Host: Welcome to the *Anesthesiology* journal podcast, an audio interview of study authors and editorialists.

Dr. James P. Rathmell: Hello, I’m Jim Rathmell, Professor of Anesthesia at Harvard Medical School and Chair of the Department of Anesthesiology, Perioperative and Pain Medicine at Brigham and Women’s Hospital. I’m one of the Executive Editors for *Anesthesiology* and you’re listening to an *Anesthesiology* podcast that we’ve designed for physicians and scientists interested in the research that appears in the journal.

Today we’re going to talk with the lead author of an original research article and an accompanying editorial view that appear in the June 2019 issue. With us today is Dr. Phillip Vlisides. Dr. Vlisides is an Assistant Professor of Anesthesiology and he works in the Center for Consciousness Science, that’s in the Department of Anesthesiology at the University of Michigan Medical School in Ann Arbor, Michigan.

Dr. Vlisides is an author on an article that appears in the June 2019 issue of the journal titled “Dynamic Cortical Connectivity during General Anesthesia in Healthy Volunteers” and there’s a second article in the same issue that looks at cortical connectivity in anesthetized surgical patients. Dr. Vlisides, thank you for joining us.

Dr. Phillip E. Vlisides: Thank you very much for having me. It’s a pleasure to be here.

Dr. James P. Rathmell: Also with us today is Dr. Jamie W. Sleigh. Dr. Sleigh is Professor of Anaesthetics and Intensive Care in the Department of Anaesthesia and Pain Medicine at Waikato Clinical School of the University of Auckland in Hamilton, New Zealand.

Dr. Sleigh wrote an editorial view that accompanies Dr. Vlisides’ research article in the June 2019 issue of the journal and it’s titled “Syncopated Tempis of the Anesthetized Brain.” Dr. Sleigh, thank you for joining us.

Dr. Jamie W. Sleigh: Well, thank you. It’s great to be able to join in.

Dr. James P. Rathmell: Dr. Vlisides, congratulations on the publication of your work. I’d first like for you to describe the research group you’re working in; it’s called the ReCCognition Study Group. Tell us about the group: what clinicians and scientists are members and how it functions and what you’re trying to study in this group.

Dr. Phillip E. Vlisides: Sure. So, the ReCCognition Study Group is a multidisciplinary group of investigators largely from the University of Michigan, the University of Pennsylvania and Washington University in St. Louis. And our broad objective is to better understand how consciousness and cognition are reconstituted after general anesthesia through advanced EEG analytic techniques.

And as you might imagine, there are many unanswered clinical and scientific questions in this realm and I think for clinicians, on a daily basis, who are trying to study in this group.

Dr. Phillips E. Vlisides: And we have a diverse group of investigators with backgrounds in anesthesiology, physics, psychiatry, pharmacology and so on to try to address some of these questions from different backgrounds and disciplines and it’s been a great experience.

Dr. James P. Rathmell: So, I want to start by giving listeners a bit of context about your study. We already know from prior studies that anesthetic-induced loss of consciousness is accompanied by changes in functional connectivity within and between brain networks. What did you set out to specifically learn when you designed this new study?

Dr. Phillip E. Vlisides: So, a number of groups have studied connectivity among brain regions in the context of anesthetic-induced unconsciousness and it appears that connections between the frontal cortex and posterior brain region may become functionally disrupted during general anesthesia. Some of that work comes from our department with investigators like George Mashour, UnCheol Lee, Tony Hudetz and many others worldwide.

The problem is many prior studies in protocols have examined advanced EEG oscillatory patterns for only a short timeframe. So, often participants will be induced with propofol, they’ll lose responsiveness and then over a short period of time—often minutes to several minutes—participants then wake up and emerge and we analyze EEG data over that short period of time.

We’re not sure whether disruptions in connectivity are still there or appreciated over a much longer period of time; for example, several hours, which might parallel the duration of a major surgical procedure.

And, in fact, there’s some emerging evidence from some groups, Drew Hudson at UCLA does some of this work to demonstrate that it might be that brain-state connectivity patterns might dynamically change independently during a stable anesthetic.

