**Introductory Neuroscience and Neuro-Instrumentation**
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**Lecture No. 22**
**Introduction to Event Related Potentials – 2**

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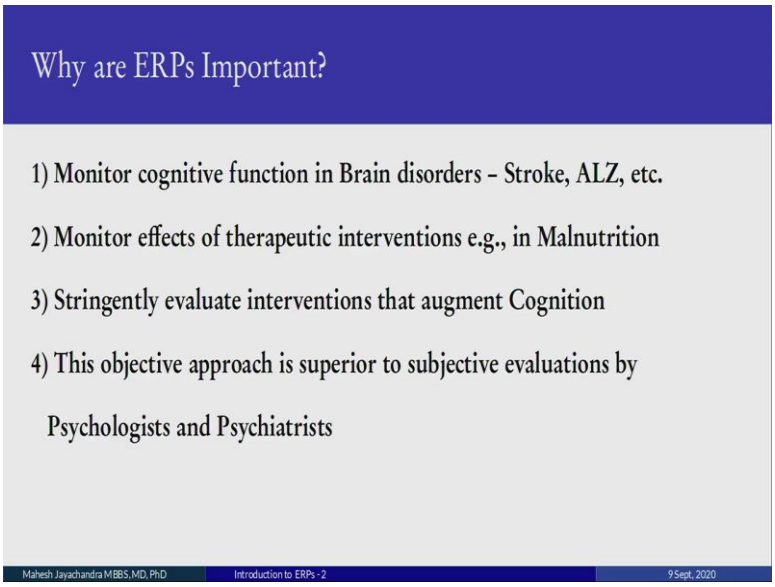


So, Introductory Neuroscience and Nero-Instrumentation: Event-Related Potentials, lecture 02. So we went through a few ERPs in our last lecture and the question arises, why are they important? We talked about monitoring the auditory, the visual system, and during surgery but also, cognition. So, we can monitor cognitive functions in brain disorders like for example, stroke or Alzheimer's disease, etcetera. Typically, to do cognitive testing you need a clinical psychologist who runs a battery of tests and you cannot do it in one session.

There are multiple sessions of 45 minutes, 1 hour each. And there is just not enough clinical psychologist in India or in the world to do this. So, we need instrumentation and clinical neurophysiology and stuff to supplement mental health professionals. The other thing is therapeutic interventions. You get, for example, a lot of children are malnourished, not so much anymore in India but in Africa and other countries.

And a lot of companies have interventions, nutritional interventions which they say makes the brain better, but there is no way to monitor them objectively except through psychological testing which as I mentioned is difficult because of the porosity of trained people or ERPs. And then, you have newer things, marketing strategies which suggest that this organic compound that plant compound, that hamburger is good. It augments cognition.

So, to evaluate it stringently we need objective metrics and ERPs are objective, you cannot sham through an ERP, you cannot, suppose you ask a person, can you hear this? He can hear it and he might say no, I cannot, and pretend to be deaf. But if you have your P1N1, P2 complex, you know that the brain is responding to the stimuli. So, these kinds of objective evaluations are superior to subjective evaluations by mental health professionals, typically psychologists or psychiatrists. So, that is why they are important. Also, they are quick, they are easy to do, they are invasive, it is not such a big deal.

And I have to mention one other thing that in India especially, there is a huge social stigma to go to a psychologist or psychiatrist. It is real, people especially outside the metros they will not consider marrying into your family if they know that somebody is going to a psychiatrist. It is very real. So, ERPs are objective and they tend, there is no social stigma attached to them.

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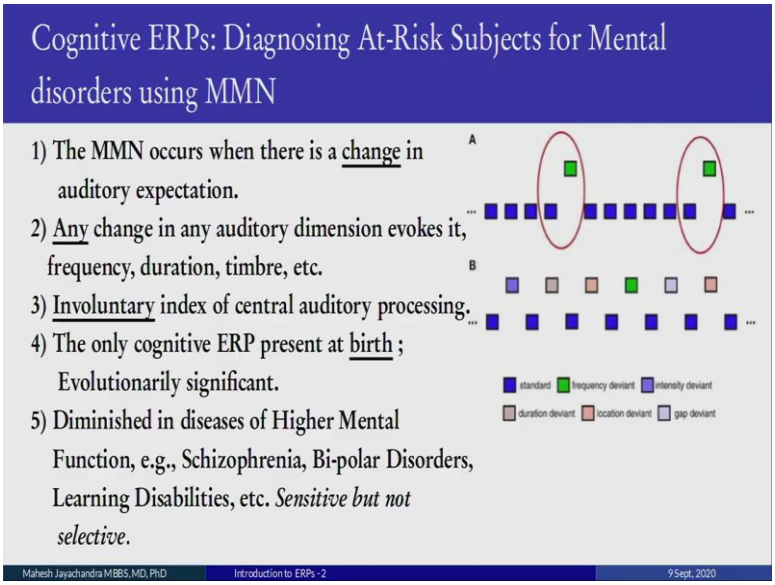


So, let us talk about a cognitive event-related potential called the miss-match negativity. So, consider a stimulus, beep beep beep boop, beep beep beep boop. So, these are the beeps and this is the boop, these are the beeps and this is the boop. So, what we do is we average all the beeps, we average all the boops and we subtract it. When we subtract it, you get the miss-match negativity, it is a negative potential and it shows the miss-match signal.

