Consciousness Unbound

Toward a Paradigm of General Anesthesia

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THEORIES of general anesthetic mechanism have evolved from the unitary hypothesis of Claude Bernard in the nineteenth century to our current understanding of the multiple receptors and neural systems affected by anesthetic agents. As the scientific study of general anesthesia has progressed, it has become clear that early unifying theories of anesthetic mechanism, although elegant, do not account for the many specific actions of anesthetic agents. Studies of general anesthesia over the past years have ranged from the level of single-channel dynamics,[1] to the analysis of neural systems controlling sleep,[2] to neuroimaging.[3] Although general anesthesia may be mediated by complex pharmacologic and neurologic mechanisms, we should not abandon the quest for a unitary hypothesis. Although such frameworks may be simplified, the lack of a guiding paradigm may ultimately impede the development of investigation.

A paradigm of general anesthesia should be able to:

1. describe the effects of anesthetic agents in terms of a final common mechanism
2. accommodate the broad range of data on specific anesthetic action
3. integrate the scientific study of anesthesia with that of other states of consciousness
4. provide new direction for future investigation

The present article attempts to establish a neuroscientific framework of anesthesia that satisfies these criteria by utilizing the concepts of cognitive binding and unbinding.

The Cognitive Binding Problem

The clinicopathologic correlations of the nineteenth century by such luminaries as Broca and Wernicke established a foundation for modern cognitive neuroscience by demonstrating that discrete brain regions are responsible for specific functions. Since that time, we have continued to develop a sophisticated understanding of the distinct neural areas and pathways mediating sensory, motor, cognitive, and affective phenomena. As the diversity of neural processing systems continues to be elucidated, however, a yet deeper problem arises. If the anatomic substrate of cognitive processing is functionally and spatially discrete neuronal subpopulations, how is information ultimately synthesized? For example, although evidence suggests that the brain subdivides perceptual processing into modality (*e.g.*, the visual, the tactile) and submodality (*e.g.*, color, temperature), our perceptions themselves are unified. What mechanism, therefore, mediates the unity of our experience? This quandary is referred to as the *cognitive binding problem*, a term attributed to Christof von der Mahlsburg.[4] Cognitive binding is thought to occur at virtually all levels of cognitive processing and is thought to be a crucial event for consciousness itself.[5]

There has often been confusion in the literature resulting from the multiple uses of the term *binding problem*.[6] First, the binding problem is a scientific problem for us: it is we who have yet to elucidate the steps between the observed division of labor in the brain and our unified experience. A second use of the phrase denotes the brain's difficulty in synthesizing information when multiple stimuli are presented in a rapid manner.[7] This difficulty results in "illusory conjunctions," the incorrect combination of features from distinct objects that can occur even in the absence of any neural pathology. Finally, lesions of the parietal cortex leading to neurologic deficits such as Balint syndrome may result in difficulties of visual binding.[8] Patients with Balint syndrome (bilateral parietal lesions) demonstrate simultagnosia, the inability to process two different objects at the same time. In this article, the term *binding problem* is used in the first sense described, denoting the problem of neuroscientific investigation itself.

Possible Solutions to the Binding Problem

There have been various neuroscientific solutions proposed for the cognitive binding problem, which can be summarized as binding by convergence, binding by assembly, and binding by synchrony.

Binding by Convergence

This approach suggests that information from various lower order neurons is bound by higher-order neurons

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that collect the responses and fire as a "binding unit" when the full set of inputs converge. Consider the analogy of a factory, in which the division of labor leads to the production of component parts. These parts are then sent to a single processing area (*i.e.*, they converge there) and are combined to form a final product. A similar process is posited to occur in the brain, as component cognitive processing in different areas of the neural "factory" converge to a higher-order neuron or set of neurons. This is a hierarchic model in which each stage of processing performs specialized functions dependent on the information entered from the previous stage.[9] The most extreme example of binding by convergence is the concept of the "grandmother cell," a single neuron that processes all features of a single object (*e.g.*, your grandmother). In support of this solution to the binding problem, cells or clusters of cells (a binding unit) have been identified that respond preferentially to single objects.[10,11]

