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Review Article

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Messages from the Brain Connectivity Regarding Neural Correlates of Consciousness

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Consciousness has become a legitimate theme of neuroscientific discourse over the last two decades. Neuroscientific investigation seeking neural correlates of consciousness (NCC) has ranged from the neuronal level to the system level. Regarding system level studies, there is a large body of evidence supporting the idea that functional connectivity studies can help in examining NCC. Functional connectivity studies have suggested the involvement of the thalamo-cortical, frontoparietal, and other cortico-cortical connectivity under anesthetic-induced unconsciousness and in disorders of consciousness. Likewise, effective connectivity has been used to investigate the causal interactions among elements of functional connectivity in various consciousness states, and provided a deeper understanding of NCC. Moreover, as an extended version of connectivity studies, complex network methods have also been used for studies on NCC. In this review, we focused on the aspect of the brain system level of NCC including functional and effective connectivity networks from methodological perspectives. In addition, as for states of consciousness, anesthetic-induced unconsciousness and disorders of consciousness are the main subjects. This review discusses what we have learned from recent studies about the exploration of human brain connectivity on consciousness and its neural correlates.

Key words: consciousness, neural correlates of consciousness, functional and effective connectivity, brain network

INTRODUCTION

The question 'what is consciousness' is the most challenging issue of the human brain yet to be resolved. It is true that efforts seeking the answers to questions about consciousness have mainly been considered in the field of philosophy until the 1990s. In 1994, the first Tucson discussions and debates toward the science of consciousness [1] triggered a number of events reinvigorating the study of consciousness and the emergence of the science of consciousness, leading to the legitimate scientific pursuit of consciousness being re-established [2]. That is, as neuroscientific technologies have developed, consciousness *per se* has become a fascinating research theme in the field of neuroscience, which could be characterized by the approach searching for the "neural correlates of consciousness (NCC)". Since the phrase "neural correlate" indicates the specific and minimally adequate brain state or neural system [2], NCC can be defined as the minimal set of neuronal mechanisms [3] or a specific brain state of consciousness. Some of the initial candidates for the NCC that developed in the 1980s and 1990s are well summarized in previous literature [2, 4]. It implies the diversity of possible NCC ranging from the neuronal level to the neural system level, and provides good evidence on how difficult it is to specify NCC in a word. Clinically, disorders of

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consciousness can be caused by damaged function from extensive areas of both cerebral hemispheres, or impairment of structures lying in the paramedian diencephalon and upper brainstem, or involvement of both the hemispheres and brainstem together [5].

Consciousness is not a one-dimensional concept. It has dual aspects to the dimensions of wakefulness (arousal) and awareness [6]. Wakefulness corresponds to the level of consciousness, and awareness is regarded as the content of consciousness [6]. Usually, these two components of consciousness are positively correlated [7]. Awareness indicates the state of perceiving, feeling or experiencing sensations [8], which can be divided into external awareness referring to sensory or perceptual awareness of the environment and internal (or self-) awareness referring to stimulus-independent thoughts, mental imagery and inner speech [7, 9]. The 'qualia' (as the elements of conscious experience, or the specific perceptual qualities of experience [2]), or 'claustrum' (a brain structure proposed by Crick and Koch [10] which might account for properties of consciousness) would be the putative concept for external awareness. External awareness network encompasses lateral frontal and parietal cortices, and its activity is crucial for conscious external stimuli perception [7]. Self-awareness network is distributed over the posterior cingulate/precuneal cortices, medial frontal cortex, and bilateral temporoparietal junctions [7]. On the other hand, the conscious states, like anesthesia-induced unconsciousness or vegetative state can be located on the axis of the level of consciousness.

As mentioned above, the research areas for NCC range from the neuronal level to the brain network level. In this review, we will more focus more on the aspect of the brain network level of NCC including the functional and effective connectivity networks from a methodological point of view. Moreover, as for the states of consciousness, anesthetic-induced unconsciousness and disorders of consciousness are the main subjects that were reviewed. This review will discuss what we have learned from recent studies on the exploration of human brain connectivity on consciousness and its neural correlates, and which step should be followed in order to bring us one step closer to understanding the nature of consciousness.

