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Biological Computations in Human Cortical Pyramidal Neurons: A Literature Review

As put forward in the opening chapter of *The Principles of Neuroscience*, the ultimate challenge of life science lies in the understanding of the biological basis of how the brain works. Every scientific inquiry starts with a hypothesis. For the inquiry into the human brain, a reasonable hypothesis would be the following: based on current observations, it's proper to claim that human brains give rise to a level of intellectual achievement not found in any other species. In particular, humans should have brain features not found in even the most closely-related fellow non-human primates, so as to explain the difference in the level of cognitive capabilities. The natural question to ask next, then, is this: In what ways are human brains different from that the brains of humans' next of kin? Examining these key differences might hold the key to understanding what exactly makes us human.

The first noticeable difference lies in the size of the brain. Human brains are large, even compared to other primates – human brains, weighing on average 1,400 grams, are nearly three times larger than those of the great apes (Verendeev and Sherwood, 2017). Yet, there are much bigger brains out there: elephant brains are at 4.5–5 kg, while whale brains go up to 7–9 kg (Herculano-Houzel et al., 2014; Whitehead, 2018), reducing the convincingness of the size argument. Arguing from the position of human's larger brain-to-body mass ratio isn't fruitful either, since human's ratio (1:40) is comparable to that of rodents, which are both much smaller than those of birds (1:12) and ants (1:7) (Seid et al., 2011).

But continuing down the same vein of investigating size and proportions, researchers are successful in identifying one feature that distinguishes humans: the disproportionally-expanded human neocortex. In comparison to non-human primates, the human neocortex is significantly enlarged than expected for primates of comparable brain size to ours (Rilling and Insel, 1999). A human cortex is reported to have 14-16 billion neurons, while a chimpanzee cortex is estimated to have around 7-8 billion neurons (Kenneth, 2011; Collins et al., 2017). Given this key difference, it can be properly hypothesized the expansion of the human neocortex is a major evolutionary leap in the history of neurodevelopment. Then this question follows: what are the attributes of human cortical pyramidal neurons that could make these cells central to human intellectual achievement?

1. Non-linear Computation in Cortical Neurons Dendrites

The first and most notable of the attributes is the capability of cortical neurons in performing nonlinear computations. Gidon et al. (2020), in their *Science* paper "Dendritic action potentials and computation in human layer 2/3 cortical neurons," reported the discovery of a class of calcium-gated action potentials in the dendrites of human layer 2 and 3 neurons in the cerebral cortex. These action potentials, referred to as dCaAPs by researchers, have never been previously found in research related to other mammalian species. dCaAPs are different from the typical all-or-none action potential by generating the maximum amplitude at the threshold stimuli strength but soon diminishes with stronger stimulus. A pyramidal neuron with two or more dendrites exhibiting dCaAPs could essentially function as an XOR gate, giving individual neurons the ability to classify linearly-inseparable datasets. How would this ability contribute to the overall computing power of the human brain?

Georgescu et al. (2020), in an arxiv preprint article “Non-linear Neurons with Human-like Apical Dendrite Activations” modeled the aforementioned findings computationally. They presented converging evidence that validates that a single neuron employing the novel apical dendrite activation can achieve 100% accuracy in learning XOR logical functions. Through cross-comparison with other models, the researchers found that the single neuron model implementing the novel type of activation function from Gidon et al.’s research surpasses various architectures, including multi-layer perceptions (MLPs) and convolutional neural networks (CNN), when processing high dimensional datasets. One would certainly be curious about the mechanism behind such results, namely, how exactly would nonlinear activation function resembling dCaAPs enhance the performance of the neural network. While explanations weren’t given in the two mentioned papers, a recent review paper by Acharya et al. (2022) from *Neuroscience* helps shed light on this question. Acharya et al. identified four main implications of dendritic nonlinearities: improved expressivity of single neurons, improved use of neuronal resources, utilization of learning signals, and enabling of continual learning. Equipped with nonlinearity, a single neuron can essentially perform classification that traditionally requires the use of two-layer artificial neural networks. It would thus not be hard to conceive how the four implications sketched above could be true on an intuitive level.

To come back to Gidon et al.’s research, as inspiring as their paper is, many questions are also left unresolved:

1) How are neurons with simple vs. complex dCaAPs different? What factors could influence whether the dCaAPs are coupled or not with the somatic action potentials?

2) The paper mentions that 4 out of 12 cells showed the inverse behavior where stronger stimuli resulted in decreased somatic firing. What about the remaining 8 of the 12 cells? Are

there correlations between the cells that exhibit such quality? Are dCaAPs universal in layer 2/3 neurons of the human cortex or are they more found in specific parts of the cortex? What, in turn, does this tell us more about the function of such action potentials in human neurons?

3) The authors kept referring to the fact that dCaAPs have not been found in the study of rodents, but could they possibly exist in the brain of primates? Is the non-linear feature of neurons special to humans only or can it be found generally within primate species?

