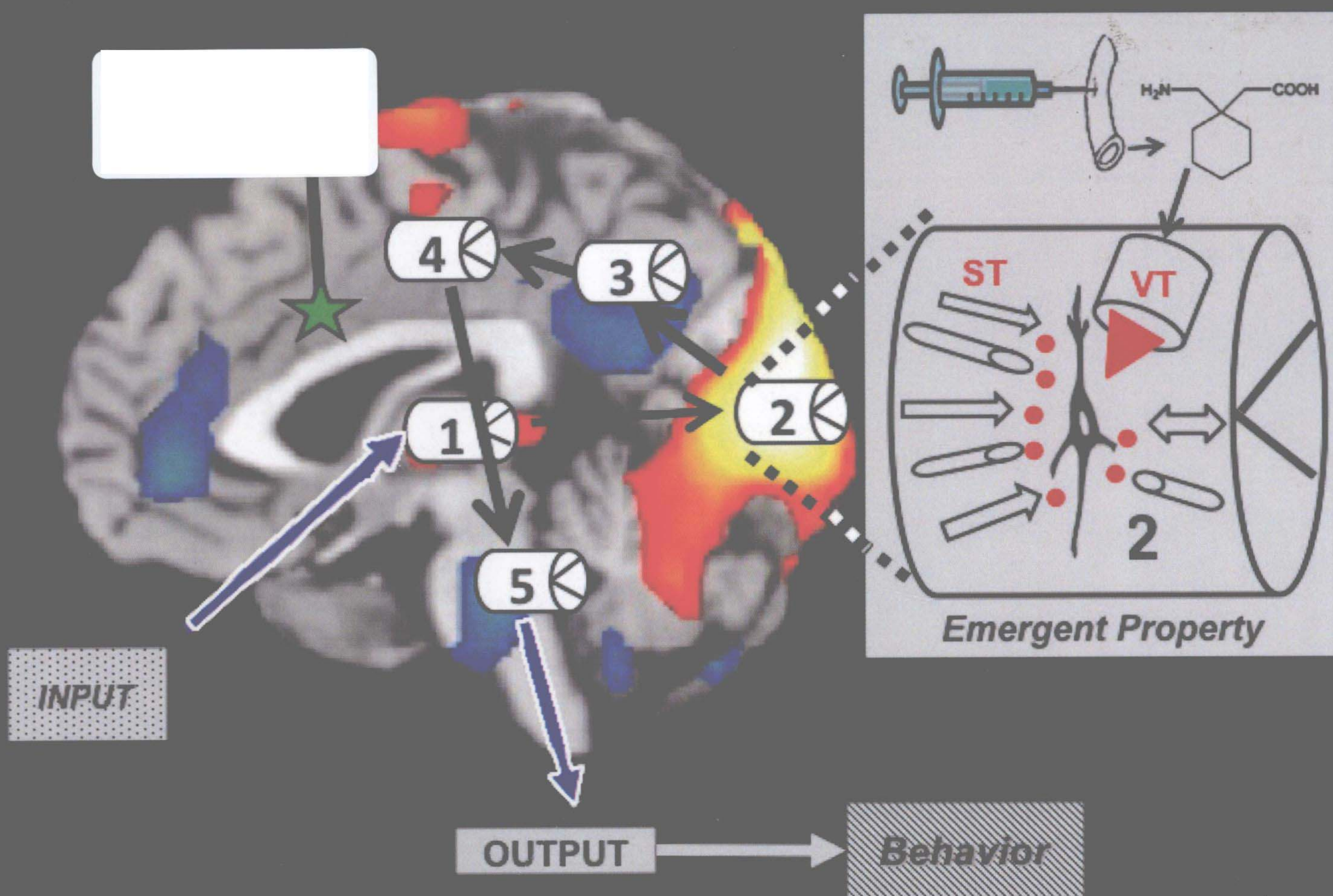

EDITED BY CARL FAINGOLD AND HAL BLUMENFELD

Neuronal Networks in Brain Function, CNS Disorders, and Therapeutics

NEURONAL NETWORKS IN BRAIN FUNCTION, CNS DISORDERS, AND THERAPEUTICS

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Dedications

I would like to express my profound appreciation and love to my wife, Carol Faingold, for her caring and unwavering support throughout my career, and especially during this project, which has been an impossible dream and a true exercise in tilting at windmills of the mind. The graduate students, post doctoral fellows, and colleagues who participated in the research from my laboratory deserve much of the credit for our work, but we all ultimately recognize that nature is the true professor and we are all but students. I want to thank the National Institutes of Health (NINDS and NIAAA), Citizens United for Research in Epilepsy, and Epilepsy Foundation for funding our research, and the Southern Illinois University School of Medicine for providing the scientific home, where all our research was carried out. This project would not have been completed without the assistance of my current and former secretaries, Gayle Stauffer and Diana Smith, who labored with me and our coeditor as well as all the authors to make this book a reality. I would also like to thank my family, my sons Scott, Rob, and Chuck; my daughter-in-law Trisha; and my grandkids, Noah, Samantha, Ryan, and Manny for their support. I would also like to thank my late parents, Charles and Anne Faingold, for starting me on the path of my three score and ten year journey to *tikkun olam*. As a life-long sufferer from a neurological disorder, I can only hope that application of the ideas expressed in this book can help advance the treatment of serious brain disorders that plague so many other patients.

Carl L. Faingold, PhD

I would like to dedicate this book to my family—the wonderful love of my life Michelle, our children Eva, Jesse, and Lev who keep a smile on my face, my parents who continue to make me proud, sister who is always there for me, loving in-laws, and all the other family members sharing our journey through life.

Hal Blumenfeld, MD, PhD

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CARL L. FAINGOLD, HAL BLUMENFELD

CHAPTER

1

Introduction to Neuronal Networks of the Brain

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INTRODUCTION

In recent years, it has become clear that an understanding of the brain's neuronal networks is a critical requirement for understanding normal brain function. In addition, an understanding of how neuronal networks are altered in central nervous system (CNS) disorders is yielding improved insights on the mechanisms of these disorders. Finally, knowledge of the properties of neuronal networks has a significant potential to improve the targeting of therapies for these CNS disorders, as discussed in Chapters 31 and 32.

