

# Effects of Anesthesia on Effective Connectivity in the Brain

Xinyu Xu<sup>1</sup>, Guolin Wang<sup>2\*</sup>, Xin Tian<sup>1\*</sup>

<sup>1</sup>Laboratory of Neurobiology in Medicine, School of Biomedical Engineering, Tianjin Medical University, Tianjin, China

<sup>2</sup>Department of Anesthesiology, Tianjin Medical University General Hospital, Tianjin Institute of Anesthesiology, Tianjin, China

Email: \*[wang\\_guolin@hotmail.com](mailto:wang_guolin@hotmail.com), \*[tianx@tmu.edu.cn](mailto:tianx@tmu.edu.cn)

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## Abstract

The brain constitutes a formidably complicated structural network. There are three main types of connectivity used to describe neuronal networks, which reflect three parallel levels of investigation: anatomical connectivity, functional connectivity and effective connectivity. Effective connectivity indicates the direct influence that a node exerts on another, and in the context of neuronal circuits, a causal relationship between the activities of two nodes. Since its definition, effective connectivity analysis has been used to describe causal relationship across multiple spatial scales in PET imaging, fMRI, electroencephalography (EEG) and magnetoencephalography (MEG), single-unit, and local field potential. There are diverse literatures which probe the anesthetized state using effective connectivity analysis over the past two decades. The examination of effective connectivity in the anesthetized state is of relevance to both anesthesiologists and neuroscientists, as it has the potential to elucidate still unclear mechanisms of anesthesia while offering insight into intrinsic functional activity in the brain. The present review attempts to examine, elucidate, and integrate the insight that effective connectivity analysis of the anesthetized state has generated thus far.

## Keywords

Effective Connectivity, Anesthesia, Granger Causality, Consciousness

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## 1. Introduction

Since the nineteenth century, we have known that the neuronal elements of the brain constitute a formidably

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\*Corresponding author.

complicated structural network [1] [2]. Such networks are thought to provide the physiological basis for information processing and mental representations [3]-[6].

A network is defined by nodes, which are the elements of the network, and links (edges) connecting the nodes and defining structure. The nodes can be the neurons, neuronal ensembles and brain regions. There are three main types of connectivity used to describe neuronal networks, which reflect three parallel levels of investigation: anatomical connectivity, functional connectivity and effective connectivity. Anatomical connectivity indicates physical connections (*i.e.* chemical and electrical synapses, etc.) among nodes. Functional connectivity indicates a statistical dependence between the activities of two nodes without any assumption of the mechanism by which these relationships are mediated. Effective connectivity indicates the direct influence that a node exerts on another, and in the context of neuronal circuits, a causal relationship between the activities of two nodes [7]. Although effective connectivity can be also considered as one kind of functional connectivity, a distinction is usually made between functional connectivity and effective connectivity. Only the effective connectivity takes explicitly into consideration the existence of a causal link between two or more brain regions [8].

## 2. How Is Effective Connectivity Determined?

Effective connectivity research has branched into two formally distinct approaches: Dynamic Causal Modeling (DCM) [9], and Granger Causality (GC) [10].

The basic idea of DCM is that neural activity propagates through brain networks as in an input-state-output system, where causal interactions are mediated by unobservable neuronal dynamics. This multi-input multi-output neuronal model is augmented with a forward, or observation model that describes the mapping from neural activity to observed responses. Together neuronal and observation model comprise a full generative model that takes a particular form depending on the data modality. DCM was mainly used for analyzing fMRI.

From its introduction within econometrics, GC has been applied in neuroscience partly because it is simple to estimate, given (stationary stochastic) time series. GC also has some useful properties including a decomposition of causal influence by frequency and formulation in an ‘ensemble’ form, allowing evaluation of GC among multivariate sets of responses [11]. GC has provided useful descriptions of effective connectivity in EEG [12], MEG [13] and local field potentials [14]. But the application GC to fMRI is more controversial because of the slow dynamics and regional variability of the haemodynamic response to underlying neuronal activity [15] [16].

Other measures related to spectral GC have been proposed, such as the Directed Transfer Function (DTF) [17], the Partial Directed Coherence (PDC), which might be numerically and computationally advantageous when compared to any of the above measures [18]. Both DTF and PDC lend themselves to a multivariate approach and produce valid spectral causality estimates [19] [20].

The Phase Slope Index (PSI) is based on the idea that interactions between variables are not instantaneous and need time to propagate [21]. For example, two variables X and Y, and provided that the propagation speed is constant, the phase difference between X and Y increases with frequency and the phase spectrum is expected to have a positive slope if X drives Y and a negative slope if Y drives X. Another useful feature of PSI is insensitivity to mixtures of non-interacting sources which leads to a lower number of false positives when compared to GC.

