Essay - The Basic Unit of Information in the Brain

In this remarkable era of molecular neurobiology and neuropharmacology, it is easy to forget that the brain is basically an electrical device. The brain encodes, processes, and transmits information electronically. Neurotransmitters, and their associated synaptic vesicle and receptor systems, basically are a means of transferring the information between the electrical devices known as neurons. Neurotransmitters, which are the basis for most of pharmacological interventions, are just the messenger; they are not the message. To be sure, the actions of the neurotransmitters are precisely controlled in space and time, but this control most often is exerted by the electrical action potentials that arrive at the synaptic terminals. The message containing the information (or misinformation) is encoded in the sequence of action potentials.

The fundamentally electrical nature of the nervous system was readily appreciated since the work of Luigi Galvani in the late 1700's who applied electrical stimulation from static electricity generators with electrostatic charges stored in Leyden jars (basically a capacitor). It was not until the mid-1900's that the neurochemical transmission of activities between neurons supplanted what was thought to be electrical in nature. The demonstration that certain chemicals, such as acetylcholine, could mimic the effect of vagal nerve stimulation on the heart argued for a neurochemical intermediary in the neural control of the heart (Valenstein 2005). The logic follows from the syllogism:

The heart is slowed by the agent acetylcholine

Vagal nerve stimulation slows the heart

Therefore vagal nerve stimulation is the agent acetylcholine

The logic derives its certitude from linking the major premise, *The heart is slowed by the agent acetylcholine,* to the conclusion, *Therefore vagal nerve stimulation is the agent acetylcholine,* through the middle term, *heart slowed,* in both the major premise and the minor premise, *Vagal nerve stimulation slows the heart,* with *acetylcholine* being the major term and *vagal nerve stimulation* being the minor term. The validity of the argument depends on whether the middle term, heart slowed, is exactly the same in both the major and minor premises. If they are not, then there are four terms in the argument: the major term, acetylcholine, the minor term, vagal nerve stimulation, and one middle term that is heart slowed specific for acetylcholine and another middle term, heart slowed for vagal nerve stimulation. If these two versions of the middle term are not exactly the same (as in Leibniz's Law on Identity of Indiscernibles where two [or more] entities are identical if every property and every consequence of each are exactly the same), the argument is victim of the Fallacy of Four Terms.

Consider the following syllogism relating DBS to the effects of the neurotransmitter, dopamine:

> *Improvement of Parkinson's disease is from the application of dopamine (through its prodrug – levodopa)*
>
> *DBS improves Parkinson's disease*
>
> *Therefor DBS is an application of dopamine*

This syllogism would valid only if improvement in the context of the application of dopamine is exactly the same consequent to DBS. If not, there are four terms (two versions relating to different improvements) and the syllogism results in the Fallacy of Four Terms. It is clear that the improvement associated with the application is not the same as that provided by DBS and consequently, the syllogistic reasoning is invalid.

Despite the demonstrated fallaciousness of the reasoning, many still equate DBS and the neurotransmitter dopamine, specifically, but also neurotransmitters in general. This is not to say that the neurotransmitters are irrelevant. The neurotransmitters are relevant in the same way as electrons are relevant in an electrical computer. However, no one would say that a computer and an electron are synonymous or equivalent. There is nothing inherent in an electron that would determine whether 2 + 2 = 4 as opposed to 3 + 3 = 6.

Neurotransmitters talk typically allude to excitatory or inhibitory effects which is inaccurate and misleading. Rather, neurotransmitters typically cause depolarization or hyperpolarization of the post-synaptic membrane. These changes frequency, but not necessarily, result in an increase or decrease of the information output of the neuron, which is the sequence of action potentials traveling out the axon to other neurons. In some instance, particularly within the basal ganglia-thalamic-cortical system, initial hyperpolarizations induced by the actions of the neurotransmitter, GABA, are followed by a rebound depolarization that can result in a net increase in action potentials generated in the postsynaptic membrane. Similarly, a prolonged subthreshold depolarization can reduce the probability of action potentials being generated.

