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1 An introduction to classic studies in behavioral neuroscience

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There have been literally tens of thousands of papers on brain organization and function published over the past 100 years, but the majority have focused on reducing complex phenomena of brain function to simpler (and often molecular) terms yet do not help our understanding of brain organization and function, and few stand out as "classics." The classics are distinguished by introducing new ideas that shape the direction of subsequent research.

Such was the book *The Treatise of Mind*, written by the French philosopher René Descartes in the 1600s, that proposed that the brain makes an important contribution to behavior. In contrast to earlier ideas about the control of behavior, Descartes placed the control of behavior in the brain, although he made a distinction between "mind" and "brain". For Descartes, the nonmaterial mind controlled the body through the brain and received information about the body from the brain, a position now referred to as dualism. Cartesian ideas were influential, and although there were difficulties with the details of his theory, it was dominant until the theory of materialism emerged in the mid-nineteenth century with the writings of Wallace and Darwin. Materialism held that rational behavior did not require a separate mind but instead could be explained simply by the activities of the brain and nervous system.

Yet a major problem remained – how was the brain organized and how did it work? Early ideas dating back to the phrenology of Gall and Spurtzheim in the 1800s suggested that functions were localized in the cerebral hemispheres. Although Gall placed no emphasis on the study of cases with brain damage, the neurologists of the latter part of the nineteenth century began to describe evidence from brain-damaged people purporting to show that at least language was localized, epitomized by Broca's claim that language was localized in the third frontal convolution, which came to be known as Broca's area. Although many neurologists were seduced by the idea of localization of functions in the late nineteenth and early twentieth centuries, there were other writers – most notably John Hughlings Jackson and Karl Lashley – who argued that many functions were distributed and the brain could not be understand by any strict theory of localization.

The emergence of noninvasive imaging techniques in the late twentieth century has reinforced this view, and the emphasis has shifted more to networks of cerebral functioning and away from earlier debates about localization of function. Nonetheless, big questions regarding how the brain is organized remained to be formalized.

This book identifies 17 papers and one book that we consider should be considered classics because they provide key insights into the big questions related to brain and behavior. We wanted to show how these classics have influenced current ideas about brain and behavior, so we selected active researchers or research groups whose research interests were related to specific classics and asked them to write a chapter on the relevant classic study, explaining its influence on subsequent research.

Selecting the classic studies by anyone is obviously biased, and in our case this is related to our experience both as researchers and textbook writers. Undoubtedly some people may wonder why some studies were not included and why others were. We did our best to include those writings that in our view had the most influence on subsequent research and on current thinking about the big questions in behavioral neuroscience. We divided our search into four general categories: cerebral organization, cortical functions, chemicals and behavior, and brain plasticity. Although it was tempting to include topics that occupied many researchers at specific times over the past 100 years – such as the fundamental regulatory mechanisms of feeding and drinking and the organization of the synapse – we decided to focus on those topics that we felt had had the largest impact on our understanding of the broad questions of psychology and behavioral neuroscience. What is striking about these chapters is the unique interpretations on the development of brain research that feature in each of the contributions.

CEREBRAL ORGANIZATION

As we set about writing the original edition of *Fundamentals of Human Neuropsychology* in the late 1970s, we were struck by the absence of a coherent theory of how the brain was organized as a whole. There were early attempts to do this but most had little lasting impact. Several more modern writers, however, did have an impact. In a series of books and papers Alexander Luria provided the first clear theory of the functional organization of the brain, and especially the cerebrum. Although his model may seem simple today, we found it empowering both because students could understand it easily and because it led others to consider this very big question. The idea that there are functional maps in the cerebrum is obvious today, but the original studies by Wilder Penfield and his colleagues were groundbreaking, and although they were wrong in details they revolutionized how we think about the organization of the sensory and motor systems.

Later work, especially by Jon Kaas and his many colleagues using more sophisticated electrophysiological techniques, showed that Penfield's early maps were

far more complex than they first appeared, leading to a shift in thinking that remains today on how cerebral maps represented the external world. But how is the map information related to the rest of the brain? This is where the anatomical and behavioral studies of Leslie Ungerleider and Mort Mishkin led to an influential shift towards parallel streams of cortical processing in the visual system, a story that has had a major influence on the past 25 years of thinking on cerebral organization. Finally, although Broca suggested that there was lateralization of language in the brain, it was the split-brain studies of Sperry and his students that revolutionized our thinking about cerebral asymmetry and the lateralization of cognitive functions.

