The Global Neuronal Workspace Model of Conscious Access: From Neuronal Architectures to Clinical Applications

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Abstract While a considerable body of experimental data has been accumulated on the differences between conscious and non-conscious processing, a theory is needed to bridge the neuro-psychological gap and establish a causal relationship between objective neurophysiological data and subjective reports. In the present review, we first briefly outline the detailed postulates and predictions of our working hypothesis, referred to as the *global neuronal workspace* (GNW) model. We then compare these predictions to experimental studies that have attempted to delineate the physiological signatures of conscious sensory perception by contrasting it with subliminal processing, using a variety of methods: behavioral, PET and fMRI imaging, time-resolved imaging with ERP and MEG, and finally single-cell electrophysiology. In a final section, we examine the relevance of these findings for pathologies of consciousness in coma and vegetative states.

1 Introduction

In recent years, experimental methods have become available to investigate conscious and non-conscious processing, and a considerable body of experimental data has accumulated aiming to establish a causal relationship between objective and subjective data on conscious access. In parallel, computational neuroscience has developed as a fast-moving discipline, with the aim of building up formal mathematical or simulation models, expressed in terms of neuronal networks, that link

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S. Dehaene and Y. Christen (eds.), *Characterizing Consciousness: From Cognition to the Clinic?* Research and Perspectives in Neurosciences,
DOI 10.1007/978-3-642-18015-6_4,

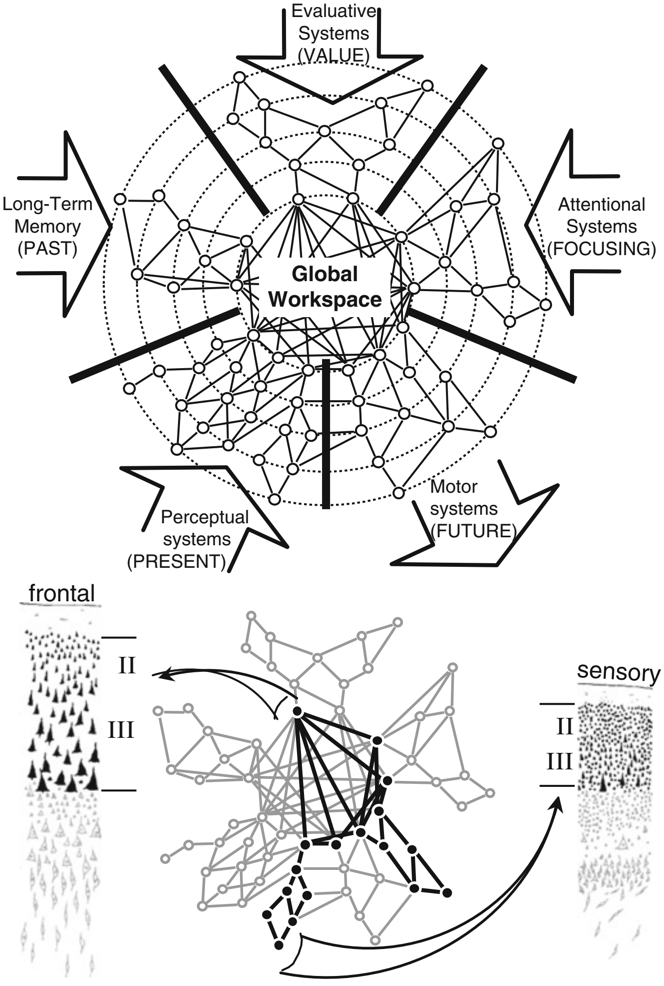
together the molecular, neuronal, physiological and behavioral/mental data in a coherent, non-contradictory though minimal form (Changeux and Dehaene 1989). Implemented as "formal organisms", these neuro-computational models should ultimately address the challenge of decades of attempts to account for subjective experience, which provides a unified or global mental scene where a synthesis between past, present and future takes place and where multimodal perceptions, emotions and feelings (present), evoked memories of prior experiences (past), together with anticipations of actions (future) become subjectively integrated in a continuously changing and dynamic stream of consciousness (Baars 1989; Crick and Koch 2003; Dehaene et al. 1998; Dehaene and Naccache 2001; Edelman 1989; James 1890).

In the present review, we first briefly outline the detailed postulates and predictions of our working hypothesis, referred to as the global neuronal workspace (GNW) model. We then examine the experimental studies that have attempted to delineate the physiological signatures of conscious sensory perception by contrasting it with subliminal processing, using a variety of methods: behavioral, PET and fMRI imaging, time-resolved imaging with ERP and MEG, and finally single-cell electrophysiology. In a final section, we examine the relevance of these findings for pathologies of consciousness in coma and vegetative states.

2 A Brief Overview of the GNW Model

The GNW model in its original formulation (Dehaene and Changeux 2005; Dehaene et al. 1998, 2003, 2006; Dehaene and Naccache 2001) relies upon a few simple assumptions. Its main postulate is that conscious access is global information availability (see Baars 1989): what we subjectively experience as conscious access is the selection, amplification and global broadcasting, to many distant areas, of a single piece of information selected for its salience or relevance to current goals.

From a neuronal architecture standpoint, two main computational spaces are distinguished within the brain, each characterized by a distinct pattern of connectivity (see Fig. 1): (1) a processing network, composed of a set of parallel, distributed and functionally specialized processors (Baars 1989) or modular subsystems (Shallice 1988) subsumed by topologically distinct cortical domains with highly specific local or medium-range connections that "encapsulate" information relevant to its function. Processors typically operate non-consciously and in a bottom-up manner, although local top-down projections may also contribute to their operation by providing local predictions and prediction errors (see e.g. Bekinschtein et al. 2009); and (2) a global neuronal workspace (GNW), consisting of a distributed set of cortical neurons characterized by their ability to receive from and send back to homologous neurons in other cortical areas horizontal projections through long-range excitatory axons. Such long-range cortico-cortical connections



Dehaene, Kerszberg & Changeux 1998

Fig. 1 Schema of the global neuronal workspace (GNW) model. The GNW model proposes that associative perceptual, motor, attention, memory and value areas interconnect to form a higher-level unified space where information is broadly shared and broadcasted back to lower-level processors. The GNW is characterized by its massive connectivity, made possible by thick layers II/III with large pyramidal cells sending long-distance cortico-cortical axons, particularly dense in PFC (after Dehaene et al. 1998)

include callosal connections and mostly originate from the pyramidal cells of layers 2 and 3 that are particularly elevated in prefrontal, parieto-temporal and cingulate associative cortices, together with their thalamo-cortical relationships (Von Economo 1929). GNW neurons typically accumulate information through recurrent top–down/bottom–up loops, in a competitive manner such that a single representation eventually achieves a global conscious status. Because GNW neurons are broadly distributed, there is no single brain center where conscious information is gathered and dispatched but rather a brain-scale process of conscious synthesis achieved when multiple processors converge to a coherent metastable state.

According to the GNW hypothesis, conscious access proceeds in two successive phases (see also Chun and Potter 1995; Lamme and Roelfsema 2000). In a first phase, lasting from ~100 to ~300 ms, the stimulus climbs up the cortical hierarchy of processors in a primarily bottom–up and non-conscious manner. In a second phase, if the stimulus is selected for its adequacy to current goals and attention state, it is amplified in a top–down manner and becomes maintained by sustained activity of a fraction of GNW neurons, the rest being inhibited. The entire workspace is globally interconnected in such a way that only one such conscious representation can be active at any given time (see Sergent et al. 2005; Sigman and Dehaene 2005, 2008). This all-or-none invasive property distinguishes it from peripheral processors in which, due to local patterns of connections, several representations with different formats may coexist. Simulations, further detailed below, indicate that the late global phase is characterized by several unique features. These predicted "signatures" of conscious access include a sudden, late and sustained firing in GNW neurons [referred to as conscious "ignition" in Dehaene et al. (2003)], a late sensory amplification in relevant processor neurons, and an increase in high-frequency oscillations and long-distance phase synchrony.

