So formal statistical definition of a mediator is a variable that lies between other variables and influences the relationship with them, but it doesn’t necessarily by itself point to causation. So there’s a very good book called The Book of Why written by Judea Pearl, and he talks a lot about mediators, particularly in relation — the example he used is that of scurvy. And so you can show a statistical association between going on long sea voyages and getting scurvy, so you can say that statistically scurvy is mediated by long sea voyages, however, you really need to know the actual physical cause of scurvy, which is obviously lack of vitamin C, and was only discovered much later on in history.

And so you can think of science as a kind of exploration to find out what is true mediators; actually how something is causing something else. And this study which we’re talking about today is a step in that direction in trying to narrow down mediation with exactly how anesthetics might be causing postoperative delirium.

Dr. BobbieJean Sweitzer: Thank you. So Dr. Johnson Akeju, can you tell us a bit more about this previous so aptly named trial, the MINDDS trial, in which you analyzed the data for this (inaudible)?

Dr. Oluwaseun Akeju: Yes, so the MINDDS trial is a 370 patient randomized controlled trial, so in the parent trial, the MINDDS trial, what we’re trying to do is understand or evaluate the efficacy of a single nighttime dose of dexmedetomidine, so one mcg/kg given at night, to prevent delirium. I think one of the important things is that we don’t know a lot about the pathophysiological mechanisms of delirium, so what the MINDDS trial is also structured to do is give us a firm understanding of perhaps the cellular and molecular mechanisms underlying delirium through analysis of serum, RNA and DNA samples, and also to investigate whether intraoperative EEG signatures, such as burst-suppression that we’re discussing today, are associated with delirium.

Dr. BobbieJean Sweitzer: So do you think we can agree on some well-defined risk factors for delirium or is this complication still a total mystery?

Dr. Oluwaseun Akeju: You know, I think we can certainly agree on risk factors for delirium. I think a lot of great work has been done to make clear some of those risk factors; I think some of the common risk factors for delirium include cognitive deficits, dementia, older age, critical illness, infections, medications such as benzodiazepines, immobility, sensor impairment and frailty. However, I want to just qualify that to say, you know, more work really needs to be done to clearly refine our understanding of what delirium is. Perhaps some of those risk factors are much more prevalent in certain subtypes of delirium. We certainly know enough, but I think there are opportunities for fundamentally advancing our understanding of delirium and the risk factors.

Dr. BobbieJean Sweitzer: So you chose a setting of patients having heart surgery, I believe, are there different risk factors for delirium in these patients, for example having cardio pulmonary bypass compared to other surgeries?

Dr. Oluwaseun Akeju: Yes, so we chose patients having heart surgery because of the homogeneity in terms of surgical procedures, anesthetic management and the inflammatory response from cardio pulmonary bypass is rather unique. It provides us an opportunity to study the mechanisms underlying delirium without allowing for too much in terms of confounds. And I say confounds such that, you know, a lot of studies of delirium in our ICU settings are obviously confounded by critical illness such as, you know, sepsis. And I think at some fundamental level that perhaps it’s challenging to tease out or disentangle the underlying mechanisms of delirium. So that’s why we chose patients who are rather homogenous to get at the mechanisms underlying delirium in our patient cohort.

Dr. BobbieJean Sweitzer: Makes a lot of sense. So Dr. Sleigh, I wanted to talk a little bit about burst-suppression with both of you, but I’m going to start with you. I think other studies have shown that burst-suppression on association between the number of gray hairs in my beard and the expansion of the universe. That’s a kind of pointless statement. What you really need to understand is the flow of real causation amongst the variables.

So formal statistical definition of a mediator is a variable that lies between other variables and influences the relationship with them, but it doesn’t necessarily by itself point to causation. So there’s a very good book called The Book of Why written by Judea Pearl, and he talks a lot about mediators, particularly in relation — the example he used is that of scurvy. And so you can show a statistical association between going on long sea voyages and getting scurvy, so you can say that statistically scurvy is mediated by long sea voyages. However, you really need to know the actual physical cause of scurvy, which is obviously lack of vitamin C, and was only discovered much later on in history.
EEG during anesthesia is associated with delirium. So what was novel about Dr. Akeju’s study?

