STRESS: *PHYSIOLOGY, BIOCHEMISTRY, AND PATHOLOGY*

HANDBOOK OF STRESS | VOLUME 3

EDITED BY GEORGE FINK

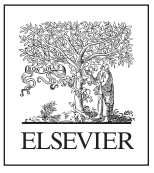
STRESS: PHYSIOLOGY, BIOCHEMISTRY, AND PATHOLOGY

HANDBOOK OF STRESS VOLUME 3

Edited by

GEORGE FINK

Florey Institute of Neuroscience and Mental Health
University of Melbourne
Parkville, Victoria, Australia



ACADEMIC PRESS
An imprint of Elsevier

Academic Press is an imprint of Elsevier
125 London Wall, London EC2Y 5AS, United Kingdom
525 B Street, Suite 1650, San Diego, CA 92101, United States
50 Hampshire Street, 5th Floor, Cambridge, MA 02139, United States
The Boulevard, Langford Lane, Kidlington, Oxford OX5 1GB, United Kingdom

Notices
Knowledge and best practice in this field are constantly changing. As new research and experience broaden our understanding, changes in research methods, professional practices, or medical treatment may become necessary.

Practitioners and researchers must always rely on their own experience and knowledge in evaluating and using any information, methods, compounds, or experiments described herein. In using such information or methods they should be mindful of their own safety and the safety of others, including parties for whom they have a professional responsibility.

To the fullest extent of the law, neither the Publisher nor the authors, contributors, or editors, assume any liability for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions, or ideas contained in the material herein.

Library of Congress Cataloging-in-Publication Data
A catalog record for this book is available from the Library of Congress

British Library Cataloguing-in-Publication Data
A catalogue record for this book is available from the British Library

ISBN: 978-0-12-813146-6

Publisher: Nikki Levy
Acquisition Editor: Natalie Farra
Editorial Project Manager: Pat Gonzalez
Production Project Manager: Paul Prasad Chandramohan
Cover Designer: Mark Rogers

Typeset by TNQ Technologies

Contributors

Tamas Bartfai Department of Biochemistry and Biophysics, Stockholm University, Stockholm, Sweden

Sarah L. Berga Division of Reproductive Endocrinology and Infertility, Department of Gynecology and Obstetrics, University of Utah School of Medicine, Salt Lake City, UT, United States

Sondra T. Bland Department of Psychology, University of Colorado Denver, Denver, CO, United States

Enrrico Bloise Department of Morphology, Federal University of Minas Gerais, Belo Horizonte, Brazil

Jenna E. Boyd Department of Psychology, Neuroscience, and Behaviour, McMaster University, Hamilton, ON, Canada; Mood Disorders Program, St. Joseph's Healthcare Hamilton, Hamilton, ON, Canada; Homewood Research Institute, Guelph, ON, Canada

Brandy A. Briones Princeton Neuroscience Institute, Princeton University, Princeton, NJ, United States

Maria Alexandra Brito Research Institute for Medicines, Faculty of Pharmacy, Universidade de Lisboa, Lisboa, Portugal

Wilson C.J. Chung Department of Biological Sciences, School of Biomedical Sciences, Kent State University, Kent, OH, United States

Iain J. Clarke Neuroscience Program, Monash Biomedical Discovery Institute, Department of Physiology, Monash University, Clayton, VIC, Australia

Daemon L. Cline Northern Medical Program, University of Northern British Columbia, Prince George, BC, Canada

Everly Conway de Macario Department of Microbiology and Immunology, School of Medicine, University of Maryland at Baltimore-Institute of Marine and Environmental Technology (IMET), Columbus Center, Baltimore, MD, United States; Euro-Mediterranean Institute of Science and Technology (IEMEST), Palermo, Italy

R.A.L. Dampney School of Medical Sciences (Physiology) and Bosch Institute, University of Sydney, Camperdown, NSW, Australia

Clémence Disdier The Alpert Medical School of Brown University, Department of Pediatrics, Women & Infants Hospital, Providence, RI, United States

Klaus P. Ebmeier Department of Psychiatry, University of Oxford, Warneford Hospital, Oxford, United Kingdom

Elizabeth Gould Princeton Neuroscience Institute, Princeton University, Princeton, NJ, United States

Sarah L. Gray Northern Medical Program, University of Northern British Columbia, Prince George, BC, Canada

Matthew W. Hale School of Psychology and Public Health, La Trobe University, Melbourne, VIC, Australia

Robert J. Handa Department of Biomedical Sciences, Colorado State University, Fort Collins, CO, United States

Anthony J. Hannan Florey Institute of Neuroscience and Mental Health, Melbourne Brain Centre, University of Melbourne, Parkville, VIC, Australia; Department of Anatomy and Neuroscience, University of Melbourne, Parkville, VIC, Australia

Belinda A. Henry Metabolism, Diabetes and Obesity Program, Monash Biomedical Discovery Institute, Department of Physiology, Monash University, Clayton, VIC, Australia

Holger Jahn Department of Psychiatry and Psychotherapy, University Medical Center Hamburg-Eppendorf, Heiligenhafen, Germany

Naomi Kakoschke Monash Institute of Cognitive and Clinical Neurosciences, Monash University, Melbourne, VIC, Australia

Hagar Kandel Laboratory of Neurobiology and Behavior, The Rockefeller University, New York, NY, United States

Ruth A. Lanius Department of Psychiatry, University of Western Ontario, London, ON, Canada; Department of Neuroscience, University of Western Ontario, London, ON, Canada; Imaging Division, Lawson Health Research Institute, London, ON, Canada

Sonia J. Lupien Center for Studies on Human Stress, Research Center of the Montreal Mental Health University Institute, Montreal, Canada; Department of Psychiatry, Faculty of Medicine, University of Montreal, Montreal, Canada

Alberto J.L. Macario Department of Microbiology and Immunology, School of Medicine, University of Maryland at Baltimore-Institute of Marine and Environmental Technology (IMET), Columbus Center, Baltimore, MD, United States; Euro-Mediterranean Institute of Science and Technology (IEMEST), Palermo, Italy

Nicola Maggio Department of Neurology and Neurosurgery, The Sackler Faculty of Medicine, Tel Aviv University, Israel

Marie-France Marin Center for Studies on Human Stress, Research Center of the Montreal Mental Health University Institute, Montreal, Canada; Department of Psychology, Faculty of Social Sciences, Université du Québec à Montréal, Montreal, Canada; Department of Neurosciences, Faculty of Medicine, University of Montreal, Montreal, Canada

Cristina Martin-Perez Mind, Brain and Behavior Centre, Universidad de Granada, Granada, Spain

Stephen G. Matthews Department of Physiology, Obstetrics & Gynaecology and Medicine, University of Toronto, Toronto, ON, Canada

M.P. Mattson Department of Neuroscience, Johns Hopkins University School of Medicine, Baltimore, MD, United States

Anthony L. McCall Division of Endocrinology & Medicine, University of Virginia (Emeritus), Charlottesville, VA, United States; Division of Nutritional Sciences, Cornell University, Ithaca, NY, United States

Bruce S. McEwen Laboratory of Neuroendocrinology, The Rockefeller University, New York, NY, United States

Michael J. McKinley Florey Institute of Neuroscience and Mental Health, University of Melbourne, VIC, Australia

Margaret C. McKinnon Mood Disorders Program, St. Joseph's Healthcare Hamilton, Hamilton, ON, Canada; Homewood Research Institute, Guelph, ON, Canada; Department of Psychiatry and Behavioural Neurosciences, McMaster University, Hamilton, ON, Canada

Christina Mo Florey Institute of Neuroscience and Mental Health, Melbourne Brain Centre, University of Melbourne, Parkville, VIC, Australia; Department of Neurobiology, University of Chicago, Chicago, IL, United States

Donald W. Pfaff Laboratory of Neurobiology and Behavior, The Rockefeller University, New York, NY, United States

Daniela Rabellino Homewood Research Institute, Guelph, ON, Canada

Catherine Raymond Center for Studies on Human Stress, Research Center of the Montreal Mental Health University Institute, Montreal, Canada; Department of Psychology, Faculty of Social Sciences, Université du Québec à Montréal, Montreal, Canada; Department of Neurosciences, Faculty of Medicine, University of Montreal, Montreal, Canada

Thibault Renoir Florey Institute of Neuroscience and Mental Health, Melbourne Brain Centre, University of Melbourne, Parkville, VIC, Australia

Philip J. Ryan Florey Institute of Neuroscience and Mental Health, University of Melbourne, VIC, Australia

Mathias V. Schmidt Max Planck Institute of Psychiatry, Munich, Germany

Menahem Segal Department of Neurobiology, The Weizmann Institute, Rehovot, Israel

Helmut Sies Institute of Biochemistry and Molecular Biology I, Heinrich-Heine-University Düsseldorf, Düsseldorf, Germany; Leibniz Research Institute for Environmental Medicine, Heinrich-Heine-University Düsseldorf, Düsseldorf, Germany