The state of activation of GNW neurons is assumed to be globally regulated by vigilance signals from the ascending reticular activating system that are powerful enough to control major transitions between the awake state (GNW active) and slow-wave sleep (GNW inactive) states. In the resting awake state, the brain is the seat of an important ongoing metabolic activity (Gusnard and Raichle 2001). An important statement of the GNW model is that the GNW network is the seat of a particular kind of brain-scale activity state characterized by spontaneous "ignitions" similar to those that can be elicited by external stimuli, but occurring endogenously (Dehaene and Changeux 2005). A representation that has invaded the workspace may remain active in an autonomous manner and resist changes in peripheral activity. If it is negatively evaluated, or if attention fails, it may, however, be spontaneously and randomly replaced by another discrete combination of workspace neurons, thus implementing an active "generator of diversity" that constantly projects and tests hypotheses on the outside world (Dehaene and Changeux 1989, 1991, 1997). The dynamics of workspace neuron activity is thus characterized by a constant flow of individual coherent episodes of variable duration, selected by specialized reward processors.

Several explicit formulations and computer simulations of the GNW architecture and physiology were successively developed (Dehaene and Changeux 2005; Dehaene et al. 1998, 2003, 2006; Zylberberg et al. 2009), leading to specific experimental predictions.

3 Simulations of the Neural Signatures of Conscious Access

The GNW has been implemented as explicit computer simulations of neural networks (Dehaene and Changeux 2005; Dehaene et al. 1998, 2003; see also Zylberberg et al. 2009). These simulations incorporate spiking neurons and synapses with detailed membrane, ion channel and receptor properties organized into distinct cortical supragranular, granular, infra-granular and thalamic sectors with reasonable connectivity and temporal delays. Although the full GNW architecture was not simulated, four areas were selected and hierarchically interconnected (Fig. 2). Bottom–up feedforward connections linked each area to the next whereas long-distance top–down connections projected to all preceding areas. Moreover, in a simplifying assumption supported by recent data (Self et al. 2008), bottom–up connections impinged on

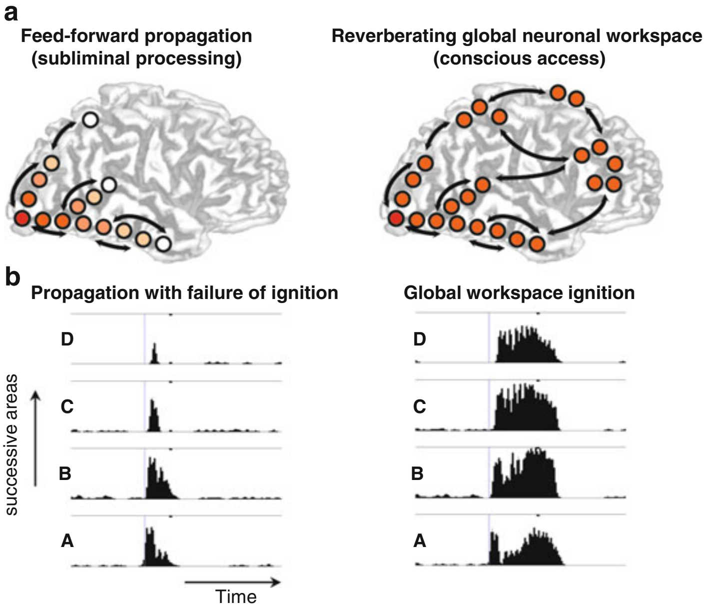


Fig. 2 Events leading to conscious access according to the GNW model. (**a**) Main postulated differences between subliminal and conscious processing. During feed-forward propagation, sensory inputs progress through a hierarchy of sensory areas in a feed-forward manner, successively contacting diverse and not necessarily compatible representations corresponding to all probabilistic interpretations of the stimuli. Multiple signals converge to support each other's interpretation in higher-level cortical areas. Higher areas feedback onto lower-level sensory representations, favoring a convergence towards a single coherent representation compatible with current goals. (**b**) Simulation of two single trials in which an identical pulse of brief stimulation was applied to sensory inputs (Dehaene and Changeux 2005). Fluctuations in ongoing activity prevented ignition in the left diagram, resulting in a purely feedforward propagation dying out in higher-level areas. In the right diagram, the same stimulus crossed the threshold for ignition, resulting in self-amplification, a global state of activation, oscillation and synchrony, and a late long-lasting wave of late activation reaching back to early sensory areas

glutamate AMPA receptors whereas the top–down ones, which are slower, more numerous and more diffuse, primarily involved glutamate NMDA receptors (yet does not include, at this stage, the functionally and pharmacologically important set of metabotropic glutamate receptors; see Niswender and Conn 2010). In higher areas, inputs competed with each other through GABAergic inhibitory interneurons, and it was assumed (though not explicitly simulated) that the winning representation would be broadcasted by additional long-distance connections to yet other cortical regions.

Our simulations first explored the sequence of activity leading to conscious access. When sensory stimulation was simulated, using a brief depolarizing input at the lowest thalamic level, activation propagated according to two successive phases (see Fig. 2): (1) 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; and (2) in a second stage, mediated by the slower NMDA-mediated feedback connections, the advancing feed-forward wave amplified its own inputs in a cascading manner, quickly leading the whole network into a global self-sustained reverberating or "ignited" state. This ignition was characterized by an increased power of local cortico-thalamic oscillations in the gamma band (Dehaene et al. 2003), as well as increased synchrony across distant regions (Dehaene, unpublished simulations). Thus, this second phase of the simulation reproduces the signatures of conscious access detailed in the empirical section – late, all-or-none, cortically distributed potentials involving prefrontal cortex (PFC) and other high-level associative cortices, with simultaneous increases in high-frequency power and synchrony (e.g. Gaillard et al. 2009). GNW simulations capture both the initial linear response and the late perception threshold present in experimental data (de Lafuente and Romo 2006; Del Cul et al. 2007).

Further simulations indicated that ignition could fail to be triggered under specific conditions, thus leading to simulated non-conscious states. For very brief or low-amplitude stimuli, a feed-forward wave was seen in the initial thalamic and cortical stages of the simulation, but it died out without triggering the late global activation because it was not able to gather sufficient, self-sustaining reverberant (Dehaene and Changeux 2005). Even at higher stimulus amplitudes, the second global phase could also be disrupted if another incoming stimulus had been simultaneously accessed (Dehaene et al. 2003). Such a disruption occurs because, during ignition, the GNW is mobilized as a whole, some GNW neurons being active while the rest are actively inhibited, thus preventing multiple simultaneous ignitions. A strict seriality of conscious access and processing is therefore predicted and has been simulated (Dehaene and Changeux 2005; Dehaene et al. 2003; Zylberberg et al. 2010). Overall, these simulations thus captured the two main types of experimental conditions known to lead to non-conscious processing: stimulus degradation (e.g., masking) and inattention due to a simultaneous task (e.g., attentional blink).

The transition to the ignited state could be described, in theoretical physics terms, as a stochastic phase transition – a sudden change in neuronal dynamics whose occurrence depended in part on stimulus characteristics and in part on spontaneous fluctuations in activity (Dehaene and Changeux 2005; Dehaene et al. 2003). Pre-stimulus fluctuations in neural discharges only had a small effect on the early sensory stage, which largely reflected objective stimulus amplitude and duration, but they had a large influence on the second stage, which was characterized by a bimodal, “all-or-none” distribution of activity, similar to empirical observations (Quiroga et al. 2008; Sergent et al. 2005; Sergent and Dehaene 2004). Across trials, the very same stimulus did or did not lead to global ignition, depending on the precise phase of the stimulus relative to ongoing spontaneous activity. This notion that pre-stimulus baseline fluctuations partially predict conscious perception is now backed up by considerable empirical data (e.g., Boly et al. 2007; Palva et al. 2005; Sadaghiani et al. 2009; Super et al. 2003; Wyart and Tallon-Baudry 2009).