There are several difficulties with the hypothesis of binding by convergence.[12-14] Even higher-order neurons are still responsive to lower-order features, which brings into question whether unambiguous binding can exist in a single cell. The convergence theory may also be limited because it requires a higher-order neuron or binding unit for every set of inputs that must be bound. Even if this were the case, it would limit flexibility of higher-order neurons, because they would have to be specific for a particular object. Furthermore, how would novel objects then be bound? This framework would require a population of uncommitted neurons maintaining latent connections. In short, binding by convergence does not seem to be a complete explanation, although it has been suggested that it is a possible binding strategy for highly specialized representations.

Binding by Assembly

In this proposed solution, the single neuron or binding unit is replaced by a self-organizing Hebbian cell assembly whose interconnections define a set of neurons that must be bound for a particular feature or object.[15,16] Such assemblies were posited by the Canadian psychologist Donald Hebb, who correctly hypothesized that the strength of synaptic connection between two neurons is enhanced by synchronous activity.[17] As the adage goes, neurons that *fire* together, *wire* together. This increase of synaptic strength results in an interconnected system of neurons that is a stable anatomic and functional structure. There is evidence for this form of sensory binding by ensembles of neurons in distinct areas of the cortex.[18,19] This organization allows a more dynamic flexibility than the previously described schema, because the same neuron is capable of participating in more than one cell assembly and thus could participate in multiple binding patterns rather than for just one particular object. This flexibility, however, also results in a potential

ambiguity called "the problem of superposition."[4,20] If a neuron in an assembly can participate in the binding of features for more than one object, it may not be able to function properly when both objects are presented at once (*i.e.*, when they are superposed). How is a particular neuron to be specifically associated with a single binding assembly, especially in the situation of superposed binding demands? In other words, if neuron "A" is a member of two different cell assemblies that bind the features for oranges or tangerines, in which assembly does neuron A function when both oranges and tangerines must be simultaneously represented? This problem of superposition is thought to be a limiting feature of binding by assembly. It may be argued that such difficulties of binding do exist, such as the illusory conjunctions discussed previously. Such incorrect combinations of features from distinct objects may in fact demonstrate that binding by assembly does occur and is limited by problems of superposition.

Binding by Synchrony

Correlation of neurons in the temporal dimension has been proposed as a mechanism of unambiguously defining them as part of a binding assembly.[4,20] The temporally correlated cell assembly would have yet more flexibility than the Hebbian cell assembly described previously. Hebbian cell assemblies are unitary anatomic structures, in which neurons within the assembly interact more strongly than those outside of it. The temporal rather than spatial construction of an assembly could correlate different groups of neurons processing particular features in a more flexible arrangement while unambiguously defining the assembly by simultaneous firing. Thus, binding by synchrony allows the flexibility that solves the problems of binding by convergence while resolving the problems of superposition found in binding by assembly.

To understand binding by synchrony better, consider the analogy of a symphony orchestra. Individual musicians or groups of musicians are spatially arranged but nonetheless separated on a stage, with each processing musical information in a particular way. The final product is coherent music rather than meaningless noise because of the temporal organization that is achieved by the direction of the conductor. There is ample evidence for different scales of temporal coherence in the brain,[14] and evidence of neural synchronization associated with perceptual events has been obtained using magnetoencephalography and electroencephalography.[21-23] Furthermore, distinct neuronal subpopulations of the cortex (the individual musicians) may be synchronized by resonance with a common structure that rhythmically oscillates (the conductor), such as 40-Hz γ-band pacemaker neurons in the thalamus.