Dr. Jamie W. Sleigh: The novelty really was the application of a causal approach to think about and sift through the variables. So typically in a multivariate analysis, people try and find the best combination of variables that gives you the maximum predictive power, but don’t actually think about the causation. And so the first step is to make a picture, which is called a causal diagram or technically a directed acyclic graph, and use a whole lot of variables that basically sit upstream from the suppression and tend to be removed from the multivariate model when burst-suppression is put into it.

Now there’s obviously these analyses are surprisingly complex, and I think this is really just the first step in the causal approach to move from association to causation. Because there’s a lot of unknown and unmeasured confounders, which as just been mentioned, you want to reduce by kind of looking at a really narrow surgical group.

Dr. BobbieJean Sweitzer: So Dr. Johnson Akeju, I think you mentioned earlier that burst-suppression was essentially an overdose of anesthesia. So was the burst-suppression intentional or just happened to occur during these anesthetics in these patients that you were looking at?

Dr. Oluwaseun Akeju: You raise a very important point. So burst-suppression is typically encountered after the induction of general anesthesia. I think this is largely driven by the fact that we administer large doses of hypnotics to rapidly induce general anesthesia. For this study we chose to study non-intentional burst-suppression by analyzing the EEG for burst-suppression during cardiopulmonary bypass. And the reason we chose to do this is cardiopulmonary bypass is a period with stable and controlled anesthetic and physiological management. This, if you will, allowed us to study unintentional burst-suppression.

Dr. BobbieJean Sweitzer: I understand, but Dr. Sleigh can you maybe tell us exactly what burst-suppression is and is it always a bad thing?

Dr. Jamie W. Sleigh: As its name suggests, burst-suppression is the name we give to a pattern of the EEG with a period of suppression, which is electrical silence, interspersed with bursts of activity. Burst-suppression is probably both good and evil, as alluded to in the paper. There are probably a number of different flavors of burst-suppression. It’s generally caused by hypnotic drug and other pathological processes which generally involve metabolic or mitochondrial dysfunction. Examples would be brain ischemia or hypoglycemia. But whether the induction of burst-suppression fits in, a secondary vicious cycle of further neurological damage is a bit unclear. Certainly it’s common practice to actually therapeutically induce burst-suppression near anesthesia if you want to try and protect the brain during a temporary clipping of an aneurism or something. Obviously the idea here is you’re inducing metabolic demand by poisoning the mitochondria a bit. And so you have to prolong that safe ischemic time.

As just mentioned, burst-suppression is very common in younger patients and seems to be relatively harmless. But in older cohort of patients here I think it’s safe to say burst suppression is certainly a marker of brain frailty. It is also an indicator of bad things to come and probably unhealthy pathological processes. And these results have been pretty similar to those reported in quite a few studies. They almost always show a strong association between burst-suppression and postoperative delirium.

Dr. BobbieJean Sweitzer: Dr. Johnson Akeju, what were the predictors of burst-suppression in this cohort of patients that you looked at?

Dr. Oluwaseun Akeju: For the predictors for burst-suppression in the cohort of patients we analyzed were age, ASA physical status, objective assessment of cognitive status using the Montreal cognitive assessment, measure of physical function, measures of mental health, actually pain, sleep, and then we used some other metrics such as EEG power during general anesthesia but before the onset of cardiopulmonary bypass. We used the length of cardiopulmonary bypass, and also temperature during cardiopulmonary bypass. It’s important to know that these predictors were the same predictors for delirium. The only difference was we added burst-suppression as an additional predictor. We were trying to figure out the association between all these predictors and delirium.

Dr. BobbieJean Sweitzer: So I think that it’s fairly well-known that, you know, older age, higher ASA physical status, worse preoperative cognitive function; that all are associated with a higher risk. But you mentioned a few things I guess I want to clarify. You talk about pain, sleep and temperature. Can you specifically tell us if more pain was associated with more burst-suppression or delirium post-op or both?