In GNW simulations, conscious broadcasting manifests itself as a slow depolarization of layer II/III apical dendrites of pyramidal dendrites in a subset of target GNW neurons. The many post-synaptic potentials evoked by this long-distance, cortico-cortical signalling would therefore create slow intracellular currents travelling from the apical dendrites towards the cell’s soma, summing up on the cortical surface as negative slow cortical potentials (SCPs), which have indeed been suggested to be associated with conscious processing (for review, see He and Raichle 2009). In scalp EEG measurements, negative potentials indeed predominate over regions dense in active GNW neurons, and their topography reflects which content is currently active in working memory (e.g., Vogel and Machizawa 2004). However, ignition does not imply that all GNW neurons are simultaneously active. In the simulations, a subset of neurons is activated while the rest is strongly suppressed by lateral inhibition via GABAergic interneurons, thus leading to attentional blink and serial processing (Dehaene et al. 2003). Which neurons are active and which are inactive defines the current conscious content. The impact of this broad GNW inhibition may perhaps be easier to detect at the scalp level, particularly if a sparse code is used, where the set of active neurons is relatively small, e.g., 10% (for neurophysiological evidence, see e.g., Deco et al. 2007). Inhibition, by the same logic as above, should result in broad *positive* surface potentials. As already noted by Rockstroh et al. (1992, p. 175), “the surface positivity corresponding to these inhibited networks would then dominate over the relatively smaller spots of negativity caused by the reverberating excitation.” Thus, the GNW hypothesis, combined with elementary physiological arguments, can explain why the P3b component (a broadly distributed scalp positivity) is a frequent neurophysiological signature of conscious access and can draw attention to the important putative role of GABAergic interneurons and their neuromodulatory control in conscious processing.

4 Simulations of the Impact of Vigilance on Conscious Access

Further simulations explored the impact of vigilance on access to the GNW (Dehaene and Changeux 2005). Changes in vigilance, including the transition between the awake and asleep states, are regulated by various diffuse ascending neuromodulatory systems located in the brainstem, hypothalamus, and basal forebrain and by liberating substances such as acetylcholine, noradrenalin, serotonin, and histamine in the cortex and thalamus. For simplicity, we summarized these complex effects of ascending neuromodulatory inputs by a change in a single parameter, the amount of depolarizing current injected into both thalamic and cortical pyramidal neurons (Dehaene and Changeux 2005).

The model exhibited two interesting changes when the neuromodulatory current was increased. First, there was a threshold value of ascending neuromodulation below which very little spontaneous activity was seen but above which structured neuronal activity emerged in the form of spontaneous thalamocortical oscillations in the gamma band. This GNW prediction fits with the sudden emergence of a broad network of GNW areas, including PFC and its thalamic connections, during awakening or recovery from vegetative state (Balkin et al. 2002; Laureys et al. 2000), and its drastic disruption during anesthesia, coma, or slow wave sleep (reviewed in Laureys 2005, and further discussed below).

Second, when a fixed external sensory stimulus was presented, the threshold for global ignition of the GNW network decreased as the strength of the ascending neuromodulation signal increased (Dehaene and Changeux 2005). At one extreme, very low levels of ascending inputs prevented any ignition, even by long and intense stimuli: in this case, only a small transient activation was seen in the lower levels of the model. These simulations can be compared with empirical observations of sensory processing during the vegetative state, where activation can be seen in the thalamus and early sensory cortices, but fail to extend to the prefrontal, parietal, and cingulate regions seen in awake normal subjects (see below).

5 Simulations of Spontaneous Activity and Serial Processing

One last important feature of the GNW model is the occurrence of highly structured spontaneous activity. Even in the absence of external inputs, the simulated GNW neurons are assumed to fire spontaneously, in a top–down manner, starting from the highest hierarchical levels of the simulation and propagating downwards to form globally synchronized ignited states (Dehaene and Changeux 2005). When the ascending vigilance signal is large, several such spontaneous ignitions follow each other in a never-ending stream and partially prevent access to external stimuli, possibly capturing empirical observations of inattentional blindness (Mack and Rock 1998) and mind wandering (Christoff et al. 2009; Mason et al. 2007; Smallwood et al. 2008).

In initial simulations, a spike-rate adaptation current was solely responsible for the interruption of an ignited state and its replacement by another. However, more complex network architectures have also been simulated in which a goal state is set and where structured patterns of activity are spontaneously generated until the goal is attained (Dehaene and Changeux 1997; Zylberberg et al., 2010). In these simulations, ignited states are only metastable and can be destabilized by a negative reward that signals deviation from the current goal, in which case they are spontaneously and randomly replaced by another discrete combination of workspace neurons, thus implementing an active generator of diversity that constantly projects and tests hypotheses on the outside world (Dehaene and Changeux 1989, 1991, 1997). The dynamics of such networks is characterized by a constant flow of individual coherent episodes of variable duration, selected by reward signals to achieve a defined goal state. Architectures based on these notions have been applied to a variety of tasks (delayed response: Dehaene and Changeux 1989; Wisconsin card sorting: Dehaene and Changeux 1991; Tower of London: Dehaene and Changeux 1997; Stroop: Dehaene et al. 1998), although a single architecture common to all tasks is not yet in sight (but see Rougier et al. 2005). They provide a preliminary account of why GNW networks are spontaneously active, in a sustained manner, during effortful tasks that require series of conscious operations, including search, dual-task and error processing.

In summary, simulations of the GNW architecture explain the close similarity of the brain activations seen during (1) conscious access to a single external stimulus, (2) modulation of conscious access by changes in vigilance and (3) effortful serial processing, even in the absence of an external stimulus. In all of these cases, the GNW provides a working memory space that can be temporarily detached from incoming stimuli and operates in an autonomous manner.

6 Anatomy of the GNW

The main anatomical premise of the GNW model is that it consists of "a distributed set of cortical neurons characterized by their ability to receive from and send back to homologous neurons in other cortical areas horizontal projections through long-range excitatory axons mostly originating from the pyramidal cells of layers 2 and 3" (Dehaene et al. 1998). It is grounded in the "special morphology" of the pyramidal cells from the cerebral cortex already noted by Cajal et al. (1892/1988), who mentioned their "long axons with multiple collaterals" and their "very numerous and complex dendrites", and also noted that these fibers of association form "the main mass of the white matter." Recent investigations have confirmed the view that the cortico-cortical and callosal fibers primarily (though not exclusively) arise from layer II–III pyramids. Von Economo (1929) further noted that the cerebral cortex is not uniform in structure and that these large pyramidal cells in layers III and V are specially abundant in areas "spread over the anterior two-thirds of the frontal lobe, (. . .) the superior parietal lobule" and "the cingulate cortex", among other cortical areas.

Pyramidal cells comprise over 70% of all neurons in the cerebral cortex (DeFelipe and Farinas 1992) and display a remarkable diversity. Quantitative analyses of the dendritic field morphology of layer III pyramidal neurons revealed a continuous increase of complexity of the basal dendrites from the occipital up to the PFC within a given species (DeFelipe and Farinas 1992; Elston and Rosa 1997,

1998) and from lower species (owl monkey, marmoset) up to humans (Elston 2003). Consistent with its proposed role in the GNW, the PFC receives the most diverse set of cortico-cortical inputs from a multitude of areas involved in processing all sensory modalities (Cavada et al. 2000; Fuster 2008; Kringelbach and Rolls 2004; Pandya and Yeterian 1990; Petrides and Pandya 2009). In particular, mapping of long-range connections in the monkey cerebral cortex revealed long-range connections linking, among others, the PFC (area 46), the superior temporal sulcus, parietal area 7a and the hippocampus, together with the contralateral anterior and posterior cingulum, area 19 and the parahippocampal gyrus (Goldman-Rakic 1988). These circuits were suggested to contribute to working memory and the central executive (Goldman-Rakic 1996). In addition, areas within PFC are multiply interconnected (Barbas and Pandya 1989; Preuss and Goldman-Rakic 1991), and the superficial layers in PFC are characterized by the abundance of horizontal intrinsic axon projections that arise from supragranular pyramidal cells (Kritzer and Goldman-Rakic 1995; Melchitzky et al. 1998, 2001; Pucak et al. 1996), thus exhibiting the massive and recurrent interconnectivity needed to sustain workspace states.

