

Is prefrontal cortex required for conscious perception? Challenging classic ideas with new experimental evidence

Module A1: Cognitive Neuroscience

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Introduction

Conscious perception is one of the highest functions of the human brain and a central matter for the humankind. Historically it has also been a source of debate both in humanistic forums and more recently in the ongoing scientific discussion. Consciousness is difficult to approach from a scientific, rationale perspective because of the lack of tools and appropriate behavioural paradigms to probe it. The first relevant scientific contributions to the field were made during the first half of the twentieth century. Psychiatrists and neurologists commenced psychological studies of patients with cortical lesions in order to evaluate the extent to which they were aware of their surrounding world. Early work by Dandy, Brickner, Penfield, Hebb and others uncovered that lesions in the prefrontal cortex (PFC) may impact conscious state and conscious access to stimuli. However, early studies were unclear and controversial, and researchers failed to address an agreement on the role of PFC in conscious perception. More than fifty years later, thanks to the development of new techniques we have accumulated a vast amount of experimental evidence either supporting or refuting a role of PFC in consciousness. However, even today the scientific community struggles to address this central question for Neuroscience: What is the role of the PFC in consciousness (if any)?

This essay will first review the current dominant hypotheses in the field and briefly summarize some notorious early lesion studies, to then move on to discuss frontoparietal and frontotemporal networks. Finally, this essay will break down two recent papers and discuss the implications of their findings in relation to the role of PFC in consciousness.

Consciousness: Hypotheses, theories and framework

In order to avoid misconceptions and maximise precision of the terminology, it is necessary to first settle down some definitions. In the past, incongruent and poorly defined terms in combination with incorrect interpretations of experimental outcomes have caused long-standing debates in the field of consciousness. This is preferable avoided by conveying ideas into terms which we all understand as the same thing, and by giving clear, non-ambiguous definitions of such nomenclature. The aim of this section is to define, explain and clarify relevant concepts that will be used along the essay.

To begin with, the concept of neural correlates of consciousness (NCC) refers to the minimal anatomical substrate sufficient for sustaining any one conscious percept (Crick and Koch, 1990).

We can further subdivide the NCC into content-specific NCC, which account for particular phenomenal contents within consciousness, such as colour or faces (Boly et al., 2017). Such substrates are defined using a wide variety of techniques ranging from lesion studies, to neuronal recordings to neuroimaging experiments.

In relation to current frameworks, in the field of experimental psychology, the classical framework used to explain whether stimuli are perceived is signal detection theory (SDT) (Green and Swets, 1966). It hypothesises that any stimulus gives rise to a stochastic signal propagating over time, which may reach a certain threshold, triggering perception, or may decay after some time, being lost. SDT transforms a quantitative measure of the stimulus into a binary outcome, namely, to be or not to be perceived. The mathematical implementation of SDT is in essence similar to the drift-diffusion model, which is widely used as a computational model for decision making (Bogacz et al., 2006). SDT alone does not point to specific NCC, nor to specific neural computations involved determining the threshold. By contrast, global neuronal workspace theory (GNWT) proposes that a requirement for awareness is the propagation of stimuli from primary sensory areas to higher associative levels of the cerebral cortex (Dehaene and Changeux, 2011). In these areas, the propagated activity can lead to an ignition event that then allows information to be sustained and broadcasted back (Lamme and Roelfsema, 2000). So, how may a stimulus fail to drive perception in the GNWT framework? On the one hand, the stimulus may be lost if it only elicits weak propagation of activity from lower, primary sensory cortical areas to higher ones. On the other hand, the stimulus might as well not reach perception if ignition fails – for example, due to low arousal levels or because attention has been directed to another stimuli. I will explore these two hypotheses in detail in a later section in the context of a recent study.

The frontal lobe hypothesis postulates that the neural correlates of consciousness are found in the frontal lobe, in particular in the PFC, as it has access to encoded processed stimuli and projects to cortical areas associated with motor planning (Koch and Crick, 1998). This hypothesis predicts that a patient with extensive bilateral prefrontal damage will be completely unconscious. However, this is very difficult to be directly tested due to two limitations. First, such extent of damage is rare among clinical patients. Second, and more importantly, even if such patient existed, and because of the central role of PFC in cognition, it would be really difficult to subject the patient to any task as he or she would be completely irresponsive, not to mention the inevitable associated strong cognitive impairment. In relation to the frontal lobe hypothesis, several authors have noted that feedback from frontal cortex may be a signature of consciousness (Boly et al., 2011).