Although cognitive binding has been investigated for its role in perceptual processing, it has also been sug-

gested that binding is essential for consciousness itself. The association of binding and consciousness is strengthened by the observation that different states of consciousness are associated with different states of binding. Dream states, for example, have been characterized by alterations in 40-Hz oscillations detected by magnetoencephalography.[24] The alert state is characterized by "sweeps" or "scans" of cortical 40-Hz oscillations that travel from frontal cortex to occipital cortex and back again. Such sweeps can be reset by the thalamic input in the waking state, whereas dream sleep is characterized by oscillations evidencing thalamocortical dissociation. Although sensory input relayed through the thalamus usually modulates the 40-Hz scans, in the dream state, this thalamic input is not functionally integrated into the cortical activity. Interestingly, evoked potentials demonstrate that the thalamus may actually receive sensory input in dreaming states as well as waking states. In the dream state, however, this information remains dissociated from the cortex.

Another altered state of consciousness associated with altered cognitive binding is chronic hallucination after the use of lysergic acid diethylamide. The presence of chronic visual hallucinations in these patients was correlated with abnormally increased electrical coherence in regions of the occipital cortex.[25] The increase in local binding was associated with reduced coherence between the occipital cortex and more distant brain regions. The correlation of aberrant visual perceptions with aberrant occipital hypersynchrony supports temporal binding as a mechanism for visual consciousness. Abnormal electroencephalographic coherence and "thalamocortical dysrhythmia" have also been observed in a variety of psychiatric and neurologic disorders.[26,27] In summary, various forms of temporal binding have been described in both normal and aberrant perceptual activities.

Binding by synchrony, however, may nonetheless be an incomplete explanation. It has been suggested that temporal synchrony in itself may be insufficient for the computational integration required for complex perceptions.[28] Furthermore, recent evidence has demonstrated that motion detection in an area of primate brain is not associated with neuronal synchrony.[29] Although binding by synchrony is an important contender as a solution to the binding problem, multiple mechanisms are clearly involved, with potential contributions by all three modes of binding. Furthermore, it should be clear that these three modes of binding might interact with one another. For example, an area of convergence may be a crucial link in maintaining the synchrony of two distinct areas in the brain. Alternatively, the synchrony of a system may allow information to converge on a small number of cells. Synchrony may also lead to increases in synaptic strength and the formation of a Hebbian assembly, potentially converting one form of binding into another.

Finally, neural synchronization is present from extremely small to global scales in the brain, suggesting that it may play a role in other levels of binding.[30] Although these three mechanisms of binding have been separated for clarity, there are likely complex relations between them.

General Anesthesia as "Cognitive Unbinding"

As the paradigm of cognitive binding has provided a framework for integrating multiple processes leading to consciousness, so might the paradigm of "cognitive unbinding" provide a framework for integrating multiple processes leading to anesthesia. The phenomenon of general anesthesia requires a paradigm that can incorporate both molecular and systems data and be consistent with other models and states of consciousness. Temporal binding and unbinding of 40-Hz oscillation is of clear relevance to a unified framework and has been demonstrated in various states of consciousness and unconsciousness. Various forms of cognitive binding by 40-Hz oscillation have been correlated with perceptual tasks in the waking state,[21] aberrant hallucinatory states,[25] and dream states.[24] Importantly, cognitive unbinding in which 40-Hz synchrony is interrupted has been correlated with nondreaming delta sleep[24] and anesthesia.[31,32] The interrupted 40-Hz coherence in non–rapid eye movement sleep is of interest, considering the recent elucidation of anesthetics affecting sleep systems in the brain.[2]

