"An Exploration of the Biological Mechanisms Contributing to Higher-Order Cognitive Processes"

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Abstract

In this paper, we will discuss uniquely human biological features that are thought to contribute to higher cognitive abilities. More specifically, we will look at four papers that investigate Pyramidal Neurons in humans, and how they could lead to very large events, and how those events have plasticity which allow learning to occur. In each of these papers, the authors used human neurological tissue and found biological features that are unique to humans and could explain the higher level of cognitive abilities that humans possess.

1. Introduction

Over the years there have been many theories as to what biological reasons contribute to humanity's ability to have higher cognitive abilities. Brain size was an initial metric for comparison, as people thought larger brains corresponded to increased intelligence. This theory is easily debunked, however, as whales have much larger brains than humans but do not possess an obvious increase in cognitive ability. Taking another step along this line of reasoning, people began comparing ratio of brain mass to body mass in an organism, which was used to create the encephalization quotient (EQ). Organisms with a higher EQ were considered to be more intelligent, which was supported by the fact that humans have the highest EQ of all mammals. Though EQ is a predictor for intelligence, it does not give any indication about what features in the brain correspond with higher cognitive abilities. Additionally, it fails to explain how there could be such variation in intelligence among people who all share the same EQ[2].

After looking more at the anatomy of the brain, people began seeing correlations between the intelligence and the thickness of the cerebral cortex. Part of the cerebral cortex, and unique to mammals, the neocortex is responsible for language, sensory perception, cognition, and other higher-order brain functions. A large neocortex relative to overall brain size has been shown to correlate with more complex social behaviors in mammals. Humans have a large neocortex to overall brain size compared to other mammals[6]. The neocortex has six layers, and is made up of cortical columns, which is a group of connected neurons which have identical receptive fields. The cortical columns give a hierarchical organization to the neurons in the brain, and a higher number of cortical columns has been thought to correlate with higher cognitive ability[3].

Now that we have identified a specific area of mammalian brains that correspond to higher-order cognitive functions, we can look at the smaller structures in the brain - neurons,

axons, and dendrites. Another metric for looking at intelligence is how connected are the neurons in the brain. Neurons with larger dendritic trees tend to have more synaptic inputs, which overall increases the cortical connectivity. A common cell in the cerebral cortex, Pyramidal cells are found in 5 of the 6 layers in the neocortex, and can have dendritic trees that cross over multiple layers. The dendritic spine on a Pyramidal cell are responsible for the majority of excitatory synapses in the neocortex. There are significant differences between the pyramidal cells in humans versus other primates. Pyramidal cells in humans have a higher number of dendritic spines, especially in the prefrontal cortex, than other primates, and they also have more volume[4]. A higher number of human dendritic spines could point to a higher number of excitatory synapses in humans versus other primates, though it is unclear if this contributes to more intelligent beings.

Though there are many avenues to explore when examining the source of higher-order cognition, pyramidal neurons in the cerebral cortex has been a natural next area of research. In this paper, we will look at studies that focus on pyramidal cells in humans, and how they differ from other primates and mammals. These differences could contribute to the cognitive abilities that make humans different from other animals. In section 2, we will introduce four papers that examine pyramidal cells from human neurological tissue, and describe the various methods used in their experiments. The results of those experiments will be described in section 3. In section 4 we will discuss the collective results and how it relates to the mystery of higher-order cognitive processes. The closing remarks will be presented in section 5.

2. Approaches in the Literature

In this section, we will introduce four papers that investigate pyramidal neurons in humans. In each of these papers, the authors used human neurological tissue to identify properties and characteristics that are unique to humans, and could contribute to humanity's ability to have higher order cognitive processes. In the first two papers, the authors look at the physical structures of the pyramidal neurons, and try to identify ways in which the dendritic structures are different in the human tissue versus the monkey and mouse tissue they are comparing against. The third paper investigates what happens after a pyramidal neuron fires, and compares monosynaptic and polysynaptic potentials. Finally, the fourth paper investigates the long term depression (LTD) that can occur after a pyramidal cell triggers a very large glutamatergic ESPSs (VTE). This LTD could give an indication if the plasticity and learning that is occurring in the brain, that affects its functioning based on previous events. Each of these papers is a step in the direction of identifying uniquely human traits of pyramidal cells that could contribute to intelligence.

