The Dynamical Signature of Conscious Processing: From Modality-Specific Percepts to Complex Episodes

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The search for neural correlates of human consciousness in past decades has been based on different assumptions and methods. Some researchers assume that conscious functions are localized in brain circuits, and ultimately pinned down to single neuron selective firing at the millisecond range, while others search for dynamic patterns, as the synchrony of neural potentials or slow waves in brain tissue. We raise and review evidence for the hypothesis that the composition of conscious processes has a dual dynamics: (a) Information processing carried by neuronal spike trains generating modality-specific contents and (b) the formation of complex episodes by dendritic fields synchronized in multiple frequencies and interacting with the astroglial calcium wave. On the basis of this evidence, we hypothesize an explanation for the coordination of the 2 types of processes: Oscillatory frequencies compose a multiplexing mechanism promoting the insertion of specific contents into a global hydroionic standing wave in brain tissue, which feeds back on dendritic fields, in a process that takes around 2 s to form 1 unitary conscious episode. A dynamical signature of conscious processing can be identified by means of a mathematical analysis of how the faster brain rhythms are nested in the slower ones.

Keywords: consciousness, EEG, brain rhythms, astrocytes, calcium waves

The scientific study of conscious phenomena requires an interdisciplinary approach that encompasses physics, biology, psychology, and other human sciences, as well as conceptual contributions from philosophy. As conscious phenomena are directly accessible only to the first-person perspective, phenomenological considerations are well positioned to guide the investigation of consciousness (Velmans, 2009), along with sophisticated psychophysiological and brain imaging techniques (as functional MRI [fMRI] and fluorescence microscopy combined with optogenetic techniques).

A phenomenological analysis of conscious experiences (as in, e.g., Husserl, 1991; James, 1890/1983) reveals a complex of sensory and mnemonic elements combined in space and time, forming complex *episodes*. The formation of an experiential "gestalt" can be analyzed in two steps: first, the interpretation of sensory elements as an *event*, and second, the *feeling* of the event from the perspective of the experiencer (the first-person perspective; see Nagel, 1984). The entire process can be summarized as "the feeling of what happens" (Damasio, 1999). For instance, within a conscious episode, a stone building can be interpreted as a house, and a person may *feel at home* inside, if the house is (or is similar to) the place where she lives.

In the above example, a report of the recognition of the stimulus as being a house is con-

sidered to be sufficient for identifying neural correlates of the conscious experience. Nevertheless, we know from our everyday experiences that the integration of percepts in conscious episodes involves the "binding" of modality-specific contents (e.g., visual images, sounds, smells, and other sensory qualities) and their integration with mental representations derived from memories, perspectives on future events, representations of the physical and social environment, abstract concepts, emotional reactions, as well as ethical and aesthetic appraisals.

The "binding" of these components (involving several modalities, as discussed by Treisman, 1996) form a conscious "gestalt" that develops over the course of time. For example, it takes a few hundred milliseconds to see and recognize a small white ball entering a hole in the ground (a modality-specific conscious content), whereas it takes a few seconds to integrate the visually registered event in a complex episode, as follows: (a) it is a golf game, (b) someone earned a score of 82, (c) she may win the game, and (d) if she wins the game, then she will move to the first position in the ranking. To identify the perceiver's conscious episode as "The event when X won the final game of cup" requires a degree of abstraction from the visual percept, while retaining the relevant information conveyed by the visual representation.

In terms of time scaling in which dynamic processes unfold, abundant neuroscientific evidence provides support for the thesis that modality-specific conscious contents (body sensations, objects located in space and their movements, shapes, colors, sounds, smells) are formed in the range of one hundred or a few hundreds of milliseconds, as is the case in the human visual system we will discuss. Microstate theory (Lehmann, 2013), for example, identifies from the electroencephalogram (EEG) record "atoms of thought" that take a few milliseconds to be formed and change abruptly. Important lines of research using single cell recording and/or arrays of microelectrodes have succeeded in detecting firing patterns that correlate with conscious processes (see, e.g., Bachmann, 2015; Quiroga, Mukamel, Isham, Malach, & Fried, 2008).

Psychophysical studies, in turn, indicate that complex conscious episodes require around 3 s to be formed (Pöppel, 1994, 2002, 2004; Pöppel, Ruhnau, Schill, & Steinbuchel, 1990). These studies are corroborated by neuroscientific approaches, such as the slow cortical potential (SCP; He & Raichle, 2009) based on fMRI and EEG data, which relate conscious processing with slow oscillations in the range below 1 Hz. Moreover, researchers have used blood–oxygenation-level-dependent (BOLD)-type fMRI. BOLD fMRI measures differences in blood oxygenation level, to access brain correlates of conscious processing in the range of seconds (Farrant & Uddin, 2015; Price, 2012). The fMRI temporal resolution parallels closely the timing of the SCP and astroglial calcium waves (see Pereira & Furlan, 2009), critical aspects of what we will argue is the process related to the formation of free-flowing complex conscious episodes over the course of time.

It bears emphasis that modality-specific contents are not necessarily devoid of episodic implications. Nevertheless, they do not derive their experiential qualities only from the sensory information being processed. *Making sense* of an episode often includes multimodal and amodal constructs that take a longer time to be formed. These constructs can constrain the specific contents from which they are built. For example, in the color phi phenomenon, "when two colored disks are presented spatially displaced in rapid succession, it appears as if one disk moves between the two positions and changes color in the middle of its trajectory"; therefore, "a stimulus that had been presented first can even be perceived occurring after a stimulus presented later in time" (Herzog, Kammer, & Scharnowski, 2016, p. 2). In this example, the illusion of the moving disk (an episodic feature) constrains the perception of the second disk (a modality specific—i.e., visual—feature). Another example is an experimental result by Krusemark, Novak, Gitelman, and Li (2013) showing that during an induced anxious state subjects report as aversive/unpleasant the experience of stimuli previously considered to be neutral. This change in conscious experience was accompanied by changes in brain activity registered with fMRI.

In this article, we will argue that the basis for the experience of the unitary flow of consciousness resides in the continuity between the processes in the brain related to modality-specific contents and complex episodes. Kozma and Freeman (2003) and Buszáki (2006) have em-

phasized the complementarity of fast and slow brain processes, considered to be two phases in the process of brain self-organization that generates necessary conditions for the existence of conscious activity. Following this line of thought, we summarize two major goals in developing our arguments as follows.

