COVID Information Commons (CIC) Research Lightning Talk

Transcript of a Presentation by Judy Ford (University of California, San Francisco) January 30, 2024

Title: Event-related brain potentials reveal neurological slowing following COVID-19 infection

VA Award #: I01CX002322-01A1

YouTube Recording with Slides

Winter 2024 CIC Webinar Information

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Transcript

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I'm going to present preliminary data. This study is ongoing - we probably have another year and a half in which to be recruiting patients for the study. I've listed my co-authors on this on this work. Also, I want to note my the other PI on the VA Grant - the VA has funded this work through the Merit Review grant program - that is Lynn Pulliam and she's responsible for the all of the variables associated with blood.

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Let me get started here - I'm going to be talking about neural slowing following COVID-19. It's a much bigger proposal - a much bigger project than just what I'm going to show. There's MRI, there's clinical assessment, there's neuro-psych testing, there's all of the stuff that Lynn does with the plasma, APOE, but today - also, it's a work in progress, I want to be sure everybody gets that. Today, I'm just going to be talking about the EEG based event related potentials or ERPs. Also, just so you know this is a - as you can imagine, this is a full day protocol - they come in early, they give blood, they have EEG collected, they go to the MR scanner, they do neuro-psych testing, and then they then they go home. In one order or the other.

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I'm just going to give you - for those of you who don't know and there are probably plenty of you who don't - sort of the brief history of recording EEG. Almost a hundred years ago, in Yana, Germany, Hans Berger invented the electroencephalography. His hope was to communicate with his sister telepathically across hundreds of miles. Needless to say, that did not work but the technique was picked up by others

because they were interested in the fact that you could actually record brain activity from the scalps of human volunteers. About five years later Hallowell Davis and Don Lindsay started recording EEG in their Lab at Harvard. By the 1960s, auditory ERPs (again, ERP is event related potentials) were used to test hearing. Since the 1970s, which was actually when I first got involved, they have been used as an objective measure of cognitive function. That's what I'm going to be focusing on today.

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Here is a little example of how you would calculate an event related potential, in this instance that is an auditory event related potential. Auditory event related potentials are derived by averaging together EEG segments - little snippets time locked to the onset of a sound.

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This is a specific example of what we do with the people that come in for our study. We have a very frequent sound that is actually sounds kind of like a cat purring and that happens 80% of the trials. Then on 10% of the trials, they hear a tone a high-pitched thousand hertz tone, it actually happens to be the the tone that is that is best heard by humans - the tone frequency. Then we also have these novel sounds. They have dog barks, horns honking, machine sounds, doors slamming, etc. Those are infrequent tones just like the targets and subjects are not supposed to press a button to it. They do press a button every time they hear a target tone. We record the reaction time to that sound.

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Here's an example I got from the internet that I thought was pretty good. Just imagine that the EEG is going along here on the top row and you get a tone, you get another tone, you get another tone. After about 40 or 60 or 100 of those tones, you cut them into little snippets over here and you average them all together. You get something called an ERP. This is an average different related potential waveform. If there's a dog barking or if there's the target tone, you really get this big p300. P stands for positive, 300 reflects the time that it takes to peak, which is 300 milliseconds. This is really quick. You're really hardly aware that this is happening in your brain. We are today going to look at the novelty p300 and the target p300. They both reflect the allocation of attention to the event. They can be either elicited passively, like in the case of the novelty p300, or with effort as in the case of the target p300. The latency, which I'm going to be focusing on today, reflects the neural processing speed of both of these events. Again, P3 latency is an objective measure of cognitive function - how quickly that cognitive function happens. Again, we press a button and we get a reaction time. The reaction time is kind of a dirty measure, if you will. It reflects not only the neural speed of how long it takes you to make that decision, it also reflects the motor speed that could be slowed down by any number of things, including difficulty getting to the button, difficulty making finally finalizing that decision, etc. We have the p300, and that's an objective measure of cognitive function, and then the reaction time, which is a combination of both of those two things.

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For our study, and again this is ongoing, we have collected data from 39 people that we are considering Neuro-COVID. What does it take to be in the Neuro-COVID group? We ask them these questions:

Compared to before you got COVID, is it harder to concentrate? Is it harder to remember things? Are you more depressed than you used to be? Are you more anxious than you used to be? If you say yes on any of those questions, we put you in the Neuro-COVID group. We also have a smaller group of people that are we are considering the control COVID patients. These are people who have COVID, have had COVID, but they have not experienced any of those four things. Then, because we weren't sure whether we could actually collect data from anybody who had never had COVID, we have another group of people that we call the Legacy Controls. These are data that we collected on that paradigm I just showed you at Yale before the pandemic. There are 83 people in that group. So we have the Neuro-COVID group, who have complained of one of these kinds of neurological things. We have the control COVID group who had COVID but don't have any complaints. Then, we have the pre-pandemic Legacy Controls.

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I just want to point out one important thing and that is that the Legacy Controls are a little bit older than the Neuro-COVID and the control COVID patients. We have statistically removed the effects of normal aging from the COVID subjects using z-scoring, but I'm not going to go into that. The Neuro-COVIDs had worse depression and anxiety, as you might expect, than the control COVIDs. However, they actually performed better on tests of working memory, and we're still sorting through that - those kinds of data. Those are data that are clinical data collected from Beck Depression Inventory, the Beck Anxiety Inventory, and Matrix Cognitive Battery.

