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Research Report

A FRAMEWORK FOR INVESTIGATING THALAMOCORTICAL ACTIVITY IN MULTISTAGE INFORMATION PROCESSING

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A framework for investigating information processing in cortico-thalamocortical (cortico-TC) networks is presented, that in part can be used to model and interpret individual changes in electroencephalographic spectra and event-related potentials such as those from the Brain Resource International Database. Scientific work covering neurophysiology, TC firing modes, and TC models are explored in the framework to explain how the brain might process complex information in a multistage process. It is proposed that the thalamus and the cortico-TC system have unique ionic properties and transmission delays (in humans), which are suited to the function of taking "snapshots" or samples of complex environmental stimuli, rather than continuous data streams. This leads to careful and sequential coordination of stimulus and response processes, and increases the probability of information transfer and the resulting information complexity in higher cortical regions. Given the scope of this framework, the multidimensional and standardized Brain Resource International Database provides a pertinent set of measures for both testing hypotheses generated from the model, and for fitting the model to experimental data to investigate mechanisms underlying information processing.

Keywords: Thalamus; consciousness; acetylcholine; EEG; ERP; model; neurotransmission; burst firing; evolution; feed back.

1. Introduction

Human evolution has resulted in an anomaly in the development of the cerebral cortex; a trebling of brain size, but comparatively minimal expansion of subcortical structures. An exception appears to be the thalamus, not in terms of size, but in terms of functionality. All sensory input (excluding olfaction) passes through the

thalamus to topographic and modality specific areas across the cortex where it is processed and relayed further onto other cortical regions via cortico-thalamocortical (cortico-TC) fibres [13, 72, 73, 104, 111]. Studies utilizing imaging modalities such as functional resonance imaging (fMRI) show the activation of the thalamus during numerous sensory and cognitive processes [40, 63, 122, 128]. Depth electrode studies in awake animals have also measured bursting activity in TC neurons in response to sensory and cortical input [22, 87, 90, 103, 114, 125]. Therefore, many authors would agree that the TC system plays a crucial role in higher cognitive functions [11, 65].

Others have questioned the level of involvement of the thalamus in cortical processes given TC input represents only 5–20% of the total number of synapses in the recipient cortical areas [20, 26, 135] and with some estimates as low as 1% in humans [79]. Therefore, while changes in human evolution has seen synaptic and neural numbers significantly increase in the neocortex, the relative proportion of TC input has not, rather it has decreased. This presents us with the question, how can such a relatively small TC input exert potent effects on cortical function?

This paper presents a framework to discuss some of the primary neural mechanisms that may have evolved to increase the efficacy of TC input and how these may change as a function of automated and effortful processing. The framework is not aimed at providing a detailed set of hypotheses or predictions, but rather a plausible explanation of the above processes with reference to scientific data which are largely confirmed and listed in references. It also presents a general framework in which to begin to interpret many of the imaging and psychophysiological findings discussed in this current issue.

For brevity, we leave out many of the details which can be accessed in the cited references and we do not consider all factors that can influence levels of information processing and attention such as the reticular activating system and the brainstem. Instead, we consider what we believe to be the primary components by discussing our work from Robinson and colleagues on a computational and neurophysiological realistic model of global cortical dynamics [91, 93, 96, 97, 99], and integrating this with important studies on cholinergic neurophysiology [9, 25, 52, 60, 106], and bursting and tonic modes of TC firing [74, 103, 114]. In a previous issue of this journal, we have used the model to infer underlying neurophysiology [22, 35], and by fitting the model to individual electroencephalographic (EEG) spectra from large databases such as the Brain Resource International Database [97, 98, 99]. Current work is also aimed at applying the model to the BOLD (Blood-Oxygenation Level Dependent) response in fMRI to permit the inference of more realistic neurophysiological changes underlying BOLD activity. Therefore, it presents a verified model upon which to develop a more comprehensive framework of cortical function.

2. The General Framework

The general framework proposes some key features with respect to cortical processing and attention; (i) Sensory input travels rapidly and unconsciously to the sensory cortex and is then relayed to other higher cortical regions via corticocortical