Our first goal is to review evidence for the thesis that conscious processes are associated with dual dynamics consisting of (Hypothesis 1_a) information processing carried by neuronal spike trains that generate modality-specific contents of consciousness and (Hypothesis 1_b) complex conscious episodes formed by synchronized dendritic fields that interact with astroglial calcium waves. Our second goal is to explain the coordination of the dual dynamic processes we identified. More specifically, we hypothesize that (Hypothesis 2_a) synchronized oscillatory frequencies comprise *a multiplexing mechanism* (Buszáki, 2006; Cariani, 2004) that generates conscious event-related potentials (ERPs) by means of phase-locking of frequencies and the resulting summation of electric currents, and (Hypothesis 2_b) the multiplexing mechanism requires a spatiotemporal substrate to receive and integrate the messages carried by the synchronous oscillations. Based on findings pertaining to mental (cognitive and affective) functions carried by the astroglial network, we propose an original thesis that the SCP and related ionic waves in brain tissue are the global substrates of conscious episodes. These waves feed back on dendritic fields, modulating the resulting spike trains that reach muscles and glands and determine behavioral patterns.

Experimental Results About the Formation of Conscious Percepts in the Visual System

We begin our analysis with an examination of the formation of conscious percepts in the visual system. The study of visual consciousness in cognitive neuroscience is based on establishing correlations between three parameters: properties of visual stimuli, brain activity, and reported conscious states of the experimental subject.

As conscious systems operate in the domain of interaction with the environment, perception and action are conceived respectively as providing inputs and outputs for the conscious mechanism. The time needed for a conscious behav-

ioral reaction to a presented stimulus (the *reaction time*) is relative to the perceptual modalities involved, and proportional to the intermodal and amodal cognitive processes necessary to generate the response. Reaction times are typically shorter for single-modality signal detection, and progressively longer for multimodal integration and for tasks that require cognitive processing and/or selection of alternatives. According to classical findings obtained by Libet (1973) and Soon, Brass, Heinze, and Haynes (2008), the conscious feeling of the will to act may occur 500 ms after the beginning of the motor response. Because of this kind of temporal lag, the temporal dynamics of conscious perceptual processing cannot be accessed only by taking into consideration the behavioral responses. Pöppel and Logothetis (1986) measured reaction times to visual stimuli and calculated that perceptual processing operates in units of 30 ms. A few years later, Pöppel and colleagues proposed a model of conscious perceptual processing with two temporal constraints. The basic unit is estimated to be around 30 ms, while conscious episodes composing the "conscious present" can be extended to periods of 2 or 3 s (Pöppel, 1994; Pöppel et al., 1990).

The ERP paradigm is an experimental approach to access the timing of conscious processing. ERPs are changes in electrical voltage recorded from many sites over the surface of the scalp and time-locked to the occurrence of a particular stimulus. These electrical potentials reflect underlying neural activity, mostly dendritic graded fields. Components of the resulting waveform can be used to differentiate different cognitive conditions (Coull, 1998).

ERP components are characteristic of conscious tasks; their amplitude increases in response to stimuli that are conscious, compared with stimuli that are not. The ERP P300 and N400 components are related to working memory and/or attention functions that involve conscious processing (Coull, 1998; Knight, 1997). The timing of brain events correlated with conscious processing evoked by stimulus presentation can be found in ERP studies. We use an example of an experiment of puzzle solving, composed of the tasks of listening to or reading a question, finding an answer and then selecting one picture (among five) that best matches with the answer to the question (Pereira, Foz, & Rocha, 2015; Rocha, Foz, & Pereira, 2015). The

corresponding progression in the EEG register begins with potentials related to modality-specific contents and evolves to potentials related to the processing of multimodal and amodal conscious contents (see Figure 1).

Del Cul, Baillet, and Dehaene (2007) used an ERP paradigm to evaluate how supraliminar stimuli combined with backward masking to determine the sequence of brain events necessary to form a reportable conscious visual state. The target stimulus consisted of a single digit (a number) projected for 16 ms (a supraliminar stimulus). The mask was a group of numbers projected soon after, for 250 ms, at the same visual location. The authors varied the time interval between stimulus onset and the presentation of the mask, from 16 to 100 ms. Shorter intervals were predicted to cause backward masking by means of a perturbation of the sequence of brain events necessary to generate the corresponding conscious state, whereas longer intervals were predicted to not perturb the brain processing of the stimulus. High-density ERP recordings showed that below 16 ms, the performance was at chance level, suggesting that the presented digit was completely masked by the second. In the 16- to 33-ms interval, performance in the forced-choice task was above chance, whereas in the 33- to 66-ms interval, both the forced-choice and the (conscious) visibility ratings increased nonlinearly. Above 66 ms, there was not a significant change in visibility, and the participants consistently had conscious access to the presented stimulus. The authors looked for ERP components temporally correlated with the transition in visibility elicited by the 50-ms interval and found activity within a fronto–parieto–temporal network to be strongly correlated with the conscious phenomenon about 270 to 300 ms after target onset.

Quiroga et al. (2008) conducted a study with similarities and differences from Del Cul et al. (2007). In terms of differences, Quiroga et al. (2008) made single and multiunit recordings; in this case, measurement of axonal activity by means of invasive microelectrodes implanted in epileptic patients, instead of relying on the EEG. Second, the data secured were restricted to axonal firing in the medial temporal lobe. Third, the experimenters presented complex stimuli (pictures of faces and buildings) for longer and varied times. These differences aside, the findings across studies are similar in that the medial temporal response measured by Quiroga et al. (at approximately 300 ms after stimulus onset) occurs simultaneously with or soon after the frontal response measured by Del Cul et al. (at 270–300 ms). Still, two interpretations of this compatibility are possible: (a) Both responses (frontal and medial temporal) occur at the same time and both support visual consciousness equally, and (b) one of the responses occurs first and supports visual consciousness, whereas the other response serves another function (e.g., the Del Cul et al., 2007, response may be related to short-term memory, and the Quiroga et al., 2008, response may be related to triggering the formation of long-term memory).