Transfer Entropy (TE), based on the information theoretic context, was proposed [22] as a model-free, non-parametric measure of information transfer between two variables and has been applied to fMRI and EEG data [22]-[24]. The transfer entropy (TE) from the source to destination can be interpreted as the average mutual information between the previous state of the source and a future state of the destination, conditioned on past states of the destination.

## 3. Why Study Effective Connectivity in Anesthesia?

Despite advances in the understanding of anesthetic-receptor interactions for a variety of anesthetics, the specifics of why general anesthesia causes unconsciousness remain unclear [25]. Findings had indicated that different anesthetics produce the various components of anesthesia to varying degrees and with different dose responses [26]. Effective connectivity has provided one manner to assess the effects of various types and doses of anesthetics, for it provides not only the last effective networks to disappear prior to the onset of anesthetic-induced unconsciousness but also the first effective networks to reappear upon the recovery of consciousness [27]. More generally, effective studies provide a means of investigating the information flowing from one brain region to

another at varying levels of anesthesia and, accordingly, the modulation of those networks by the various components of anesthesia.

#### 4. Studying Mechanisms of Anesthesia through Effective Connectivity

Functional neuroimaging work on mechanisms of anesthesia has focused on understanding the specifics of the brain state corresponding to anesthesia-induced loss of consciousness (LOC). There are a number of hypotheses to consider. First and most simply, it may be possible to find regions of the brain in which activity is suppressed during AIU that wholly or partially account for LOC. A second possibility is that there may be impaired communication between specific brain regions that accounts for the LOC. Effective connectivity mapping is a highly appropriate means to search for this second type of finding.

##### 1) Thalamus, thalamocortical connectivity, and consciousness

The thalamus plays a uniquely privileged role in the brain because all sensory information (except olfaction) passes through it. This unique location has made the thalamus a prime candidate to be the site of integration of percepts into a unified experience that we refer to as consciousness [28]. Many investigations have corroborated the concept that thalamic activity is significantly modulated in anesthesia. In 1993, Angel researched evoked potential recordings indicating that a blockade or disruption of sensory processing in the thalamus may be involved in LOC [29]. Soon after, Volkow and others showed that the depression of thalamic metabolism correlated with level of sedation induced by benzodiazepine lorazepam [30]. In 1999, Alkire and others demonstrated significant decreases in thalamic metabolism during halothane anesthesia, while Fiset *et al.* showed a correlation between thalamic activity and level of consciousness during propofol anesthesia [31] [32]. Those results gave more weight to the idea that thalamus switch on consciousness.

Thalamocortical networks play an important role in information integration during consciousness [33] [34]. How does anesthetic affect on the thalamocortical connectivity? In order to find the answer, in 2012, Andrada and others recorded neuronal action potentials from cerebral cortex and thalamus before, during, and after infusion of either propofol or etomidate [35]. The result showed that neurons in the cortex and thalamus were similarly depressed by propofol and etomidate. Although Andrada work demonstrated anesthetic depression of neuronal activity likely contributes to anesthetic-induced unconsciousness, more work is needed to determine how anesthetic effects on thalamocortical interaction to produce unconsciousness. Then, Kim *et al.* used granger causality to investigate information flows in the thalamocortical network [36]. The result showed that 65% of the thalamocortical information flows were changed by anesthesia-induced LOC. Specifically, the information flows from the primary motor and somatosensory cortex to the ventral lateral thalamus before LOC whereas flows from the ventral lateral thalamus to the primary motor cortex and somatosensory cortex after LOC.

Based on the above research, suppression of thalamus by anesthetics may in fact follow in time the anesthetic suppression of cortical activity, suggesting an indirect role [37]. Thus, the thalamic effects of anesthesia are more likely to be consequential, secondary to the cortical effect of anesthetics.

##### 2) Frontoparietal connectivity

Frontoparietal connectivity has been noted consistently as a neural correlate of consciousness [38]-[40].

To assess the effects of general anesthesia on frontoparietal connectivity, in 2005, Imas and others recorded event-related potentials from rat the primary visual cortex, parietal association and frontal cortex [41]. They used transfer entropy to examine the effect of two common volatile anesthetics, halothane and isoflurane, on information transfers between primary visual, parietal and frontal cortex. The result provided direct evidence that inhalational anesthetics impair frontal-posterior parietal cortex information transfer at high gamma frequencies in rats. In 2009, Lee *et al.* studied EEG signals from frontal and parietal scalp areas of human subjects under propofol anesthesia [42]. Effective connectivity was computed in both the awake and anesthetized states. The result showed that the anesthetized state greatly reduced feedback connectivity (frontal→parietal), indicating that higher order processing involving top-down selection and contextual interpretation of sensory information were impaired in anesthesia. In 2013, Lee *et al.* also demonstrated except propofol and sevoflurane, ketamine disrupt frontal-parietal communication, despite molecular and neurophysiologic differences [43]. Another EEG study also demonstrated impaired frontal to parietal, top-down information processing during anesthesia [44]. Analysis of effective connectivity in frontal-parietal pathway could provide a common metric of general anesthesia and insight into the cognitive neuroscience of anesthetic-induced unconsciousness.

