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Review

Conscious Processing and the Global Neuronal Workspace Hypothesis

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We review the central tenets and neuroanatomical basis of the global neuronal workspace (GNW) hypothesis, which attempts to account for the main scientific observations regarding the elementary mechanisms of conscious processing in the human brain. The GNW hypothesis proposes that, in the conscious state, a non-linear network ignition associated with recurrent processing amplifies and sustains a neural representation, allowing the corresponding information to be globally accessed by local processors. We examine this hypothesis in light of recent data that contrast brain activity evoked by either conscious or non-conscious contents, as well as during conscious or non-conscious states, particularly general anesthesia. We also discuss the relationship between the intertwined concepts of conscious processing, attention, and working memory.

Introduction

The nature and mechanism of conscious processing is arguably one of the most intriguing questions in 21st-century neuroscience. The past two decades have witnessed substantial progress in the field, which has been driven by an array of conceptual and experimental advances (Dehaene and Changeux, 2011; Koch et al., 2016). Just over 20 years ago, two of the authors (J.-P.C. and S.D.) proposed a simple and neurobiologically informed theoretical framework for conscious processing, termed the "global neuronal workspace (GNW) hypothesis" (Dehaene et al., 1998). In the present review, we describe its central tenets, neuroanatomic basis, and recent studies supporting or challenging its explanatory power in answering questions of key relevance to conscious access.

Given the rich and often confusing nomenclature related to consciousness, it will be beneficial to clarify some basic terminology that will be used. One distinction relates to "phenomenal consciousness" versus "access consciousness" (Block, 2005). Phenomenal consciousness, by definition, involves a hypothetical and idealized situation of pure subjective experience (also called "qualia") without further associated information processing (and, therefore, no need for verbal report). Access consciousness refers to the fact that conscious information, unlike unconscious information, is accessible to numerous cognitive processors, such as those mediating working memory, verbal report, or motor behavior. The importance of this distinction remains hotly debated, but it has been suggested that "global availability of information (…) *is* what we subjectively experience as a conscious state" (Dehaene and Naccache, 2001). Thus, unless otherwise specified, the term "consciousness" in this review will be replaced by conscious access. Note that conscious access can occur with or without overt behavioral report. Although a report is often needed to decide whether a stimulus was consciously perceived, "no-report" paradigms are emerging in which conscious access can be de-confounded from traditional behavioral responsiveness (Aru et al., 2012).

Another distinction relates to the level and content of conscious processing, two dimensions that are distinct though not fully dissociable (Bachmann and Hudetz, 2014). Level refers to the overall state of an individual (e.g., being awake versus drowsy, asleep, or comatose), whereas content refers to the information that is currently experienced (e.g., seeing a red rose versus a yellow sun). We will address the relevance of the GNW to both level and content of conscious processing in the course of this review.

Central Tenets and Neuroanatomical Basis of the GNW Hypothesis

The central thesis of the original global workspace theory was proposed by Baars (1988). It is a psychological construct arguing that perceptual contents, which are acted upon by localized processors, only become conscious when they are widely broadcasted to other processors across the brain. Broadcasting implies that the information in the workspace becomes available to many local processors, and it is the wide accessibility of this information that is hypothesized to constitute conscious experience. Baars's global workspace involves processors related to the past (memory), present (sensory input, attention), and future (value systems, motor plans, verbal report) (Figure 1A). Thus, the global workspace achieves experiential integration that is, in terms drawn from the philosophy of mind, both synchronic (at a particular point) and diachronic (over time).

Baars suggested the diffuse, extended reticular-thalamic activating system as the main brain structure forming the global workspace. However, Baars's instantiation of the hypothesis does not distinguish between the level of conscious processing (under the control of the reticular formation) and the content. By contrast, the GNW hypothesis, as initially proposed by Dehaene et al. (1998) and later simulated (Dehaene and Changeux, 2005; Dehaene et al., 2003), proposes a defined brain network as the neural instantiation. In addition to localized, specialized, and modular cortical areas that process specific perceptual, motor, memory, and evaluative information, a second computational space is composed of widely distributed excitatory neurons (called GNW neurons) with long-range axons, forming reciprocally connected tracts able to "selectively mobilize or suppress, through descending connections, the contribution of specific processor neurons." This distributed population of neurons is postulated to possess the ability to receive bottom-up information from and transmit top-down information to any of the various processors, thus selecting and broadcasting information. At the neuronal level, the GNW hypothesis postulates a key role for large pyramidal cells in cortical layer II/III (Figure 1B) but also a contribution of pyramidal cells in deeper layer V, as illustrated by recent studies (see below).

Another important feature of the hypothesis is that the GNW activates in a non-linear manner called "ignition" (Dehaene et al., 2003). Ignition is characterized by the sudden, coherent, and exclusive activation of a subset of workspace neurons coding for the current conscious content, with the remainder of the workspace neurons being inhibited. Ignition may be triggered by an external stimulus, as part of a cognitive task, or it may occur spontaneously and stochastically at rest. In the latter case, even during the unstimulated resting state, simulations show that the GNW is subject to a continuous stream of stochastic spontaneous activity (Dehaene and Changeux, 2005), thereby implementing a source of diversity that can continuously activate mental representations in an endogenous manner. This property of the model fits with the constant variations in fMRI and electroencephalogram (EEG) functional connectivity that are observed in the awake resting brain and that vanish during anesthesia or in patients with disorders of consciousness (Barttfeld et al., 2015; Demertzi et al., 2019).

It is important to note that the GNW hypothesis is not a localizationist approach to conscious access, nor is conscious access posited to exist solely in a given node of the GNW (for recent discussions of localization and conscious access, see Boly et al., 2017; Odegaard et al., 2017). Rather, the GNW acts as a distributed "router" associated with millions of neurons distributed in many brain regions through which information can be amplified, sustained, and made available to specialized sensory processors and thalamocortical loops. The prefrontal cortex (PFC) is posited to play a key role in the GNW because of the greater density of neurons thought to be critical for global broadcasting of information, but it is not proposed as the exclusive territory for conscious access. The GNW was, indeed, initially suggested to include the dorsolateral prefrontal and inferior parietal cortex together with a set of specialized and modular perceptual, motor, memory, evaluative, and attentional processors. Other cortical hubs, such as the anterior temporal cortex, anterior and posterior cingulate cortex, and precuneus, may be equally important. Note that these areas are neither identical nor redundant: each has their own functional specificity and connectivity pattern, yet the communication between them is so extensive and rapid that any information available to one is quickly made available to others. Their tight bidirectional connectivity creates the conditions for ignition, i.e., the triggering of a sudden collective and reverberant coordinated activity that mediates global broadcasting. Tracer studies in non-human primates indicate that these areas indeed connect together as a "high-efficiency cortical core" with high-density connectivity (Markov et al., 2013) (Figure 1C).

Simulations of the Global Workspace

The 1998 GNW model was initially applied to the computer simulation of the classical word-color Stroop tasks. This simulation showed that workspace activation increased during the acquisition of a novel task, its effortful execution, and after errors. Those simulations led to predictions for spatiotemporal activation patterns for brain imaging, particularly the contribution of the dorsolateral PFC and anterior cingulate to the workspace. An interesting property of that network is its ability to maintain an active, sustained state of workspace and processor unit activity for some duration in effortful tasks in which the response must be postponed after the stimulus has been terminated.

Another set of simulations within the GNW framework was designed to simulate two conditions leading to a loss of conscious perception: masking and inattention (Dehaene and Changeux, 2005; Dehaene et al., 2003). Those simulations involved spiking neurons with realistic receptor dynamics embedded in a multicolumn cortical architecture with four hierarchical levels interconnected by corticocortical bottom-up and top-down connections with two representations at each level. Initially, a brief wave of excitation progressed into the simulated hierarchy through fast AMPA-mediated feedforward connections, with an amplitude and duration directly related to the initial input. In a second stage, assumed to be mediated by the slower NMDA-mediated feedback connections, the advancing feedforward wave amplified its own inputs in a cascading manner, quickly leading the whole stimulus-relevant network into a global, self-sustained, reverberating, or ignited state. This ignition was characterized by an increased power of local corticothalamic oscillations in the gamma band and their synchrony across areas (Dehaene et al., 2003).

A recent modeling study (Joglekar et al., 2018), with a theoretical starting point largely independent of the GNW hypothesis, confirmed that ignition emerges naturally in a network with reciprocal projections. Importantly, this study evaluated the propagation of visual information in the macaque brain, derived from numerous tracing studies, whose connectivity suggests a workspace-like central core of densely linked associative areas (Markov et al., 2013). This network includes feedforward projections forming the basis for fast sensory processing from V1 to higher visual, temporal, or prefrontal cortices, as well as reciprocal and