Another strategy to find neural correlates of conscious processing is to identify the timeframe for the onset of oscillatory synchrony. In
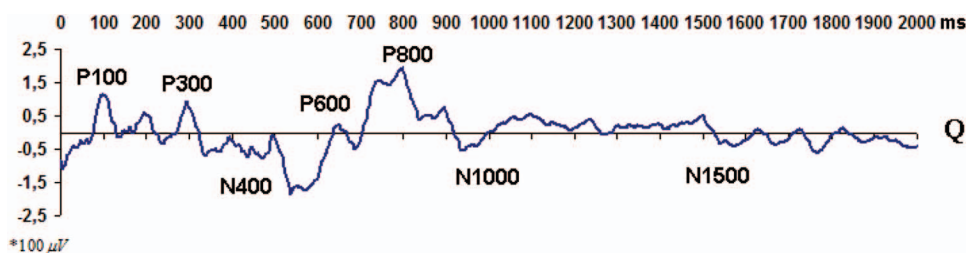

Figure 1. Temporal waveform of human conscious processing. In the task of listening or reading to a question (first section of 1,000 ms) and reasoning before making a decision (second section of 1,000 ms), a common type of waveform with a similar distribution of event-related potentials was obtained. Data was obtained with 20 scalp electrodes in 40 human subjects; individual registers were averaged. Figure adapted from Rocha et al. (2015). See the online article for the color version of this figure.

a face recognition experiment, Rodriguez et al. (1999) found that gamma (40 Hz) synchronous oscillations occurred at 230 and 800 ms after external stimulation. The first synchronous period correlated with the visual conscious processing, whereas the second period correlated with the motor response.

Melloni et al. (2007) found that an early "long-distance synchronization" of gamma occurred from 80 to 120 ms after stimulus presentation. They recorded the EEG during a delayed matching-to-sample task in two conditions: The target stimulus, a word presented for 33 ms, was either preceded or followed by a mask for each presentation. The experimenters varied luminance to render the stimulus (consciously) visible or invisible (but still processed). The matching with another word was performed 533 ms after the presentation of the target. Visible words were correctly recognized in 94.5% of the cases, whereas invisible words were recognized at chance level (52.2%). However, the behavioral measurement did not check for conscious perception at the time of the early synchronized phase; the relation of conscious visibility and the early gamma synchronized phase (considered to be a sign of conscious processing; see Rodriguez et al., 1999) recorded by the EEG was inferred from the fact that such a phase only occurred for visible words. An interpretation could be that the early synchronous phase is necessary to *prepare* the conscious visual state, which is completed later. Such a synchronous firing may be necessary to broadcast local patterns to other parts of the brain, because the integration of information required by the conscious process may depend on the interplay of local and global activities (Buzsáki, 2007).

Our interpretation of the chronology of events reported in the above studies is the following: (a) Under 80 ms after stimulus onset, stimulus-evoked receptor field responses occur in the primary sensory cortex, without conscious perception of the stimulus (because conscious perception was not reported for this time window). (b) Around 100–120 ms after stimulus onset, preconscious priming occurs, as suggested by Melloni et al. (2007). This priming phase is necessary to trigger the conscious process, but does not generate the full conscious visual state. The priming is facilitated by a transient stimulus-evoked gamma synchroniza-

tion, encompassing primary sensory, higher sensory, and associative cortical areas. (c) Between 130 and 270 ms, a stimulus-evoked, feed-forward gamma synchronous firing from sensory to associative areas occurs (as suggested by Samonds & Bonds, 2005). (d) Around 270–300 ms, sparse responses to the visual stimulus occur in higher associative areas, related to the P3 component, as recorded by Del Cul et al. (2007), and to the P300 component (Melloni et al., 2007). (e) Beyond 300 ms, reentrant signaling from higher associative back to sensory areas reach previously potentiated neuronal assemblies. Gamma oscillations become phase-locked with alpha and theta (Palva & Palva, 2007), generating brainwide coherence of postsynaptic potentials. At this moment, visual awareness of the stimulus occurs; that is, the formation of a modality specific conscious content. The reviewed data do not support the hypothesis of formation of complex conscious episodes, including the pattern of a given stimulus, in a temporal interval below 300 ms of presentation.

A Biophysical Substrate for Global Workspace Theory

Correlates of conscious episodes are not reducible to a single event or type of event, but rather involve a complex chain of distinct phases, as assumed in global workspace theory (GWT; Baars, 1988, 1997). When a conscious episode is formed several parts of the brain carry different cognitive tasks in parallel (Freitas da Rocha, Pereira, & Bezerra Coutinho, 2001). Results of the distributed activity are posted on a "blackboard" substrate and then selected, according to their relevance for the agent in the context of adaptive behavior. Selected contents compose a unitary flow, which is broadcasted to the entire system, thus promoting access to the memory and motor systems.

What is the spatiotemporal mechanism that corresponds to the computational workspace where specific contents are registered, selected, and integrated? Current neuroscience is well positioned to understand the 'binding' mechanism underlying the integration of specific contents, a process that is not directly addressed by GWT. Assuming a biological version of GWT, which relates its computational operations to

the functions of the human prefrontal cortex, Gaillard et al. (2009) used intracranial EEG to examine the brain correlates of conscious activity beyond the 300-ms threshold. The researchers found that a sustained potential is required for conscious word processing. Additionally, they reported sustained spectral power and late increases in long-range phase coherence (Gaillard et al., 2009). These findings imply that multimodal and amodal contents are formed closer to the range of $1+$ s after the presentation of the stimulus.

The SCP described by He and Raichle (2009) also implies that conscious processing occurs in the range of seconds. The authors propose that the physiological unit that instantiates conscious processes is a whole-brain fluctuation with a duration of less than 1 Hz, corresponding to a time window with the duration of more than 1 s. The conclusion from both Del Cul et al. (2007) and Quiroga et al. (2008) should be that conscious activity extends beyond perceptual snapshots in the millisecond range into a more complex processing in range of seconds, the result of which corresponds to the phenomenological richness of our conscious experiences. In other words, the spatiotemporal workspace responsible for the formation of conscious episodes involves a progressive integration of processed patterns into complex episodes, taking a few seconds to be completed.

Two additional questions relevant to the formation of conscious episodes with respect to spatial and temporal integration are as follows: (a) How are multiple neuronal assemblies spatially coordinated? and (b) How is the activity of the assemblies shaped in time to acquire the global pattern of amplitude modulation found in the well-known progression of ERPs? Answers to these questions require an explanation of brain mechanisms involved in the generation of conscious episodes, as discussed in Rocha, Pereira, and Massad (2005).

