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.

In the simulations, the populations of the network begin in their baseline attractor states. A stimulation period follows corresponding, for example, to the presentation of a sensory memorandum in a delay working memory task. This stimulation is input to the network with different spatial configurations: 1) Stimulation received directly by a single population, 2) stimulation received directly by multiple local populations, and 3) stimulation received directly by multiple spatially distributed populations. Stimulation is also given and the networks resulting behavior is analyzed systematically across a range of temporal characteristics of the input. Specifically, stimuli are given both as periodic (frequency range from 1 to 100 Hz) and continuous (period of 0 Hz), over a range of different duration (1 to 500 ms) and amplitudes (1 to 4000 arbitrary units). After termination of the stimulus, a delay period of several seconds ensues, during which information of the stimulus or working memory behavior activity is to be maintained through selective persistent activation of populations. Following the delay period, a second stimulation is input to the network with a range of spatial and temporal characteristics as during the memorandum period, and the ability of this second stimulation to terminate persistent activity, or in some cases to examine the networks ability to transition to a different persistent memory state, is examined. This second stimulus in the case where it is terminating persistent working memory activity could correspond to the behavioral choice period in delay working memory tasks.

1. Normal working memory Local Network

Across a robust range of parameters, populations are selectively and persistently excited after presentation of stimuli (Figure 2). If stimulation is such that it is received directly by a single population (Figure 2A), then that population can be solely persistently activated. 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. Other populations, which have not been directly stimulated may become excited (Figure 2B), but not sufficiently so as to remain active in the presence of sufficiently strong inhibition. When a single population receives direct stimulation, that population emerges as the winner and is persistently activated, however, the activation exhibits a frequency and amplitude selectivity for the input. Specifically for sufficiently low amplitude input, persistent activation can be evoked for any frequency input. As amplitude of the input increases however, persistent activation occurs only for periodic input with frequencies occurring in bands peaking at approximately 7 Hz intervals.

When multiple populations are stimulated, with network parameters in the normal range, network heterogeneity breaks the symmetry and a particular winner emerges. From figure 2C it can be seen that in the case of multiple inputs, persistent activation exhibits a frequency dependency on the input over a significant range of stimulation amplitudes. Specifically, over the amplitude range of approximately 250 to 1500 au, a continuous stimulation will not induce the network into persistent working memory activity, but rather all populations return to the baseline state following the stimulation period. Persistent activation is evoked however for periodic stimulation over reoccurring frequency bands separated by bands whose frequencies result in a return to baseline following stimulus termination.

Figure 2D shows the results of a second stimulation period corresponding to the choice period of a delay working memory task, and the ability of the stimulation to terminate the persistent working memory state back to the baseline state. For stimulation received directly by all network populations, working memory behavior terminates and returns to the baseline state for a continuous pulse and across the range of frequencies for periodic stimuli, provided the amplitude of the stimulation is sufficiently high and of sufficient duration.

The frequency dependence observed for direct stimulation of a single population and on stimulation of multiple populations arises from the balance between slow inhibition and excitation. On each cycle of stimulation, if when the stimulation terminates the slow inhibition has grown sufficiently large so that it is above threshold it will overcome the persistent excitation of the E population and drive it towards its baseline attractor state. If on the other hand it is in a phase such that it is below threshold sufficient to drive the E population to baseline, then the activation will be sufficient to maintain itself after the stimulus has terminated.

Network activity can also be terminated through more selective input with the 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 (Figure 2A).

In the case of a second stimulation given to the non-active population of the network we determine the networks ability to transition to another memory state. This is examined when the WTA working memory persistent dynamics are characterized by a continuous single frequency, and for the oscillatory beta/gamma WTA dynamics (Figure 3). Figure 3A shows the case for transitioning from continuous WTA activity. The network successfully transitions to activation of the stimulated population along with termination to baseline of the previously active population, provided that the amplitude of the second stimulation is of sufficient magnitude. The case of transitioning from oscillatory WTA dynamics is illustrated in Figure 3B. We see here in contrast to the fixed frequency WTA dynamics, that for a secondary input above approximately 300 au, that rather than activation of the second stimulated population, that all populations are returned to their baseline state, while for moderate to low amplitude stimuli the network can successfully transition to the new population, but with a complex dependency on frequency of the input.

1. Pathological Seizure Behavior-Local Network

Our primary hypothesis is that epilepsy or seizure-like states can occur as a consequence of specific types of changes in architecture and/or critical parameters of working memory networks, observed in different epilepsies. Specific architectural changes include increased density of local connectivity between excitatory populations (e.g. such as sprouting of excitatory mossy fibers in temporal lobe epilepsy), and changes in levels of inhibition such as decreased inhibitory to excitatory (I-E) coupling (e.g. such as occurs in conjunction with mesial temporal lobe epilepsy through loss of Hilar cells following trauma), or I-E coupling strength that is increased above the normal functional range (as might occur through homeostatic mechanisms following severing inhibitory connection coming into a local network following trauma). Figure 3 shows the results of changes in I-E connection strength.

