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

Dr. James Rathmell: Hello. I'm Jim Rathmell, Professor of Anesthesia at Harvard Medical School and one of the executive editors of Anesthesiology. 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 authors of a publication that appears in the November 2016 issue of the journal. With us today is Dr. George Mashour, who is the Bert N. La Du Professor of Anesthesiology Research at the University of Michigan, where he also serves in a number of other roles, including Associate Dean for Clinical and Translational Research and Director of the Center for Consciousness Science. Dr. Mashour is the senior author on an article titled, “Neural Correlates of Wakefulness, Sleep, and General Anesthesia: An Experimental Study in Rat.” Welcome, Dr. Mashour.

Dr. George Mashour: Jim, thank you very much for having me.

Dr. James Rathmell: Also with us today is Dr. Andrew Hudson, who is now Assistant Professor-in-Residence in the Department of Anesthesiology and Perioperative Medicine at UCLA. Dr. Hudson and Dr. Kane Pryor in the Department of Anesthesiology at Weill Cornell Medical College in New York wrote an editorial view that accompanied Dr. Mashour's article, entitled, “Integration and Information: Anesthesia Unconsciousness Finds a New Bandwidth.” Dr. Hudson is going to share some of the perspective that his editorial brings to this new research. Dr. Hudson, welcome, and thank you for your willingness to share your insights.

Dr. Andrew Hudson: Thanks so much for the invitation to participate.

Dr. James Rathmell: Dr. Mashour, you first. Congratulations on the publication of your work. This is some pretty complex work, so I'm hoping you can walk us through to some basic level of understanding. To start, what you were aiming to understand better through this series of experiments was more about the neurochemical changes within the cortex of the brain, and the electrical connectivity between different regions that accompany anesthetic- and sleep-induced unconsciousness. Can you elaborate on what we know about changes that occur in the brain during the transition from awake to anesthetic- and sleep-induced unconsciousness, and how your approach aimed to add new information?

Dr. George Mashour: First of all, thank you for the very positive comments; again, for the opportunity to speak. I've been out of my training for about ten years now, and my primary focus has really been on the way the brain communicates, and how that communication within the brain helps to sustain consciousness, and what happens to that communication when we go under general anesthesia, when we fall asleep, or in situations of pathological unconsciousness.

This was a relatively undeveloped field when I was a resident. The field has blossomed; really, in some respects it's exploded, in terms of the data that have been coming out. But it has remained largely disconnected from the earlier, and ongoing, and very important work related to the molecular mechanisms of general anesthesia. And so, part of my goal with this study and with our team, was to start to build a bridge between some of the molecular and cellular changes that we know happen during general anesthesia, and some of these changes in terms of brain connectivity and brain communication. We tried to approach that by looking at and focusing on one important neurotransmitter system—namely the cholinergic system, acetylcholine—which is high in the cortex when we're awake; it is low during non-REM or slow wave sleep; and then it's high again during rapid eye movement, or REM sleep.

What we did was fairly straightforward in terms of recording EEG activity in the brains of rats. Now, unlike the EEG in humans or monitoring in the operating room, this wasn't on the scalp, but actually on the epidural surface, just covering the brain. And in addition to that, we inserted a probe for microdialysis in the prefrontal cortex. And that basically is a way of providing a window into neurochemical changes. We then had the rats in various states of unconsciousness, including propofol-induced unconsciousness, sevoflurane-induced unconsciousness, and both non-REM and REM sleep. And what we did in the analysis was to look at different ways of assessing how the brain communicates across different areas that are processing information, and what the associated neurochemical changes were.

What we found was not entirely surprising. We would predict, based on our earlier work in animals, and also in humans, that there would be a breakdown of communication during general anesthesia and sleep. And indeed, we found that. What we identified was a specific frequency bandwidth of the EEG—higher-frequency activity around 150 hertz; that is, 150 events per cycle—that there was a coherence in communication in that bandwidth that was very consistently found during wakefulness, and very consistently interrupted during general anesthesia and sleep.