Recent empirical findings point to a neuroastroglial mechanism that fulfills the basic requirements of both (spatial integration, covering all brain systems activated in conscious processing and temporal segmentation, imposing a dynamical signature of conscious processing in brain tissue. Fields (2009, 2013) has made the case that glial cells are central players in the brain processes that support mental functions. Together with other types of glial cells, oligo-

dendrocytes and microglia, astrocytes compose a signaling network parallel to neurons. Fields et al. (2014) stated that these cells "are well suited for participating in complex cognitive functions requiring broad spatial integration and temporal segmentation" (p. 426).

Astrocytes are the glial cell type with larger communication capabilities, forming large and continuous networks in the brain. The astrocyte network does not have synaptic clefts, but gap junctions that allow the intercellular flow of ions and molecules. They have channels that communicate with the extracellular space, controlling the homeostasis of transmitters and ions in brain tissue (Verkhratsky, Nedergaard, & Hertz, 2015). A major pathway for astrocytes modulating neuron activity is the control of potassium uptake (Wang et al., 2012). Astrocytes are connected to arterial capillaries and mediate the transport of glucose and hormones from the blood to neurons. They also have receptors that bind with transmitters released by the neurons, and release transmitters that bind with neuronal receptors (see Pereira & Furlan, 2010).

The participation of astroglial calcium waves in the spatial and temporal integration processes that supports the formation of conscious episodes is compatible with neuroscientific evidence. In the spatial integration process, astrocytes are involved with the genesis of oscillatory synchronies (Fellin et al., 2004; Halassa, Fellin, Takano, Dong, & Haydon, 2007; Poskanzer & Yuste, 2016) and the formation of global tissue waves related to the conscious ERPs we have reviewed in previous sections. In the temporal integration process, astrocytes are in charge of modulating neuron dendritic potentials, sustaining or depressing their activity, as discussed in the previous section. Glutamate (Glu) released from astrocytes to postsynaptic neurons binds to N-methyl-D-aspartate (NMDA) receptors that drive slow inward calcium currents (De Pittà & Brunel, 2016), causing a delayed depolarization and an increase of calmodulin-dependent protein kinase subtype II phosphorylation and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA; a membrane receptor that binds with Glu and allows the entry of sodium ions into the neuron) excitability, or, alternatively, triggering a process of long term depression (Pereira & Furlan, 2010).

The existence of astroglial calcium waves in vivo, as well as their biological and cognitive functions, are debated issues, which are recently trending to a "third wave" of thinking (Bazargani & Attwell, 2016) that favors those who argue for the view that calcium waves do contribute to mental activity, besides executing other anatomical and physiological functions (for a review of these functions, see Shigetomi, Patel, & Khakh, 2016). Calcium waves have been imaged in vivo (Resendez et al., 2016) with fluorescence microscopy and optogenetic techniques. An exploratory model of the formation of these waves was presented in Pereira and Furlan (2010). In the model, the "domino effect" describes a process of propagation of the astroglial calcium wave from a single location, bifurcating and being boosted by means of purinergic signaling and phosphorylation of molecular motors that generate traveling ionic waves in brain tissue. The "carousel effect" refers to reciprocal activations of dendritic fields and astroglial calcium waves; synchronized local field potentials generate an ensemble of small calcium waves in the adjacent astrocytes; these small waves interact and generate a global standing wave (characterized by the vibrational energy of the ions, instead of displacement or change of concentration) by means of constructive interferences; finally, the global wave feeds back on the local field potentials, modulating them and influencing the resulting behavior.

The involvement of astroglial calcium waves in the construction of conscious episodes is compatible with experimental results. Smeal, Economo, Lillis, Wilcox, and White (2012) demonstrated the existence of ultrafast traveling waves of calcium transients crossing large distances in the brain. Calcium ion patterns in astrocytes present "rich information content" (Zheng et al., 2015). Brazhe, Mathiesen, Lind, Rubin, and Lauritzen (2014) have developed methods for analyzing data from two-photon microscopy of calcium waves to reveal the information patterns being processed by the calcium wave. Additionally, Croft et al. (2016) developed a probabilistic method to understand their encoding of stimuli strength (i.e., semantic salience). Pannasch and Rouach's (2013) review focuses on mechanisms of astrocyte information processing implemented by gap junctions—connections between astroglial cells that

allow and boost the traffic of calcium waves—and hemichannels—connections between astrocytes and extracellular fluid that allow the traffic of ions and molecules. The informational gates of the network are controlled by the *connexin* family of proteins. These functional and structural features suggest that calcium waves in the astroglial network are capable of processing information in support to the formation of conscious episodes.

Several independent lines of evidence have related astroglial function to conscious perception (as argued in Pereira, 2012, 2013). Schummers, Yu, and Sur (2008) found that astrocytes in the visual cortex are more sensitive to some external stimuli than neurons. Zhang et al. (2016) claim that human astrocytes respond robustly to Glu, which carries sensory messages and impacts conscious activity. These findings imply that early in the sensory cortex the astrocyte network mediates the interpretation of modality-specific stimuli (see also Asada et al., 2015; Chen, Sugihara, et al., 2012). Besides reacting to sensory glutamatergic stimulation, astrocytes also react to electrical stimulation of the brain, mediating conscious cognitive and affective effects (Etiévant, Lucas, Dkhissi-Benyahya, & Haddjeri, 2016) confirming a classical finding that glial cells in the mammalian brain responds to electric stimuli (Tasaki & Chang, 1958).

Neurons activate astrocytes and in turn astrocytes modulate neurons. The modulation exerts effects on learning, memory, emotional responses and behavior. In this regard, Takata et al. (2011) found that astrocytes mediate cholinergic neuromodulation into cortical plasticity, and Ding et al. (2013) found that astrocyte calcium waves are activated in vivo by norephinephrine. Pabst et al. (2016) demonstrated that astrocytes mediate the cholinergic modulation of hippocampal inhibitory neurons, influencing memory formation (for the role of astrocytes in memory, see Robertson, 2013).

