Chapter

The Neurofunctional Model of Consciousness: The Physiological Interconnectivity of Brain Networks

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Abstract

The present chapter integrates neural networks' connectivity into a model that explores consciousness and volitional behavior from a neurofunctional perspective. The model poses a theoretical evidenced-based framework that organizes the brain journey of neural information flow from the ascending reticular activating system and non-specific thalamic nuclei, to cortical networks, such as the default mode network and the fronto-parietal network. These inter-connected brain networks can be divided within three hierarchical and inter-connected "functional neural loops": (1) the "brainstem-thalamic neural loop" for arousal, (2) the "thalamo-cortical neural loop" for neural information distribution throughout the brain, and (3) the "cortico-cortical neural loop" for transforming neural information into the contents of consciousness that the individual can perceive and manipulate voluntarily. These three neural loops act as a global functional neural system, and its disruption due to brain damage can cause a person to experience catastrophic outcomes, such as a coma, a vegetative state, a minimal conscious state, or other cognitive and behavioral impairments.

Keywords: consciousness, cortico-cortical system, thalamo-cortical system, brainstem, fronto-parietal network, default mode network

1. Introduction

Consciousness is a complex term to tackle objectively due to its broad epistemological spectrum. From a clinical view, consciousness has been neurophysiologically and behaviorally parameterized for its assessment [1, 2]. It is a central nervous process (reduccionism) that multiple neural long-range connections control (conexionism) and that is teleonomically goal directed. This neurofunctional point of view converges with theories about the emergence of new features in complex systems [3]. Various authors propose that high brain connectivity between distinct and distant neural groups is an elemental characteristic for the emergence of consciousness [3–5]. In this respect, consciousness is a neurophysiological phenomenon regulated by different brain networks that create *qualia*, the subjective experience of consciousness [6–11].

Consciousness should be interpreted as a physiological state of the central nervous system that changes over time and space. This functional mutability allows high-order cognitive functions to take place [6, 12, 13] to produce an overt and/or covert behavior that can be measured via direct observation or neuroimage [14–16]. All of these intermingled processes are supported via various brain networks that integrate endogenous and exogenous information with the intention of responding effectively to organic and psychological demands [6, 8, 11, 17, 18]. In this regard, acquired brain damage can impair the regular activity of brain networks, disorganizing cognition and behavior (mild, moderate, or severe brain damage), or even inhibiting the experience of consciousness (disorder of consciousness) [14, 19–21]. Therefore, from a clinical view, the structural and neurophysiological integrity of the neural substrate that underlies consciousness will determine the functional behavior of individuals [6, 22, 23]. Thus, consciousness can be described as a basal, dynamic, and transitive brain state that supports the high-order cognitive processing of information to produce suitable behaviors for environmental demands [24].

2. The neurofunctional model of consciousness

A huge number of theories seem to agree on many assumptions about consciousness, although they diverge regarding the descriptive approach. Some of them, such as the Global Neural Workspace Theory, focus on its neurophysiological components [11]. Meanwhile, others, such as the Global Workspace Theory, focus on its cognitive components [25]. In addition, the Integrated Information Theory focuses on its computational components [8, 26, 27]; the Temporo-Spatial Theory of Consciousness focuses on its inner space and time characteristics [6]; and the PFC-feedback System [28] focuses on its feedforward and feedback components. Crick and Koch introduced one of the first approaches to the study of consciousness [9]. Their approach posits that the experience of consciousness will be determined based on the long-range connectivity between the front and back parts of the brain. All of these authors and theories have shed light on the phenomena of consciousness and have probably contributed to the very first theoretical foundations for the study of consciousness objectively:

- Consciousness depends on bioelectrical and biochemical brain activity.
- Some neurophysiological processes are required to experience consciousness as awareness (i.e., the object or event has to trigger a P300 wave on the cortex).
- These neurophysiological processes are regulated via various neural groups that process information in a rapid, automatic, and stereotypical manner (back brain), as well as via other neural groups that process information in a slow and voluntary manner (front brain).
- Consciousness needs long-range connectivity between distinct and distant brain areas.
- These long-range connections (probably in beta bands) assemble distinct and distant neural groups into extended neural networks that regulate various physiological and phenomenological dimensions that are necessary for the experience of consciousness.

