Cortical Networks, Working Memory, and Epilepsy: Oscillations, Seizure Type

And Their Termination By External Network Stimulation

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Abstract

Epilepsy is one of the most common neuropathologies worldwide. Seizures arising in epilepsy or in seizure disorders are characterized generally by uncontrolled spread of excitation and electrical activity to a region of the brain, or to the entire cortex. While it is generally accepted that abnormal excessive firing and synchronization of neuron populations leads to seizures, little is known about the precise mechanisms underlying human epileptic seizures, the mechanisms of transitions from normal to paroxysmal activity, or about how seizures spread. Further complication arises in that seizures do not occur with a single type of dynamics but as many different phenotypes and genotypes with a range of patterns, synchronous oscillations and time courses. The concept of preventing, terminating, or modulating seizures and/or paroxysmal activity through stimulation of brain has also received considerable attention. The ability of such stimulation to prevent or modulate such pathological activity may depend on identifiable parameters. In this work, firing rate networks with inhibitory and excitatory populations were modeled. Network parameters were chosen to model normal brain activity particularly in working memory. Two different models of cognitive activity were developed. The first model consists of a single network corresponding to a local area of the brain. The second incorporates two networks connected through sparser recurrent excitatory connectivity with transmission delays ranging from approximately 0 ms within local populations to 30 ms between populations residing in different cortical areas. The effect of excitatory stimulation to activate working memory behavior through selective persistent activation of populations is examined in the models, and the conditions and transition mechanisms through which that selective activation breaks down producing spreading paroxysmal activity and seizure states is characterized. Specifically we determine critical parameter and architectural changes that produce the different genotypes and phenotypes of seizure dynamics as observed in the real human brain. This provides a unifying framework for understanding epileptogenesis. Because seizures arise as attractors in a multi-state system, the system may possibly be returned to its baseline state through some particular stimulation. The ability of stimulation to terminate seizure dynamics in the local and distributed models is studied. We systematically examine when this may occur and the form of the stimulation necessary for the range of seizure dynamics. In both the local and distributed network models, termination is possible for all seizure types observed by stimulation possessing some particular configuration of spatial and temporal characteristics.

**INTRODUCTION**

Epilepsy is one of the most common neuropathology worldwide, affecting between 1% and 3% of the world’s population [1]. Seizures arising in epilepsy and other seizure disorders are characterized generally by uncontrolled spread of excitation and electrical activity to a region of the brain, or to the entire cortex in the case of generalized seizures [2]. Further complication arises from the fact that epilepsy is not characterized by one specific behavior or unique electrographic signature, but rather encompasses a wide variety of behavior and electrographic abnormalities. Indeed many different phenotypes and genotypes have been described and it seems that epileptic seizures are the final common path for a broad range of pathologies.

From a network point of view, seizures may be modeled as the loss of ability to selectively activate neural networks as in normal cognitive function such as working memory [3]. In working memory, selective networks or populations of neurons must be able to be activated for a time determined by the needs of the cognitive task at hand, and that activity must be able to be terminated when the information represented by the activation of the network or populations which constitute the network is no longer required. Seizures or seizure-like dynamics can be considered to arise when these processes breaks down [4-6]. In working memory, persistent activation states are accepted as the neuronal or network correlate of working memory [Fuster et al., Wang et al]. This persistent activity is maintained, at least in part, through reverberant feedback resulting from the recurrent architecture of the networks, and the balance between excitation and inhibition. Seizure-like dynamics may arise in such networks as a result in particular perturbation in the architecture or changes in the balance of excitation and inhibition [Traub et al., Verduzco et al., 2009].

The mechanism by which seizures are generated and spread in cortical networks is not well understood. Epilepsy or seizures can arise through a variety of sources including congenital malformations, metabolic disease, brain trauma, tumors and abscesses, strokes vascular malformations or cerebral degeneration. Nearly half of all cases are idiopathic. Considerable efforts have been expended on trying to determine which neuronal network properties are important in initiating and sustaining seizure activity.