Despite all the yet unaddressed questions, Gidon et al.'s and Georgescu et al.'s papers do contribute to our confidence in the hypothesis that the attribute of nonlinearity could be central to human intellectual capabilities. This is supported by some other recent research. In the opinion piece "Cellular Mechanisms of Conscious Processing" from *Trends in Cognitive Sciences*, Aru, Suzuki, & Larkum (2020) highlight the role of nonlinearity in the direction of brain's information flow. By examining experimental evidence from several articles, they proposed the "Dendritic Integration Theory" (DIT): they believe that the hallmark of active intellectual processing is the integration of anatomically separate data streams, and pyramidal cells act as gates to control such integration. They cited their previous results from research on anesthesia patients: it's found that anesthesia put people into unconsciousness without completely shutting down synaptic transmission and neuron firing to a large degree. Aru et al. believe that this evidence implies that a critical nonlinear threshold of activation between brain areas exists that's critical to the integration of information flows, and the mechanism responsible for implementing this threshold is disturbed under anesthesia. More specifically, this hints that the decoupling of the pyramidal neurons is the general property of the unconscious state, where no active intellectual information processing would be happening (Suzuki & Larkum, 2020). This could allow us to interpret the research of Gidon et al. in a new light. The threshold of dendritic activation and the nonlinear pattern found in layer 2/3 neurons agrees well with the theory that pyramidal neurons act as gates in directing data streamflow within the brain. Hence, would different combinations of the state of gates mean different patterns of data flow? For the experimental evidence, Gidon et al. found that 17 out of 37 cells have coupled dCaAPs and the remaining 20 out of 37 have decoupled dCaAPs (whose implications the authors didn't explain), could this pattern of coupling/decoupling correspond to a specific state of information flow? If this hypothesis holds, what should follow is that each cell should have the potential to be coupled or uncoupled, with some factors triggering the switch between states. The next step in this direction could be to repeat Gidon et al.'s experiment by obtaining cell samples in the same position in the brains of different patients and see if they show differences in having coupled/decoupled dCaAPs.

2. Branched Morphology and Repeated Inputs in Cortical Dendritic Trees

In addition to the nonlinear activation potential on neurons that could advance the cortex's computational power and the control of information flow, the morphology of dendritic trees is another attribute that could play an instrumental role in aiding natural neural network's data processing. The major class of projection neurons in the human neocortex is the pyramidal neuron, which contains a triangular soma, an axon, and apical and basal dendritic trees. Compared with other primates like chimpanzees, humans are found to have cortical pyramidal neurons with significantly longer and more branched dendritic trees in all cortical areas (Bianchi et al., 2012). This key evolutionary observation has inspired researchers to investigate the functions of such dendritic trees.

Jones and Kording (2021) from the University of Pennsylvania, in their *Neural Computation* paper titled "Might a Single Neuron Solve Interesting Machine Learning Problems

Through Successive Computations on Its Dendritic Tree," designed a trainable neuron model with a dendritic tree and compared its performance on binary classification tasks with two other more standard networks: 1) a fully connected neural network (FCNN) matched in parameter size and 2) a linear point neuron (LPN) using the classic McCulloch and Pitts (M&P) model. It was found that across a range of computer vision tasks, the dendritic tree model consistently performed better than the LDA and worse than the FCNN. Jones and Kording further examined the effects of repeated inputs: increasing the number of the dendritic trees (denoted as *k*) with identical inputs connected to the neuron body. It was found that as the *k* value went up, the classification accuracy steadily increased, approaching the upper bound of FCNN's accuracy.

Several questions could stem from the description of the research above:

1) How did the researchers think of using repeated inputs? The authors described in the paper that they were inspired by anatomical observations: it's concluded empirically using electron microscopy that each presynaptic axon creates approximately four synapses with one postsynaptic dendrite – indicating the signal from an axon is repeated four times on the receiving dendrite (Kincaid et al., 1998).

2) Why exactly would repeating inputs increase the computational capabilities in both the natural and the artificial neural networks? This may be related to the concept of redundancy in machine learning research. It might even be possible that the initial inspiration for implementing redundancy in artificial neural networks originated from the observation of biological principles, as described in a 1994 paper, "Training redundant artificial neural networks: Imposing biology on technology" (Medler and Dawson), which found that ANN with redundancy achieved significantly better results than those without. The theory behind the superior performance of the redundant network is supported mathematically by Izui and Pentland (1990), whose analysis

yields the conclusion that redundant networks produce faster convergence, higher accuracy, and higher reliability.

3) If a fully connected neural network is generally of the highest accuracy across all tasks, why did evolutionary mechanisms shape the brain to be fully connected? The research by Acharya et al. mentioned in Section 1 could provide some insights: it puts forward the belief that the most important resource in the brain is connectivity – most of the brain volume is already consumed by axons, and the present connectivity in natural neural networks is still relatively sparse. A fully connected network, therefore, couldn't in any way be feasible in actual implementation settings.