Robert L. Spencer Department of Psychology and Neuroscience, University of Colorado Boulder, Boulder, CO, United States

Gregg D. Stanwood Department of Biomedical Sciences, Florida State University College of Medicine, Tallahassee, FL, United States

Barbara S. Stonestreet The Alpert Medical School of Brown University, Department of Pediatrics, Women & Infants Hospital, Providence, RI, United States

Nigel A.S. Taylor Centre for Human and Applied Physiology, School of Medicine, University of Wollongong, Wollongong, Australia

Maarten van den Buuse School of Psychology and Public Health, La Trobe University, Melbourne, VIC, Australia

Antonio Verdejo-Garcia Monash Institute of Cognitive and Clinical Neurosciences, Monash University, Melbourne, VIC, Australia

Annamaria Vezzani Department of Neuroscience, Mario Negri Institute for Pharmacological Research IRCCS, Milano, Italy

Enikő Zsoldos Department of Psychiatry, University of Oxford, Warneford Hospital, Oxford, United Kingdom

Preface

It isn't the mountain ahead that wears you out; it's the grain of sand in your shoe. ***Robert W. Service*** (***Bard of the Yukon***)

> *"One of the most striking features of our bodily structure and chemical composition that may reasonably be emphasized, it will be recalled, is extreme natural instability. Only a brief lapse in the coordinating functions of the circulatory apparatus, and a part of the organic fabric may break down so completely as to endanger the existence of the entire bodily edifice. In many illustrations we have noted also how infrequently they bring on the possible dire results. As a rule, whenever conditions are such as to affect the organism harmfully, factors appear within the organism itself that protect it or restore its disturbed balance."*

So wrote the great Harvard physiologist, Walter Bradford Cannon in his landmark *Wisdom of the Body* in which he coined the term "homeostasis" and described the "fight-or-flight" response.

Cannon continues: "*A noteworthy prime assurance against extensive shifts in the status of the fluid matrix is the provision of sensitive automatic indicators or sentinels, the function of which is to set corrective processes in motion at the very beginning of the disturbance*."

Cannon's prescience is underscored by the fact that the epilogue of his book is focused on the "relations of biological and social homeostasis," *relations* which are now the subject of intense investigation.

Notwithstanding the important principles established in the *Wisdom of the Body*, our knowledge of the physiology, biochemistry, and pathology of stress has increased exponentially since 1932 due in large part to new stress concepts, the discipline of neuroendocrinology which first matured in the 1950s (covered in Volume 2 of the *Handbook of Stress*) and astonishing new technologies such as human brain imaging, neurochemistry, genetics, optogenetics, genomics, and studies of behavior. Many of the quantum advances in stress knowledge are the subject of this volume.

I am grateful to our distinguished authors who have given so generously of their time and knowledge, Pat Gonzales for her excellent assistance in collating and preparing the chapters for Production and Natalie Farra for her encouragement, oversight, support, and wise guidance. Finally, as always, I thank Ann Elizabeth Fink for her steadfast forbearance and support and my children Naomi and Jerome who forever cheer from the sidelines.

Reference: Cannon WB 1932. *The Wisdom of the Body. WW* Norton &Co Inc, New York Pp. 1−312 (quotations from pages 268−270).

George Fink
Florey Institute of Neuroscience and Mental Health
University of Melbourne
Parkville, VIC, Australia
2018

CHAPTER

1

Arousal

Hagar Kandel, Donald W. Pfaff

Laboratory of Neurobiology and Behavior, The Rockefeller University, New York, NY, United States

OUTLINE

Several years ago, we proposed the concept of "generalized central nervous system (CNS) arousal (GA),"[3] now updated and extended.[4] There is a marked asymmetry between the concept of GA and the concept of stress: You can be aroused without stress, but you cannot be stressed without arousal. This chapter represents an update of Pfaff, Martin, and Ribeiro.[5]

KEY POINTS

- Generalized CNS arousal (GA) is the most elementary function of vertebrate nervous systems. It is a nonspecific neuronal "force" that activates ascending and descending systems, facilitating the initiation of any behavior responding to external stimulation and emotional expression
- Several components of the nervous system such as the medullary reticular formation, thalamus, and cortex contribute to GA and have been analyzed with respect to neuroanatomical pathways, electrophysiological features, and some of the most important genes involved in the generation of GA.
- GA has been given an operational definition and criteria for successful operation.
- GA is proven to exist by psychological, genetic, statistical, and mechanistic findings.
- Surprisingly, GA can be abnormally high during melancholic depression.
- GA is out of control, in association with bipolar disorders.

Stress: Physiology, Biochemistry, and Pathology
https://doi.org/10.1016/B978-0-12-813146-6.00001-1

Constant throughout has been the definition of GA:

Operational definition: A more aroused animal or human, with higher GA, is more alert to sensory stimuli in many sensory modalities (S), more active motorically (M) and more reactive emotionally (E).

One can also consider *operating requirements*: Four which can be justified on a theoretical basis: (1) GA mechanisms must work fast enough to allow the individual to escape danger, (2) there must be great convergence of inputs onto GA mechanisms so that a wide variety of incoming signals can trigger adequate behavioral responses, (3) there must be great divergence of signals emanating from GA mechanisms so that a wide variety of behavioral responses can be initiated, and (4) GA mechanisms must be robust enough so that they will not fail.

We propose that GA mechanisms work in all vertebrate brains including, of course, the human brain. GA is a primitive, undifferentiated force deeper than and additive to the usual motivational states (sex, hunger, etc.). GA contributes to many different types of behaviors, normal and abnormal. GA is the *ur-arousal*[*], the force for the initiation of behavior conceptually and mechanistically deep to all of the more superficial and individuated forces. For example, fight or flight depends on GA but is more situationally dependent than GA.

EVIDENCE FOR THE EXISTENCE OF GA

We cite four lines of evidence:

1. *Psychology.* The oldest line of evidence for the existence of a brain function called "generalized arousal" came from psychologists who study normal human behavior and personality. Virtually, all personality theorists included a dimension called "arousal" or a similar term in their description of the fundamental axes of personality.
2. *Genetics*. The newest evidence for GA comes from genetics; modification of GA, and therefore to its existence (reviewed in the study by Pfaff[4]). This genetic evidence comes from three approaches.

A perfect example of the *first approach* is the gene for hypocretin (reviewed in the study by Li et al.[6,7]) expressed in about 3000 neurons in a very restricted portion of the lateral hypothalamus. Optogenetic activation of hypocretin neurons can wake up mice from sleep. Conversely, optogenetic silencing of hypocretin neurons can induce sleep during the light phase of the daily light cycle.

Part of the power of the hypocretins in preserving wakefulness seems to lie in their ability to work through classical monoaminergic systems that serve arousal. These include noradrenergic neurons since hypocretin axons project to the noradrenergic source in the hindbrain the locus coeruleus. Another monoamine systems affected are dopamine (emanating from the ventral tegmental area), histamine (produced in the tuberomammillary nucleus in the medial hypothalamus) and serotonin (produced in neurons in the raphe neurons on the midline of the midbrain). Importantly, hypocretin neurons project to the large cholinergic neurons of the basal forebrain, neurons which are important for waking activity in the cerebral cortex.

A *second approach* to the genetics of arousal follows a different route to discovery. In the field of work just reviewed, the scientists cloned a gene involved in GA and thus stimulated an entirely new field of work: describing neuroanatomical projections, discovering cognate receptors, analyzing mechanisms of action, and so forth. This second approach comes from gene knockout studies that were initiated for a different reason, and the arousal data were eventually discovered in later, follow-up studies. For example, the gene for estrogen receptor α (ER-α) first garnered great interest because of its involvement in sexual behaviors.[8,9] Later, Joan Garey[10] extended our behavioral analyses to include arousal measurements.

[*] Ur-arousal means the oldest, most primitive and most fundamental form of CNS arousal

Other studies measuring motoric activity gave similar results. For example, we know that reduction of the ER-α gene product specifically in the neurons of the medial preoptic area reduced movement. This finding replicated early work from our lab which had also reported that gonadectomized α-ERKO (estrogen receptor knockout) females were significantly less active than α wild-type (WT) mice in open field tests, whereas beta-ERKO females tended to be more active than beta-WT mice.