While anti-epileptic drugs are the mainstay of therapy (effective on approximately 70% of patients) a significant number are intractable, responding neither to AEDs or surgery. Particularly in these cases it is paramount to understand the mechanisms by which seizures are generated and propagate to find safe new methodologies such as various forms of brain stimulation to alleviate or cure seizures in those individuals. The concept of modulating or terminating seizure activity by different forms of brain stimulation has arisen as a potentially critical and important therapeutic methodology. The ability of such external excitatory stimuli to terminate seizures and/or paroxysmal activity may depend upon identifiable parameters, which, at present, are not understood [Turner et al, Fisher et al., George et al, Lulic et al., Franaszcuk et al, Kudela et al].

In this work we present a model of brain function, particularly of working memory, although it may be interpreted more broadly as producing activity involved and useful for many cognitive and motor functions. We examine the models nonlinear dynamic behavior in normal (i.e. working memory) and seizure/epileptic pathological states. Specifically we examine how the network’s behavior transitions from selective persistent activation of populations as a result of stimulation, to that of spreading excitation and loss of selective activation of varying degrees, with a range of concomitant dynamics including synchronous oscillations in particular frequency ranges, and onsets and time courses of that activity characteristic of a range of specific epilepsy types. We comprehensively analyze how these transitions to pathological dynamics arises as a function of specific changes in network architectures and critical network parameters known to correlate with epileptogenesis. Specifically we determine effect of network dynamics as a result of changes in inhibition and sprouting of excitatory connectivity. We examine the dependence of the normal and pathological states on the frequency and pattern of stimulation to the network, and characterize the ability to terminate the different pathological seizure dynamics that arise through specific frequencies and patterns of network stimulation. We start by introducing a network corresponding to a local working memory network residing in a particular area of the brain consisting of populations of excitatory neurons with fast (AMPA) and slower (NMDA) dynamics, and separate inhibitory populations of interneurons corresponding to GABAa and GABAb (i.e. fast and slow) inhibition. The network also incorporates synaptic delays and adaptation. We determine this networks ability to exhibit normal working memory behavior consisting of the activation and maintenance of persistent elevated firing rates of selected populations in response to a salient input. Further we determine that this working memory behavior may be terminated back to baseline levels by general and selective excitatory inputs. We then systematically alter network parameters and architecture such as decreased inhibitory to excitatory (I-E) coupling and increased connectivity between local excitatory populations and analyze the transition to pathological behavior in response to stimulation of different temporal and spatial characteristics. We then systematically determine the efficacy and mechanisms for terminating the different pathological and normal states arising in response to subsequent stimulation of different temporal and spatial characteristics. We then determine the change in states and the mechanisms involved in differential spreading of seizures, and the different oscillatory dynamics that arise through the analysis of a distributed cortical model. This model consists of two coupled local cortical models as described above. The model exhibits a hierarchical structure with self-connectivity of populations having the highest density and strength, followed by the strength of connectivity between local area populations, and with inter-area populations possessing the weakest or sparsest connectivity. We determine the effect of local architectural and parameter changes as well as inter-area connectivity in the spread of seizures, the types of dynamics that they may exhibit, and the effect of stimulation of various temporal and spatial characteristic in terminating that activity.

**METHODS**

We build on a previously defined model for working memory in a neural network based on interactions between inhibitory and excitatory neurons, and including adaptation and transmission delays. The network corresponding to a given area of the cortex consists of a four dimensional system of the form:

*Equation for excitation (1)*

*Equation for GABAa inhibition (2)*

*Equation for GABAb inhibition (3)*

*Equation for adaptation (4)*

In this model, u represents the firing rate of the population of excitatory neurons, and v the firing rate of the population of inhibitory neurons. The nonlinearity is given by:

*Expression for the nonlinearity (square root)*

Network connectivity is all-to-all, hierarchical clustered….(FIGURE 1 Network Archiecture)

Coupling parameters xx are all non-negative. XX represents….