Dr. Oluwaseun Akeju: The reason we chose all of the risk factors we did was really we placed these risk factors in context with what’s been known in the literature on delirium. So certainly there’s no definitive evidence that pain is causal to delirium. However, there’s been a few studies that have shown or made clear that there are associations between pain and delirium. So that’s why we wanted to study that association in context of burst-suppression. I think we did the same thing with sleep, because certainly there’s been a few studies making clear that perhaps sleep disruption may be a risk factor for delirium. So you know, we studied these risk factors in a context of burst-suppression with the notion that we were trying to understand the causal pathway between a variety of risk factors, burst-suppression and delirium.

Dr. BobbieJean Sweitzer: Understood. So Dr. Sleigh, how bad is post-operative delirium? I mean does it predict poor outcome short term, long term? Does it predict death? Is it associated with increased costs, or what kind of adverse events are associated with delirium?

Dr. Jamie W. Sleigh: First I would say post-op delirium is usually very distressing for the family and the staff and sometimes even for the patients if they have memory of the episodes. And the other issue is that agitated delirium can sometimes undo the surgery if you’re doing free flaps or something. Conversely, if you have a hyperactive sort of inert delirium, the patients definitely have worse post-op problems. I mean you had more muscle wasting, pneumonia, deep vein thrombosis, etcetera.

There was a meta analysis a couple of years ago in Anesthesiology with suggested that postoperative delirium was associated with a fourfold increase in odds of death. Although it has to be said, this effect was a bit different when that controlled to other confounders, but it’s certainly associated with more readmissions, longer hospital stays. That’s been shown pretty consistently.

Dr. BobbieJean Sweitzer: So Dr. Johnson Akeju, you concluded in your manuscript that patients with postoperative delirium had a preexisting susceptibility to delirium. Can you elaborate on that?

Dr. Oluwaseun Akeju: So what we did was we found that there was an EEG signature that we could elicit way before patients developed burst-suppression, and that EEG signature was really a low broadband power right between 10 Hz to 20 Hz that we saw even before cardiopulmonary bypass. And I think, you know, that the ladder of inference was such that, you know, because the EEG reflects activity and state of underlying brain cells, neurons and glia, you could certainly surmise that the EEG findings, you know, which existed before the development of burst-suppression, and certainly before patients were screened positive for delirium, that these EEG findings were a marker of a vulnerable brain or a brain that’s really predisposed to developing delirium, if you will.

Dr. BobbieJean Sweitzer: Interesting. And do you think that there’s a possibility that a pre-anesthetic EEG, or was there any evidence that a pre-anesthetic EEG could possibly have markers that would predict delirium?

Dr. Oluwaseun Akeju: So I think that’s a fascinating concept and it’s a concept that we and certainly lots of other research groups are interested in. And I think the one thing is that the anesthetic drugs that we administer to patients cause a lot of changes or dynamics in the brain. And I think what’s clear is that these EEG changes are dynamics that the anesthetic drugs bring forward cause a high signal to noise ratio problem such that you could see a lot more of the brain oscillations than you would probably have seen without anesthetic drugs.
And I’ll point out to a few studies that were done in the ’90s where neurologists actually gave anesthetic drugs to patients with dementia to make clear or at least illicit EEG signatures that they could point to and use to separate patients who had dementia from normal patients. And some of those EEG signatures couldn’t be deciphered preoperatively or before the anesthetic drug, which you know, points to the fact that actually anesthesia or anesthetic drugs may actually be a probe or a tool to illicit underlying brain dysfunctions that we may not be able to tease out or at least pull apart pre-anesthesia or without anesthetic drugs. So lots of interest in this topic and I think over the next few years we probably will learn a lot more about this kind of exciting research topic.

Dr. BobbieJean Sweitzer: That’s really fascinating. Is it possible that anesthetics could become diagnostic tools?

Dr. Oluwaseun Akeju: Yes, I certainly think so.

