

Review

Theta–gamma coupling as a ubiquitous brain mechanism: implications for memory, attention, dreaming, imagination, and consciousness

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Brain rhythms are known to play a relevant role in many cognitive functions. In particular, coupling between theta and gamma oscillations was first observed in the hippocampus, where it is assumed to implement a code for organizing multiple items in memory. More recent advances, however, demonstrate that this mechanism is ubiquitously present in the brain and plays a role not only in working memory but also in episodic and semantic memory, attention, emotion, dreaming, and imagination. Furthermore, altered mental states and neurological disorders show profound alterations in the theta–gamma code. In this review, which summarizes the most recent experimental and theoretical evidence, we suggest that the substantial capacity to integrate information characteristic of the theta–gamma entrainment is fundamental for implementing many conscious cognitive processes.

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Introduction

Brain rhythms are periodic fluctuations of the electric fields in brain regions due to temporal synchronization among groups of neurons. Many studies in the past decades provide convincing evidence that brain rhythms and their

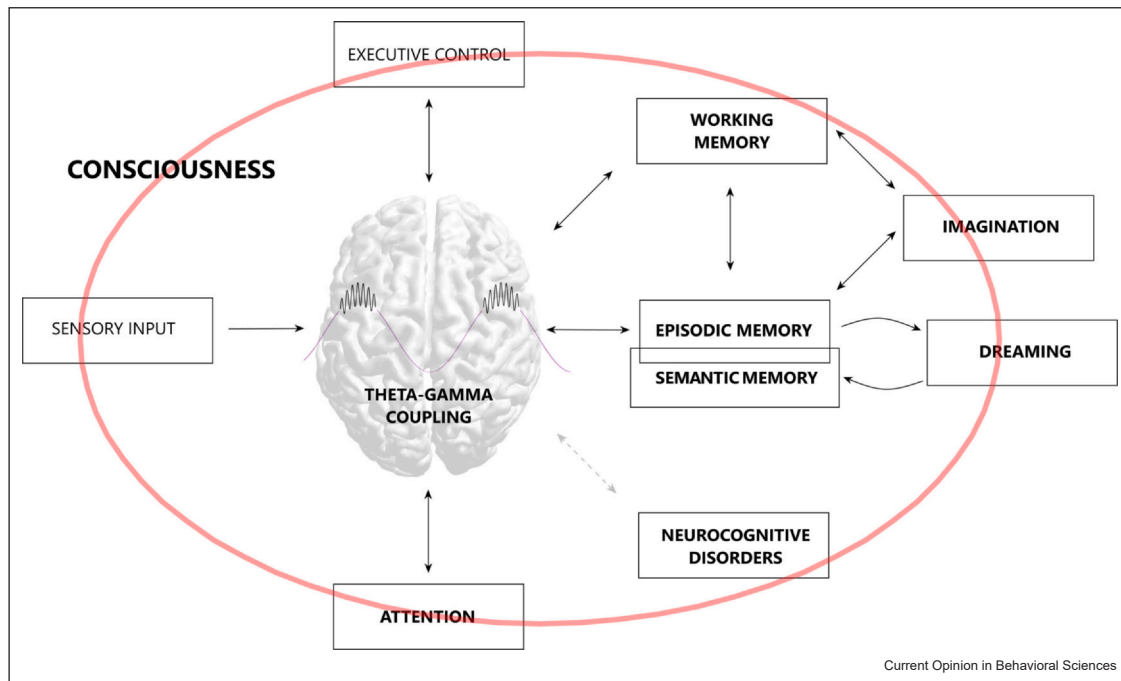
interaction (especially between theta and gamma) play a fundamental role in different mental processes [1]. The first interplay between theta (4–8 Hz) and gamma (> 30 Hz) oscillations was observed in the hippocampus, where it is assumed to implement a code for organizing multiple items in memory. Over the years, long-range phase synchronization between these different neural oscillations has come into the focus of consciousness research as a possible correlate of conscious perception [2–4]. The coupling between slow and fast oscillatory signals may, in fact, represent a primary mechanism for accessing information, integrating it on a large scale, and constructing a global workspace that, according to some influential theories, is considered essential for consciousness [5]. Consistently, the administration of anesthetic drugs (which induce altered states of consciousness) causes impairments in responses mediated by cross-frequency coupling (CFC) between theta and gamma rhythms [6].