In the course of postnatal brain development, dendritic and axonal arborizations develop progressively through nested processes of neurite outgrowth and selection through synapse selective stabilization and elimination or “pruning” (Bourgeois et al. 1994; Changeux et al. 1973; Changeux and Danchin 1976). The data are consistent with the view that most (about 2/3 in the monkey) of the cortical synaptic endowment of the GNW develops postnatally, followed by a consistent and continuous maturation manifested by a decrease of the global synaptic envelope down to the adult brain synaptic content.

Identification of the detailed anatomy of white matter pathways interconnecting cortical areas started with Theodore Meynert (1833–1892), who classified white matter fibers into association fibers connecting cortical areas within a hemisphere, commissural fibers connecting the two hemispheres, and projection fibers, ascending or descending pathways arising and terminating in the cortex. In a still up-to-date volume, Dejerine (1895) further distinguished U-shaped, short, *intra*-area association fibers that remain superficial close to the gray matter and long *inter*-areas association fibers that run more deeply in the white matter. Among this last category Dejerine distinguished five main tracts: the cingulum that connects medial frontal, parietal, occipital, temporal and cingulate cortices, the uncinate fasciculus that connects orbitofrontal to anterior and medial temporal lobes, the arcuate/superior longitudinal fasciculus that connects perisylvian frontal, parietal and temporal cortices, the inferior fronto-occipital fasciculus that connects the orbital and lateral frontal cortices to occipital cortex and the inferior longitudinal fasciculus that connects the occipital and temporal lobes. Consistent with the GNW hypothesis, four of them connect the frontal areas with other cortical areas.

The course of cortical tracts can now be confirmed by diffusion tensor imaging and tractography algorithms, yet with important limitations. Measurements typically average over relatively large voxels (a few millimeters aside) that contain a diversity of criss-crossing fibers. Current tracking algorithms suffer from severe difficulties in estimating the true course of fibers, especially when a relatively smaller tract crosses a large one. Furthermore, long-distance fibers, are typically underestimated by probabilistic tracking algorithms, unless distance compensation is introduced. Even recent articles claiming to study the entire “connectome” (e.g., Hagmann et al. 2008) suffer from a massive underestimation of the true longdistance connectivity of areas 46, 6, FEF (frontal eye fields) and LIP (lateral intraparietal sulcus), critical to GNW theory and known from macaque invasive tracer studies, careful human anatomical dissections dating from the end of the nineteenth century (Dejerine, Meynert, Flechsig), and some reliable diffusion tensor tractography methods (Catani and Thiebaut de Schotten 2008).

Because of these limitations, it is important to confirm the inferred networks using converging techniques. The correlation of cortical thickness measures at two different cortical sites across many individuals can serve as a proxy for cortico-cortical connectivity (Bassett et al. 2008; He et al. 2009). There is a remarkable convergence of this method with fMRI intercorrelation during the resting state or by phase synchrony in the beta band during either working memory (Bassett et al. 2009) or conscious access in the attentional blink (Gross et al. 2004).

Human structural and functional brain networks have been further explored using graph theory (Bassett and Bullmore 2009; Bullmore and Sporns 2009; Gong et al. 2009; Hagmann et al. 2008; Iturria-Medina et al. 2008). Here brain networks are described as composed of nodes (brain regions) linked by edges (axonal projections). The resulting undirected graph can then be characterized by parameters such as degree (number of connections from a given node), the minimal path length between any two nodes, and clustering (density of triangular connections). Graph analyses indicate that the brain lives in the small-world regime (Watts and Strogatz 1998) characterized by a small path length, indicating a high transmission efficiency, and a high level of clustering, providing a tolerance of the overall system to the failure of individual nodes or connections. Putative hubs (nodes with a high degree of connectivity) were identified within the posterior medial and parietal cerebral cortex, including the precuneus, the insula, the superior parietal cortex and to some extent the superior frontal cortex (though these results are probably limited by the biases noted above; Gong et al. 2009; Hagmann et al. 2008; Iturria-Medina et al. 2008). Particularly notable is the prominent structural role of the precuneus, a region homologous to the highly connected posteromedial cortex (PMC) in the macaque (Parvizi et al. 2006). Being an aggregate of convergence-divergence zones (Meyer and Damasio 2009) and tightly connected to PFC area 46 and other workspace regions (Goldman-Rakic 1999), the PMC may play a critical role in humans in the “generation of the self process” (Damasio 1999) and in self-referential processing (Cavanna and Trimble 2006; Vogt and Laureys 2005). As discussed below, deactivation of PMC is seen during loss of consciousness in coma and vegetative state, anesthesia and slow wave sleep (Alkire et al. 2008; Laureys 2005). In a general manner, these results are thus consistent with the GNW model assumption of a tight relation between anatomical long-distance association fibers and functional conscious access.

7 Imaging States of Conscious Access and Non-Conscious Processing

As noted by Baars (1989), the experimental study of the mechanisms of conscious access requires the definition of a minimal contrast between a situation in which information is consciously accessed and a similar situation in which the same information is only processed non-consciously. Many such contrasts are now available (Kim and Blake 2005). Our own brain imaging work relied primarily on two techniques: retrograde masking, where the stimulus is flashed for a perceptible duration but is made invisible by the subsequent presentation, at the same location, of another shape, called the "mask;" and the attentional blink (AB), where a brief target, presented for a duration that would be perceivable in isolation, becomes invisible once the participants are temporarily distracted by a concurrent task. In both cases, functional magnetic resonance imaging (fMRI), magneto-encephalography (MEG), electro-encephalography (EEG) and intracranial recordings can be used to record the progression of activation in the cortical hierarchy under conditions of conscious versus non-conscious perception.

Such a research program requires a consensus on an empirical criterion to discriminate conscious and non-conscious processing. According to a long psychophysical tradition, grounded in signal-detection theory, a stimulus should be accepted as non-conscious or "subliminal" (below threshold) only if subjects are unable to perform above chance on some direct task of stimulus detection or classification. This objective definition raises problems, however (Persaud et al. 2007; Schurger and Sher 2008). First, it tends to overestimate conscious perception: there are many conditions in which subjects perform better than chance, yet still deny perceiving the stimulus. Second, performance can be at chance level for some tasks but not others, raising the issue of which tasks count as evidence of conscious perception or merely of subliminal processing. Third, the approach requires accepting the null hypothesis of chance-level performance, yet performance never really falls down to zero, and whether it is significant or not often depends on arbitrary choices such as the number of trials dedicated to its measurement. For these reasons, our research has emphasized obtaining subjective reports of stimulus visibility, if possible on every single trial (Sergent and Dehaene 2004). Such subjective reports are arguably the primary data of interest in consciousness research. Furthermore, reports of stimulus visibility can be finely quantified, leading to the discovery that conscious perception can be "all-or-none" in some masking and AB paradigms (Del Cul et al. 2006, 2007; Sergent and Dehaene 2004). Subjective reports also present the advantage of assessing conscious access immediately and on every trial, thus permitting post-experiment sorting of conscious versus non-conscious trials with identical stimuli (e.g., Del Cul et al. 2007; Lamy et al. 2009; Pins and Ffytche 2003; Sergent et al. 2005; Wyart and Tallon-Baudry 2008). Importantly, objective assessments, wagering indices and subjective reports are generally in excellent agreement (Del Cul et al. 2006, 2009; Persaud et al. 2007). For instance, the masking thresholds derived from objective and subjective data are essentially identical across subjects ($r = 0.96$, slope ≈ 1) (Del Cul et al. 2006).