One of the main neural models that are emerging currently about neural processing is the "predictive coding model" [29, 30]. This model posits that neural processing occurs within feedforward and feedback loops between upper and lower brain structures and slices. Lower structures/slices send predictions to upper structures and these structures send back error predictions to adjust neural processes to make the ongoing behavior efficient [29–33]. Llinás has already suggested that consciousness could be more related to a close-loop neural network than to the emergent consequence of a sensory input [34]. In this sense, a functional and preserved consciousness could depend on the predictive codification between inferior (brainstem and thalamus) and superior brain structures (cortex), where the prefrontal cortex (PFC) receives "end-of-the-line" bottom-up predictions and sends top-down error predictions to the thalamus to adjust new top-down projections [24, 35–40].

Despite all of the theories and experimental evidence about the neural networks involved in consciousness, no global theoretical framework exists to describe how these neural networks operate to produce and maintain consciousness. The present chapter will introduce a neurofunctional model that organizes the interaction and functioning of the neural networks into three neurofunctional loops: (1) the Brainstem-Thalamic neural loop (B-T neural loop), (2) the Thalamo-Cortical neural loop (T-C neural loop), and (3) the Cortico-Cortical neural loop (C-C Neural Loop). Each of these loops are formed via differentiated and semi-independent neural structures that are involved in specific aspects of the phenomenological consciousness.

2.1 B-T neural loop

The brainstem plays a key role in the regulation of consciousness due to the control that it exerts to the Ascending Reticular Activating System (ARAS) and therefore to wakefulness (wakefulness and awareness are the two clinical dimensions typically related to consciousness) [41, 42]. The ARAS is composed of myriad brainstem nuclei (dorsal raphe locus coeruleus, median raphe, pedunculopontine, and parabrachial nuclei), with connections to the thalamus, hypothalamus, and basal forebrain [42–48], and even with the prefrontal areas [49] and the precuneus (Pcu) [50]. The lower dorsal ARAS connects the pontine reticular formation to the intralaminar thalamic nuclei (ILN), the lower ventral ARAS connects the pontine reticular formation to the hypothalamus, and the upper ARAS connects the intralaminar thalamic nuclei to the cerebral cortex [51–54]. Whereas hypothalamic-basal forebrain pathways regulate sleep-wakefulness cycles [48, 55, 56], the ILN, as part of the non-specific thalamic nuclei, can block thalamocortical rhythms and therefore the emergence of arousal and awareness [22, 57–60]. Baars [18] called this circuit the Extended Reticular-Thalamic Activating System, which he considered to be the principal neural assembly in the experience of consciousness.

2.2 T-C neural loop

A significant amount of evidence points out that reciprocal interactions between the thalamus and cortex are a fundamental component of the proper functioning of the thalamo-cortical system [61], which is related to consciousness [62]. This thalamo-cortico-thalamic connectivity starts to develop in the late prenatal and early postnatal stages [61, 63, 64], and the efficient deployment of these developmental processes will determine the functional state of the thalamo-cortical system in the adult stage [65]. The thalamus has been proposed as the main neural structure

of the thalamo-cortical system, as it operates as a regulator of cortical functional connectivity, whereby it is involved in the ongoing cognitive processes [66–70]. The thalamus can be divided into three nuclear groups: first-order thalamic relay nuclei, higher-order thalamic relay nuclei, or non-specific thalamic nuclei. First-order thalamic nuclei send afferent projections to the primary sensory cortical areas, whereas higher-order nuclei receive projections from the primary sensory cortical areas and send these projections back to the higher visual cortical areas forming the cortico-thalamo-cortico circuits. Finally, nonspecific thalamic nuclei are those that receive projections from the ARAS and send diffuse projections throughout the brain [71–73]. The nonspecific thalamic nuclei are composed of three main nuclear groups: the thalamic reticular nucleus (TRN), the ILN, and the midline thalamic nuclei (MTN). The TRN-ILN-MTN thalamic axis has been related to consciousness [22, 62, 74] with strong implications in the distribution of neural information throughout the brain [24].