Dr. BobbieJean Sweitzer: Your study includes some very interesting but also some challenging concepts. I’d specifically like to talk a little bit about figures one and three. I know that’s challenging if we don’t have the paper in front of us, but we encourage our listeners to, you know, sometimes have the paper in front of them when they listen to our podcast. But for figures one and three, which I think very simply and very elegantly demonstrate the essence of this study, at least to me. So figure one I think is an initial hypothetical causal model. Can I paraphrase this as representing the questions, perhaps, you tried to address?

Dr. Oluwaseun Akeju: Yes. {Laughs}

Dr. BobbieJean Sweitzer: And then I think figure three – great. Thank you. I think figure three is the final estimated causal model, which I interpret as your results. So I urge our listeners to read your article, but here we are without the benefit of those visual aids. Can you try your best to try and explain these to our listeners and what you were trying to represent in those two figures?

Dr. Oluwaseun Akeju: No, absolutely. Similar to what Dr. Sleigh mentioned earlier, we tried to address our research questions by first laying out what we thought were reasonable causal relations, and we laid those out in figure one. And what we did was we really did try to ask the question does known predictors of delirium directly cause delirium or do they end up on the causal pathway to delirium by an intermediary, if you will, and that intermediary was burst-suppression. So we laid that out in figure one, and then we let the relations suggest the analysis that was best suited to fit our implied causal relations. So although causal relations were an important part of our models, I think what we did was we decided to leave things at a level of a structural equation model framework. And in the context of figure one, we ran two-step multivariable logistic regressions where we try to understand the association model framework. And in the context of figure one, we ran two-step multivariable logistic regressions where we try to understand the association between those risk factors and burst-suppression. And then in the same vein, were those same risk factors include in burst-suppression and how they were related to postoperative delirium.

What we found out using this framework was that, you know, we were able to confirm that burst-suppression was associated with delirium, however we found that burst-suppression was an intermediary, really, on the causal path to delirium. So increase in age, poor physical function and low EEG alpha power and low temperature, obviously, were also associated with delirium by way of burst-suppression as a mediator in a statistical sense. I think in a much more practical clinical sense, we’ll say burst-suppression was just a marker of increase in age, poor physical function and et cetera. You know, we tried to highlight those contexts very well in figure three.

Dr. BobbieJean Sweitzer: I think you did a very good job. So Dr. Sleigh, what is the most important conclusion that you and you think our listeners should take away from Dr. Akeju’s study?

Dr. Jamie W. Sleigh: Well, as a clinician I would like to reiterate what Dr. Johnson Akeju was mentioning just previously. Even now if you give a patient a general anesthetic you should think of it as sort of a brain stress test. And if you see low amplitude power or not much alpha or a lot of burst-suppression, the patient is waving a flag shouting I’ve got brain frailty or high brain age, which I think we’ll mention in a minute. And what you take home is if you don’t look at an interoperative EEG, you’ll never see this information.

Dr. BobbieJean Sweitzer: And I assume when you say EEG, this is not (abyss)?

Dr. Jamie W. Sleigh: You could see it on (abyss), you’ve just got to look at the raw stream, but (abyss) will tell you most burst-suppression. So I mean whilst I agree that this can be developed further, even tomorrow or today in your operating rooms you could be looking at this and saying this person has burst-suppression and they’re on 4 mic of sevoflurane; I think they’re, you know, going to be trouble and I’m going to do various things to try and ameliorate that postoperatively.

Dr. BobbieJean Sweitzer: Excellent point. But Dr. Johnson Akeju you discuss a bit about brain age in your paper. Can you tell us more about brain age and the brain age index?

Dr. Oluwaseun Akeju: Yes, I think fortunately there’s a renaissance of some sort in anesthetic brain monitoring. So many research groups are now showing that not only can we use the EEG monitor to infer the anesthetic state, that it’s now possible, as Dr. Sleigh mentioned, to infer brain vulnerability, if you will, from interoperative EEG. So the concept of brain age, which is different from chronological age, was coined by some researchers in Boston. So what they did was they looked at thousands of EEGs that were obtained during sleep. They used a machine learning based model and they used EEG features. They fed it into this model and what they were able to show was that certain patients, and it was typically patients with neurological or psychiatric diseases, were found to exhibit increased brain age compared to healthy controls.