Those data suggest that conscious access causes a major change in the availability of information that is easily detected by a variety of subjective and objective measures.

Once criteria for conscious access are defined, one can examine how the brain activity evoked by accessed stimuli differs from that elicited by well-matched stimuli that remain subjectively invisible. Here, we successively review the four levels of analysis at which such experiments have been attempted: fMRI, time-resolved methods such as event-related potentials (ERPs) and MEG, intracranial recordings, and finally, single-cell recordings.

7.1 Brain-Scale Neuroimaging with fMRI

fMRI can provide a global image of the brain activity evoked by a visible or invisible stimulus integrated over a few seconds. Grill-Spector et al. (2000) first used fMRI to measure visual activity evoked by masked pictures presented below or above the visibility threshold. V1 activation was largely unaffected by masking, but the amount of activation in more anterior regions of lateral occipital and fusiform cortex strongly correlated with perceptual reports. A year later (Dehaene et al. 2001), a similar contrast between masked and unmasked words, now at the whole-brain level, again revealed a strong correlation of conscious perception with fusiform activity but also demonstrated extended areas of activation uniquely evoked by conscious words, including inferior prefrontal, mesial frontal and parietal sites. In more recent fMRI work, under conditions where masking followed a characteristic U-shaped curve, fusiform and midline prefrontal and inferior parietal regions again closely tracked conscious perception (Haynes et al. 2005). An important control was recently added: participants' objective performance could be equated while subjective visibility was manipulated (Lau and Passingham 2006). In this case, a correlate of visibility could only be detected in left dorsolateral PFC.

Some authors have found correlations of fMRI activation with visibility of masked versus unmasked stimuli exclusively in posterior visual areas (e.g., Tse et al. 2005). However, in their paradigm, even the unmasked stimuli were probably not seen because they were unattended and irrelevant, which can prevent conscious access (Dehaene et al. 2006; Kouider et al. 2007; Mack and Rock 1998). Overall, fMRI evidence suggests two convergent correlates of conscious access: (1) amplification of activity in visual cortex, clearest in higher-visual areas such as the fusiform gyrus, but sometimes including area V1 (Williams et al. 2008); and (2) emergence of a distributed set of areas, virtually always including bilateral parietal and prefrontal cortices (see Fig. 3).

7.2 Time-Resolved Imaging Methods

ERPs and MEG have been used to track the processing of a stimulus in time, at a millisecond scale, as it crosses or does not cross the threshold for subjective

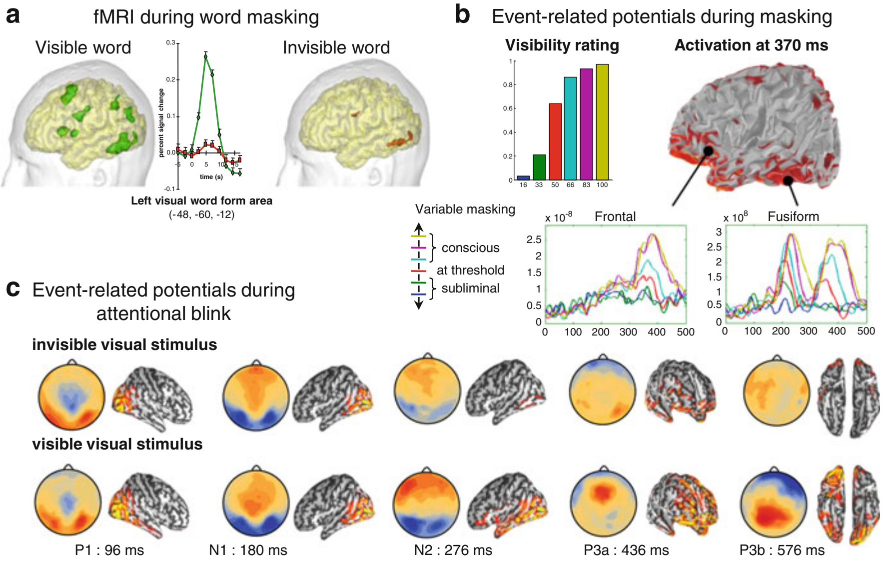


Fig. 3 Brain-imaging correlates of conscious access. (**a**) An early fMRI experiment contrasting the fMRI activations evoked by brief presentations of words that were either normally readable (*left*) or made invisible by masking (*right*) (Dehaene et al. 2001). Non-conscious word processing activated the left occipito-temporal visual word form area, but conscious perception was characterized by (1) an intense amplification of activation in relevant non-conscious processors, here the visual word form area (*left* occipito-temporal cortex; see *middle* graph); and (2) an additional spread of activation to a distributed, though restricted set of associative cortices including inferior parietal, prefrontal and cingulate areas. (**b**) Event-related potentials during masking, with manipulation of visibility by varying the temporal asynchrony between a visual stimulus and a subsequent mask (Del Cul et al. 2007). A non-linearity, defining a threshold value for conscious access, was seen in both subjective visibility reports and the P3b event amplitude. Source modelling related this P3b to a sudden non-linear ignition, about 300 ms after stimulus presentation, of distributed sources including inferior PFC, with a simultaneous re-activation of early visual areas. Note the two-stage pattern of fusiform activation, with an early linear activation followed by a late non-linear ignition. (**c**) Time course of scalp event-related potentials evoked by an identical visual stimulus, presented during the attentional blink, as a function of whether it was reported as seen or unseen (Sergent et al. 2005). Early events (P1 and N1) were strictly identical, but the N2 event was amplified and the P3 events (P3a and P3b) were present essentially only during conscious perception

report. Early visual activation can be fully preserved during masking (Schiller and Chorover 1966), a finding supported by both animal electrophysiology (Bridgeman 1975, 1988; Kovacs et al. 1995; Lamme et al. 2002; Rolls et al. 1999) and essentially all recent ERP and MEG studies (Dehaene et al. 2001; Del Cul et al. 2007; Fahrenfort et al. 2007; Koivisto et al. 2006, 2009; Lamy et al. 2009; Melloni et al. 2007; Railo and Koivisto 2009; van Aalderen-Smeets et al. 2006; for an exception, see Pins and Ffytche 2003). Evidence from the AB confirms that the first 200 ms of initial visual processing can be fully preserved on trials in which subjects deny seeing a stimulus (Sergent et al. 2005; Vogel et al. 1998; see Fig. 3).

When does a consistent correlation with subjective reports of visibility first emerge? Following the initial P1 (~100 ms) and N1 (~170 ms) waves, at around 200–300 ms, more negative voltages are seen over posterior cortices under conditions that are conducive to higher visibility (Del Cul et al. 2007; Fahrenfort et al. 2007; Koivisto et al. 2008, 2009; Railo and Koivisto 2009; Sergent et al. 2005). Koivisto and collaborators have called this event the visual awareness negativity (VAN). Lamme and collaborators (Fahrenfort et al. 2007) find an even earlier amplification in visual cortex, just posterior to the P1 wave (110–140 ms). Several arguments, however, mitigate the possibility that these mid-latency differences already reflect conscious perception. First, they are absent from several carefully controlled experiments (e.g., Lamy et al. 2009; van Aalderen-Smeets et al. 2006). Second, their profile of variation with stimulus variables such as target-mask delay does not quite mimic the subject's conscious reports (Del Cul et al. 2007; van Aalderen-Smeets et al. 2006). Indeed, they typically consist in differences in degree, modulating N1 and P2 events that remain strongly present on non-conscious trials (Del Cul et al. 2007; Fahrenfort et al. 2007; Sergent et al. 2005). Although more research is needed to clarify this point, they might represent a cascading modulation of non-conscious processing, perhaps causally related to subsequent conscious access but not yet reflective of the all-or-none process of conscious perception itself.