In particular, the relationships between consciousness, memory, and endogenous attention are still the subject of active research. Some studies argue that working memory (WM) and attention are necessary mechanisms for supporting consciousness in humans [5], and they have also recently been used as markers to identify consciousness in animals correctly [7]. However, not all current theories of consciousness support this idea (for a recent comparison of them, see Refs. [8,9]). Furthermore, episodic and semantic memory is the basis of our autobiographical experience and daily behavior; hence, understanding how these processes work together and are interrelated could be essential for comprehending consciousness.

In this review, we summarize recent experimental and theoretical evidence linking the theta–gamma code with working, episodic, and semantic memory, attention, and emotional states. Then, we further analyze the possible role of this mechanism in imagination and dreaming and its implication in the etiology of neurological diseases or altered mental states. Finally, we briefly discuss the need for a deeper understanding of its causal neural mechanisms, highlighting how computational models can play a vital role in this respect.

At present, there are not sufficient hints to sustain that theta–gamma integration is a *necessary* prerequisite for

Figure 1



The different cognitive functions that are affected by the theta and gamma rhythms. In most cases, conscious experiences are produced during these functions. However, consciousness does not necessarily cover all aspects, and some unconscious processes are possible.

consciousness. However, as documented below, the capacity to process information typical of the theta–gamma entrainments is crucial in many different cognitive processes related to consciousness. Accordingly, we suggest that a large portion of our conscious mental experience is supervised by this ubiquitous integrative mechanism. A graphical summary can be found in [Figure 1](#).

General mechanism and working memory maintenance

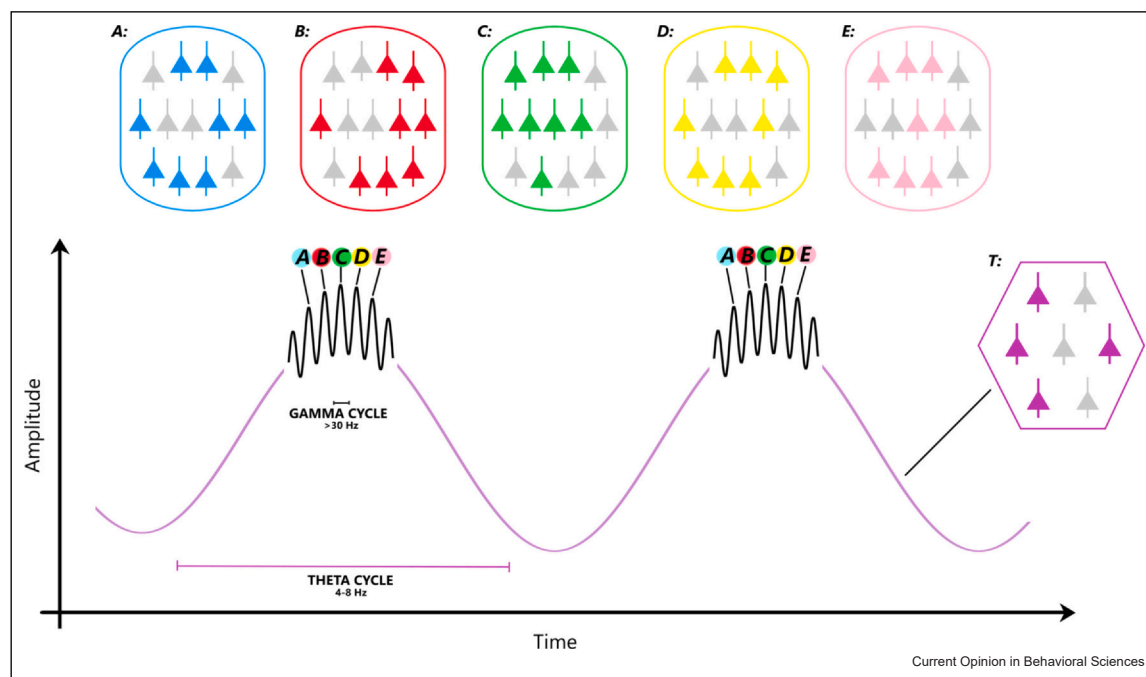
The first idea of the theta–gamma coupling originated from studies in the hippocampus, particularly on place cell firing when a rat moves on a labyrinth [10]. The common idea is that this code provides a mechanism for representing and maintaining multiple items in memory. During WM maintenance, each gamma cycle encodes the elements of an individual memory item, while multiple items can be ordered sequentially along the phase of a modulating theta wave. The general mechanism is depicted in [Figure 2](#). In recent years, new results have been gathered showing a relationship between WM capacity and the theta–gamma code not only in the hippocampus (for the hippocampus, see Ref. [11]) but also in different brain regions.