The functional extent of each nonspecific thalamic nuclei is related to the control and regulation of a specific cognitive domain [24] . The TRN is one of the main neural nodes that regulates the activity of the thalamus and therefore the activity of the entire thalamo-cortical system [75–77]. The TRN receives afferent glutamatergic projections from the entire brain, and in turn, it sends only efferent GABAergic projections to the thalamus, thus regulating thalamo-cortical and cortico-cortical activity [28, 78, 79]. On a morphological level, the TRN is divided into sensory and motor regions [80]. Whereas the sensory region modulates attentional processes via connections with the prefrontal cortex [38], the motor region is involved in limbic and motor processes due to high connectivity with the ILN-NMT, the ventrolateral, and the anterior thalamic nuclei [81–85]. Various authors have referred to the involvement of the TRN in the attentional processes as the "attention spotlight" and "attentional door" that regulate the flow of information between the thalamus and the cortex [35, 86, 87]. The capacity to control neural information throughout the brain is due to the inhibition that it exerts to the thalamic nuclei [37, 76, 86]. This inhibition mechanism underlying the "attention spotlight" selects the information needed to face psychological and physiological demands while suppressing those that are not relevant. Some authors suggest that the TRN is involved in the content of consciousness by controlling selective attentional processes and the thalamus activity [28, 86]. According to Crick [35], the short-term synaptic plasticity of the TRN could influence first-order thalamic relay nuclei in the formation of temporal connections between brain areas related to the content of consciousness [35]. Hence, this capacity to modulate the content of consciousness could be mediated by the control of attentional processes [88–90].

On the other hand, the functions of the ILN and the MTN are functionally differentiated, but their activity are highly dependent [91–95]. Regarding consciousness, both nuclei (due to its multiple connections with the ARAS) activate the excitability of the cerebral cortex to maintain vigilance and arousal [42, 58–60, 76, 91]. For instance, the ILN send and receive projections from the prefrontal, motor, and parietal cortices. Meanwhile, the MTN is connected to the medial prefrontal cortex (mPFC) and the hippocampus (HPC). These diffuse connections spread to the cortex, thus allowing the synchronization of brain activity through the adjustment of the brain waves' phases. Thus, distinct and distant neural groups assemble into cortico-cortical networks to facilitate the flow of neural information [91]. In addition, The ILN and MTN are also involved in the regulation of the striatal-thalamocortical circuits [96] due to the multiple efferent inhibitory connections that receive from the TRN, the basal ganglia, and the reticular formation of the ARAS [97–99]. These connections with the striatum, the brainstem, and the cortex highlight the relevance of the ILN

and the MTN in the motor, somatic, and visceral functions, which are essential for controlling arousal, perception, and even emotion expression [100].

Specifically, the ILN have been associated with the regulation of cortical activity and the restoration of consciousness [22, 68, 101, 102]. The anterior region of the ILN react to motor inputs [103, 104], whereas the posterior region organizes motor, limbic, and associative information [60, 97, 105, 106]. Projections to limbic structures and sensori-motor areas suggest the relevance of the integration of the affective and motor functions that underly propositional behaviors [107]. In addition, they are involved in tasks that require the focalization of attention and the selection of actions for unexpected events [108, 109]. Kinomura and colleagues pointed out that arousal and attention require the simultaneous activation of the reticular formation of the midbrain and the ILN [110]. This evidence places the ILN as the basic neural nodes for the integration of brain functions, such as arousal, attention, and motor control, to trigger high-level cognitive performance [86, 104, 110–113]. This functional characteristic of the ILN in the regulation of the arousal has been employed for deep brain stimulation in cases of minimally conscious state. Schiff [22, 114] showed that stimulating the ILN in minimally conscious state patients could improve their motor behavior, but without showing any sign of "real" consciousness [22, 114, 115]. Therefore, although the ILN seems to be involved in consciousness, it cannot produce a constant and fluent stream of consciousness by itself.

Finally, the MTN have been reported as the main "gateway" of information to the HPC and the limbic system, with a high dependence on the individual's arousal levels [116–119]. Concretely, the nucleus reuniens and rhomboid of the MTN jointly with the mPFC and the HPC form a specialized neural circuit that contribute to learning and to the cognitive flexibility [120], probably due to its relationship with the working memory [116, 117]. This circuit constituted by the MTN-HPC-mPFC could be modified via the functional state of the TRN [121] and also affect the content of consciousness [122]. Other authors propose that the circuit formed via the orbital and mPFC, the amygdala, the hypothalamus, and the MTN could also be involved in the visceral and emotional control of human behavior [123–128]. The MTN directly influences the arousal and attentional processes through its involvement in emotional regulation [129]. Thence, it is implicated in the emotional adjustment of behavior in a continuously changing environment [130]. According to these authors, the MTN could mediate the selection of the most suitable behavior depending on the emotional tone inputs received in a specific moment [118, 130]. This evidence places the MTN as a remarkable interface between the diverse structures of the limbic system to integrate memory, emotion, and cognition [100, 119, 129, 131].

