Published in final edited form as:

Anesthesiology. 2016 November ; 125(5): 830–831. doi:10.1097/ALN.0000000000001276.

Network-Level Mechanisms of Ketamine Anesthesia

George A. Mashour, M.D., Ph.D.

Department of Anesthesiology; Center for Consciousness Science; Neuroscience Graduate Program, University of Michigan Medical School, 1500 E. Medical Center Drive, 1H247 University Hospital, SPC-5048, Ann Arbor, MI 48109-5048, Phone: 1-734-936-4280, gmashour@med.umich.edu

These and previous studies recording visual and somesthetic evoked potentials appear to indicate that sensory input may reach cortical receiving areas but fail to be perceived in some of the association areas because these are depressed. This interference in proper association of afferent impulses results in “dissociation.” It is therefore suggested that the state induced by CI-581 be called “dissociative anesthesia.” Corssen and Domino, University of Michigan, 1966¹

The first clinical study of ketamine (then known as CI-581) revealed an anesthetic drug that appeared to function like no other, motivating the description of a new state of consciousness.¹ Based on behavioral observations and the results of evoked potentials, Corssen and Domino also generated prescient insights regarding the state of brain networks during ketamine anesthesia. Recent neurophysiological data in human and nonhuman primates confirm that anesthetic doses of ketamine result in a unique constellation: 1) information can still be accurately represented in primary sensory cortex,² 2) communication patterns between higher-order cortices become disrupted,³ but 3) the complexity and repertoire of brain states are still consistent with disconnected consciousness (such as dreams or hallucinations).⁴ Although there have been numerous studies of subanesthetic ketamine—as an analgesic, antidepressant, and psychotomimetic—using functional magnetic resonance imaging (fMRI), what has been notably absent is an fMRI investigation of brain networks during ketamine anesthesia. This gap in knowledge has resulted in the inability to compare network alterations induced by drugs such as propofol^{5,6} and sevoflurane,⁷ which are thought to act (to varying degrees) through γ -aminobutyric acid (GABA) receptors. Such a comparison could help answer key questions. How do the network-level mechanisms of ketamine differ from more commonly used GABAergic anesthetics? More importantly, what is the “family resemblance” that results in the same functional outcome of general anesthesia? The study by Bonhomme and colleagues⁸ addresses these questions, providing insight into how ketamine modulates the mind.

The investigators conducted a study of healthy volunteers (14 recruited, eight included in the final analysis) receiving both subanesthetic and anesthetic doses of ketamine via target-

Editorial for ALN-D-15-01384 “Resting state network-specific breakdown of functional connectivity during ketamine alteration of consciousness in volunteers”

Conflict of Interest: The author is not supported by, nor maintains any financial interest in, any commercial activity that may be associated with the topic of this article.

controlled infusion pumps. After equilibration at each targeted concentration, fMRI data were acquired in the resting state, when the brain is not actively engaged in a specific task. These data were subsequently analyzed to assess functional connectivity (the coupling of activity between different brain regions) across various networks. The analyses reveal the neural instantiation of ketamine's family resemblance to other anesthetics as well as its "black sheep" qualities. Like propofol and sevoflurane, ketamine was found to disrupt connectivity within the default mode network, primarily through a corticocortical effect between frontal and more posterior cortices. These findings are consistent with past electroencephalographic analyses identifying a disruption of frontal-parietal connectivity by ketamine, propofol, and sevoflurane.³ Also like propofol and sevoflurane, ketamine did not appear to disrupt primary auditory and visual networks. Collectively, these data support the hypothesis that general anesthesia is a higher-order phenomenon that is mediated beyond the level of the primary sensory cortex, although this clearly depends on the doses administered.

Ketamine differs in a number of ways from primarily GABAergic anesthetics³ and ketamine anesthesia is associated with a higher incidence of dreaming⁹ than is found during exposure to propofol or sevoflurane.¹⁰ Indeed, in the study of Bonhomme and colleagues,⁸ all participants subsequently reported a variety of subjective states that were attributed to the period of unresponsiveness. Although it was not possible to correlate precisely the state of consciousness and the state of the brain, ketamine anesthesia was associated with a reorganization of networks (resulting in new patterns of connectivity) and a preservation of connectivity between regions supporting distinct modalities of sensation. These cross-modal interactions between sensory regions such as the primary auditory and visual cortices are *not* preserved during propofol-induced unconsciousness—this is potentially an important finding with respect to the ability to dream or hallucinate during exposure to ketamine, despite being disconnected from the environment. It also sheds light on the role of sensory binding in the generation of consciousness and its disruption during various anesthetic states.¹¹

There are limitations to this study that are well described in the manuscript. One worth noting is the relatively low number of participants, which can statistically impede the identification of all important changes in brain networks due to ketamine. Furthermore, despite the advantage of multiple concentration targets, this investigation did not have the power to distinguish clearly between the subanesthetic and anesthetic effects of ketamine on brain networks, a current controversy in the field. Recent findings using magnetoencephalography indicate that disruptions of corticocortical connectivity can be observed during exposure to subanesthetic doses of ketamine.¹² On this basis, it has been concluded that such connectivity changes cannot account for the mechanism of ketamine anesthesia. There are, however, numerous molecular and neurophysiological events associated with the administration of anesthetics that likely occur at subanesthetic doses but that may nonetheless be mechanistically relevant after reaching a dose-dependent threshold. As an example, the binding of propofol to GABA receptors in an awake patient would not exclude the possibility of GABA being relevant for propofol-induced unconsciousness, since there is likely some degree of receptor modulation prior to loss of consciousness. What would need to be demonstrated to eliminate this candidate mechanism is *maximal* binding to GABA receptors while consciousness persists. Similarly, to exclude the disruption of corticocortical connectivity as a mechanism of ketamine anesthesia, it would need to be

shown that there is *maximal* disruption at subanesthetic doses. Further study is therefore required.