So, I think what we add to the literature with this study is a focus on this higher-frequency activity that we can't really see through our scalp EEG with humans in the operating room, and also a way of starting to build a bridge by considering the neurochemical changes along with the connectivity changes. And my hope is that, in the future, that bridge will continue to link to more molecular actions and cellular actions of general anesthesia.

Dr. James Rathmell: Well, you answered a lot of my next questions by really stepping through that — methods that you used. But I want you to focus on one particular area and try and explain to us this coherence and symbolic transfer entropy. What does that mean, and how was that used in your study to shed light on this connectivity, and even the neurochemical changes; or were they unrelated?

Dr. George Mashour: Well, first, let me give you and the listening audience the lay of the land in terms of what we mean by connectivity. There are really four types of connectivity that are generally considered when thinking about neuroscience; when thinking about the brain. The first is structural connectivity. How does one group of neurons physically connect or synaptically connect with another group of neurons? That's something that you might identify in terms of neuroimaging with diffusion tensor imaging, also called tractography, where you're getting a sense of the physical or structural connections. We don't think those are disrupted during general anesthesia. We hope that those aren't disrupted during general anesthesia. This is something that people are looking at.

But what we're more focused on is functional connectivity, and that relates to the way activities in different areas of the brain relate to one another in terms of their temporal order, or their synchrony. Now, functional connectivity is a statistical relationship between two areas of the brain, but it doesn't necessarily mean that these brain regions are in-
teracting with one another, or having a causal influence on one another. When we’re talking about communication in the brain, we’re talking about an exchange of information, where that information makes a difference in another region of the brain.

So, to try to get a handle on that, there are two other measures of connectivity. I talked about the structural connectivity; talked about functional connectivity. Trying to get a handle on that communication or information transfer is a job for what’s referred to as directed connectivity; that is, it’s not just that these two areas are related, but possibly related through another independent mechanism, but how is one region affecting the other in a more directed fashion? So, for example, the prefrontal cortex having a directed effect on the posterior parietal cortex. And also, effective connectivity, which really gets at the causal relationship; so, in the case of the prefrontal cortex, truly influencing the posterior parietal cortex.

So, our study looked at coherence, which is a form of functional connectivity, and it looked at symbolic transfer entropy, which is basically a fancy way of expressing the inference that one part of the brain is having an influence on another part of the brain. I emphasize inference, because there are lots of limitations to these techniques. This is really course recording. There’s a lot of activity going on in terms of neuronal exchange.

The way I think about it, when we get the output of these data, it’s sort of like looking at the Dow Jones in terms of a stock index, or choose your favorite stock market or stock index, that’s giving us an overall picture of a lot of rich, dynamic activity on the trading room floor. In the case of the stock exchange, the trading room floor is an exchange of shares or an exchange of money. In the brain, that trading room floor really has to do with the neuron-to-neuron interactions and the communication exchanges.

So, what we’re looking at is really more that net effect, not telling us everything about the rich dynamics that are going on. In fact, Dr. Hudson, who’s also part of this call, is, I think, an exciting leader in the new generation that is helping to draw our attention to this dynamic activity. So, what we did was really look at a surrogate for how different areas of the brain communicate with one another, and showing that this breaks down during general anesthesia.

Dr. James Rathmell: Now, you conclude by telling readers the following, and I’m quoting from your paper: “This is the first study to report suppression of electroencephalographic coherence and frontal-parietal directed connectivity in high-gamma bandwidth across multiple states of unconsciousness that include propofol anesthesia, sevoflurane anesthesia, slow wave sleep, rapid eye movement sleep,” and you compared with spontaneously occurring wakefulness. Can you explain what that means, and why it’s important, and how might that lead to new anesthetics, or better ways to test anesthetics—maybe even better ways to monitor patients during anesthesia?

