millisecond waveforms. And then the other result that we see here is the splenius and inion responses tend to modulate in the same way.

So what are we seeing in their data so far? There's an area of large magnitude activity at the parietal-occipital area contralateral to the stimulated ear. That's true for all lateral recording electrode sites. The infraocular electrodes are recording an oVEMP response when an expected large gaze effect on amplitude, but with no effective head position. The authors indicate this represents a release of cerebellar inhibition. CB splenius recording sites are similar to a cVEMP response from the sternocleidomastoid muscles. There's no gaze effect, but there is a head position effect. The authors indicate this should be a myogenic response, especially for the 17 millisecond wave. Importantly, this response from the cervical muscles modulates with head position just like the inion response and just like our responses from splenius.

The posterior occipital waveform amplitudes are greatest in neutral gaze and neutral head position. If the authors are correct about this response reflecting cerebellar inhibition, then greatest inhibition and largest amplitude may be expected in these neutral conditions. Specifically the authors state the large amplitude P10 is associated with increased cerebellar inhibition in neutral gaze. Overall, we may have more gaze effects for 10 millisecond waves and more head position effects for 17 millisecond waves. The second major part of this investigation was something called Brain Electrical Source Analysis or BESA. Basically, and I am very much simplifying this so I can understand it, all of the recorded data was analyzed using the specialized software. Since the generators of the oVEMP are known, those data were included in the algorithm, which is helpful in deriving the best fit for the generator sources.

We got to recognize that there are many assumptions when you complete this type of modeling and it's important that we understand that. It's also very complicated. And if you have specific questions about BESA, I would suggest that you email Gary Jacobson because he loves to answer those. Using the BESA analysis on their recorded data, the investigators determined that the extraocular muscles plus three

other electrical fields or dipoles provided the best fitting model. That model had the smallest residual variability. This is outlined in red for you in table three. So you see the RV in this column, that's the residual variability. That model indicated that in addition to the extraocular muscles which contribute to the oVEMP, there were generator sites from the contralateral cerebellum, the ipsilateral cerebellum, and the cervical muscles.

Figure eight is very interesting because the wave forms from the electrodes of interest are shown in column A along with MRI localized generators in column B in corresponding BESA generators in column C. For the infraocular electrodes, we see the two blue waves have a prominent contralateral extraocular muscle contribution or generator site. That's the inferior oblique. The red infraocular wave right here actually has a small ipsilateral extraocular muscle generator. In purple, we see an ipsilateral cerebellar contribution to the N7 wave. So N7 and then here's the N10. And that's close to 10 milliseconds, obviously. That's in the CB splenius trace, and it's the earlier waveform. Though smaller than in the PO waves, BESA results suggest some cerebellar contribution in this CB splenius responses, just ipsilateral cerebellum.

The other CB response is at the bottom in brown. And this is the main cervical muscle contribution with a positivity around 13 milliseconds, which is cVEMP-like, but this is coming from the splenius muscles. Finally, and perhaps most important to the investigation, there is a large contralateral cerebellar generator site for the 10 millisecond positivity recorded at the posterior occipital electrodes in which is shown in green. That's the contralateral cerebellar source. Looking more specifically, an N10 P17 waveform was recorded from the infraocular electrodes, this is the oVEMP, with largest contribution from contralateral extraocular muscles, inferior oblique, and some contribution from ipsi-extraocular muscles. This response is modulated by gaze as expected, but not so much with head position. So Todd et al would suggest there's a strong sensory component occurring related to cerebellar modulation.

It's important to remember that the response is being recorded from muscles. So another way to consider these data is that to move the eyes up. To get the most inferior oblique contraction, you must have a release of cerebellar inhibition that is otherwise attempting to hold the eyes straight ahead at zero degrees. For the splenius muscle electrodes, we see a couple of interesting results. First, there's a negative wave at seven milliseconds with a BESA generator site of ipsilateral cerebellum. So a sensory component. Gaze effects in the graph appear minimal. But considering the amplitudes under various conditions, there is a pattern inverse to the PO, P10 results. There's also a positive wave at 17 milliseconds with a cervical muscle generator.