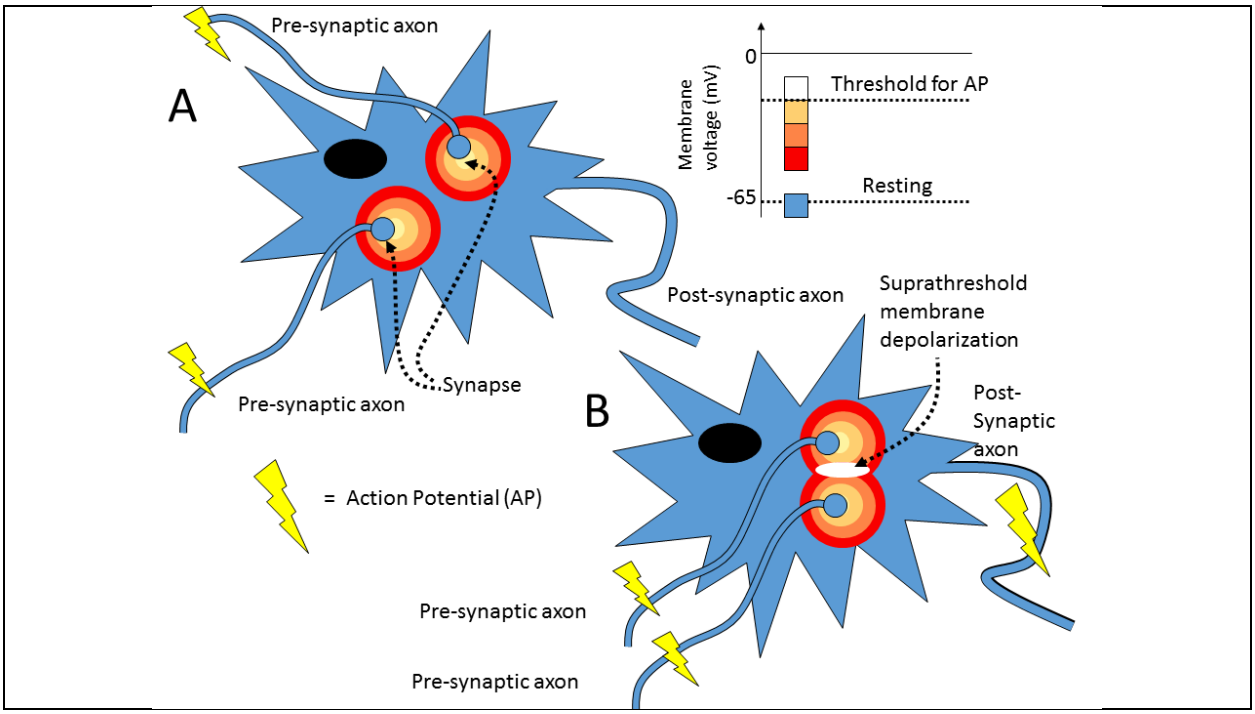
These depolarizations and hyperpolarizations summate in the individual neuron to determine whether an action potential, the unitary bit of information in the brain, is generated (like a “1” in the binary code in electronic computers) or not (like a “0” in the binary code of electronic computers). Thus, the processing of information by an individual neuron is electronic. The actions of neurotransmitters on an individual neuron only indirectly affect information processing and there are many other factors involved. The actions of neurotransmitters are not synonymous with brain information processing functions.

There is a conceptual predisposition to equate chemical neurotransmission with the physiological function of neurons (Valenstein 2005). To the degree that mediation at the neurotransmitter level (for example, replacing dopamine with doses of levodopa) reverses the symptoms of Parkinson's disease, chemical neurotransmission is, in fact, similar to physiological function. However, the remarkable success of DBS in the face the failure of clear manipulation of neurotransmission, either with pharmacological agents or biologicals, such as fetal cell transplants, to control symptoms, such as bradykinesia and akinesia, is strong evidence that chemical neurotransmission is not synonymous with brain function, and further, the electrical effects of DBS are superior to effects of pharmacological agents.