A *third line* of genetic evidence for generalized arousal is that you can breed for this function. You can't breed for a brain function that does not exist. That is, if the highest and lowest males and females are selected generation after generation according to the operational definition of arousal (mentioned previously), then successful creation of a high and a low line proves that a concept matching that operational definition must exist. Since we knew that we would be breeding mice for a multigenic function, we went for advice to behavior geneticist David Blizard of Pennsylvania State University. He advised us to start with a strain of mice that had a high-degree genetic heterogeneity. This type of strain had indeed been achieved by Gardner Lindzey and Donald Thiessen many years before. The high genetic heterogeneity had resulted from an extensive intercross of more than eight outbred strains (and was called Het-8). The generalized arousal assay in our lab featured mice housed singly and cut off absolutely from the outside world. No sound, no vibration, no odors. Using this assay and, over 10 generations, mating high arousal males with high arousal females (and low with low), it was possible to achieve a high arousal line and a low arousal line of mice.[11]

3. A third line of evidence showing the existence of GA comes from mathematical statistics. As summarized by Calderon et al.[12] principal components analyses of mouse behavioral data related to arousal reveal a large GA component which accounts, in different experiments, for between 29% and 45% of the data. That means in a differential equation which mathematically describes changes in arousal, on the right side of the equal sign, there would be one term representing GA, and many other terms representing specific forms of arousal, such as sex, hunger, thirst, fear, anger, and so on.

   Thus, the statistics of principal components analysis support the conclusion that GA exists but also indicates the importance of other, specific forms of arousal.
4. *Brain mechanisms*. You cannot have mechanisms for a function that does not exist. During the last 30 years or so, the neurobiological mechanisms for changes of state of the entire CNS—the exact opposite of specific sensory systems—has "caught up" enough to merit a book-length treatment. An example would be the neuroanatomical delineation of reticular formation neuroanatomy by the McGill University neurobiologist Barbara Jones. Brain mechanisms have spelled out and reviewed.[4]

With four independent lines of evidence for the existence of GA—psychological, genetic, statistical, and mechanistic—it is timely to theorize about GA as a physical process. It turns out that flipping from a not-aroused state appears to have the property of a physical phase transition and should demonstrate the "scaling" and accompanied "power law behavior"—behavior governed by a simple exponential equation that produces the same dynamics from tiny scales to huge scales. In laboratory mice, this prediction proves true, and this type of transition likely is universal among vertebrates.

PHYSICAL AND QUANTITATIVE PROPERTIES OF GA

Pursuing the conviction to think about arousal systems with a precision typical of the physical sciences, we turned to Penn State Professor of Physics, Jayanth Banavar. We knew we needed to generate a systematic set of hypotheses about the regulation of GA as a function that bears on virtually all aspects of human and animal behavior. These ideas were expected to apply universally among vertebrates. We started with the idea that when rapid changes of state of the CNS would be required—for example, when a rapid response to a stimulus would be important

to achieve—that linear dynamics in generalized arousal mechanisms would not be sufficient. Nonlinear dynamics, as found in chaotic systems, could provide tremendous amplification of CNS arousal signals and would also confer exquisite sensitivity to the initial state of the system. The hypothesis, therefore, that in the not-aroused state chaotic dynamics prevail, is very attractive because they are deterministic and because they link the elegant mathematics of chaos to the concept of a fundamental property of the vertebrate CNS. But for coordinated movements as part of the behaviors thus initiated, the system will have to emerge from chaos. Thus, the second idea was that as neural systems pass from the chaotic nonaroused state to aroused states, they pass through a classically defined phase transition. With the behavioral response activated, orderly movement control neurophysiology takes over.[13]

To understand this theory clearly, consider the analogy to a classical physical example of a phase transition, the liquid crystal. Arousal systems in the not-aroused or low-aroused animal are in a chaotic state. The controlled-chaotic state of Ott et al. would be perfectly appropriate. When the animal is sufficiently stimulated, the nonlinear dynamics of deterministic chaos provide exponential amplification so that CNS systems can initiate orderly movement in response. By analogy to the liquid crystal, the disordered molecules at a higher temperature go through a phase transition to the ordered, crystalline state.

Experimental scientists are beginning to think along these lines, and some evidence for our theory has accrued. For example, with magnetoencephalographic data from human subjects who were performing a finger-tapping task, a variety of mathematical approaches were used to analyze several spectral domains in the subjects' cerebral cortical activity. The results showing the degree of synchronizability of this activity demonstrated; in their words, the brain networks are located dynamically on a critical point of the order/disorder transition. That is, their networks were close to the threshold of order/disorder transformation in all frequency bands, just like our theoretical liquid crystal analogy.

Another example of the importance of thinking about chaotic dynamics in relation to neural activity comes from findings in auditory neurophysiology. Certain nonlinear equations yielding chaotic dynamics demonstrate instabilities at fixed, special values of some given system parameter called "Hopf bifurcations." Marcelo Magnasco and his colleagues have presented evidence that the tuning curves of the cochlea in the auditory system are partly shaped by a set of mechanosensors poised precisely at the threshold of a Hopf instability. This application of nonlinearity in hearing achieves the advantages of a high degree of amplification and a sharp tuning curve even at low input intensity.

Magnasco and his colleagues have extended their evidence for "dynamic criticality" to the electrical activity of the human cerebral cortex. Dynamic criticality refers to "systems that persist at the boundary between stability and instability" and is typified by "systems highly susceptible to small external perturbations." It can be argued that we need neural mechanisms to constitute an extended dynamical system that is close to a critical point and that will neither decay nor explode, thus allowing for long-range communication across the entire system. This type of system is just what is needed, theoretically, to create a GA system that protects us from dangers in the external world.

Alex Proekt (2012), now at the University of Pennsylvania Medical School, noticed that the timing of many diverse behaviors from human communication to animal foraging form complex self-similar temporal patterns reproduced on multiple time scales. We envisioned a general framework for understanding how such scale invariance may arise in nonequilibrium systems, including those that regulate mammalian behaviors. Below is described how we demonstrated that the predictions of this framework are in agreement with detailed analysis of spontaneous mouse behavior observed in a simple unchanging environment. Neural systems operate on a broad range of time scales, from milliseconds to hours. Analyses revealed that the specifics of the distribution of resources or competition among several tasks are not essential for the expression of scale-free dynamics. Importantly, we showed that scale invariance observed in the dynamics of behavior can arise from the dynamics *intrinsic to the brain*.

In physical systems, one observes scale invariance—a repetition of shape and dynamics from tiny physical scales through huge physical scales—near a critical point, for example, where water turns into steam or where the unaroused animal can become aroused. It has been suggested that the presence of power laws in diverse living systems might imply that biological systems are poised in the vicinity of phase transitions. There are, however, fundamental differences between scale invariance exhibited by biological and physical systems. Criticality, the supersensitive responses to small stimuli are is confined to a small region in parameter space, and it is not clear how diverse biological systems are fine-tuned to exhibit criticality. But, in physics, critical systems are at equilibrium, whereas most processes occurring in living systems including animal behavior are not in equilibrium.

Behavior is often conceived as serving a particular purpose or as a response to a specific stimulus. However, even in the relative absence of these phenomena, all animals including humans readily exhibit spontaneous behavior. Spontaneous activation of behavior is the simplest case of animal behavior because it avoids the complexities added by specific behavioral tasks, interactions among individuals, and the specifics of the structure of the environment. Understanding the dynamics of spontaneous behavior therefore is a prerequisite for understanding behavioral dynamics in more complex settings. This was the focus of Proekt's analysis.[14]

Proekt worked with Professor Banavar and mathematician Amos Maritan to analyze the fine structure of the movements of mice in the GA assay described previously. Importantly, systems going through a phase transition behave according to simple exponential equations called "power laws." Plotted on log: log coordinates, both the X-axis of the graph and the Y-axis of the graphs are scaled logarithmically rather than linearly, such systems yield straight lines. In accordance with theory, mice, during the dark phase of the daily light cycle, demonstrated straight lines over three orders of magnitude. These results[14] are consistent with the phase transition theory summarized previously.

Still working with the physicist Jayanth Banavar, we are now asking mathematical questions about the performance of laboratory mice as they go through the hypothesized phase transitions from the light part of the day (low CNS arousal) to the dark part (high CNS arousal) in a 12-h light 12-h dark daily cycle. Working with equipment that provides temporal resolution of 20 ms, we ask, with the data from individual mice on individual days, what mathematical curves fit their activity change and what do whose equations suggest? How can we describe individual differences? Is the phase transition from high to low arousal the mirror image of the transition from low to high? Within a few months, these new studies may offer answers to these questions.

NEUROLOGIC MALADIES AND PUBLIC HEALTH PROBLEMS FROM DYSREGULATION OF GA

There are many serious medical and public health problems resulting from failures of GA. One obvious category is disorders of consciousness. Coma is, by definition, a temporary condition. Either the patient escapes from coma and enters a vegetative state or he dies. Vegetative state patients are not uniform in their range or severity of symptoms. Recently, there has been special attention given to "high-end" vegetative state patients—those who sporadically have shown some communication—because such patients may be responsive to treatments such as deep brain stimulation. Stupor, as well, certainly involves arousal problems.