Dr. George Mashour: So, one of the neat things about this study, I think, is just the number of states that we investigated. Oftentimes, people are looking at sleep, or they’re looking at one anesthetic. We really tried to take a broad approach by looking at two clinically relevant anesthetics, propofol, by doing an intravenous infusion; sevoflurane; and looking at sleep. And we looked at it in a systematic way. One of the advantages of doing that, in addition to multiple states of wakefulness—both, you know, spontaneous wakefulness; forced wakefulness, in terms of trying to keep the animals awake; recovery wakefulness—it gives you an opportunity to see some patterns, because you have a number of different states and a number of different indices that you’re comparing.

So, I think what stood out to us, in looking at this pattern, is that this higher-frequency activity seemed to be consistently present and seemed to be important for communication during all states of wakefulness, and it was suppressed during all states of unconsciousness. So, that’s something that I think points us in a direction of thinking about what might be important for consciousness; what might be important for inducing unconsciousness, either during general anesthesia or during sleep.

Again, this was in a higher-frequency bandwidth that we don’t routinely measure, and can’t measure in the operating room. So, I don’t think it’s going to have a direct effect on monitoring in the near future, or a direct effect on new anesthetics. I think it does start to point us in the direction of what might be going on in terms of that breakdown of consciousness. And what we need to do next is to look for surrogates or signatures that we can measure in the operating room, that might help give us a sense or a window into that underlying neurobiology.

Dr. James Rathmell: Wow. Terrific. Dr. Hudson, what a terrific—and I have to add, an equally complex—editorial. You start your comments by giving readers this perspective: “Prior studies suggest that the underlying structural connectivity in the sense of the point-to-point wiring of the brain, is stable under anesthesia, but it’s reversibly rendered nonfunctional. How cortical computation becomes fragmented by anesthetics and then reconstitutes itself after recovery thus remains a vital question.” Can you elaborate on what Dr. Mashour has already described about connectivity within the brain and its importance to consciousness?

Dr. Andrew Hudson: So, I think that the really interesting line that this connectivity set of studies has led us down, is that we’re starting to approach characterizations of the brain during unconsciousness that are functional states. Now, humans have been wondering how the brain leads to the mind for eons, and plenty of smart people have tackled this question. And as we’ve developed a greater biological understanding, I think it’s become apparent that a notion that any change in consciousness must come from some change in brain state, but I don’t think that we have a consensus view of what that change in brain state would have to be.

The nice thing about looking at this at a functional level is that it gives us the chance to study consciousness in a way that could unify multiple molecular mechanisms that could cause unconsciousness. We’re constantly thinking about anesthetics as operating principally on a GABAergic or inhibitory circuit mechanism, but the standout anesthetic that always defies those explanations is ketamine.

But there’s certainly the chance that the more NMDA-dependent mechanisms, whether it’s ketamine, or to a lesser extent xenon and nitrous, could possibly cause the same sort of disruption of connectivity, and that that could be in some sense a final common pathway by which they disrupt consciousness, is very compelling. It moves us beyond just a molecular or single-neuron approach to something that is probing the functional state of the brain, which we presume has to be underlying the huge behavioral state switch that you see with anesthetics or with sleep.

And I think that that bridge that Dr. Mashour was talking about, in terms of going from the molecular to the population level, is going to be critical to our understanding of consciousness broadly, but also to our understanding of general anesthesia, as well as the sort of physiologic state switch of sleep.

Dr. James Rathmell: You tell us that newer studies have demonstrated the importance of connectivity among frontoparietal networks. How does this differ from earlier theories?