Several electroencephalography (EEG) studies (most of them summarized in Ref. [12]) demonstrate a clear association between WM and theta–gamma coupling using

different tasks (pictorial recognition tasks, verbal tasks, delayed match-to-sample visual tasks, etc.) involving the frontal, parietal, occipital, and posterior cortices. Biel et al. [13] stressed that cross-frequency phase synchronization between theta and gamma rhythms in posterior regions serves matching processes between mental templates (i.e. predictions) and expected sensation. Fernandez et al. [14] studied the relationship between WM load and CFC between frontal and posterior regions. The results showed maximal increases of theta activity in frontal areas and of fast frequencies' activity in posterior regions with the WM load, suggesting a modulation of inter-regional communications depending on the demand. The previous recent papers emphasize that frontal theta rhythm subserves a control or a WM function, while gamma rhythm mainly reflects the sensory experience and its memorization.

A way to demonstrate the involvement of theta and gamma rhythms in WM consists of modulating the WM capacity via rhythmic stimulation. Several recent studies address this aspect. For example, Köster et al. [15] enhanced memory formation processes via rhythmic visual stimulation at theta frequency. In addition, Jones et al. [16] modulated the interaction between frontoparietal theta oscillation and gamma activity through transcranial direct current stimulation and observed improved WM performance.

Figure 2



Qualitative explanation of the mechanism for encoding multiple items in a temporal sequence, exploiting the theta–gamma phase–amplitude coupling. Letters A–E represent five different items, each characterized by the activation of an ensemble of neurons (not necessarily distinct). A different ensemble of neurons (T), oscillating at a smaller frequency, generates theta rhythm (e.g. neurons encoding items may be located in hippocampal or cortical regions, while neurons producing theta rhythm may be located in subcortical structures such as the septum or the amygdala, which then send the signal to the hippocampus/cortex). All neurons in the same item are excited in synchronism during a single gamma period but at a different phase of the underlying theta rhythm. Different items occupy different phases in the theta period, thus generating a sequence. The sequence is then replicated at each new period. The mechanism allows the production of a temporal memory, in which different items unfold in time with an assigned order.

Long-term memory

A broader recent perspective proposes that WM and long-term memory mutually cooperate to realize complex behavioral patterns [17].

Indeed, much data concerning the hippocampus stresses the functional role of gamma and theta oscillations in human episodic memory (EM) as well (see Ref. [18] for a review). Recent results confirm an increase in the theta rhythm and its phase reset during associative memory tasks [19,20] and show that encoding and retrieval occur at different phases of the theta rhythm [21,22]. A differentiation between encoding and retrieval could be linked to fluctuations in acetylcholine (ACh) levels. Indeed, ACh reduces feedback synapse strength in the hippocampus and increases feedforward afferent inputs, thus favoring the encoding of new information in memory [23]. In contrast, low ACh concentration has the opposite effect, favoring the replay of previously stored items [24]. Some authors suggested that the cholinergic tone can regulate the theta rhythm [25], devising a solid relationship between ACh, theta–gamma coupling, and memory. This result opens broad perspectives,

indicating that neurotransmitters can regulate mental processes by modulating neural oscillation entrainment.

