Unified principles of thalamo-cortical processing: the neural switch

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Abstract It has been reported that cross-frequency interactions may play an important role in local processing within thalamus and neocortex, as well as information transfer between subcortical and cortico-cortical brain regions. Strong commonalities in rhythmic network properties have been observed across recording techniques and task demands, but strong neuroscientific theories to situate such observations within a unified framework with direct relevance to explain neuropathologies remain scarce. Based on a comprehensive review of animal and human literature, we probe and introduce a neurophysiological framework to explain how coordinated cross-frequency and interregional oscillatory cortical dynamics underlie typical and atypical brain activation, and the formation of distributed functional ensembles supporting cortical networks underpinning perception and cognition. We propose that local regional activation by an external stimulus via a sensory pathway entails (1) attenuated alpha (8–14 Hz) and increased theta (4–8 Hz) and gamma (30–50 Hz) oscillatory activity, and (2) increased interactions among theta and gamma rhythms. These local dynamics also mediate

the integration of activated neural populations into large-scale functional assemblies through neuronal synchronization. This comprehensive perspective into the animal and human literature indicates a further thinking beyond synchrony and connectivity and the readiness for more hypothesis-driven research and modeling toward unified principles of thalamo-cortical processing. We further introduced such a possible framework: “The ATG switch”. We also discussed evidence that alpha–theta–gamma dynamics emerging from thalamocortical interactions may be implicated and disrupted in numerous neurological and neuropsychiatric conditions.

Keywords Alpha · Theta · Gamma · Neural-switch · Local and large-scale networks · Connectivity dynamics · Cognition

1 Introduction

Sensory, motor and cognitive functions are associated with oscillatory changes within task-relevant cortical regions, as well as alterations in functional and effective connectivity between those regions associated with neuronal synchronization [1–5]. Magnetoencephalography (MEG) and Electroencephalography (EEG) have shown that brain dynamics within and between regions often differ markedly across frequencies, and that brain rhythms often interact across widely separated frequency ranges [6–14]. It has further been reported that cross-frequency interactions may play an important role in local processing within thalamus and neocortex, as well as information transfer between subcortical and cortico-cortical brain regions [15]. Strong commonalities in rhythmic network properties have been observed across recording techniques and task

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demands, but strong neuroscientific theories to situate such observations within a unified framework with direct relevance to explain neuropathologies remain scarce.

A comprehensive review into the animal and human literature indicates a further thinking beyond synchrony and connectivity and the readiness for more hypothesis-driven research and modeling toward unified principles of thalamo-cortical processing [16]. We further introduced such a possible framework: “The ATG (Alpha–Theta–Gamma) switch”. We probe this neurophysiological framework to explain in more detail how coordinated cross-frequency and interregional oscillatory cortical dynamics may underlie typical and atypical brain activation, and the formation of distributed functional ensembles supporting cortical networks underpinning sensation and cognition. We also discuss evidence that alpha–theta–gamma dynamics emerging from thalamocortical interactions may be implicated and disrupted in numerous neurological and neuropsychiatric conditions.

2 Coordinated oscillatory and cross-frequency dynamics within local and large-scale networks

Based on the current literature, we propose that a unified set of oscillatory mechanisms underpins activation of cortical regions and their integration into distributed functional ensembles. Such mediation depends on interactions between lower- and higher-frequency cortical rhythms [17] in which theta–gamma mechanisms play a role in sculpting communication among distributed, coactive constellations of neurons forming transiently-organized, functional brain networks [5, 9].

- *Local alpha oscillations and inhibition* Local alpha oscillations are classically thought to reflect cortical inhibition and/or idling [18, 19], as local alpha power reductions have been observed following stimulus presentation in various sensory modalities and cognitive context [18, 20, 21]. Modulations of alpha power within sensorimotor cortex have been further related to predict performance, spike timing, and firing rate [22]. It has also been reported however, that increases in synchronization of alpha oscillations between distant cortical regions may be related to the establishment of long-range networks further relating to working memory retention and maintenance of attention at a spatial location [23, 24]. Such results among others indicate that alpha oscillations primarily reflect cortical idling and inhibition that function to direct information flow within brain networks across diverse contexts [25].
- *Local gamma and theta oscillations and cortical activation* Local increases in gamma-band activity

have been linked to active processing within cortex across numerous contexts, consistent with the view that they play a critical role in attention and memory [26], as well as a more general role in all cortical sensory and cognitive processing [3, 27–30]. Local theta rhythms have been related to task-dependent processing in both hippocampus and neocortex [31]. The relationship between cortical theta oscillations and active processing is perhaps best documented in working memory paradigms including selective attention, navigation, and long-term memory processes [32–34]. Theta–gamma coupling has also been reported in a variety of perceptual and cognitive processes based on noninvasive recordings [8, 9, 12]. Given that alpha oscillations are locally suppressed in many of these same contexts, it is likely that task-dependent activation within a cortical region involves a shift in the dominant frequency of rhythmicity from the alpha band to the theta band.