Dr. Andrew Hudson: Well, people have been very interested in looking at the brain while you’re unconscious, for as long as people have been unconscious. And certainly, you know, as early as the ’30s, people were recording EEG to try to gain some insight as to what was happening in the brain during ether anesthesia, and there were some really exciting developments starting in the late ’40s, with Moruzzi and Magoun looking at the reticular activating system, and how you could stimulate
in various points in the reticular activating system and cause desynchronization in the EEG which was consistent with the EEG pattern you would see during wakefulness. So, rhythms would speed up, and the voltages would drop, as presumably the neuronal population stopped being synchronized, which is what you would see during anesthesia or during sleep, with slow waves in the EEG.

Very early on, with the initial application of EEG to ether anesthesia, we moved away from the notion that anesthesia is completely suppressing activity in the brain. I think someone has labeled that the "wet blanket" theory of anesthesia—that all that happens in anesthesia is, you silence all the neuronal populations. That’s clearly not true, and that’s clearly known not to be true for a long time now.

But what is going on hasn’t been clear. And so, following Moruzzi and Magoun, a lot of people felt that what anesthetics might be doing is disrupting these brainstem arousal centers that all contribute to cortical activation, and that anesthetics must be acting either on locus coeruleus, or dopaminergic nuclei, or the basal forebrain with their acetylcholine outputs, or the nonspecific thalamus, and that these were all parts of the reticular activating system that contribute to wakefulness, and that withdrawal of activity in those areas would lead to loss of consciousness.

And later work in the ’90s and early aughts by a number of people, including Michael Alkire, led to sort of a thalamic switch hypothesis, that maybe what is critical for anesthesia is shutting down of the thalamus, and if you were to shut down the thalamus you would remove input to cortex, and that would lead to unconsciousness. And it’s certainly true that if you lesion thalamus, you get an acute coma. The areas that are most important for producing coma from a thalamic lesion are the same nonspecific thalamic nuclei that Moruzzi and Magoun were reporting, so it was a nice and consistent theory.

But, again, we’ve now started to look at these connectivity questions as being perhaps a better marker of unconsciousness, and starting to appreciate that maybe there could be direct cortical effects of the anesthetics that could explain unconsciousness by disruption of cortico-cortical connectivity; and whether that’s mediated through the thalamus or not is an open question, but the two are not mutually incompatible.

But this question of, can we look at a cortical level and explain at a cortical level what disruptions might be caused by broad classes of anesthetics, I think is a very exciting potential. And the chance to start to work together from this bottom-up notion of these brainstem nuclei contributing to cortical activation on a broad level, but informing our notion of network connectivity from a molecular level, is what’s really exciting about this study by Dr. Mashour and colleagues.

Dr. James Rathmell: But the crucial question about how loss of connectivity during anesthesia or sleep states leads to reduction in consciousness, remains. You describe something called integrated information theory, or IIT—a mathematical characterization of consciousness that might help explain how loss of connectivity leads to reduction in consciousness. Can you explain that for us, and in a way that your average anesthesiologist might understand [laughter]?

Dr. Andrew Hudson: I have to admit, every once in a while I will read an IIT paper and scratch my head a bit as well, so — I picked that particular theory dimension because it has been embraced by the anesthesia community. And part of the reason for that, I think, is that the proponent of the theory, Giulio Tononi and his colleagues, have done a great job of going back and trying to continually rework the theory to come up with a better description of their insight into what they think consciousness is.

And what integrated information theory proposes is essentially that, for a system to be conscious, it’s got to do two things. Those two things are, it’s got to have a wide range of information that it can convey; and it’s got to integrate whatever that information is into a single state at a time. And so, it’s got to be informative, in that it has to have lots of multiple states, and it has to integrate them together into a single final percept, if you will. It’s, in a way, moving the goalposts. It’s redefining what consciousness is, as this integrated information.

And in some senses that’s problematic. If you go to the insight of what consciousness is, that you and I have as daily beings who are conscious, it — consciousness is intrinsically phenomenological. It’s intrinsically got a point of view. It’s intrinsically about the experience of being conscious. And that’s not a part of integrated information theory.

