Wireless Communication in the Brain: IV. Evidence from Seizure Progression

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Abstract

Recent studies have provided compelling evidence that widely separated microdomains are not synchronized at the seizure onset. Their synchronization increases as the seizure progresses. This paper shows that the long range synchronization could be achieved by electromagnetic (EM) stimulation primed by the extracellular electric field (ECEF). ECEF, which arises from non-radiative ionic motions, decreases with the **square of the distance**. Its value becomes negligible at long distance (> 300 μm). By contrast, the EM field, which is radiated from the accelerated ions as they pass through ion channels, decreases with the distance. The slow distance dependence enables EM fields to mediate long range synchronization. However, available evidence indicates that the EM fields generated by brain activities are insufficient to excite a neuron from its resting state. Neurons should first be "primed" by ECEF and/or synaptic inputs to a subthreshold state such that the EM fields can simultaneously excite them to achieve zero-lag long range synchronization among these neurons. A seizure could be terminated by the inhibition of free tubulin which are produced from microtubule depolymerization due to calcium overload - the same mechanism as the initial decrease in excitability following traumatic brain injury (Paper 13). This notion is supported by the findings that both trauma and seizure caused a refractory period of roughly 4 hours.

Introduction

In order to explain the zero-lag long range synchronization, Paper 1 introduces two novel concepts: (1) Microtubule Model for Excitability (MTME), and (2) electromagnetic (EM) stimulation primed by the extracellular electric field (ECEF). MTME is supported by ultrasound

stimulation (Paper 12), traumatic brain injury (Paper 13), and the hyperexcitability implicated in neurodegeneration (Paper 4). This paper will present evidence for the ECEF-primed EM stimulation from the studies of seizure progression. Further evidence will be provided in the next several papers which explore memory retrieval, attention and other brain functions.

Recent studies have revealed that a seizure starts from several hyperactive microdomains (< 1 mm in diameter) distributed in the brain. At the seizure onset, neurons are synchronous within a microdomain, but not between microdomains. As the seizure progresses, synchronization between distant neurons increases. At certain level of large-scale synchronization, the seizure suddenly terminates (Jiruska et al., 2013). Its underlying mechanism is discussed below.

Extracellular Electric Fields vs. Radiative EM Fields

Neural activity is accompanied by ionic motions at dendrites, soma and axon, resulting in fluctuation of electric fields at the extracellular space. The extracellular electric field (ECEF) gives rise to electroencephalogram (EEG) when recorded from the scalp, or local field potential (LFP) if measured by microelectrodes in the brain (Buzsáki et al., 2012). The cell-cell interaction mediated by ECEF is known as **ephaptic coupling**. Since ECEF acts instantly without any time delay, the ephaptic coupling might be used for zero-lag long range synchronization. However, experiments have found that the ephaptic coupling extends only up to a few hundreds of μm (Anastassiou and Koch, 2015). This could be due to the rapid decrease of ECEF with distance, as $1/r^2$.

An action potential is associated with ionic fluxes through ion channels. The accelerated motion of these ions will generate radiative EM fields with frequency around 10 MHz (Paper 1). Such high frequency EM fields were not picked up by EEG or LFP, which typically filtered out frequencies higher than a few KHz. The ion channel in a polarized membrane resembles a "dipole antenna" where the radiated electric field is known to **decrease with distance**, rather than the **square of the distance** (Wikipedia). The slow distance-dependence makes the radiative EM field well suited for long range synchronization. Furthermore, its light speed enables it to achieve spike synchronization with zero phase lag.