In the working world, GA plays especially important roles in certain jobs that require high and sustained vigilance. The military is one example. It is said that even a trained sniper cannot maintain the necessary level of attention for longer than about 30 min. Shift work in which an individual rotates through two or three daily shifts takes its toll because of the challenge to the individual's circadian rhythms. Dangerous occupations like slicing meat or fish explode the size of the potential losses—for example, decreased

arousal resulting in even a moment of lapsed attention can cause the loss of a limb.

Public health failures like elevated lead concentration in drinking water can reduce cognitive performance through routes that included decreased GA. Perhaps, the mysterious "fatigue states" are related. Thus, some scientists think that they can follow certain environmental exposures that lead to chronic fatigue syndrome, fibromyalgia syndrome, and Gulf War Syndrome. The first two are much more common among women and the third in men, but they all share many symptoms, one of which is decreased GA.

Almost all the foregoing conditions depend on underperformance of GA mechanisms. But for some patients, *reducing* arousal level is necessary. Here are two examples. First, it is estimated that about 15%–20% of American adults have sleep problems: some cannot get to sleep, while others have badly fragmented sleep or wake up too early. Second, anesthesia, as for surgery, is a highly sophisticated branch of medicine. The regulated reduction in arousal level was mentioned earlier in this chapter.

NEURONS CRITICAL FOR GA

Evidence has piled up that large medullary reticular neurons in a group called nucleus gigantocellularis (NGC; also called reticularis gigantocellularis) are crucial for maintaining CNS arousal levels and for the initiation of a wide variety of behaviors. Elevating electrical activity in these glutamatergic neurons is associated with the activation of behavior[15] and with an aroused electrical pattern in the cerebral cortex (the electroencephalogram [EEG]). Decreased activity has the opposite effect. Large medullary reticular neurons express genes for arousal-related neuropeptide receptors.[16] We now have the entire transcriptome expressed by a subset of NGC neurons, demonstrating a unique expression of one gene and an unusually intimate relation to the nearby vasculature.

The hypothesis has been put forth[4] that these NGC neurons function in a large anterior/posterior integrated network. In terms of the connectivity of individual neurons within the network, they may have a "scale-free" property; in that many neurons have few connections, while only a few, like NGC, have a large number of connections.

AROUSAL AND PSYCHIATRIC DISORDERS

Arousal regulation in the human brain is a complex phenomenon; it describes a dynamic process of cortical and behavioral activation in response to varying degrees of stimulation; and accordingly, the relationship between stress, cortical activity, and performance. Its dysregulation has been implicated in different psychiatric disorders.[17,18]

Classically, beginning with the pioneering work of Professors Tarchanoff, Peterson, and Jung, researchers started to study dysregulation of arousal in different psychiatric disorders.[19]

The Research Domain Criteria (RDoC) project of the National Institute of Mental Health develop new ways of classifying mental disorders for research purposes; they shift away from symptom-based diagnoses toward a transdiagnostic neurobiological focus in the study of mental disorders. The major RDoC framework consists of Matrices; there are five domains in it: Negative Valence Systems, Positive Valence Systems, Cognitive Systems, Systems for Social Processes, and Arousal/Regulatory Systems.[20–22]

The Arousal construct group defines arousal as a continuum of sensitivity of the organism to stimuli both external and internal; it facilitates interaction with the environment; it can be evoked by either external/environmental stimuli or internal stimuli; it can be modulated by the physical characteristics and motivational significance of stimuli; it varies along a continuum that can be quantified in any behavioral state; it is distinct from motivation and valence; it may be associated with increased or decreased locomotor activity; and it can be regulated by homeostatic drives. The group identified a number of genes, molecules, circuits, and neurotransmitter

systems that were relevant to arousal, which are included in the arousal matrix.[23]

Arousal can be assessed by

- Autonomic measures: heart rate variability (HRV; Beauchaine and Thayer[24]), electrodermal responding.[25]
- Cognitive measures: psychomotor vigilance task[26] and the Vigilance Algorithm Leipzig (VIGALL); where different EEG vigilance stages from full alertness to sleep onset can be separated during rest.[27,28,29,30]
- Psychological measures: the Arousal Predisposition Scale[31] and the Scale of Trait Arousability.[32]

This part of the chapter presents examples of different psycho–patho–physiological proposed mechanisms that potentially can contribute to discoordination of arousal regulatory systems, leading to hyper or hypo arousal in different psychiatric disorders.

PSYCHIATRIC DISORDERS ASSOCIATED WITH HYPERAROUSAL

Major depressive disorder (MDD) is a mental disorder characterized by at least 2 weeks of pervasive depressed mood, loss of pleasure in daily activities, weight loss, insomnia, agitation, fatigue, feelings of worthlessness or guilt, attentional problems, thoughts of death, and suicidal ideation.[33]

The arousal regulation model of affective disorders denotes that the upregulation of arousal—negative emotional arousal—is a central pathogenic factor in MDD. This is paradoxical at first glance, but this model provides a simple explanation, that withdrawal and sensation avoidance in depression are proposed to be a reaction to the tonically high brain arousal. It explains several clinical phenomena typically seen in MDD such as prolonged sleep onset latencies, avoidance of arousal-increasing external stimulation and the response to therapeutic sleep deprivation.[34] In line with this model, wakefulness-promoting cytokines, "especially IL-13," were found to be significantly associated with hyper-stable EEG vigilance recording in MDD patients.[29]

Severe depression drastically reduces the amount of time spent in Stage 4 (delta) sleep. Furthermore, depressed patients have more reduced rapid eye movements (REM) sleep, and REM sleep occurs earlier in the night (reduced REM latency), indicating increased arousal.[35] This can open the door for future evaluation of vigilance measures as a biomarker in MDD.

Zobel and colleagues found that genetic factors, elevated neuroticism, and HPA dysregulation moderate as risk factors for depressive disorders and also reflect a predisposition toward coping less effectively with stress and its related challenges.[36] Animal evidence indicates that stress exacerbates the effects of reduced brain-derived neurotrophic factor (BDNF) on both hippocampal networks and autonomic arousal.[37]

The effects of the interaction of the BDNF Val66Met polymorphism and exposure to early life stressors (ELS) on neural circuitry and autonomic arousal pathways that in turn predict syndromal depression and anxiety have been identified by Gatt et al. They found that BDNF Met carriers exposed to greater ELS have smaller hippocampal and amygdala volumes ($P = .013$), heart rate (HR) elevations ($P = .0002$), and a decline in working memory ($P = .022$), also the combination of Met carrier status and exposure to ELS predicted reduced gray matter in hippocampus ($P < .001$), and associated lateral prefrontal cortex ($P < .001$) and, in turn, higher depression ($P = .005$). Higher depression was associated with poorer working memory ($P = .005$) and slowed response speed. The BDNF Met–ELS interaction also predicted elevated neuroticism and higher depression and anxiety by elevations in body arousal ($P < .001$).[38]

Schmidt et al. studied arousal regulation between depressed patients and healthy controls and also responders and nonresponders to antidepressant "Escitalopram" using the VIGALL 2.1. In 65 unmedicated depressed patients; 15-min resting-state EEGs was recorded. In 57 patients, an additional EEG was recorded 14 ± 1 days following onset of escitalopram.

There were 29 responders and 36 nonresponders. They found that responders and nonresponders differed in distribution of overall EEG vigilance stages ($P = .009$), with responders showing significantly more high vigilance stage A and less low vigilance stage B. They concluded that responders to antidepressants show a higher brain arousal level compared to nonresponders and that could confirm the hypothesis of a higher brain arousal level in responders compared to nonresponders to antidepressant treatment.[39]

Olbrich et al. investigated the hypothesis of a decline in CNS and autonomic nervous system (ANS) arousal by treating depressed patients with selective serotonin reuptake inhibitor (SSRI). The data were derived from a small, independent exploratory dataset ($N = 25$) and replicated using data from the randomized international Study to Predict Optimized Treatment Response in Depression (iSPOT-D; $N = 1008$). CNS arousal was assessed using VIGALL (see previously). Analysis of the exploratory dataset revealed a significantly more negative CNS arousal slope ($P < .03$; Cohen's $d = 0.84$) and a trend for a faster declining ANS arousal ($P < .06$; Cohen's $d = 0.94$) in responders compared with nonresponders to SSRI treatment after 2 weeks. Analysis of iSPOT dataset results were not significant for CNS arousal slope ($P = .57$; Cohen's $d = 0.34$) but were for ANS arousal slope ($P < .04$; Cohen's $d = 0.86$).[40]

Taken exploratory dataset and iSPOT dataset together, when the means of ANS and CNS arousal parameters were used to assign subjects to SSRI or SNRI treatment retrospectively, response rates for SSRI treatment increased from 63.5% to 73.3%, and remission rate increased from 47.1% to 58.4%. For treatment with the SNRI, response rates increased from 64.7% to 72.3%, and remission rates increased from 43.2% to 46.5%. These findings underline the importance of the RDoC announced by the National Institutes of Health and validate CNS and ANS arousal systems as future potential predictive biomarkers to guide positive treatment outcome in MDD patients.[40]