It has been demonstrated that general anesthetics of distinct pharmacologic properties affect electroencephalographic coherence in an invariant way during unconsciousness, an effect that is reversed on the return of consciousness. In 176 cases of human surgical anesthesia using volatile anesthetics (nitrous oxide, desflurane, isoflurane, and sevoflurane), as well as propofol, etomidate, and barbiturates, there were similar changes in the electrical uncoupling of brain regions. Multivariate analysis of quantitative electroencephalography showed that gamma oscillations (35–50 Hz) of rostral and caudal regions of the brain became uncoupled from one another.[31,32] In other words, the γ-band synchronization that is typically observed between cortices (*e.g.*, frontal and parietal cortices) in the conscious state was interrupted in the anesthetized state. These changes were associated with the onset of anesthesia, intensified with increasing depth of anesthesia, and reversed with the termination of anesthesia. The rostrocaudal dissociation is of particular relevance, given the proposed scans of 40-Hz binding that sweep from the frontal to occipital cortex and back again. In addition to this functional rostrocaudal disconnection, the hemispheres themselves became functionally disconnected. There were shifts to low-frequency waves, with spectral power shifting to anterior

regions. This power shift to rostral regions has often been termed *frontal predominance*.[33] Associated with the decoupling was the profound and reversible inhibition of the medial orbital and dorsolateral prefrontal and frontal cortex, anterior cingulate cortex, paracentral gyrus, amygdala, and basal ganglia. This was assessed with variable electromagnetic tomographic analysis, and the finding of frontal and cingulate cortex inhibition was consistent with previous positron emission tomography findings of propofol-induced anesthesia.[34]

Another recent study in the rat suggests that general anesthesia induced by halothane, isoflurane, and propofol is associated with a decrease of gamma rhythms in the hippocampus.[35] It has also been shown previously that sevoflurane inhibits gamma activity in the medial temporal lobe.[36] These data are relevant to the amnestic effects of anesthetics, because the hippocampus is known to play an essential role in memory consolidation. Indeed, isoflurane has been shown to inhibit long-term potentiation in the hippocampus, a mechanism of memory formation that is thought to be mediated by Hebbian cell assemblies.[37] Of further interest is that increased gamma activity was found in the hippocampus during behavioral hyperactivity, which was posited to model delirium in stage II anesthesia. These studies indicate an important role of general anesthetics on gamma activity in the hippocampal system.

Anesthetics may also interrupt mechanisms of binding other than neural synchrony. Recall that binding by convergence is the synthesis of perceptual information by higher-order neurons or clusters of neurons. There is evidence that cognitive unbinding of convergence may be a mechanism of anesthetic activity. For example, in a cortical area of nonhuman primate brain, isoflurane was shown to shift visual pattern recognition to component recognition.[38] In other words, anesthetic action at this site interrupted the ability of these neurons to bind patterns from their component parts. It was observed that neurons in this area were still responsive to component signals in the anesthetized state but were not able to synthesize them into a complete representation. This might be an important example of cognitive unbinding at the level of convergence and suggests that neural processing of elemental sensory data may occur under anesthesia while the formation of complete representations is inhibited.

There is also a more speculative perspective on the role of convergence in the generation of consciousness that may be affected under anesthesia: the "observing homunculus." Crick and Koch[5] have suggested that there is a rostral homunculus that binds input from caudal and spinal inputs into one snapshot perception. Based on split-brain experiments, Gazzaniga[39] has posited a homunculus in the left hemisphere that formulates interpretation of bihemispheric input and conceptually binds perceptions over time. It is of interest that both these rostrocaudal and interhemispheric axes were shown to be functionally uncoupled by general anesthetics.[31,32]

Cognitive unbinding may thus be a framework that can incorporate the actions of anesthetics at the cellular (convergence), systems (assembly), and global (synchrony) scales of the brain. This framework furthermore suggests that discrete information processing may persist in the anesthetized state, whereas anesthesia itself is effected by the inhibition of representation that results from the binding of this information.

Discussion

This article has considered the origin and definition of the cognitive binding problem, three neuroscientific solutions to the problem, and the relevance of these solutions to consciousness and anesthesia. The proposition of cognitive unbinding as a paradigm for general anesthesia satisfies the criteria enumerated previously.