Now when I say beep and boop, I am changing the frequency. But any change in the auditory dimension evokes it like frequency or duration or timber. So for example, you have beep, beep, beep on a guitar and then you have beep on a piano, you get the miss-match negativity.

So, it is pretty much involuntary and it is an index of central auditory processing. It kind of reflects auditory short-term memory or auditory echoic memory. This is the memory if I call you and I give you a phone number and you do not have a pencil, you just repeat it in your mind, go, have a pencil, paper and you write it down.

Now if I ask you a day later what it was, you would not remember it, it is very transitory. So, it is a kind of auditory, sensory auditory echoic memory, that kind of memory. Also, it is the only event-related potential present at birth. And hence, it is evolutionarily significant. Why? The baby has to recognize the mother's voice. Babies who have not, who do not recognize their mother's voice, probably have died or in evolution. So, it is very important.

And the other thing is most mental health dysfunction like schizophrenia, bipolar disorder, learning disabilities, MMN is reduced. So, it is sensitive but not selective. For those of you who are from a medical background, it is something like a blood test where you have sensitivity but no selectivity like erythrocyte sedimentation rate, ESR. It is very sensitive. It goes up, if there is an infection, it goes up if there is the chronic disability, but it does not tell you which chronic disability or which infection.

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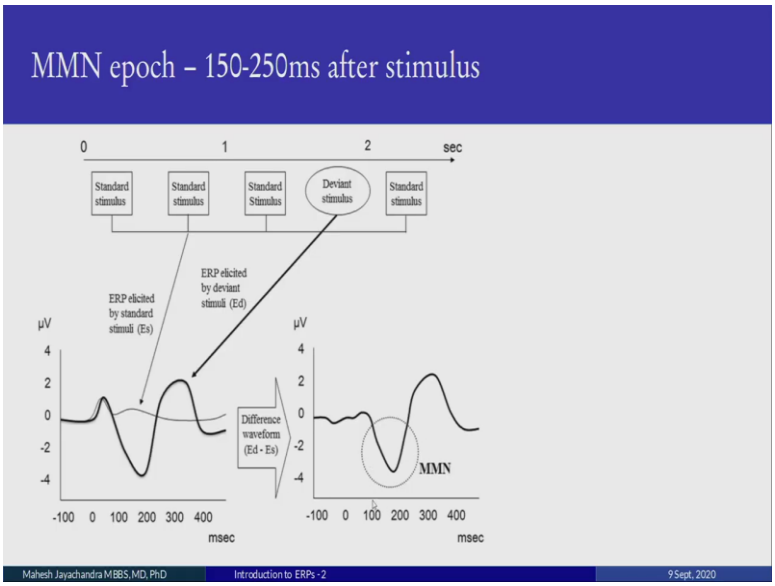


So here, it is positive-up, it is pretty unusual and this is your normal beep. It just generates the auditory evoked potential. This is the boop, and these are average responses, not single responses because a single response will be too noisy to see any of these. And when you subtract it, you get the MMN. And the MMN usually occurs somewhere between 150 to 300 milliseconds, in that zone.

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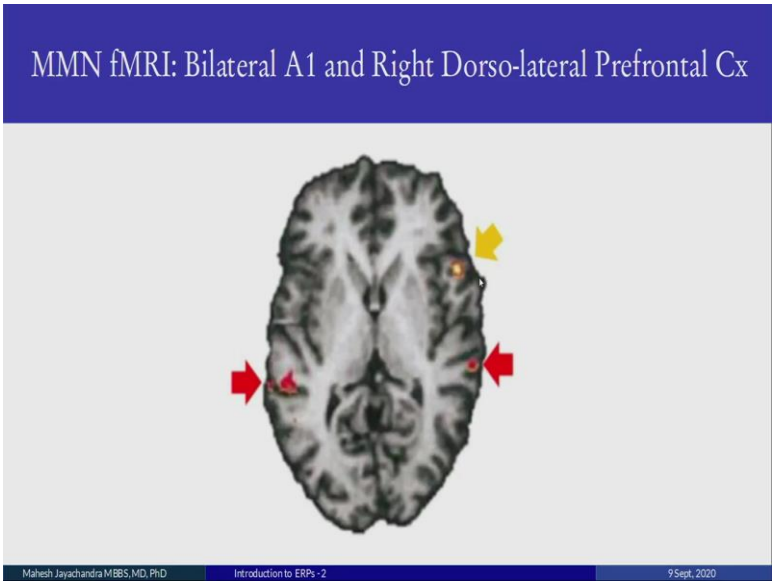


And which parts of the brain are involved in MMN? So, consider a section like this going right like this and you are looking at it, the brain from the top. So, both the auditory cortices on both sides are activated but there is also another additional area which is activated which senses the miss-match signal and that is in the right dorsolateral prefrontal cortex depicted by the yellow arrow over here. The red arrows depict the auditory evoked potential areas.