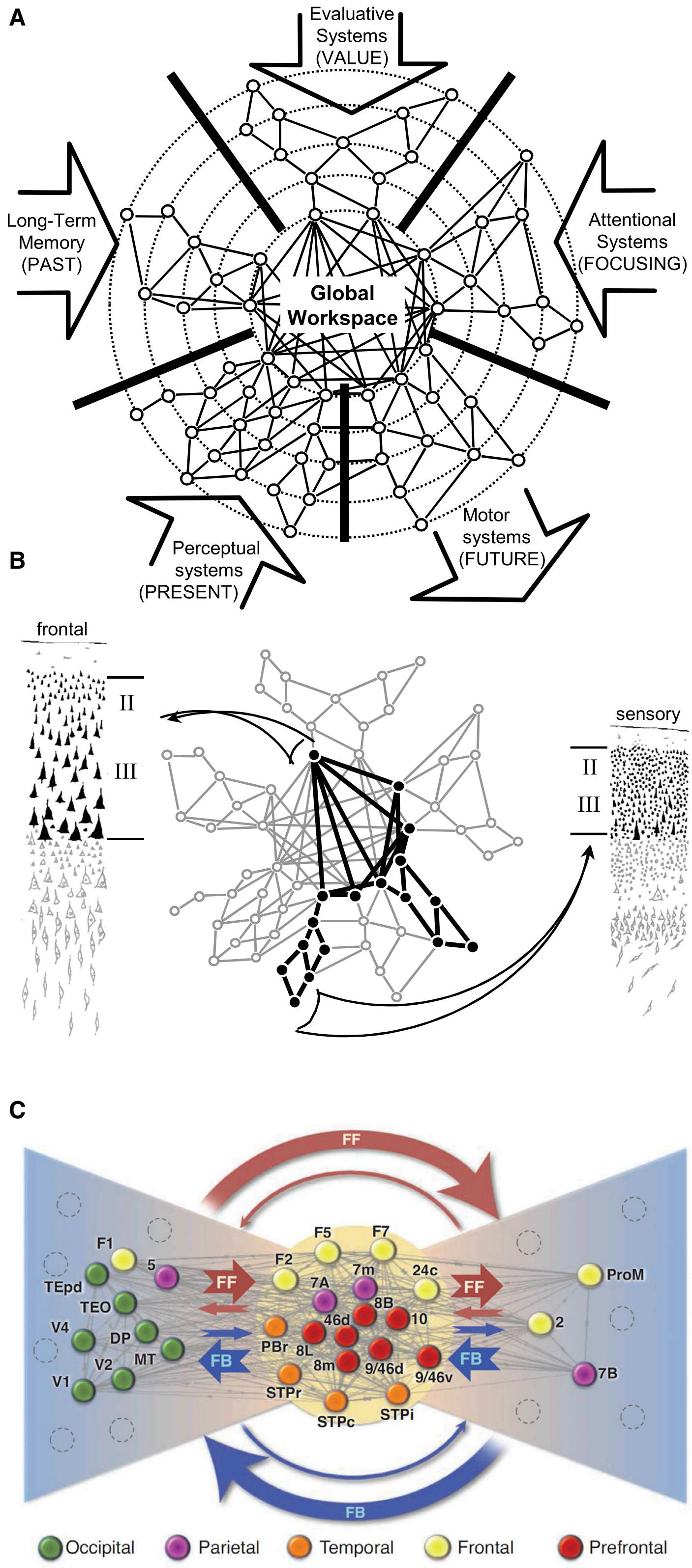

Figure 1. The Global Neuronal Workspace (GNW) Hypothesis

(A–C) Original schemas from Dehaene et al. (1998) illustrating the main tenets of the GNW hypothesis: local, specialized cortical processors are linked, at a central level, by a core set of highly interconnected areas (A) containing a high density of large pyramidal neurons with long-distance axons (B). At any given moment, this architecture can select a piece of information within one or several processors, amplify it, and broadcast it to all other processors, thus rendering it consciously accessible and available for verbal report. Recent tracer studies of global feedforward and feedback cortical connectivity confirm a bow-tie architecture with a central core set mostly comprised of parietal and prefrontal areas and forming a structural bottleneck capable of routing information between other cortical processors (C) (Markov et al., 2013).

horizontal recurrent connections linking those regions. Although there are recurrent loops even within the visual cortex that are considered important for experience, feedback connections from higher-level areas, such as the PFC, may be critical for amplifying and sustaining relevant stimuli (see Dehaene et al., 2003). The simulations showed that, if feedforward connections are carefully balanced by local inhibitory influences, incoming stimuli elicit a stable cascade of activity characterized by a late and sudden ignition. Importantly, and in agreement with the GNW model (Dehaene et al., 2003), the feedforward signal must be strong enough to reach the PFC, which in turn leads to the activation—or ignition—of a reverberant network involving the posterior parietal cortex. It is this reverberation that allows the signal to be sustained over time. Addition of layer-specific connectivity in simulations (Mejias et al., 2016) leads to the emergence of frequency-band-specific patterns of causality (bottom-up gamma arising primarily in supragranular layers versus top-down alpha-beta arising primarily from bottom layers), which have been observed empirically across the cortical hierarchy in both human and non-human primates (Bastos et al., 2015; Michalareas et al., 2016; van Kerkoerle et al., 2014).

In the above models, the exchange of bottom-up and top-down signals is not associated with specific computations. However, the GNW framework can be combined with Bayesian inference (Keller and Mrsic-Flogel, 2018; Kersten et al., 2004; Rao and Ballard, 1999), leading to a more precise functional interpretation of top-down broadcasting. In this view, GNW neurons, lying at the top of a deep feedforward network, provide a compressed, high-level symbolic model of an aspect of the external world; top-down signals broadcast the predictions that this model makes to lower-level areas; and bottom-up signals convey sensory signals and may either amplify the signals predicted by top-down input (Moore and Armstrong, 2003; Poort et al., 2016) or measure the mismatch between predicted and observed data, allowing the central model to be updated. Through such loops, the GNW achieves a coherent model of incoming sensory information, integrating all available multisensory and memory cues.

This framework predicts that, while some signals within modular pathways may persist under non-conscious conditions, global top-down signals related to the content of working memory depend on the availability of a conscious model. This prediction has received experimental support in the auditory and motor domains. Auditory areas generate an unconscious local prediction error (mismatch negativity) to a rare oddball sound, and this response can be preserved in coma, sleep, or inattention; however, higher-level temporal and prefrontal regions generate a later prediction error (P3 wave) when the global sequence is violated only under conscious conditions (local/global paradigm) (Bekinschtein et al., 2009; Chao et al., 2018). In the motor domain, the supplementary motor area and/or anterior cingulate generate an error-related negativity whenever a subject presses the wrong button but only if the stimulus that led to the error was consciously perceived, thus allowing a conscious top-down intention signal to be compared with the ongoing action (Charles et al., 2013).

Empirical Evidence in Support of the Ignition Concept

Over the past 15 years, abundant neurophysiological and neuroimaging studies in humans have provided evidence in support of the ignition concept. These investigations reported the existence of a sudden divergence in brain activity, around 200 to 300 ms after stimulus onset, between trials with or without conscious perception, with an intense propagation of additional activity, particularly toward the prefrontal and parietal cortex, on conscious trials (for a review of the early work, see Dehaene and Changeux, 2011). This non-linear divergence occurs regardless of the stimulus modality or paradigm used to manipulate consciousness (e.g., reduced visibility, masking, inattention). For instance, Noel et al. (2018) tested three putative signatures of conscious access for auditory, visual, and audiovisual trials in human EEG. They found that sudden late ignition was the only clear signature common to all three conditions. Similarly, Sanchez et al. (2019) evaluated conscious perception in the visual, auditory, and tactile modalities. Multivariate decoders trained to classify perceived versus unperceived stimuli identified a late sudden ignition (>200 ms) that generalized across modalities. Importantly, the supramodal activity patterns signaling conscious perception included late activity in sensory regions belonging to other modalities (for instance, auditory detection could be detected from visual areas), compatible with the idea that consciously perceived stimuli were broadcasted globally in a top-down manner.

The first 200 ms of brain activity, corresponding to early perceptual processing, can be fully preserved on trials without conscious perception, particularly under inattention conditions (Marti and Dehaene, 2017; Marti et al., 2015; Sergent et al., 2005). Instead, conscious appraisal correlates with late events that typically lag stimulus onset by at least 200 ms, such as the P300 or “late-positive” component of scalp-event-related potentials (Dehaene and Changeux, 2011). For instance, the crossing of the threshold for auditory or visual conscious perception is associated with a sudden increase in the P300 component, and only this component vanishes almost entirely under inattention conditions (Berkovitch et al., 2018; Charles et al., 2014; Del Cul et al., 2007) or during sleep (Strauss et al., 2015). The latency for conscious access can in fact be delayed by much more than 300 ms when attention is temporarily distracted by a secondary task (dual-task conditions) (Marti et al., 2012, 2015). Even a “retro-cue” coming as late as 900 ms after a flashed stimulus can lead to the retrospective conscious perception of a stimulus that would otherwise have been too weak to be perceived (Sergent et al., 2013; Thibault et al., 2016). These convergent findings indicate that conscious access is not attached to early sensory processing but instead relates to a late stage whose timing is often decoupled from the timing of the actual stimulus. Recent work in healthy humans supports the hypothesis that visual consciousness is mediated in higher-order brain areas that are anterior to the visual cortex (e.g., Liu et al., 2019).

In our previous review (Dehaene and Changeux, 2011), we stressed the P3b (a late-positive component of event-related potential) as the most consistent scalp-recorded correlate of conscious ignition, common to auditory and visual, as well as many paradigms (masking, attentional blink, etc.). This proposal received support but also criticism, because an earlier negative event (variably called N2, N3, or even “visual awareness negativity” [VAN]) peaking at ~260 ms and with a total duration of

~200 ms is also often observed when contrasting conscious to unconscious stimuli (Eklund and Wiens, 2018; Koivisto and Revonsuo, 2010; Pitts et al., 2012, 2014). VAN has been suggested as the earliest electrophysiological correlate of visual awareness (Koivisto and Grassini, 2016), and this claim has been corroborated with magnetoencephalography (MEG) (Andersen et al., 2016). It remains unclear whether P3b is correlated with awareness (Salti et al., 2012), post-perceptual processes (Andersen et al., 2016; Koivisto et al., 2016), or both. In many experiments, the N2 simply precedes the P3b, and their succession may index the spread of global ignition as reflected in intracranial and MEG signals. However, the two waves occasionally dissociate. Most importantly, only the N2 remains under conditions where the stimuli are task-irrelevant yet reported to be consciously perceived (Pitts et al., 2012, 2014). The (unresolved) controversy surrounds the issue of whether one can ascertain that such stimuli are truly seen as opposed to being merely potentially visible but unattended: intermediate-latency sustained negativities may reflect a neural state of information accessibility, whereas the P3b would reflect genuine conscious access and processing (for discussion, see Pitts et al., 2018).

In terms of mechanisms, the current understanding is that during visual processing, activity from lower visual areas is fed forward to higher areas and then fed back to form recurrent loops. The early recurrent loops occur in lower areas (Lamme and Roelfsema, 2000) and may correspond to VAN (Koivisto and Revonsuo, 2010). As later recurrent loops involve higher areas, including the frontal-parietal network, global recurrent processing ensues. This process may be captured by the late positive (Koivisto and Grassini, 2016), and it enables subjects to report their awareness (Lamme, 2006). Although non-response tasks may be a promising approach to separating neural correlates of awareness from those of post-perceptual processes (Tsuchiya et al., 2015), experimental findings so far do not resolve this discussion.

Unseen, subliminal stimuli may also result in a long series of evoked brain activations, sometimes lasting over one second and even extending for several seconds, i.e., in the temporal range of working memory (King et al., 2016; Soto and Silvanto, 2014; Trübutschek et al., 2017). The difference, however, is that subliminal stimuli do not evoke a sudden ignition but rather a slowing, decaying wave of activity. Thus, researchers are increasingly describing conscious access in terms of system dynamics, with distinct trajectories for seen and unseen trials. In this framework, ignition is seen as a sudden, high-speed divergence of the trajectories on trials reported as consciously perceived, generating a series of metastable activity states (Baria et al., 2017; He, 2018; King et al., 2016). Importantly, the observed dynamic states are not just non-specific correlates of attention and perception; they demonstrably contain detailed, decodable information about the specific stimulus that was consciously seen (Baria et al., 2017; King et al., 2016; Salti et al., 2015; Trübutschek et al., 2017).