and cortico-TC networks following a hierarchical neural structure. The level up the hierarchy which the stimulus travels depends upon the attentional capacity that is allocated to the stimulus and whether the stimulus requires further processing. (ii) This process involves a series of static "snapshots" or stages where perception and stimulus evaluation occurs in discrete epochs rather than a continuous stream of data [15]. For example, the illusion of a rotating wheel suddenly appearing to rotate backwards in continuous light suggests the visual system processes information in a series of sequential episodes [86]. The duration and frequency of the snapshots are unlikely to be constant but may coincide with stimulus activity and the primary theta or alpha EEG rhythms [15, 119]. These rhythms are found to arise from thalamocortical networks in the Robinson *et al.* model and the underlying mechanisms have been explored and will be discussed further below [91, 93, 96, 97, 99]. We also suggest that frequencies may vary according to the level of processing with more automated and attentional processes resulting in rhythms in the alpha range and more effortful and later stage processes resulting in rhythms in the theta range. Other authors have also made such suggestions and have shown these relationships in psychophysiological studies [4, 46, 71, 88, 119]. (iii) Information processing might be elicited by some type of neural firing that reaches a threshold such as a sustained high rate, a synchronization of firing, or burst mode of firing. (iv) Special ionic properties involving an increase in chemicals such as Ca^{2+}, or re-entrant circuitries may be required to maintain threshold activity. Here, the low threshold Ca spike of thalamic neurons and associated burst firing is considered as a primary component, and in the following section we discuss the importance of re-entrant circuitry and feedback loops that contribute to this process. (v) Synchronized firing of cell populations including increased firing rates and burst activity may increase the probability of information transfer and the exact timing of the arrival of a spike may have an advantage over earlier or later spikes [74, 103, 114].

3. Continuum EEG Model

The EEG presents an excellent measure for modelling global cortical dynamics given it is commonly used in clinical and experimental studies and changes in EEG activity are often associated with various cognitive and sensorimotor processes [2, 4, 34, 71, 127]. However, despite this there are few research groups that have managed to provide objective models of global cortical activity in humans and most studies examining the EEG remain atheoretical. A good exception is the research of Robinson and colleagues on continuum based models, which is based in part on earlier work by a number of authors [23, 27, 44, 56, 59, 76, 78, 95, 120, 130, 132]. The Robinson *et al.* model directly models the EEG in the form of mean-field potentials using primary neurophysiological principles and structures; including axonal transmission delays, synapto-dendritic rates, separate excitatory and inhibitory neural populations, firing thresholds, nonlinearities, range-dependent connectivities, and cortical and TC networks [91, 93, 96, 97, 99]. The architecture of the model is

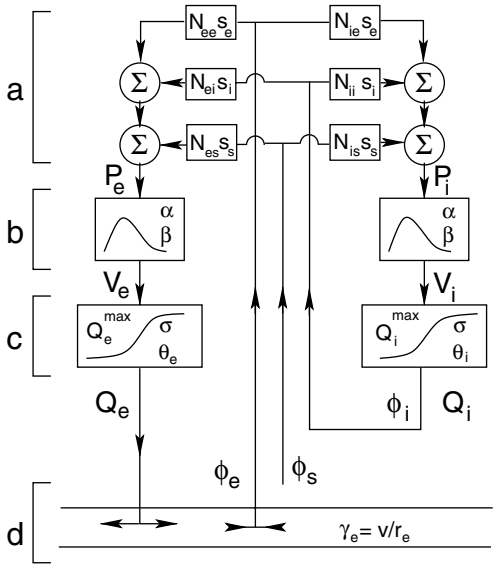

Fig. 1. This schematic shows the interconnection of a single cortical unit with excitatory neuron on the left and an inhibitory neuron on the right. The four transformations that occur within neurons are represented by boxes: (a) spatial summation of pulse density fields ϕ_b ($b = i, e, s$) from inhibitory and excitatory subcortical (s, or thalamic relay) and cortical neurons (i, e), and a multiplication of afferent action potentials by synaptic numbers N_{ab} and strengths s_b; (b) synapto-dendritic activity parameterized by dendritic rate constants α and β induces perturbations of the somatic membrane potential V_a ($a = e, i$) at the cell body; (c) resulting in firing rate Q_e, which is related to the membrane potential V_a by a typical sigmoidal function, characterized by threshold θ_a, width σ_a, and maximum firing rate $Q_a^{\max}$; and (d) propagation of excitatory impulses throughout the cortex as fields ϕ_a along axons according to a 2-D wave equation with damping rate γ_e parameterized by conduction velocity and axonal range [97].

illustrated in Figs. 1 and 2, and a description of the model is in the Appendix. The full mathematical and physiological details of the model are provided in a prior issue of this journal [97] and in earlier references [91, 93, 96, 99]. Figure 1 shows the detailed physiological components of a single unit in the model, but for now Fig. 2 requires more attention given it is these primary pathways and structures from which EEG rhythms such as alpha and theta can arise, whereas more local populations are more associated with higher frequency rhythms such as gamma. The neural activity of the primary pathways is parameterized in terms of gains which parameterize the differential number of neural pulses out per pulse in, and describe the effect of input perturbations from the various afferent neural fields ϕ_b on the firing rate Q_a of excitatory and inhibitory neurons ($a = i$, e) [95, 96].