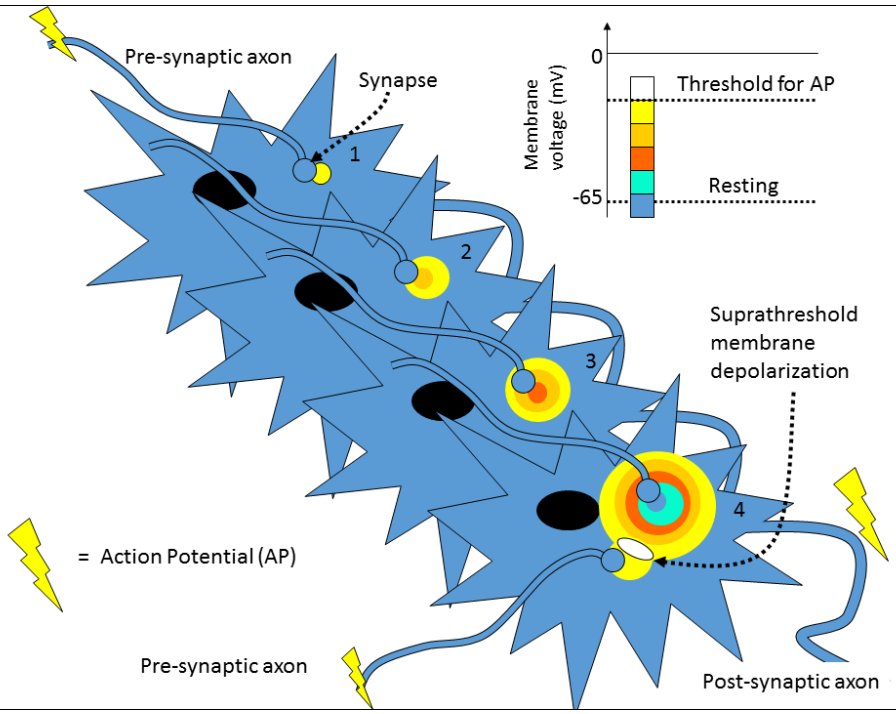
Critics of this conclusion note that not every symptom is directly caused by a failure of dopamine neurotransmission and, consequently, these symptoms should not be expected to respond completely. However, such an explanation does not account for the failure of pharmacological and biological treatments for symptoms that previously responded to dopamine. Further, the delayed excitation of Vop neurons after inhibition by the action potentials arriving from the GPi could not have been predicted by knowing that the neurotransmitter involved is GABA (Montgomery 2006).

Neurotransmitters released at the synaptic junctions are just the messengers; they are not the message. One merely has to consider the time scale of operations to understand the difference between electrical and pharmacological effects. DBS operates on the order of milliseconds. For example, the time difference between effective DBS at 130 pps and ineffective DBS at 100 pps is 2.3 ms, which is the difference in the inter-stimulus pulse intervals. Pharmaceutical agents operate over minutes to hours and cannot replicate the precise timing of information in the brain.

Considerable evidence indicates that this pattern of DBS is important in its therapeutic effect (Montgomery 2005; Montgomery and Gale 2008) and consequently, the patterns of action potentials induced by the DBS are the key to efficacy. The time scale of these patterns is very different from the time course of pharmacological or biological agents, as described above. Information is encoded in the patterns of action potentials and information is processed by electronic integration of information encoded by action potentials, translated by neurotransmission at the synaptic junction, and then re-translated to changes in the electrical properties of the post-synaptic membrane. The change in the neuronal electrical membrane potentials (voltages) are integrated over space and time to allow information processing. Hypothetical examples are shown in **Figures 1** through **4**. These examples are not based on processes that actually occur in the brain. Rather, their purpose is to attest to the computational power of the neurons integrating electrical phenomena.