As you would expect, head position influences this component with head down, especially. The results here suggest this is more of a mixed response with a sensory slash cerebellar contribution at N7 in a myogenic contribution at P17. This is interesting because the responses here are very similar to the inion response and Todd et al suggests at least early components of the inion response could be sensory. These electrodes at the posterior occipital sites are over the anterior cerebellar hemispheres and those are the locations with the largest activity in the neutral position. There's a large positive wave at 10 milliseconds and a negative wave at 17 milliseconds. P10 is modulated with gaze in its largest at neutral gaze with neutral head position.

This is where you would expect the greatest cerebellar inhibition and potentially the largest cerebellar response. As the eyes look upward or downward, there needs to be a release or decrease of cerebellar inhibition on the extraocular muscles to allow for adequate contraction to move the eyes. So the P10 gets smaller in those cases. There's actually a similar response pattern when the wave amplitudes are considered with change in head position. Could this reflect a similar change in inhibition to allow neck muscle contraction? It does seem possible. To view these results one last way, we can see that largest N10 of the oVEMP occurs with gaze up, the gaze up condition. There is a similar increase in N7 of the CB electrodes, reflecting ipsilateral cerebellar

influence, may be excitation, but there is a decrease in P10 of the PO electrodes from reduction of contralateral cerebellar inhibition.

P13 of the splenius muscles is really unaffected because the neck muscles are not changing in these task comparisons since the head is kept in the neutral position. Now in these waves, the eyes are maintained at zero degrees while the head is positioned upward or downward. N10 of the oVEMP is really not changing, which is what we would expect. N7 of the splenius muscle electrodes, so here's your N7, are larger in the head up or head down conditions, or there could be a need for excitation of the cervical muscles from ipsilateral cerebellum. P10 of PO electrodes doesn't really change much for head up and neutral, but there is a decrease in amplitude for head down, which should correlate to a decrease in cerebellar inhibition and the largest amplitude P13, so on this panel, from the CB electrodes does occur there.

These results to me, at least, suggest cerebellar inhibition is modulating extraocular muscle activity as well as cervical muscle activity. Both the N7 of the CB electrodes and P10 of the PO electrodes seem to reflect cerebellar activity. The work of Todd et al indicates a likely vestibular cerebellum potential can be recorded from the posterior occipital area, which, again, is just above the anterior cerebellar hemispheres. There's a primary positive wave at 10 milliseconds and a negative wave at 17 milliseconds. The BESA identified generator source is the contralateral cerebellum and the response amplitude is largest for the electrode contralateral to the stimulated ear. The response amplitude is largest for neutral gaze in head position. Presumably, these conditions would be expected to generate the largest cerebellar inhibition and thus should be a sensory response.

There's another likely cerebellar potential recorded from the splenius muscles with primary negative wave at N7 and positive wave at P17. The BESA identified generator source for N7 is the ipsilateral cerebellum, and the response amplitude is smallest with

neutral gaze and neutral head position. This could suggest it's an excitatory cerebellar response. The N17 is from the neck muscles. Given the close association between the potentials from the CB electrodes on splenius muscles and the inion response recorded from Iz, there could be some sensory cerebellar contribution to the inion response for the earlier waves, though the later waves are myogenic coming from the neck muscles. The results here by Todd et al or interesting enough that more work is needed to confirm and explore these likely vestibular cerebellum responses. And Daniel's gonna talk about some of the work that we've done related to this. Thank you.

- Thank you, Richard. I would sort of like to now discuss some of the current work that we're doing here at Vanderbilt University Medical Center within the vestibular lab, pertaining to the cerebellar potential. But before I do that, I want to kind of briefly talk about a couple of studies that have recently looked at this potential. Now, Richard nicely laid out that when an EEG cap was used, you know, many evoked potentials could be observed around various locations on the scalp. At the top of that figure you can see, of course, what we use every day in the clinic, that is the oVEMP. But you can also see a wide variety of different evoked potentials that are measurable as the stimulus is coming in and as it's producing this vestibular input.