As conscious activity is a state-dependent process (see Lehmann, 2013), when the physiological state of the brain changes, conscious experience also changes. Neural plasticity (the mechanism of structural changes in synapses) allows the reshaping of synapses according to conscious experiences. The astroglial modulation of synapses in neural plasticity phenomena indicates a relation between the activity of these

cells and cognitive processing (Dallérac & Rouach, 2016). Han et al. (2013) inserted human astrocytes in the mouse forebrain and found an improvement of their learning capabilities and cognitive performance, and Lee et al. (2014) determined that toxic selective deactivation of astroglial functions impairs recognition memory; considering that neurons were not impaired by the toxin, it is legitimate to conclude that these conscious functions were carried by non-neuronal cells in the brain. Additionally, astrocytes appear to modulate *critical neuronal integrative features*, such as baseline visual responses and orientation selectivity to visual stimuli (Perea, Yang, Boyden, & Sur, 2014).

Astrocytes appear to be involved in the instantiation of emotional feelings and psychosomatic stress responses (Pearson-Leary, Osborne, & McNay, 2016) associated with conscious episodes, as in the case of chronic neuropathic and inflammatory pain (see Chen, Kress, et al., 2012, 2014; Ji, Berta, & Nedergaard, 2013). Bull et al. (2014) found that astrocytes mediate neural processes of reward and motivation (related to conscious sensations of pleasure) at the *nucleus accumbens*. Researchers have related reduced Glu uptake in astrocytes to anxiety (Zimmer et al., 2015) and found that astrocytes are involved in the generation of the effects of hormonal changes on conscious processing. Alterations of brain activity leading to the loss of consciousness, or to an abnormal pattern of construction of conscious episodes (in the case of mental disorders), have been closely related to the activity of the astrocyte network. Thrane et al. (2012) found that astrocytes, compared with neurons, are more sensitive to three commonly used general anesthetics, implying that loss of consciousness caused by the drugs begins with the impairment of astrocyte activity. Sfera, Osorio, Price, Gradini, and Cummings (2015) argue that conscious delirium derives from a combination of cholinergic inflammatory processes and astroglial function failure. The discovery of astroglial mediation of neuroinflamatory processes suggests the involvement of these cells in the impairment of related conscious processing, such as the loss of recent memory and reduction of conscious cognitive functions in Alzheimer's disease (Osborn, Kamphuis, Wadman, & Hol, 2016).

Taking into consideration the above experimental results, the role attributed to the astroglial network as a central mechanism of spatial integration and temporal segmentation of brain activity does not conflict with GWT, but, to the contrary, supplements Baars' theory in contending that the spatiotemporal global workspace is in the domain of neuro-astroglial interactions. How are unitary conscious episodes formed from modality specific, multimodal and amodal contents? The roles of the prefrontal cortex and the SCP are clues to the answer, but knowing that they play some role is not tantamount to providing a theoretical or mechanistic account of how information processing is executed by brain cells. The same kind of limitation is found in the information integration theory of consciousness (Tononi & Koch, 2008), because this theory provides a formalism for detecting information integration, but does not address the brain mechanism that is responsible for the operation.

Finding an experimental answer to the question is difficult because investigating the question requires the usage of different methods of measurement of brain activity. Modality-specific conscious contents are generated by the interplay of spiking patterns elicited by information external to the central nervous system with dendritic fields that match them with previous states of the system. The spiking patterns can be measured with tiny electrodes placed at the axon of neurons, or electrode arrays that capture firing patterns. Dendritic fields can be measured with the orthogonal electromagnetic signal that is registered by electrodes places at the scalp, or by means of invasive electrodes that measure differences of potential around the dendrites, the local field potentials (LFPs; see discussion in Pereira and Furlan (2009). The localization of activity can mapped with fMRI with temporal resolution in the range of seconds. Calcium waves can be imaged with two-photon microscopy, but require a hole in the skull to detect the optical signal.

According to Cariani (2004), Buzsáki and Draguhn (2004), and Buszáki (2006), conscious processing is supported by multiple brain rhythms (neural oscillations, the corresponding electric currents and orthogonal magnetic fields, and their registers as EEG waves), composing a multiplexing mechanism. Neural oscillations in a single frequency cannot support the "binding" of multi-

dimensional objects (Goldfarb & Treisman, 2013). Evidence for simultaneous multitasking can be found in an analysis of data by means of mapping the distribution of frequencies. Different frequency bands in the same cortical regions (Palva & Palva, 2007) imply that neuronal assemblies running at different frequency cycles contribute to the formation of the 2-s waveform, in a cooperative action of a large number of cell assemblies. The 2-s interval corresponds to a whole-brain cycle of 0.5 Hz. Nested in this cycle, we find the SCP with 1 Hz and the nested EEG waves with different frequencies. The 2-s waveform, corresponding to the whole cycle of the calcium wave, contains two cycles of the SCP, which can (roughly, for the purposes of this paper) be analyzed as: in the first second, the formation of the calcium wave, and in the next second the calcium wave feeds back on the ensemble of dendritic fields that generated it.

Phase-locking means a temporal coincidence of oscillations that occur at different frequencies. Considering that the EEG register is determined by a summation of currents from many internal sources generating the orthogonal electromagnetic fields that reach the scalp (Buzsáki, 2006), phase-locked frequencies are likely to determine the main changes in amplitude. Neurons at the cortical columns are disposed perpendicularly to the cortical surface and because of that the local ionic currents i_i of the neurons of each column are summed up. Activity of adjacent synchoronously activated columns in a certain cortical area generate n local ionic currents i_i, then a huge number n of local ionic currents i_i that are summed up in a large resulting current $i_r = \sum_{i=1}^{n} i_i$ that propagate to the skull creating an electrical field $v_j(t) = wj^*i_r$ under each electrode e_j (positioned outside the skull) that may be amplified and recorded. The value of $v_j(t)$ depends on the value of the electrical resistance between the electrode and the site of the activated columns. If columns at different cortical areas are simultaneously activated then $v_j(t)$ becomes dependent on the activity at all these distinct areas, the contribution of each of them depending on the distance between the area and the electrode.

Phase-locking of the frequencies is likely to give a stronger contribution to the EEG, because the temporal coincidence of the oscillations implies the summation of currents at specific moments of time. For instance, the P300 is formed by the completion of the first cycle of delta, summed with the completion of two cycles of theta, five cycles of alpha, 10 cycles of beta, and more contributions from gamma. The combinations of phase-locked frequencies during repeated cycles within 2 s generate the observed ERPs, as in the example presented in Figure 2.