Additional data suggest that theta–gamma coupling can affect other types of long-term memory, including semantic and procedural ones. A causal relationship between theta–gamma coupling and motor acquisition skills was demonstrated by Akkad et al. [26] via transcranial alternating current stimulation (tACS) and by Diedrich et al. [27], who obtained significant improvements in nondeclarative visuomotor skills after tACS treatment. Other works probe the functional role of theta–gamma coupling during verbal long-term memory encoding [28] and adaptive control of motor commands [29]. Mellem et al. [30] analyzed the oscillatory dynamics of lexical-semantic processing. They suggested that gamma power reflects activation of local functional networks supporting semantic representations, while theta coherence indicates dynamic coupling of anterior and posterior areas. Marko et al. [31], using tACS, suggest that theta band oscillatory brain activity supports the binding of semantically linked representations via a phase-dependent modulation of semantic activation or maintenance.

Attention and emotion

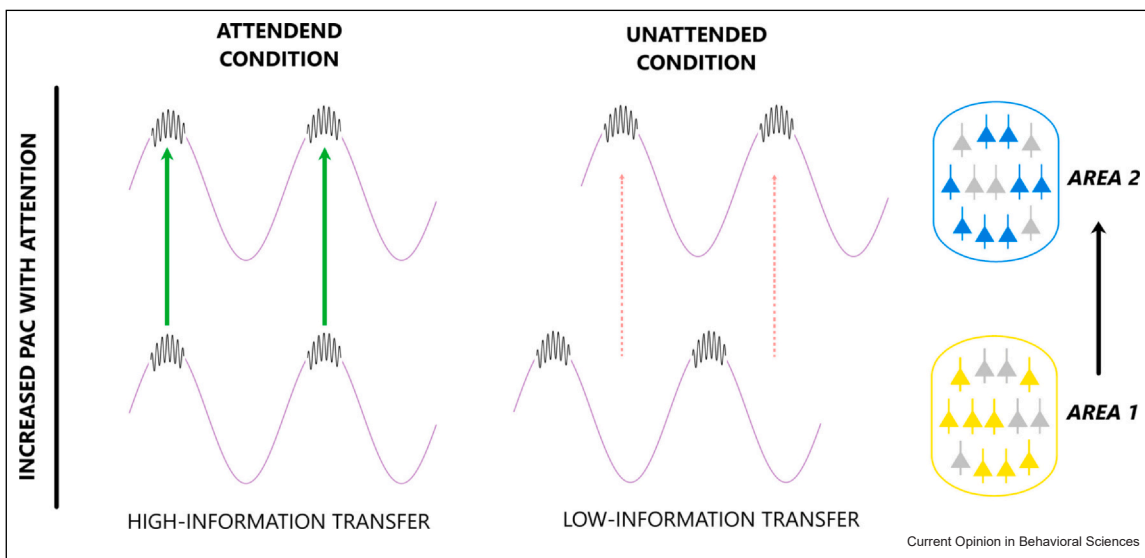
The previous studies underline the pivotal role of theta–gamma coupling in memory. Others enlarge the role of brain rhythms to additional problems, particularly attention. The results, summarized by Helfrich et al. [32], suggest that the neural bases of attention are fundamentally rhythmic and that theta rhythmicity plays a central role in the attention network via a top-down control directed to goal-reaching. Chen et al. [33] emphasize the role of theta–gamma coupling in attention as a mechanism to resolve conflict-processing tasks. Pappioannou et al. [34] measured cortical theta–gamma coupling in three conditions (a WM task, an attention task, and a passive perception condition) and found similar levels of theta–gamma coupling in all of them. This result suggests that gamma–theta entrainment has greater relevance than expected, being also implicated in attentional and perceptual processes, and so may represent a more generic mechanism for signal processing in the brain. Cansler et al. [35] examined the olfactory attention network in rats. They observed an increase in the power of gamma oscillations and their coupling with theta phase as rats switched their attention to odors. Esghaei et al. [36] summarized much previous work on the role of CFC in visual attention and formulated two interesting hypotheses. First, distinct frequency bands could play different roles in visual information handling

by implementing different submodalities of sensory processing: enhancing discrimination or improving communication. An example of how the theta–gamma code can favor or jeopardize communication between two areas is summarized in Figure 3. Second, different rhythms would process distinct sensory feature dimensions (for instance, color vs visual motion).