CORTICAL FUNCTIONS

Although behavioral neuroscience encompasses both cortical and subcortical regions, it is our view that it is the organization of the cerebral cortex, and its relationship to subcortical regions, that are central to our understanding of brain organization. We begin with Donald Hebb's book, the *Organization of Behavior*. We would be hard pressed to identify any other single paper or book that has so influenced our thinking about brain and behavior in the past 100 years. Owing to the importance of Hebb and his book, Richard Brown's chapter is somewhat broader than the others as it includes historical information related to Hebb, his book, and his legacy. Arguably Hebb's most influential student, Brenda Milner, combined with William Scoville to present the case of H.M. – a case that changed our understanding of memory. At about the same time Paul MacLean's writings on the limbic system and motivation had an equally influential impact on how we currently view the control of emotion. While many of the details of the Scoville and Milner and MacLean papers are now known to be wrong, these publications have had an amazing impact, with Scoville and Milner being cited over 5,400 times.

Perhaps the only case in behavioral neuroscience that is as well known as H.M. is that of Phineas Gage. It is descriptive rather than scientific but the impact on our understanding and study of emotional behavior and the frontal lobes is extraordinary, leading to a rich literature on neurology and psychology. Finally, the 2014 Nobel Prize in physiology or medicine went for research on the brain's Global Positioning System, which began with the studies of John O'Keefe and his colleagues.

CHEMICALS AND BEHAVIOR

This is a huge topic but there are two papers that stand out as classics. The first is by Charles Phoenix and colleagues who transformed how sex differences in sexual behavior were believed to develop. Looking at the field more than 50 years later, this paper clearly led to extensive work that has had an enormous impact on

the fundamental topic of sexual differentiation, which continues to fascinate students and researchers. The second is Roy Wise and colleagues' paper on catecholamine theories of reward. Like the Phoenix et al. paper, the Wise et al. paper stimulated a lot of new research that has moved the field to a completely different place than it started from – that it was not just the structure of a specific brain region but also its chemical function that shapes behavior. The question of why things are rewarding remains central to the whole field of motivated behavior.

BRAIN PLASTICITY

One of the fundamental paradigm shifts in behavioral neuroscience was the development of the concept, and now the field, of brain plasticity. A PubMed search under brain plasticity has over 29,000 papers, which is truly remarkable. It was a challenge to choose classic papers, but we settled on five. Harry Harlow was ranked by a 2002 survey as being the 26th most cited psychologist of the twentieth century. While he also did influential work on learning, it was his work on the role of maternal deprivation in infant development that had a transformational role in our understanding the role of attachment in brain and behavioral development. Some of Harlow's early work may now seen to be dramatic, but developmental influences are often dramatic. His original findings clearly were serendipitous and classic.

About the same time that Harlow was studying development in infant monkeys, the Berkeley group including David Krech, Mark Rosenzweig, Edward Bennett, and Marion Diamond made the remarkable finding that experience produced neurochemical and neuroanatomical changes in the brain. Although initially greeted with skepticism, their work was seminal in showing that experience can chronically change the brain. This research did not include electrophysiological studies, but the paper by Timothy Bliss and Terje Lømo revealed a different way to study plasticity, a phenomenon now known as long-term potentiation (LTP). LTP has become the most widely-studied experimental model of how the brain stores memories.

We noted above that Penfield's studies of brain stimulation revolutionized the study of the organization of cerebral maps. The study by Timothy Pons and his colleagues took advantage of the brain stimulation technique to demonstrate unexpectedly large changes in the somatosensory maps of monkeys (known as the Silver Spring monkeys) with chronic deafferentation of an arm. Like Harlow's work, the Silver Spring monkey studies were controversial, but the final chapter in their legacy has had an important and lasting impact on ideas of brain plasticity.

Finally, Per Roland and colleagues were among the first to show plastic changes in the activity of the human brain during the performance of a simple motor task. While primitive by today's standards, this work set in motion a new way to examine

plastic changes in brain functioning – the brain could be directly observed as it did its business. Neuroimaging has advanced rapidly since the Roland studies of the 1980s, and no doubt there will be more advances as current techniques are improved and new techniques are developed, but the key point remains that cerebral blood flow and metabolism change with experience.

CONCLUSION

Behavioral neuroscience is an exciting and rapidly changing field. However, one central point is that big questions in behavioral neuroscience are not new and not likely to change very much in the near future. The classic papers that we chose range from 1937 to 1988 but most are from the 1960s and 1970s. The key issues revolve around how the brain is organized, how the cerebral cortex works as a unit, and how the brain changes with experience. If we fast forward ahead 30 years, there will be thousands more papers but most will be focused on specific issues and not on the big questions of brain and behavior, and those that are on those questions will have originated from the classic studies highlighted here.

One of the fundamental pieces of advice for students of the brain is that understanding the big questions means reading old books and papers. Many if not all of these papers are not easily available as PDF files, but that is no reason not to revisit them. Their wisdom will continue to guide us for a long time. While most of us will do experiments looking at smaller questions, understanding what the big questions are is essential both to understanding the organization of the brain and behavior.