2.1 Comparing Pyramidal Cell Structures in Humans, Mice, and Monkeys

In a 2015 publication, Mohan et. al studied the size and shape of human dendrites and axons, by obtaining human neural tissue from a resection surgery[4]. They used living brain tissue from the human temporal cortex in 28 patients from 19 to 66 years of age. Undamaged

slices of the neural tissue were selected for electrophysiology, and were then mounted and stained. A similar method was used with the neural tissue of mice.

Using the Matlab statistics toolbox, Mohan et. al. created dendrograms of the neural tissue. They were able to digitally reconstruct the neuron with the apical and basal dendrites, as well as the axon, by dying the neuron during a patch-clamp recording from the neuron in the living brain tissue. They also applied Nissl staining to the samples in order to view the different layers in the tissue from the temporal cortex. Additionally, they targeted pyramidal neurons with biocytin loading, and then selected 91 of those neurons for 3D dendritic reconstruction. The neurons that were selected were neurons where the apical dendrite was intact and not truncated. After the reconstruction, the neurons were checked for accuracy.

2.2 Comparing Dendritic structure between Human and Monkey

In order to compare the dendritic structure between humans and monkeys, Elston et. al. obtained human neural tissue from the left hemisphere of a 48 year old male 2 hr postmortem[1]. They also obtained neural tissue from the prefrontal cortex of marmoset and macaque monkeys. In each group, occipital, temporal, and prefrontal tissue was used. The neurons were then injected with Lucifer Yellow and then processed with an antibody. Elston et. al. used concentric circles to count the number of dendrites that intersected with the circles, in order to determine the branching pattern of the neurons. They measured the dendritic field area by calculating the area of a polygon formed by joining the outermost distal tips of the dendrites. By counting the number of spines per 10μm of 20 horizontally projecting dendrites of different cells in the same area, they were able to calculate the density of spines on the dendrites of pyramidal neurons. Finally, they calculated the average number of spines found on the pyramidal basal dendrites, by multiplying the average number of spines in a specific region of the dendrite, by the average number of branches, and then dividing by the total dendritic arbor.

2.3 Pyramidal Cells can cause very large glutamatergic EPSP (VLE)

In a paper describing the large events caused by a single neuron in the cerebral cortex, Molnár et. al. obtained nonpathological cortical samples from 58 patients aged 18 to 73 years[5]. In layer 2 and 3 of the tissue slices, they applied dual, triple, and quadruple whole-cell recordings. In 681 pyramidal cells, they evoked presynaptic action potentials, and looked for potentials in target pyramidal neurons, and interneurons. They targeted more interneurons (481) than pyramidal neurons (252), and were interested in monosynaptic and polysynaptic potentials.

In order to test whether pyramidal cells only initiate postsynaptic spikes in GABAergic neurons, they measured the amplitude of unitary excitatory postsynaptic potential (EPSP) that were created by local pyramidal cell, through simultaneous paired recordings. In particular, they looked at local pyramidal cells that target other pyramidal cells or fast-spiking interneurons.

2.4 VLEs are highly plastic

Interested in verifying the work of Molnár et. al., while also hoping to understand the biological mechanisms involved in the plasticity of pyramidal cells, Szegedi et. al. obtained neurological tissue of 31 patients age 10 to 85, from the frontal and temporal area of the right and left hemisphere[7]. The tissue was immediately stored in a cold solution after removal, and then slices were cut with a microtome at a thickness of 350μm. Recordings were performed in a submerged chamber, and micropipettes of an intracellular solution were used for whole-cell patch recording. Current and Voltage clamp recordings were performed, and action potentials were initiated with 2-3ms suprathreshold depolarizing paired pulses, in paired cell recordings. The postsynaptic cells were held at a resting membrane potential, but in some experiments it was depolarized. A concentric bipolar electrode was applied for extracellular stimulation.

3. Results in the Literature

The results of the previous papers will be discussed in this section. In the first two papers, there were significant biological differences between human pyramidal neurons, and the pyramidal neurons examined in monkeys and mice. These biological differences could be an indication of more excitatory synapses on pyramidal cells. The second two papers examine the results of a single action potential in a pyramidal neuron, how that can trigger additional neurons to fire, and how long term depression and learning can occur.