The involvement of theta–gamma coupling has also been recently observed during the reorienting of attention in motor execution [37] and in the auditory cortex, where it is related to speech comprehension [38].

Interestingly, a recent paper by Costa et al. [39] points out the role of theta–gamma coupling in handling emotions. Using intracranial recording on patients, the authors observed that memory encoding of aversive events depends on the relationship between the amygdala theta phase and hippocampal gamma activity and suggested that this represents a general mechanism through which the amygdala informs distant brain regions of the emotional valence. Another recent study supports this idea using optogenetic stimulation and determining a causal role by the amygdala in influencing declarative memory by eliciting theta–gamma coupling in the hippocampus [40].

Figure 3



An example of how theta–gamma coupling can affect information transmission among different brain regions by realizing temporal windows of excitability (freely modified from Esghaei et al., 2022). We assume that activity in a first region (represented by the signal at the bottom) is transmitted to another region (whose activity is represented by the signal at the top). Information is coded by the gamma rhythm. We further assume that the valley of the theta oscillation corresponds to a condition of inhibited activity, and so excitation can occur only during theta peaks. In the left configuration, transmission is optimal, and gamma activity in the first region can substantially affect activity in the second region. Conversely, in the right configuration, the transmission is impaired since gamma activity in the first region reaches the second region during an inhibition period. Moreover, the gamma activity in the second region, during its window of excitability, does not receive substantial information from the other region. Therefore, this mechanism can be used to gate information or implement a selective attention mechanism.

Dreaming and imagination

In recent years, the role of brain rhythms and their CFC has also been investigated in particular conditions of the human mind, such as our ability to dream or imagine.

During sleep, consciousness fades away, but it quickly recovers when dreams begin. Interestingly, theta–gamma coupling becomes especially prominent during rapid eye movement (REM) sleep [41,42], when dreams show greater length and narrative organization, also being influenced by breathing [43]. Furthermore, the theta activity dominating REM sleep (when Ach levels are high) has been proposed to support memory consolidation, particularly when emotion is involved [44]. Also, current psychiatric research, summarized in Scarpelli et al. [45], assigns a pivotal role to the theta and gamma rhythms during REM sleep, probably related to emotional processing.

Unfortunately, there are still few recent studies that directly analyze the relationship between brain waves and dreaming (however, see Scarpelli et al. [45] for some arguments). These authors hypothesize that dreams could represent a simulation of reality, providing the possibility to create a new scenario for reprocessing and assessing emotional mastery elements. We think that theta–gamma coupling could play a role in this process of simulating temporal events.

Much effort in recent years has been devoted to other mental states, such as lucid dreaming [46], meditation [47,48], or mind-wandering [49–51]. Some authors argue that mind-wandering could be triggered during quiescent states by the interplay of neuromodulators and brain rhythms [52] and be understood as a weaker version of dreaming [53] or perception [54] with which it could, therefore, share the same oscillatory mechanisms. In support of this possibility, two recent articles find an increase in long-range phase synchronization between prefrontal theta and posterior gamma rhythms during mind-wandering [55] and imagination tasks [56].

Neurological diseases and altered mental states

Recent studies additionally indicate a deep relationship between impairments in theta–gamma rhythmicity and aging, neurological disturbances, or altered conscious states. They link abnormal theta and gamma oscillations to several neurological disorders, including Alzheimer's disease (AD), Parkinson's disease, epilepsy, and schizophrenia [57–59].