By modeling the EEG waveforms and spectra, and auditory event related potentials (ERPs), Robinson and colleagues have illustrated how primary networks contribute to cortical dynamics. In particular, the importance and strength of TC inputs and its influence upon cortical dynamics [91, 93, 96, 99]. The mechanisms and findings described by Robinson and colleagues provide insight into how sensory

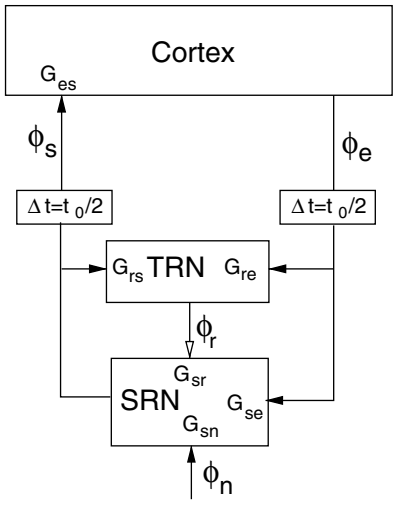

Fig. 2. Schematic showing primary pathways between the cortex, specific and secondary relay nuclei (SRN) and the thalamic reticular nucleus (TRN). The interconnections are shown with arrows; either solid (excitatory) or open (inhibitory). These provide two partially overlapping cortico-thalamocortical feedback pathways: one direct and excitatory (+) between the cortex and SRN with total gain $G_{ese} = G_{es}G_{se}$; and one indirect and inhibitory (−) pathway from cortex to TRN to SRN to cortex with total gain $G_{esre} = G_{es}G_{sr}G_{re}$. Intrathalamic feedback between the TRN and SRN is also possible, with gain $G_{srs} = G_{sr}G_{rs}$. Propagation between cortex and thalamus involves delays of $t_0/2$ ($\sim$40 ms), and additional small delays are induced by each nucleus due to synapto-dendritic filtering. The firing rate in each pathway is ϕ_a, $a = e, r, s$ and $\phi_{\rm N}$ is an independent source of signals [97].

information may be processed within cortico-TC loops in conjunction with the generation of alpha and theta rhythms.

3.1. *Cortical idling and alpha activity*

The dominant frequency that occurs in the human EEG (e.g., eyes-closed) is the alpha rhythm and this often referred to as *cortical idling* [83–85]. Robinson *et al.* show that alpha activity in the cortex is related to the delay time ($\sim$100 ms) that is inherent in the cortico-TC loops and the relatively high gains of the neurons in this circuitry. This delay estimate is based on the conduction velocity of myelinated glutamatergic neurons (pyramidal and thalamic relay), the length of cortico-TC fibres and the associated dendritic delays induced by nuclei, and has been verified in experimental studies by Rowe *et al.* [98–99]. The estimate is reasonable given the general dimensions of the cortex, the average conduction velocity of myelinated fibres $\sim$10 ms^{-1} [10, 19, 77], and the short dendritic time constants of GABAergic and glutamatergic neurons [61, 113, 116]. An increase in cortico-TC feedback has the effect of amplifying and sharpening (*tuning*) the resonance of cortical fields to a frequency ($\sim$10 Hz) approximately equal to the inverse of the total cortico-TC loop delay time. This resonance is strongest at large spatial scales and appears

as "synchronous" alpha rhythm [96, 99]. This rhythm reflects a mechanism which involves periodic modulation of the mean membrane potential over a large area of the cortex [58, 129]. This presumably favors "non-specific" and broad cortical activation (idling), rather than "focal" activation and suppression [14, 53, 67, 134].

3.2. *Sensory processing and alpha, beta & gamma rhythms*

The advent of sensory processing (e.g., eyes-opening) has been associated with the phenomenon of alpha desychronization or alpha blocking and associated enhancements in theta, beta and gamma bands [47, 70, 82, 99]. Strictly speaking, alpha desychronization involves a detuning of the alpha rhythm, given that alpha activity across the cortex is at most only phase locked for no more than a fraction of a second. The effect is to reduce the dominance of the peak alpha frequency, leading to a more irregular time series. This phenomenon occurs in the model as direct (via SRN) positive corticothalamic feedback decreases and the proportion of indirect negative corticothalamic feedback through the TRN increases (see Fig. 2). The resultant effects on the net gain of neocortical fields are complicated [see 96 for details]; however, in summary, what occurs is a *detuning* of the alpha resonance, with possible enhancement of delta-theta resonance depending on the relative strength of negative versus positive corticothalamic feedback. This phenomenon may be a reflection of distinct processing stages as can be seen in the ERP modeling discussed further below; broad and focal cortical activation induced by variant positive and negative corticothalamic feedback that is required to relay signals to specific cortical regions in response to incoming sensory stimuli [14, 107, 124, 134]. More effortful processes inducing longer cortical delays and more focal cortical activation in multiple areas of the cortex may require more active inhibitory action by the TRN, thereby inducing delta-theta resonances, rather than alpha resonances.