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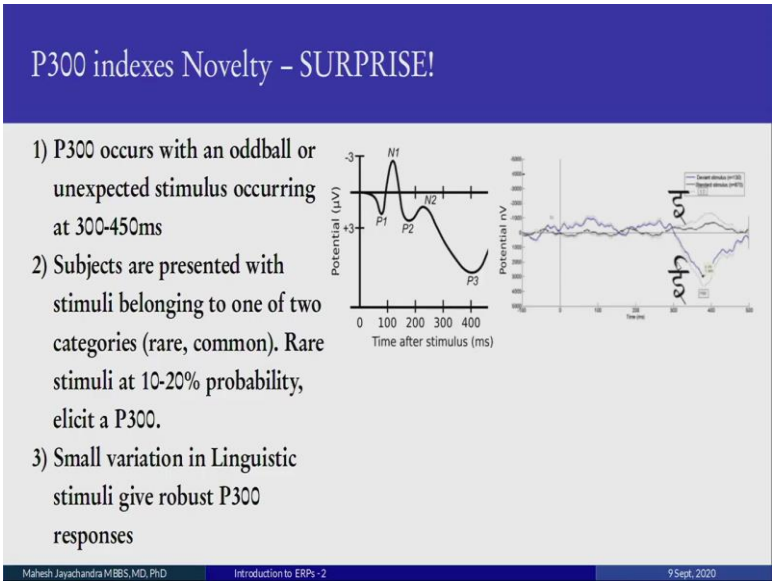


So, that was the miss-match. Now if you look at PubMed and if you put a miss-match, you would get more than 5,000 references. It is being studied very intensively and it was first described by the professor from Finland. Another evoked potential which is even more popular and has got more than 10,000 references on PubMed P300. So, the P300 index is

novelty like surprised by something, something unusual in the environment. It is called an oddball stimulus. So, that evokes the P300 and this occurs a little later than the miss-match negativity about 300 to 450-500 milliseconds.

It is very constant in a single subject and it tries using a single subject but between people, there could be variations. So, you have two stimuli in the typical P300 experimental paradigm. A common stimulus and a rare stimulus that comes randomly, and the rare stimulus usually has a probability of 10 to 20 percent. So, even small variations, now we are talking of the visual P300. Even small variations can give the P300. So, here you have a canonical P300 negative is up, that is a neurophysiological tradition.

And you have the P1N1, P2 response and this is the P300 response. This is not an individual response. This is an average response probably grand averages from many runs and many subjects. I did this experiment with my lab where I use the common stimulus as the E and the rare stimulus is the badi E. And you see the common stimulus you have this response and the badi E you have a massive P300 response. And the only difference between these two stimuli is the thing on top, the little matra on top. So, even small variations give rise to this.

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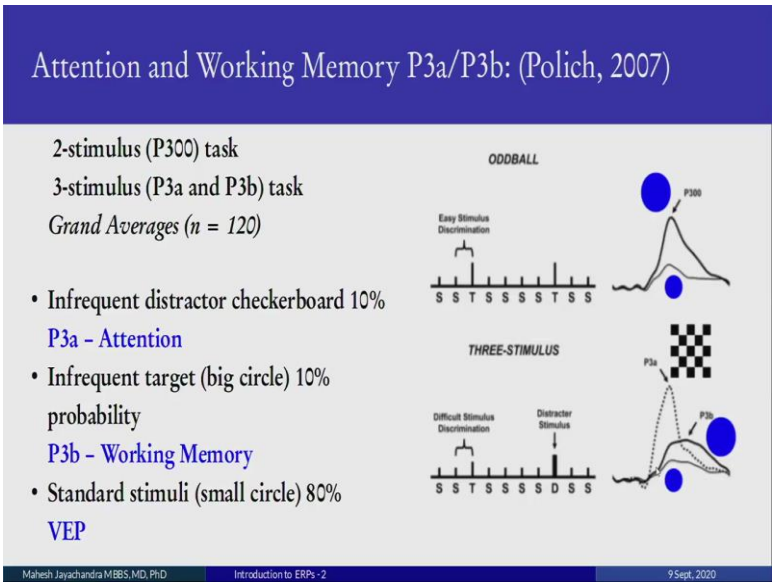


So, we can extend the experiment by instead of having just a rare and a common stimulus, which is the 2-stimulus P300 task which you saw before, we can have a 3-stimulus task where you have, this is the 2-stimulus, you have the standard response which you are supposed to ignore and then you have the target which you are supposed to press the key. So,

the standard stimulus is usually a small blue ball. The target is a big blue ball. And this comes at a probability of 80 and the target comes at a probability of 10 percent.

But in the remaining 10 percent, you have a checkerboard that suddenly pops up and which you are not supposed to react to. So, coming to what it all means, the standard stimulus is a visual evoked potential. So, you get a visual evoked potential over that, that is this guy. Now the target which is the infrequent blue ball, that reflects working memory and you get this response which is P3b because you have to keep in mind there is a small ball, there is a big ball. When the big balls come, I have to press the buttons. So, this is working memory.

The checkerboard on the other hand is a distractor. It is unexpected and unusual, so it reflects attention. Are you paying attention or not? And you can use these metrics to see, to evaluate a person's short-term memory, his attention besides the visual evoked potential. So, the P3a comes a little early. The P3b comes a little later. And this dissociation with 3-stimuli allows us to look at 3 things; attention, working memory, and the visual evoked potential pathways.