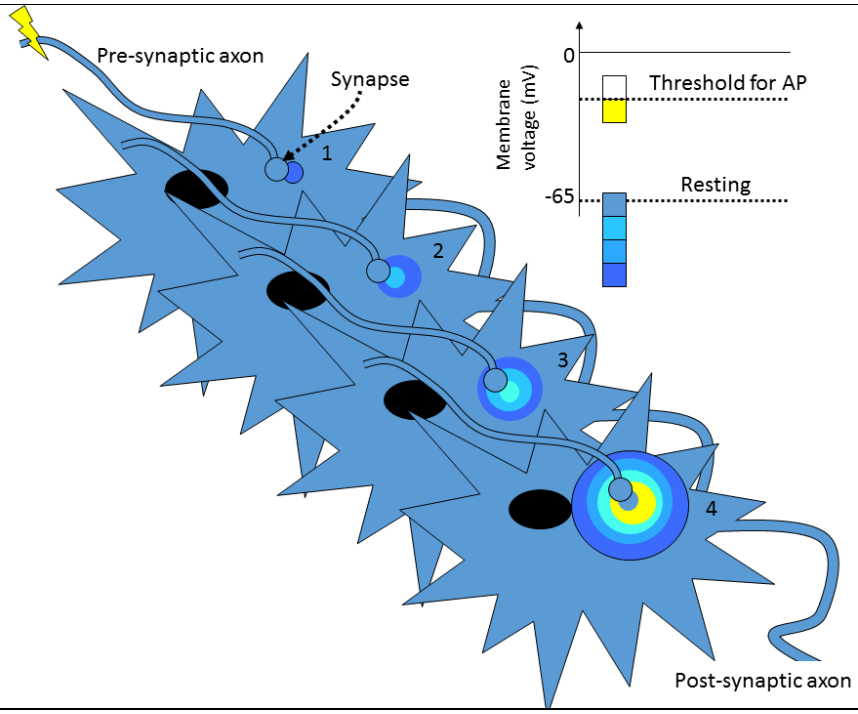


Figures 1. Hypothetical example of the actions and integrations of electrical changes in the post-synaptic membrane associated with excitatory inputs. This figure represents two neurons. In one case (A), there are two excitatory synapses that are relatively far apart. The synaptic inputs cause a spread of depolarization (indicated by the color codes) but these do not overlap to have an adding effect. By contrast, neuron B has two excitatory synapses that are relatively close. As the depolarization from each synaptic event spread out, they overlap. The additive effect of their overlap is sufficient to cause an action potent in the axon of neuron B. Also, spatial summation as described above could be considered an example of Boolean logical operators. If two (or more) synapses are required to have sufficient spatial summation to generate an action potent, this would be an example of an "AND" logical operator; input 1 AND input 2 both must be true equivalent to excitatory inputs or the logical values of "1", for the output to be true, equivalent to an action potential or logical value of "1", as shown in neuron B. Re-consider neuron A. If either synaptic input was sufficient itself to result in an action potential, then the neuron A would fire with one or both synapses were depolarized. This would serve the logical operator, "OR," where if any input is true, equivalent to a sufficient excitatory input or the logical value "1", then the output is true, equivalent to an action potential or the logical value of "1". *See Chapter 4 - Principles of Electrophysiology, Montgomery Jr. EB, Deep Brain Stimulation Programming: Mechanisms, Principles, and Practice, Oxford University Press 2016* for discussion of how changes in the neuronal membrane potential (voltage) cause action potentials.