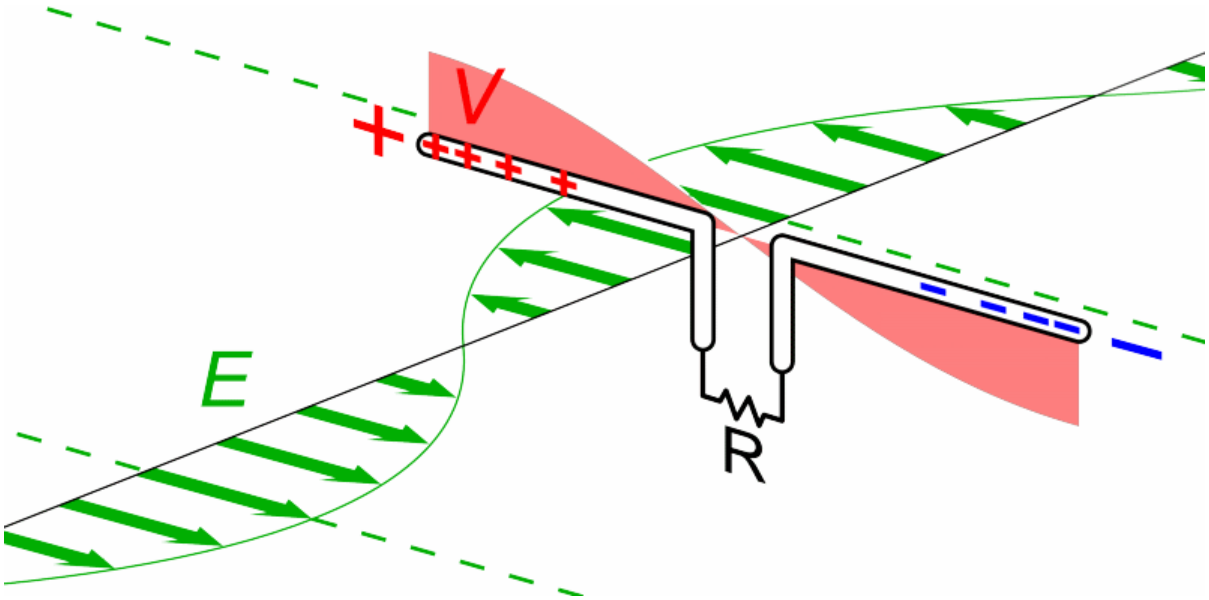

Figure 1. The interaction between the electric field (E) of the EM wave and a metal antenna commonly used in receiving radio or television signals. In this figure, E exerts a force on the electrons inside the metal antenna, producing electric currents. In the brain, the oscillating electric field can also exert a force on the highly negatively charged microtubules at AIS, resulting in their partial or complete dissociation from the AIS membrane, thereby enhancing excitability. [Source: Wikipedia]

According to MTME, both non-radiative ECEF and radiative EM field (wave) are capable of modulating neuronal excitability by interacting with the microtubules at the axon initial segment (AIS). In the brain, EM fields are generated by the accelerated ions as they pass through ion channels which act like transmitting antennas while the AIS microtubules serve as receiving antennas. The EM field is composed of oscillating electric and magnetic fields. Figure 1 shows the interaction between the electric field (E) and a metal antenna commonly used in receiving radio or television signals. E may exert a force on the electrons inside the metal antenna, producing electric currents. For microtubule antennas, no electric current would be produced. Rather, the electric field of the EM wave may exert a force on the highly negatively charged microtubules at AIS, resulting in their partial or complete dissociation from the AIS membrane, thereby enhancing excitability (see Paper 2 and Paper 12).

In ultrasound stimulation and traumatic brain injury, the mechanical force alone would be able to excite neurons from the resting membrane potential. However, evidence from various studies suggests that, under normal physiological conditions, the EM force alone is insufficient to elicit action potentials from the resting state. The neuron should first be "primed" by ECEF and/or synaptic inputs to a subthreshold value such that the EM force can simultaneously excite primed neurons to achieve zero-lag long range synchronization among these neurons. During normal operation, the brain may employ this simple mechanism to select proper neurons for memory retrieval, attention and other functions. In the case of seizures, the uncontrolled hyperactive neurons could provide ECEF and/or synaptic inputs to adjacent neurons, facilitating EM stimulation.