So, you know, the inference is that you could use the EEG and infer brain vulnerability or brain frailty from the EEG. So as we mentioned that anesthetics are some sort of a stress test of the brain, we anticipate that this concept in the future could be applied to, you know, every day work in the OR to infer which ones of our patients or what patients are at high risk.

Dr. BobbieJean Sweitzer: So there appear to be a few modifiable risk factors (inaudible) that you have discussed and that we have identified. For example, preexisting – or non modifiable such as preexisting, you know, age and cognitive function. We may not be able to change that. Do you think from your work, though, that we can maybe both reliably predict and prevent post-op delirium by either, I guess, modifying the existing risk factors or changing anesthetics or what ideas do you have for us?

Dr. Oluwaseun Akeju: So I think a lot more work needs to be done to get us to a place where we could reliably reduce the incidence of delirium in all patient populations by a certain percentage. However, what we do have right now like a readily accessible tool are these multicomponent non-pharmacological interventions for the prevention of delirium. I think what a lot of multicomponent interventions entail is ensuring that our patients don’t have sensory deprivation. So, you know, you give your patient their hearing aids and make sure they have their glasses and make sure there is a family member around as soon as they need to. Make sure you treat pain.

From a pharmacological perspective, nighttime administration of low-dose dexmedetomidine has been shown in a few studies to be associated with a decreased incidence and duration of delirium. It’s unclear how it works. Perhaps it’s an immune modulator. Perhaps it helps people sleep better. But we look forward to more studies of these non-pharmacologic and perhaps combined with pharmacologic approaches in various patient populations.

Dr. BobbieJean Sweitzer: So Dr. Sleigh I want to ask if you have any thing to add to those excellent suggestions that Dr. Johnson Akeju made, and also perhaps pose, you know, any suggestions or thoughts you have for future research to help us sort of get to some more practical answers.

Dr. Jamie W. Sleigh: I would entirely agree that you need to do a whole lot of things. There’s no single magic bullet that will treat postoperative delirium. The issue is that we’re stuck in our causal understanding, similar to, perhaps, sort of the 19th century understanding of scurvy that we found
various things that ameliorate it. You know, they knew various things like lime juice would reduce scurvy. But essentially I think our research is we need more mechanistic understanding of the pathological processes so we can actually reach down and treat the brain. I mean if burst-suppression is telling us the presence of mitochondrial stress, then maybe we have to give drugs that are some sort of mitochondrial rescue treatments. You know, I think there’s a lot of different avenues we can go down. I’m very happy to hear that the MINDDS study will be looking at some of these mechanistic things; gene expression, etcetera. So I look forward to hearing the final results of that study.

**Dr. BobbieJean Sweitzer:** Dr. Johnson Akeju, you get the final comments here.

**Dr. Oluwaseun Akeju:** No, I think it’s important to close by making it clear that delirium is now increasingly being recognized as a public health priority. But I think despite the fact that it’s a public health priority and there potentially may be a modifiable approach to reducing the burden of delirium on our public health system, we have numerous knowledge gaps that need to be addressed before we could advance our approach to preventing or treating delirium. And I’ll give you a few of them.

So at present we don’t have a reference standard for identifying subtypes of delirium. So it’s possible that delirium is just not one unitary disease or diagnosis, but that there are different subtypes of delirium with different pathophysiological mechanisms. And so I think we need well coordinated interdisciplinary research for continued advances in delirium research.

**Dr. BobbieJean Sweitzer:** Well said. I hope today’s discussion will interest many of our listeners and lead you to read these important articles to learn more. Thank you Drs. Johnson Akeju and Sleigh for discussing your work with us today. I wish you well as you continue your efforts to enhance the practice of anesthesiology and strive to improve the care of our patients.

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