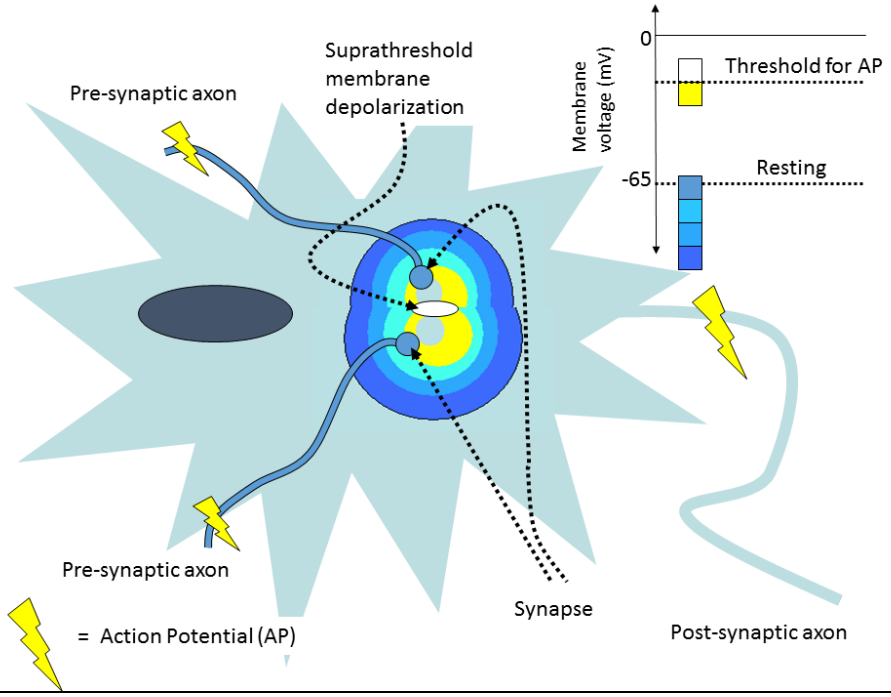
Figures.2. Hypothetical example of temporal summation. A single neuron is represented over time (time intervals 1 through 4). In this case, a single excitatory input is received (time interval 1) and causes a membrane depolarization, but it is insufficient to cause an action potential. However, this change induced in the neuronal membrane voltage spreads out over time (time intervals 1 – 4). Later, if another synapse causes a post-synaptic excitatory potential (time interval 4), resulting in a subthreshold depolarization, this second potential by itself would not be sufficient to cause the neuron to fire and create an action potential. However, if the depolarization of the second synaptic input overlaps with the lingering subthreshold depolarization induced by the first synapse (time interval 4), the combined effect may exceed the threshold and generate an action potential. This arrangement of interactions is well suited to detecting subtle timing information in the inputs to the neuron. *See Chapter 4 - Principles of Electrophysiology, Montgomery Jr. EB, Deep Brain Stimulation Programming:*

Mechanisms, Principles, and Practice, *Oxford University Press 2016* for a discussion of how changes in the neuronal membrane potential (voltage) cause action potentials.



Figures 3. Hypothetical example of a post-synaptic inhibitory input. This figure schematically represents a single neuron over time intervals 1 –4. An action potential reaching the pre-synaptic axon terminal and releasing an inhibitory neurotransmitter changes the post-synaptic neuronal membrane potential. The neuronal membrane beneath the synapse becomes more negative (hyperpolarized). The hyperpolarization spreads over the surface of the neuronal membrane. In many neurons, hyperpolarization activates a group of ionic conductance channels (*See Chapter 4 - Principles of Electrophysiology, Montgomery Jr. EB, Deep Brain Stimulation Programming: Mechanisms, Principles, and Practice, Oxford University Press 2016*) that cause a subsequent depolarization as seen at time 4 (the yellow filled circle). In this case, the depolarization is insufficient to generate an action potential. However, there are

some circumstances where it can and actually result in an action potential. In these cases, the inhibition actually becomes a type of delayed excitation.



Figures 4. Hypothetical example of spatial summation of post-synaptic inhibitory inputs and post-inhibitory rebound excitation (the generation of an action potential). This figure schematically represents a hypothetical neuron that receives two inhibitory synaptic inputs at relatively the same time. Action potentials reaching the two pre-synaptic axon terminals release inhibitory neurotransmitters. The neuronal membrane beneath the synapse becomes more negative (hyperpolarized). The hyperpolarization spreads over the surface of the neuronal membrane. In this neuron, the hyperpolarizations summate sufficiently to activate a group of ionic conductance channels (*see Chapter 4 - Principles of Electrophysiology, Montgomery Jr. EB, Deep Brain Stimulation Programming: Mechanisms, Principles, and Practice, Oxford University Press 2016*) that cause a subsequent depolarization sufficient to

initiate an action potential. This hypothetical neuron serves as the Boolean logical operator, “NAND,” in which if two inputs are false, equivalent of an inhibitory synaptic event or the logical value of “0”, then the output is true, equivalent to an action potential or the logical value “1”. This example is interesting because nearly every logical operation can be constructed of various combinations of "NAND" operations.