3 Unified mechanism of thalamo-cortical activation

If the cortex is a finely-tuned dynamic network in which interactions among oscillatory rhythms sculpt the flow of information and control, then the current literature [see 5, 7, 9, 13, 14] is consistent with a general framework supporting information processing in the brain: activation of a local neural population involves a shift away from the dominant alpha rhythm toward both lower frequency (theta) and higher frequency (gamma) oscillations (Fig. 1). In particular, accumulating evidence indicates prolonged alpha desynchronization in parallel with theta synchronization and periodic, recurrent gamma activation during auditory/visual discrimination processing using EEG recordings (Fig. 1a), sustained alpha desynchronization in parallel with a prolonged theta–gamma activation/synchronization in specific sensory and non-specific or non-sensory cortical areas during sustained attention to response task using EEG (Fig. 1b), event-related EEG power changes after onset of stimulus in a face recognition memory task with sharp increases in theta and gamma bands, followed by more sustained decrease in alpha band (Fig. 1c), significant lateralized gamma-band connectivity (using phase locking values—PLV) between occipital cortex and other distant brain areas when alpha power is decreased and gamma power is increased in occipital cortex using EEG (Fig. 1d), and gamma power and its connectivity are modulated by theta phase using EEG with oscillatory phase coupling and PLV measures (Fig. 1e). These findings indicate that activation of a cortical region

Fig. 1 Current literature is consistent with a general framework supporting information processing in the brain: Neurophysiological examples: **a** Prolonged alpha desynchronization in parallel with theta synchronization and periodic, recurrent gamma activation during auditory/visual discrimination processing using EEG recordings. *Left* Spectrogram: changes in power (Hz) over time; *Right* event-related spectral changes over time. (Modified with permission from [7]). **b** Sustained alpha desynchronization in parallel with a prolonged theta-gamma activation/synchronization in specific sensory (occipital cortex) and non-specific or non-sensory (left anterior cingulate) cortical areas during sustained attention to response task using EEG. Red/blue dots in left column represent individual subjects' dipole

involves (1) partial slowing from alpha to theta (2) enhanced area-specific theta- and gamma-band oscillatory activity, (3) coupling between theta and gamma oscillations, which mediates task-dependent processing, and (4) resulting partial global desynchronization of alpha rhythms. This can be described as a “neural switch” from a

locations from two separate experiments. (Modified from [13]). **c** Event-related power changes (averaged across Fz, Cz, Pz, Oz EEG channels) in various frequency bands after onset of stimulus in a face recognition memory task. Sharp increases in theta and gamma bands are followed by more sustained decrease in alpha band. (Modified with permission from [14]). **d** Significant lateralized gamma-band connectivity between occipital cortex and other distant brain areas (*black lines in left*) is greatest when alpha power is decreased and gamma power is increased in occipital cortex (*right*). (Modified from [9]). **e** Gamma power (*left*) and gamma connectivity (*right*) are modulated by theta phase. (Modified with permission from [5, 9]). (Color figure online)

local resting/idling alpha oscillatory state to a task-specific active mode dominated by interacting theta and gamma rhythms, within a stimulus- and task-relevant set of distinct local neural ensembles within thalamo-cortical networks, spanning a few hundred milliseconds: the alpha–theta–gamma (ATG) switch.