Acute stress disorder (ASD) characterized by presence of nine (or more) of symptoms from any of the five categories of intrusion, negative mood, dissociation, avoidance, and arousal, beginning or worsening after the traumatic event(s), experienced during the first month of the trauma. Arousal symptoms include sleep disturbance, irritable behavior, and angry outbursts (with little or no provocation), typically expressed as verbal or physical aggression toward people or objects, hypervigilance, problems with concentration, and/or exaggerated startle response.[33]

Recent evidence points to hyperarousal being a critical component of the acute trauma response, and that hyperarousal is associated with acute psychopathology levels. Nixon and Bryant provide evidence that re-experiencing is directly associated with elevated states of arousal, by investigating Civilian trauma survivors with ($n = 18$) and without ASD ($n = 14$), using hyperventilation provocation test (HVPT) and Physical Reactions Scale (PRS). They found that significantly more ASD participants described flashback experiences (72%) than non-ASD participants (29%), $\chi^2(1, n = 32) = 4.40$, $P < .05$. Similarly, ASD participants were more distressed as a result of the HVPT procedure (72%) than non-ASD participants (7%), $\chi^2(1, n = 32) = 11.04$, $P < .001$. ASD participants had more intense flashback-type experiences ($M = 2.23 \pm 0.73$) than non-ASD participants ($M = 1.25 \pm 0.50$, $t(15) = 2.50$, $P < .05$).[41]

ASD participants reported higher arousal as a result of the HVPT on the PRS ($M = 17.28 \pm 11.91$) than non-ASD participants ($M = 9.36 \pm 9.24$, $t(30) = 2.05$, $P = .05$). ASD participants reported greater avoidance of trauma-related thoughts during the experiment ($M = 6.04 \pm 2.33$) than non-ASD participants ($M = 3.67 \pm 1.99$, $t(30) = 3.05$, $P < .005$). Pearson correlations indicated that the number of intrusions was positively correlated with PRS scores ($r = 0.42$, $P < .05$). The findings provide evidence that re-experiencing of the trauma is directly associated with elevated states of arousal.[41]

Stress Trauma Symptoms Arousal Regulation Treatment (START) is a short manualized structured intervention to stabilize and modulate arousal for highly stressed minor refugees through working with them immediately on arrival to Germany. It is used for children and

adolescents suffering from intense stress and acute tension or desperation. START was accepted by the refugee children and adolescents and observed to reduce stress in children and supervising professionals. Its efficacy and effectiveness are currently targets of a standardized pre- and post-test evaluation.[42]

Posttraumatic stress disorder (PTSD) criteria include exposure to a stressor beyond the normal range of human experience, symptoms clustering in three areas that interfere with daily functioning: re-experiencing the trauma, avoiding the stimuli associated with the trauma, and experiencing increased arousal levels. Those symptoms typically remain more than 4 weeks.[33] Hyperarousal can manifest itself as sleep difficulties, hypervigilance, startle response, and intrusive thoughts.[43]

PTSD brain dysfunction has been presented under a frontolimbic model that includes the amygdala, medial prefrontal cortex (mPFC), and hippocampus as core-implicated structures. This model explained that an overactive amygdala is responsible for heightened arousal and exaggerated fear, aggravated by loss of top-down inhibition due to a dysfunctional mPFC; the hippocampus fails to identify safe or otherwise nonthreatening situations thereby contributing to avoidance and re-experiencing.[44]

Akiki et al.[45] tried to present the evidence of functional alterations in the broader framework of large-scale network dysfunction—the salience network (SN), which is involved in the detection of salient internal and external stimuli. Core structures that are part of the SN are the amygdala, insula, and dorsal anterior cingulate cortex. Within the SN, based on the perceived threat level, the anterior insula is thought to modulate the dynamics between central executive network (the middle frontal gyrus, precuneus, and parts of the premotor cortex) and default mode network (posterior cingulate cortex, ventromedial prefrontal cortex, and medial temporal lobe, including the hippocampus). Consequently, this dysfunction in the SN may alter the threat detection functions and could underlie behaviors such as hyperarousal.[45]

BDNF, which is known to regulate neuronal survival, growth, differentiation, and synapse formation hence the plasticity of the brain, can also regulate the stress response. It has been implicated in a number of psychiatric disorders, such as MDD and PTSD. A common single-nucleotide polymorphism in the BDNF gene leading a valine to methionine substitution at position 66 (Val66Met) influences human hippocampal volume, memory, and susceptibility to PTSD.[46,47]

Startle is a core symptom of hyperarousal in PTSD observed to be associated with polymorphism. The association between BDNF Val66Met and the startle score of PTSD Checklist has been studied by Zhang et al. Met/Met frequency distribution was significantly different between subjects with and without exaggerated startle. The frequency of the Met/Met genotype was almost fourfold (12.2% vs. 3.3%) higher in subjects with exaggerated startle than in those without exaggerated startle. In addition, the frequency of the Met allele was higher in subjects with exaggerated startle than in those without exaggerated startle (24.4% vs. 15.3%), indicating that Met/Met is associated with hyperarousal vulnerability.[48]

Chronic hyperarousal can lead to abnormal levels of stress-related hormones such as norepinephrine and cortisol or change in the number or sensitivity of receptors to these substances as it makes victims of past traumatic events more vulnerable to current life stressors through a process of sensitization or it may alter certain brain structures, such as the hippocampus.[49] There is evidence that corticotropin releasing factor (CRF) and norepinephrine (NE) interact to increase fear conditioning and encoding of emotional memories, through a feedforward circuit connecting the amygdala and the hypothalamus with the LC, to enhance arousal and vigilance and integrate endocrine and autonomic responses to stress.[50]

Baker et al. measured CRF in CSF using serial cerebrospinal fluid (CSF) sampling in a group of 11 combat veterans with PTSD and 12 matched normal volunteers, they found high basal CSF CRH concentrations in veterans than in normal subjects (55.2 pg/mL $\pm$ 16.4 vs. 42.3 pg/mL $\pm$ 15.6); no correlation was found between CSF CRH concentrations and PTSD symptoms,

while there was no significant difference between groups in 24-h urinary-free cortisol excretion, the correlation between 24-h urinary-free cortisol excretion, and PTSD symptoms was negative and significant (Baker et al., 1999). In various animal models, increased CNS CRF activity may promote certain cardinal features of PTSD, as conditioned fear responses, increased startle reactivity, sensitization to exposure to stressors, and hyperarousal.[50]

Several studies have demonstrated the efficacy of alpha-1 adrenergic blocker in reducing nightmares and hyperarousal related to PTSD. Raskind and colleagues tested 10 Vietnam combat veterans with chronic PTSD and severe trauma-related nightmares, using prazosin and placebo in a 20-week double-blind crossover protocol. They found that subjects were more improved when they were taking prazosin ($M = 9.5$ mg/day at bedtime ± 0.5) than when they were taking placebo on the primary outcome measures of nightmares, sleep disturbance, and global change in PTSD severity and functional status. Moreover, prazosin was more effective for re-experiencing, avoidance, and hyperarousal symptom cluster scores as well as total scores on the Clinician-Administered PTSD Scale. Effect size analyses for dependent variables showed robust and clinically meaningful reductions in symptoms across all outcomes measured.[51]

It is hypothesized that yohimbine (an alpha-2 adrenergic receptor antagonist) increases noradrenergic activity and so emotional distress during prolonged exposure therapy (PE), which is considered a gold-standard treatment for PTSD. Yohimbine facilitates enhanced emotional engagement with trauma memories in PTSD so that PE "can correct information by pairing them with distress for new learning to occur".[52]

Tuerk and colleagues[52] conducted a randomized placebo-controlled double-blind clinical trial for 5 years. The trial investigated the effects of pairing one 21.6 mg oral dose of yohimbine with the first imaginal exposure in PE on trauma-related HR reactivity (primary outcome) and on the slope of patient-rated PTSD, depression, and exposure-related distress throughout the remaining course of treatment (secondary outcomes) in the intention-to-treat sample.

The sample consisted of 26 male combat veterans of Operations Enduring Freedom and Iraqi Freedom, they found that participants randomized to yohimbine were more likely to experience an increase in HR from the time of drug administration to 1 h later, compared with placebo ($\chi^2 = 3.91$, $N = 26$, $P < .04$, adj. $P = .09$), with 43% of the yohimbine group, and only 8% of the placebo group experiencing an increase of at least five beats per minute. Participants randomized to yohimbine also evidenced increased systolic BP 1 h after drug administration compared with placebo ($t = 2.17$, df = 23, $P = .02$, adj. $P = .04$, $d = 0.66$), with an average increase of 7.5 mm Hg (± 8.06, 95% confidence interval [CI]: 2.85−12.15) and no increase for placebo, 0.58 mm Hg (± 7.23, 95% CI: −4.01 to 5.18). Yohimbine resulted in increased physiological arousal and subjective distress during the drug/exposure visit compared with placebo led to significantly lower trauma-cued HR reactivity 1 week after administration and greater between- and within-session declines in distress.[52] Further studies are needed to replicate the findings.