All of this evidence points out that the TRN-ILN-MTX thalamic axis and its connections throughout the brain are essential components for being conscious and aware of our surroundings due to the axis's capacity to place the T-C neural loop in an optimal functional state [24, 35]. In this sense, it is important to distinguish between "be aware" and the "formation of consciousness." Being aware of something means that our cognitive systems are prepared to receive and manipulate the content of consciousness, but the formation of the content of consciousness depends on other neural processes. The content of consciousness is formed mainly in the posterior cortex [132, 133] through cortico-thalamo-cortico circuits, which facilitate connections among various sensory cortical areas in the "content-specific Neural Correlates of Consciousness (NCC)" [70, 133–136]. Regardless of the content-specific NCC, when it comes to accessing consciousness, some neurophysiological requirements, such as a late P300 wave, are needed to ignite a global brain

activation that will trigger awareness [137]. The conscious perception of the content of consciousness is the end of the concatenation of neurophysiological events that propagate from the back to the front cortex [6, 138]. It would be like a competition among various neural coalitions to access consciousness, and once a winning coalition exists (the first to break neurophysiological requirements), a specific representation or the content of consciousness can be perceived as generating a genuine experience of consciousness [137]. Afterward, this content of consciousness is controlled by high-order cognitive functions and is incorporated into plans, desires, and/or thoughts [6, 139].

2.3 C-C neural loop

Once the content of consciousness is created in the back brain [132, 133], various cortico-cortical networks consciously manipulate the information [140]. One of the main cortico-cortical networks, which is broadly documented, is the Default Mode Network (DMN) [141–144]. This network is formed by the anterior and posterior cingulate cortex, the mPFC, the orbital PFC, the medial temporal lobe (parahippocampal cortex and HPC), the retrosplenial cortex, and the inferior parietal lobe [145] . The DMN is a rest neural network, whose activity is maximum when the subject is awake and the cognitive demand is low (low-level processing of exogenous information) [146]. Moreover, the DMN is characterized by a high metabolism during rest states [147–150], a progressive deactivation when more cognitive resources are needed to process information [147], and a high connectivity with other cortico-cortical networks to exchange information [140, 143, 151]. Traditionally, the DMN has been related to internal processes, such as self-reference thoughts and mind-wandering [152–154], although some studies currently link its activity to extrinsic processes, such as certain attentional processes [155] and the recall of memories [156–159]. Recently, it has been posed that the DMN could also be involved in the integration of spatial, self-reference, and temporal information, thus generating episodic memories [160]. These authors suggest that, henceforth, the DMN is mostly activated in all of the cognitive processes [160].

One of the key points for understanding the role of the DMN in consciousness is to conceive it as a cognitive system that modulate cortico-cortical activity through its mediation in the transfer of information from resting states or task-negative networks to cognitively active states or task-positive networks [140, 147, 156, 161–164]. When a subject is resting (with the low-level processing of exogenous information), the DMN controls cortical activity with the posterior cingulate cortex (PCC) and the precuneus (Pcu) as their main neural nodes. However, as long as elaborated processing is required and the load of the working memory increases, the physiological burden of the DMN decreases in favor of task-positive networks: the fronto-parietal central executive network (FPN), the dorsal attention network (DAN), and the salience network (SN). The FPN includes the dorsolateral PFC, the mPFC, the anterior insula (aINS), the Pcu, and the interior parietal lobe [140, 165–167]. On the other hand, the DAN is formed by the frontal eye field and the intraparietal sulcus [168], and the SN by the aINS, the dorsal anterior cingulate cortex, the amygdala, the ventral striatum, and the ventral tegmental area of the mesencephalon [169]. All of these networks share overlapping regions whereby they can exchange neural information depending on the ongoing cognitive activity [147, 149, 150, 170–173] . The outcome of the continuous interactions among the cortico-cortical networks will define the functional conscious state of the individual [163].

The FPN, DAN, and SN play a key role in conscious behavior due to its capacity to operate jointly and synchronically in a highly coordinated and temporally accurate manner [140, 165, 174]. For instance, the DAN has been related to focalized attention

and working memory, whereas the SN has been related to social communication, social behavior, and self-consciousness [171, 175–178] . When all of these task-positive networks are operating, the DMN needs to deactivate [179–181] to facilitate the transition from low-energy cognitive states to high-energy cognitive states [147]. In these high-energy cognitive states, the mPFC takes control of the global brain activity at the expense of the PCC and the Pcu [170, 182]. Therefore, the alteration of structural and functional connectivity "within and between cortico-cortical networks" could cause the individual to experience a broad spectrum of neuropsychiatric and neurocognitive disorders [162, 163, 180, 183, 184].