In the EEG model the beta rhythm is a harmonic of the alpha rhythm and so it behaves functionally very similarly, with strong alpha rhythms being associated with strong beta rhythms. Further enhancements in beta and gamma activity can also arise due to an increase in sensory (e.g., eyes-open) related synapto-dendritic activity. In the EEG model this effect occurs due to an increase in the synapto-dendritic rate parameters or faster time constants [101]. In terms of physiology, this effect is very realistic given such an increase in "synaptic background activity" can in turn result in a greater fraction of voltage-gated ion channels being open at any instant, causing a drop in average membrane resistance, and thus reducing the dendritic time constant [48, p. 416]. A similar phenomenon has been observed by Ho and Destexhe [37] where high amplitude fluctuations in membrane potential and smaller dendritic time constants (effectively higher α and β) due to AMPA-mediated synapses lead to an enhancement in the responsiveness of pyramidal neurons, so that they are presumably more sensitive to afferent inputs.

3.3. *Gamma activity*

The gamma rhythm has recently become an extremely important phenomenon in neuroscience given its presence is associated with higher order functions such as cognition and binding [7, 30, 54, 115]. In general, it is thought to arise from the short delays induced by re-entrant feedback loops in localized cortical networks [80, 92, 123]. This seems reasonable given the dendritic response times for the change in membrane potential for primary AMPA, NMDA, and $GABA_A$ synapses in these local networks range from 3–44 ms, corresponding to 23–333 Hz [61, 113, 116]. Axonal delays of these local neurons are negligible due to the very short propagation times along local axons [93, 99] giving a resonant frequency of intracortical loops that can potentially generate 20–80 Hz gamma rhythms and higher [92].

Of relevance is the work by McDonald *et al.* [62] who show in their experiments that selective stimulation of discrete sectors of the TRN can evoke focal "gamma" oscillations in the somatosensory cortex corresponding to a localized area of the receptotopic map, acting via TC projection cells. This focal activation is consistent with the above description of alpha detuning and the searchlight hypothesis [14], where the TRN acts to focus the searchlight onto target neural networks. What this suggests is that global circuits are involved in the activation and long range synchronization of gamma activity [80], but it is not intrinsically generated from these long range networks.

3.4. *Event-related potentials*

ERPs (see Fig. 3) have been used to understand the sequence of cognitive processes and their modulation by attention, given their excellent temporal resolution. Relatively early ERP components occurring within 200 ms post-stimulus (such as the P1 and N2) have been found to index automated processing of salient stimuli, while the later components such as the P3 may reflect more voluntary and effortful processes

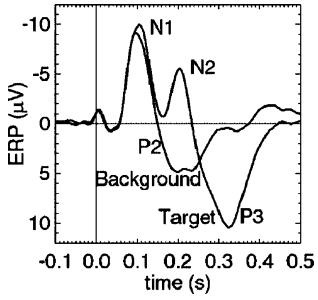

Fig. 3. A typical example of an evoked response or event-related potential (ERP) obtained from and oddball paradigm in response to an auditory background (irrelevant stimuli) versus a target (rare) stimulus. The stimulus onset occurs at 0 ms, with components N1, P2, N2 and P3 typically occurring at 100 ms, 160 ms, 210 ms, and 320 ms, respectively.

[127]. ERPs may also reflect different stages of processing that can be considered consistent with the proposal that the brain processes information at periodic intervals, gradually moving up a hierarchy [15]. Rennie *et al.* [91] using the same EEG model of Robinson and colleagues, show that the ERP components from the oddball paradigm may arise through the cycling of positive (via relay nuclei) and negative (via the inhibitory TRN) TC volleys, which occur periodically at approximately 100 ms. Rennie *et al.* refer to the searchlight hypothesis [14] to explain the cognitive significance of these mechanisms, suggesting focal enhancement together with general inhibition of the cortex via TRN underlies attention [91].

The model can be used to suggest that preattentive and late processing as can be reflected in ERP components occurs in the following manner: (i) Sensory input gives rise to an initial preattentive TC volley at ∼30 ms post stimulus leading to cortical activation (i.e., searchlight) of pyramidal cells in a specific part of the cortex, resulting in the first N1 peak. (ii) Shortly thereafter the natural rhythmicity of the cortico-TC loop leads to the P2 ERP component. This is enhanced by a general reduction in cortical excitation, mediated by negative feedback via the TRN. (iii) For significant or novel stimuli requiring attention, a greater proportion of the relay nuclei are assumed to be disinhibited such that the second corticothalamic volley will once again act as a search light, activating a larger and more distributed proportion of the cortex. This leads to a greater proportion of positive corticothalamic feedback and the resulting N2 component. (iv) As in (ii), this is followed by general cortical inhibition plus focal excitation (narrowing the searchlight) mediated by the TRN and corticothalamic feedback. Once again, this results in a signal inversion and a reduction in the N2 component and generation of the P3 component. Interestingly this proposal builds on familiar EEG rhythms: the earlier components are separated by periodic intervals of approximately 100 ms, consistent with the alpha rhythm, whereas the later P3 component is further delayed to a frequency closer to the theta rhythm. This final P3 component is of greater amplitude and more extended presumably as a reflection of the cognitive processes involved in reacting to the target stimulus. This is suggested to entail greater action of the TRN with active refinement of TC relay nuclei and their transfer of corticothalamic and sensory input.