4 Neurophysiological foundation and mechanism of a neural switch within thalamo-cortical networks

Thalamocortical interactions are important and involved in the generation of alpha-, theta- and gamma-band oscillations [35]. Mathematical modeling of the thalamo-cortical system further showed that the dynamics of the cortical networks were turbulent and desynchronized when intrinsic thalamic activity was excluded from the model [36]. The onset of a thalamic pacemaker input organized the system into a more coherent spatio-temporal behavior and further provided evidence for the significance of coupling and connectivity of oscillatory activity within thalamo-cortical systems. Neurophysiological mechanisms linking oscillatory slowing and cross-frequency interactions may be further explained in detail by such a thalamo-cortical network model [37, 38], in which an iteration of task-related partial slowing into the specific thalamo-cortical system via cortical layer IV activates local task-relevant neurons at gamma and theta rates with a alpha desynchronization, and then followed by further slowing into task-related non-specific thalamocortical networks via layer I combined with further ongoing alpha desynchronization (Fig. 2). Activation of such task-related cortical network dynamics, via layer I throughout cortex, at gamma and theta rates in a timely manner [35], integrates then “content into context” [37] as earlier hypothesized.

Based on the current literature we have reasons to believe that in normal brain function, the neural ATG switch represents a fundamental mechanism mediating network activation and integration, underlying the transition of local oscillatory activity from an idling or inhibited state to one promoting selective information processing (Fig. 2). This allows the task-dependent integration of well-trained specific local circuits into long-range connectivity across the entire brain (including thalamo-cortical [TC], cortico-cortical [CC], cortico-thalamic [CT], and thalamic–thalamic [TT] systems), by integrating “content into context” or “core into matrix” [35]. Moreover, these interactions between the specific and non-specific thalamic loops support the idea that, rather than simply being a relay station (just gating sensory information into cortex), the thalamus represents a hub (interactive interplay) from which any site in the cortex can communicate with any other site(s) [39, 40]. The neural ATG-switch, then, may represent a fundamental mechanism within thalamo-cortical networks underlying sensory, perceptual, and cognitive processing.

5 GABA-ergic modulation and brain network organization

These thalamo-cortical network dynamics may further emerge from cortico-thalamic feedback inhibition and subsequent cortical GABAergic disinhibition relevant for

gamma oscillations mediating information processing and network integration. The conceptual model of the neural ATG switch with proposed brief and selective inhibition to alter functional states of networks relating to perception and cognition, adds to our understanding of selective network area activation through inhibition. This role for neuronal inhibition was earlier suggested by Buzsáki and colleagues [41], who postulated that long-range-projecting inhibitory GABA-ergic neurons might be an ideal substrate to precisely coordinate brain activity between distant cortical brain regions. Recent findings in animals have indeed identified and characterized long-range GABA-ergic neurons that provide bi-directional hippocampal-entorhinal inhibitory connectivity and preferentially target GABA-ergic interneurons [42], to modulate neural activity through disinhibition (inhibitory inhibition). In parallel, a series of studies of human brain structure reports on the segregation of semi-autonomous building blocks, defined by genetics [43]. This incredible structural complexity underlies functional segregation in the cerebral cortex, a mosaic of hundreds of interconnected and microscopically identifiable areas that controls perception, cognition and behavior. Taken together such evidence indicates that a mechanism of neural inhibition that promotes consequent selective coordination of various task-specific brain areas is quite plausible, and we propose that the neural ATG-switch may play a major role in such selective activation dynamics.

6 Permanently altered neural switch: neuropsychiatric pathologies

Typically, the ATG-switch operates only transiently from the “OFF” to the “ON” position and back to the “OFF” position during a few hundred milliseconds depending on the required information processing in a specific sensory-motor or cognitive task (Fig. 2). There is reason to believe, however, that under some (pathological) circumstances it can become abnormally stuck in the “ON” position, resulting in persistently altered oscillatory dynamics within thalamocortical networks, regardless of processing needs. Such a pathological instantiation of the ATG switch may further provide a more detailed understanding for our earlier discovered thalamocortical dysrhythmia [6]. Our earlier research indeed demonstrated that in several neurological and neuropsychiatric populations, resting-state peak-power oscillatory frequency was persistently slowed from an alpha to a theta rate, theta and gamma power was persistently increased, and persistent cross-frequency coupling was observed among theta and gamma rhythms within pathology-specific networks. This is understood to result from either (1) a deafferentation of thalamus, i.e. in amputee patients with chronic pain, causing a switch to be