3.1 Comparing Pyramidal Cell Structures in Humans and Monkeys

When comparing the dendritic structures at L2 and L3 in the neurological samples, Mohan et. al found a gradual increase in total dendritic length, but at the L3 - L4 border there was a decrease. Using their reconstructions of the human and mouse neurons, as well as well as previously published morphologies of the dendrites in the crab-eating macaque, Mohan et. al. were able to compare L2 and L3 pyramidal neurons from the temporal cortex of each of the groups. Overall, the total dendritic length was three times larger in the human samples than in both the mice and the macaque which had a similar total dendritic length. As the macaque has a larger cortical thickness than the mouse, this shows that there is no correlation between the total dendritic length of the pyramidal neurons and cortical thickness. Overall, the apical oblique dendrites, apical tuft, and basal dendrites were bigger in humans than in the mouse. The basal and oblique dendrites also had more branch points in the human neurons than in the mouse neurons.

Using an unlabelled pool of the mouse and human dendritic morphologies, Mohan et. al. performed an unsupervised cluster analysis using Euclidean distance and the Thorndike procedure[8]. The cluster analysis resulted in two primary clusters, one containing 88% of the human L2 and L3 neurons, and the other containing the other 12% of the human neurons, along with 100% of the mouse neurons. Since the majority of the human neurons were clustered

separate from the mouse neurons, which were all clustered together, this is an indication that human neurons have a distinct dendritic structure.

3.2 Comparing Dendritic structure between Human and Monkey

Overall, Elston et. al studied 344 L3 pyramidal cells, and found that human pyramidal cells were the most branched out of the three groups. The prefrontal human cells were the most branched out of all the cells studied, as humans had a higher number of dendritic intersections and also dendritic field area, as seen in Figure 1[1]. Additionally, the human pyramidal neurons had more spines than both the macaque and marmoset in the occipital, temporal, and prefrontal cortex.

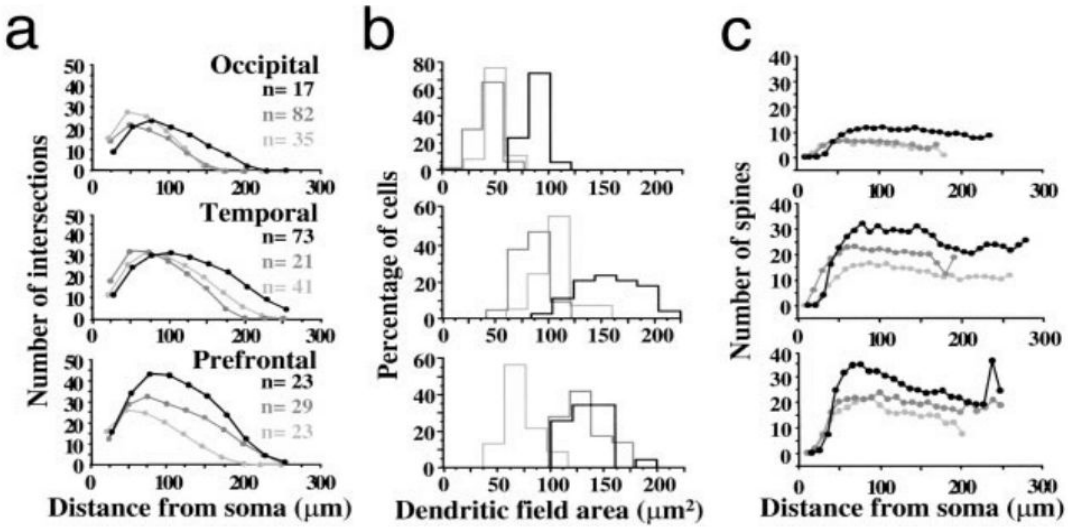

Figure 1. Plots of the human (black), macaques (dark gray) and marmosets (light gray) L3 pyramidal cells from the occipital (top), temporal (middle) and prefrontal (bottom) cortex. This plot looks at the number of intersections (a), the percentage of cells (b), and the number of spines (c) in each region.[1]