The most consistent correlate of visibility appears to be a late (~300–500 ms), broadly distributed, positive component called P3 or sometimes P3b (to distinguish it from the focal anterior P3a, which is thought to reflect automatic attention attraction and can occur non-consciously; see, e.g., Muller-Gass et al. 2007; Salisbury et al. 1992). This component is reproducibly observed as strongly correlated with subjective reports, both when varying stimulus parameters (e.g. Del Cul et al. 2007) and when comparing identical trials with or without conscious perception (e.g., Babiloni et al. 2006; Del Cul et al. 2007; Fernandez-Duque et al. 2003; Koivisto et al. 2008; Lamy et al. 2009; Niedeggen et al. 2001; Pins and Ffytche 2003; Sergent et al. 2005). A similarly late effect is seen in MEG (van Aalderen-Smeets et al. 2006). The generators of the P3b are thought to involve a highly distributed set of simultaneously active areas, including hippocampus and temporal, parietal and frontal association cortices (Halgren et al. 1998; Mantini et al. 2009), that are proposed as components of the GNW.

7.3 Intracranial Recordings

The high spatial precision and signal-to-noise ratio afforded by intracranial recording in epileptic patients, combined with the human ability to perform objective and subjective perception tasks, provided a unique window into the neuronal correlates of conscious access (Fisch et al. 2009; Gaillard et al. 2009). Gaillard et al. (2009) contrasted the fate of masked (subliminal) versus unmasked (conscious) words while recording from a total of 176 local sites using intracortical depth electrodes in ten epileptic patients. Four objective measures of conscious perception were identified: (1) late (>300 ms) and distributed event-related potentials contacting sites in PFC; (2) large and late (>300 ms) increases in induced power (indexing local synchrony) in high-gamma frequencies (50–100 Hz), accompanied by a decrease in lower frequency power (centered on 10 Hz); (3) increases in long-distance cortico-cortical synchrony in the beta frequency band 13–30 Hz; and (4) increases in causal relations amongst distant cortical areas (Granger causality), bidirectionally but more strongly in the bottom–up direction.

Gaillard et al. (2009) noted that all four signatures coincided in the same time window (300–500 ms) and suggested that they might constitute different measures of the same state of distributed "ignition" of a large cortical network, including PFC. Compatible with the GNW concept of "global broadcasting", seen stimuli had a global impact on late evoked activity virtually anywhere in the cortex: 68.8% of electrode sites, although selected for clinical purposes, were modulated by the presence of conscious words (as opposed to 24.4% of sites for non-conscious words).

Intracranial recordings clearly refute an early speculation concerning the neural correlates of conscious access (Crick and Koch 1990): local gamma oscillations are *not* unique to conscious states, being clearly present on non-conscious trials, particularly during the first 200 ms of stimulus processing (Fisch et al. 2009; Gaillard et al. 2009; see also Melloni et al. 2007). Gamma-band power merely shows a relative increase on visible relative to invisible trials (Doesburg et al. 2009; Gaillard et al. 2009; Melloni et al. 2007; Rodriguez et al. 1999; Schurger et al. 2006; Wyart and Tallon-Baudry 2009). In recent visual intracranial recordings, for instance, gamma-band power increases were present in the 150–200 ms time window on non-consciously perceived trials but were significantly enhanced on consciously perceived trials, turning into an all-or-none pattern after 200 ms (see Fig. 6c in Fisch et al. 2009).

While time-frequency *power* increases occur in a very broad band (up to 100 Hz and above), in several intracranial MEG and EEG studies, *synchrony* across distant cortical sites tends to appear in the lower frequency range, either in the beta band 13–30 Hz or in the low-gamma band around 30–40 Hz, and to be a more specific indicator often exclusively seen during conscious access (Doesburg et al. 2009; Gaillard et al. 2009; Gross et al. 2004; Kranczioch et al. 2007; Rodriguez et al. 1999). With their slow period (25–80 ms), these frequencies may be more appropriate for forming brain-scale assemblies across long cortical distances and time delays (Fries 2005).

7.4 Neuronal Recordings

Animal single- and multi-unit recordings have examined changes in spike trains evoked by detected or undetected stimuli. These studies have largely supported and enhanced the conclusions drawn from human neuroimaging studies, and particularly the distinction between an early time window, dominated by stimulus-induced non-conscious processing, and a later window, dependent on long-distance interactions with higher association areas and reflecting conscious perception (Lamme and Roelfsema 2000).

A pioneering research program was conducted by Logothetis and collaborators using monkeys trained to report their perception during binocular rivalry (Leopold and Logothetis 1996; Sheinberg and Logothetis 1997). By recording from V1, V2, V4, MT, MST, IT and STS neurons and presenting two rivalling images, only one of which led to high neural firing, they identified a fraction of cells whose firing rate increased when their preferred stimuli was perceived, thus participating in a conscious neuronal assembly. The proportion of such cells increased from 20% in V1/V2 to 40% in V4, MT or MST, to as high as 90% in IT and STS. This finding supports the hypothesis that subjective perception is associated with distributed cell assemblies whose neurons are denser in higher associative cortices than in primary and secondary visual cortices.

Other paradigms afforded a precise measurement of the timing of information progression and conscious access in the visual system. In area V1, multi-unit recordings during both threshold judgments (Super et al. 2001) and masking paradigms (Lamme et al. 2002) identified two successive response periods. The first period (approximately 30–80 ms) was phasic, time-locked to stimulus onset, and reflected objective properties such as stimulus orientation, whether or not they were detectable by the animal. The second period, starting at 80–160 ms and extending for several hundreds of milliseconds, was associated with a late, slow and long-lasting amplification of firing rate that correlated tightly with stimulus detectability. Only this late amplification vanished under anesthesia (Lamme et al. 1998). Thus, although different forms of masking can affect both initial neural responses and late sustained discharges, in both awake and anesthesized monkeys (Macknik and Haglund 1999; Macknik and Livingstone 1998), the work of Lamme and colleagues suggests that it is the late phase that is most systematically correlated with conscious visibility.

In the infero-temporal cortex (IT), similarly, even when an image was presented extremely briefly and masked at a very short time interval (20–40 ms, thus probably subliminal), neurons still showed a brief pulse of firing, extending ~ 60–160 ms post-stimulus and carrying significant information about the masked image (Kovacs et al. 1995; Rolls et al. 1999). However, the mask image interrupted the firing train and prevented the emergence of a late discharge period (>200 ms post-stimulus), during which stimulus information was amplified.

Perhaps the clearest evidence for a two-stage process was obtained in the FEF in two macaque monkeys trained to detect faint and masked stimuli (Thompson and Schall 1999, 2000). A signal-detection analysis was applied, separating hits, misses, false alarms and correct rejections. A first firing peak (~80–100 ms post-stimulus), locked to stimulus onset, mostly tracked objective stimulus presence, although it was partially modulated according the monkey's eventual decision (i.e., higher on hits than on misses, and on false alarms than on correct rejections). A subsequent slow-firing modulation, starting around 100 ms and lasting several hundreds of milliseconds and thus bridging between visual and motor responses, was present only when monkeys detected a target, as indexed by their ocular responses.