Beyond MEG and EEG, ignition has been demonstrated in neural firing, both in human and non-human primates. In humans, the so-called concept cells in the anterior temporal lobe, which fire after 300 to 400 ms to specific pictures and words such as ‘‘Bill Clinton’’ or ‘‘the World Trade Center,’’ do so with stronger and longer-lasting firing rates when the corresponding stimulus is consciously perceived (Gelbard-Sagiv et al., 2018; Kreiman et al., 2002; Quiroga et al., 2008; Reber et al., 2017) or recalled (Gelbard-Sagiv et al., 2008). Due to clinical constraints, such human recordings are largely confined to the temporal lobe. In monkeys, however, recordings in the PFC show that prefrontal neurons encode, in firing patterns, the specific current content of consciousness during binocular rivalry and related paradigms (Panagiotaropoulos et al., 2012). Importantly, those data were obtained in a no-report paradigm in which the monkey passively watches stimuli, and thus, the results are not confounded by working memory or effects related to reporting.

A recent empirical study (van Vugt et al., 2018) investigated the neuronal correlates of conscious access by recording the propagation of spiking activity elicited by weak visual stimuli in areas V1 and V4 and the dorsolateral PFC of monkeys (Figure 2). The animals were trained to report visual stimuli of various contrasts. In some trials, they perceived the stimuli and reported it by making a saccade to their location, and in others, they failed to perceive the same stimuli and made a default saccade to a fixed location. Both perceived and unperceived stimuli caused activity in V1 and V4, but only the perceived ones elicited a sudden, strong, and sustained activity in the frontal cortex akin to ignition. For non-perceived stimuli, signal propagation could be lost at several successive stages en route to the frontal cortex. Very weak stimuli tended to be lost in the transmission from the primary visual cortex (area V1) to area V4, whereas stronger stimuli reached the mid-level area V4 but were not propagated well enough to the frontal cortex to elicit ignition (Figure 2B). Importantly, there were also false alarm trials in which the monkeys reported that they had seen a stimulus that was not there; on these trials, spontaneous PFC ignitions were observed (blue curves in Figure 2B).

Why did the same stimuli sometimes lead to perceptual reports and sometimes not? The van Vugt et al. (2018) results revealed that a minimum amount of activity needs to reach PFC before it elicits ignition, thereby establishing a relationship between the GNW and the classic signal detection theory (SDT) (King and Dehaene, 2014). SDT is a psychological theory that describes how subjects distinguish between the presence and absence of weak sensory stimuli. It incorporates three key constructs: a noisy internal representation of the stimulus, a sensitivity parameter (d’) that indexes how well the stimulus is separated from the noise, and an adjustable decision threshold. On trials with a stimulus, the average internal signal strength is higher than on trials without. If a stimulus causes the internal signal to cross the threshold, the subject reports perceiving it (hit); if the signal stays below the threshold, the subject reports not perceiving it (miss). On trials without a stimulus, the signal usually stays below the threshold so that the subject reports not seeing it (correct rejection), but if it does cross the threshold, the subject commits a false alarm.

The van Vugt et al. (2018) data indicated that the SDT threshold corresponds to the threshold for ignition in the PFC. Sensitivity, on the other hand, depended on how efficiently the sensory stimulus was propagated to the PFC. Sensitivity could be predicted even prior to stimulus onset by taking pre-stimulus

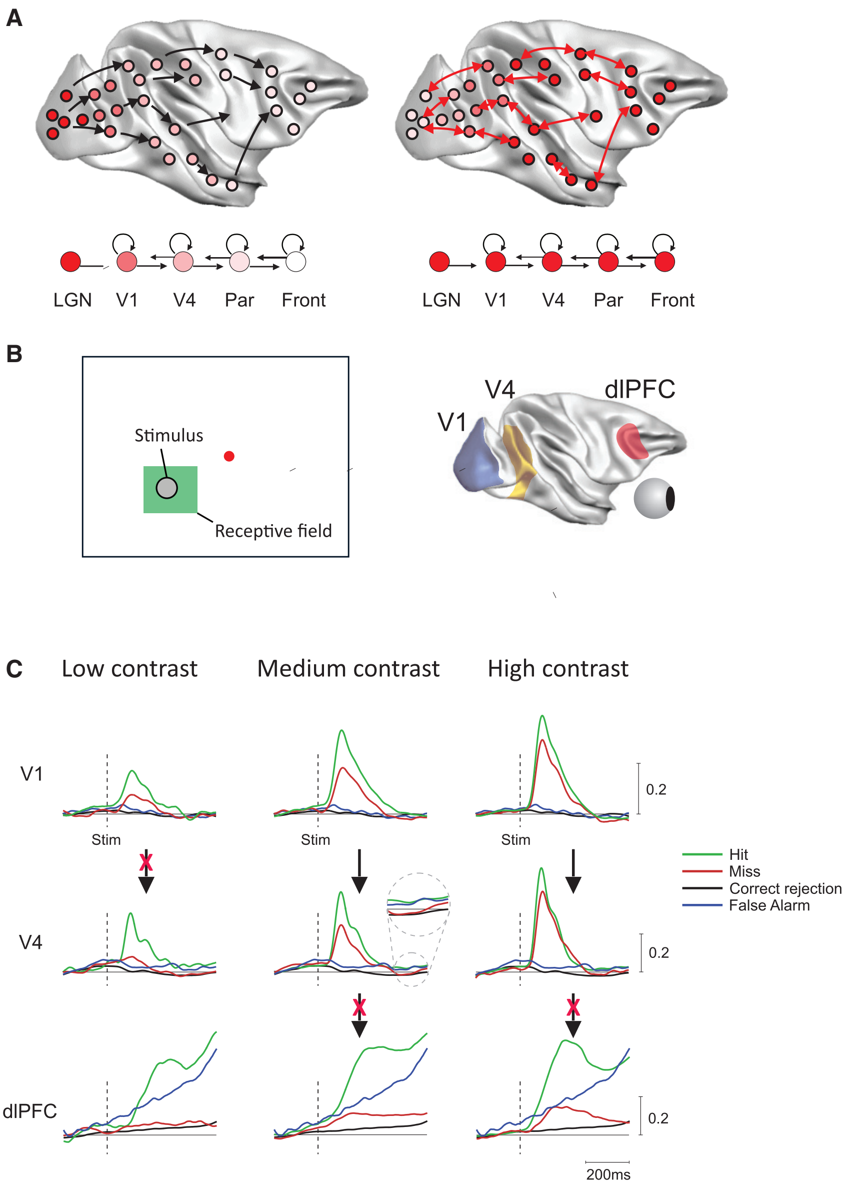

Figure 2. Dynamics of Neural Ignition in the GNW

(A) Elementary simulations of networks with feedforward propagation and a higher set of areas with elevated recurrent excitation and feedback projections predict two dynamic states for an identical stimulus: either the incoming activity cascades upward in a self-amplified manner, ultimately igniting the entire network, thus corresponding to conscious access (A, right) or the propagating activity remains below the threshold for ignition and induces only a progressively decaying wave of activity in higher regions, corresponding to subliminal processing (A, left).

(B and C) Electrophysiological test of those predictions in awake macaque monkeys. Recordings were performed in V1, V4, and PFC while monkeys attempted to detect a weak stimulus of variable contrast placed in the neurons' receptive field (B). Monkeys reported target presence with an eye movement, thus resulting in four trial types: hits, misses, correct rejections, and false alarms (C). Depending on their strength, the missed stimuli could evoke strong early transients in V1 and V4, indicating that such firing was not sufficient for a consciously reportable representation. The main difference between conscious stimuli (hits and false alarms) versus non-conscious stimuli (misses and correct rejections) was late, sustained activity in PFC (green and blue curves) together with small but significant concomitant late sustained activation in V1 and V4 (see inset in middle panel). Missed stimuli evoked only transient, decaying PFC activity.

Modified from data in van Vugt et al., 2018.

brain-state markers, including the monkeys' motivation, pre-stimulus firing rates, and frequency bands in the EEG into account. Finally, these pre-stimulus brain-state markers also predicted the probability of a false alarm (the bias to say "yes" in SDT). A high probability of false alarms was associated with a higher pre-stimulus firing rate of neurons in all brain regions examined, bringing the system close to the threshold for ignition.

Thus, the SDT and GNW are not independent theories. Rather, the psychological constructs of SDT map onto specific pre-stimulus and post-stimulus states of GNW neuronal activity. Van Vugt et al. (2018) also provided elementary simulations of the GNW model and showed how the observed pattern of neuronal activity across the visual and frontal cortex was well described by a model in which perceived stimuli ignite a self-sustained pattern of activity that reverberates between the frontal and other cortices (Figure 2A). The experimental findings also cohered with a more realistic modeling study previously described, demonstrating that the propagation of neuronal activity from the visual to the frontal cortex benefits from a "balanced amplification" regime, in which the feedback excitation from top-down sources is balanced by local inhibition (Joglekar et al., 2018). Together, these results suggest that conscious access depends on recurrent interactions between higher cortical areas (e.g., the frontal and parietal cortex) that can maintain a representation of a weak stimulus as persistent activity until a behavioral response is required by the task.