So, put very simply, our broad objective was to characterize connectivity patterns during both an anesthetic depth and timeframe that would parallel surgical anesthesia and that’s what we set out to do.

Dr. James P. Rathmell: So, your study minces the depth and duration of actual surgical anesthetics and you were really looking at functional connectivity patterns to see if there were correlates with general anesthesia during this longer exposure. What was your actual original hypothesis about cortical connectivity during general anesthesia?

Dr. Phillip E. Vlisides: Yes, that’s exactly right. And so, we initially hypothesized a (sounds like: priority) that functional connectivity pattern between anterior and posterior brain regions would be disrupted during general anesthesia and that those disruptions would persist throughout the full anesthetic maintenance phase.

Specifically, I think we were expecting to see reduced connectivity between anterior and posterior regions for the full duration of anesthesia—and I’m sure we’ll talk about this in a moment—but the results were a bit more interesting and nuanced than that, so.

Dr. James P. Rathmell: Well, tell us how you conducted the study. You analyzed electroencephalographic data in 30 healthy participants during general anesthesia. How did you actually assess for functional connectivity?

Dr. Phillip E. Vlisides: That’s right. So, the 30 participants were induced with propofol; an LMA was placed and then they were maintained at 1.3 MAC of isoflurane for three hours. And it’s first important to point out that there was no other stimulation during this time. So, this was 1.3 MAC of isoflurane anesthesia: no noxious pain or surgical stimulation, no auditory stimulation. So, a very stable anesthetic maintenance phase for three hours.

So, in terms of connectivity—and I think it’s a great question—so, what we’ve done in the study and what we’ve done in the past, many other groups have done this: we’ve used EEG and we’ve used brainwave data from the EEG to try to determine whether certain areas of the brain remain functionally connected or disconnected during general anesthesia.

So, what we’re doing is the following: we focused on frontal channels and posterior channels in this phase based on the hypothesis we just discussed. And then we analyzed electrical activity from frontal channels and posterior channels and then we sought to determine whether the electrical activity from the front of the channels remained synchronized to the posterior activity.

And we did that with a tool called weighted phase lag index and that’s an advanced mathematical tool to basically help us determine whether oscillations from the frontal channels were still synchronized with oscillations from the posterior channels.

And weighted phase lag index does that by examining the phase of the brainwave patterns to see if they’re in sync from different regions and the weighted phase component helps us to determine not just if a few regions potentially (sounds like: aren’t) synced, but the extent to which they (sounds like: aren’t) synced.

I do think it’s important to point out, though, that this is an indirect measure of connectivity and that we’re assessing EEG data from these channels that are situated on the scale, but we really can’t make direct anatomical or structural inferences. So, it is important to point out that this is an indirect statistical inference about connectivity.

And as we’re assessing these patterns, if these regions seem to remain in sync, the premise is that if those regions are in sync, they’re potentially functioning like connected and thus exchanging information. So, that’s the framework as far as how we assess connectivity.

Dr. James P. Rathmell: Well, then you went on to define discrete states of cortical connectivity. Can you explain that and how you use this k-means framework as far as how we assess connectivity.
Dr. Phillip E. Vlisides: Sure. And I think this was certainly, I think, a very challenging and complex analytic technique, especially for a clinician like myself. And so, just to step back and give a big-picture overview, as you can imagine, this is a fairly large robust dataset. So, we have 30 participants, three hours of isoflurane anesthesia with whole-scalp EEG data.

So, what we wanted to do was first determine how the data clustered together over time to determine if brain regions may be functionally connected regionally. So, we used techniques called principal component analysis image clustering, as you mentioned.

And principal component analysis, it’s a statistical technique that examines the entirety of the dataset including all this variability. And then over time, PCA, as we call it, helps us to determine how data clusters organize themselves over time.

K-means clustering is a supplemental approach to that and it’s actually a machine-learning algorithm and when we apply it to the dataset, it does something similar where it reviews all the datapoints over time and examines how datapoints—so, in this case EEG data and activity data—how they best cluster together over time. And these rhythms recur their analysis hundreds and thousands of time to see if their results are stable and consistent.

