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Obituary

In Memoriam: Francis H.C. Crick

I never saw Francis Crick in an immodest mood. He was a towering figure, both in science and in person, and was quick to get to the bottom of an issue; his only immodesty was his choice of scientific problem. In *What Mad Pursuit: A Personal View of Scientific Discovery*, he wrote that at an early stage in his scientific career:

> Quickly I narrowed down my interests to two main areas: the borderline between the living and the nonliving, and the workings of the brain. Further introspection showed me that what these two subjects had in common was that they touched on problems which, in many circles, seemed beyond the power of science to explain.
>
> —Francis Crick, 1988, p. 17

Crick was trained in physics and during World War II worked on acoustic and magnetic mines for the British Admiralty at Teddington, so when his interests turned back to science, he was older than most PhD students. He was fortunate to get a studentship in Max Perutz's group in the Cavendish Laboratory at Cambridge University, where he learned about X-ray crystallography. The discovery of the structure of DNA by James Watson and Francis Crick and, later, the structures of proteins by Perutz's group set the stage for the extraordinary advances in molecular biology that have occurred in the last 50 years. He once mentioned to me that it had never occurred to him during the years he worked on the genetic code that the human genome would be sequenced in his lifetime.

Crick's interest turned to neuroscience after moving from Cambridge to the Salk Institute for Biological Studies in 1976, where he began to think about the workings of the brain. His approach to the brain focused on perception, particularly visual perception (Crick, 1979). His preferred way to attack a problem was to read the literature, which he knew better than most experts, and to discuss the details directly with the authors. In preparing a paper on the distribution of long-range horizontal connections within the visual cortex, for example, he visited Jennifer Lund's laboratory and asked to see her raw anatomical data (Mitchison and Crick, 1982). I vividly recall his visit to the Johns Hopkins University in 1982. He had arrived unprepared to give a lecture but gave an insightful one on the visual system using borrowed slides.

Crick was skeptical that theoretical approaches could provide a breakthrough in our understanding of the brain but saw brain modeling as a useful technique for sharpening our thinking.

> Hence an important role for theory in neurobiology is not merely trying to create correct and detailed theories of neural processing (which may be an extremely difficult task) but pointing to which features it would be most useful to study and in particular to measure, in order to see what kind of theory is needed.
>
> —Francis Crick, 1979

Francis H.C. Crick (1916–2004)

He once said that the ultimate goal of a theory was not to explain the brain directly but indirectly by asking the right question and designing a key experiment that would "give the game away." An early interest in the molecular basis of memory led him to ask: Do spines twitch? (Crick, 1982). His prediction that synaptic spines might be motile and that actin might be found in them was recently confirmed (Matus, 2000). He also explored the issue of what was responsible for the stability of memories despite the rapid turnover of protein in neurons. He suggested that proteins might be found at synapses with stable binary states (Crick, 1984b). Autophosphorylation of an important molecule in the postsynaptic spine, Ca^{2+}/calmodulin-dependent protein kinase, was found to have the predicted properties (Miller et al., 1988). In a study on the function of dream sleep (Crick and Mitchison, 1983), he used an associative network model to explore the possibility of "unlearning" during sleep. Evidence that memory consolidation occurs during sleep is getting stronger, and the question of how this happens is a topic of growing interest (Power, 2004).

Crick developed an anatomically-based model of attention, called the searchlight hypothesis (Crick, 1984a), which focused on the thalamic reticular nucleus—a thin layer of inhibitory neurons surrounding the principal thalamic nuclei. In his model, this nucleus was given a star role in synchronizing spikes in thalamic and cortical neurons that form cell assemblies, creating a searchlight of attention though intrinsic ionic mechanisms that promote bursting (see the Figure). Recordings from awake and behaving monkeys indicate that the synchronization of cortical activity may indeed accompany focused attention (Fries et al., 2001) and that synchronization may

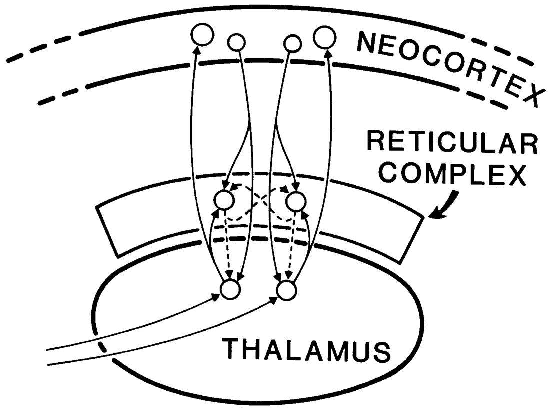

Diagram of the Main Connections of the Thalamic Reticular Nucleus

Solid lines represent excitatory axons. Dashed lines show GABAergic (inhibitory) axons. Arrowheads represent synapses. The reticular neurons are inhibitory and receive collaterals of ascending thalamocortical axons and descending corticothalamic projections. The only output from this nucleus is to the thalamic relay neurons (Crick, 1984).

enhance the impact of those neurons downstream (Salinas and Sejnowski, 2001). Whether bursts in thalamic neurons are involved in focused attention, are a means for detecting weak inputs (Sherman, 2001), are a prelude to memory consolidation during sleep spindles (Destexhe and Sejnowski, 2001), and/or have other functions remains an active area of research.