Generalized anxiety disorder (GAD) is characterized by excessive anxiety or worry over more than 6 months. That is present most of the time regarding many activities with inability to manage these symptoms and at least three of the following: restlessness, fatigue, problems concentrating, irritability, muscle tension, and problems with sleep. These symptoms result in problems with functioning.[33] To diagnose GAD using ICD-10, at least one from autonomic arousal symptoms must be preset (palpitations or pounding heart or accelerated HR, sweating, trembling or shaking, dry mouth [not due to medication or dehydration]).

Barlow has termed the fundamental process to conceptually understand anxiety disorders as "anxious apprehension." Anxious apprehension refers to a future-oriented mood state in which one becomes ready or prepared in an attempt to cope with upcoming negative events. This mood state is associated with a state of high negative affect and chronic overarousal, a sense of uncontrollability, and an attentional focus on threat-related stimuli. The content of anxious

apprehension varies from disorder to disorder (e.g., anxiety over future panic attacks in panic disorder, anxiety over possible negative social evaluation in social phobia).[53]

Pathological worry shifts the nature of the cognition toward negative verbal thoughts as denoted by "the Cognitive Avoidance Theory," which proposes that worry is implemented by patients as an avoidance strategy, aimed at controlling physiological arousal engendered by anxiety.[54,55] Makovac and colleagues used resting-state functional magnetic resonance imaging and measure HR variability (HRV) in 19 patients with GAD and 21 control subjects to define neural correlates of autonomic and cognitive responses before and after induction of perseverative cognition.

They found that patients with GAD have higher HR compared with the healthy control (67.35 ± 8.83 vs. 61.65 ± 7.63, $P < .001$), with baseline HR being lower compared with HR after the induction (63.84 ± 9.3 vs. 65.37 ± 8.63, $P < .05$). Compared with HC subjects, patients with GAD reported lower connectivity between the right amygdala and right superior frontal gyrus, right paracingulate/anterior cingulate cortex, and right supramarginal gyrus. They link functional brain mechanisms to parasympathetic autonomic dyscontrol, highlighting overlap between cognitive and autonomic responses in patients with GAD.[56]

One of the two principal components that should form the targets of a treatment intervention for GAD is the persistent overarousal accompanying the uncontrollable worry. Brown and colleagues' relaxation training in their treatment protocol for GAD taught patients the rationale that relaxation is aimed at alleviating the symptoms associated with the physiological component of anxiety, partly via the interruption of the learned association between autonomic overarousal and worry.[57]

Obsessive–compulsive disorder (OCD) is characterized by presence of obsessions, compulsions, or both. Obsessions are defined by recurrent, persistent, intrusive and unwanted thoughts, urges, or impulses, causing marked anxiety or distress, and the individual attempts to ignore, neutralize, or suppress such thoughts, urges, or images, with some other thought or action. Compulsions are defined by repetitive behaviors or mental acts that the individual feels driven to perform in response to an obsession or according to rules that must be applied rigidly; they are aimed at preventing or reducing anxiety or distress.[33]

The neurobiological basis of emotional experience is based on the interaction between the limbic brain areas and prefrontal control mechanisms to appraise salient stimuli and adequately regulate emotional responses; exaggerated anxiety in OCD has been linked to functional changes in these brain areas.[58,59] Besides abnormal neural activity in those brain areas during threat processing, clinical anxiety is also characterized by excess attention to threatening stimuli; enhanced processing of phobic stimuli is reflected in the late positive potential (LPP) in the event-related potential (ERP). The LPP shows its maximum effect over centro-parietal scalp sites and is enhanced by emotional compared with neutral pictures.[60]

This was investigated by Paul et al.[61] 24 patients with OCD and 24 HC were studied using ERPs to disorder-relevant, to record aversive and neutral pictures while participants were instructed to either maintain or reduce emotional responding using cognitive distraction or cognitive reappraisal. They found that relative to OCD patients, HCs showed greater regulation effects in the LPP for both distraction ($t(46) = 2.25$, $P = .03$) and reappraisal ($t(46) = 1.81$, $P = .08$). OCD patients rated aversive pictures as less arousing when using reappraisal compared with distraction ($t(23) = 3.18$, $P = .01$), which was absent in HCs ($P = .99$), and only distraction reduced arousal in response to neutral pictures in HC ($t(23) = 2.53$, $P = .06$), while reappraisal failed to reach significance ($P = .17$). This should draw more attention for further investigation because quickly responding to aversive stimuli has proven to be critical for survival.[61]

Further studies showed morphometric gray matter abnormalities in regions associated with the frontal-subcortical loops, and functional neuroimaging studies demonstrated activation of the orbitofrontal and anterior cingulated loops that are associated with provocation of OCD symptoms.[62] Gonçalves et al. investigated 15 patients with OCD, and 12 healthy controls

underwent functional magnetic resonance imaging acquisition while being exposed to emotional pictures, with different levels of arousal. They found that patients with OCD when compared with healthy controls showed significantly less activation in the superior occipital gyrus, the right precentral gyrus, left paracentral lobule, left superior occipital gyrus, and left fusiform gyrus. That means OCD patients show evidence of altered basic survival circuits, particularly those associated with the visual processing of the physical characteristics of emotional stimuli.[63]

Olbrich et al.[64] studied unmedicated OCD patients altered vigilance regulation during a 15-min resting-state EEG recording in comparison to healthy controls. Thirty OCD patients and 33 HC enrolled. The post-hoc Scheffé test revealed a significantly higher EEG vigilance for OCD patients in comparison to HCs for minutes 9–12 ($P < .003$).[64] This finding may be in line with study showed increased cortisol and adrenocorticotropic hormone,[65] which represents the neuro-endocrinological analogy of altered EEG vigilance regulation in OCD.

Differences in sleep behavior have been documented in patients with OCD, especially delayed sleep phase disorder (DSPD) in patients with severe OCD.[66] Nota et al. examined quantitative information about the sleep of patients with OCD in comparison to healthy individuals by doing a meta-analysis including 12 articles. They found that sleep duration was shorter in individuals with OCD compared with healthy individuals. The magnitude of this difference is in the medium range ($g = -0.60$; 95% CI: −0.90 to −0.31); heterogeneity among studies was low and not statistically significant ($Q = 11.81$, $P = .22$; $I^2 = 23.81\%$), and the prevalence of DSPD in the individuals with OCD was also significantly greater than healthy individuals. The magnitude of this difference is large ($g = 2.28$; 95% CI: 1.28, 3.27); heterogeneity among studies was moderate but not statistically significant ($Q = 4.72$, $P = .09$; $I^2 = 57.61\%$).[67] Further studies are needed to clarify these findings.

A retrospective study was performed by Dohrmann et al. to examine whether EEG-based CNS arousal markers differ for patients suffering from OCD that either respond or do not respond to cognitive behavioral therapy (CBT), SSRIs, or their combination using VIGALL, and to identify specific response-predictors for the different therapy approaches, Clinical Global Impression scores were used to assess response or nonresponse after 3–6 months following therapy (CBT, $n = 18$; SSRI, $n = 11$; or combination, $n = 22$). Fifty-one patients enrolled. These results revealed that there is a significant difference between responders and nonresponders only for stage 0 with $F(1, 49) = 5.76$, $P < .02$, but for no other stage, responders spent significant less time at highest CNS-arousal stage 0. Comparisons between the wakefulness profiles of responders of the three treatment groups revealed that subjects with lowest wakefulness profiles (i.e., lowest amounts of high arousal stages) were more likely to respond to a combined treatment approach than to SSRI or CBT treatment alone.[68]

CONDITIONS FEATURING AROUSAL DYSREGULATION

Bipolar affective disorder involves the alternation between manic, hypomanic, and depressive episodes. Manic episodes are characterized by abnormally elevated mood lasting at least 1 week, together with inflated self-esteem, talkativeness, and flight of ideas, distractibility, increased goal-directed activity, decreased need for sleep, and excessive involvement in pleasurable activities. Hypomania is distinct from mania in that there is no significant functional impairment and lasting at least four consecutive days.[33]

The vigilance regulation model denotes that in vulnerable subjects, "genetically" an unstable vigilance—the term vigilance denotes tonic neurophysiologic arousal—induces exaggerated autoregulatory behavior "sensation and novelty seeking, hyperactivity, talkativeness, distractibility, and impulsivity." This behavior overrides the physiological tendency to seek sleep, thus aggravating the sleep deficits and therefore the instability of vigilance. A pathogenic vicious circle is started, which then contributes to full-blown mania.[34]

HRV as one of arousal regulation measures has been reviewed by Faurholt-Jepsen et al. in a meta-analysis included 15 articles, for it being an important risk factor for coronary heart disease, atherosclerosis, heart failure, and arrhythmias when it is reduced. Reduced HRV ($g = -1.77$, 95% CI: −2.46 to −1.09, $P < .001$, 10 comparisons, $n = 1581$) was observed in patients with bipolar disorder compared with healthy control individuals.[69] It is possible that a reduced HRV in bipolar disorder could predict sudden cardiac death in this population, further prospective and retrospective studies are needed to further investigate it.