3.5. *Summary*

Important key features come out of the studies by Robinson and colleagues; (i) The alpha rhythm (e.g., eyes-closed) arises due to the cycling of neural signals through cortico-TC loops at an interval of ∼100 ms, which is the delay time that is inherent in this circuit. This also involves a greater proportion of positive corticothalamic feedback via thalamic relay cells, rather than negative feedback via the TRN, in a state that is known as cortical idling. (ii) Upon the processing of sensory stimuli (e.g., eyes-open) signals are relayed with broad cortical activation followed by focal excitation and inhibition, which can initiate local gamma activity in the neocortex,

presumably relating to high order processing of the stimulus. (iii) The mechanism behind this involves TC volleys and differential positive and negative cortico-TC feedback which arises partly due to action of the TRN. (iv) This results in a detuning of the alpha rhythm and enhancement of delta-theta rhythms as the proportion of negative cortico-TC feedback increases via the TRN. Note that increased firing of GABAergic neurons in TRN leads to inhibition of TC relay cells, reducing their tonic firing activity and increasing their potential for hyperpolarization and a burst mode of firing. This effect is an important component of the framework and this is discussed further below in Section 5. (v) The periodic cycling of neural signals via cortico-TC loops approximates 100 ms and the timing of ERP components. This suggests that the cortex may process information at a given cortical location in stages or periodic intervals.

4. Cholinergic System

The question remains how such a relatively small number of TC synapses can have such a large influence on cortical activity. The cholinergic system appears to play a crucial role in this process. Cholinergic cells from pedunculopontine tegmental nucleus (PPTg) and the laterodorsal tegmental nucleus in the mesopontine tegmental area provide widespread innervation of the thalamus [33, 49, 81, 101] showing an organized system of afferents [12, 33, 50]. Neurons of the PPTg are also predominantly myelinated [89, 105] allowing for high signal velocities and rapid modulation of recipient cells, particularly via ionotropic nicotinic acetylcholine receptors (nAChRs). Cholinergic projections to the TRN also occur in discrete locations, which in turn project to specific regions of the dorsal thalamus including midline, ventromedial, ventrolateral, mediodorsal nuclei, and the lateral geniculate nucleus [49]. These recipient regions of the thalamus also show modality specific sectors and receptotopic mapping through to the cortex [13, 72].

The activation of the PPTg has also been shown to enhance the amplitude of glutamatergic TC impulses in response to visual stimuli [118], and PPTg damage leads to the impairment of such processes [17, 21]. More detailed studies of synaptic connections reveal large numbers of nAChRs on TC neurons and their afferent terminals [25, 52, 100, 106], and muscarinic AChRs on cortical neurons [25, 36, 100]. The nAChRs and mAChRs appear to have complementary roles in enhancing the reliability of TC information transfer, and the associated cortical signal to noise ratio: (i) mAChRs can suppress the firing activity of dominant cortical neurons to facilitate activation due to local TC inputs rather than intrinsic cortical activities [25, 35, 36, 45, 121], while (ii) nAChRs can enhance the transmission of neural signals via the TC terminals [25, 28, 51, 52, 55]. These mechanisms are considered crucial for reliable transfer of information from the thalamus to the cortex. However, the firing mode of TC cells also appears to be another important factor for increasing the probability of information transfer.

5. Firing Modes of Thalamic Cells

The final component of the framework refers to the firing modes of TC cells which include *burst* (oscillatory) and *tonic* (relay) modes [103]. These distinct modes of neural firing arise due to variations in modulatory inputs from the cortex and a number of brainstem nuclei including cholinergic and noradrenergic fibres [38, 65, 69, 126]. The tonic or "relay" mode is characterized by regular depolarizations, in which TC cells fire repetitive single spikes of action potentials [68, 103]. The firing rate is directly linked to the excitatory postsynaptic potential (EPSP) such that larger EPSPs can elicit higher firing rates. In contrast, the firing rate of TC neurons in the "burst" or "oscillatory" mode is an all-or-nothing response and the firing density (number of actions potentials) within the burst does not change according to the voltage level of the EPSP [103].