What we found was that over time brain regions that seemed to remain connected and in sync with each other seemed to gravitate to the frontoparietal channel and then also the prefrontal-frontal channels, particularly in alpha and beta bandwidth.

So, PCA and k-means clustering are advanced statistical and data science tools to examine how neurophysiologic data cluster together over time. And for any data scientists and statisticians out there, I do apologize for my crude description, but that’s, I think, the basic framework of the analysis.

Dr. James P. Rathmell: Well, alright. Let’s move on to what you found. What did you learn about cortical connectivity during general anesthesia?

Dr. Phillip E. Vlisides: To me this is really interesting and I think in the manuscript itself Figure 3 I think tells a story. We report connectivity patterns over time for all 30 participants and looking at the figure, it becomes readily apparent that these connectivity states really dynamically change and toggle pretty frequently throughout the whole three hours of isoflurane anesthesia.

And again, this is 1.3 MAC of isoflurane and no other stimulation and looking at these figures we basically see that there continues to be synchronous activity between frontal and parietal channels, and also prefrontal and frontal channels and there’s this toggled dynamic activity that inherently happens over those three hours.

And so, I think for me, conventionally in the past, naively, I always think of slow-wave anesthesia as this single dimensional state of alpha wave, beta wave. But I think we’re realizing that the patterns are more dynamic and discernible than that and the brain-state connectivity patterns, they seem to appear pretty dynamic during general anesthesia.

So, very interesting and certainly a number of questions we can ask from this point onwards.

Dr. James P. Rathmell: Yes, really fascinating. So, cortical connectivity was dynamic throughout the maintenance period of general anesthesia, even without any changes in depth or stimulation. So, what did you conclude? What does the work tell us about the brain during general anesthesia?

Dr. Phillip E. Vlisides: For me, one major takeaway is that looking at single dimensional measures of connectivity or oscillations, that might not be enough to really distinguish levels of consciousness.

If you look at our baseline figures in data, we characterize connectivity, as I said, by weighted phase lag index and those are quantitative numbers on a continuous scale. And if you really look at the figures in our data, patients would achieve their baseline connectivity values at some point during the anesthetic maintenance phase.

So, I think my takeaway is that it might not just be the connectivity itself that changes during anesthesia. We might need to look deeper at things like network shape and structure and pathology—and those are questions and topics we didn’t really address in the study—but if you look just at connectivity, that probably isn’t enough. We need to probably look at more complex perhaps network measures.

So, again, I think a lot of interesting questions that remain to be resolved.

Dr. James P. Rathmell: But no single discernible EEG pattern that can be used to identify when the brain’s anesthetized?

Dr. Phillip E. Vlisides: Yes, I mean, I think based on these data and then if you look at our surgical manuscript that was, as you mentioned, published in the same issue, at least in the context of this study looking at our connectivity data, it’s interesting, I mean, frontoparietal connectivity both in alpha and beta bandwidth would intermittently reappear during maintenance phases.

And then interestingly, we’d see these prefrontal connectivity states during general anesthesia, but then at times that would go away as well and there’d be this toggling between prefrontal-frontal synchronous states and frontoparietal synchronous states.

So, at least based on my interpretation, I can’t look at any of these indices or values and say if you look at just this characteristic or this number we can reliably tell that someone’s unconscious. It’s probably quite a bit more nuanced than that.

Dr. James P. Rathmell: Dr. Sleigh, I want to turn to your editorial view. It’s titled “Syncopated Tempi of the Anesthetized Brain” and you co-authored this with Dr. Rebecca Pullon. I encourage those who are listening to the podcast to read this elegant essay. To try to demystify the complexity of this research, you use a metaphor to compare the function of the conscious brain to that of an orchestra playing music. Can you walk us through your wonderful explanation?

Dr. Jamie W. Sleigh: The idea of an analogy between music and brain function is really because the brain consists of a lot of different regions and different hierarchies that are all producing various oscillations and nonoscillatory activity. And clearly the brain’s function is related to the coordination of this activity. So, it seemed that an orchestra kind of does something analogous to that.