The Mechanism of Seizure Progression

Initially a cluster of neurons located within ~ 300 μm may become hyperactive due to a variety of abnormalities such as reduced GABA inhibition, increased glutamate excitation, excess 4-repeat Tau, etc. Their synchronization could be mediated by ephaptic coupling, gap junctions or GABA interneurons (see this article). However, these mechanisms cannot account for long range synchronization. Therefore, at the seizure onset, widely separated microdomains are not synchronous (Jiruska et al., 2013).

Consider two widely separated (> 300 μm) brain areas A and B. In each area a neuronal cluster A_1 or B_1 is abnormally active. Initially neurons are synchronous within A_1 or B_1 but not between A_1 and B_1. The synchronized A_1 would generate EM fields to act on the AIS microtubules of any neuron in the brain. Such EM fields are normally too weak to elicit an action potential from the resting state. In the mean time, the cluster B_1 would also generate EM fields to act on the AIS microtubules of any neuron. However, the EM field propagates at the speed of light. It would leave the brain almost instantly after being generated by action potentials (spikes). Since clusters A_1 and B_1 are not synchronous, the EM fields generated by B_1 activity would not be able to facilitate EM stimulation by A_1.

In addition to generating radiative EM fields, the B_1 activity also produces ECEF to act on adjacent neuronal population, say cluster B_2. ECEF does not go away immediately because it is governed by slow ionic motions in

the extracellular space. Therefore, it may facilitate B_2 activation by the EM fields from A_1 activity even though clusters A_1 and B_1 are not synchronous. If both EM fields and ECEF are sufficiently strong, long range synchronization between clusters A_1 and B_2 can be established. The synchronized cluster B_2, in turn, may produce ECEF to recruit cluster B_1 and other adjacent neurons into the long range synchronization. The ECEF-primed EM stimulation could eventually build up a large scale synchronization unless the seizure is terminated by inhibitory mechanisms.

The Mechanism of Seizure Termination

As discussed in Paper 13, excessive neural activities may cause calcium overload, resulting in microtubule depolymerization, which produces free tubulin. The free tubulin has the capacity to penetrate the actin/spectrin layer just beneath the AIS membrane. Since tubulins are highly negatively charged, their close contact with the membrane would be able to inhibit neuronal firing. This mechanism has been proposed to explain the initial decrease in excitability caused by long-lasting optogenetic stimulation (Evans et al., 2015) and traumatic brain injury (Ping and Jin, 2016). The trauma-induced hypoexcitability starts to recover after 4 hours, suggesting that the tubulin inhibition is only temporary, possibly due to tubulin degradation or re-polymerization into microtubules. Remarkably, after seizure termination, there is also a refractory period that lasts about 4 hours (Minabe et al., 1989). This supports the hypothesis that seizure could be terminated by tubulin inhibition. Further evidence comes from the finding that biallelic mutations in *TBCD* (encoding the tubulin folding cofactor D) reduces free tubulin level (Flex et al., 2016), and causes intractable seizures (Pode-Shakked et al., 2017).

Figure 2 summarizes the proposed mechanisms for seizure initiation, progression and termination.