During burst mode, TC neurons cycle through states of hyperpolarization resulting in intermittent bursts of Na and K mediated axonal spikes of two to seven action potentials in very rapid succession (200–500 Hz), known as the low threshold Ca spike (LTS) [66, 103, 112]. The bursting mode occurs due to the interplay between the slow hyperpolarization-activated currents I_{H} (mixed Na^{+}-K^{+}, inward rectifying current) and the low threshold Ca current I_{T} (T-type Ca^{2+} current) occurring in TC neurons [1, 68]. Hyperpolarization by inhibitory projections of the TRN of approximately 100 ms or longer de-inactivates I_T [41, 42] and the neuron becomes highly sensitive to synaptic input. When triggered, Ca flows rapidly into the cell, creating a transient inward Ca current I_T, resulting in an "all-or-none" depolarization or LTS [18, 66, 103]. This type activity is found to occur during stage 2 sleep [3, 109] due to intrathalamic interactions between the burst firing of TC relay neurons and those of the TRN [3, 5, 108]. With the transition to slow wave sleep, the hyperpolarization period of TC neurons lengthens (170–200 ms), leading to an increase in the occurrence and regularity of spike bursts, and a "clock-like" delta-theta (1–5 Hz) activity in TC networks and the EEG [1, 108, 110]. This is consistent with the Robinson *et al.* model in that generation of delta-theta activity also relies on involvement of the TRN.

An important finding here is that the minimum hyperpolarization period of 100 ms coincides with the cortico-TC delay time. The discussion which follows focuses on the incidence of burst firing during waking states and the possible significance of this relationship. We will suggest that a synergy between burst firing and the cortico-TC delay time may have become an important evolutionarily adaptation in humans by enabling the precise timing of temporal events through cortico-TC loops with the burst mode of TC neurons.

6. Functions of Burst and Tonic Firing Modes

6.1. *Burst mode and orienting*

Recent experimental studies suggest the occurrence of burst mode firing during awake states increases the gain and relay properties of TC relay cells [74, 103, 114].

Many studies also show that the probability of post-synaptic activity generating multiple cortical impulses is much greater for bursts than for tonic trains of TC impulses [39, 57, 114]. TC cells in burst mode also become "hypersensitive" to a single stimulus event, once again increasing the likelihood of a cortical response [22, 75]. These findings are relevant to the case of novel or changing stimuli; since the impulse burst is much more likely to generate a post-synaptic response, this may be important for initiating more diverse patterns of cortical activity required for adaptation or orienting to new environmental contingencies.

6.2. *Hyperpolarization interval and cortico-TC delay time*

After the burst impulse or LTS, the TC cells become temporarily incapable of responding to fast sequences of incoming impulses until they return to a tonic mode of firing or until they are hyperpolarized for $\sim$100 ms [22, 75]. This suggests the exact timing of the arrival of a spike has an advantage over earlier or later spikes. Also, when TC cells fire, the resulting EPSPs via TC collaterals can activate cells in TRN, providing inhibitory feedback that subsequently inhibits TC relay cells [24, 31]. These effects collectively result in stimulus gating regulating the flow of information between the thalamus and the cortex [64, 117]. If burst impulses do reflect the transfer of neural information, then these results suggest that TC cells in burst mode must relay input signals at fixed intervals that approximate the "hyperpolarization–inhibitory" period ($\sim$100 ms) and the cortico-TC delay time. This timing suggests the cortex via corticothalamic feedback and TC bursts can recruit a large number of cortical neurons with increased probability and high entropy. By this we mean that the information complexity of the resulting widespread cortical activity is likely to be much higher, presumably reflecting higher order cortical processes. More effortful processes are likely to involve more active involvement of the TRN and corticothalamic feedback leading to an increase in the burst firing mode of TC cells and associated activation in the cortex. This is consistent with the ERP model of Rennie *et al.* where the later ERP component representing an index of mental activity such as novel stimulus evaluation involves increased action of the TRN.

7. Integration of Findings

As mentioned above, the minimum hyperpolarization period required to switch TC cells to burst mode coincides with the cortico-TC delay time in humans allowing the synchronization of TC burst firing with corticothalamic feedback. This may permit the human cortex to recruit a larger proportion of cortical neurons with increased probability of effect. Therefore, the synergy between ionic physiology and cortical architecture may reflect an evolutionary adaptation that has contributed to the capacity to perform complex cognitive and sensorimotor actions. This has been suggested to be very important in humans given the proportion of TC synapses to cortical synapses in the target Layer 4 of the neocortex has not evolved to a

significantly greater number (∼10%) than in other animals and small rodents, but is actually estimated as less ∼1 % [79]. This is surprising given our superior processing capabilities and our highly evolved frontal lobes. Therefore, other mechanisms, as suggested and described further below, may have evolved to provide humans with superior processing capabilities.