It is often assumed that consciousness must be confined to a structure or group of structures in the brain. However, it has recently been noted that a more useful way of understanding the NCC could be by linking them to specific computations in the brain, rather than to brain regions (Sandberg et al., 2016). This way, the PFC would be necessary for conscious perception in the sense that its recruitment as a trigger for perception might be a necessary condition, but not because all conscious computations are performed there. Indeed, the idea of consciousness implemented as a sparse cortical network has gained strength over the last years. Some researchers have highlighted the importance of consciousness as an integrative element, as it requires multimodal integration of all classes. In this sense, Crick and Koch note that “*a key property of conscious sensations is their integrated nature. You are not aware of isolated percepts, but of a single, unifying experience*” (Crick and Koch, 2005).

For the sake of clarity and brevity this essay will not cover in depth the contributions of subcortical structures to conscious perception. However, it is important to demarcate that PFC receives strong innervation from both brain-stem and diencephalon, including the habenula (Hoover and Vertes, 2007). Indeed, cholinergic stimulation of PFC, although not noradrenergic stimulation, recovers consciousness in unconscious rats anaesthetised with sevoflurane, an oral general anaesthetic (Pal et al., 2018). Interestingly however, in this experiment noradrenaline did produce electroencephalographic activation without alteration of conscious state. Stimulation of the posterior parietal cortex – mainly constituted by the somatosensory cortex in rodents – or the medial parietal association cortex with either of the two modulatory neurotransmitters did not recover consciousness (Pal et al., 2018). This result demonstrates that input from the brainstem to the PFC, but not to other cortical areas, modulates conscious state. Such modulation is most likely related with the level of arousal rather than with conscious access to specific sensory stimuli.

Revisiting lesion studies: To be or not to be frontal

In 1922, Dandy performed the first unilateral frontal lobectomy (Dandy, 1922). He reported no observable post-operative mental disturbances of such patient. Some years afterwards another article documented the same surgical procedure for two new patients, one on the non-dominant hemisphere and the other on the dominant hemisphere (German and Fox, 1932). The first did not develop any observable intellectual deficits after the surgery, whereas the second showed “*definite impairment of intelligence, characterized chiefly by a paucity of spontaneous motor response*”. Other

reports noted changes in behaviour, conscious state and cognitive abilities – ranging from mild to severe – of patients that underwent unilateral frontal lobectomies (Ackerly, 1935; Brickner, 1952; Penfield and Evans, 1932, 1935).

Brickner reported the first patient to undergo a complete bilateral frontal lobectomy (Brickner, 1952). According to the article, he showed no observable alterations to conscious state after the surgery, providing the first strong evidence that lesions to PFC do not impair consciousness at all and settling a dispute that would last until the days of today. However, in a recent opinion article Odegaard *et al.* argue that, contrary to Brickner's claim that most of the subject's frontal lobe had been removed, careful visual inspection of the patient's post-mortem brain reveals that portions of the right lobe's dorsolateral PFC remained almost intact (Odegaard et al., 2017). In another study it was reported the clinical case of a young man with intractable epilepsy, K. M., that also underwent bilateral prefrontal lobectomy (Hebb and Penfield, 1940). The neurosurgeons performing the operation estimated a loss of around 14% of cerebral mass after the surgery – around one third of the whole frontal lobe – which included brain tissue from the frontal pole to, approximately, the central fissure of Rolando (**Fig. 1**). Surprisingly, after postoperative recovery K. M. showed no signs of unconsciousness or cognitive impairment and epileptic seizures almost disappeared. Moreover, it was reported that his intelligent coefficient improved. These two clinical cases strongly clash with the initial conception that the PFC might be required for conscious perception.