WHY STUDY BRAIN CONNECTIVITY SEARCHING FOR NCC WITHIN THE SCIENCE OF CONSCIOUSNESS?

Functional segregation and integration are two major organizational principles of the cerebral cortex [11-16] and are applied in almost all cognitive domains [17]. They look like two sides of the same coin, since we cannot understand the brain function seeing only one aspect between these two features. Functional segregation is known for the basis for neuroimaging, which implies how a brain region is statistically distinct from another and thus indicates the segregated functional specialization within brain regions [16]. There is a general consensus that functional segregation is a multi-scale phenomenon, ranging from specialized neurons to neuronal populations and cortical areas [17].

On the other hand, most complex cognitive processes require the functional integration of widely distributed brain areas for coherent behavioral responses and mental states [17]. Although the coexistence of segregation and integration is indispensible for the proper functioning of large-scale neurocognitive networks [17], a majority of neuroimaging studies had mainly focused on the speculation of segregation until the mid-1990s (see Fig. 2. in ref. [16]). However, the proportion of studies looking at integration has been gradually increasing during the last two decades (see Fig. 2. in ref. [16]). Since functional integration can be characterized in terms of functional and effective connectivity [16], connectivity plays an important role in neuroscience fields such as neuroanatomy, neurodevelopment, electrophysiology, and the neural basis of cognition [18].

In terms of general anesthesia and consciousness, current theories to explain general anesthetic mechanism have focused on functional processes related to the NCC, for instance, the information processing theory of Flohr [19], the unified theory of narcosis based on the finding of disrupted thalamo-cortical circuits of Alkire [20], and anesthetic cascade mechanism that linked to the cognitive unbinding paradigm of John and Prichep [21]. The idea of disruption of higher-order large-scale cerebral connectivity while preserving lower-order sensory networks [22] is also an another explanation about the mechanisms of anesthetic-induced unconsciousness from the functional brain connectivity standpoint.

There is a large body of evidence supporting the idea that functional connectivity studies can shed light on functional networks involved in various conscious states [7, 23, 24]. Functional connectivity studies have been applied examining the thalamo-cortical [3, 25-27], frontoparietal [26,28-30], and other cortico-cortical connectivity [31,32] under anesthetic-induced unconsciousness and in disorders of consciousness. Likewise, effective connectivity has been used to investigate the causal interactions among elements of functional connectivity [33-38] in various consciousness states. Moreover, as an extended version of connectivity studies, the complex network methods have also been used in studies on NCC [39-41].

Consequently, based on the implications from previous literature, the investigation of the brain connectivity looking for NCC is crucial for extending our understanding of the mechanism of

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consciousness.

NCC FROM FUNCTIONAL CONNECTIVITY PERSPECTIVE

Functional connectivity indicating the exploration examining temporal correlations of spontaneous neuronal activity between spatially remote neuronal units is one way to investigate the integration in the brain across multiple spatial scales ranging from local field potential recordings to electroencephalography (EEG) and magnetoencephalography (MEG), and functional magnetic resonance imaging (fMRI) techniques [42-44]. A set of brain regions demonstrating temporal correlations has been interpreted as a functional network or as representative of a specific mode of brain function [23].

Functional connectivity is also known as a highly appropriate method to look at the possibility of impaired communication between specific brain regions that account for anesthetic-induced unconsciousness [23]. In fact, functional brain connectivity studies have allowed substantial progress in the understanding of anesthetic-induced alteration of consciousness [22, 33], and also intrinsic brain activity in altered state of consciousness such as coma, vegetative state and minimally conscious state [7, 24].

Anesthetic-induced unconsciousness

Thalamo-cortical functional connectivity is one of the well-known networks explaining NCC. It has been supported by reports of thalamic lesions [45] and impaired thalamo-cortical connectivity under anesthetic-induced unconsciousness [3, 33]. In fact, the thalamus is the region associated with anesthetic effects [3, 46, 47], and thus may serve as a key component of the anesthetic-induced consciousness switch [48]. However, thalamic activity alone may not be a sufficient basis for consciousness. Instead, the explanation about the cause of anesthetic-induced unconsciousness by functional disconnection between subregions of the thalamo-cortical complex seems to be a more reasonable one describing the influence of the thalamus on the underlying mechanism of anesthetics-induced unconsciousness [49]. Recently, Martuzzi and others [25] demonstrated a contradictory finding of increased connectivity between the thalamus and the motor and somatosensory areas [25]. They presumed that the reason for their contradictory findings to previous studies [3, 33] might be due to the lack of a concordance of anesthetic doses, anesthetic types, and depths of anesthesia [25]. Thus, careful consideration might be required when searching for NCC under anesthetic-induced alteration of consciousness from the functional connectivity perspective.