Wittekind and colleagues investigated brain arousal regulation in different affective episodes in patients with bipolar disorder using VIGALL (see previously). Twenty-eight patients with bipolar disorder received a 15-min resting EEG during a depressive episode, 19 patients received the same during a manic/hypomanic episode and 28 healthy control subjects. When comparing patients and controls, unstable arousal regulation was highest in patients with manic episodes, who showed significantly less stable arousal regulation than controls ($P = .004$, $\eta^2 = 0.168$); however, patients with depressive episodes showed significantly more stable arousal regulation than patients with manic episodes ($P \leq .001$, $\eta^2 = 0.257$). By comparing the groups, they revealed that manic patients had the lowest vigilance level, with the mean vigilance values being significantly lower than that in the control sample ($F(1, 45) = 4.981$, $P = .031$, $\eta^2 = 0.100$), while depressive patients showed the highest vigilance level with a significantly higher mean vigilance than both manic patients ($F(1, 45) = 19.246$, $P \leq .001$, $\eta^2 = 0.300$) and healthy controls ($F(1, 54) = 4.213$, $P = .045$, $\eta^2 = 0.072$).[70]

Brain arousal-stabilizing drugs have been studied in the last decade for their potential to stabilize vigilance dysregulation in manic and attention deficit hyperactivity disorder (ADHD) patients.[71–77] Based on these findings, an international randomized placebo-controlled clinical trial was started to assess efficacy and safety of treatment with methylphenidate in mania.[78] Forty-two patients were randomly assigned to receive 20–40 mg per day of methylphenidate or placebo. Futility was declared for methylphenidate, as there was no significant difference between both groups $F(1, 37) = 0.23$; $P = .64$; difference from placebo = −4.50 points; effect size (Cohen's d) = −0.48; 95% CI: −1.08 to 0.14. Given this result, the randomized controlled trial was stopped.[79]

Those results are in line with the cohort done using linked Swedish national registries on 2307 adults with bipolar disorder who initiated therapy with methylphenidate between 2006 and 2014. They found that manic patients on methylphenidate monotherapy displayed an increased rate of manic episodes within 3 months of medication initiation (hazard ratio = 6.7, 95% CI: 2.0–22.4), while patients taking mood stabilizers, the risk of mania was lower after starting methylphenidate (hazard ratio = 0.6, 95% CI: 0.4–0.9).[80]

PSYCHIATRIC DISORDERS ASSOCIATED WITH HYPOAROUSAL

ADHD is childhood-onset psychiatric disorder, which is characterized by age-inappropriate levels of the core symptoms inattention, hyperactivity, and impulsivity.[33]

The presentation specifiers for ADHD are predominantly inattentive subtype and predominantly hyperactive–impulsive subtype. The inattentive subtype can be explained by unstable arousal regulation. In the combined presentation, additional autoregulatory aspects supervene with sensation seeking and hyperactivity as an attempt to stabilize arousal, according to vigilance regulation model "which denotes that in vulnerable subjects an unstable vigilance induces exaggerated autoregulatory behavior as hyperactivity, talkativeness, and distractibility," so we can explain hyperactivity not as a primary disorder per se, but as an auto-regulatory response, which may or may not be present.[81–83]

Hypoarousal in ADHD has been documented for many years started by the work of Satterfield and Dawson; they illustrated a lower general skin conductance level—an established indicator of autonomic arousal—in ADHD patients at

rest.[84] Several resting EEG studies have also suggested ADHD-associated hypoarousal in children and adults by demonstrating excess of slow frequencies, especially increased theta and reduced faster alpha and beta activities.[85–87] The increased ratio of theta-to-beta activity (TBA) during rest has perceived as a marker of the disorder indicating hypo arousal.[88–90] Further studies are needed to examine TBA and its correlation to executive functions.[91–93]

Unstable vigilance and behavioral variability in ADHD might be due to altered connectivity between regions of the default mode network, which is a distributed set of brain regions in frontal (inferior frontal cortex), parietal (precuneus, inferior parietal cortex), temporal (inferior temporal gyrus, amygdala), and medial regions.[94–96]

When arousal mechanisms are performing at a low level, it is claimed that arousal-related neurons utilizing NE and DA and pyramidal neurons in the prefrontal cortex are unable to distinguish important neuronal signals from unimportant signals. These patients cannot focus on one thing and cannot sustain attention because it is easy to be distracted from one signal to another, as if all signals are the same.[97]

Psychostimulants therapeutic effects are well established in treatment of ADHD. The rapid effects of stimulants could be explained by their arousal-stabilizing properties, which could interrupt the autoregulatory hyperactivity and sensation-seeking behavior.[98–100]This effect was documented by reduction of EEG slow-wave activity under treatment.[101] Children having less beta activity show a good response to treatment with methylphenidate.[102]

Ludyga and colleagues[103] examined the effect of acute moderately intense aerobic exercise on cognitive flexibility and task-related HRV in children with ADHD ($n = 18$) and healthy controls ($n = 18$) in a cross-over design. The analysis indicated a lower HR during cognitive testing following the control condition (78.8 ± 10.3 bpm) compared with aerobic exercise (85.8 ± 10.2 bpm); $F(1, 32) = 26.5$, $P < .001$, $\eta^2 = 0.45$. Regarding the acute effects of exercise on task performance, the results revealed a significant multivariate main effect for condition, Wilks's $\lambda = 0.725$, $F(4, 29) = 2.8$, $P = .047$, $\eta^2 = 0.28$, and power to detect the effect was 0.68, these effects indicated higher scores following aerobic exercise compared with the control condition. In this respect, acute intense aerobic exercise might be seen as a complementary treatment, which allows a temporary enhancement of executive function beyond the normal range.[103] Further studies are needed to replicate the finding.

SUMMARY

Changes in arousal are associated with many neuropsychiatric disorders. For example, hyperarousal is associated with major depression, GAD, and PTSD; while hypoarousal correlates with ADHD. Arousal can be assessed by cognitive, psychological, or autonomic measures. Shedding the light on the brain mechanisms for fine tuning of arousal levels potentially can help in the understanding and treatment of certain psychiatric disorders.

References

1. Moruzzi G, Magoun H. Brain stem reticular formation and activation of the EEG. *Electroencephalogr Clin Neurophysiol*. 1949;1(4):455–473.
2. Steriade M. Arousal: revisiting the reticular activating system. *Science*. 1996;272:225–226.
3. Pfaff DW. *Brain Arousal and Information Theory: Neural and Genetic Mechanisms*. Cambridge, Mass: Harvard University Press; 2006.
4. Pfaff DW. *How Brain Arousal Mechanisms Work: Paths toward Consciousness*. Cambridge: Cambridge University Press; 2018. in press.
5. Pfaff DW, Martin EM, Ribeiro AC. Relations between mechanisms of CNS arousal and mechanisms of stress. *Stress*. 2007;10:316–325.
6. Li SB, Jones JR, de Lecea L. Hypocretins, neural systems, physiology, and psychiatric disorders. *Curr Psychiatry Rep*. 2016;18(1):7.
7. Li SB, Giardino WJ, de Lecea L. Hypocretins and arousal. *Curr Top Behav Neurosci*. 2017;33:93–104.
8. Ogawa S, Eng V, Taylor J, et al. Roles of estrogen receptor-alpha gene expression in reproduction-related behaviors in female mice. *Endocrinology*. 1998a; 139:5070–5081.
9. Ogawa S, Washburn T, Taylor J, et al. Modifications of testosterone-dependent behaviors by estrogen receptor-alpha gene disruption in male mice. *Endocrinology*. 1998b;139:5058–5069.