Figure 4 shows the states of the local network across different I-E coupling strengths and excitatory connection densities for various inputs. It can be seen that, independent of input, that normal working memory behavior dominates for sufficiently sparse inter-population excitatory connection density (p), and that maintenance of working memory dynamics requires increasing levels of I-E coupling strength as density increases. Equivalently, decreases in I-E coupling strength results in transition to the regime of the phase space where the system losses the ability to selectively activate populations persistently. The behavior exhibited is one in which selectivity is lost and all local populations in the network become simultaneously active or seizure-like. As I-E coupling becomes too high in the local network however, the dominant behavior of the network is that populations are unable to be maintained persistently active, returning to the baseline state for most stimulation configurations after the input terminates. An exception to this occurs for relatively low amplitude stimulation directly to a single population (100 au) where for high I-E coupling strengths at sufficiently sparse levels of inter-population excitatory connection densities, the system exhibits oscillatory WTA dynamics (Figure 2B). Figure 4B shows the bifurcation diagram of the system as a function of changing I-E coupling at a fixed level of interpopulation connection density. For all values of the parameter the baseline state remains stable. For high values of I-E coupling (i.e. >43) the system exhibits bistability with a persistent elevated firing rate state. At approximately gie = 34 the system undergoes a hopf bifurcation and the emergence of an additional persistent elevated working memory state takes place in which the elevated state exhibits persistent oscillations around the low gamma range. As gie continues to decrease additional working memory states emerge until approximately gie =15. At this point a xxxxxx bifurcation occurs with the emergence of with the emergence of a seizure state in which all populations are persistently activated. This state coexists along with normal working memory down to extremely low values of I-E coupling (e.g. gie approximately equal to 2). In Figure 4C we examine the bifurcation diagram of system as a function of changing inter-connection coupling density (p)….

1. Termination of Local Seizure States

The fact that the baseline state and normal working memory states coexist along with the seizure state in the local system, suggests that appropriate stimulation of the system transition the system from a seizure state to one of those other normal states. Figure 5 shows the effect of stimulation to terminate the possible seizure activity observed in the isolated local network. The system can transition directly from seizure states to its baseline through selective inhibitory input, however excitatory inputs directly to populations cannot produce transitions to the baseline state. A selective input directly to a single population of sufficient amplitude however can causes the system to transition from the seizure state to a persistently activated working memory state with the population receiving direct stimulation exhibiting the persistent WM activity. From the working memory state then, a subsequent stimulation of appropriate amplitude and frequency can return all populations in the network to their baseline state. The mechanism for termination of seizure state is similar to the mechanism by which the seizure state is generated (Figure 5D). When a single input is stimulated with the network in an asynchronous seizure state, slow inhibition can increase to a sufficient amplitude to shut-down the other populations not receiving direct excitatory stimulation as occurs in the normal activation of working memory activity. The other active populations are also receiving stimulation, however their amplitude does not rise to the threshold level to overcome the rising slow inhibition driven by the directly stimulated population. In contrast, when multiple populations are receiving excitatory stimulation, their amplitudes all increase to levels such that the slow inhibition does not rise to a sufficient level to shut down the activity, and thus the system remains in an “all up” seizure state and thus termination of the seizure state fails for such general stimulation.

1. Normal working memory—Distributed Network

We next turn our attention to consider how seizures may spread beyond a local area, and the modulation of states resulting from a distributed architecture.

In the distributed network, as in the case of the local network, selective populations are persistently excited after presentation of a stimulus across a robust range of the critical parameters (Figure 7). If stimulation is such that it is received by a single population, then that population in the particular local network may be solely persistently activated, or can activate a selective distributed network consisting of that population directly receiving the stimulation along with populations to which that the stimulated population projects in the other cortical area (Figure 7A). The persistent working memory WTA activity evoked can occur with the same types of dynamics observed in the local network—specifically continuous frequency WTA, and oscillatory WTA—along with an additional WTA dynamics which consists of beta/gamma oscillatory modulation of a WTA elevated firing state (Figure 7B).

As in the case of the local network, the persistent working memory can be terminated or transitions made to different network activation through subsequent stimulation (Figure 7C)

Figure 8 shows the states of the local networks (and thus together the state of the entire system) across different local network excitatory connection densities and inter-area connection densities for levels of I-E connection strength. At values of I-E connection strength within a “normal” range (Figure 8A), working memory behavior dominates over a significant range of interpopulation and inter-are connection densities. As local connection density increase with sparse inter-area connection densities, the system network transitions first to a region where focal seizures dominate with synchronous gamma oscillations. As the local excitatory connectivity further increases, the system may transition to focal seizures exhibiting synchronous theta oscillations, quiescence, or a generalized seizure with synchronous oscillations, depending on variations in the level of the inter-area connectivity density. As the connection density becomes sufficiently large (e.g.> 0.55) the system exhibits seizure dynamics with asynchronous firing.