Frontoparietal connectivity has been regarded as another strong candidate for NCC [50-52], which is not surprising given the multiple roles of this system in consciousness, attention, and memory [52]. Frontal cortex may not be essential for anesthetic unconsciousness, but recently, Lee et al. [39] demonstrated the effect of general anesthesia on frontoparietal connectivity (Since this study was performed with effective connectivity tools, it will be discussed more precisely later.). Other target regions for anesthetic-induced unconsciousness are mesial parietal cortex, posterior cingulate cortex (PCC), and precuneus [53]. In addition to those, deactivation or disconnection a lateral temporo-parieto-occipital complex of multimodal associative areas centered on the inferior parietal cortex was also found in many anesthetics [49]. Moreover, Boveroux and others [26] showed that connectivity in lower-order sensory networks is relatively preserved, although interactions between auditory and visual sensory modalities are altered. Intriguingly, they presented evidence of a dose-dependent reduction in default mode network and executive control network connectivity over medial and dorsolateral frontoparietal regions.

Disorders of consciousness

Thalamo-cortical connectivity revisits in cases of disorders of consciousness such as a vegetative state, minimally conscious state and coma. It has been supported by the reports on thalamic lesions [45] and impaired functional connectivity between the thalamus and the association areas of the cortex in the brain of a patient in a vegetative state [27]. The relevance of the thalamus to consciousness has gained more credibility through studies showing that midline thalamic damage can cause a vegetative state [54], and recovery from a vegetative state is accompanied by the restoration of functional connectivity between the thalamus and the cingulate cortex [30]. Vegetative states are "disconnection" syndrome [6] based on the studies of brain-injured patients in vegetative states indicating fragmented cerebral activity [55]. Since there is no known brain region exclusively associated with vegetative states, a connectivity or network of frontal, cingulate, association cortices and thalamus is a good approach in understanding the state of vegetative state [6]. In 2000, Laureys et al. [27] described a restoration of the connectivity of the thalamo-cortical functional connectivity after recovery from vegetative states, providing key evidence for the importance of functional connectivity in consciousness. The resonance of thalamo-cortical circuits has been proposed as the dynamic core of consciousness by Edelman [56] and is in line with cognitive temporal binding by gamma oscillations [57, 58].

Frontoparietal areas, which are deactivated during anesthetic-induced unconsciousness, are also deactivated in vegetative states but are the first to reactivate in those who recover [30].

Table 1. Summary of functional connectivity studies in anesthetic-induced unconsciousness and disorders of consciousness

State of consciousness	Study	No. of subject	Group	Anesthetic agent	Modality	Main findings
Anesthetic-induced unconsciousness	Fiset et al. (1999)	5	Healthy subjects	Propofol	PET	Impaired thalamo-cortical connectivity
	Martuzzi et al.(2010)	14	Healthy subjects	Sevoflurane	fMRI	Increase in thalamo-cortical functional connectivity
	Boveroux et al. (2010)	19	Healthy subjects	Propofol	fMRI	Thalamo-cortical and cortico-cortical in frontoparietal disconnections correlate with consciousness level
Disorders of consciousness	Laureys et al. (1999)	3	VS	-	PET	Impaired connectivity between PCC and other cortical areas
	Laureys et al. (2000)	Not described	VS	-	PET	Thalamo-cortical disconnection but restoration after recovery from VS
	Lauerys et al. (2002)	15	VS	-	PET	Cortico-cortical disconnection
	Schiff et al. (2002)	5	VS	-	PET	Metabolism correlate with the severity of state
	Boly et al. (2009)	8	6 Healthy subjects, 1VS and 1 coma	-	fMRI	Decreased frontoparietal connection in VS, disappearance of long-range functional connectivity in coma patient
	Cauda et al. (2009)	3	VS	-	fMRI	Frontoparietal disconnection
	Vanhaudenhuyse et al. (2010)	13	4 VS and 5 coma 4 MCS	-	fMRI	Frontoparietal disconnection correlate with consciousness level

PET, positron emission tomography; fMRI, functional magnetic resonanceimage; VS, vegetative state; MCS, minimally conscious state; PCC, posterior cingulate cortex.