The Role of Recurrent Activity

The neural activity patterns that are associated with feedback projections and horizontal connections have been referred to in the literature as reafferent, recurrent, re-entrant, or reverberant processing (Edelman, 1992; Lamme and Roelfsema, 2000). Such recurrent circuits permit ignition and persistent neuronal firing and can either be built from local cortical circuits or include neurons in different cortical areas (Wang, 2001). The GNW hypothesis emphasizes the role of long-range loops between cortical areas, which are linked with feedforward and feedback connections. These more widespread corticocortical

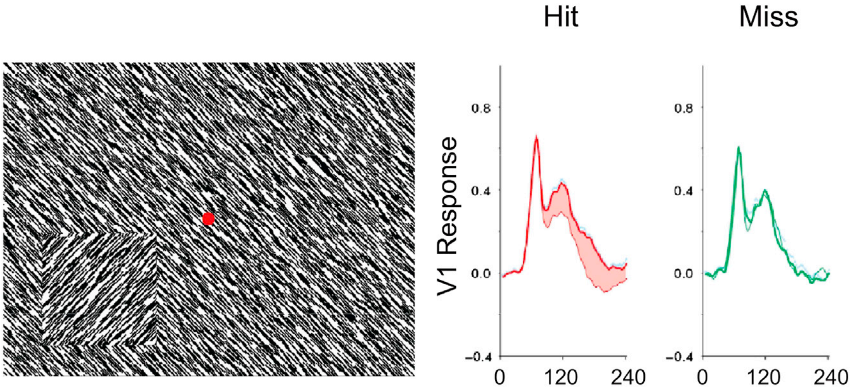

Figure 3. Late Feedback to V1 Reflects Conscious Figure-Ground Segregation
A square figure is composed of line elements of one orientation superimposed on a background with line elements of the opposite orientation. Initial feedforward activity is strictly identical whether the figure is placed within V1 neurons' receptive field (thick curve) or when the receptive field falls on the background regions (thin curve). Only the later sustained activity, dependent on top-down cortical signals, discriminates figure from ground but only when the monkey detected the figure (hit), not when it failed (miss). Modified from data in Supèr et al., 2001.

connections originate from cortical layers II/III and V/VI and permit the communication between widely distributed cortical processors. In agreement with the GNW, the effects of recurrent processing are indeed most pronounced in layers II/III and V of the primary visual cortex of monkeys (Self et al., 2013; van Kerkoerle et al., 2017), and recent studies using high-field fMRI demonstrated corresponding profiles of laminar activity in humans during the conscious perception of visual illusions (Kok et al., 2016; Muckli et al., 2015).

Interestingly, recent experimental evidence indicates that the reverberatory loops for persistent neuronal activity not only involve corticocortical interactions but also loop through subcortical regions with an important role for the thalamus and cerebellar nuclei (Gao et al., 2018; Guo et al., 2017). These recent findings imply that conscious access is not a purely cortical phenomenon and provide support for the involvement of neurons in the deep cortical layers in the GNW as hypothesized in the original GNW paper (Dehaene et al., 1998).

There are several reasons why conscious processing might rely on recurrent loops between distributed processors. First, recurrent connections can help *amplify* a signal through recurrent excitation, thereby making it available for other cortical processors. Second, recurrent loops can *sustain* a signal, e.g., such that it could be maintained in working memory. In accordance with this view, studies that examined tactile perception in mice revealed that it is associated with the reverberation of activity between the frontal cortex and somatosensory cortex that is accompanied by NDMA-receptor-driven calcium events in the distal dendrites of sensory neurons (Larkum, 2013). Feedback from the frontal cortex thereby amplifies neuronal activity elicited by tactile stimuli in the somatosensory cortex and this amplification predicts successful perception (Sachidhanandam et al., 2013; Takahashi et al., 2016). If the feedback from a higher cortical area, the mouse secondary motor cortex, to somatosensory cortex is silenced optogenetically, the late amplification in the somatosensory cortex is selectively attenuated and perception is prevented (Manita et al., 2015). Although most experiments on conscious perception are correlational in nature and merely observe neural ''correlates'' or ''signatures'' of conscious perception, some studies (Manita et al., 2015; Sachidhanandam et al., 2013) provide evidence for a causal role of top-down inputs in perception.

An important question is whether primary sensory areas are invariably members of the set of areas that need to engage in recurrent interactions before a sensory stimulus can reach awareness. The van Vugt et al. (2018) data were explained well by a late difference in PFC activity between stimuli that were and were not reported, with only modest (but significant) differences in the late recurrent activation of visual cortex (see inset in Figure 2C). However, the situation may differ for tasks that rely on fine-grained visual information processing and that may critically depend on recurrent loops involving V1. For example, in one study (Supèr et al., 2001), monkeys performed a texture-segregation task in which they detected a figure composed of line elements of one orientation superimposed on a background with line elements of the opposite orientation (Figure 3). The initial feedforward activity elicited in the visual cortex was driven by the texture elements in the neurons' receptive fields, whereas later activity reflected successful figure-ground perception; figures that reached awareness elicited more V1 activity than the background, but figures that stayed subliminal did not. This delayed response enhancement is thought to be caused by feedback from higher visual areas to V1 (Christophel et al., 2017; Klink et al., 2017; Lamme and Roelfsema, 2000). On trials in which the monkeys failed to perceive the figure-ground stimulus, they presumably saw the texture elements, which were of high contrast, and only failed to perceive that the line elements defined a figure. Accordingly, the initial visually driven response did not depend on figure-ground perception (unlike in the contrast detection task of Figure 2B). In contrast, the delayed figural response enhancement was absent on missed trials, implying that failures of figure-ground perception are associated with a lack of recurrent interactions between V1 and higher brain regions. Taken together, these findings suggest that the critical brain regions engaging in the recurrent interactions for conscious perception may be task and stimulus dependent: whereas recurrent, metastable activity in the PFC and interconnected associative areas may be systematically present during conscious perception, recurrent interactions with primary sensory areas may play a role or not, depending on the task's emphasis on high-resolution sensory information (for a similar argument in the field of mental imagery, see Kosslyn et al., 1995). In tasks that rely on recurrent interactions between V1 and higher areas, V1 neurons become part of the GNW, and the fine-grained visual percepts can enter into conscious awareness.

A related proposal is that feedback processing within sensory cortices (e.g., during figure-ground segregation) could be important for phenomenal consciousness (Lamme, 2006), whereas more global feedback (e.g., in frontal-parietal networks) is important for access consciousness (Lamme, 2018). At present, however, short of an experimental method for producing conscious experience in the absence of conscious access, this proposal remains untested.

Recent studies have also started to elucidate the neurobiological mechanisms that underlie the propagation of activity in the feedforward and feedback directions. Pharmacological studies indicate that, in agreement with the GNW hypothesis (Dehaene and Changeux, 2005), the initial feedforward sweep predominantly relies on AMPA glutamate receptors, whereas NMDA receptors play a dominant role in the later feedback effects (Self et al., 2012). This observation is important because modulating NMDA receptors, by using ketamine, for instance, may selectively affect ignition and conscious perception, mimicking the impairment of conscious perception observed in schizophrenia (Berkovitch et al., 2017). In fact, a severe form of encephalitis due to antibodies against NMDA receptors leads to psychotic symptoms followed by a complete loss of consciousness, suggesting a causal link between NMDA-mediated top-down connectivity and conscious perception.

Global Neuronal Workspace, Attention, and the Content of Consciousness

The GNW implements a process for broadcasting information in order to make it available to distributed cortical processors (Figure 3). The flow of information across distributed processors has many commonalities with two interrelated cognitive functions that are central topics in neuroscience and psychology: attention and working memory. Attentional signals select a particular piece of information by amplifying its activity and reducing that of other competing stimuli, whereas persistent neuronal activity keeps information online in working memory (Roelfsema, 2005; Roelfsema et al., 2000; Zylberberg et al., 2011). Attention and working memory reflect "what is on the mind." Indeed, GNW models (Dehaene et al., 2003) share many features with models for attention and working memory (Hamker, 2005), which also require interactions between neurons in widespread networks. However, the relationship between attention, working memory, and conscious awareness is complex and warrants careful consideration.

An important role of attention is to establish relationships between features represented in different brain areas and bind them into coherent representations (Treisman and Gelade, 1980). Cortical and subcortical neurons coding for the various features of attended objects enhance their firing rate, and these attentional effects are widespread: they occur in all cortical regions, ranging from primary sensory areas to the motor cortex. A cortical area devoid of attentional influences on neuronal firing rates remains to be discovered. Attention is object based, which means that the attentional selection of one feature of a perceptual object, represented in one brain region, causes the co-selection of other features of the same object, represented in different brain regions (Duncan et al., 1997; O'Craven et al., 1999; Reynolds and Chelazzi, 2004; Roelfsema, 2006; Roelfsema and Houtkamp, 2011; Zylberberg et al., 2011). In the visual modality, the spread of enhanced neuronal activity through the network of corticocortical connections enables binding operations, which establish the relations between visual features. One example is visual search, where the subject determines the location of a cued shape in the visual field. In a search task, enhanced neuronal activity spreads from shape representations in the inferotemporal and frontal cortex to the representations in the retinotopic cortices to enhance the activity of neurons that code the location of the to-be-found object (Bichot et al., 2015; Deco and Rolls, 2004; Zhou and Desimone, 2011). Another example is the determination of a shape at a cued location. In this case, activity spreads in the opposite direction from regions that represent the location of the cue to the brain regions that represent the cued shape (Everling et al., 2002; Moran and Desimone, 1985). Thus, models of attentional feature integration share the GNW's aim to integrate information across distributed cortical processors. The binding mechanisms co-select distributed feature representations that are part of a single object and explain why the object representations that become part of conscious experience are usually coherent and integrated.

The precise relationship between attention and awareness remains an active topic of ongoing research. Several studies have dissociated attention from awareness, for example, by demonstrating that attention can be summoned to a location by a subliminal cue so that the perception of stimuli at that location is improved (for reviews and discussions, see Dehaene and Changeux, 2011; Koch and Tsuchiya, 2007). Other studies instructed subjects to direct attention to a particular location and presented stimuli that were consciously perceived or stayed subliminal. In these studies, the neuronal correlates of attention and conscious perception differed if assessed with fMRI (Watanabe et al., 2011) or MEG (Wyart et al., 2012; Wyart and Tallon-Baudry, 2008). It should be recognized that what we call "attention" is actually a diverse set of temporal, spatial, and cognitive filters; thus, many of these filters may operate non-consciously, with only the final one gating entry in the global workspace. However, we note that the spatial location that was attended to in some of these experiments differed from the feature for which consciousness was established (e.g., a grating at that location), implying that the dissociation was incomplete: subjects presumably could not direct feature-based attention to features that failed to enter consciousness, and conversely, they were most likely aware of the location to which they had to attend.

Irrespective of the precise interpretation of these experiments, the final result of attentional selection enters consciousness, where it can use the GNW to activate all features that belong to the same object even if they are represented in different cortical areas (Roelfsema and Houtkamp, 2011), allowing conscious perception to be occupied by coherent, multifeature, and multimodal objects (Figure 4). In this view, the establishment of coherent objects by labeling their features with enhanced neuronal activity causes these objects to enter into awareness (Roelfsema and Houtkamp, 2011), which is a hypothesis that could be tested in future work.