Ketamine induces a unique brain state compared to the commonly used agents that work primarily through GABA receptors. Although traditionally marginalized as a black sheep, it is now becoming clear that this drug can provide key insights into the neurobiological family resemblances that might represent invariant mechanisms of otherwise diverse general anesthetics. The study of Bonhomme and colleagues is an important advance in this line of investigation.

Acknowledgments

Funding: Dr. Mashour's work on ketamine anesthesia and brain networks is supported by the National Institutes of Health, Bethesda, MD, grant R01GM111293.

References

1. Corssen G, Domino EF. Dissociative anesthesia: further pharmacologic studies and first clinical experience with the phencyclidine derivative CI-581. *Anesth Analg*. 1966; 45:29–40. [PubMed: 5325977]
2. Schroeder KE, Irwin ZT, Gaidica M, Bentley JN, Patil PG, Mashour GA, Chestek CA. Disruption of corticocortical information transfer during ketamine anesthesia in the primate brain. *Neuroimage*. 2016; 134:459–465. [PubMed: 27095309]
3. Lee U, Ku S, Noh G, Baek S, Choi B, Mashour GA. Disruption of frontal-parietal communication by ketamine, propofol, and sevoflurane. *Anesthesiology*. 2013; 118:1264–1275. [PubMed: 23695090]
4. Sarasso S, Boly M, Napolitani M, Gosseries O, Charland-Verville V, Casarotto S, Rosanova M, Casali AG, Brichant JF, Boveroux P, Rex S, Tononi G, Laureys S, Massimini M. Consciousness and complexity during unresponsiveness induced by propofol, xenon, and ketamine. *Curr Biol*. 2015; 25:3099–3105. [PubMed: 26752078]
5. Boveroux P, Vanhaudenhuyse A, Bruno MA, Noirhomme Q, Lauwick S, Luxen A, Degueldre C, Plenevaux A, Schnakers C, Phillips C, Brichant JF, Bonhomme V, Maquet P, Greicius MD, Laureys S, Boly M. Breakdown of within- and between-network resting state functional magnetic resonance imaging connectivity during propofol-induced loss of consciousness. *Anesthesiology*. 2010; 113:1038–1053. [PubMed: 20885292]
6. Jordan D, Ilg R, Riedl V, Schorer A, Grimberg S, Neufang S, Omerovic A, Berger S, Untergehrer G, Preibisch C, Schulz E, Schuster T, Schroter M, Spoormaker V, Zimmer C, Hemmer B, Wohlschlagel A, Kochs EF, Schneider G. Simultaneous electroencephalographic and functional magnetic resonance imaging indicate impaired cortical top-down processing in association with anesthetic-induced unconsciousness. *Anesthesiology*. 2013; 119:1031–1042. [PubMed: 23969561]
7. Palanca BJ, Mitra A, Larson-Prior L, Snyder AZ, Avidan MS, Raichle ME. Resting-state functional magnetic resonance imaging correlates of sevoflurane-induced unconsciousness. *Anesthesiology*. 2015; 123:346–356. [PubMed: 26057259]
8. Bonhomme V, Vanhaudenhuyse A, Demertzi A, Bruno MA, Jaquet O, Ali Bahri M, Plenevaux A, Boly M, Boveroux P, Soddu A, Brichant JF, Maquet P, Laureys S. Resting state network-specific breakdown of functional connectivity during ketamine alteration of consciousness in volunteers. *Anesthesiology*. 2016 In Press.
9. Grace RF. The effect of variable-dose diazepam on dreaming and emergence phenomena in 400 cases of ketamine-fentanyl anaesthesia. *Anaesthesia*. 2003; 58:904–910. [PubMed: 12911367]
10. Leslie K, Skrzypek H, Paech MJ, Kurowski I, Whybrow T. Dreaming during anesthesia and anesthetic depth in elective surgery patients: a prospective cohort study. *Anesthesiology*. 2007; 106:33–42. [PubMed: 17197843]

11. Mashour GA. Cognitive unbinding: a neuroscientific paradigm of general anesthesia and related states of unconsciousness. *Neurosci Biobehav Rev.* 2013; 37:2751–2759. [PubMed: 24076246]
12. Muthukumaraswamy SD, Shaw AD, Jackson LE, Hall J, Moran R, Saxena N. Evidence that subanesthetic doses of ketamine cause sustained disruptions of NMDA and AMPA-mediated frontoparietal connectivity in humans. *J Neurosci.* 2015; 35:11694–11706. [PubMed: 26290246]