The hypothesis that consciousness is an emergent property of frontoparietal connectivity [6, 59] could be derived from the functional connectivity studies showing that the vegetative state is a cortico-cortical disconnection syndrome [31, 32]. In addition, there is the convergence of findings supporting the frontoparietal disconnections in brain death [28] and decreases in vegetative state [9, 28, 29] in an fMRI study. Moreover, frontoparietal disconnection is correlated with consciousness level [30]. Diminished cerebral glucose metabolism by PET in PCC and impaired connectivity between PCC and other cortical areas in the anesthetized state was also reported [31]. More precisely, it demonstrated that in vegetative patients various prefrontal and premotor areas in common are less tightly connected with the PCC than in the normal controls [31].

Loss of interhemispheric connectivity in large-scale systems organization of the whole human brain was also found in an independent resting-state fMRI study on a minimally conscious patient compared to healthy volunteers [60], which is also supported by the study of Peltier and others [61]. A vegetative state showed a marked reduction of connectivity between the premotor, prefrontal, and posterior parietal areas at rest [62].

Taken together, disconnection of functional connectivity over cortico-cortical and thalamo-cortical networks seems to be a converged finding based on neuroimaging studies explaining the underlying mechanisms for the disorders of consciousness. Table 1 presents the summary of the studies.

NCC FROM THE EFFECTIVE CONNECTIVITY PERSPECTIVE

Effective connectivity referring to the causal interaction between distant structures in the brain [54, 63] is another way to unveil functional integration. Functional and effective connectivity could be considered complementary properties of brain function, thus effective connectivity can be viewed as an extension of functional connectivity given some underlying neuroanatomic assumptions [64]. In fact, effective connectivity attempts to go beyond functional connectivity by identifying causal influence among components of a network, and thus its beauty comes from the fact that it endeavors to reveal the causes driving observed patterns of neural activity [32].

Anesthetic-induced unconsciousness

Based on the disruption of functional interactions within neural networks involving the thalamus and cerebral cortex, an attempt to interpret the cortico-cortical and cortico-thalamo-cortical connectivity from the effective connectivity perspective was performed by White and Alkire [33] in a PET study using structural equation modeling. They revealed significant state-related changes

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in effective connectivity which primarily involved impairment of the thalamo-cortical and cortico-cortical connectivity, especially between the frontal cortical areas when comparing before and after general anesthetic-induced unconscious state. It is noted that as described in the previous section, there is a recent contradictory finding reporting an increase in thalamo-cortical connectivity in the anesthetized state [25], unlike White and Alkire [33]'s suggestion. From these findings, we learned that the anesthetic doses, anesthetic types, and depths of anesthesia might affect the connectivity pattern under anesthetic-induced unconsciousness.

According to another effective connectivity study on NCC with steady-state EEG signals during propofol-induced anesthesia [36], a significant increase in bidirectional Granger Causality between anterior and posterior cingulate was found especially in the beta and gamma frequency bands and moreover, was observed consistently across subjects. It looks to be contradictory to existing findings demonstrating the association with decreased connectivity regardless of functional or effective ones during anesthetic loss of consciousness [6, 20, 27, 33, 55, 61]. However, the authors insisted that because they assessed the connectivity between only two areas, it could not cover the large-scale network which is likely to represent decreased connectivity. It implies that the types of network either local- or large-scale might influence the results.

Ferrarelli et al. [34] examined effective connectivity during midazolam-induced loss-of consciousness by examining TMS-evoked cortical currents, and revealed a breakdown of cortical effective connectivity during unconsciousness. During the awake state, TMS-evoked EEG responses consisted of small-amplitude, long-lasting oscillations involving several brain areas beyond the premotor cortex, but it was followed by the initially larger local but short-lived responses. In addition, the disruption of frontal-parietal feedback connectivity is also suggested under general anesthesia by means of EEG [35].