Fig. 2 Conceptual model for the neural “ATG-switch” to activate and mediate the assignment of transient functional connectivity within distributed large-scale networks in a task-specific and selective way: (1) the classical resting state (alpha; shown in green and concentrated over occipital areas); (2) following stimulus (or internal/intrinsic input from CT feedback, during an activated task-mode or during “an internally activated” spontaneous or default-network mode) brief inhibition on task-specific part of thalamus, resulting in a brief slowing of that part of thalamus and the related task-specific TC network to the theta band frequency (shown in red), inducing via cortical layer IV a dysinhibition and increased local theta-driven cortical gamma-band synchronization (shown in yellow) and coupling (correlated theta/gamma band activity), in parallel with a slightly-delayed related partial background alpha desynchronization (shown in light green) due to slowing (shift from partial alpha to theta); (3 and 4) further sequential task-specific intrinsic partial inhibition (probably through CT or TT networks) and induced slowing to theta band in task-related non-specific TC networks via layer I, inducing additional

or different spatially segregated local theta-driven gamma-band synchronization and coupling, further mediating functional long-range cortical network interactions and connectivity by theta-gamma synchronization, probably involving related CC/CT/TC loops; (5) after termination theta frequencies restore back to alpha frequency band and baseline-mode (resting state or non-activated mode). Conceptually (as indicated at the bottom), a series of switches would turn on in a task-specific sequence over a certain time period, i.e.; first, one switch activating one set of networks (*one yellow circle* in 2), then together with a second switch activating two set of networks (*two yellow circles* in 3) and/or with an additional third switch activating three sets of networks (*three yellow circles* shown in 4), and then turn off to resting-state. In neuropathological conditions these series of ATG-switches will be symptom-specifically and permanently activated (in any combination of scenarios 2, 3, or/and 4), resulting in permanent theta/gamma band correlation relating to a particular symptom-specific pathology. (Color figure online)

stuck in the “ON” position activating symptom-specific somatosensory networks with persistent increase and coupling of theta and gamma power, or (2) an excess inhibition of thalamic activity, i.e. in Parkinson’s Disease, also causing a switch to be stuck in the “ON” position but activating symptom-specific motor networks, also with persistent increase and coupling of theta and gamma power as discovered earlier [6, 44]. Rather than functioning in a “normal” transient and task-dependent fashion, the ATG-switch in such patients may be permanently and inappropriately activated within these pathology-related networks due to persistent inhibition or dysfacilitation of symptom-specific thalamic areas [45–48]. In this view, focal increases in gamma, which are implicated in perception and cortical activation, induce the (illusory) experience of

positive symptoms depending on the pathology-specific anatomical location of the excessive gamma oscillations [35].

7 Summary and conclusions

Thinking beyond synchrony We propose that the neural ATG-switch reflects a basic biological mechanism that generally implicates a switch from “resting state” or “stand-by mode” to the activation of local and task-related distributed functional networks relating to sensory perception and cognition, and thus represents a fundamental attribute of oscillatory dynamics that arises from network properties in thalamocortical and cortico-cortical circuits.

Further, its malfunction is proposed to be responsible for a range of neurological pathologies.

The conceptual model of a neural switch and all the related literature supporting it, may revisit the dominant view in neuroscience regarding sensory stimulation and cortical activation. The ATG-switch may rather suggest that sensory stimulation or cognitive processing results in “brief inhibition” on the thalamocortical network, causing brief slowing and resulting in local synchronization in the theta- and gamma-bands and coupling of theta/gamma oscillations integrating local and distributed networks. This is consistent with the view that upon stimulation the brain may not undergo an activation per se, but rather a local inhibition and related cortical disinhibition and subsequent synchronization/integration of existing ongoing intrinsic activity.

Concept of brain activation revisited This idea represents a more specific form of earlier proposals [37, 49, 50] that new stimuli interact with ongoing brain activity to integrate external information and generate modified intrinsic activity patterns rather than simply stimulating new activity in a quiescent brain.

Outlook Based on the current literature, we propose the neural ATG switch as a first step towards a basic biological mechanism that has to be further explored and expanded in detail. There are yet some outstanding questions to be resolved by future research studies using multimodal structural, functional and dynamic brain imaging and clinical assessments. Such questions include of how the beta rhythm does relate to the ATG switch, since beta oscillations are frequently reported to be desynchronized similar to alpha oscillations. Another question relates to the alpha–gamma coupling; besides the well-known and well-documented theta–gamma coupling, there are also few reports on the alpha–gamma coupling in human and in monkeys [51–53]. An initial explanation could be that the increase in alpha power, relating to the establishment of task-related long-range networks, is coupled with parallel increases in local theta–gamma activations, therefore demonstrating secondary gamma–alpha coupling being overall consistent with the ATG switch model.

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Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest.

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