Large hippocampal gamma waves are suggested to contribute to seizures, while low-amplitude gamma activity is found during general anesthesia [60].

Various data in the literature suggest that GABA-ergic inhibition is impaired in schizophrenic subjects [61]. Since inhibitory GABA signaling between parvalbumin-positive GABAergic basket cells and excitatory pyramidal cells is required to generate robust gamma oscillations [62], this alteration can affect the gamma–theta code and WM. Koshiyama et al. [63] found a distributed network of temporal and frontal brain regions exhibiting gamma phase synchronization in control subjects and demonstrated that this network is disorganized in schizophrenia. Abnormality in gamma and theta oscillations in schizophrenia is the subject of a wealth of recent studies (see Refs. [64,65] for a few of them).

A direct relationship between altered theta–gamma coupling and WM has been suggested for individuals with AD and dementia [66,67]. Recently, gamma entrainment using 40 Hz stimulation (auditory or visual) has been proposed as a potential treatment for AD [68].

Furthermore, a compromised precision in the coupling between gamma power and theta phase may be related to memory impairment in old age [69]. Accordingly, invasive frequency-tuned stimulation to modulate long-range theta synchronization improves WM performance in older adults [70].

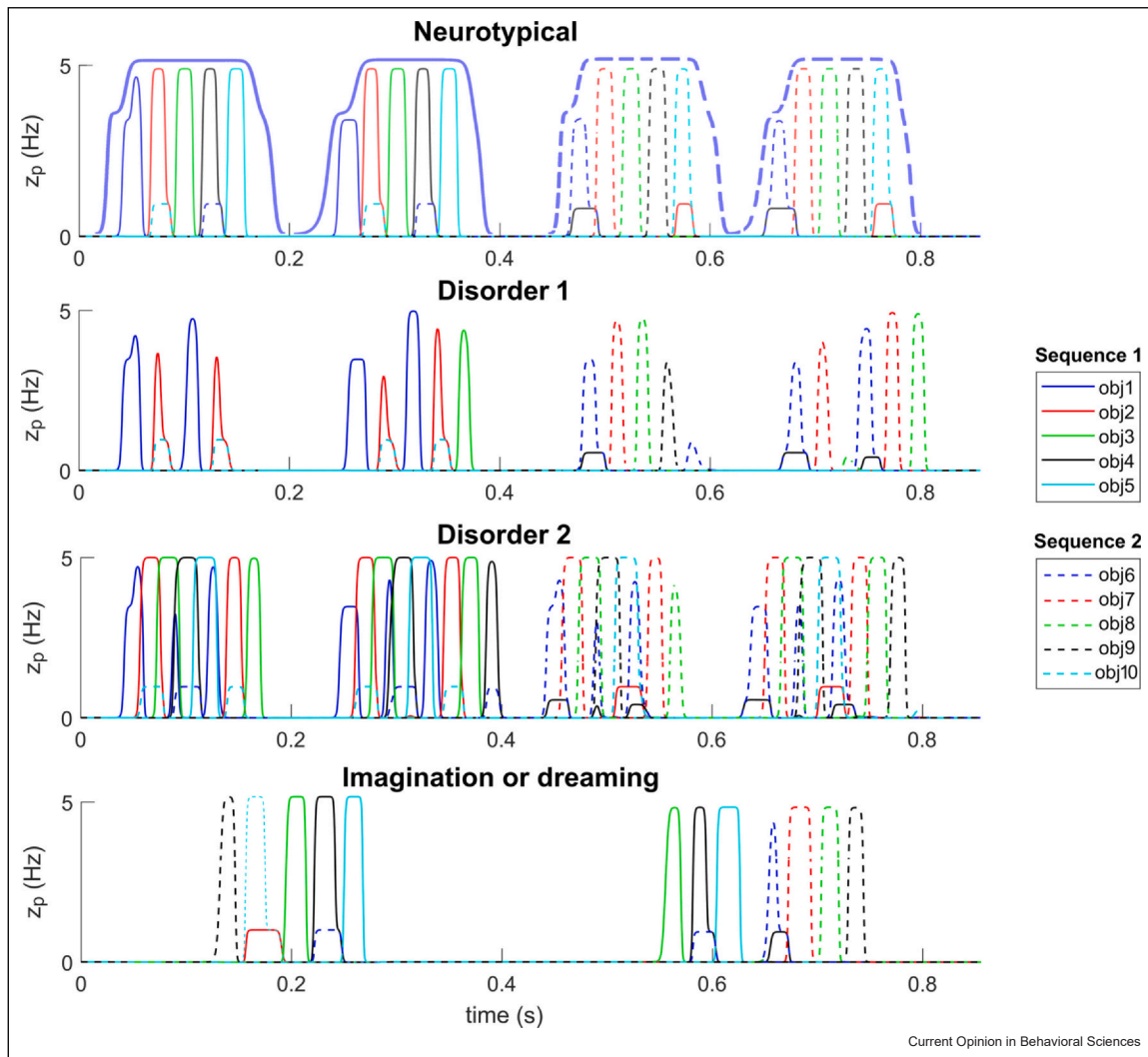
Finally, many altered mental states are associated with modifications in the entrainment of theta and gamma rhythms. For example, they have been observed during anesthesia-induced loss and recovery of consciousness (following administration of ketamine [71] or propofol [6]), and after the use of cannabinoids [72]. It is widely established that psychedelics act mainly on serotonergic receptors in the corticothalamic circuits. Notably, subcortical serotonergic innervations to the hippocampus serve a prominent role in the modulation of the hippocampal theta and gamma rhythm [73].