The local network involves coupling a pair of excitatory populations…

These are connected to a pool population with weak connectivity….

Heterogeneity is incorporated through….

We use model parameters that are consistent with independent physiological and anatomical measures [reference]. We examine the transition from stable linear dynamics via linear instability to non-linear behavior.

We simulate working memory activity tasks with the network in an initial baseline state. A stimulus lasting several hundred milliseconds is applied to the populations [figure 2]. After this there is a delay period during which the stimulate population(s) are to maintain persistent elevated activation. In some cases we examine the ability for the network to transition to other memory states via the stimulation of other populations within the network. We determine also the ability for the network to be returned to its baseline state via an inhibitory or a synchronizing excitatory pulse given for several hundred milliseconds, corresponding to activity of the response period of delay task during normal working memory. This second stimulation also examines the possible parameters for a stimulus to terminate pathological seizure states such as is applied in various forms of neurostimulation.

We describe the classes of activity and how they depend on the main parameters of the model: particularly the excitatory, slow inhibitory, and fast inhibitory synaptic gains in recurrent feedback loops from interneurons to pyramidal cells and in the control of fast inhibitory interneurons by slow ones.

We analyze dynamical changes observed in signals through a parameter sensitive study of the model that uses an exhaustive procedure aimed at uncovering from simulations disjoint regions in the space of parameters, each region being associated with a particular type of model activity. As the parameter space is of dimension xx, the planes (gie, nu1), (d, nu1) (d, gie) are explored varying the parameter values step-by-step. The resulting behavioral state resulting in the network is automatically classified among the possible classes of normal working memory and pathological activity. The association of a specific color to each class of activity allows for graphical representation of results in the form of colored diagrams or activity maps. Transitions between activities encountered in real cases can be interpreted as possible paths connecting corresponding colored regions on the activity maps.

Finally we examine the possible pathways to terminate normal and pathological activities through external stimuli varying the temporal and spatial pattern of the input. Specifically we comprehensively characterize the result of stimulation through step-by-step variation in frequency, amplitude, duration, and the distribution of stimulation (different degrees of local and distributed stimulation).

**RESULTS**

The essential accepted neuronal substrate of working memory is that a network consisting of selective neuronal populations, both within a local brain area and/or between populations in remote cortical areas, can exhibit elevated firing activity above baseline levels in response to a stimulus representing some memorandum, and maintain persistently that elevated activity after the stimulus is removed. Almost all models of this phenomena involve selective bistability between a quiet resting state and a state of sustained activity. Essentially, if a specific stimulus arises, then the population of neurons that best responds to that stimulus will turn on and suppress other populations of neurons. Recurrent excitatory connections enable the stimulated population(s) to maintain activity after the stimulus is terminated so that the network can “remember” which population was stimulated.

1. *Normal working memory parameters and architecture—Local Network*

Across a robust range of parameters (Figure 2) a single population can be persistently excited after presentation of a stimulus. This is achieved from the excitatory to inhibitory coupling (E-I) and strong local inhibition I-E in the network. If a single population is sufficiently stimulated, then the slow synaptic excitation for that population will build up and allow it to remain high once the stimulus is removed. The other populations which have not been directly stimulated will become excited but not sufficiently so to remain active in the presence of sufficiently strong inhibition.

