



Articles

Quest for Consciousness.

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In Stuart Hameroff's review of my book, *The Quest for Consciousness: A Neurobiological Approach*, he praises many attributes of its empirical program to explore the neural basis of consciousness that the late Francis Crick and I have been advocating for years. Stuart also cites instances where he and I differ as to which evidence to favor and what seems reasonable or not in the search for the material roots and causes of consciousness. This is fair enough. However, there are three specific points in Stuart's essay that do not give a correct reading of the extant data. Let me address these.

Gap junctions and consciousness

As Stuart correctly points out, a flurry of studies over the last handful of years have shown that electrical gap junctions play a much larger role in cortex than previously realized (for a review, see Bennett and Zuki, 2004). The focus has been on gap junctions mediated by the Connexin family of proteins (which has at least 10 members expressed in the mammalian central nervous system); they provide a low-resistance, electrical pathway between two neurons – hence their common alias, electrical synapses. The most important connexin of the adult brain is Cx36. These proteins link groups of local, inhibitory interneurons into large networks (forming a “hyperneuron”), restricted to specific layers in neocortex and hippocampus. Different from their conventional chemical synapses that would serve to inhibit the firing activity of their postsynaptic targets, gap junctions can cause the membrane depolarization in one interneuron to spread to others. This has given rise to the hypothesis that Cx36 gap junctions synchronize the firing of these interneurons, enabling the entire population to fire in lock step in the 30-70 Hz (gamma) range. If such synchronized and rhythmic firing is important for certain aspects of attention, perception and consciousness, then mice that lack gap junctions should show major

deficits.

It has been possible to breed mice that lack the gene for the Cx35 protein. In these knockout mice, interneuron coupling is greatly reduced; this goes hand-in-hand with a loss of spike synchrony among them (however, gamma range oscillation persist, albeit at a reduced amplitude). The animals have decreased retinal function at low light levels (as expected from a loss of gap junctions in the retina) and reduced reproductive rates, but otherwise no major behavioral deficiencies; they display no obvious loss of motor coordination, and can stay on a rotating cylinder (rotorod test) as well as normal, wildtype mice. By and large, the Cx36 knockout mice have a relatively benign phenotype. Of course, it is quite possible that the behavioral assays used so far are too crude to detect perceptual pathologies or other deficits in rodent consciousness. For example, it may be possible that these mice can be conditioned using aversive delay, associative (Pavlovian) conditioning but not using the more sophisticated form of trace conditioning (in which there is an interval between the end of the tone and the onset of the foot shock (Han et al., 2003).

The idea that the firing activity of groups of interneurons, possibly extending over several cortical columns, is tightly synchronized and may underlie the coalitions of neurons that are sufficient for any one conscious percept is a fascinating one to me. However, no positive evidence links neuron-to-neuron coupling in cortex via gap junctions to perception, let alone consciousness. Thus, the cautionary statement in my book, “Not enough is known about this phenomenon to implicate it in conscious perception.” remains true today. This may always change in the future, of course.

Dendrites and consciousness
Stuart criticizes my neglect of dendrites, the extended appendages formed by all nerve cells and that carry the majority of synapses. He states his opinion flat out as “Consciousness occurs in dendrites, and the results are conveyed elsewhere by axonal spikes.

I do not understand this statement. Does he mean to imply that the dendritic tree of any one neuron is sufficient for consciousness? Or that dendrites, collectively, are essential to understanding the neuronal correlates of consciousness? Furthermore, I have never stated “that axons reverberate via cell bodies, bypassing dendrites altogether”. In my PhD thesis, I modeled nonlinear computations occurring in the dendritic trees of retinal ganglion cells. I am the author of a textbook “Biophysics of Computation: Information Processing in Single Neurons” (Oxford University Press, 1999) whose topic is the large repertoire of mathematical operations available to single neurons, implemented by voltage- and ligand-dependent channels, and particular synaptic architectures coupled to complex dendritic tree morphology. In 2002, we published empirical evidence in Nature that a single neuron in the locust’s

visual system multiplies its two inputs within its dendritic tree (Gabbiani et al., 2002). Finally, in footnote 22 of Chapter 15, I point out a specific coincidence-detection mechanism within the apical tuft of large, layer 5 pyramidal neurons in neocortex. This operation might be the crucial ingredient for feedback from the front of the cortex to its back that is, so I argue, an essential requirement for the NCC. I don't discuss these ideas in more depth given 1) our lack of knowledge (by-and-large, dendritic trees of cortical neurons remain offlimit to the intrusive inspection by intracellular electrodes in behaving animals) and 2) our extremely limited ability at this point in time to interfere in a delicate, deliberate, reversible and transient manner with dendritic mechanisms under in vivo conditions. What is needed are not general statements about the importance of dendrites – clearly dendritic trees are an integral part of the nervous system and the brain wouldn't work without them – but specific, biophysically plausible, proposals.

The action of anesthesia Stuart disagrees with my statement that “So far, they [i.e. anesthetics] have proven to be too blunt of a tool to help in our quest, though that may change in the future. “ (p. 96), in particular as applied to volatile, inhaled gas anesthetics (e.g., ether, nitrous oxide).

All of the recent evidence implicate specific proteins, in particular voltage- and ligand-gated ionic protein channels as the site action of such volatile agents (e.g. Sonner et al., 2003). This does not rule out that some anesthetics may exert some of their diverse effects in a global, unspecific manner, compatible with the Meyer-Overton lipid solubility relationship (see, for example, Tang and Xu, 2002). Whether or not quantum mechanical effects play any role at all in their action, as asserted by Stuart, remains speculative.

Stuart claims that at just the right concentration, gas anesthetics only inhibit consciousness. This is news to me. More than one hundred years of experience has shown that the majority of anesthetic agents act in a dose-dependent manner, first causing analgesia, then amnesia, followed by loss of purposeful response, immobility and finally autonomic stability. Somewhere along this concentration gradient consciousness begins to be progressively reduced until it is finally abolished. At any given therapeutic concentration, a host of bodily processes is affected (e.g. cardiac or pulmonary function). The discovery of an agent that would turn consciousness off and back on again, without affecting other brain and body functions, would revolutionize the practice of anesthesiology and the study of the neuronal roots of consciousness. Unfortunately, to the best of my knowledge, no such substance exists today. As I noted in my book, one attractive spin-off of discovering the neuronal correlates of consciousness would be the design of such substances. This, I challenge Stuart to provide evidence of loss of consciousness without concomitant loss of pain perception, memory impairment,

pulmonary function and so on.

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