Disorders of consciousness

Since one way to gauge effective connectivity among thalamo-cortical circuits involves perturbing directly a subset of cortical neurons with transcranial magnetic stimulation (TMS) and recording the reaction of the rest of the brain with millisecond resolution by means of EEG [38], Rosanova and others [38] investigated a TMS-EEG combined method to evaluate the level of consciousness in patients with disorders of consciousness. In a patient with a vegetative state, TMS triggered a simple, local response indicating a breakdown of effective connectivity, whereas in minimally conscious patients, TMS triggered complex activations that involved distant cortical areas [38]. This study implies that the thalamo-cortical connectivity would be the NCC, since TMS triggered responses are related to the level of consciousness associated with disorders of consciousness, although TMS has a limitation that it is indirect inference of effective connectivity.

A recent breakthrough in an effective connectivity study on NCC using cortical electrophysiological signals, that is, EEG, was carried out by Boly et al. [37]. They provide a new insight into the NCC using effective connectivity in disorders of consciousness. In this study, the assumption that the level of consciousness may rely on the integrity of the backward (top-down) connection was made since feed-forward connectivity is sufficient to generate short-latency ERP components and long-latency components are mediated by the backward connection. As a result, patients in a vegetative state presented the statistically reduced fronto-temporal backward connectivity revealed by dynamic causal modeling compared with patients in minimally conscious states and healthy subjects. In a previous study, abnormal magnetic evoked responses to external auditory and somatosensory stimulation in patients in a persistent vegetative state were reported [55]. However, the authors were not able to provide any information on the direction of the connectivity. However, this study [37] suggested the impairment of top-down connectivity in a vegetative state by taking advantage of the effective connectivity method. Table 2 summarizes the previous studies.

RECENT ADVANCES IN THE UNDERSTANDING OF NCC REVEALED BY COMPLEX NETWORK THEORY

Since a set of brain regions demonstrating temporal correlations has been interpreted as a functional network [23], it is natural to expand the connectivity approach to the network level. In the past few years, a diverse group of scientists, including mathematicians, physicists, computer scientists, sociologists, and biologists, have been actively studying the new research field of network science [65, 66]. We presume that there is no doubt that the human brain is perhaps the most complex entity known to science. Since any complex system in nature can be modeled as a network where nodes are the elements of the system and the edges represent the interactions between them [67], the human brain also can be modeled as a network. From this basis, the application of network analysis based on graph theory to diverse human brain signals such as functional MRI, magnetoencephalography (MEG), and electroencephalography (EEG) provides the feasibility for the complex systems approach to the study of brain functional networks [68]. In other words, knowledge about brain networks is necessary for a more complete understanding of the brain as an

Table 2. Summary of effective connectivity studies in anesthetic-induced unconsciousness and disorders of consciousness

State of consciousness	Study	No. of subject	Group	Anesthetic agent	Modality	Main findings
Anesthetic-induced unconsciousness	White and Alkire (2003)	11	Healthy subjects	Halothane or Isoflurane	PET	Impaired cortico-cortical and thalamo-cortical connectivity
	Ferrarelli et al. (2010)	6 out of 11	Healthy subjects	Benzodiazepine midazolam	TMS+EEG	TMS-evoked activity was local and of shorter duration than wakefulness
	Ku et al. (2011)	18	Patients for abdominal or breast surgery	Propofol or Sevoflurane	EEG	Disruption of dominant feedback connectivity from frontal to parietal regions
	Barrett et al. (2012)	7	Healthy subjects	Propofol	EEG	Increases in bidirectional Grager Causality between anterior and posterior cingulate cortices during unconsciousness
Disorders of consciousness	Boly et al. (2011)	21	13 MCS, and 8 VS	-	EEG	Impaired fronto-temporal backward connectivity
	Rosanova et al. (2012)	12	VS	-	TMS+EEG	Breakdown of thalamo-cortical connectivity

PET, positron emission tomography; EEG, electroencephalography; TMS, transcranial magnetic stimulation; VS, vegetative state; MCS, minimally conscious state; PCC, posterior cingulate cortex.

integrated system [18].