In order to overcome methodological limitations of EEG methods, Jordan *et al.* recorded simultaneously resting-state EEG and blood oxygen level-dependent fMRI of healthy subjects during consciousness and propo-

fol-induced LOC [45]. They found that changes in functional connectivity in fMRI during unconsciousness correlate with simultaneous changes in effective connectivity in EEG. Their work indicates that one underlying mechanism of functional decoupling of “higher-order” frontal and “lower-order” parietal processes during unconsciousness is the breakdown of directional feedback connectivity.

### 3) Posterior cingulate cortex

A third brain region that has been consistently implicated in studies examining activity modulations in anesthesia is the posterior cingulate cortex (PCC). Laureys and others reported diminished cerebral glucose metabolism by PET in PCC and noted impaired connectivity between PCC and other cortical areas in the anesthetized state when compared to controls [46]. But Stamatakis reported that increasing plasma propofol concentrations did not significantly modulate connectivity within posterior cingulate, the medial prefrontal cortex and bilateral parietal cortices. On the contrary, it was associated with significant increases in connectivity between the PCC and other areas (such as the motor/somatosensory cortices, the anterior thalamus, and the pontine tegmentum in the brainstem [47].

How is it possible to reconcile these two findings of PCC? The first reason is the difference of anesthesia. Laureys researched the patient who was in coma after suicide attempt using insulin and benzodiazepines, while Stamatakis used propofol on patients. The second argument point to a potentially more fundamental difference is physiological signals used for constructing connectivity. Laureys utilized PETs, and Stamatakis made use of fMRI.

## 5. Studying Mechanisms of Postoperative Cognitive Dysfunction through Effective Connectivity

Postoperative cognitive dysfunction (POCD) is now recognized as one such complication, often detected by an abnormality on neuropsychological testing [48]-[50]. It may manifest clinically as memory loss, psychomotor derangement, dementia, delirium or depression, difficulties with fine-motor coordination and impaired higher-level cognitive functions [51] [52].

Working memory refers to the temporary storage and manipulation of information necessary for performance of complex cognitive tasks [53] [54]. Prefrontal cortex participates in working memory, and plays an active role in the shift of attention and task switching [55] [56]. Xu and others had researched the effect of propofol anesthesia on the working memory through gamma band LFPs in rat prefrontal cortex [57]. The result showed that prominent inhibition of working memory function was induced by propofol anesthesia, which mainly inhibited the effective connectivity of gamma-band LFPs in prefrontal cortex.

In 2013, Chi and colleagues found that postoperative pain contributes to the development of memory deficits after anesthesia and surgery via up-regulation of hippocampal NMDA receptors in aged rats [58]. Further, the synaptic NMDA receptor 2B level was reduced in the medial prefrontal cortex of adult mice suffering from surgical pain, which might contribute to POCD [59]. These findings suggest that postoperative pain may be one of important factor leading to POCD. In order to find out the mechanism that pain leads to POCD, Cardoso-Cruz H and others recorded LFPs from rat medial prefrontal cortex and dorsal hippocampus during a food-reinforced spatial working memory task, before and after the establishment of the spared nerve injury model of neuropathy [60]. The results show that the nerve lesion caused an impairment of working memory performance and revealed that chronic pain reduces the overall amount of information flowing in the prefrontal cortex-hippocampal circuit. Cardoso-Cruz’s work demonstrates that effective connectivity disturbances in the prefrontal cortex-hippocampal circuit are a relevant cause for pain-related working memory deficits. Based on the above work, Cardoso-Cruz also researched the effective connectivity between prefrontal cortex and the mediodorsal thalamus through the same method [61]. The most relevant finding of his study is that the onset of chronic pain caused a global decrease in prefrontal cortex and the mediodorsal thalamus effective connectivity, and the decrease occurs over a wide frequency range and in both directions of the circuit, albeit more evidently from mediodorsal thalamus to prefrontal cortex.