In contrast with large inter-area connection densities (e.g. above 0.4), as local excitatory connection density increases, the network dynamics changes from that of normal working memory, (i.e. losing selectivity) and transitions directly to a generalized seizure state, first with synchronous oscillations in the theta range, and then to an asynchronous seizure state. Thus with I-E coupling strength within the range producing normal working memory, the network can transition to seizure dynamics through several pathways. With normal levels of local connectivity density and I-E coupling strength, normal working memory behavior dominates exclusively. For increasing local connectivity the pathway to focal seizure and then generalized seizures occurs for sparse inter-area connectivity, while for high levels of inter-area connectivity generalized seizures occur when local sprouting exceeds a threshold. The transition to generalized seizures for sparse d passes first through a regime of focal gamma oscillations seizures, while for high d the system transition directly to generalized seizures first with theta oscillations and then asynchronous dynamics.

For increased levels of I-E coupling (Figure 8B), working memory behavior still dominates at sparse normal levels of local excitatory connection densities. However, the working memory dynamics exhibited occurs over a reduced range and exhibits oscillatory WTA dynamics. As p increases the system transitions directly to generalized seizures with synchronous gamma oscillations with no dependence on inter-area projections with the exception of minimally at the transition boundary between normal working memory and seizure dynamics behaviors.

For decreased I-E coupling strengths (Figure 8C) the range of local connection densities over which the network can sustain working memory behavior is decreased. As was the case for the system with normal I-E coupling strengths (Figure 8A) with inter-area connection density is relatively sparse, as local excitatory connection sprouting occurs, the network transitions first into focal seizures, and then as sprouting further increases, the system transitions to generalized seizures. Also as was the case for normal I-E coupling strengths, for high inter-area connection densities, the system transitions directly from normal working memory dynamics to generalized seizures.

1. Termination of Seizures Distributed Network

Termination of seizures through secondary input depends highly on the dynamics of the seizures. The system exhibits a number of different seizure states consistent with that observed in human epilepsy. These include seizures exhibiting focal and generalize synchronous beta and gamma oscillations, theta oscillations, and asynchronous firing seizure states.

*Generalized seizures:*

For seizures exhibiting high frequency (beta/gamma) synchronous oscillatory dynamics if all populations of the network are stimulated the seizure may be terminated regardless of frequency or continuous, provided the amplitude of the stimulation is of sufficient magnitude (figure xx) the mechanism here is that…

The seizure dynamics may also be terminated with more selective excitation (not stimulated all populations which may be impractical or impossible). In this case however, depending on the particular configuration of stimulation the results have a strong frequency and amplitude dependence. Seizure dynamics may be switch off even with input to a single population. Figure 7xx shows this condition. While this stimulation is insufficient to directly terminate the seizure, the system can be transitioned to selective activation of populations (i.e. working memory dynamics). Following this a secondary stimulus may then transition the system to a baseline state (show this). This transition occurs with a frequency dependence with frequency bands reoccurring with harmonics at approximately 10 Hz intervals. In the case of stimulation of a local area only, the system may be stimulated to baseline, and this occurs for very specific frequencies (as opposed to over intervals or bands). If this stimulation is spread across networks (but at the same level or number of populations stimulated) termination can occur over a wider range, but continues to show a frequency dependency (Figure 7 xxx).

*Focal Seizure Synchronous gamma oscillations:*

For the state of a focal seizure exhibiting synchronous gamma oscillations, there is an additional degree of freedom in that the network may be stimulated at the focus of the seizure, or the network not exhibiting seizure dynamics may be stimulated. Examining the situation where the “normal” network is stimulated with a single population receiving direct stimulation, the result is that the normal network stimulates persistent working memory activation in the local population, while a transition in the seizing network from synchronous gamma oscillations to synchronous theta oscillations occurs. The mechanism by which this transition occurs is… Thus a very specialized or localized stimulation will not terminate the seizures for this case. Next consider stimulated the entire pathological network revels that termination of the seizure may be accomplished but only at high amplitudes of stimulation and at very specific frequencies. In contrast, stimulating all populations of the connected normal network results in termination of the seizure with the network returned to baseline state. If the stimulation is of sufficiently high amplitude, termination occurs essential frequency independent. For moderate to low stimulation amplitudes however, the frequency dependency arising from… is present. It is of not that for very low amplitude stimulation of this configuration, the seizure may be transitioned from a generalized seizure to a local seizure, with the normal stimulated network exhibiting WTA behavior, and the pathological network continuing to exhibit synchronous gamma oscillations. For the case of a distributed stimulation with the same degree of stimulation as a local stimulation, the result is the same as a single stimulus to the normal network.

***Focal Seizures Theta Oscillations:***

**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**