The thing to bear in mind is both the MMN and the P300, they also work for other modalities. Like you can have a P300 paradigm using auditory stimuli which is what we do at initial science. You can have an MMN with visual stimuli, you can have an MMN with somatosensory stimuli. For example, you keep touching, touch, touch, touch, and then poke. So, the difference between the touch and the poke is somatosensory MMN.

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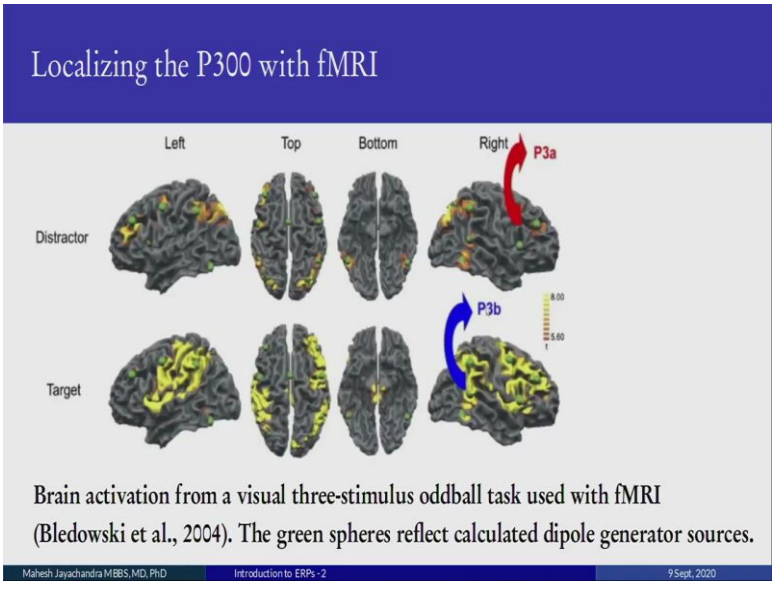


So, which parts of the brain are the MMN produce? So, please ignore the left, top, bottom, and just look at the extreme right figures of the MRI. The P3a, the attention comes from the

dorsolateral prefrontal cortex. The P3b which is working memory comes from behind, the parietal cortex. And you can calculate the dipole, this can be assumed to be dipoles, electromagnetic dipoles. And these gray, green spheres show the dipoles, calculated dipoles.

There is no actual dipole over there. The cells when they act together, they give rise to a feeling which looks like a dipole. This is the other view of the brain; the top, the bottom, the left, right but the most important is the thing to take home is that the P3a attention occurs in the front dorsolateral prefrontal cortex, the P3b occurs in the parietal areas.

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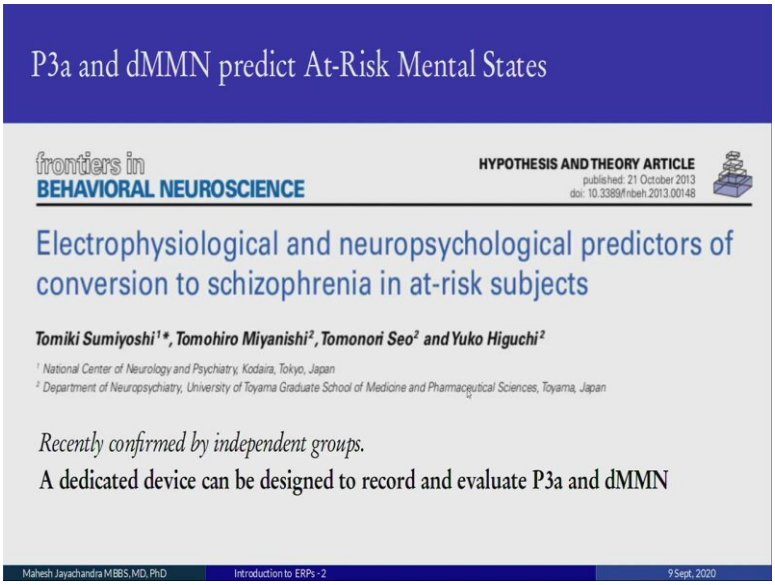


So recently, the dream is to use these potentials to see if there is some problem or to predict or to scan or to screen patients with future problems. And recently, the P3a attention and the dMMN, dMMN is duration MMN. fMMN is frequency MMN. Frequency MMN is beep, beep, beep, boop, beep, beep, beep, boop. dMMN is beep, beep, beep, beep, beeep, beep, beep, beeep. So, duration MMN, so if you combine these two, it seems that you can predict subjects at risk for future psychosis.

And this is fairly recent and but independent rules have confirmed it. So, if you can make a device and you guys are interested in neuroscience and with an engineering background, a dedicated device to record and evaluate P3a and dMMN, well, you have a screening device to quickly go through large sections of the population and separate them. If they have a propensity for this, then you send them to the psychiatrist or the clinical psychologist. But this would be able to be done at the village level by an Asha worker.