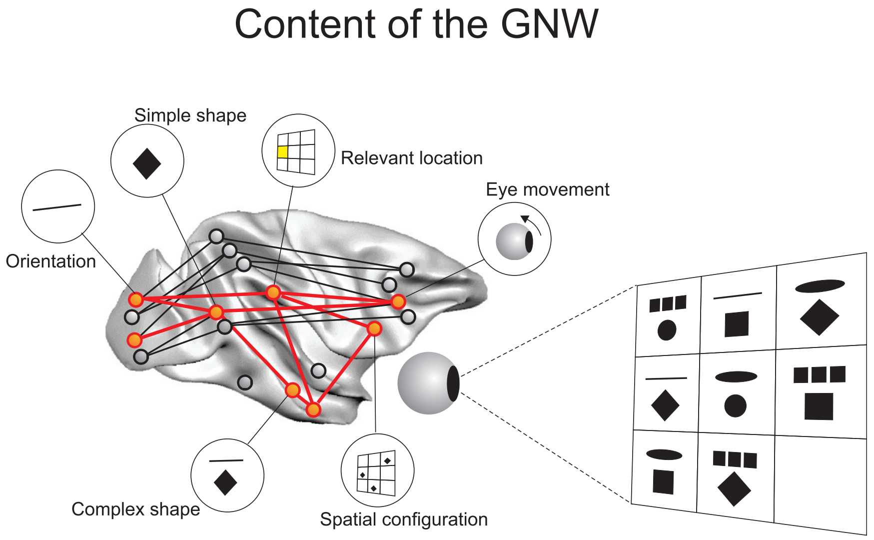

Figure 4. Proposed Integration of Multiple Features of the Same Conscious Object in a Single GNW State

Many tasks require the interaction between different cortical processors with distinct functions. The GNW interconnects these processors and enables them to exchange information about the object that lies at the current focus of attention. The Raven's progressive matrices test is one of many tasks that depends on such information exchange. In this task, the observer forms hypotheses about the relations between the cells of the matrix and predicts the configuration in the empty cell that completes the matrix in a regular manner. It requires the analysis of simple and complex features, feature counts, and feature constellations and spatial locations. The observer may, for example, notice that there are three diamonds and three squares but only two circles in the matrix by successively directing feature-based attention to these shapes and counting their number (a form of visual search). The underlying attentional operations require interactions between the representations of features, spatial positions, and spatial configurations. According to the GNW hypothesis, the attended information corresponds to what is in the observer's awareness.

Conscious Representations and Working Memory

Interactions between cortical processors also take place long after a sensory stimulus is gone in order to enable mental operations in working memory. The effects of working memory on neuronal firing rates occur in many cortical areas (Christophel et al., 2017), ranging from primary sensory cortices that code for the memories of elementary sensory features (Mendoza-Halliday et al., 2014; van Kerkoerle et al., 2017) to the frontal cortex, where neurons code for more abstract aspects of sensory stimuli (de Lafuente and Romo, 2005, 2006; Vergara et al., 2016), object categories (Freedman et al., 2001), motor intentions (Alexander and Crutcher, 1990; Thura and Cisek, 2014), and task instructions (Wallis et al., 2001). Persistent neuronal activity allows the nervous system to bridge the time between sensory stimuli, task instructions, and actions that need to take place at a later point in time (Fuster, 1997). Its widespread presence is important for the large diversity of contents that can enter into working memory (Christophel et al., 2017).

Recent studies gained insight into the neuronal mechanisms of working memory by investigating concept cells. These cells are found in the medial temporal lobe of humans and activate when subjects perceive or think about specific concepts. A central finding is that concept cells fire when concepts are held in working memory (Kamiński et al., 2017; Kornblith et al., 2017) and become active when these concepts are retrieved from long-term memory (Gelbard-Sagiv et al., 2008). Medial temporal neurons code for associations, i.e., the transitions between specific working memories (Ison et al., 2015; Sakai and Miyashita, 1991). For example, if subjects learn an ordered list of concepts, neurons in the medial temporal lobe start to activate if they are tuned to an upcoming item in the list (Reddy et al., 2015) and similar "prospective coding" effects have been observed in the frontal cortex of monkeys (Rainer et al., 1999). Thus, our experience builds associative memory networks, in which activity can spread from one concept to the next, a function that resembles the spread of activity for attentional operations described above. Working memory operations can thereby execute the successive mental steps required to solve a task and permit mental simulations, i.e., subjects can navigate through sequences of working memory states to explore the future consequences of actions (Pezzulo and Cisek, 2016). The machine-learning field develops efficient ways to train artificial neuronal networks to form task-relevant sequences of memory states (LeCun et al., 2015), and researchers have also started to model the formation of relevant working memories and the transitions between them in the brain (O'Reilly and Frank, 2006; Rombouts et al., 2015).

Recent evidence in rodents demonstrated that the persistence of neuronal firing rates for working memory storage is not a purely cortical phenomenon but instead relies on the interactions with subcortical structures, including the thalamus (Guo et al., 2017) and cerebellar nuclei (Gao et al., 2018). The interactions between these brain structures enable distinct attractor states for the maintenance of different items in memory (Inagaki et al., 2019). We hypothesize that coherent working memory states can be created by the coordination of multiple persistently firing loops representing various aspects of a memory, a function directly related to the proposed broadcasting role of the GNW. The relation between persistent firing, ignition, and conscious awareness is supported by a study that measured the activation of concept cells in the medial temporal lobe during shortly presented visual stimuli that were followed by a mask (Quiroga et al., 2008). Stimuli that could be consciously reported elicited a response from concept cells, whereas stimuli that remained subliminal did not.

Psychological theories of working memory distinguish between several activation states (Cowan, 2001; Oberauer, 2002). The most active memory item is considered to be in the focus of attention. When items are stored in working memory, they are initially in the focus of attention and this special state also allows them to be manipulated or updated. In addition to the attended item, a few other items can be present in a memory store with a limited capacity. These items can readily enter in the focus of attention to be used and updated. Finally, there is a larger set of activated long-term memories, which are in a more dormant state and for which retrieval requires more elaborate mechanisms (Oberauer, 2002). Our understanding of the neuronal mechanisms for the different states in working memory is incomplete (Kamiński and Rutishauser, 2019; Olivers et al., 2011) but highly relevant for our understanding of the relationship to the GNW.

We propose that the attended working memory item is conscious and uses the GNW for broadcasting. Attended memory items can activate subsequent memory states in order to retrieve an association or as part of a cognitive routine when, for example, a mental image is transformed during mental rotation (genuinely meriting the name ''working'' memory) (Zylberberg et al., 2011). At a neurophysiological level, the attended memory item is maintained as the persistent firing of neurons across cortical and subcortical structures so that they can exert their influence on the firing rate of other neurons. The data of van Vugt et al. (2018) indicate that ignition characterizes the transition of a weak sensory stimulus into the attended working memory state. Furthermore, a recent experiment used MEG and multivariate decoding to investigate the relation between conscious perception and memory for brief stimuli. Maintenance in working memory gave rise to similar MEG signatures as conscious ignition (Trübutschek et al., 2017), supporting the view that conscious ignition is a first step leading to the entry of information into working memory.

The neuronal mechanisms underlying the maintenance of the items that are outside the focus of attention are under intense investigation (Kamiński and Rutishauser, 2019). Some of these accessory memory items are also coded with persistent activity in the medial temporal lobe (Kornblith et al., 2017) and PFC (Warden and Miller, 2010). However, persistent firing for these items is weaker than that of the attended item (Konecky et al., 2017), which may explain why they are more difficult to pick up with non-invasive methods, such as fMRI and MEG (Stokes, 2015; Trübutschek et al., 2017, 2019). Mongillo and colleagues proposed that the additional working memory items can also be stored as short-term changes in synaptic weights so that their representation can be quickly reinstalled when useful (Mongillo et al., 2008), a form of working memory that is called ''activity-silent.'' If the synaptic weights decay, they can be refreshed by reactivating the neuronal assembly. Such periodic refreshing may correspond to early psychological conceptions of working memory as a decaying buffer that requires regular rehearsal to be refreshed (Baddeley, 2012).

Thus, we propose that working memory is conscious only when it is coded by global, highly distributed persistent neural firing, as occurs during both initial encoding, during the later refresh stage, and when the memory item influences other mental processing steps. Working memory items that fall outside the focus of attention are coded by weaker persistent firing within local processors or by activity-silent synaptic mechanisms (Trübutschek et al., 2017). The latter remain unconscious until they are reinstated as globally distributed and sustained firing patterns. Crucially, this view predicts that activity-silent working memories, although capable of bridging over delays, differ in an important way: only active neural states can be mentally transformed, e.g., by mental rotation, whereas activity-silent states merely store previously computed states (and thus should be more appropriately termed short-term memory). Recent experiments support this view; whenever the information in working memory must be transformed, an active form of working memory is reinstated, and a decodable state of activity reemerges, accompanied by classical signatures of conscious access (Trübutschek et al., 2019).

Global Neuronal Workspace and the Level of Consciousness

Any theory of conscious processing should enable specific predictions regarding pharmacological, pathological, and physiological states in which the *level* of consciousness is disrupted. Indeed, there has been accumulating evidence that the GNW hypothesis accounts for disruptions of conscious processing. Here, we examine the empirical data related to this prediction in three domains: general anesthesia, disorders of consciousness following brain injury, and sleep.

General Anesthesia

Clinically, the two major therapeutic traits of the anesthetized state are hypnosis and amnesia. However, there is a cognitive continuum of possible phenomenology associated with general anesthesia, which depends on the specific agent and dose. On one end of the spectrum, anesthetics can render the brain persistently isoelectric, thereby completely disrupting information processing. On the other end of the spectrum, just across the threshold of lost responsiveness (Sanders et al., 2012), there can still be fragments of experience or disconnected states of conscious processing (Huang et al., 2018b; Ní Mhuircheartaigh et al., 2013). Indeed, even the routine administration of general anesthesia for surgery is associated with dream states and other disconnected states of conscious processing (Leslie et al., 2007; Sanders et al., 2016). It can therefore be argued that disruption of conscious access is the primary therapeutic effect of general anesthesia. Such a disruption would reduce the probability of information being available to other cognitive systems, including working memory, which may comprehensively account for the functional outcome of general anesthesia in routine clinical care.