During the burst mode, the TC relay cells become much more sensitive to inputs and their target cells are much more likely to respond due to a triggered impulse burst compared with tonic firing modes. Therefore, during each snapshot or stage, information is more likely to be transferred to the cortex, potentially activating a larger number of recipient cells [39, 57, 114]. The snapshot of information can be expected to vary according to the modality-specificity and salience of the stimulus information, corticothalamic and intrathalamic (TC collateral) feedback, and various neuromodulatory systems that are activated in response to specific environmental variables such as state of arousal or threat. In humans, the interval between each snapshot will primarily be a factor of the transmission delay for a TC impulse to be processed at "higher levels" in the neocortex before returning as corticothalamic feedback to the thalamus and corticofugal feedback to the subcortex and spinal tract. This is ∼100 ms and coincides with the minimum pre-inhibitory (hyperpolarization) period required to switch recruited neurons to burst-mode.

The occurrence of delays in cognitive processing presumably occur due to the action of neocortical networks, including inhibitory neurons, which function to focus cortical activity onto discrete cortical macrocolumns [6, 32], until the appropriate or modality specific neural pattern has been generated. Once this occurs, disinhibitory processes may permit the relay of activity to corticocortical, corticofugal and corticothalamic networks. More effortful cognitive processes requiring more complicated patterns of activity would be expected to take longer to generate within neural assemblies, while the brain searches for the optimal neural pattern required for the current task or process. This would lead to a delay in the following corticothalamic and corticofugal impulse. In turn, lengthier "cognitive" delays would permit greater hyperpolarization of TC cells by the TRN, thereby switching them to burst mode, resulting in a stronger enhancement of delta-theta rhythms. Various cholinergic mechanisms such as preterminal receptors may also have the capacity to shunt away spurious inputs [16, 133] until a strong corticothalamic input is received that overcomes presynaptic suppression permitting the flow of sensory information, corticothalamic feedback and the next snapshot or burst of activity.

More rapid processes requiring lower level cognitive or automated processing may lead to faster cortico-TC cycling and shorter transmission delays, less TRN activity, and a smaller number of TC cells that can be hyperpolarized, leading to a more tonic or relay mode of activation, and a stronger enhancement EEG activity in the alpha-beta range. In this sense, more automated responses and routines that do not require extensive processing or "higher level" cognition will indirectly maintain TC cells in relay mode. In contrast, more effortful and slower processes, which require

greater information transfer, will lead to longer delays and a switching of TC cells to burst mode.

In summary, a sensory induced TC impulse may transmit a snapshot of information. Depending on the complexity and salience of the stimulus, this may be a very rapid process leading to a predominantly relay mode of TC function. More complex and effortful processes will induce processing delays, which may lead to an increase in the potential hyperpolarization of TC cells. This can switch TC cells to burst mode and increase the probability of information transfer, with a subsequent increase in the number of cortical cells activated during the next "snapshot" or TC volley. This process will reflect a mixture of corticothalamic feedback and environmental input. In the case of orienting to novel stimuli, a TC burst may gather additional information in the context of corticothalamic feedback, such that information transmitted to the cortex is more likely to facilitate a change in the response routine or act as a "wake-up" call. This is expected to increase the information complexity of the resulting activity.

8. Conclusion

The above framework of thalamocortical activity and information processing has attempted to provide an integrated understanding of how discrete components of this system interact to generate sensorimotor and cognitive experience. This has required simplifying various aspects of the system down to a sequential and cyclic process, involving cortico-TC volleys and periodic hyperpolarization of TC relay cells. No doubt this process is much more complicated and the cycling of cortical activity in cortico-TC and cortical networks is expected to be parallel and asynchronous, as various networks dedicated to specific neural processes overlap and operate at different time intervals. The concepts raised in this discussion may also be very difficult to test empirically in humans, but noninvasive measures such as EEG & fMRI provide an excellent medium for the examination of global cortical activity in humans and for concepts of attention, consciousness and information processing.

The Brain Resource International Database provides the first fully standardized integration of both EEG and fMRI data [29]. This provides a means to test these concepts with complementary measures of high temporal and spatial resolution in the same subjects by fitting and simulating individual data using neurophysiologically based models. The EEG and fMRI measures are provided for both resting (tonic) and active (phasic) states, and can be related to a wide range of behavioral and cognitive measures in the database to further test hypotheses about relationship between thalamocortical systems and cognition. The continuum based EEG models provide an excellent method for testing predictions relating to the neurophysiological and haemodynamic mechanisms underlying changes in the EEG [93, 97, 98, 99] and fMRI [29]. Current work is aimed at applying the ERP model to the BOLD response in fMRI to permit the inference of more realistic neurophysiological changes

underlying BOLD activity. This may provide further insights into brain activity and permit the formulation of testable hypotheses relating to both temporal and spatial properties of the brain.