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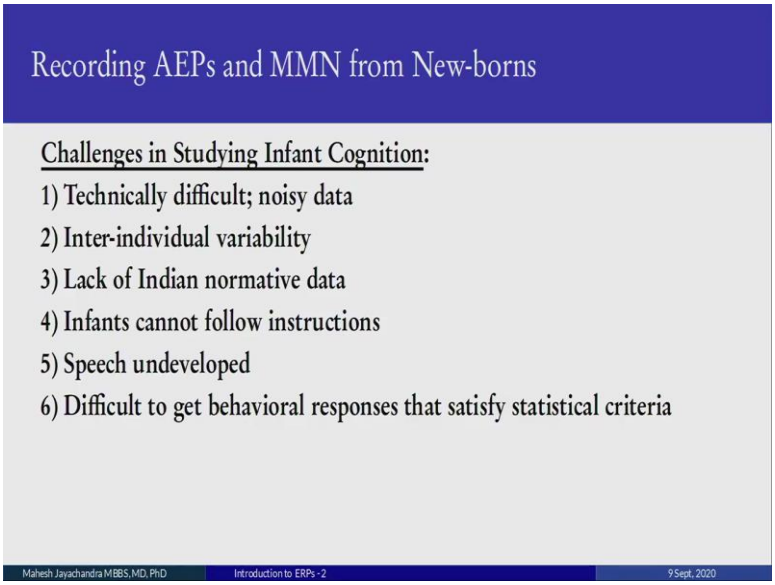


So, coming to AEPs and MMN recording from infants, why do we record from infants? Because catch them young as I say if you can catch an infant with a hearing deficit immediately after birth, most probably you should be able to treat it because lots of them for example, have treatable causes like a thyroid deficiency. So, all you need is thyroid supplementation and the baby is fine and grows up to be fine.

If this is delayed by a few months then it becomes permanent, the deficits. And the longer you delay, the more difficult it is to reverse it. So, if you can catch it when the baby is born within 48 hours instead of, we can start thyroid supplementation and prevent conginental difference due to thyroid deficiency. So, this is just one example. There are many such conditions. However, it is difficult to study infant cognition because it is technically difficult, the data is very noisy because babies just come out and everything is just kind of settling in.

There is a lot of variabilities and in India, we do not have normative data. So, each time you do something, you have to do the normative data bit first. Infants cannot follow instructions, they come and hold their head straight, keep dangling and there is no speech and you cannot get a behavioral response for statistical criteria, what you can do with children, with adults? You cannot do it because they are not sure. So, there are a lot of challenges in studying infant cognition, please keep that in mind. But it can be done.

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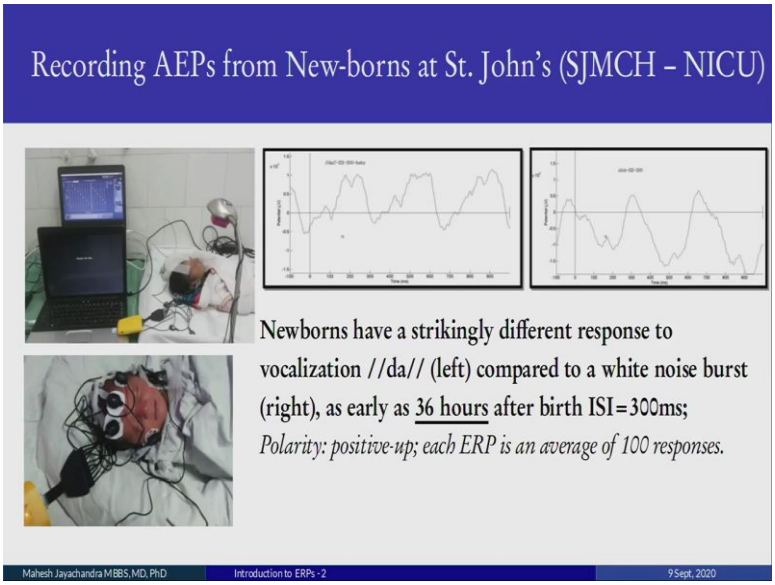


So, these are recordings done by my group at St. John's. The St. John's medical college hospital, NICU, neonatal ICU. So, you have a stimulating computer, you have the, I am, this is the recording computer, this is stimulating computer and this is the (())(15:09) which I showed in the previous lecture where we are using just the electrodes and this is the Wi-Fi device which communicates with this computer.

And this is typically a placement. It is difficult to place electrodes on an infant's scalp because you have the anterior frontal as the bones have infused, so it is a little dicey but the forehead is fine. The forehead is just fine and the recordings would be a little distorted but we can work around it. So, over here you have data from a newborn. This is the baby was 36 hours old and remember the da stimulus from nenocross lab.

So, this is da stimuli given over here three times in a second. So, it is about 300 milliseconds you get this da stimulus. And you have clicks and notice that even though the baby is just 36 hours old, there is a clear difference it can recognize between da and clicks. Here the polarity is positive-up. So, it can be done. So, we can make a headband, abstract all this and we can record ERPs from the newborn.

There are some technical challenges, they will cry, this, that. So typically, you have a period of 20 minutes or 15 minutes between feeds when the baby is fed by the mother. You have 15 minutes to do the recording and then that is your interval but that is enough.