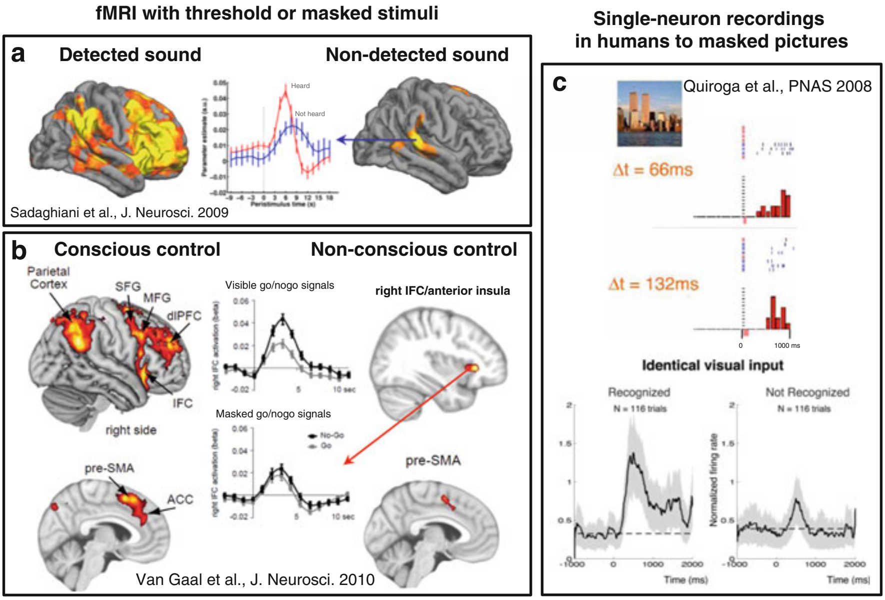


Fig. 4 Converging evidence from multiple methodologies for a global ignition during conscious access. (**a**) fMRI study of threshold-level noises, approximately half of which were consciously detected (Sadaghiani et al. 2009). Bilateral auditory areas showed a non-conscious activation that was amplified and spread to distributed inferior parietal, prefrontal and cingulate areas (for similar results with tactile stimuli, see Boly et al. 2007). (**b**) fMRI study of conscious versus non-conscious inhibitory control (van Gaal et al. 2010). Subjects were presented with masked visual signals, at the threshold for conscious perception, some of which occasionally required inhibiting a response (go/nogo task). Small activations to the non-conscious no-go signal were detected in the inferior frontal and pre-SMA cortices, but inhibitory control by a conscious no-go signal was associated with fMRI signal amplification (see the difference between no-go and go signals in middle graphs) and massive spread of the activation to additional and more anterior areas including prefrontal, anterior cingulate and inferior parietal cortices. (**c**) Single-cell correlate of all-or-none conscious access for masked pictures (Quiroga et al. 2008). Neurons were recorded from the human medial temporal lobe and hippocampus during presentation of masked pictures, with a variable target-mask delay. A single cell that fired specifically to pictures of the World Trade Center and did so only on trials when the patient recognized the picture (*dark blue* raster plots) and not on trials when recognition failed (*red* raster plots). In the plot of firing rate averaged across all neurons (bottom), transient firing could be seen on unrecognized trials, and conscious perception was characterized by a massive and durable amplification of activity (for complementary results in occipito-temporal areas, see also Fisch et al. 2009)

Thompson and Schall note that FEF neurons project back to extrastriate cortex and speculate that, “this top–down modulation (. . .) is a critical event to make explicit the interpretation of the ambiguous sensory input.”

Only a single study to date has explored single-neuron responses to seen or unseen stimuli in human cortex (Quiroga et al. 2008). Pictures followed at a variable delay by a mask were presented while recording from the medial temporal lobe in five patients with epilepsy. In this hierarchically high area, a very late response was seen, peaking around 300 ms and extending for 1 or 2 s. This late firing reflected tightly the person's subjective report to such an extent that individual trials reported as seen or unseen could be categorically distinguished by the neuron's firing train (see Fig. 4). Such a late categorical response is consistent with the hypothesis that conscious access is “all-or-none”, leading either to a high degree of reverberation in higher association cortex or to a quickly decaying response (Sergent et al. 2005; Sergent and Dehaene 2004). Zhang and Luck (2008, 2009) have similarly observed that working memory operates in an all-or-none manner: only up to three “slots” are available, and manipulations that degrade memory, such as set size or masking of the targets, merely change the storage probability, not the number or precision of the memory.

Single-cell electrophysiology has also contributed to a better description of the mechanisms of formation of global brain-scale assemblies, confirming the key role of synchronization in conscious access. Within a single area such as V4, the degree to which single neurons synchronize with the ongoing fluctuations in local-field potential is a predictor of stimulus detection (Womelsdorf et al. 2006). Across distant areas such as FEF and V4 (Gregoriou et al. 2009) or PFC and LIP (Buschman and Miller 2007), synchrony is enhanced when the stimulus in the receptive field is attended and is thus presumably accessed consciously. Consistent with human MEG and intracranial studies (e.g., Gaillard et al. 2009; Gross et al. 2004), synchronization involves both gamma and beta bands, the latter being particularly enhanced during top–down attention (Buschman and Miller 2007). During the late phase of attention-driven activity, causal relations between distant areas are durably enhanced in both directions but more strongly so in the bottom–up direction from V4 to FEF (Gregoriou et al. 2009), again similar to human findings (Gaillard et al. 2009) and compatible with the idea that sensory information needs to be propagated anteriorly, particularly to PFC, before becoming consciously reportable.

8 Clinical Application to Coma, Vegetative State and Non-Communicative Disorders

The exploration of patients suffering from disorders of consciousness (DOC patients) such as comatose, vegetative state (VS) or other related states is motivated by two major goals. First, such translational research could eventually lead to major medical improvements in the way we (1) diagnose consciousness in non-communicating patients prognosis, (2) predict recovery of consciousness and cognitive abilities, (3) enable a bidirectional communication in these patients, and (4) facilitate recovery from impairments of arousal and consciousness. Second, these studies on such extreme situations offer a unique opportunity to test crucial theoretical predictions of our theories and to discover additional neural mechanisms involved in the physiology of consciousness. One such ancient but major discovery is the dissociation between arousal and consciousness as observed, for instance, in the vegetative state (see below). We will now briefly describe the various states observed in DOC patients and in general anesthesia and review some of the major findings related to this field.

8.1 Varieties of Disorders of Consciousness

Coma, from the Greek "deep sleep", is a drastic loss of responsivity, eye opening, visual pursuit and communicative acts, yet with a preservation of several reflexes. It is characterized by a failure of the arousal system caused by a structural or metabolic lesion of the brainstem reticular system or by widespread bilateral cerebral damage (Tshibanda et al. 2009, 2010). Coma is usually a transient condition that lasts no longer than a few days or weeks and evolves either to brain death, vegetative state, or regaining of consciousness. Contrary to coma patients, vegetative state (VS) patients exhibit preserved autonomous functioning, including spontaneous or stimulus-induced arousal and sleep–wake cycles (Laureys 2005). They may cry, smile, or move their eyes, head and limbs but in a meaningless, "automatic" manner and without any apparent voluntary or conscious response to verbal cues. Minimal consciousness (MCS), finally, is characterized by occasional but often unreliable voluntary responses to verbal commands or goal-driven eye movements (Giacino 2005). Unfortunately, the borders between these categories remain poorly defined, and even fully conscious but paralyzed patients with locked-in syndrome can remain undetected. It is therefore of interest to see if objective neural measures and GNW theory can help discriminate them.

8.2 Testing GNW Theory in Disorders of Consciousness

In coma and VS, as with general anesthesia, global metabolic activity typically decreases to ~50% of normal levels (Laureys 2005). This decrease is not homogeneous, however, but particularly pronounced in GNW areas including lateral and mesial prefrontal and inferior parietal cortices – a network that strongly reactivates, together with thalamo-cortical activity, upon recovery from VS (Laureys et al. 1999, 2000). Anatomically, prediction of recovery from coma relies on the comprehensive assessment of all structures involved in arousal and awareness functions, namely, the ascending reticular activating system located in the postero-superior part of the brainstem and structures encompassing thalamus, basal forebrain, and fronto-parietal association cortices (Tshibanda et al. 2009, 2010). Lesion or inhibition of part of this system suffices to cause immediate coma (e.g., Parvizi and Damasio 2003). Studies on traumatic coma patients with conventional MRI showed that lesions of the pons, midbrain, and basal ganglia were predictive of poor outcome, especially when they were bilateral (Tshibanda et al. 2010). In relation with the GNW model, it is noteworthy that prediction of non-recovery after 1 year could be calculated with up to 86% sensitivity and 97% specificity when taking into account both diffusion tensor and spectroscopic measures of cortical white matter integrity (Tshibanda et al. 2009).