NCC from the complex network perspective

As for NCC, anesthetic-induced alteration of consciousness is associated with changes in local and global networks in the brain [39,40], which was found through an EEG study. However, it does not necessarily mean a complete network failure since the adaptive reconfiguration of the network during general anesthesia maintaining the temporal organization was found [41]. The phenomenon of adaptive reconfiguration of a functional network has been seen in various task-related paradigms in MEG [69] or EEG [70] studies, which also includes the abnormal functional reorganization of brain networks caused by disorders such as schizophrenia [71], and focal hand dystonia [72]. It is known that different processing demands and task domains are associated with the dynamic reconfiguration of functional or effective brain networks [73, 74]. The multifunctional nature of the network nodes of the brain leads to the idea that functions do not reside in individual brain regions but are accomplished by network interactions that rapidly reconfigure, resulting in dynamic changes in neural context [73,74]. Considering these ideas, it seems that the brain network under anesthesia should adopt its network configuration depending on the changes induced by the anesthesia, resulting in the adaptive reconfiguration. In addition, robustness of temporal structures of scale-free brain activity and modulation by task performance were revealed in an ECoG study [75]. It implies that the adaptive reconfiguration of the network during general anesthesia might also be due to the nature of brain networks as scale-free dynamics, which is an intrinsic feature of the human brain network.

Another study published by the same group as a previous research was done by means of graph theory to see the properties of the whole brain network during state transitions from awake to anesthetized states. This graph theory based approach on the issue of whether anesthetic state transitions are continuous or discrete suggested the coexistence of both continuous and discrete processes of anesthetic state transitions, particularly in the parietal cortex rather than in the frontal cortex where most cerebral functional monitors have been taking measurements in clinical environments [76]. Dissociation of the parietal cortex might lead to the breakdown of awareness, since awareness is related to the activity of a widespread set of frontoparietal associative areas [7].

Moreover, network theory especially, using small-world network, was used to explain the well-known theory of disruption of cortical integration in anesthetic-induced unconsciousness [49]. Since small-world networks have mostly local connectivity with comparatively few long-range connections, the thalamo-cortical system may be especially vulnerable to anesthetics due to its small-world organization. Anesthetics need only to disrupt a few long-range connections to produce a set of disconnected components [49], which was also supported by a simulation demonstrating a rapid state transition at a critical anesthetic dose, in fact, consistent with a breakdown in network integration [77].

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CONCLUSIONS AND FUTURE CHALLENGES

Involvements of cortico-cortical and thalamo-cortical connectivity as the NCC could be characterized by functional and effective connectivity studies in various consciousness states either anesthetic-induced or due to disorders. However, the connectivity pattern may vary depending on the anesthetic methods and the severity of the disorders. Moreover, as an advanced approach, a network analysis can contribute to finding NCC at the brain system level.

In order to elucidate NCC from the brain connectivity and network point of view, studies trying to discover the core elements of functional connectivity network would be a good future research topic. According to a recent EEG study, Chu and others [78] suggested the possibility of the existence of a core functional organization underlying spontaneous cortical processing and providing reference network templates on which unstable, transient, and rapidly adaptive functional networks changes. It leads us to the idea that speculation about the core of the NCC would make an intriguing future study on NCC in terms of brain connectivity and network.

We presume that given the recent research trend of examining brain connectivity and its network would exert a strong influence on the field of the science of consciousness to understand the nature of consciousness. From this sense, recent studies [41, 76] are well appreciated regardless several limitations. More carefully designed studies in various situations, such as graded delivery of anesthetic agents during surgery or applying external passive stimulation to evoke the endogenous or exogenous responses in brain regions related to adaptive network reconfiguration, could provide some guidance for us on how to deal with the NCC and help us gain a better understanding of the NCC.

Development of a new measure for determining the depth of anesthesia based on the brain connectivity or diagnostic methodology for discriminating among various disorders of consciousness like between a minimally conscious state and vegetative state would be one example of a clinical application.

In summary, brain connectivity studies will provide a better understanding of the consciousness and its neural correlates. Due to the importance of its clinical relevance, further investigation on the NCC from the perspective of brain connectivity networks should be carried out.

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