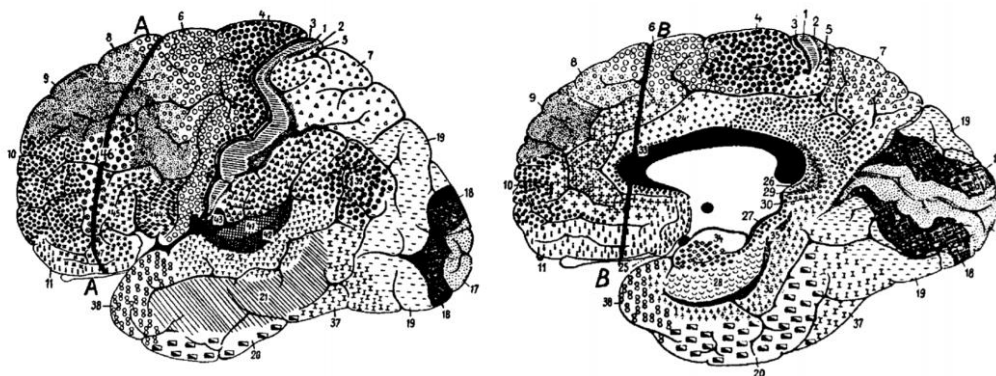


Figure 1. Drawings showing the extent of removal of K. M.'s frontal lobe in a cytoarchitectonic diagram of Brodmann areas. AA indicates the estimated line of section on the lateral convexity of the brain of both sides, and BB the line of section in the median longitudinal fissure. Reproduced from Hebb and Penfield (1940).

On the other hand, it has also been reported that patients with bilateral damage to lateral or dorsolateral PFC appear to be almost completely disconnected from, and unaware of, the

external world (Odegaard et al., 2017). In this same article Odegaard *et al.* criticise misinterpretation of classic lesion studies, arguing that in most cases the authors reported incomplete frontal lobectomies, including in many cases failure to resect the dorsolateral PFC entirely. In a response to Odegaard *et al.* a group of well-known researchers in the field of consciousness wrote that “*the frequent assumption that PFC is essential for consciousness seems largely due to neuroimaging studies that do not distinguish between subjective experience and task performance*” (Boly et al., 2017). Recently some of these same authors reported two perioperative clinical cases that once again challenge the idea of PFC being the NCC (Sanders et al., 2018). The first one, a patient showing severe, bilateral frontal injury with signs of mild cognitive impairment and memory deficits but being completely conscious. In the report the authors do not offer any evidence to prove that the patient was completely conscious, but they write that “*while he showed some evidence of cognitive impairment, including memory issues, he was obviously conscious when he presented for the procedure*” (Sanders et al., 2018). The second patient, who had no apparent brain damage, showed slow wave activity in the PFC during anaesthesia recovery while being partially conscious, a functional signature normally attributed to unconscious state. In particular, the authors report that she was able to execute simple motor actions in response to simple commands and nod on request while they were observing this slow-wave activity in the PFC. As seen, this matter is still subject of intense debate in the field of Neuroscience.

Functional studies: Frontoparietal or frontotemporal networks?

To the extensive list of unresolved issues surrounding the role of PFC in consciousness we have to add the dispute of whether consciousness recruits frontoparietal or frontotemporal networks. In one influential study, recordings in the macaque brain showed that neuronal activity in the lateral PFC correlated well with visual awareness (Panagiotaropoulos et al., 2012). Following this idea, stimulation of the frontal cortex by means of transcranial alternating current stimulation (25 and 40 Hz) was shown to increase conscious awareness during sleep (Voss et al., 2014). These two articles were the first to provide powerful functional evidence of the coupling between PFC and conscious access to visual stimuli. Also, dreaming during REM has been associated with high frequency activity in the PFC (Siclari et al., 2017). Interestingly, frontoparietal networks show enhanced resting-state functional connectivity in individuals experiencing frequent lucid dreaming (i.e. reflective consciousness while dreaming) (Baird et al., 2018). To illustrate this point we can also gather evidence from the mechanism of action of general anaesthetics. As a matter of fact, many general anaesthetics disrupt fronto-parietal

networks (Lee et al., 2013), and a number of them also suppress feedback from the PFC to occipital and parietal cortical areas (Imas et al., 2005, 2006).

These studies and others show that visual awareness recruits frontoparietal networks. Surprisingly however, two independent groups studying the hemodynamic correlates of sound perception found that a bilateral frontotemporal network, but not a frontoparietal network, is associated with the awareness of such perception modality (Brancucci et al., 2016; Eriksson et al., 2006). Other minor studies report similar results. Therefore, it seems that the specific NCC depend on the sensory modality.