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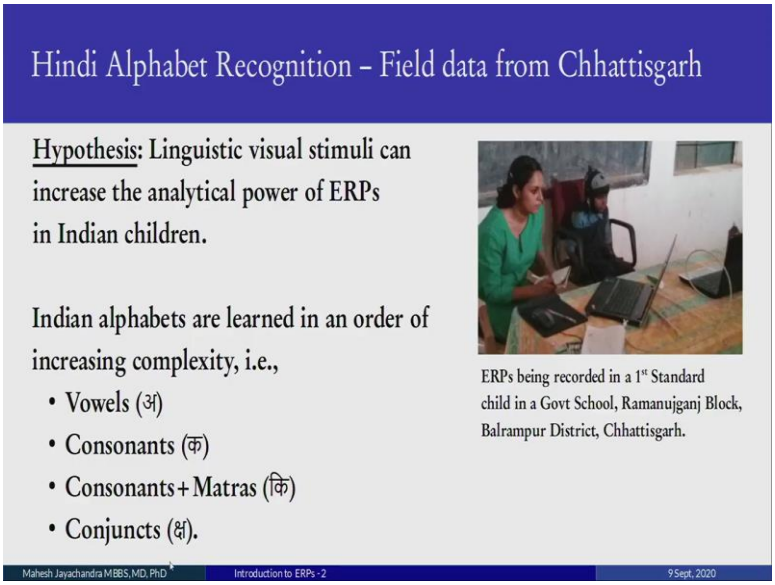


Coming to a slightly older age group, here if you remember, a stimulus where even a slight change in the stimulus properties and if you are using linguistic stimuli, you have a huge P300 response. So, the hypothesis was this, can we use Indian language stimuli to increase the power, the analytical power of ERPs in Indian children? We cannot use it in non-Indians because they do not know Indian languages.

So, most Indian languages are learned in an order of increasing complexity. First, you learn the vowels, a, aa, e, ee, then you learn the consonants ka, kha, ga, gha and then the constants plus matras kaa, ki, ku, etcetera and finally, the conjuncts, ksha, tra, pra, etcetera. So, we went to the field because we can do it. After all, this is the whole lab and just two computers and MATLAB over there and stimuli and stuff. This can be easily used in the field to record data.

So, we took it to the field, went to Chhattisgarh and we recorded from I Std. children in a government school in Ramanujganj Block, in Balrampur in Chhattisgarh. And this is here from my lab, Shilpa who helped with collecting the data and this is the I Std. kid looking at these stimuli being presented by this computer. Why did we use I Std.? I Std. is where they first get exposed to the language and the argument being that any differences would show up in the beginning when kids are exposed to something new, kids with problems would have a problem which you can see on ERPs.

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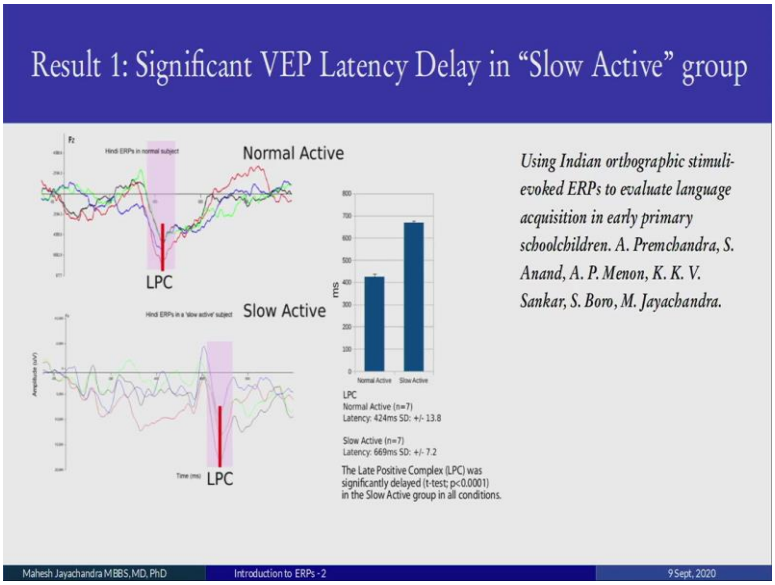


So, this is the data we got, these were normal active children and the P1N1, P2 complex we call it the LPC, late positive complex. So, for normal kids it occurred at one particular latency of about 425 milliseconds, 10 of these and 10 of these. But in kids who are slow, they are active, everything is fine. They are talking nicely on stuff but the ERPs were slow and the teacher told us that these kids were lagging.

You see a huge difference, there are LPCs are at nearly 670 milliseconds, and in neurophysiological terms that is a massive difference by a marker for normal kids and slow active kids. And bar graphs show statistically highly significant differences between, you can barely see the error bars. And so it was significantly delayed between slow active and normally active. And this is what we have presented the society for neuroscience.

The point being that we can use simple things like an ERP to straightaway say if a child has learning problems and what problem it has is the next step, dyscalculia, etcetera but we can straightaway screen a vast set of children. Why is it important? It is important because there are 130 million primary school children in India and 10 percent are estimated to have dyslexia and we do not have the number of clinical psychologists, psychiatrists to handle this, to even screen, forget about diagnosing.