Specifically, he mentioned a location known as the PO8 that is measured in the parietal-occipital region, most originating from the cerebellum or thought to be more originating from the cerebellum. To give you an idea of where this parietal-occipital eight region is on the scalp, specifically, here is a figure to sort of show from one of the follow-up studies out of this Australian group to show where this PO8 location lies on the actual scalp. And so you can see it's in that parietal-occipital region, just lateral to what we know is the inion potential, which Gary nicely talked about. And so in a few subsequent studies, what the research group was actually observing was a more reliable location to actually record this potential during their pilot investigations.

This location lies slightly inferior and medial to the original PO8 site. And they described these locations as the Iz and CBz locations. And so as we go forward, I'll be referencing some of those actual location sites 'cause we sort of piggybacked on those same identical sites to record the cerebellar potentials in our own lab. And so there's been a couple of different studies since the one Richard talked about out of this Australian group. And one of the more notable studies is this one by Govender et al in 2020 called mapping the vestibular cerebellar revoked potential following air and bone conduction stimulation. And this response, this cerebellar potential has now sort of been dubbed the name the vestibular cerebellar evoked potential, so you'll sort of see it referred to as the VsCEP throughout the remainder of the presentation.

And their goal was really to do some further mapping of the response. And what they observed was that this response was best measured, best recorded, and they defined best recorded as the areas that were yielding the largest peak-to-peak amplitudes. But they noticed that the largest amplitudes were being measured on the back of the scalp at these Iz and CBz locations contralateral to the ear that was being stimulated. And this was both true for their air and bone-conducted transducers. So that essentially brings us to our study. Given that much of this research on the cerebellar potential or on the VsCEP has come out of one research lab, we thought it would be important to really replicate several different components of previous investigations.

That is we wanted to determine where on the scalp is this response best recorded. Most previous investigations have defined what is best or what is optimal as those areas yielding the largest peak-to-peak amplitudes. We decided to define best recorded as yes, as those areas given us the largest peak-to-peak amplitudes, but we also wanted to add the areas that gave us, that yielded the highest response rates. Response rate is something that is going to be crucial going forward, especially if this potential does have any clinical utility in the future. And so we defined best recorded as

that area yielding the hot largest peak-to-peak amplitude as well as the highest response rate.

We also wanted to ensure that the response was not dependent on any particular reference electrode location. We know that with much of our myogenic potentials, there are certainly differences in peak-to-peak amplitudes, response rates, depending on where that reference electrode lies, and so we wanted to look at a couple of different sites. Most commonly in the previous investigations have used the contralateral ear lobe, so we included that as well. But we also wanted to use the tip of the nose given its advantages in measuring wide variety of different other potentials. And so we wanted to compare, measure these responses and compare between both the tip of the nose electrode, reference electrode, and ear lobe reference electrode locations.

And so our participants, we had six participants that were recruited just for this initial study with the mean age of 26 and standard deviation of 2.1. We had five females, one male, and all participants reported no known history of any hearing or balance disorders. So well below any potential aging effects or any other things that could potentially interfere or negatively impact our ability to measure the VsCEP. Here are some of our methods that we used. We use a standard 125 dB peak SPL, 500 hertz tone bursts that was delivered through insert earphones. Because similarly to other studies, we wanted to also minimize any potential myogenic contributions that is measurable from the posterior neck muscles. And so we had the participant lay in a supine position on a pillow with their head and neck relaxed, and we had them fixate on a one inch target right in front of them just to sort of give them something to sort of visually fixate on.

That's been pretty common in some of the previous investigations and so we wanted to include that as well. We measured these responses when both the left and right ear were being stimulated, and we did this for both a contralateral ear lobe reference as

well as that tip of the nose. And so these are just some of the standard protocols that we use to initially investigate the recordability of this response. Now here is essentially the layout of our active or non-inverting electrode a electrode sites. So this is the electrode that is actually going to pick up that response. And we had 10 different electro locations, each separated by three centimeters, left and right from medial to lateral.