3.3 Pyramidal Cells can cause very large glutamatergic ESPSs

By initiating presynaptic action potentials in pyramidal cells, Molnár et. al. found that monosynaptic EPSPs in pyramidal cells and interneurons were recorded with latencies of 0.91 +/- 0.46 ms and 0.86 +/- 0.32 ms. They also found that polysynaptic postsynaptic potentials were measured in pyramidal neurons and interneurons with latencies that were much longer than the monosynaptic events (Figure 2.E)[5]. These latencies were 10.02 +/- 6.83 ms and 8.54 +/- 6.19 ms respectively. The polysynaptic events were both excitatory and inhibitory(Figure 2.D)[5]. In 27% of the samples from 93% of the patients, polysynaptic events were detected from a single presynaptic spike. There was no correlation between the age, diagnosis, and medications of the patient, and where the slices were cut. Molnár et. al. also found highly correlated pairs of events

containing IPSP and EPSP sequences in a human axo-axonic cell (Figure 2.C)[5]. These coupled events work together so the latency of the events can be temporally referenced to intermediate synaptic events. This suggests that other neurons are firing, even if they did not receive direct input from neuron that initially spiked .

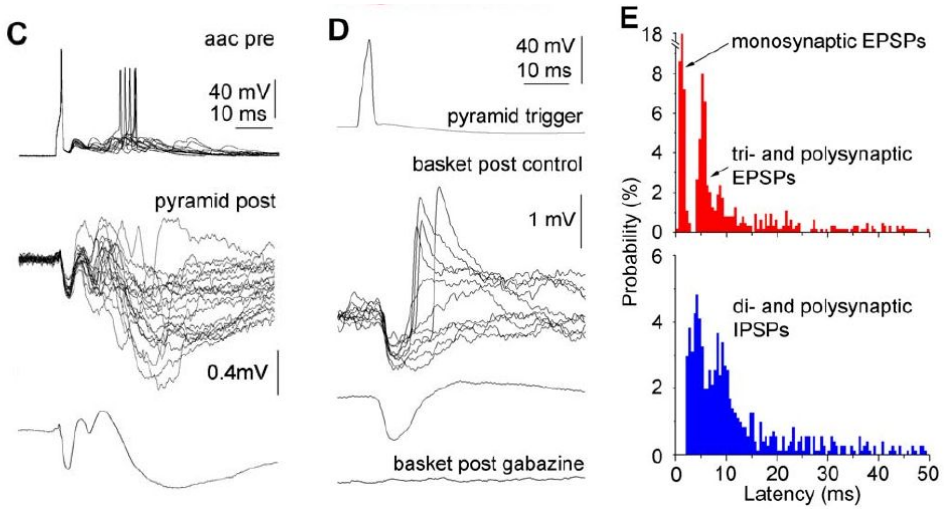

Figure 2. (C) Response to the firing of a single pyramidal cell (top) is displayed in the middle. The average of the responses can be seen in the bottom. In response to the initial firing, there was a monosynaptic IPSP, followed by a disynaptic EPSP, and then a sequence of polysynaptic events in the postsynaptic cell. (D) The firing of a presynaptic pyramidal cell creates a polysynaptic IPSP and EPSP in a postsynaptic fast-spiking basket interneuron. (E) The temporal response of IPSP (bottom/blue) and EPSP (top/red) after a single spike in a presynaptic pyramidal neuron. After an initial monosynaptic EPSP response, there were di-and polysynaptic IPSPs, and tri- and polysynaptic EPSPs in response to the single firing.[5]

When testing if the pyramidal cells create postsynaptic spikes in GABAergic neurons, Molnár et. al. found that there was no spike transmission between pyramidal cells, but there was spike-to-spike coupling between pyramidal cells with fast spiking interneurons with a resting membrane potential of -59 +/- 3mV (Figure 2.D and Figure 3)[5].

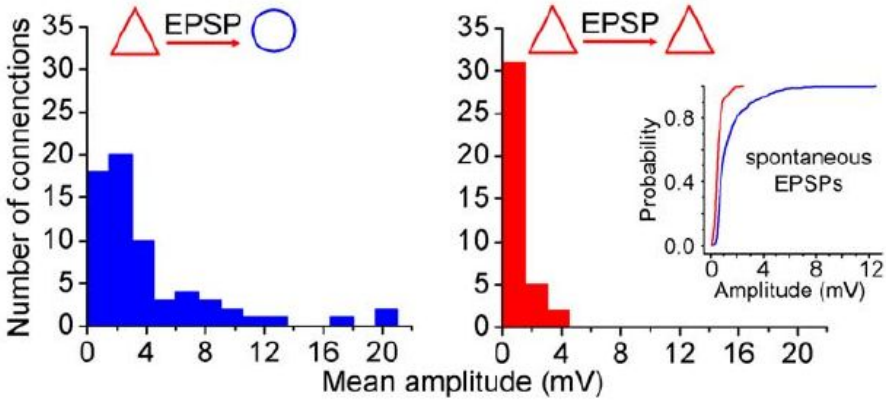

Figure 3. The chart of the left displays the amplitude distribution of unitary EPSPs arriving at interneurons (blue), whereas the chart on the right displays the amplitude distribution of unitary EPSPs arriving at pyramidal neurons (red).