So, that is why engineers like you guys must devise things like these. So, inexpensive, cost-effective but very reliable and based on hard science to screen our pediatric population.

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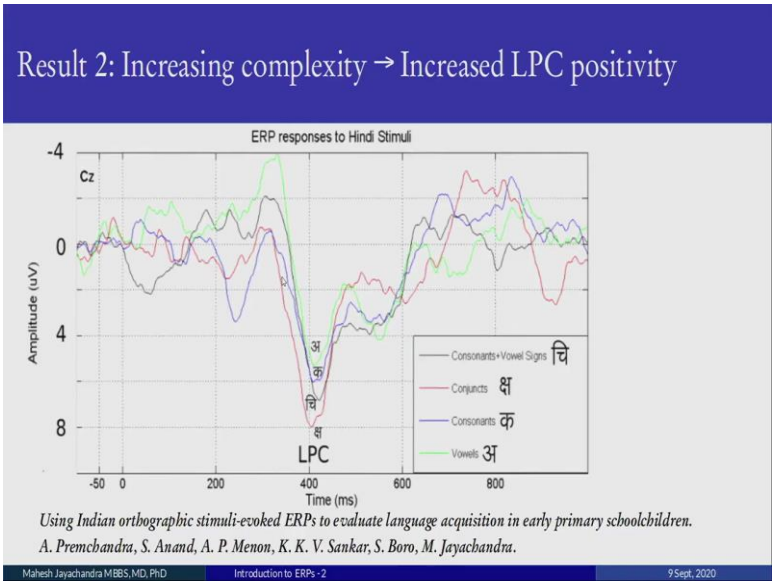


So, this is the other experiment we did where we, we have these different groups of visual stimuli, vowels, consonants, consonants plus vowels and conjuncts. So, we noticed that there was an increasing, as the complexity increased, the LPC negativity also increased. I am, the LPC positivity also increased. Here it is negative-up and this is the Cz electrode. So, between these and these, we have a way to monitor.

First of all, the child has a problem, and secondly, where is the problem? Is the problem with the conjuncts or is the problem basic with the vowels itself? And depending on what data you get the teacher can focus on the deficit and make sure, give some extra time to the child and make sure that the child overcomes this challenge.

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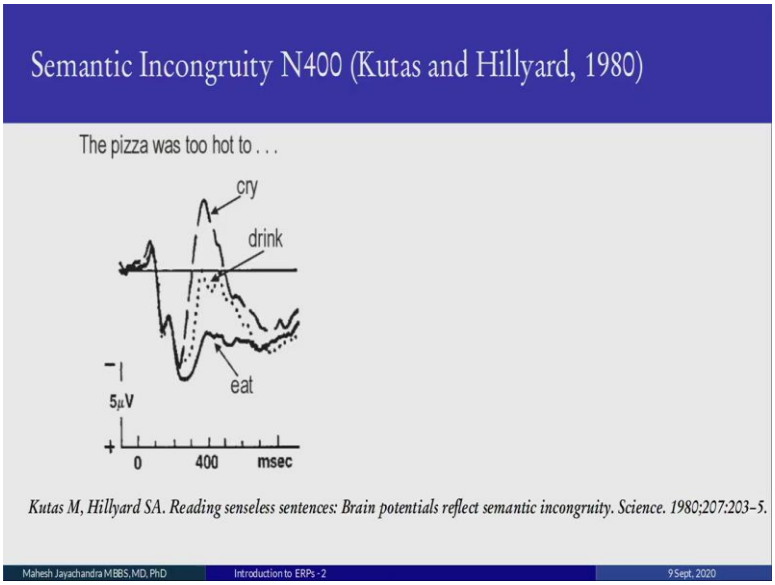

So, these are the next experiments we want to do. We want to do semantic incongruity or called the N400. So, negativity at 400 milliseconds. So, consider a sentence, the pizza was too hot to eat, that is just fine. And if you say the pizza was too hot to drink, you have at N400 you have this dotted line negativity happening. And if it is really weird and incongruous, the pizza was too hot to cry, you have a huge N400.

Now, this could be applied to middle schools where you have sentences in Hindi, in Kannada, in Tamil, in Malayalam where the last word is off and quickly again there is no question of shaming, there is no question of malingering. These are involuntary potentials. Put the cap on, flash all the sentences to the child and find out if there is a problem with the N400 or not. If the N400 is there, that means the child can distinguish between obvious grammar issues in the sentence. If it is not there, then the child has to be investigated further.

Again, all these ERP based can be done by minimally trained mental health workers. Once the screening is done by them, then they go to the next level to St. John's, to AIMS what have you.