Cognitive Unbinding Describes the Effects of Diverse Anesthetic Agents in Terms of a Final Common Mechanism

The demonstration of invariant 40-Hz uncoupling by diverse inhalational and intravenous anesthetic agents supports cognitive unbinding as a final common mechanism for these anesthetics. Importantly, cognitive unbinding is also seen at the cellular level, as in the case of isoflurane interrupting the synthesis of visual information in a discrete set of neurons. Thus, cognitive unbinding provides a common principle of anesthetic activity not simply among different types of pharmacologic agents but at different levels of neural processing.

Cognitive Unbinding Can Accommodate the Broad Range of Data on Specific Anesthetic Actions

Prior unified theories of general anesthesia have not been consistent with the particular effects of individual anesthetic agents.[40,41] Because cognitive unbinding is proposed as a common neuroscientific principle of anesthetic activity rather than a specific pharmacologic action of anesthetic activity (*e.g.*, lipid perturbation), it may allow the coherent organization of diverse data obtained at multiple levels of neural processing. For example, particular actions at neurotransmitter receptors may be evaluated from the perspective of how they inhibit binding in certain neural subpopulations rather than as an array of isolated molecular events. Cognitive binding seems to occur at the cellular, assembly, and global brain level, allowing a broad but thematically unified framework within which to incorporate data describing its interruption under anesthesia.

Cognitive Unbinding Integrates the Scientific Study of Anesthesia with that of Other States of Consciousness

It has been suggested that general anesthesia cannot be understood until consciousness itself is understood and that, in fact, these two endeavors should be linked.[40] The framework of binding and unbinding allows the natural integration of these two lines of investigation. For example, multiple states of consciousness such as alert perception, dreaming, and hallucination can all be considered as different modes of binding by synchrony (in particular, gamma activity). The description of general anesthesia as an uncoupling of gamma activity can thus be situated in the spectrum of cognitive neural activity.

This attractive feature of the proposed paradigm also leads to a difficulty: if anesthesia is cognitive unbinding in the brain, what about the known effects of anesthetics on the spinal cord? There is evidence that the hypnotic and amnestic effects of anesthetics are mediated in the brain, whereas immobility is mediated in the spinal cord.[41] Indeed, the previous discussion describing the cognitive unbinding of gamma activity in the cortex and hippocampus accounts only for hypnosis and amnesia, respectively. It has been demonstrated, however, that volatile anesthetics acting exclusively in the brain may cause immobility, albeit at higher concentrations than are typically used.[42] It is my own bias that general anesthesia be considered a brain-based phenomenon, but it is also clear that spinal input is inextricably linked to brain activity. Indeed, the dissociation of information between the periphery and the brain may itself be considered the most basic form of cognitive unbinding. Reconciling the effects of anesthetics in the brain with those in the spinal cord and the periphery is a matter for further consideration and touches on the deeper question of how we define the phenomenon of general anesthesia.

Cognitive Unbinding Provides New Direction for the Future Investigation of Anesthesia

First and foremost, this paradigm suggests that the investigation of general anesthesia should be linked to the investigation of cognitive binding. As cognitive neuroscientists come to a greater understanding of how the brain synthesizes information so as to generate conscious states, anesthesiologists should evaluate these data for their relevance to the generation of surgical unconsciousness. As the neural mechanisms for cognitive binding become elucidated, the targets for more precise unbinding by rational anesthetic design must also be considered. Future investigation should also include prospective studies that test the effects of anesthetics on known mechanisms of cognitive binding. These effects may also be measurable in the intraoperative setting, enabling monitoring capability that reflects deeper levels of information dissociation and thus deeper levels of anesthesia. Indeed, the use of the Bispectral Index® monitor may be a prototype for the intraoperative measurement of cognitive unbinding, because it has been suggested to reflect γ-band desynchronization.[43]

In conclusion, the concept of cognitive unbinding provides a paradigm of general anesthesia that is unitary while allowing for diverse activities of anesthetic agents. Future investigation of general anesthesia should be linked to cognitive binding and unbinding so as to facilitate a deeper scientific understanding of the phenomenon and to provide direction for rational anesthetic design and improved intraoperative monitoring.

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