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So these are the data. Again, P3 latency is a reflection of neural speed. I'm not sure whether you can see the things in my upper, sorry, in the upper right hand corner where my picture. On the Y axis, we have P3 latency. The slower you go, the bigger the number and the faster, the smaller the number. So these are all slower P3 latencies than these. Right here, you can see that to the novel sounds, the Neuro-COVIDs and the control COVIDs both had delayed P3 latencies compared to the Legacy Controls. This is something that I wish weren't true, and we've hoped this would go away, but so far it hasn't gone away. The COVID controls - those are people who do not have Neuro-COVID symptoms - have slower neural responses to both target tones and novel sounds compared to the legacy controls. The Neuro-COVIDs also have slower neural responses but only to the novel sounds, which is a puzzle for us. They seem to have normal speed target tones.

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Moving on to reaction times. The reaction times the target tones are actually slower in the Neuro-COVIDs. So despite having normal latency in your neural responses, the Neuro-COVIDs are delayed in pressing the button. I'll just remind you of the picture I just showed you - you can see that they actually - it looks a little - they are not slowed down significantly in their response to the target sounds, but they do have a slower reaction time. So because they did not have any evidence of neural slowing to the target tones, the slowing in the reaction time probably reflects processes happening after the brain has registered that something important happened.

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What other conditions cause slowing of P3 latency? As luck would have it, long ago I did some studies in aging and dementia. This is a picture from one of those studies. This appeared in 1997. So you can see here that both the target and the novel P3 are later in older people. These are the older people, these are the younger people. So you can see again, latency is getting longer. The novelty P3 is later in older people than in younger people and the target P3 is later in older people than in younger people. It gets even later with dementia. This makes me wonder what is going on with the people who have COVID. What is what is causing the P3 latency to be longer and prolonged?

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Let me also point out another paper I wrote a long time ago. Reaction times are also slower in older people and the lag between when the p300 happens, between the neural decision and the time you actually get around to pushing that button, is also bigger in older people.

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Here's another - so I went to the literature. I remembered an old colleague named John Polich (?). He had done an HIV study. He found that people who were HIV positive also had slower P3 latencies. It increased with viral load. Looking further, there are hepatitis - there's a literature on chronic hepatitis P3 latency. It is also slower in people with chronic hepatitis. Interestingly, P3 latency improves after direct antivirals in hepatitis C patients. This P3 latency delay that we're seeing in people with COVID, it may reflect the the persistence of the virus. It may reflect, actually, an accelerated aging process going on. One other thing - there's been a lot of talk lately about whether long COVID has anything to do with chronic fatigue syndrome. There have been several papers on P3 latency in people with chronic fatigue syndrome. There's no evidence of P3 latency delay in chronic fatigue syndrome, so it's more along the HIV, hepatitis C line that you see P3 delays in these patients.

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In summary, regardless of whether you have Neuro-COVID symptoms, if you had COVID you may still have slower neural responses to sounds. It's not much slower, you know, it's 50 milliseconds, maybe 100 milliseconds slower, but it's a significant slowing. We're trying to figure out what it might mean and what you do about it.

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Here's one thing suggested by Courtney [Baird] - maybe you should wear a mask. Not a bad idea. Neuro-COVID patients also have slower reaction times beyond what you see in people without symptoms. Again, not sure what that means but it is something that we do see in older people, elderly, and probably even more so in dementia. Like I said, these patterns are seen in hepatitis, HIV, aging, and dementia. The question I ask is if it is related to accelerated aging? I mean, I hope not because I had COVID. Will it reverse with time? Again, we're actively looking at this. We do have information about the timing between infection and the time they were tested and we're going to see if, in fact, the people who have a longer delay between infection and testing, whether the P3 latency will begin to be restored to

its more youthful pattern. And, of course, is there a treatment. That, I think, is awaiting on the pharmacology industry and perhaps even behavioral interventions.

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The next steps. Again, this is a work in progress. We definitely need to collect more data from COVID controls. This is something I I keep hoping - this finding will go away. I don't like the finding but there it is and there doesn't seem to be much I can do about it. We also are going to assess the other ERP components. I don't know if you remember that picture I showed from the internet? There all sorts of other components. We do have data from the early N1 component that also seems to be sensitive to COVID, but I didn't have time to talk about that. We're going to look at the ERPs to the standard cat purr sounds. We used that stimulus for a reason - it's seems to be that the response to that sound seems to be very sensitive to schizophrenia, which is what I really study, And we need to start relating all of the ERP findings to the blood data that Lynn is collecting and analyzing. Of course, we need to start relating all of this to brain structure and brain function. One of our colleagues is looking at microbleeds in the structural MRIs maybe that has something to do with what we are seeing in the neural slowing in these patients.

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Again, there's a lot to this study and we are just sort of - this was just a tip of the iceberg.

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I want to thank the VA for funding this work and all the people who participated. It's a very long day and thank you for listening. I look forward to questions later in the session.