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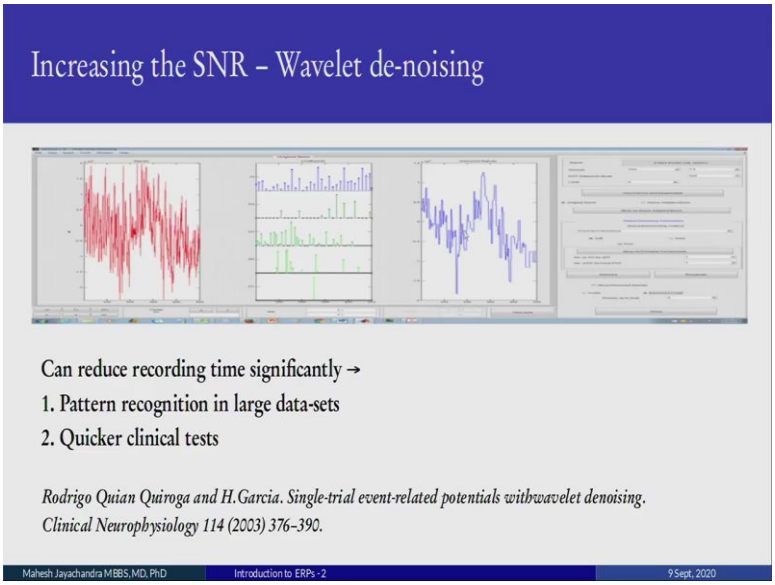


So, we talked about different kinds of cognitive potentials and talked about how they could be used in clinical medicine for societal good, so on and so forth. But what about analyzing? So, we talked about ERPs, how you have a time log stimulus, you epoch it, you filter it, you average it. After artefact rejection you average it. There is another way to denoise the data called Wavelet analysis.

So, Wavelet is a kind of frequency analysis which takes off where FFTs, Fourier analysis leaves off. And this can reduce recording time significantly and you can do pattern recognition in large datasets and the implication is you can do the first clinical test. And one of the pioneers in the application of this to EG analysis is Rodrigo Quian Quiroga and he did some very important work in the early part of the century, 2005 to 2008, where he nailed this down.

So, this is a typical P300 response which is not average, which is full of noise, the artefacts are there. And after the Wavelet's analysis is done, you have different components. You can take off components that are not useful and you can get the P300 and this is amazing because you see it on a single sweep. Normally, you have to average a 100 but here you see it on a single sweep.

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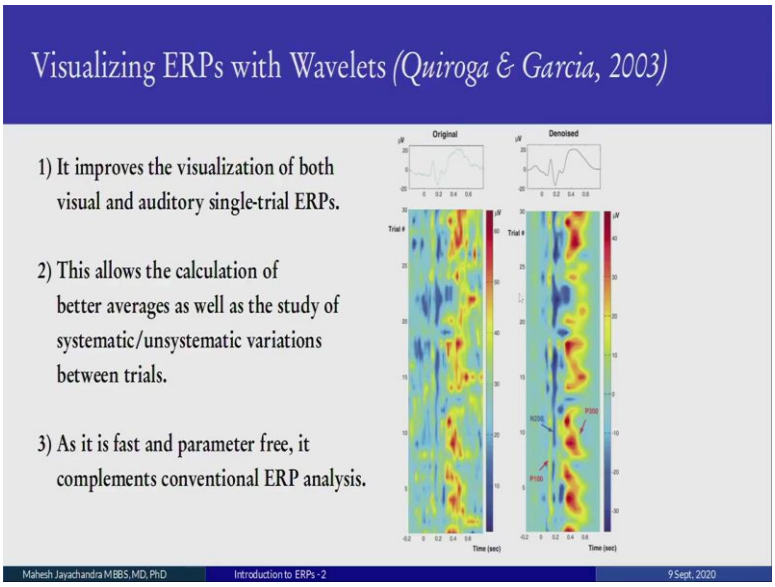


And again, this is from Quiroga and Garcia, 2003, so this is the original ERP. It is a bit noisy. After they do Wavelet denoising, you see a nice smooth response with the P1N1, P2, so on and so forth. And consider this a zipped file. If you unzip it, you have all these trials from 0 to 30. Each one is a single trial, there is some interpolation. But it is a bit noisy. It is all, if you do wavelet analysis, it is straightaway the noise disappears and you can see the P1, you can see the N1, you can see the P300 and you can see how these potentials evolve.

So in the beginning, the N200, is the N1 is not brilliant but it gets better and better. The P1 seems to be invariant and the P300, the response to some surprise in the environment that also seems invariant. So, this improves visualization of both visual, auditory, single trial,

ERPs and you can apply these to all ERPs from auditory evoked potential, visual evoked potential, somatosensory evoked potential to MMN to P300 to N400 what have you.

So, besides allowing the calculation of better averages you can also study systematic or non-systematic variations. And as it is fast and parameter-free, it complements conventional ERP analysis which is this on top. So, what is conventional ERP analysis? We look at latencies, how fast this potential occurs? We look at amplitudes, what is the amplitude of this potential? I mean we have to put a baseline over the, what is the amplitude of this potential, or we look at the area under the curve.

But usually, we stay with latencies and amplitudes. So this is an alternative way. And as I said, this is the unzipped, this is the zipped file. This is the unzipped version where you can see single events, single responses. So, applications of this could be many from looking for patterns, any kind of patterns in large datasets. For example, you have cameras on the border, you want to see if there are any intruders, P300. And if you can get individual responses then there is something unusual in the environment that needs further study.

So, thank you. So, that was the event-related potential lecture and we will have demos where we will show different ERPs, which will be uploaded to the website. Thank you very much.