## 6. Effective Connectivity and Intrinsic Brain Activity

### 6.1. Hippocampus, Prefrontal Cortex, Hippocampus-Prefrontal Cortex

The involvement of the hippocampus and the prefrontal cortex in cognitive processes and particularly in learning and memory has been known for a long time. There exists of a direct monosynaptic pathway from the ven-

tral CA1 region of the hippocampus to prefrontal cortex in anatomy [62]. However, the medial prefrontal cortex, in rats and other species, has no direct return projections to the hippocampus, and few projections to parahippocampal structures including the entorhinal cortex. At present, the nucleus reuniens is well established to represent a critical link from the medial prefrontal cortex to the hippocampus [63].

In 2001, Fell and others showed effective connectivity between the hippocampus and the neocortex accompanies successful memory encoding [64]. Based on Fell work, Jones *et al.* disclosed theta frequency coordination of LFP between hippocampus and mPFC during behavioral epochs was presumed to construct effective communication between these two structures [65].

In 2007, Baeg and others demonstrated that the hippocampus-neocortex network is a primary conduit for cerebral information flow for learning and memory [66]. Then Adhikari *et al.* constructed effective connectivity between ventral hippocampus and prefrontal cortex during rat working memory task, and demonstrate that the ventral hippocampus leads the prefrontal cortex in the theta-frequency range [67]. Interestingly, under anesthesia, Taxisidis and others had demonstrated that there exists a continuous information flow from hippocampus towards prefrontal cortex [68]. How to explain the results? After training, Rats in Adhikari work had formed long-time memory, which was mainly consolidated in hippocampus [69]. So information in the hippocampus-neocortex network flowed from hippocampus to prefrontal cortex during rat working memory task. There are more densely anesthetic receptors located in the neocortex than in the hippocampus, and the prefrontal cortex is inhibited by anesthetic preferentially in the neocortex than in the hippocampus [70]-[72]. As to Taxisidis work, information in the hippocampus-neocortex network flowed from hippocampus to prefrontal cortex during rat anesthesia.

Based on the above work, information flows between hippocampus and prefrontal cortex is fundamental for learning and memory, and disruption of such communication is likely to generate behavioral impairments.

## 6.2. Cortex and the Striatum

Nakhtnikian and others characterized directed influence between cortex and striatum using LFPs recorded in primary motor cortex and dorsal striatum from awake, unrestrained rats [73]. In addition to observing free behaviors, they recorded during sleep and anesthesia in order to compare rest states to spontaneous behavior and to each other, and to assess the neural correlates of drug induced and natural inactivity. They found that effective connectivity became bidirectional in freely behaving animals. In agreement with Sharott A report, effective connectivity was unidirectional, from cortex to striatum, during natural sleep and anesthesia [74].

## 6.3. Amygdala and Emotion

Alkire *et al.* used structural equation modeling of the PET data revealing that anesthesia suppressed amygdala to hippocampal effective connectivity [75]. The behavioral results show that anesthesia blocks emotional memory, and connectivity results demonstrate that anesthesia suppresses the effective influence of the amygdala. Collectively, the findings support the hypothesis that the amygdala mediates memory modulation by demonstrating that suppressed amygdala effectiveness equates with a loss of emotional memory.

## 7. The Continued Study of Effective Connectivity in Anesthesia

In discussing the effective connectivity of the brain and its application in anesthesia issue, we have come across a number of issues that can and should be addressed in future studies.

### 1) Dosage of anesthesia

Although anesthesia has the LOC as a potential endpoint, there are many levels of anesthesia, all of which have potential relevance to the study of effective connectivity in the brain.

Most studies of effective connectivity in the anesthetized state have reported the anesthesia by the standard of minimum alveolar concentration (MAC) or a behavioral endpoint. Although both of the methods are useful, there is one obstacle hindering comparisons across studies. For example, the induction of one kind anesthesia in one subject may not be complete at one dosage, whereas it may be in another subject. The key point may leave out critical information for the interpretation of that study.

### 2) Type of anesthetic

Although it may seem that the endpoint of surgical anesthesia is sufficiently similar across anesthetics, this cannot and should not be assumed in effective connectivity studies, because there is not a common effective

connectivity similar across anesthetic types. So, it is important to continue to assess effective connectivity across a variety of anesthetic types, at least consisting of a single representative of three or four major classes of anesthetics.

### 3) Method of assessing effective connectivity

Although many methods have offered the ability to assess effective connectivity, each method has its strengths and weaknesses. GC and methods based on GC (such as DTF and PDC) remain the most heavily used methods of computing effective connectivity relations. Regardless of the methodology used, however, the need for effective connectivity studies across anesthesia and consciousness state remains significant, as they provide unique insight into both potential mechanisms of anesthesia and intrinsic functional activity in the brain.

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## Conflict of Interests

The authors have declared that no conflict of interests exists.

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