The top row and bottom row were separated by two centimeters. We wanted to try to remain, as possible to some of the previous investigations that looked at this response. So we placed all of our electrodes along five different locations along that Iz electrode line. And then right below that, that CB electrode location. And so we had two electrodes at midline, and we also had two electrodes to the right, two electrodes to the left, both for that Iz and CB locations. And then, of course, with our reference electrodes placed both at the contralateral ear lobe and tip of the nose. We also considered the responses to be present if both negative and positive peaks were visually identified well above that noise floor, and waveforms were marked for both the P1 and N1 latencies as well as our peak-to-peak amplitudes.

And I'll sort of dive into what that waveform looks like here in a short second. And we also calculated our response rates. So here is essentially what the waveform looked like of the VsCEP. Along that x-axis is time and y-axis is amplitude. And so what we can see is that the waveform is typically defined by a positive peak occurring around 11 milliseconds, followed by a negative peak occurring around 17 milliseconds. Now this is not a waveform that is measured from underneath the eyes like oVEMPs or on that sternocleidomastoid muscle. This is waveform collected and measured from the back of the scalp using a tone burst. Here is sort of the grand figure of everything of all the waveforms that we collected for every single electrode site for both the left and right ear.

So the top portion of that figure is going to be when the right ear is stimulated, the bottom portion's gonna be when that left ear is stimulated and the waveforms corresponding to each different electrode site. And what we generally observed is that the responses that yielded, at least the largest amplitudes occurred over both the midline and contralateral areas of the scalp relative to the stimulated ear. And so what we consistently shown was that, or we consistently observed was that we were yielding the largest responses contralaterally to that ear, which is again consistent with some of the previous investigations. So this is all the waveforms referenced to the contralateral earlobe. And as we look at all the waveforms referenced to the tip of the nose, we can see that generally, just visually, the waveforms are still present, they're still visible, and statistically, we didn't show any obvious statistical differences between either electrode site.

So here are some of the raw data pulled from every single electrode location for both the left and right ear stimulated and between each reference electrode. So essentially, just to kind of break this down a little bit, we did not see any significant differences in latency regardless of reference electrode location, which is consistent with what previous reports have suggested. And just like I showed you in the previous figures, we were measuring statistically larger responses in terms of peak-to-peak amplitude over that midline and contralateral regions. Now, one of our main findings was significant variability in peak-to-peak amplitude. So I just mentioned that we recorded larger peak-to-peak amplitudes, but we also just found a lot of significant variability and that can easily be seen here in this figure.

So along that x-axis, we have our each reference or each of our active electrode locations, and along that y-axis, we have our amplitude. And we have this for both the left side of the scalp, mid, and right side for both our ear lobe and our nose references. And so what you can immediately pick up on is how variable those peak-to-peak amplitudes are. We can see that yes, on average, at least our mean amplitudes are

larger on that contralateral side for both the ear lobe and nose references. But just looking at those error bars, you can see how variable those responses are. And we did end up seeing that statistically, it was statistically supporting increased significant variability.

As far as how consistently we were able to measure this response, this figure just shows the response rate for all of our different conditions, all of our different possibilities here when we're measuring. And what we observed was that over the midline and contralateral regions, that not only were they providing the largest peak-to-peak amplitude, but they also were providing the largest response rates. So it was these regions, both the midline and contralateral regions were sort of giving us the best of both worlds. It was giving us those larger amplitude and response rates, and we're defining response rates as essentially the percentage of participants in which we were able to measure the response. And so over these two regions, we essentially were able to measure this response in 66% of people within our sample.

And we'll talk about some of the significance of that just a little bit. So overall, we recorded our largest or best responses, quote, unquote, best responses, defined as the larger peak-to-peak amplitudes and response rates over the midline and contralateral regions relative to the ear being stimulated. We also did not necessarily see any latency differences and all of our latency and amplitude values were also consistent with previous published reports. And really, this is to our knowledge, this was really the first initial study to really show equal response rates when both the left and right ears were being stimulated. Some of the previous reports have shown that response or at least there was a side preference or an ear preference, but at least in our initial study, we were not seeing any significant preferences between the ears or any significant ear difference.