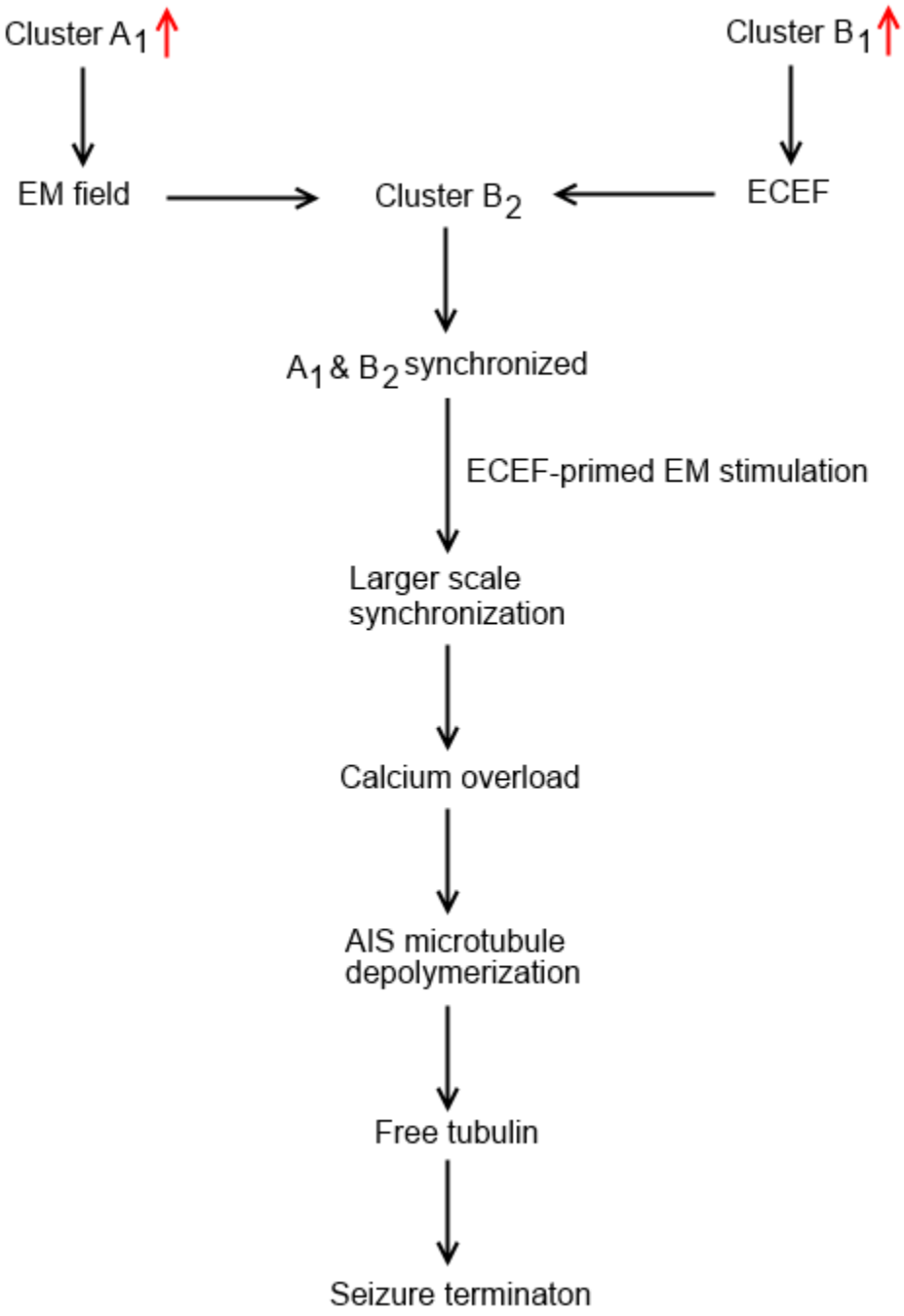

Figure 2. The proposed mechanisms for seizure initiation, progression and termination.
(1) A few neuronal clusters are abnormally active. Only two widely separated clusters A_1 and B_1 are shown for clarity. Neurons are synchronous within A_1 or B_1, but not between A_1 and B_1.
(2) A_1 may generate radiative EM fields acting on distant B_2. At the same time, B_1 can produce ECEF to "prime" adjacent B_2 such that B_2 can be excited instantly by the EM fields

from A_1, establishing their long range spike synchronization.
(3) Other neuronal clusters could be recruited into larger scale synchronization via the ECEF-primed EM stimulation.
(4) The hyperactive neurons would cause calcium overload, resulting in microtubule depolymerization at AIS.
(5) The free tubulin produced by microtubule depolymerization may penetrate the actin/spectrin layer to inhibit neuronal firing, consequently terminating the seizure.