3.4 VLEs are highly plastic

After verifying Molnár et. al.'s results that a single pyramidal cell can cause VLEs in fast spiking interneurons (FSIN), Szegedi et. al. discovered that the VLE postsynaptic spikes from FSIN were followed by a 3-5 ms delay, but there was a longer delay in non-FSIN. They also found that a single action potential from a pyramidal cell created disynaptic $GABA_AR$-mediated inhibitory currents (dIPSCs). Though the probability and delay of the dIPSCs were stable in long recordings of paired pyramidal cells, Szegedi et. al. discovered that there was rapid and permanent reduction in dIPSC after a 40Hz burst firing in the presynaptic cell (Figure 4)[7]. This indicates that there is plasticity in the activation patterns of VLEs through long term depression (LTD).

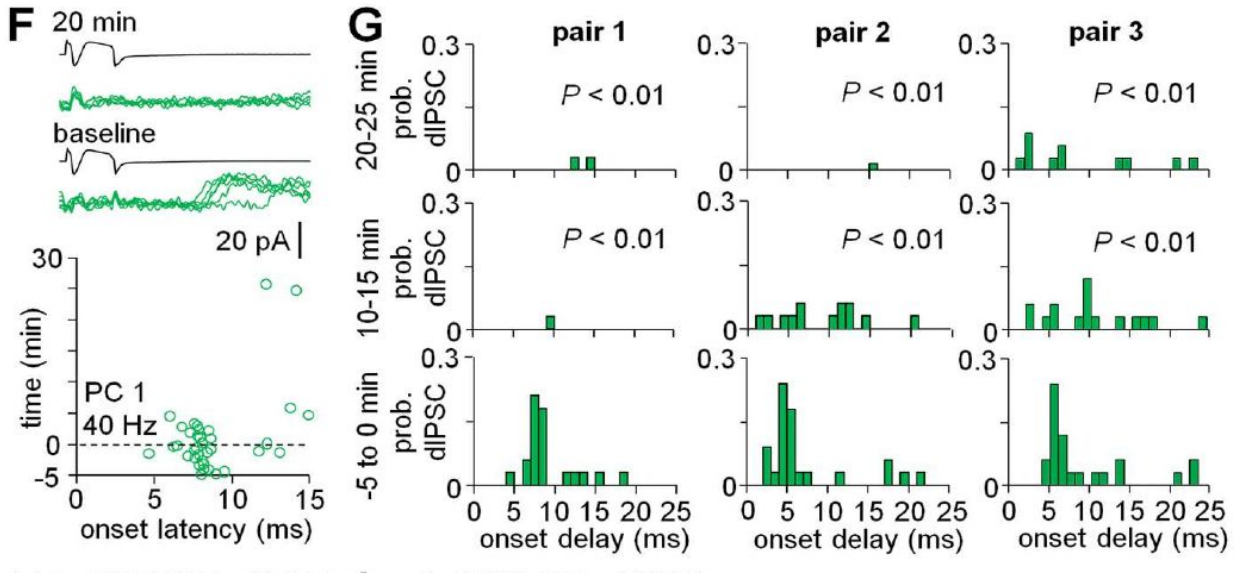

Figure 4: The two plots F and G show the dIPSC as a result of presynaptic Pyramidal cell 40Hz firing. In F, at time 0 (the dotted line) the 40Hz spike bursts then permanently reduces the occurrence of dIPSC. Even after 20 min, there is no occurrence of dISPC. In G, three similar experiments also display the reduction of dIPSC, even after 20 minutes, following the 40Hz spike burst.[7]

4. Discussion

In the first paper, Mohan et. al investigated the architecture of the pyramidal cells in human neurological tissue, and compared it against that of a mouse and macaque. Overall the dendritic length of the neurons in the human tissue was much larger, and the basal and oblique dendrites also had more branch points in the human neurons than in the mouse neurons.