According to the above reasoning, the progression of ERPs is not a random process, but follows precise mathematical ratios. The same ERPs are present in any multielectrode register of brain activity during the performance of conscious tasks. The mathematical ratios—to be identified with precision with the progress of neuroscience—comprise *a dynamical signature of conscious processing*.

It may be useful to speculate to reveal the potential of mathematically analyzing the dynamical signature. Buzsáki (2006, p. 354, footnote 41) analogizes the ratios with respect to the Fibonacci series. To illustrate this kind of mathematical pattern, the progression of frequencies during the 2-s time when a conscious episode is formed can be covered by the recursive equation $Y = 2X + 0.5$. Beginning with a frequency of 1 Hz (corresponding to the SCP, and also to the formation of calcium waves in brain tissue), we have for the first six recursions the series: 2,5; 5,5; 11,5; 23,5; 47,5 and 95,5 Hz, which roughly correspond to brain rhythms involved in conscious processing. These rhythms are as follows: delta (δ), frequencies smaller than 4 Hz; theta (θ), frequencies between 4 and 7 Hz; alpha (α), frequencies between 8 and 13 Hz; beta (β), frequencies between 16 and 30 Hz; slow gamma (Sγ), frequencies between 25 and 50 Hz; and fast gamma (Fγ), frequencies above 90 Hz. This kind of approach was anticipated by Kozma and Freeman (2003) and Buzsáki (2006, pp. 369–370; see also Buzsáki, 2006), who have suggested that a recursive operation underlies the brain self-organizing oscillatory activity necessary for conscious experience.

Operative Mechanisms in the Formation of Conscious Episodes

Based on the above evidence, we propose a physiological mechanism for the "broad spatial integration and temporal segmentation" processes (Fields et al., 2014) necessary for the formation of conscious episodes. In the central nervous system, perceptual processes begin with the stimulation of an ensemble of special-
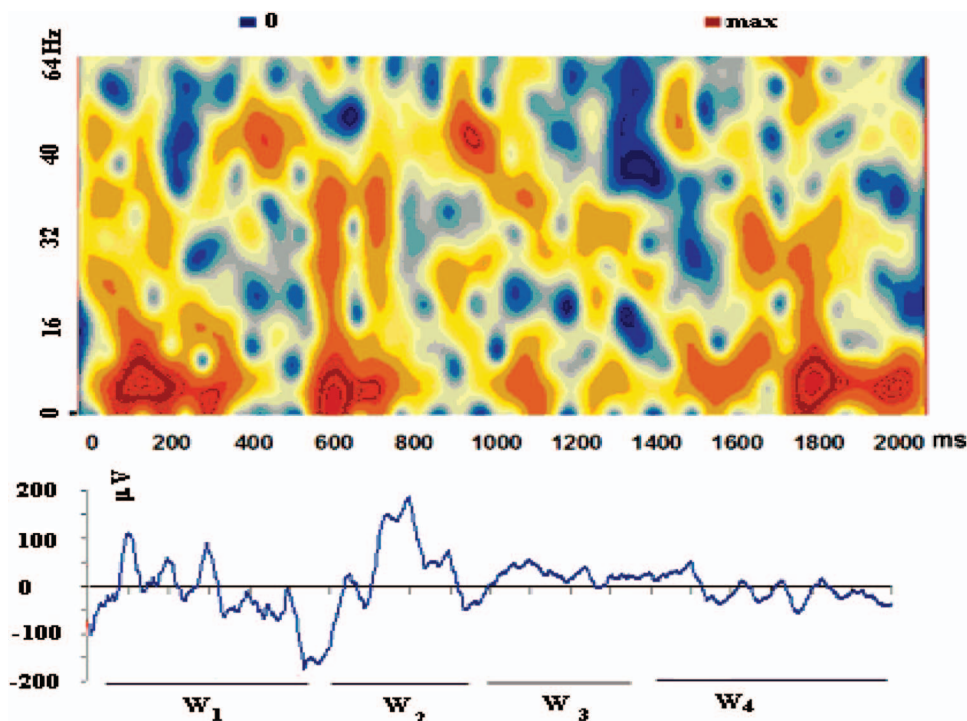
Figure 2. An example of electroencephalogram power spectrum displaying summation of currents in all frequencies. Top: Variation of the power of frequencies (Hz) in time (ms). Conventions: blue (darker) = minimum amplitude; red (lighter) = maximum amplitude. For instance, at 600 ms, there is phase coupling and amplitude summation of several frequencies, from 1 to 40 Hz. Bottom: Total amplitude (μV) variation in time, displaying four types of amplitude-modulated wave patterns $W_{1,2,3,4}$, corresponding to the steps in the formation of a conscious episode: W1 = processing the question, W2 = finding an answer; W3 = processing the pictures, and W4 = choosing a picture that best matches the answer. (Original figure made with data from Rocha et al., 2015.) See the online article for the color version of this figure.

ized receptive fields in primary sensory areas, by means of afferent spike trains, or by an endogenous brain signals that excite them beyond baseline. Each sensory neuron (or each small-scale functional assembly in cortical tissue) responds to one aspect of the stimulus.

LFP are complex phenomena reflecting simultaneous slow synaptic activities of neuronal populations. Departing from the initial excitation that produces an ensemble of LFP spatially distributed in primary cortical areas, neuronal mechanisms promote the amplification of the signals necessary for their access to consciousness. In recurrent circuits, excitatory loops are formed: initial excitatory postsynaptic potentials (EPSPs) generate spike trains that activate other neurons that generate spike trains that reinforce the initial EPSPs (Freitas da Rocha et al., 2001). Glu excitatory

loops are counterbalanced by the activation of inhibitory interneurons. Oscillatory synchronies at different frequencies produce "carrier waves" (Freeman, 2003) that allow the modulating signal to be broadcasted to the entire brain. The broadcasting benefits from the brain's "small-world" architecture, a pattern of connection that allows signaling from any node to any other node of the network in a few steps (see Baars, Franklin, & Ramsoy, 2013; Buszáki, 2006; Shanahan, 2006, 2012). In this kind of network, locally processed patterns reach a vast neural assembly by means of a few steps covered by action potentials.