Crick was also a strong proponent of neuroanatomy and, in particular, argued for the development of new techniques to study the anatomy of the human brain (Crick and Jones, 1993). His approach to complexity in biological system was to start with its structure, whether it was the structure of a molecule or the anatomical structure of a brain region, and to work out the implications. He was often frustrated when a physiologist showed him recordings from an interesting cortical neuron but could not tell him what layer of the cerebral cortex it came from. Even when the layer was known, he would point out that similar looking neurons in the same layer projected to different parts of the brain. He advocated the development of new techniques to answer these questions and suggested that techniques from molecular genetics would have a revolutionary impact on systems neuroscience—a prediction that is being fulfilled.

Along with V.S. Ramachandran at the University of California at San Diego and Gordon Shaw at the University of California at Irvine, Crick founded the Helmholtz Club, a group of researchers in Southern California who have been meeting monthly since 1982. Guests include visitors and students who participate in extended discussions on topics that revolve around vision and, more generally, systems neuroscience. The most penetrating questions were often from Francis, who really wanted to know the answers and kept us all focused on the important issues. His playful nature was evident, his quick mind shining brightly. But most of all it was his generosity of spirit that left a lasting impression.

During the last two decades, Crick became increasingly interested in the question of human consciousness. In close association with Christof Koch he focused on one aspect of consciousness—visual awareness—that was particularly amenable to experimental inquiry. They coined the term "neural correlates of consciousness," or NCC, and spurred a number of illuminating experiments aimed at one of the most elusive mysteries in science. The voice of Francis Crick appears in the last chapter of Christof Koch's recent book on *The Quest for Consciousness* as an interviewer:

> **I:** I see. The function of consciousness, therefore, is to handle those special situations for which no automatic procedures are available. Sounds reasonable. But why should this go hand-in-hand with subjective feeling?
>
> **C:** Aye, there is the rub. Right now, there are no set answers. Or, to be more precise, there is a cacophony of answers, none of them persuasive or widely accepted.
>
> —Christof Koch, 2004, p. 318

During the last month of his life, Francis Crick revisited the claustrum, an enigmatic region of the brain. In his book on *The Astonishing Hypothesis* (Crick, 1994), he pointed out that the claustrum, which has topographically organized loops with the cerebral cortex, was well positioned to perform a global function, perhaps orchestrating patterns of activity in distant parts of the cortex to produce a unified state. With waning energy but fierce determination, he pursued the claustrum in his characteristic way, making detailed notes on old papers, calling on colleagues who might help him track down anatomical facts, inspiring researchers to undertake new experiments.

Crick helped to build a strong neuroscience program at the Salk Institute. To honor his contributions, the Crick-Jacobs Center for Theoretical and Computational Biology was recently inaugurated through a gift from Irwin Jacobs, a founder of Qualcomm. The goal of the Center is to bring together researchers using molecular genetic techniques and computational approaches to study higher brain function. Francis Crick took a strong interest in the scientific direction of the Crick-Jacobs Center, and it is my privilege to serve as its founding director. Faculty and Junior Fellows will explore new research directions, along the lines that Francis envisioned.

My laboratory has a daily tea, and during the 1990s Francis regularly attended. He would initiate discussion on a wide range of topics that sometimes led to new research directions. Once, he started a discussion with the announcement that the seat of the Will in the brain had been discovered—at or near the anterior cingulate cortex (Crick, 1994, p. 267). (Since then, interest in the anterior cingulate cortex has greatly expanded, with hundreds of papers written each year. A wide range of cognitive functions has been attributed to the anterior cingulate cortex, but Crick's description still captures the essential features most succinctly.) This led to a wide ranging discussion: What is the Will? If the cortex is bilateral, could there be two centers of the Will? The childlike joy in his voice is what I most remember about those teas.

When Francis Crick died on July 28, 2004, we lost a great scientist and a valued friend. His achievements will live on in science and his spirit will live on in our memories, to influence future generations.

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