One argument that would support the disruption of the GNW as a satisfactory explanatory framework for general anesthesia would be the identification of a drug-invariant signature of the anesthetized state in key cortical nodes composing the GNW. Identifying such a common mechanism of general anesthesia has been elusive since the first use of anesthetics in the mid-19th century (Perouansky, 2012) because these agents are structurally and pharmacologically diverse, with distinct molecular targets and ostensibly distinct effects on neural systems. These targets include post- or extra-synaptic neurotransmitter receptors (such as the $GABA_A$ receptor), voltage-gated ion channels, pre-synaptic machinery, mitochondria, and cytoskeletal elements (Hemmings et al., 2019). Evidence now suggests that, despite a diversity of root causes, there is possibly a common proximate cause that disrupts the reverberant networks of the GNW that have been posited to enable conscious access (Mashour, 2013). Frontal-parietal networks are of particular

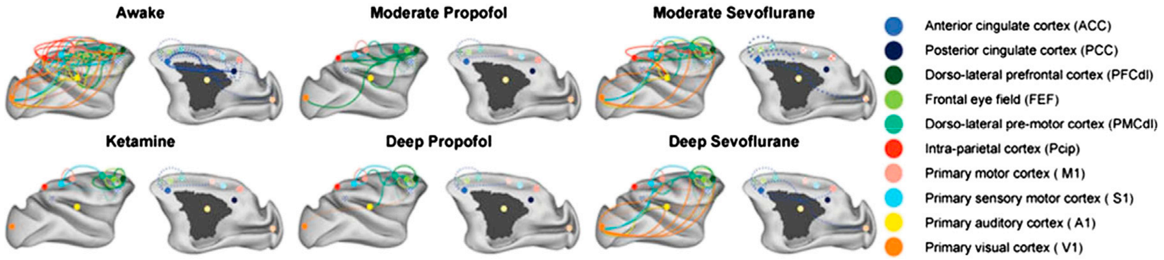

Figure 5. General Anesthesia Suppresses the GNW

Schematic representations of functional connectivity across nodes of the GNW in the right hemisphere of the macaque brain, as derived from functional magnetic resonance imaging in awake and anesthetized monkeys (from Uhrig et al., 2018). The rich functional interactions across these nodes in the awake monkey are reduced due to the dose-dependent effects of the intravenous anesthetic propofol and the inhaled anesthetic sevoflurane. Importantly, the intravenous drug ketamine has a similar effect on the GNW, despite the molecular and neurophysiological differences of this anesthetic compared to propofol and sevoflurane. These data suggest that the functional connectome of the GNW might be a drug-invariant target of general anesthetics.

importance in this regard and have been found to be metabolically depressed, disrupted, or functionally disconnected by all major classes of general anesthetics (Hudetz and Mashour, 2016). The diverse drugs propofol (primarily GABA_A receptor positive allosteric modulators), sevoflurane (strong GABA_A agonism with diverse molecular targets), and ketamine (non-GABA anesthetic antagonizing NMDA receptors and HCN1 channels) have all been found by fMRI to functionally disconnect the PFC and posterior parietal cortices (such as the precuneus) in humans (Bonhomme et al., 2016; Boveroux et al., 2010; Palanca et al., 2015). Several lines of evidence also suggest that anesthetics preferentially affect feedback connectivity originating in the frontal cortex, as might be predicted by the GNW hypothesis (Lee et al., 2013; Moon et al., 2015). In addition to human investigations, this finding has been replicated across species, from monkey (Papadopoulou et al., 2019) to ferret (Wollstadt et al., 2017), rodent (Imas et al., 2005), and *Drosophila* (in which a higher-order nucleus was the source of feedback) (Cohen et al., 2018).

More recent investigations into primate brain networks during general anesthesia have employed multimodal imaging and techniques to capture dynamic connectivity patterns. Simultaneous EEG and fMRI investigations in humans have confirmed the functional disconnection of the PFC from the posterior cortex during propofol and sevoflurane anesthesia by fMRI, with a concomitant reduction of feedback connectivity identified using symbolic transfer entropy based on EEG signals (Jordan et al., 2013; Ranft et al., 2016). One multimodal neuroimaging study of propofol revealed a functional disconnection of the dorsal anterior insular cortex from both the dorsolateral PFC and the inferior parietal lobule (Warnaby et al., 2016). Correlated with this was the functional disconnection of activity in EEG electrodes over the dorsolateral PFC and the inferior parietal lobule, but not neighboring electrodes. Importantly, these functional disconnections occurred after loss of overt behavioral responsiveness but during a period of preserved evoked potentials suggestive of maintained primary sensory processing. These findings are consistent with the possible preservation of fragmented cortical representations that are not experienced because, without a functional GNW, they cannot be broadcast. In addition to the functional disconnection of the dorsolateral PFC and the inferior parietal lobule, there are other specific frontal-parietal circuits that have been shown to be affected by general anesthetics. For example, Ma et al., (2019) found hypersynchrony, also a mechanism that would restrict information transfer, between frontal eye fields and the lateral intraparietal area in monkeys anesthetized with propofol. General anesthesia with diverse agents also induces functional disconnections between the primary sensory (S1) and motor (M1) cortex, which represents the frontal-parietal divide across the central sulcus. Electrocorticography during propofol (Malekmohammadi et al., 2018) and ketamine (Schroeder et al., 2016) anesthesia in human and non-human primates, respectively, reveals disrupted functional connectivity across the S1 and M1 cortex, as well as altered beta oscillations, which are typically associated with feedback processing (Bastos et al., 2015).

Recent work in non-human primates demonstrates that the functional relationships between critical nodes in the GNW—such as prefrontal, posterior parietal, and cingulate cortices—are stereotypically altered during propofol, sevoflurane, and ketamine anesthesia (Barttfeld et al., 2015; Uhrig et al., 2018). In the wakeful resting state, cortical networks were characterized by ceaseless fluctuations in functional connectivity patterns significantly more diverse than the fixed anatomical connectivity matrix. This suggests that the spontaneous stream of consciousness is associated with a dynamic succession of a broad repertoire of activity states arising from the fixed anatomical scaffolding. Crucially, all three anesthetics drastically reduced this dynamic diversity of functional connectivity patterns, especially across GNW nodes, to more inflexible patterns that "adhered" to anatomical connectivity patterns (Figure 5). This dynamic signature of conscious processing was initially discovered in fMRI studies of awake versus anesthetized monkeys (Barttfeld et al., 2015) and later found to generalize to humans in vegetative or minimally conscious states (Demertzi et al., 2019). This finding explains observations in humans of reduced frontal-parietal connectivity, as well as observations in primates that general anesthetics across multiple drug classes stabilize cortical dynamics (Solovey et al., 2015) or are associated with a deviation from critical dynamics (Lee et al., 2019). Still, it is important to note that the anesthetized brain is not just in a fixed state; recent observations found it to be more dynamic than previously considered, with metastable oscillations or connectivity patterns that appear to reflect intrinsic dynamics rather than pharmacokinetic instability or external stimuli (Hudson et al., 2014; Li et al., 2019; Vlisides et al., 2019). Simulations indicate that the spontaneous activity patterns already present during anesthesia may undergo a sudden phase transition toward a vastly more diverse and dynamic repertoire of states in the awake state (Hansen et al., 2015).

Even assuming some degree of preserved functional architecture among nodes of the GNW during anesthesia (as in Figure 5), disruptions in the temporal coordination and functional connectivity within these nodes would prevent the normal pathways of ignition. In other words, during general anesthesia, it is the pharmacologic action of the anesthetic drug rather than the normal spontaneous fluctuations or evoked potentials that is defining the functional relationship between these different areas. The disrupted connectivity and communication patterns induced by general anesthesia lead to the loss of organized long-latency activity that is hypothesized to be mediated by the GNW. In the clinical setting, for example, it is well known that long-latency-evoked potentials are preferentially susceptible to general anesthesia, whereas short-latency potentials are preserved (Banoub et al., 2003). This has been explicitly confirmed in more detailed basic science studies of neural spike activity, with a specific focus on visual-evoked potentials (Hudetz et al., 2009).

The disruption of functional interactions of the GNW during general anesthesia may, in part, be mediated by effects on the thalamus, which is depressed by virtually all sedative-hypnotic drugs (with the exception of ketamine) (Mashour and Alkire, 2013a). In addition to its role in transmitting arousal and sensory signals, non-sensory nuclei of the thalamus are thought to play a role in working memory (outlined above) and to facilitate the coordination of cortical communication (Saalmann et al., 2012, 2014), which is important to a functional GNW. Indeed, electrical stimulation of the central thalamus has recently been shown to reverse the anesthetized state in non-human primates, in association with a return of corticocortical connectivity (Donoghue et al., 2019; Redinbaugh et al., 2020; J. Tasserie et al., 2019, Soc. Neurosci., conference).).

Disorders of Consciousness following Brain Lesions

Pathologic states associated with unconsciousness or reduced conscious processing also reveal implications for the GNW hypothesis. First, it has long been recognized that there can be isolated islands of metabolic and cognitive activity in conditions such as the vegetative state (now often referred to as unresponsive wakefulness syndrome) (Schiff et al., 2002). In other words, pathologic unconsciousness is not necessarily a complete suppression of information processing but rather a network dysfunction that could create inhospitable conditions for global information exchange and broadcasting. This has been supported by several key studies employing neurophysiological techniques. In one study of 181 recordings of high-density EEG in humans (Sitt et al., 2014), mid-range and long-range weighted symbolic mutual information (a measure of information sharing) indexed levels of consciousness across the vegetative state, minimally conscious state, and recovery of consciousness. There have also been attempts to assess the reduced network repertoire of conscious states using a perturbational approach involving transcranial magnetic stimulation and high-density EEG. One key study demonstrated a reduction in the length and complexity of response to stimulation that distinguished patients with a diagnosis of vegetative state from those in a minimally conscious state or healthy controls (Casali et al., 2013). Remarkably, this reduction, identified by the perturbational complexity index, was consistent across pathologic unconsciousness, sleep, and general anesthesia. Subsequent investigation revealed that the perturbational complexity index might be useful in stratifying patients with pathologic disorders of conscious access (Casarotto et al., 2016). Although this experiment was inspired by an alternative theory of consciousness (integrated information theory [IIT], discussed further below), the results are fully compatible with the GNW, which predicts that the conscious state leads to a deeper and more prolonged propagation of activation through long-distance connections compared to the unconscious state.

Recent fMRI data also suggest that long-range functional connectivity in networks supporting the GNW is consistently depressed during deep anesthesia and pathologic states of unconsciousness (Demertzi et al., 2019; Huang et al., 2018a). Anatomical injuries to long-distance corticocortical pathways are also frequently reported to disrupt conscious perception. Because the GNW relies on a highly distributed set of neurons, focal lesions are unlikely to lead to a complete loss of consciousness similar to coma or anesthesia, except the most severe cases of bilateral damage (for discussion, see Odegaard et al., 2017). However, simulations show that any reduction in the number of GNW neurons, their interconnectivity, or their synaptic strength makes the ignition threshold more difficult to attain. Indeed, an elevated threshold for conscious perception has been reported in patients with frontal-lobe syndrome, neglect, multiple sclerosis, or schizophrenia and related to abnormal long-distance fiber tracts, as measured by diffusion tensor imaging (Del Cul et al., 2009; Pettersson-Yeo et al., 2011; Reuter et al., 2007, 2009; Thiebaut de Schotten et al., 2005).