4) How does branched morphology help the neural network achieve a higher level of performance? While Jones and Kording didn't tackle this question in the paper's discussion section, the research by Eyal et al. (2018) titled "Human Cortical Pyramidal Neurons: From Spines to Spikes via Models" could provide viable explanations. By studying six human Layer 2/3 pyramidal cells obtained from biopsy, Eyal et al. were able to present a detailed model of the human neocortex. They found that the large dendritic trees, which give rise to a substantial number of dendritic terminals, endow human cortical pyramidal neurons with the "ability to support a large number of independent NMDA spikes," which could lead to a significant increase in the network's storage capacity. This is derived from the computer science theory that the number of patterns that could be learned in the network is positively correlated with the number of edges in the network – $O(E^2)$ or $O(E*\log(E))$, depending on different output neuron (Shalev-Shwartz and Ben-David, 2014). A further question basing off of this: is such enhancement of performance from dendritic tree branching mechanistically equivalent to the

creation of a deeper neural network as compared to a single-layer one, so as to achieve more effective feature extraction when performing classification?

To further complicate the picture, Jones and Kording found that constructing neuron models based on neurobiology of the humans doesn't always result in better performance: when they tried introducing asymmetry in the dendritic tree, mimicking the real situation in the human brain where asymmetry is prevalent, they found such asymmetry made the performance considerably worse. They speculated that biological structure imposes restraints on the effectiveness of the artificial neural network. Yet, since biological organisms are evolutionarily selected to include asymmetry in neural systems, they must exist for some logical reason. A direction of next-step research could be to identify biophysically or prove computationally how dendritic tree asymmetry is conducive to the overall functioning of the human brain.

3. Genetic Control on Cortical Organization

Moving from the cellular level to the genetic level, one can discover another research finding on the difference between human cortical neurons and their counterparts in chimpanzees: Gomez-Robles et al. (2105), in a *PNAS* paper, reported experimental evidence that supports the brain of humans are genetics-dictated to a lesser degree than that of apes, resulting in the former's larger room for plasticity.

Through methods including Magnetic Resonance Imaging (MRI), quantitative genetics analysis, and principal components analyses (PCAs) of shape variation, Gomez-Robles et al. were able to calculate heritability scores for brain size and shape for both humans and chimpanzees. While the heritability of brain size for humans is larger, the heritability is significantly lower heritability for brain shape, which is related to the cortical organization. Such data are in line with the proposition that humans are evolved to have relaxed genetic control on cortical organization, which could facilitate neural development under cultural and environmental influences under altricial conditions.

How do these genetic inheritability patterns affect the computational behavior of human cortical neurons on a cellular level? With a larger brain size at birth, more neurons, and an expanded neocortex, along with less existing organization and therefore stronger plasticity, human brains have more capacity in forming the cortical circuits it would need to carry out computational tasks related to socially and culturally demanding tasks. This mechanism is supported by the research of Bianchi et al. (2013), which also comparatively studied, taking a more cellular approach, the early development of cortical pyramidal neurons in macaque monkeys, chimpanzees, and humans. Using immunohistochemistry against synaptophysin, a protein from presynaptic vesicles, Bianchi et al. tracked the process of synaptogenesis – the formation of synapses. They were able to identify more rapid and prolonged synaptogenesis in species known to equip with relatively higher socio-cognitive functions.

One would surely be tempted to continue asking next: which genomic loci led to these differences in heritability? If having identified the loci, is it theoretically possible to genetically engineer chimpanzees with higher plasticity in the cortical organization so as to create ape species that behave more like humans for understanding evolution better? These could all be plans for the next step of research.

While this paper strives to provide a comprehensive review of aspects that distinguishes human cortical pyramidal neuron, it's in no way all-encompassing. Due to limitations, some other attributes of cortical pyramidal neurons are not covered, the most notable of which being the unique membrane capacitance in neocortical neurons, as published by Eyal et al. (2016)

on *eLife*. The researchers were able to show that the capacitance of human L2/3 cortical neurons is only half of the capacitance of common cell membranes (*Cm* of ~0.5 $\mu F/cm^2$, as compared to the "universal" value of ~1.0 $\mu F/cm^2$). The lower capacitance is important in the signal processing of the neocortical cells as it, according to electrochemical principles, enhances both the charge-transfer process and charge propagation along the axon, contributing to the efficiency of signal transduction and neuron's overall excitability. As one wasn't able to find studies examining membrane capacitance in non-human primates, it's not possible to conclude whether such a feature is special to the human species.

To come back to the question from the start: what are the attributes of human cortical pyramidal neurons that could make them central to human intellectual achievement? Gidon et al.'s illuminating research revealed the attribute of dendritic nonlinearity, which has been validated to contribute to the computational capability of the neural network and could potentially be significant in directing neural information flow during active processing. The modeling from Jones and Kording highlighted the attributes of branched morphology and repeated inputs, both of which are supported by mathematical theories to enhance the performance of networks. Heritability analysis from Gomez-Robles et al. points to the attribute that human cortical neurons are less genetically-dictated, which lends these neurons greater freedom in developing cortical circuits that factor in external environmental influences. These attributes collectively distinguish the human cortical pyramidal neuron from its counterparts in the human species' next of kin, making this neuron type a viable candidate for explaining the origins of intellectual capabilities that makes us who we are. Many lingering questions, raised throughout the paper, along with the hope of ultimately understanding the human brain, provide exciting prospects in this field and are directions of further inquiry.

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