The FPN and SN, especially in the prefrontal regions, regulate the cognitive processes involved in the achievement of conscious goals through the regulation of the physiological *equilibrium* between the DMN and the rest of the cortico-cortical networks (cognitive control) [140, 165–167, 185, 186]. Some studies point out that the mPFC and aINS regulate physiological *equilibrium* among brain networks [178, 187]. For instance, Crone and colleagues compared the activation/deactivation of the DMN in vegetative states (currently known as "unresponsive wakefulness state"), minimally conscious states, and individuals with preserved and functional consciousness (control subjects) [182]. They suggested that although the deactivation of the DMN was normal in control subjects, the same deactivation was significantly diminished in overlapped areas between the DMN and the FPN in a minimally conscious state, and it was absent in unresponsive wakefulness state patients. In other words, the cohesive and functional integrity between the DMN and the task-positive networks is a crucial factor in the transition between rest states (those with a low cognitive burden) to high-demand cognitive states (those with a high cognitive burden) [147]. Our team conducted an investigation whereby we compared cortical connectivity between minimally conscious states and severe neurocognitive disorders [4]. Our results revealed how the degree of connectivity between the anterior and the posterior cortex in the beta band was essential for maintaining a preserved consciousness. In this investigation, patients with minimally conscious states showed a low connectivity between the posterior and the anterior cortex, which could explain why their consciousness fluctuates over time [4]. In contrast, subjects with preserved consciousness showed a high connectivity between the anterior and the posterior cortex, whereby they can operate continuously without the absence of consciousness [4]. In this sense, in a case study, an unresponsive conscious patient emerged to a minimally conscious state when connectivity between the anterior and the posterior cortex increased [188]. Thus, the integration of the posterior and the anterior cortex into long-distance cortico-cortical networks is one of the principal prerequisites for maintaining functional consciousness [9, 182, 189, 190].

3. Assumptions for the neuroFunctional Model of Consciousness (nFMC)

1. The nFMC is a theoretical and referential framework from which the study of consciousness can be tackled in all of its operative dimensions: neurophysiological, clinical, neuropharmacological, and phenomenological.

2. Consciousness is a global neural process that keeps the individual in an optimal and continuous functional state, thus allowing qualia and high-order processes to take place to drive behavior.