Elston et. al found that the prefrontal human neural cells were more branched than the macaque and marmoset, and that human dendrites had a higher number of intersections and also dendritic field area, in addition to more spines. A higher number of spines in a dendritic tree indicate that there is a higher number of excitatory inputs, which could be a contributor to the difference in cognitive abilities. The other factors, a difference in total dendritic length, number of branches, and dendritic field area, also point to potential differences in the electrical, chemical, and physical properties of the pyramidal neuron and its synapses. All of these factors could contribute to higher complexity in cognitive functioning.

Mohan et. al.'s clustering analysis confirmed that 88% of the human pyramidal neurons had physical properties that were distinctly different than the neurons in the mouse. Since the remaining human neurons were found in a cluster of mouse neurons, it brings up the question of if there are different types of pyramidal neurons, and if this clustering analysis could be a way of differentiating the different groups. Tying in with the results from Molnár et. al., could this clustering analysis be a way of finding pyramidal neurons that initiate VLEs? More research is needed on the different types of pyramidal neurons, and if certain physical properties make a pyramidal neuron more prone to initiating VLEs.

By discovering a VLE response to a single spiking pyramidal neuron, Molnár et. al. support the idea that some neural pathways are stronger than other pathways.The IPSP and EPSP sequences following a presynaptic action potential provide a foundation for the action potential to propagate to neurons farther removed from the source. These sequences of connections and firing events could be important to cognitive functioning. Molnár et. al.'s research also emphasized the importance of interneurons in relation to the pyramidal neurons when evoking VLEs. This relationship, especially when comparing humans to other species, could be another avenue to research when looking for answers to higher cognitive functioning.

By confirming the existence of plasticity in these connections, Szegedi et. al. found evidence to support the existence of Hebbian Theory and Hebbian Learning in the cerebral cortex, in which the synaptic strength is modified due to the simultaneous activation of cells. Through the modulation of VLEs, the human neocortex can create specialized microcircuits which may be essential for achieving higher-order cognitive functionality.

All of these studies are important to understanding the biological reasons of why the human neocortex is unique. It should be noted, however, that there are difficulties in acquiring human neurological tissue which overall makes these studies have a small smaller sample size. The human neurological tissue is these studies were generally obtained from sick patients, although each study is careful to select non pathological samples for their research. There is also a wide age range of the patients, and they come from both genders which could affect the results. Despite these obstacles, each of these studies has provided valuable insight into a topic that is difficult to study, but is essential to humans understanding ourselves.

5. Summary and Conclusion

Though it is still unclear what biological factors are behind humanity's ability to have higher-order cognitive functioning, there has been much research over the years dedicated to finding what differentiates humans from other animals. Despite the fact that many animals share the same building blocks of neurons and synapses, there is much variation in behaviors and cognitive awareness across the multitude of species, indicating that there is something about the type and structure of neurons and synapses that contribute to intelligence. As far as we can tell, the human brain is the best example of one that possesses higher-order cognitive abilities. In this paper we have looked at four papers that were dedicated to finding features in the brain that are uniquely human and could contribute to higher-order cognitive functioning. As pyramidal cells are the majority of the neurons in the neocortex, all of these papers investigate specific properties of pyramidal cells that could contribute to higher cognitive ability.

In the first two papers, there were significant differences in the structure of pyramidal cells between humans and other primates, as well as humans and mice. These structural differences of longer dendritic length, higher number of spines, and others, overall point to a higher number of synapses, connectedness, and potential communication between neurons in the human tissue. In the third paper, Molnár et. al. investigated the neurological events that can happen from the firing of a single pyramidal neuron. They found that a single neuron can cause a chain of neurons to fire, in a large synaptic event that is only seen in humans. These types of large synaptic events are complex enough to contribute to the higher-order cognitive processing that separates humans from other animals. Finally, Szegedi et. al. found that spiking pyramidal cells involved in VLEs are followed by long term depression that can permanently affect the activity of postsynaptic cell. This means that the VLEs are modulated by learning and plasticity to previous neural events.

More research needs to be done to understand how the pyramidal neuron's dendritic structure affects the ability of an action potential to propagate. It is still unclear what types of pyramidal neurons cause VLEs, and also how or if the VLEs contribute to higher-order information processing. The occurrence of VLEs, and the plasticity of the connections is promising, however, as it is in line with Hebbian Theory, and could be a uniquely human trait that contributes to humanity's higher cognitive functioning.

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