In the simulations, all of the populations of the network begin in their baseline attractor state. Stimulation is given under three general conditions 1) stimulation given to a single population and 2) stimulation given to all excitatory populations 3) stimulation given to populations in selective distributed manner (Figure 1B—***Network stimulation protocols***). Stimulation is given over a range of frequencies ranging from 0 Hz (a continuous pulse) to 100 Hz, and over a range of durations (1 to 500 ms) and amplitudes (1 to 4000 Arbitrary Units). Figure 2A shows the behavior of the network with parameter values falling in the range producing normal working memory behavior. After removal of the stimulus (i.e. corresponding to the presentation of a memorandum as in a working memory delay task) a delay period of several seconds ensues during which the network undergoes winner-take-all (WTA) persistent working memory behavior. When a single populations is stimulated, that populations emerges as the winner and exhibits persistent activation for any frequency or amplitude of input. When multiple populations are stimulated, network heterogeneity breaks the symmetry and a particular winner emerges (Figure 2B). From figure 2 it can be seen that in the case of multiple inputs, the network exhibits frequency-selectivity working memory for input above a given threshold amplitude. For normal ranges of network connectivity and I-E strength, persistent WTA behavior occurs over specific frequency bands while other frequencies between bands do not result in the network attaining persistent activation and returning to baseline firing rate levels after removal of the stimulus. The frequency dependence arises from…

At the end of the delay period, a second excitatory stimulation is presented to the network corresponding to the activation observed for example in the response period of a working memory delay task. Stimulation is again examined under the different stimulation conditions across a range of stimulation frequencies (0 to 100 Hz), durations (1-500 ms) and amplitudes. For stimulation to all populations, working memory behavior terminates and returns to the baseline state for a continuous pulse and across the range of frequencies provided the amplitude of the stimulation is sufficiently high and of sufficient duration (Figure 2C). Network activity can also be terminated through excitatory stimulation of the persistently active population. In this case termination results if the frequency of stimulation falls within the bands of frequencies that do not produce persistent activation.

***We examine the behavior for the network possessing both 2 and 5 excitatory populations??? (MAYBE)?***

1. *Pathological behavior-Single Network*

Our primary hypothesis is that epilepsy or seizure-like states occur as a consequence of specific changes in network architecture and parameters of working memory networks observed in different epilepsies. Specifically architectural changes include increased amounts of connectivity between local excitatory populations (such as sprouting of excitatory mossy fibers which occurs in hippocampus in temporal lobe epilepsy), changes in long-range projections (e.g. increased axonal spreading in inter-area projections) and decreased inhibition (for example resulting from loss of inhibitory Hilar cells in temporal lobe epilepsy) through reduction in I-E coupling, or excessive I-E coupling (as may occur through homeostatic mechanisms following severing inhibitory connections coming into a local network following trauma). ***We also consider the effect of changes in slow inhibition (i.e. slow GABAA) and changes in local transmission delays.***  Figure 3 shows the results of changes in I-E connection strength.

***For normal levels of inter-population connectivity (Figure 3A), the network exhibits normal persistent activation working memory behavior with frequency selectivity occurring at approximately alternating 5 Hz bands provided I-E connectivity is at normal levels (i.e. 15 or greater). As I-E strength becomes too large input is insufficient to excite working memory behavior. A continuous input is able to stimulate working memory behavior however at much higher levels of I-E input with very low frequency inputs (i.e. 1-3 Hz) able to stimulate the network even at very high I-E levels (i.e. up to 50).***

***For low levels of I-E connection strength the network alternates between pathological activities as a function of frequency of the stimulus. As I-E strength decreases below a threshold level, the working memory frequency dependence behavior of the network changes to transitioning to the stimulation of different types of seizure dynamics across frequency bands. For intermediate low values of I-E strength There is a band of activity for WM frequency stimulating bands that activates oscillatory synchronous activation (approximately in the gamma range). As I-E coupling strength continuous to decrease below a critical range (approximately 10) the synchronous oscillatory states transition to non-oscillatory seizure activation states (i.e. all populations active without showing synchronous oscillations).***