The above mechanisms (recurrent networks and oscillatory synchrony) need the collaboration of the astroglial network. The insertion of dendritic patterns in synchronous carrier waves requires them to be *sustained* during a sufficient

time period (Buszáki, 2006; Pereira & Furlan, 2007). Each LFP that participates in generating a conscious episode should be sustained after the decay of sensory stimulation. These activities include the formation of excitatory and inhibitory postsynaptic potentials, membrane afterpotentiation, and recurrent signaling from associative areas; however, all these mechanisms are not sufficient to sustain the EPSP up to 2 seconds, allowing the inclusion of the sensory pattern in a conscious episode. Another causal factor is necessary to induce and support synchronous oscillations, allowing the phase-locking discussed previously. This factor was called *metapotentiation* and related to neuron–astrocyte interactions (Pereira & Furlan, 2007). Metapotentiation is the sustaining of dendritic graded potentials up to 2 seconds by astrocytes, *exclusively* for the conscious function. In the absence of consciousness, this activity would not occur: the EPSP decays after 150 ms, when the excitatory input fades out; or after 300 ms, when recurrent signaling also fades.

A description of common mechanisms of postsynaptic activity will clarify when and how metapotentiation enters the scene. Presynaptic axonal spikes contribute to generate EPSPs by releasing excitatory neurotransmitters at the axon terminal to bind with postsynaptic membrane ionotropic receptors. This is the usual pathway by which an increase in presynaptic firing rates engenders increases in postsynaptic excitation. However, studies on subliminal perception (e.g., Murphy & Zajonc, 1993) reveal that the temporal duration of the presentation of a stimulus is important to determine if it is conscious or unconsciously perceived. A visual stimulus presented for only 5 ms and followed by a mask is not consciously perceived, although it may have unconscious priming effects. This requirement implies that the existence of incoming signals is not sufficient for perceptual consciousness, because the excited neuronal population returns to baseline or becomes hyperpolarized by an inhibitory interneuron soon after receiving the signal and propagating it to other brain areas.

Several molecular mechanisms of neurons are known to be involved in sustaining of dendritic fields, such as (a) the interaction of different kinds of membrane receptors, (b) the opening of voltage-dependent channels (ion channels that open when the membrane potential reaches a threshold), and (c) the action of neuropeptides, a kind of hormone secreted by brain cells and responsible for triggering basic sensations, as hunger and maternal care. However, none of these mechanisms can sustain dendritic potentials beyond 150 ms (see discussion in Pereira & Furlan, 2007). Considering that an action potential lasts around 5 ms (Hochner, Klein, Schacher, & Kandel, 1986), the addition of time intervals required for the series of neuron-to-neuron signaling required in the task (e.g., from retina to thalamus, and then to occipital, parietal, temporal and frontal cortices, and back to occipital if needed) hardly surpasses 100 ms, whereas most conscious ERPs are from 300 ms forward.

The shape of ERP progression in the 2-s time interval is a whole-brain temporal waveform with amplitude variations, but not small sequential excitations. Although neuron cognitive mechanisms are sufficient to broadcast a locally processed pattern, the shape of the amplitude modulated waveform containing the ERPs suggest that a common substrate is involved. Recent findings from astroglia research indicate that these cells participate in glutamatergic tripartite synapses (Haydon & Carmignoto, 2006), contributing to the onset of synchrony (Fellin et al., 2004). Considering that consciousness requires the coordination of local and global patterns of brain activity, experimental findings qualify neuro-astroglial mechanisms to be the link between local and global brain activities.

In the previously proposed model (Pereira & Furlan, 2007, 2009, 2010), which is based on a review of experimental results, the excitatory period supporting consciousness begins with presynaptic neuronal Glu release and binding with postsynaptic AMPA. The opening of this ionotropic receptor triggers several excitatory activities, such as the opening of NMDA channels. NMDA is another ionotropic receptor, which depends on both Glu and membrane depolarization to be opened, letting calcium ions from the extracellular milieu to enter the neuron. This is considered to be the initial step in the formation of long-term memory. While the interneuronal glutamatergic excitation lasts, transmitters released by the presynaptic neuron also bind with astroglial receptors, inducing calcium waves. These small waves, produced at the astrocyte processes, interfere and generate larger waves by means of constructive interfer-

ence. These waves can, in turn, promote the release of astrocytic Glu (Glu released from astrocytes to neurons), which binds with neuronal receptors. The opening of these receptors elicits slow inward currents of calcium ions in the neurons. These ions enter the cell and bind to calmodulin and calmodulin-dependent kinase II, two calcium receptors, which completes the sustaining cycle by phosphorylating AMPA receptors and keeping the neuron at excited (depolarized) states. Astrocytes also activate potassium uptake receptors that control the extracellular concentration of potassium. The conjoint effect of these actions is that astrocytes modulate local fields (Tewari & Parpura, 2016), determining the timing of the spike trains generated by neurons and influencing the neuronal control of muscles and glands.

In the Pereira and Furlan model, the processing cycle from neurons to astrocyte and back to neurons putatively corresponds to the generation of a phenomenal conscious episode. There are complementary approaches to the same phenomena, as Freitas da Rocha et al. (2001) and Rocha et al. (2005), proposing that quantum computations triggered by calcium ion entry in a distributed population of neurons supports the process of information integration that generates conscious episodes, but here we focus exclusively on the putative function of the astroglial calcium wave in the context of neuroastroglial interactions.

Broadcasting requires a common receptor to integrate the signals. What is the *substrate*, or the *receptor system* that receives the multiplexed signals carried by synchronized neurons in different and combined frequencies? In the Baars' GWT model, the receptors are the same neurons that processed the specific signals, but it is not clear how the integration occurs. We assume *a common substrate*: the brain tissue *hydroionic wave* (an energy standing wave composed by ions in the gel formed by water interacting with proteins; see Fernandes de Lima & Pereira, 2016). Neurons cannot propagate this kind of wave, because they are separated by the synaptic cleft, where the electrical signal is transduced to the chemical signal.

The conjecture that glial cells support a slow energy wave that crosses brain tissue has been raised for decades. Forbes, Renshaw, and Rempel (1937) argued that slow brain waves are not produced by a summation of axonal spikes.