I think Phil’s work certainly has shown that even during slow-wave anesthesia we think not much is happening; the brain is quite active and it’s evolving through a lot of different phases and types of activity. So, that’s more like a process than a state that the brain is in.

Dr. James P. Rathmell: One of the surprising aspects of this study is that they couldn’t find a prolonged and reliable decrease in frontoparietal connectivity during the maintenance phase of general anesthesia and that’s in stark contrast to the prevailing view, that loss of this frontoparietal connectivity is pathognomonic for loss of consciousness. Can you explain why this new study might different from the prevailing view?

Dr. Jamie W. Sleigh: Well, I mean, I don’t know, I guess maybe 10 or 20 studies in the last 5 or 10 years that have shown you get this change in connectivity. But all of the studies have been with basically with healthy volunteers having various types of ketamine or propofol or sevoflurane anesthesia.

And they’ve shown similar effects, whether you’re doing an EEG analysis or whether you’re doing a functional MRI analysis. So, there’s really quite a strong body of evidence that this might be going on, that unconsciousness is related to this loss of frontoparietal connectivity.

So, I think it is interesting that when you get real patients having real surgery in the real operating room, that some of the things that we see in volunteer subjects might not occur quite the way we think it’s occurring.

Dr. James P. Rathmell: Toward the end of your editorial you say, “To continue [with] the music metaphor, reducing the measurement of consciousness to a single number is like a music critic describing the success of a performance of a symphony by the loudness of the double basses.” You seem to suggest that this study might be overly simplistic in trying to use discrete connectivity states to define anesthetic effects. In the future, how might we refine indices of anesthetic effects?

Dr. Jamie W. Sleigh: Consciousness is a high-level phenomenon that emerges from low-level neural activity. I think we mustn’t forget this. To take a literary analogy, it’s like trying to understand the works of Shakespeare by analyzing the color of the ink he used.

So, I think from the back of our minds we’ve got to be aware there’s this—it’s an emergent phenomenon that’s fairly different in a lot of ways from basically the brainwaves, an electrical phenomenon that we’re measuring.

In the future, we have to have ways of describing a dynamic flow of states, as Philip has found in his studies. So, I think it’s quite problematic. I mean, how do you quantify the beauty of a piece of music? It’s to do with a
whole lot of phenomena like the variation in the music, the predictability and the unpredictability.

So, these things may be the way ahead where we’re not just looking for the mean of some derived number, but we’re looking for some way of describing an evolving structure.

I guess that’s pretty abstract for clinicians and I’m not enormously hopeful that we’ll have a solution anytime soon, but I think that’s the direction we need to be heading.

**Dr. James P. Rathmell**: Terrific. Well, Dr. Vlisides, what comes next for you and your research group?

**Dr. Phillip E. Vlisides**: So, I think very pragmatically the clinician; and so, I think one of the first questions that has arisen for me is, what do these changes mean clinically? If we look at these dynamic connectivity changes, does that tell us something perioperatively as far as in maybe cognitive reserve or cognitive recovery?

So, something we’re currently looking at is we’re trying to correlate these dynamic measures with postoperative cognitive recovery and delirium and we’re trying to determine whether some of these dynamic measures of connectivity correlate with cognitive reserve, age and so on.

And so, we’re trying to determine if some of these findings might actually have some clinical implications and correlations. So, I think as we said, if it’s a challenging topic – and I think at this point we probably still have more questions than answers, but we’re trying to understand these scientific and clinical relevance of these findings.

**Dr. James P. Rathmell**: I hope today’s discussion will lead many of you listening to read this new article and the editorial view that appear in the June 2019 issue of *Anesthesiology*. You can learn more about cortical connectivity during general anesthesia in both healthy volunteers and surgical patients.

Dr. Jon Wanderer from Vanderbilt and I created an infographic that attempts to explain better this volunteer study. It’s called “Anesthesia without Surgery: Unconsciousness is Metastable.”

Dr. Vlisides and Sleigh, thank you for joining me today and for the terrific explanations.

**Dr. Phillip E. Vlisides**: Thank you very much.

**Dr. Jamie W. Sleigh**: Thank you.

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