As concerns the processing of external stimuli, GNW theory predicts that the initial but not the late stages of processing may be preserved in coma and VS patients. Indeed, several fMRI activation studies and $H_2{}^{15}O$ positron emission tomography (PET) studies in VS patients have shown that high-intensity electrical stimulation (experienced as painful in controls) still causes robust poststimulus activation restricted to brainstem, thalamus and primary somatosensory cortex (Laureys et al. 2002a; Tshibanda et al. 2010). Using fMRI, auditory, visual, tactile and pain-induced activations have been observed (Laureys et al. 2005; Owen et al. 2005). However, sensory areas appear to be functionally disconnected from “higher order” associative multimodal areas that fail to activate, such as, in the case of pain, secondary somatosensory, insular, posterior parietal and anterior cingulate cortices (Boly et al. 2008; Laureys et al. 2002a). The VS may thus be interpreted as resulting from a functional disconnection from the GNW circuits.

Two major predictions of GNW theory deal with the non-linearity of consciousness. First, we predict transitions between conscious and non-conscious states (intransitive consciousness) to be all-or-none in response to linear progressive increases (or decreases) of arousal, and second we predict that, in a conscious subject, access to an initially non-conscious representation should follow a sudden non-linear ignition process (conscious access). A recent study (Velly et al. 2007) recorded both cortical (scalp EEG) and subcortical (intracerebral local field potentials, LFP) activities during propofol anesthesia in Parkinsonian patients implanted with deep intracerebral electrodes. While subcortical structures showed a progressive linear decrease of the complexity (dimensional activation) of neural activity in response to progressive increase of propofol, cortical activity showed a brutal decrease of complexity. In the same vein, Ferrarelli et al. (2010) used an elegant EEG/TMS approach to demonstrate that, while a single TMS cortical pulse caused both a local early response and a late distributed pattern of cortical activity in distant areas including in particular frontal regions, the very same stimulations only caused the early local response when subjects had lost consciousness secondary to midazolam anesthesia. In VS patients, Laureys et al. (2002b) were the first to show that, while nociceptive stimuli could cause local patterns of cortical activation in somatoensory areas, only conscious subjects showed long-distance patterns of cortical activity with a strong functional connectivity between sensory areas and fronto-parietal cortices. Recently, it was also reported that loss of consciousness observed during epileptic seizures originating from the temporal lobe is a brutal event associated with a sharp increase of long-distance cortico-cortical and cortico-thalamic synchronization (Arthuis et al. 2009).

8.3 Clinical Application of the Signatures of Conscious Access

Can the observed signatures of conscious access in normal subjects be used to improve our ability to probe consciousness in DOC patients in whom behavioral manifestations are very limited? The existence of various forms of non-conscious patterns of cortical activity raises a challenging issue: how can we separate conscious and non-conscious patterns of brain activity? Progress in the cognitive neuroscience of conscious processing offers the hope of using markers of brain activity constrained by the specific properties of conscious processing to address this issue.

Using fMRI, a patient initially classified as vegetative by clinical signs showed essentially normal activations of distributed long-distance cortical networks during speech processing and mental imagery tasks (Owen et al. 2006). Recently, four more VS patients (out of 23) showed distinct cortical activation when asked to imagine playing tennis or navigating in a known place. Furthermore, one patient could voluntarily control the activation of these networks to provide yes/no answers to simple personal questions, clearly indicating some degree of preserved conscious processing (Monti et al. 2010). These important results confirm that some conscious patients are misclassified as “vegetative” and offer an empirical means of identifying them. However, they do so with a task whose relation to conscious processing is not founded in any precise theory.

In an effort to isolate such a theoretically validated scalp signature of conscious sensory processing, Bekinschtein et al. (2009) recorded ERPs to local versus global violations of an auditory regularity. As previously demonstrated (e.g., Fischer et al. 2004), when hearing a deviant tone after a sequence of repeated standard tones (sequence XXXXY), a local mismatch response was elicited non-consciously even in coma and VS patients. When this sequence XXXXY was repeatedly presented, however, such that the final tone change could be expected, the presentation of a deviant monotonic sequence (XXXXX) engendered a P3b wave in normal subjects that was absent in coma patients and in most VS patients but could still be observed in minimally conscious and locked-in patients. This paradigm, founded upon previous identification of the P3b component as a signature of conscious processing, still requires extended validation as a means of identifying residual conscious processing in patients. Recently, we reported the results of this test in a population of 31 VS patients. While most VS patients were negative on this test, we could identify 2 patients showing this neural signature of consciousness. Interestingly, these 2 patients showed unequivocal clinical signs of consciousness within the 3-4 days following ERP recording (Faugeras F et al. 2011).

Can the emerging understanding of conscious processing eventually propose novel therapeutic and pharmacological tools for patients suffering from impaired consciousness? Deep brain stimulation (DBS) in the thalamus, upper brain stem, and associated targets is advanced as a method to restore consciousness after loss of consciousness (LOC) due to severe brain injury (Cohadon and Richer 1993; Hassler et al. 1969a, b; Schiff et al. 2002, 2008; Sturm et al. 1979). Animal experimentation has demonstrated behavioral improvements when central thalamic stimulation is applied at the level of the anterior component of the intralaminar system, where neurons collect afferents from the brainstem arousal systems and connect to medial frontal cortices (Schiff et al. 2002). In a recent report (Schiff et al. 2008), electrodes were implanted bilaterally into the central thalamus of a single human subject who had remained in a minimally conscious state for 6 years following a deep traumatic brain injury. Over a 6-month period, communication, cognition, movement control and oral feeding improved during periods in which DBS was on as compared with periods in which it was off. This study is in great need of extension with more patients and with neuroimaging measures of recovery mechanisms. The GNW model predicts that improvements should relate to the reactivation of long-distance prefrontal and parietal networks, not just local thalamic effects. In VS, indeed, spontaneous recovery is accompanied by a functional restoration of a very broad frontoparietal network (Laureys et al. 1999) and some of its cortico-thalamo-cortical connections (Laureys et al. 2000). Furthermore, DTI (diffusion tensor imaging) in a patient who had been in a minimally conscious state but recovered verbal communication nearly two decades after a traumatic brain injury revealed an unanticipated axonal regrowth (Voss et al. 2006).

9 Conclusions

The project of relating subjective reports of conscious perception to objective behavioral and neuroscientific findings is now under way in many laboratories throughout the world. The GNW hypothesis provides one possible coherent framework within which these disparate observations can be integrated. It is exciting to see that this research program not only leads to novel experimental predictions in normal subjects but also, most importantly, to new clinical tools. Proving the efficacy of this approach in a broader group of patients will be a crucial endeavor for the coming years.

Acknowledgment This chapter is based in part on an earlier draft of a review article by S. Dehaene and J.P. Changeux, entitled “Experimental and Theoretical Approaches to Conscious Processing”, to appear in Neuron in May 2011. We gratefully acknowledge extensive discussions with Sid Kouider, Jérôme Sackur, Bechir Jarraya, and Pierre-Marie Lledo as well as commens on previous drafts by Stuart Edelstein, Raphaël Gaillard, Biyu He and Henri Korn. This work was supported by Collège de France, INSERM, CNRS, European Research Council and Human Frontiers Science Program (S.D.), and Skaggs Research Foundation at UCSD School of Pharmacy (J.P.C.).

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