Galambos (1961) originally proposed the participation of astrocytes as a medium for the slow propagation of brain potentials based on his experimental work: "an evoked slow wave could not possibly be a summation of nerve-cell electrical activity . . . we hold the glia cells responsible for the slow waves and neurons for the spikes" (Galambos, 1961, p. 132). In the introduction to the first book on astrocyte information processing supporting mental functions, Hansson, Olsson, and Rönnbäck (1997) wrote that because "astrocytes are intimately connected to the synaptic region . . . determining their role in the forming of the various EEG-signals is an intriguing matter" (p. 10). How does the astroglial calcium wave have a complementary role in the formation of the episodes? Although neural communication is sufficient to promote the broadcasting of conscious contents in the 100-ms range, the formation of complex episodes requires the integration of the patterns by a substrate with the property of allowing multidirectional interference. Axonal communication by means of action potentials are point-to-point and lead to an infinite transmission of binary pulses (firing/not firing) without a common target where the messages could be fused as the feeling of the whole episode. Dendritic fields synchronized at several different frequencies need such a *common substrate* with the capacity of nesting them in a regular mathematical proportion (the "dynamical signature").

The reason why slower waves compose the required substrate is simple. The temporal cycles of faster frequencies cannot embed the slower ones, but the slower ones can embed the faster ones. The slow potential with period with the duration of 1 s, and the astroglial calcium wave, with a period of 2 s, possibly operate as the common substrate where the patterns processed by distributed neural circuits are integrated.

In the big picture of brain function we are proposing (see Figure 3), the calcium wave assumes the role of the "searchlight" (attributed by Crick, 1984, to the thalamic complex) that highlights a part of brain-processed information, which becomes conscious. In this picture, being broadcasted is a necessary, but not a sufficient condition, for a pattern to be included in a complex conscious episode; the sufficient condition (when taken conjointly with the nec-
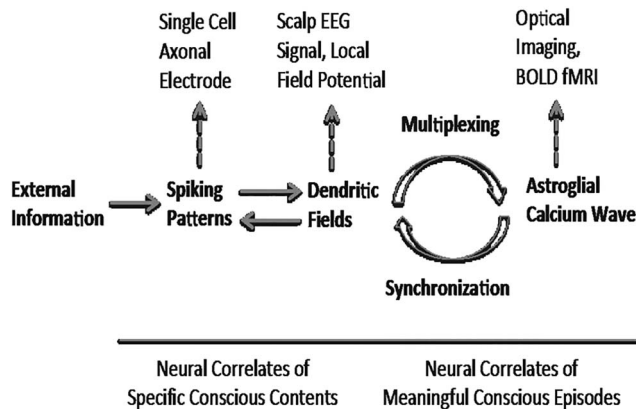
Figure 3. Dynamics of conscious processing: The flow diagram shows the main steps of conscious processing in the human brain. It is composed of two kinds of process, one that corresponds to the formation of modality-specific conscious contents (the interplay of spiking patterns with dendritic fields), and the other that corresponds to the formation of complex episodes with the duration of approximately 2 s.

essary one) is being embedded in the SCP and respective astroglial calcium wave.

According to the theoretical framework displayed in the figure, complex conscious episodes are generated by cyclical interchanges between a spatially distributed ensemble of dendritic fields and astroglial calcium waves. The cycles begin with the induction of local waves by means of dendritic fields; these waves interfere constructively, forming a global wave that feeds back on the ensemble of neurons, modulating their activity and influencing behavior. The waves can be detected by means of optical techniques, and indirectly by means of BOLD fMRI; astrocytes control the arterial blood flow that determines the patterns of fMRI registers (see Pereira & Furlan, 2009).

Concluding Remarks

We reviewed findings that provided evidence for neural correlates of consciousness in the ranges of milliseconds and seconds, and sketched an explanation of the mechanism connecting the fast distributed processing of modality-specific contents and the relatively slow integration and formation of conscious episodes. In regard to the latter, we argued that the symphony of brain rhythms shapes a brain tissue hydroionic wave that supports the subjective experience of complex conscious episodes.

Our theoretical framework affords some predictions.

(a) Once the dynamical signature of conscious processing is precisely defined, specific spatiotemporal amplitude-modulated patterns present in the EEG can be associated with specific kinds of conscious processing. Two examples are recent findings by Nieminen et al. (2016), showing that during non-REM sleep (a phase of sleep without conscious activity, i.e., mostly without dreams) there is a negative deflection of the EEG with a dominance of delta rhythms in the posterior associative cortex, while in REM sleep (with reported dreams) the same regions display faster rhythms; and the findings by Beukema et al. (2016), showing altered ERP auditory progression in vegetative and minimal conscious state patients.

(b) The dynamic patterns of hydroionic waves/oscillations found in optical registers of brain calcium waves have a complex structure able to support the neural aspect of "qualia" ("neural" includes both neuronal and glial activities). Using the three-pillars method of cognitive and affective neuroscience (the combination of registers of brain activity with controlled stimulation and subjective report of experiences by the subjects), statistically significant correlations between kinds of "internal" mental states (not directly related to stimuli in the body and

external environment) and kinds of hydroionic patterns at the mesoscopic scale can be found.

(c) Recent results point toward the possibility of developing methods for in vivo control of the waves/oscillations for the treatment of disorders of conscious emotion, improvement of cognitive and motor performance, and aesthetical experiences. For instance, effects of electric and magnetic brain stimulation are arguably mediated by astroglial calcium waves (Monai et al., 2016; Ruohonen & Karhu, 2012).

(d) If a digital machine is endowed with a biological tissue that instantiates the right kinds of hydroionic waves, then it should be conscious of the information it processes, as discussed in Pereira and Almada (2011).

As the brain correlates of each step of conscious processing is measured by means of a different technology, their respective results should be related to afford a full picture of the complexity of brain cognitive and affective functions. An important application of our theoretical framework is the comparison of simultaneous astroglial calcium with EEG spatiotemporal waveforms during conscious processing, taking into consideration phenomenological reports to identify the role of these waveforms in conscious experience. The fine analysis of astroglial calcium and EEG waveforms in vivo during conscious processing can reveal unknown details about how the brain carries the processes, and facilitate the development of more specific and accurate models in the field of the psychology of consciousness. These scientific tasks demand more intensive efforts in the near future to promote the construction of realistic models of conscious processing in computational neuroscience, benefiting from the large database that is emerging from research on glial cells and their functions.

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