***As sprouting increases (Figure 3B—P = 0.8?), normal working memory responses become less consistent and more erratic in its input frequency dependence—particularly at higher frequencies above 50 Hz in which there is scattered working memory behavior. Pulse and very low frequency response of WM behavior however becomes more robust. Seizure states (both synchronous oscillatory and “all up” become more prominent. REVISE THIS—(FIGURE 3C: P = 0.7: As sprouting continues to increase, normal working memory behavior at normal values of I-E strength losses almost all of its frequency dependence and responds primarily only for pulse and very low frequency input. Oscillatory seizure states become a more continuous transition band, and low I-E coupling becomes highly dominated by seizure all up states with small bands of schizophrenic behavior intermittent. As p becomes sufficient low seizure states become the overwhelming dominant response with only very small regions of non-responsiveness.***

***This same essential behavior occurs for single inputs to a particular population as well as for multiple inputs (i.e. both populations receive input).***

1. *Normal working memory parameters and architecture—Distributed Network*

For normal ranges of I-E coupling (i.e. 15 to 35) and inter-area connectivity (i.e. 0.15 – 0.35)—Figure 4--normal working memory behavior dominates the network response to stimulation…

*The dynamics exhibited by the network depend on the particular range of parameters. The specific dynamics exhibited by the system also may vary depending on the particular pattern (i.e. spatial distribution of the input) and characteristics of the stimulation (i.e. frequency, amplitude, and duration). Figure 4 shows the state maps for the distributed network as a function changes in critical parameters. Figure 4a shows the states of the system for changing inter-area connectivity density and local I-E connectivity (with normal I-E levels fixed for the rest of the system) and for normal delays and GABAa excitation levels. The response of the network with inter-area connectivity and local I-E coupling strength within normal ranges (d approximately 0.25 to 0.5 and gie approximately 20 to 35) is normal persistent working memory activation for essentially any frequency (or continuous) input (Figure 5a).*

***STOPPED HERE!!!!!!!***

*As inter-area connectivity densities increase, and/or I-E coupling strengths below or above the normal range, working memory persistent activity states co-exist with seizure states with a range of dynamics as observed in actual epilepsies. The activation of normal working memory vs. particular seizure dynamics depends on the frequency and amplitude of the stimulation. We see for example for d= 0.2 and normal I-E coupling (gie=15) that generalized seizures are evoked by stimulation particularly around 20 Hz, with dynamics characterized by spike and wave bursts and synchronous oscillations. For normal inter-area connection densities and increased I-E connection strengths (gie = 25) normal working memory behavior is evoked by stimuli at specific repeating frequency bands, while stimulation outside those bands either fails to evoke persistent activity (i.e. system returns to baseline) or evokes generalized seizures with synchronous gamma activity.*

1. *Pathological behavior-Distributed Network*

As inter-area connectivity increases within this range of I-E coupling however, seizures exhibiting high frequency (e.g. gamma range) synchronous oscillations in their activity occur. Normal working memory behavior can be recovered however by an associated increase in I-E coupling proportional to increases in inter-area coupling, perhaps through homeostatic mechanisms.

Within the range of normal inter-area coupling, seizure behavior dominate for both low I-E coupling as well has high I-E coupling as has been reported previously. For low I-E coupling with normal values of inter-area coupling, the network exhibits generalized seizure behavior with asynchronous firing. For high values of I-E coupling (once again which could result from homeostatic mechanisms following changes in architecture as a result of trauma for example) the network can exhibit seizures with high frequency gamma oscillations.

For low I-E coupling and low inter-area connectivity the network can exhibit generalized seizures, with high-frequency oscillations dominating one area, and nested theta synchronous oscillations dominating the other area.

Termination of seizure states through secondary stimulation revealed that…

The mechanism for the termination of seizures was determined through an analysis of … The results are…

1. *Mechanism for transitions from focal to generalized seizures*

Analysis reveals the conditions for the occurrence of generalized and focal seizures. Generalized seizures dominate for high values of inter-area coupling with asynchronous or high-frequency synchronized oscillations. For normal ranges of inter-area coupling, asynchronous generalized seizures dominate for low values of I-E coupling, while focal seizures with high frequency oscillations can occur for high values of I-E coupling. Thus for example as I-E coupling increases through homeostatic mechanisms following for example trauma, this could lead to focal seizures.