"SILOS" IN CNS NETWORK RESEARCH

Much of recent brain-related research has emphasized molecular, genetic, and single-channel recording techniques. As valuable as these approaches are, it has become clear that research at the network and the network interaction levels are also vitally important to understanding brain function. However, much of the network-related research that does occur has involved evaluating "single-function" networks, such as the visual or auditory systems. No one can deny the importance of these approaches and the need for further research in these specific functional areas, some of which are covered in several of the chapters in this book. Unfortunately, this approach can yield a "silo" effect, where one area of research rarely considers the *interaction* of the specific network with other brain networks. A possible critique of the network interaction idea is that the level of knowledge of each single network is still incomplete, so it is premature to try to connect them, which may explain why potentially important "cross-silo" research is relatively uncommon. However, it is a major thrust of this volume that a better understanding of brain function, brain disorders, and therapy of these disorders is needed now to alleviate human suffering from the disorders, many of which involve cross-silo network interactions.

TYPES OF NETWORK INTERACTIONS

Network interactions can take several different forms and occur to varying degrees (Chapter 29). The main types of interactions are positive and negative interactions, as shown in the simplified diagram in Figure 1.1. Positive network interactions can involve the projection of an individual network, which can activate another network. In the example in Figure 1.1, Network 1 is shown as not undergoing a significant degree of self-organization, and Network 2 is depicted as capable of self-organization. The degree of self-organization is a critical network property, which can lead to an important network characteristic—an emergent property—which is discussed in this chapter and in detail in Chapter 30. Activation of Input 1 activates Net 1 and leads to Function 1. An example of Input 1 might be a simple acoustic stimulus to the auditory network (Net 1) and results in Function 1, perception of the acoustic stimulus. Net 2 could be the network that controls locomotion, which is subject to a considerable degree of self-organization and in nonexigent states maintains postural control or mediates ambulation (Function 2). Self-organization, which is a major feature of many neuronal networks, can lead to nonlinear amplification of network function (see Chapters 28 and 32). Net 1 and Net 2 can interact in a positive or negative way. Thus, an intense sensory stimulus, which is potentially exigent for the organism, can cause a major motor response by activating the locomotion network. An example of this is the acoustic startle