In summary, the key finding is that information processing in the brain appears to rely on important temporal events that have arisen from ionic neurophysiology and cortical evolution. The bursting mode is important for the initiation or switching of an information processing event in response to critical or novel stimuli and is primed to detect incoming stimuli and to increase the probability of information transfer. The cortex has also evolved such that this mode of activity can be synchronized with corticothalamic feedback, and the synergy between these two systems appears to make the brain ideally suited to processing information at periodic intervals or as "snapshots" rather than continuous data streams.

Appendix

An overview of the model by Robinson and colleagues is illustrated in Figs. 1 and 2. In the cortex, action potentials from various neurons, represented as neural fields ϕ_e, ϕ_i and ϕ_s, arrive at the dendritic tree [Fig. 1(a)]. A typical dendritic impulse response is used to model the temporal spread and conduction delay within the dendritic tree of an individual neuron [Fig. 1(a)], leading to the membrane potential V_a at the cell-body [59]. Dendritic rate constants β and α parameterize the rise and decay rate of the impulse response [Fig. 1(b)]. The mean firing rate Q_a (or *pulse density*) of neurons occurring at the cell body [Fig. 1(c)] is assumed to vary according to a sigmoid function that relates firing rate to the average membrane potential V_a. Action potentials propagate away from the cell body along a branching axon forming the neural fields or pulse densities ϕ_a [Fig. 1(d)]. On average, the potentials propagate at a velocity $v_a \sim 10\,\mathrm{ms}^{-1}$ [10, 19, 77], with decreasing effect at greater distances due to decreasing terminal density, where r_a is the characteristic range of axons of type a [43, 95].

The EEG is assumed to arise primarily from the membrane voltage fluctuations of excitatory pyramidal cells ϕ_e in layers 3 and 5 in the cortex. Given their large numbers, size and regular orientation these cells represent the principal source of the local field potentials [78, 132]. Other cortical and subcortical structures ϕ_i and ϕ_s in the model, such as the thalamus are shown to exert significant effects upon these cells altering the frequency and strength of the EEG signal over long and short time scales [91, 93, 95]. The TC and corticothalamic connections are illustrated in Fig. 2. The axons from pyramidal cells form dense synaptic connections with the local neurons including stellate cells and other pyramidal cells, but also form long range corticocortical and subcortical connections, which decrease in synaptic density as axonal range increases. This property of the pyramidal neuron is reflected in the equation for axonal propagation in [7], which implies that terminal density decreases at an approximately exponential rate at long ranges [95, 96] in accord with experimental work [8].

The signals ϕ_s returning to the cortex from subcortical structures are a mixture of sensory signals and activity from corticothalamic pathways. The neurophysiology of the subcortical excitatory and inhibitory neurons remains the same as previously explained. However, the additional nuclei in the pathways and the associated axonal projections induce further delays in signal propagation that contribute to the resonant properties of the system. Figure 2 shows the primary corticothalamic and intrathalamic pathways used in the model, plus the inherent transmission delays $t_0/2 \sim 0.04\,\mathrm{s}$. In each direction the various gains G_{ab}, with additional type b neurons — s, r, and n referring to specific relay nuclei (SRN), the thalamic reticular nucleus (TRN), and external signals, respectively, with ϕ_n including both brain stem reticular activation and stimuli.

The corticothalamic feedback path is comprised of neural activity generated by excitatory corticothalamic efferents ϕ_e that synapse with thalamic relay nuclei (with gain G_{se}) and then return to the cortex via thalamocortical afferents (with gain G_{es}). Activation of the pathway involving G_{es}, G_{se}, and dendritic filtering induces a signal delay time of approximately 0.1 s, resulting in a strong alpha (10 Hz) resonance when the loop gain is adequate. The total gain $G_{ese} = G_{es}G_{se}$ is positive since both G_{es} and G_{se} are gains of excitatory neurons. There is also a negative feedback pathway involving corticothalamic signals that pass through the inhibitory thalamic reticular nucleus (with gain G_{re}), then the relay nuclei (G_{sr}), before returning to the cortex via thalamocortical afferents $\phi_s(G_{es})$, with overall gain $G_{esre} = G_{es}G_{sr}G_{re}$. The inhibitory reticular neurons means that G_{sr} and the total loop gain G_{esre} are negative. At high values, this loop gain can lead to strong resonance within the theta (5–7 Hz) band due to the inversion of the positive corticothalamic feedback signal and the resultant modulation of ϕ_e in the cortex. The third and final loop illustrated in Fig. 2 is the intrathalamic loop with total inhibitory gain $G_{srs} = G_{rs}G_{sr}$. This pathway has a very short delay time such that adequate gain may lead to strong resonance corresponding to the spindle frequency ∼12–15 Hz occurring during sleep [94, 96].

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