These frontier results further emphasize the strict relationship between brain rhythms and consciousness.

Underlying neural mechanisms: a neurocomputational approach

A critical aspect that deserves much future study and may guide the research in the coming years concerns reaching a deeper understanding of the neural circuits at the basis of theta–gamma coupling. This achievement requires the development of neurobiological models to bridge the gap between a purely phenomenological description, often exploited in today's neuroscience, and the underlying causal mechanisms. Such models should be neurobiologically grounded based on the biophysics of neurons and synapses and be able to integrate multiscale data from the molecular aspects to the system or cognitive level. Moreover, they must provide testable

Figure 4



Example of some simulations obtained from the model by Ursino et al. (2023). Two different sequences of five objects each have been previously stored in a temporal order using Hebbian mechanisms. It is worth noting that objects are not orthogonal but exhibit some common features (see Ursino et al. for more details). In these simulations, the value 5 signifies that all properties of the object have been restored. *Upper row*: normal model functioning in the retrieval modality. At the instant 0 s, the WM receives a cue belonging to object 1. All objects in the first sequence are correctly recovered in memory and oscillate at different phases of the theta rhythm (shown overlaid only in this row for simplicity). At the instant 0.4 s a cue from object 6 is given. The WM is reset, and the second sequence is correctly reconstructed starting from this cue. *Second and third rows*: model behavior when some synapses are altered to simulate a pathological condition. In the second row, the network fails to correctly reconstruct all objects, simulating a case of dementia; in the third row, the model fails to desynchronize properties of different objects, resulting in superimposed objects, hence a scenario of hallucinations or distorted thinking. *Bottom rows*: the network is now isolated from the external environment and receives only internal noise. A list of objects previously memorized is recovered independently of the input, and new lists are recombined, linking different sequences together on the basis of partially superimposed objects (imagination or dreaming).

predictions and anticipate the effect of external maneuvers, parameter manipulations, or pathological alterations.

At the cellular or molecular level, they can exploit information from chemogenetic, optogenetic, or advanced imaging techniques to elucidate the role of specific cell types, microcircuit configurations, and synaptic dynamics. In recent years, using exact firing rate models,

some authors proposed theoretical ideas about the formation of theta and gamma rhythms [74], phase synchronization [75], the role of neuromodulators [76], and N-methyl-D-aspartate (NMDA) receptors in the genesis of altered perception or hallucinations [77].