The neuronal processing resembling the logical operation of a “NAND” gate in **Figure 4** is particularly interesting. The logical “NAND” gate holds that when two (or more) statements (inputs) are all false (and all need to be false), then the conclusion (output) is true. Any other combination results in the conclusion being false. In terms of neuronal operations, this process could mean that when a sufficient number of simultaneous inputs to the neuron are actively inhibiting, the result will be an action potential in the output of the neuron. This phenomena is seen in post-inhibitory rebound excitation which is prominent in many neurons of the basal ganglia-thalamic-cortical system. “NAND” gates also can be implemented in silicon transistors that make up the Central Processing Units (CPUs) of digital computers. Indeed, every logical operation (which also combines to perform all mathematical operations) can be implemented as some combination of “NAND” gates. Thus, any computer operation basically uses various combinations of “NAND” gates. If the most sophisticated computers can operate on these elemental logical operations, just think of what billions of neurons, in remarkable complexities and interconnections, can achieve.

The computational power of neurons is further increased by variations in synaptic efficiencies. For example, synaptic inputs closer to the axon initial segment, where action potentials are generated, have a greater probability of initiating an action potential than will

synaptic inputs far away on the dendrites. The synaptic inputs close to the axon initial segment are more likely to function as logical "OR" gates, whereas synaptic inputs further out on the dendrites are likely to act as logical "AND" gates (see **Figure 1**).

Synaptic efficiencies can be modulated dynamically, meaning over relatively short time periods. For example, the magnitude of electrical responses in the post-synaptic membrane can be increased, as in long-term potentiation (LTP), or decreased, such as in long-term depression (LTD) by repetitive activations, thus constituting a form of learning. LTP can cause an excitatory input to go from subthreshold to threshold, generating an action potential. LTD can cause the converse.

The computational power based on the logical operations of individual neurons can be greatly increased with small-scale and large-scale interconnections. Indeed, the computational methods of neural networks are based on the patterns of interconnections between relatively simple operators analogous to neurons (Rumelhart, McClelland et al. 1986). The computational power lies in the patterns of interconnections. Neural networks can learn in a manner analogous to LTP and LTD, in which connection strengths (synaptic efficiencies) between computational units are varied. Further, these neural networks can learn operations for which there is no set of instructions. For example, backing up a truck and trailer is highly counterintuitive skill that requires considerable practice. A novice attempting this task, even with an experienced expert providing advice, would still have difficulty. Yet a network of 25 simple computationally simulated neurons can learn the task (Nguyen and Widrow 1989).

Just as much of the computational power of a computational neural network lies in the dynamic patterns of interconnections, with varying connection strengths, so does the computational power of the brain. Indeed, studies in non-human primates show that

physiological functions, such as responding to a “go” signal or contracting a muscle, are not consistently represented in the behaviors of any signal neuron (Montgomery, Clare et al. 1992). Rather, a neuron’s activity may be related to one physiological function in one context and to another function in a different context. The remaining candidate for the consistent representations of physiological functions is in the pattern of interconnections.

The capacity of neurons and networks of neurons to process and transmit information electronically may be the basis of the therapeutic mechanisms of action of DBS. DBS can improve information content by increasing the signal to noise ratio by resonant amplification or suppress misinformation (see Montgomery and Gale, 2008). Understanding disorders of the brain as consequences of misinformation is a new conceptualization. Traditionally neurology generalized disorders as positive or negative symptoms or symptoms of disconnection. Positive symptoms typically were associated with excessive function, such as a seizure or spasticity. Negative symptoms were associated with a loss of function, such as paralysis of blindness. Relatively new are the disconnection syndromes where separate structures that depended on each other were separated as a consequence of disease. An example is alexia without agraphia. Hopefully, in the future, neurologists and psychiatrists will come to understand brain disorders foremost as misinformation. This will result in radically different approaches to treatment.

References:

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