New experimental evidence disentangles old misconceptions

A recent study modelling the macaque cortex found that weak inputs to V1 activated only local networks, but strong inputs resulted in the activation of the PFC (Joglekar et al., 2018). This study points to a role of GNWT in cortical signal propagation and also – and perhaps more importantly – the authors observed that excitatory feedback projections can amplify signals but are balanced by local inhibitory processes. These findings reflect the fact that, even assuming that the anatomical correlates of SDT were to be found in the PFC, this still has to be compensated by a sufficiently strong enough stimulus that propagates activation of local circuits across cortical areas.

In another recently published study, the authors recorded from V1, V4 and dorsolateral PFC of awake monkeys performing a fixation-and-saccade task (van Vugt et al., 2018). The main objective of this study was to disentangle SDT from GNWT and probe the role, if any, of the dorsolateral PFC in conscious report of stimuli. They made three important discoveries:

1. The study reported strong and sustained activation of the three areas during visual awareness. Moreover, the strength and length of activation depended on how difficult it was to discern the stimulus from random noise, indicating that the NCC of visual awareness are sparse and encoded along the dorsal stream.
2. Loss of sensory information of nonreportable stimuli occurs at several stages along the occipitofrontal propagation of information. They concluded that, in order to translate information into conscious experience, there must be an active component, which can also be seen as a feedback signal from the PFC to more caudal occipital areas.
3. In the second part of the study, the authors performed low frequency (200 Hz) weak electrical microstimulation of V1, which produces phosphenes – spatially restricted illusory

light patches (Winawer and Parvizi, 2016) –and recorded again in V4. They found that V4 activity was increased in trials in which monkeys reported the artificial stimulus but tended to be lost if the stimulation strength in V1 was not sufficient. This resolves a long-standing question posed more than two decades ago, namely whether we are aware of activity in V1 (Crick and Koch, 1995). The answer is negative; we are aware of percepts that surpass the V1 filter and reach higher cortical areas in the visual hierarchy and parietal association areas, only when these stimuli also coincide with conscious ignition (i.e. a feedback signal from the PFC).

Taken together, these studies suggest that, in order to allow information flow from the back to the front of the brain, it is necessary a trigger or ignition from the PFC (feedback signal) as well as a sufficiently strong enough stimulus that propagates activation of local circuits across cortical areas (feedforward signal). This new evidence unifies SDT and GNWT into a single framework, in which the SDT threshold is encoded in the PFC and equals the amount of neural activity required for ignition (Mashour, 2018). This threshold is dynamic and depends on cortical state and can be viewed as a major factor that drives arousal levels. As already mentioned, arousal state is actively modified by modulatory inputs to the PFC from the brainstem and habenula. Therefore, we can conclude that the SDT threshold encoded in the PFC is strongly influenced by subcortical modulation, a causality which should undoubtedly be further studied. However, it is important to note that the threshold is only one of the parameters that play a role in this joint SDT-GNWT picture and that it does not explain how conscious perception is encoded, but rather whether perception arises or not for a certain stimulus under a certain cortical state.

Conclusion

Despite the controversy caused by doubtful neuroimaging studies and classical lesion studies, it seems unlikely that the PFC does not play any role at all in consciousness. True to be said, all evidence pinpoints to the fact that the NCC are not in the PFC. However, a recent report seems to settle down the role of PFC as the neural substrate for SDT threshold (van Vugt et al., 2018), without excluding the companion GNWT theory, indicating that consciousness indeed arises from a sparse cortical network comprising, at least for visual awareness, occipital primary and higher sensory visual cortices as well as parietal association areas. However, there are still many unresolved matters. For example, how do the results from Van Vugt *et al.* and Joglekar *et al.* apply to sensory processing outside visual awareness or in the absence of thalamic sensory input

(i.e. in internally generated experiences such as dreams)? Is a combination of SDT and GNWT the underlying mechanism across all sensory modalities? Does this new data suggest new possible mechanisms for the loss of consciousness induced by general anaesthetics?

In this essay it has also been shown that frontoparietal networks seem to be recruited during visual awareness, whereas frontotemporal networks fill the equivalent role for sound perception. What are the equivalent networks for somatosensory sensation?

Finally, Odegaard *et al.* made an important observation in relation to the frontal lobe hypothesis: Patients with bilateral complete damage to the dorsolateral PFC seem to be disconnected from reality (Odegaard et al., 2017). Does this suggest that the NCC for the STD trigger are in particular located in the dorsolateral PFC?

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