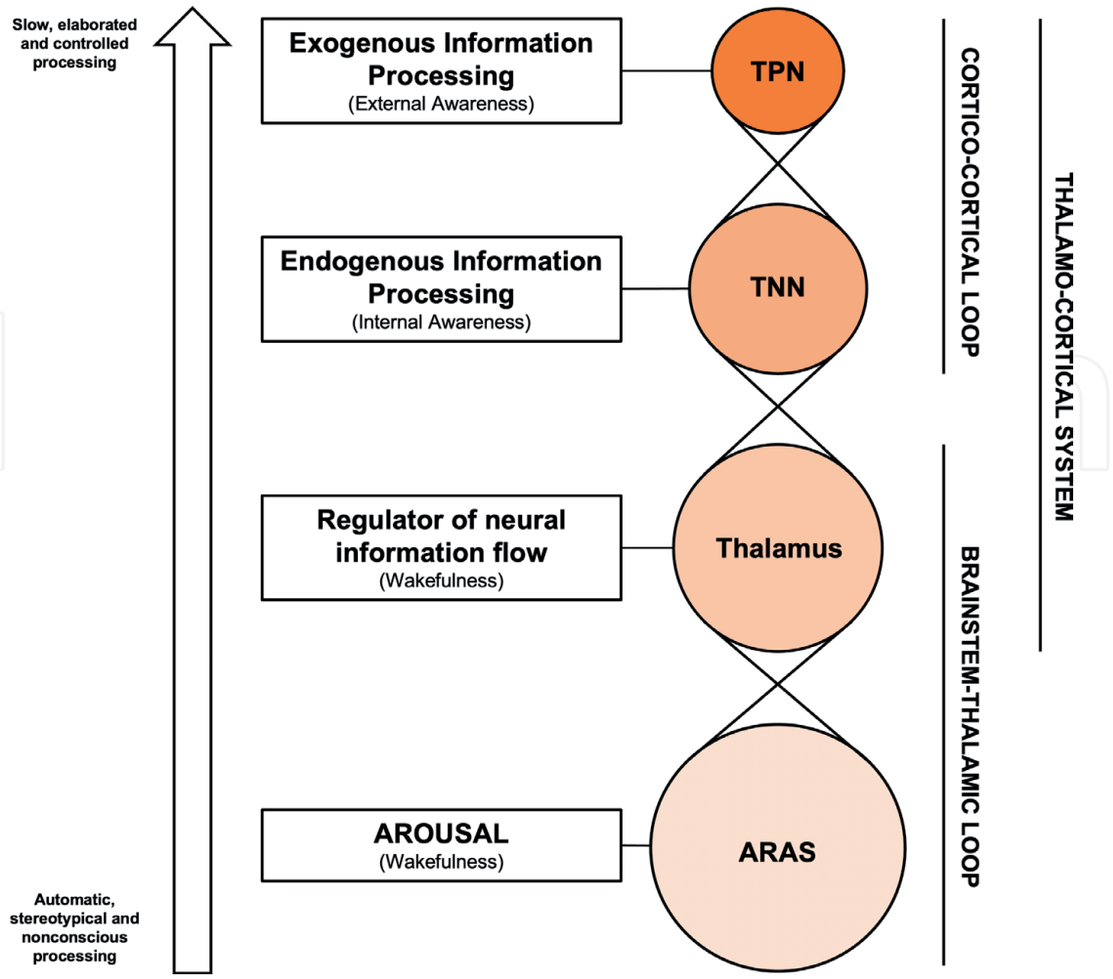

Figure 1.
*Consciousness is the phenomenological quality of human existence that arises from a hierarchical, parallel, and serial activation of long-distance brain networks [7], which operate as neural loops that "inform" upper and lower levels about their own operations [29, 30]. These loops receive input from lower levels (which contains new information/predictions) and input from upper levels (error predictions). The loop will integrate all of this new information, updating its own functional state and, consequently, also the functional state of the rest of the loops and the brain [29–32, 191]. **ARAS:** Ascending reticular activating system; **TNN:** Task-negative networks; **TPN:** Task-positive networks.*

3. The nFMC divides global neural activity into three large systems, or functional loops, that are morphologically differentiated (although they share overlapped areas) and have semi-independent neurophysiological processes: the B-T neural loop, T-C neural loop, and C-C neural loop (see **Figure 1**).

4. Cognitive, behavioral, and emotional expression due to brain damage will depend on the location and extension of the lesion within the neural loop, thus leading to clinical outcomes that they may vary from a mild cognitive impairment to a disorder of consciousness, such as a coma, minimally conscious state, or unresponsive wakefulness state.

5. Each neural loop is activated hierarchically and sequentially by its preceding level, thus extending a representation of the neural processes that took place in the lower level, as well as integrating and transforming this neural representation into new information.

6. The nFMC is in accordance with predictive coding models that present brain activity as a system in which lower brain structures project predictions/signals

via bottom–up processing, and where higher cortical areas send prediction errors back via top-down processes.

7. Neural processes (both automatic and controlled) related to consciousness (such as P300, brain rhythms, and neurotransmitter discharges) can be localized within either of the neural loops or in their reciprocal interactions.

8. The nFMC is complementary and comprises several assumptions considered in previous theories and investigations of consciousness:

   - Consciousness can be deemed a Global Neural Workspace in which distinct neural networks compete to access consciousness [11, 25, 192].

   - Consciousness is the result of functional units or complexes that integrate information and that are activated or deactivated depending on the ongoing sensorial/visceral necessities [8, 26, 27].

   - Consciousness is a neurophysiological continuum commanded by inner spatio-temporal brain laws [6].

9. Regarding the neural mechanisms or processes involved in the formation of the content of consciousness, the nFMC aligns with models and evidence that posit that the contents of consciousness are formed in the back brain via cortico-thalamo-cortical connections [70, 132–136]. In addition, the nFMC recognizes that PFC top-down connections could modulate the selection and even the formation of the content of consciousness [28].

4. Conclusion

Human behavior has to be understood as a global brain activity dominated by complex and hierarchical neural processes that cannot be divided and explained by isolated functional units. Consciousness is the "operating system" running underneath the "interface" of overt and covert human behavior, and it is dominated by the interactions of various neural levels composed of differentiated and semi-independent neural networks. Thence, the nFMC gathers reliable knowledge generated in the study on neural correlates of consciousness, providing a novel theoretical and referential framework that will help clinicians, researchers, and even students to localize the neural processes of interest within a global brain activity model. A further proposal should extend the structures and connectivity involved within and between each neural loop introduced in the nFMC.

Conflict of interest

The authors have no conflict of interest to declare.

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