Those studies therefore reinforce the role of the frontal cortex and its associated long-distance fiber tracts in conscious perception and processing. However, they provide correlational rather than causal evidence. It is therefore important to mention that there are now several pioneering studies that attempt to restore conscious access via central thalamic and/or prefrontal stimulation. A first positive result was reported by Schiff et al. (2007), who induced a slow but long-term recovery of conscious processing in a patient with minimal conscious syndrome following stimulation of the central thalamus (the nuclei of which target many high-level cortical regions, including the PFC). This is consistent with recent animal studies demonstrating the reversal of the anesthetized state with stimulation of the central thalamus (Donoghue et al., 2019; Redinbaugh et al., 2020), leading to a return of functional corticocortical connectivity.

Transcranial direct-current stimulation of the dorsolateral PFC may also transiently enhance the level of consciousness in some patients in a minimally conscious state (Thibaut et al., 2014, 2015), and similar observations exist in normal subjects (Douglas et al., 2015). The role of the PFC in controlling levels of consciousness is also supported by recent studies using general anesthesia. In rats anesthetized with clinically relevant concentrations of sevoflurane anesthesia, cholinergic manipulation of the medial PFC—but not two areas of the posterior parietal cortex—was sufficient to restore wakefulness despite continuous administration of the general anesthetic (Pal et al., 2018). This finding complements work in mice showing that nicotinic cholinergic receptors in the PFC regulate ultraslow fluctuations across consciousness and anesthesia (Koukouli et al., 2016). Of note, reversal of anesthesia by pharmacological stimulation of the cortex does not restore electroencephalographic measures of functional connectivity (Pal et al., 2020), which may relate to site of stimulation or technique of neural recording.

Sleep

Although there is an abundance of neuroimaging studies focused on pathologic disorders of consciousness, it remains difficult to draw firm conclusions regarding support for specific theories of conscious processing because of the heterogeneity of lesions and the possibility of covert consciousness in the setting of behavioral unresponsiveness. Sleep, however, creates the possibility of correlating the quality and richness of conscious experience with various neural substrates. Recent data suggest that reductions of low-frequency activity in posterior confluence of the sensory and association cortex (the so-called ''hot zone'' of consciousness) were associated with dreaming during rapid-eye-movement (REM) sleep and non-REM sleep (Siclari et al., 2017). However, neural correlates of dreaming during REM sleep differentially included higher-frequency gamma activity in the frontal and prefrontal cortex. This is notable because the phenomenology of REM sleep is arguably more consistent with the richness of waking conscious processing than the more phenomenologically impoverished dream states of non-REM sleep. Indeed, it is dreaming during REM sleep that has been argued to represent ''proto-consciousness,'' a building block for conscious experience during wakefulness (Hobson, 2009). Thus, a key correlate of REM-sleep dreaming involves structures of the GNW, and, importantly, this correlation happens in the absence of report (which occurs only after waking).

The distinction between REM-sleep dreaming and lucid dreaming, during which the agent is aware and has some degree of control over the experience, is also of relevance to the GNW. As noted, REM-sleep dreaming, during which there is a metabolic deactivation of the dorsolateral PFC (Maquet et al., 1996), is still associated with high-frequency activity in the PFC. Lucid dreaming is associated with further increased gamma activity and coherence in the dorsolateral PFC relative to REM sleep, approaching levels consistent with waking (Voss et al., 2009). In support of a causal role for this activity, one study found that external entrainment of low-gamma oscillations during REM sleep enhanced self-awareness and lucidity (Voss et al., 2014). Another study showed that transcranial direct current stimulation of the dorsolateral PFC is associated with enhanced lucidity during REM sleep (analogous to the above-cited studies of minimal conscious access; Stumbrys et al., 2013). Given that lucid dreaming is considered a hybrid of REM sleep and waking (Voss et al., 2009), studies demonstrating a causal role for the PFC in lucid dreaming thus also support a role for the PFC in waking consciousness.

During sleep, the brain not only loses its normal level or state of conscious processing (and occasionally gains access to internally generated dreams), but also loses the capacity to access specific sensory contents. The nature of this loss has been investigated with MEG (Strauss et al., 2015). In agreement with the GNW hypothesis, the first ~200 ms of sensory processing have been found to be largely preserved, though weakened, during stage 1 and stage 2 sleep. Instead, once again, the loss of consciousness and responsivity that occurs when we fall asleep has been associated with a sudden loss of ignition and the late P3 wave that normally appears after a rare, unexpected auditory stimulus.

The GNW Hypothesis and Other Theories of Consciousness

Although the present paper is focused on reviewing 20 years of research on the GNW, it is useful to briefly consider it in light of three theories of consciousness: IIT, recurrent processing theory (RPT), and higher-order thought (HOT) theory. In Table 1, we summarize the main similarities and differences (for recent descriptions of those theories, see Brown et al., 2019; Lamme, 2018; Tononi et al., 2016).

The early formulation of IIT proposed that the ''neural correlate'' of consciousness is an ever-changing ensemble of neurons, called the ''dynamic core,'' which is defined as a subset of neurons that interact more strongly with each other than with other neurons yet without specifying particular neuronal networks for conscious processing (Tononi and Edelman, 1998). The theory further attempted to address two key properties of consciousness: integration (the unity of a conscious experience) and differentiation (the large number of states available) (Oizumi et al., 2014; Tononi, 2004; Tononi et al., 2016). IIT is primarily a mathematical theory: it introduces a quantity called Φ, which quantifies the degree of consciousness of any system, biological or artificial, and suggests that at any given moment, the neural correlate of consciousness is a complex yielding a maximum of irreducible, intrinsic cause–effect power (Oizumi et al., 2014; Tononi et al., 2016; Tononi and Sporns, 2003).

Although the GNW and IIT are superficially aligned regarding certain aspects of how conscious processes are generated—e.g., both require integrated neural processing beyond the level of primary sensory cortex—these two theories are grounded in foundationally different perspectives of brain function. The GNW relies upon well-defined neuronal architectures, including cellular and molecular mechanisms of information processing that extract, represent, and manipulate information originating from both outside the brain (from interactions with the environment) and inside the brain (from spontaneous activity patterns). The GNW hypothesis is representational in nature and views consciousness as an evolved neurocomputational system that enables the global sharing of representations. By contrast, IIT proposes that the system (e.g., the brain, in a biological instantiation) is closed and non-representational; information is abstractly generated by the system and for the system.

Both the GNW and IIT ascribe importance to neural activity beyond early sensory cortices, neural information sharing, and recurrent connections as a mechanism of integration. However, the neuronal mechanisms of conscious processing also differ between the GNW hypothesis and IIT. As noted, the PFC is one of the nodes of the highly distributed GNW

Table 1. Comparison of Theories of Consciousness

Theory	A conscious process corresponds to…	Neural mechanisms include…	The role of the prefrontal cortex is…	Consciousness can be measured in humans by…	Consciousness can be disrupted when…
Global neuronal workspace	information, initially encoded in one or more specialized processors, that enters a large-scale reverberant network and is globally accessed by the other specialized processors	sudden ignition of a brain-scale network of high-level cortical areas linked by long-distance re-entrant loops	an important hub of the global neuronal network contributing to the integration of higher brain functions and their diversification, and contributing to non-linear ignition	late (~300 ms) global ignition of distant areas, global information sharing, and other markers of long-distance information sharing across the workspace network	the function of cortical hubs or reverberant connectivity is disrupted, particularly top-down amplification of signals
Integrated information[a]	information that is both integrated and differentiated, and that cannot be decomposed into causally independent parts	a confluence of posterior sensory and association cortices that represent a “hot zone” of neural processing	not essential for experience itself but contributes to post-conscious cognitive processing, such as planning or verbal report	surrogates of information integration and differentiation, such as Φ or the perturbational complexity index	integration or differentiation is suppressed, leading to a reduction in the repertoire of possible states
Higher-order thought[b]	any first-order representation X that enters into a second-order, metacognitive representation (e.g., “I currently see X”)	neural circuits that that meta-represent information arising from other areas	for some regions (e.g., Brodman area 10), essential in generating second-order, metacognitive representations	not determined	activity of anterior prefrontal regions and other areas involved in higher-order metacognitive representations is suppressed (e.g., due to a lesion)
Recurrent processing[c]	any neural code that is shaped by recurrent loops from higher-order to lower-order areas and back	feedback connections in sensory pathways	not essential for experience itself but contributes to cognitive processes associated with post-conscious processing, such as planning or verbal report	top-down signals reaching back to sensory areas due to recurrent loops	top-down, re-entrant processing is selectively suppressed

[a] Tononi et al., 2016.
[b] Brown et al., 2019.
[c] Lamme, 2018.

network. IIT, on the other hand, minimizes the relevance of the PFC and, based on anatomical considerations, considers a posterior complex—the so-called posterior cortical ''hot zone''—to be sufficient for conscious experience. Furthermore, IIT is ostensibly a theory of phenomenal consciousness, whereas the GNW hypothesis is focused on conscious access and processing, and furthermore brings into question the very distinction between phenomenal and access consciousness.

The theories also differ in testability. IIT is framed at an abstract mathematical level and does not easily capture specific cognitive neuroscience phenomena, such as masking, attentional blink, or psychological refractory period. IIT's Φ cannot be easily computed from large-scale data, making it difficult to test the theory (for attempts, see Oizumi et al., 2016 and Tajima et al., 2015). Nevertheless, IIT has served as a theoretical framework for more practical measures, such as the perturbational complexity index, which has been successful in differentiating levels of consciousness in the setting of physiological, pharmacological, and pathological perturbations (Casali et al., 2013). Furthermore, some surrogate measures of Φ have been successfully applied to altered levels of consciousness in humans (Kim et al., 2018) and also shown to relate to network factors such as topological modularity (Kim et al., 2018) or critical dynamics (Kim and Lee, 2019).