We were seeing the same overall results regardless of which ear was being stimulated. We did not see any significant difference between the contralateral ear lobe, or ear lobe, or nose, tip of the nose references. Again, that 66 response rate, and I want to come back to that because it's going to mean so much, I think, whether or not this response may be useful clinically, you know, to, just to remind you, this is a young, healthy population and our study, along with other studies have consistently shown about a 50 to 66% response rate. And so, you know, there's obviously, I think, something, some uncounted variable that we feel is unaccounted for that is contributing to this lower or less desirable response rate.

And so, you know, what could be contributing to this, to less than 100% response rate? Well, it could be a combination of different factors. Is there a myogenic contribution here that may be degrading the response? Gary and Richard both have suggested possible myogenic potentials being recorded near or around the same area or contributing to possibly some of the later portions of that waveform. Is the reason, you know, not because... Is the reason due to this not necessarily being a true physiologic stimulus like you would be stimulating the vestibular system to its natural form like during rotational chair, during other things? is that the reason why this is not contributing? When I say not an affection, I mean not enough motion stimulus.

Some of the previous studies have shown that this response can actually increase in amplitude when there is an optokinetic or when there is a sensation of motion presented to the participant at the same time that the response is being recorded. So is the target that they were looking at just not producing that sensation of motion enough. Skull thickness, is there a difference in, you know, our ability to sort of lay over the area of that cerebellum? Are there other things that could be contributing? We know that we're measuring these surface electrode responses and a lot of those factors then come into play. Or is it a combination of many of these different things? It's likely a combination.

There's just more, I think more or less has to be kind of fleshed out at this point. So here are a few study limitations, of course. We used a single stimulus, acoustic only. Some studies have shown that bone conduction stimulus may be preferable. We did have a smaller N in this study, and that may have contributed to some of the variability that we were seeing in some of the responses. So we may want to increase subsequent studies, may want to increase that sample size and again, fixed one-inch target I mentioned, that it could be not producing that motion stimulus that has shown to increase the amplitude and does it increase the response rate? So we certainly wanna explore some variables contributing to the response rate.

We also want to investigate really the clinical utility of this response at some point in the assessment of dizzy patients because there is a movement right now really to explore vestibula potentials beyond those originating from myogenic or subcortical centers. You know, we have these myogenic potentials, the ocular and cervical vents that have been used for, you know, 10, 20 years now. And, you know, there is a movement to sort of show that yes, these vestibular signals when the vestibular system is stimulated, it sends multiple bits of information to different higher cortical areas up in the brain. And, you know, we wanna really continue to, it's both exciting and we want to continue to investigate this as well as other potentials going forward to really utilize these, see what their clinical utility is in the assessment of management of dizzy patients. So yeah, with that, I will toss it back to Gary, and thank you all for your time.

- Well, we've taken a little journey today. And you just never know what's going to happen when you see something new, when, in this case, a new evoked potential. Sometimes, you know, we start off thinking that we've, you know, sort of hit the mother lode, the vein of gold, scientifically speaking, and sometimes, you don't. And it will take time for us to sort out whether this is the sort of response that we've described today, whether this is going to actually represent the first electrophysiological test of a part of

the central vestibular system and specifically the cerebellum or whether it isn't. Of course, you know, from a diagnostic standpoint, we hope that this does turn into a central vestibular test, and it would give us an opportunity to study, not just the end organs of the vestibular system, but central areas that process the information that is sent to it from the periphery.

Time will tell. And we feel we've got our foot in the door. And, you know, as happens often, you know, you do a study and it generates more questions and so you start off with a single study and then next thing you know, you blink your eyes and 10 years have gone by, and you're still asking questions about that same test that you investigated long ago. And I think it's also interesting that this is a evoked response that was discovered so long ago. And quite literally, if you go through PubMed, and you search on the inion response, you'll find these papers and that will be the sum total of the knowledge base on this. So those of you who are interested, if we piqued your interest, if you have questions, please feel free to contact us.

I am gary.jacobson@vumc.org. And if you have questions, and you want to funnel them through my email address, I will be happy to pass them on to whomever you would like to see the questions. So with that, again, in our gratitude to Continued, you always make it look simple. I know it isn't. Thank you.