Focal seizures also may occur for low values of inter-area coupling and normal ranges of I-E coupling. While seizure exhibiting multiple frequency oscillations (e.g. gamma and theta) may occur for low values of inter-area coupling and low values of I-E strength.

Figure 6a—Bifurcation Diagram (Single network no delays)

Figure 6b—Schematic Bifurcation diagram from plots (Distributed network).

The mechanism by which…

1. *Termination of Seizures Single Network (Figure 7a All up, Figure 7B up-gamma osc.)*
2. *Termination of Seizures Distributed Network (Figure 8 a) All up,B) gamma oscillations, C) Theta Oscillation,D) nested oscillations left focal, right generalized for each)*

**DISCUSSION**

In this work we have investigated the ways that cortical working memory networks may give rise to epilepsy and seizure-like dynamics. Expanding previous work on local networks, we investigated the transition to seizures in both local and distributed working memory networks. In local working memory networks, the networks exhibit bistabilty in which a selected winner-takes-all dynamics is exhibited, or may allow for binding with multiple states stimulated to become simultaneously active. These persistently activated states may be terminated by a excitatory synchronizing pulse such as observed in actual working memory experiments [Fuster et al., Bodner et al., Goldman rakic et al., Romo et al., Zhou et al]. This “normal” working memory dynamics can occur with populations exhibiting “continuous” firing, or periodic firing in the theta and gamma ranges as observed in the cortex of human and non-human primates [ref]. As observed in the cortex the higher frequency gamma oscillations occur at lower amplitude than the lower frequency theta oscillations.

As I-E coupling strength is decreased, or excitatory connectivity strengths increased, the local systems exhibit bifurcations to seizure-like states. These states are characterized by a loss within the network of the ability to selective activate selected populations through appropriate stimulation. As in normal working memory dynamics, the networks may become persistently active in a non-periodic fashion, or may exhibit oscillatory synchronization in the theta range or gamma range. Such range of activities are observed in the cortex during actual seizures. For example theta synchronization is associated with absence seizures, while gamma oscillations are observed in grand mal seizures [reference]. In addition to seizure states arising as a result of decreases in I-E coupling below normal operating ranges, it is found that seizure states may also arise as a result of increased I-E coupling beyond normal operating ranges. This is consistent with findings in humans and animal models of seizures in which an increase in GAGAergic inhibition can lead to seizures through the complex temporal dynamics between excitation and bursting paroxysmal states [Wendling et al., 2005; Klaassen et al., 2006]

Expanding the spatial architecture to examine distributed working memory networks, we find that the local dynamics may be expanded to include selective activation and binding of states in different cortical areas during selective stimulation. For example the activation of a particular population residing in a given network which could represent a population in primary sensory cortex, can selectively activate and maintain active a population in another network to which it projects (e.g. representing a population in prefrontal cortex). Such a population can thereafter maintain persistent activation even in the absence of continued activation of the associated population in primary sensory cortex as indicated in reversible lesions studies. We selectively model changes in network architecture which may be associated with trauma (e.g. increased connectivity in projections from one cortical network and within a cortical network) as well as those which may be associated with idiopathic seizures such as changes in I-E connectivity or inhibitory synapse speed.

Previously we had indicated that particular seizure dynamics may be terminated or prevented through appropriate counter stimulations. Here we have investigated this phenomenon more systematically to determine the relationships between counter stimulus and specific types of seizure dynamics and parameters (e.g. focal vs. local, petit mal low frequency, and grand mal high frequency generalized seizures etc.) The present results indicate that seizures may always be terminated through some particular temporal and spatial configuration of external excitation. Particularly we find…

Future work needs to address several limitations of the current models such as examining the long-term effects of learning (e.g. Hebbian learning mechanisms) on the long-term behavior of the networks as a result of external stimulation.

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**Figure Captions**

**Figures**