The RPT of consciousness (Lamme, 2006, 2010) also shares with the GNW the postulate that, given a hierarchically ordered neurocognitive architecture, feedforward processing is not sufficient for conscious processing, whereas feedback from higher-order to lower-order areas is critical. The key difference, however, is the extent to which these recurrent networks are thought to be involved. In RPT, which has focused primarily on the visual modality, re-entrant or feedback processes within sensory processing pathways are considered sufficient for phenomenal experience. By contrast, the GNW proposes that conscious access requires a more extensive architecture of reverberant loops, including frontal-parietal regions that enable access of a given representation to a wider array of modular processors.

HOT theories (Lau and Rosenthal, 2011) are similar to the GNW in that they generally posit a central role for the PFC in consciousness (Brown et al., 2019). However, the role of the PFC in these two classes of theory is markedly different. For HOTs, the role of the PFC is to generate a second-order, metacognitive representation of a first-order state (e.g., one generated by primary sensory cortex). Since, for HOT theories, the meta-representation is the mechanism by which a first-order representation becomes conscious, the PFC is the ultimate source of consciousness. Thus, although the two theories both ascribe importance to the PFC as a *structure*, the key differences lie in what is proposed as the *function*. Furthermore, global broadcasting is an important function associated with consciousness according to the GNW hypothesis. By contrast, there is no clear function assigned to consciousness according to HOT theory.

Given the relatively coarse-grained tools of both basic and clinical neuroscience, it is difficult to adjudicate experimentally among these four related theories. For example, the effects of general anesthetics in suppressing recurrent processing (both locally and globally) are broadly consistent with all four theories. Similarly, surrogate measures, such as the perturbational complexity index that have shown promise (Casali et al., 2013), might have originated in one theory (in this case, IIT), but, as noted earlier, the results are consistent with other theories, e.g., the GNW, which also proposes that conscious processing critically depends on the integration of differentiated processors across a network. Indeed, approximations of Φ show an inverse correlation with global modularity during depressed levels of consciousness (Kim et al., 2018), which is also consistent with the GNW hypothesis. Causal interventions in animal models and experimental protocols designed to test multiple theories using the same dataset will be critical in empirically differentiating theories that possess shared features.

Future Directions

The GNW hypothesis—even in its simple and limited original formulation—has thus far received substantial experimental support. Yet, there are several issues that remain to be understood and new future directions that remain to be explored. Here, we discuss two open issues: the development of conscious processing and the mechanisms of self-consciousness.

Development of Consciousness

How the long-distance networks forming the GNW develop and when they first become functional to generate consciousness are crucial areas for further research. All of the properties of conscious processing that were detailed above do not appear all at once but emerge progressively during fetal and postnatal life, which is why it appears useful to distinguish a few nested levels with the development of the human brain, behavior, and consciousness (Barresi and Moore, 1996; Casey et al., 2005; Changeux, 2006; Dehaene-Lambertz and Spelke, 2015; Dehaene and Changeux, 2011; Filippetti et al., 2015; Gogtay et al., 2004; Gopnik et al., 2001; Lagercrantz and Changeux, 2009; Zelazo, 2004).

25- to 30-week preterm babies can already process tactile and painful stimuli in the sensory cortex (Bartocci et al., 2006), discriminate sounds (Mahmoudzadeh et al., 2013), and perceive pain (Bembich et al., 2016). The data are insufficient to determine whether those processes correspond to the type of sensory processing that is known to be preserved in coma patients or whether a lowest level of minimal consciousness, as characterized in adult disorders of consciousness (Chennu et al., 2017), may already exist in preterm infants (Lagercrantz et al., 2010).

At birth, all major long-distance fiber tracts are already in place (Dubois et al., 2016), although still immature in terms of both their terminal connectivity and their myelination. Within the first year of life, all GNW areas quickly become active, including the PFC, although their lack of myelination renders them very slow to process information (Dehaene-Lambertz and Spelke, 2015). An electrophysiological signature of conscious processing—homologous to ignition in adults—was recorded in 5-, 12-, and 15-month-old human babies using a masked-faces paradigm. In all age groups, event-related potentials revealed a late non-linear slow wave that shifted from a weak and delayed response in 5-month-olds (starting around 900 ms) to a more sustained and faster response in older infants (around 750 ms as compared to ~300 ms in adults)

(Kouider et al., 2013). It is quite possible, but currently untested, that a similar ignition, delayed but present, would be found at birth. These results therefore reveal that the elementary mechanisms underlying ignition are already present in infancy—although they undoubtedly undergo a maturation and an acceleration during development, in addition to the development of more elaborate higher-order processes.

Importantly, the baby brain is not a miniature adult brain; regional changes of brain connectivity and differential myelination take place that are asynchronous and protracted (Dehaene-Lambertz and Spelke, 2015; Dubois et al., 2016). Primary sensorimotor areas develop earlier than adjacent unimodal associative cortices, whereas higher-order associative regions and their long-range connectivity further develop later and slowly over decades (Dubois et al., 2014; Lebenberg et al., 2019). In other words, the brain connectome becomes progressively integrated within a constantly evolving GNW architecture (Changeux, 2017; Collin and van den Heuvel, 2013).

Higher Levels: Recursive and Self-Consciousness

Although the GNW hypothesis is primarily concerned with issues of conscious access and conscious state, one of the most fascinating and underexplored facets of the human brain is its ability for self-consciousness. Here, the content of consciousness is not an external stimulus impinging on the senses nor a memory of such a perceived object or event but rather an internal representation of the perceiver itself in the act of perceiving or processing. There is currently no good theory of how the brain achieves such meta-representations, although algorithmic models are beginning to be formulated within the abstract framework of lambda calculus (Goodman and Frank, 2016).

Understanding self-consciousness may require a human-specific investigation into the capacity for recursive thought (thinking about one's own thoughts). Human behavior, in many domains, such as language, mathematics, or theory of mind, is characterized by recursive or self-embedded representations (Dehaene et al., 2015; Hauser et al., 2002). Such recursion is absent or very limited in other animals; although they may acquire some language-like symbolic abilities, they do so at a very slow pace and only up to a limited level (Jiang et al., 2018; Yang, 2013). Correspondingly, only limited self-representation abilities are found in non-human primates, such as a rudimentary capacity to acquire mirror self-recognition (Chang et al., 2017; Mashour and Alkire, 2013b). The deciphering of the evolutionary and neural bases for recursive and reflective self-consciousness, and its uniquely human aspects, are therefore priorities in ongoing and future work on the GNW.

A core set of brain areas involved in self-referential processing has been identified through neuroimaging studies using various modalities (Lou et al., 2017; Posner et al., 2007). It primarily involves the mobilization of a paralimbic network of medial prefrontal and anterior cingulate as well as the medial parietal and posterior cingulate cortices (see Rømer Thomsen et al., 2013 and Tang et al., 2016), as well as the lateral temporoparietal junction (Kelly et al., 2014; Vogeley et al., 2001). Interestingly, the same regions appear to be involved during self-consciousness and during the representation of other people's thoughts (theory of mind). Social relationships, which appear altered in autism and autism spectrum disorder, are thought to affect the GNW architectures for conscious processing (Bourgeron, 2015; Graziano and Kastner, 2011). Social consciousness is assumed to engage cortical areas, including the superior temporal sulcus, temporoparietal junction, and medial PFC, mostly in the right hemisphere (Graziano and Kastner, 2011). Although these data appear broadly consistent with the GNW hypothesis, significant work is required to specify exactly how neural firing in these areas encodes self-knowledge.

Just like the simple paradigm of threshold-level visual perception afforded great progress in understanding conscious access, self-consciousness should perhaps be approached from a much simpler operational perspective, for instance, by studying how the brain becomes aware of its own errors. In simple motor tasks, erroneous responses elicit an early error-related negativity (ERN) arising from the pre-supplementary motor area and the dorsal anterior cingulate cortex (Fu et al., 2019), followed by a later ignition of a late positive response (the error-positivity [PE], similar to the P3 wave). As in sensory access, the first ~200 ms of firing, corresponding to the ERN, can occur even for non-conscious errors, whereas the late ignition occurs only when the error is consciously detected (Nieuwenhuis et al., 2001). Furthermore, intracranial recordings indicate that the early ERN is not predictive of whether subjects will react more slowly on the next trial but rather that such bridging across time, putatively associated with error awareness, relies on late sustained, integrative, and synchronous neural firing (Fu et al., 2019). Thus, the example of error awareness suggests that theorizing about self-consciousness may only require a minor extension of the standard GNW hypothesis of sensory consciousness.

But how does the brain detect its own errors? Is it an internal rather than external signal? The current hypothesis is that of a simple consistency check between two simultaneous processes: a fast, non-conscious route linking perception to action and a slower, conscious route that computes the intended response. When the conscious intention and the actual ongoing response diverge, as may occur due to differential noise or conflicting stimuli, an error is detected (Charles et al., 2013, 2014). This model, whereby a conscious internal model of one's computations is compared to the objectively ongoing ones, might be extended to other more complex forms of self-knowledge. For instance, the human brain may also host an internal model of its own attention, an ''attention schema'' similar to the ''body schema,'' that serves as a basis for our subjective sense of awareness (Graziano et al., 2019).

Conclusions

More than two decades after its original formulation, the GNW hypothesis remains robust. As reviewed above, its main tenets (late ignition, metastable sustained activity, long-distance cortical projections, top-down mobilization) have begun to receive extensive support from neuroimaging and electrophysiological studies in normal wakefulness as well as other states such as sleep, anesthesia, or disorders of consciousness. Indeed, the GNW hypothesis is bringing considerable coherence to otherwise distant fields of research. Most importantly, a small but growing set of studies have begun to demonstrate causal links between PFC ignition and conscious processing. Furthermore, direct empirical tests of the GNW against other theories of consciousness using the same dataset are emerging (e.g., Noel et al., 2019). A multisite, preregistered, adversarial collaboration testing the main predictions of the GNW versus IIT using fMRI, MEG, and intracranial recordings during passive viewing and active dual-tasking is currently underway (Reardon, 2019).

The current state of the art thus renders us cautiously optimistic; clearly, the problem of consciousness has replaced its status as impenetrable mystery with that of an exciting, solvable scientific question. Yet, the field has not yet achieved the high standards of Richard Feynman, who famously stated, ''what I cannot create, I cannot understand.'' In the future, it will be fascinating to see whether some of the present ideas can be made precise enough to be implemented in an actual computational device (Dehaene et al., 2017). Further understanding of the relationship between the evolution of the human genome and its connectome may also help to decipher the neural architectures involved (Changeux, 2017).

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DECLARATION OF INTERESTS

S.D. is a co-author on European patent EP 2 983 586 B1 ''Methods to monitor consciousness.'' Other authors declare no competing interests.

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