A different class of models, acting at the mesoscale or system level by making use of neural masses, has been employed to mimic the collective dynamics of entire

populations of neurons. They have been used to simulate how gamma rhythm can emerge from the interaction between fast-spiking GABAergic neurons and pyramidal neurons [78,79] and how this rhythm in the hippocampus can be modulated by a slower rhythm emerging from subcortical structures such as the medial septum [80]. A large-scale model for consciousness research was presented by Bensaid et al. [81], and the implications of these models are discussed in Modolo et al. [82] and Köster and Gruber [83]. Starting from a previous model of place cell precession in the hippocampus [84], we recently proposed two different models based on traditional neural masses, which exploit hippocampal connectivity and Hebbian learning [80,85] to simulate how different items can be simultaneously reconstructed and maintained in memory (using gamma band desynchronization), or several episodes can be sequentially ordered in time (exploiting theta–gamma coupling). The results stress the relationship between working and EM, providing an integrated view of different memory functions. Furthermore, the models can simulate a phase of imagination or dreaming when isolated from the external world and can mimic hallucinatory and memory impairment scenarios following some synaptic parameter changes (see Figure 4 for a summary of the different behaviors of the models).

The advancement of these recent models and the stimulating results obtained underscore the emerging need for theoretical studies to work in parallel with experimental neuroscience to provide deeper insights into the neurobiological basis of CFC. Neurocomputational models can formulate hypotheses in rigorous quantitative terms, provide a deeper understanding of the genesis of neural rhythms and their alterations, study how oscillatory mechanisms can support cognitive phenomena, and make predictions about pathological conditions.

Conclusions

The previous results underline that theta–gamma code plays a relevant role in many brain functions not only in working, episodic, and semantic memory but also in speech, visual and auditory perception, attention, emotion, imagination, and dreaming. Moreover, several studies point to an impairment of this mechanism in the etiology of different neurocognitive disorders. In all these cases, conscious states are produced, or their alterations are experienced.

At present, we have no element to indicate that integrating gamma and theta rhythms is *necessary* for consciousness. However, we strongly suggest that the capacity to process information typical of the theta–gamma code is relevant for many conscious cognitive processes.

Among the different possible functions of this mechanism, we can mention the remapping of real-time events into a faster neural time scale, the maintenance of information in WM, the encoding of new information and the consolidation of recent memory traces into long-term memory, and the replay of previously stored items such as during imagination or dreaming. By sequentially ordering items, this mechanism can implement a predictive code to drive behavior not only in spatial navigation but more generally to predict and organize future events in our lives. Following Ach or other neurotransmitter changes, it can govern attention sampling, switching between encoding and retrieval in a flexible manner and can control the optimal transmission or gating of information, implementing time windows of higher or smaller excitability.

Some outstanding questions remain: why is theta–gamma coupling so ubiquitously present? Which crucial functions does this mechanism play? We can formulate two possible hypotheses, both valuable and not contradictory. First, theta–gamma coupling appears as a natural way to implement a sequential WM, that is, it implements a buffer representing multiple items in a segregated (via gamma synchronization) and sequential (via theta phase) fashion. This is essential to maintain consistency in our living representation across time and space. Hence, a plausible possibility is that such a temporal WM is somewhat implicated in the aforementioned cognitive functions as a necessary substrate for information processing. Second, CFC is a powerful mechanism for transferring information among brain regions, favoring coordination, binding, segregation, and Hebbian learning. The theta–gamma code can furnish a valuable solution to both aspects, which can justify its frequent role in conscious cognition.

Hence, it is reasonable to conclude that a large portion of our conscious mental life is under the supervision of this ubiquitous and powerful processing mechanism.

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CRedit authorship contribution statement

Mauro Ursino: Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Writing – original draft, Writing: review & editing.
Gabriele Pirazzini: Conceptualization, Data curation, Investigation, Methodology, Visualization, Writing – review & editing.

Data Availability

Data will be made available on request.

Declaration of Competing interest

None.

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- of special interest
 - of outstanding interest
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