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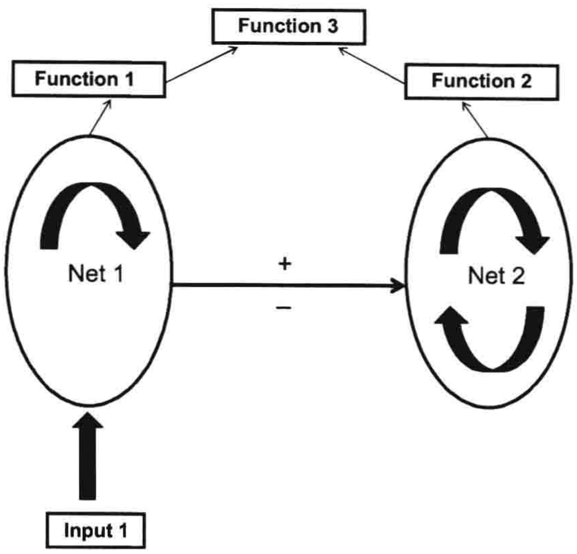

FIGURE 1.1 Simplified diagram of potential network interactions and mechanisms. Both positive (+) and negative (−) interactions can occur, as indicated by the signs above and below the arrow. The two networks are symbolized by the ovals (Net 1 and Net 2). Net 1 has an exogenous and/or endogenous input (Input 1). For simplicity, the input to Network 2 is omitted, but it may be spontaneously active. Each network is considered to have a function and behavior that it controls (Function 1 and Function 2). Net 1 is shown as not undergoing a significant degree of self-organization, as illustrated by the convention of a single semicircular arrow, and Net 2 has paired semicircular arrows and readily undergoes self-organization. Positive network interactions can involve the activation of one individual network, which then activates the second network. For example, Net 1 could be the auditory network, which is responsible for the organism's ability to perceive acoustic stimuli, and Net 2 could be the locomotor network responsible for the organism's ability to move. An example of the interaction of these networks is the acoustic startle response, in which an intense or unexpected auditory stimulus results in projection from the auditory network to the locomotor network that results in a rapid motor movement (jump or flinch), which would be Function 3. A second major form of network interaction that occurs is a negative interaction. This is where the activation of one network can interfere with the function of a second network. An example of a negative network interaction between these same networks would occur if the acoustic stimulus were a creaking noise underfoot when the organism is walking that causes it to stop moving, because it may indicate an unsteady walking surface and a cessation of Function 2—mediated ambulation. Sometimes, two networks can be activated at overlapping times without apparent behavioral consequences.

response, in which an intense or unexpected acoustic stimulus induces a motor movement (jump or flinch) (Function 3). This is an example of a positive interaction of elements of the auditory network with elements of the locomotor network. A second form of network interaction that occurs is a negative interaction. This is where the activation of one network can interfere with the function of a second network. An example of a negative network interaction between these same networks would occur if the acoustic stimulus were a creaking noise underfoot when the organism is walking that causes it to stop moving, because it may indicate an unsteady walking surface and a cessation of Function 2—mediated ambulation. Interactions of different stimuli within the same network can also occur and lead to changes in function. An early prototype of a negative network interaction is the "gate theory of pain" at the spinal cord level[1] (see Chapter 23). Network interactions can exert a beneficial or harmful effect for the individual, depending on the situation. Sometimes, two networks can be activated at overlapping times, but there are no apparent behavioral consequences for the individual. For example, innocuous auditory and visual events can often occur in close temporal proximity, but, unless this sequence of events is repeated or one of the stimuli is not innocuous, no effect on the individual's behavior is observable.

EPILEPSY AS A TEMPLATE FOR NETWORK STUDIES

Some of the most prominent examples of network interactions are seen in the group of CNS disorders called the epilepsies, and these diseases will be emphasized in this book. The question that could be raised is "Why emphasize epilepsy?" Epilepsy has long been considered an important research window into brain mechanisms.[2] Modern human brain research started in earnest with the original studies of Berger, who discovered the human electroencephalogram (EEG),[3] which was followed by pioneering research on the EEG of epileptic patients,[4] elucidating both normal and abnormal EEG patterns. Invasive studies have proven critical to evaluating brain function; these were pioneered by the eminent neurosurgeon Wilder Penfield,[5] who was the first to successfully map the cortical surface in awake patients. This exploration could be done ethically because these patients had intractable epilepsy that potentially required neurosurgery, which can be curative. The leading role of epilepsy studies in neuroscience research and particularly in neuronal network research[6] has extended from the 1950s to today. The recording of single neuronal firing in the awake brain, which is highly instructive of brain function and dysfunction,[7,8] has been done almost exclusively in epilepsy patients. For ethical reasons, the use of neuronal recording is possible in patients in few other CNS disorders. However, this recording technique can greatly facilitate subsequent epilepsy surgery, which remains an important treatment modality for seizure control in intractable epilepsy cases. Finally, the nature of essentially all forms of epilepsy involves disordered network function,[6] often on such a pervasive scale that the