That’s both a strength and a weakness of integrated information theory, is an attempt to characterize what consciousness is. And you can think of integrated information theory as a list of properties that a conscious system seems to have.

The strength of integrated information theory in relation to these studies of connectivity, I think, comes from the fact that we know that conscious systems—namely, brains—integrate a lot of information into a single unified moment of consciousness; a unified experience. And if we can attempt to look at connectivity and look at measures of information, it may very well be that when the brain is unconscious, there may be a reduction in the total amount of information that the brain is able to relay, and it may be that the connectivity measures that we are now finding useful might similarly drop off.

And so, I think that it’s an interesting and provocative theory. I think that it’s not the only theory that would potentially explain the results that we have, but it’s currently the most popular one. And it’s consistent with the findings of Dr. Mashour. But I don’t think that it’s at all been proven yet, so I don’t want to give it the weight of force that this is the definite answer about why the brain is conscious, or why the brain is capable of being conscious. But I think that it’s an interesting touchstone to relate these results back to, and test. So, if integrated information theory is explanatory of what is required for consciousness, then the results of Dr. Mashour have to be explained within the context of integrated information theory.

So, I think that this is a nice test case to bring back to IIT and say, how does the theory do with this set of phenomena that we see across multiple anesthetics and sleep? When we are seeing a change in frontoparietal connectivity, and we are seeing this high-frequency change with loss of consciousness, can that be explained within the context of integrated information theory?

Dr. James Rathmell: I think I follow you. But, Dr. Mashour, can you follow up, maybe, with a sentence or two of how you take integrated information theory in relation to your findings?

Dr. George Mashour: Sure. First of all, I’ve long been interested in this theory. I think I was probably the first to actually introduce it into our literature of anesthesiology with some early papers, so I’ve been following it closely. I do think it’s very relevant, and I think the basic principle that we need to get information together to have the kind of complex, unified conscious experience that we have—I think that’s a sound principle. And the thought that breaking up that synthesis could be sufficient for unconsciousness is a belief — a principle that I’ve long held, and articulated at around the same time that IIT came out.

Now, there are many aspects to the theory that are difficult to get your head around, that are going to require a lot of future work and complex mathematics that is certainly beyond what we’re working on right now. I do think that this work in animals, and the work in humans that we’ve conducted, generally supports the theory.

But, as Drew mentioned, it actually supports a number of other theories—predictive coding; higher-order thought; global neuronal workspace theory—I’m just throwing out some other more cortically based perspectives of unconsciousness that our data are consistent with as well. So, I think we’re going to need to start to develop more refined tools to...
really differentiating among these different theories of consciousness, but I think using anesthetics really is a great way to probe them. I think the experimental paradigms are going to have to get more refined.

The other thing that I want to point out for the sake of completeness is that it’s still unclear, even from this paper, that this breakdown of connectivity necessarily relates to consciousness, or perhaps some other cognitive functions. So, for example, attentional mechanisms. This might also be mediated by this higher-gamma frequency, and we would expect that this higher cognition would also be breaking down when we went into these various states.

So, that’s another challenge, is having more sophisticated experimental paradigms to differentiate between different theories, and also differentiate between different cognitive processes. We’re looking for neural correlates, but we still don’t know if what we’ve found is a neural correlate, is a neural prerequisite, is a neural consequence, or neural cause, of either consciousness or anesthetic-induced unconsciousness.

Dr. James Rathmell: Wow. Well, thank you both. This is complex stuff. Very interesting; but what else would we expect when we’re probing human consciousness? I hope today’s discussion will lead many of you listening to read this new article about neural correlates of wakefulness, sleep, and general anesthesia.

Drs. Mashour and Hudson, you gave us some great explanations in a complex and hard-to-understand realm. I wish you well as you continue your efforts to probe the neuronal and neurochemical underpinnings of consciousness.

Dr. George Mashour: Jim, thank you very much.

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