10. Garey J, Goodwillie A, Frohlich J, et al. Genetic contributions to generalized arousal of brain and behavior. *Proc Natl Acad Sci USA*. 2003;100(19):11019−11022.
11. Weil ZM, Zhang Q, Hornung A, et al. Impact of generalized brain arousal on sexual behavior. *Proc Natl Acad Sci*. 2010;107(5):2265−2270.
12. Calderon DP, Kilic M, Maritan A, et al. Generalized CNS arousal: existence, mechanisms, and submission to quantitative analysis. *Neurosci Biobehav Rev.* 2016; 68:167−176.
13. Pfaff DW, Banavar JR. Hypotheses: a theoretical framework for CNS arousal. *Bioessays*. 2012;29(8):803−810.
14. Proekt A, Banavar JR, Maritan A, et al. Scale invariance in the dynamics of spontaneous behavior. *Proc Natl Acad Sci*. 2012;109(26):10564−10569.
15. Martin EM, Pavlides C, Pfaff DW. Multimodal sensory responses of nucleus reticularis gigantocellularis and the responses' relation to cortical and motor activation. *J Neurophysiol*. 2010;103(5):2326−2338.
16. Martin EM, Devidze N, Shelley DN, et al. Molecular and neuroanatomical characterization of single neurons in the mouse medullary gigantocellular reticular neurons. *J Comp Neurol*. 2011;519(13):2574−2593.
17. Robbins TW, Granon S, Muir JL. Neural systems underlying arousal and attention: implications for drug abuse. *Ann NY Acad Sci*. 1998;846(1):222−237.
18. Mayes LC. A developmental perspective on the regulation of arousal states. *Semin Perinatol*. 2000;24(4):267−279.
19. Peterson F, Jung CG. Psycho-physical investigations with the galvanometer and plethysmograph in normal and insane individuals. *Brain*. 1907;30:153.
20. Insel T, Cuthbert B, Garvey M, et al. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. *Am J Psychiatry.* 2010; 167(7):748−751.
21. Cuthbert BN, Insel TR. Toward the future of psychiatric diagnosis: the seven pillars of RDoC. *BMC Med*. 2013;11:126.
22. Anderzhanova AC, Kirmeier BT, Wotjak AC. Animal models in psychiatric research: the RDoC system as a new framework for endophenotype oriented translational neuroscience. *Neurobiol Stress*. 2017;7:47−56.
23. National Institute of Mental Health. *Arousal and Regulatory Systems: Workshop Proceedings*; 2013. http://www.nimh.nih.gov/research-priorities/rdoc/rdoc arousal regulatory systems workshop.pdf.
24. Beauchaine TP, Thayer JF. Heart rate variability as a transdiagnostic biomarker of psychopathology. *Int J Psychophysiol*. 2015;98(2):338−350.
25. Boucsein W, Fowles DC, Grimners S, et al. Publication recommendations for electrodermal measurements. *Psychophysiology.* 2012;49(8):1017−1034.
26. Basner M, Mollicone D, Dinges DF. Validity and sensitivity of a brief psychomotor vigilance test (PVT-B) to total and partial sleep deprivation. *Acta Astronaut*. 2011;69(11−12):949−959.
27. Hegerl U, Stein M, Mulert C, et al. EEG-vigilance differences between patients with borderline personality disorder, patients with obsessive-compulsive disorder and healthy controls. *Eur Arch Psychiatry Clin Neurosci*. 2008;258:137−143.
28. Olbrich S, Mulert C, Karch S, et al. EEG-vigilance and BOLD effect during simultaneous EEG/fMRI measurement. *Neuroimage*. 2009;45:319−332.
29. Schmidt FM, Pschiebl A, Sander C, et al. Impact of serum cytokine levels on EEG-measured arousal regulation in patients with major depressive disorder and healthy controls. *Neuropsychobiology.* 2016;73(1): 1−9.
30. Huang J, Hensch T, Ulke C, et al. Evoked potentials and behavioral performance during different states of brain arousal. *BMC Neurosci*. 2017;18(1):21.
31. Coren S, Mah KB. Prediction of physiological arousability: a validation of the arousal predisposition scale. *Behav Res Ther.* 1993;31(2):215−219.
32. Mehrabian A. Theory and evidence bearing on a scale of trait arousability. *Curr Psychol*. 1995;14(1):3−28.
33. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Arlington, VA: American Psychiatric Publishing; 2013.
34. Hegerl U, Hensch T. The vigilance regulation model of affective disorders and ADHD. *Neurosci Biobehav Rev.* 2014;44:45−57.
35. Ware JC, Morin CM. Sleep in depression and anxiety. In: Pressman MR, Orr WC, eds. *Understanding Sleep: The Evaluation and Treatment of Sleep Disorders*. Washington, DC: American Psychological Association; 1997:483−503.
36. Zobel A, Barkow K, Schulze-Rauschenbach S, et al. High neuroticism and depressive temperament are associated with dysfunctional regulation of the hypothalamic−pituitary−adrenocortical system in healthy volunteers. *Acta Psychiatr Scand*. 2004;109(5):392−399.
37. Duman RS, Malberg J, Thome J. Neural plasticity to stress and antidepressant treatment. *Biol Psychiatry.* 1999;46:1181−1191.
38. Gatt JM, Nemeroff CB, Dobson-Stone C, et al. Interactions between BDNF Val66Met polymorphism and early life stress predict brain and arousal pathways to syndromal depression and anxiety. *Mol Psychiatry.* 2009;14:681−695.
39. Schmidt FM, Christian Sander C, Dietz ME, et al. Brain arousal regulation as response predictor for antidepressant therapy in major depression. *Sci Rep*. 2017;7: 45187.
40. Olbrich AS, Tränkner AG, Surova AG, et al. CNS- and ANS-arousal predict response to antidepressant medication: findings from the randomized iSPOT-D study. *J Psychiatry Res*. 2016;73:108−115.
41. Nixon RD, Bryant RA. Induced arousal and reexperiencing in acute stress disorder. *Anxiety Disorders*. 2005;19:587−594.

42. Dixius A, Möhler E. START - development of an intervention for a first stabilization and arousal-modulation for highly stressed minor refugees. *Prax Kinderpsychol Kinderpsychiatr.* 2017;66(4):277−286.
43. Briere JN, Elliot DM. Immediate and long-term impacts of child sexual abuse. *Future Child*. 1994;4:54−69.
44. Rauch SL, Shin LM, Phelps EA. Neurocircuitry models of posttraumatic stress disorder and extinction: human neuroimaging research—past, present, and future. *Biol Psychiatry.* 2006;60(4):376−382.
45. Akiki TJ, Averill CL, Abdallah CG. A network-based neurobiological model of PTSD: evidence from structural and functional neuroimaging studies. *Curr Psychiatry Rep*. 2017;19:81.
46. Matsuoka Y, Nishi D, Noguchi H, et al. Longitudinal changes in serum brain-derived neurotrophic factor in accident survivors with posttraumatic stress disorder. *Neuropsychobiology.* 2013;68:44−50.
47. Zhang L, Li X, Hu X. Post-traumatic stress disorder risk and brain-derived neurotrophic factor Val66Met. *World J Psychiatry.* 2016;6(1):1−6.
48. Zhang L, Benedek DM, Fullerton CS, et al. PTSD risk is associated with BDNF Val66Met and BDNF overexpression. *Mol Psychiatry.* 2014;19:8−10.
49. Kendall-Tackett KA. Physiological correlates of childhood abuse: chronic hyperarousal in PTSD, depression, and irritable bowel syndrome. *Child Abuse & Neglect*. 2000;24(6):799−810.
50. Heim C, Nemeroff CB. Neurobiology of posttraumatic stress disorder. *CNS Spectr*. 2009;14(1):13−24.
51. Raskind MA, Peskind ER, Kanter ED, et al. Reduction of nightmares and other PTSD symptoms in combat veterans by prazosin: a placebo-controlled study. *Am J Psychiatry.* 2003;160:371−373.
52. Tuerk PW, Wangelin BC, Powers MB, et al. Augmenting treatment efficiency in exposure therapy for PTSD: a randomized double-blind placebo-controlled trial of yohimbine HCl. *Cogn Behav Ther.* 2018;15:1−21.
53. Barlow DH. *Anxiety and its Disorders: The Nature and Treatment of Anxiety and Panic*. New York: Guilford Press; 1988.
54. Borkovec TD. The nature, functions, and origins of worry. In: Davey GCL, Tallis F, eds. *Worrying: Perspectives on Theory, Assessment and Treatment*. Oxford, England: Wiley; 1994:5−33.
55. Borkovec TD, Alcaine O, Behar ES. Avoidance theory of worry and generalized anxiety disorder. In: Heimberg R, Mennin D, Turk C, eds. *Generalized Anxiety Disorder: Advances in Research and Practice*. New York: Guilford; 2004:77−108.
56. Makovac E, Meeten F, Watson DR, et al. Alterations in amygdala-prefrontal functional connectivity account for excessive worry and autonomic dysregulation in generalized anxiety disorder. *Biol Psychiatry.* 2015; 80(10):786−795.
57. Brown TA, O'Leary TA, Barlow DH. Generalized anxiety disorder. In: Barlow DH, ed. *Clinical Handbook of Psychological Disorders, 3rd Edition: A Step-by-step Treatment Manual*. New York: The Guilford Press; 2001.
58. Milad MR, Rauch SL. Obsessive−compulsive disorder: beyond segregated cortico-striatal pathways. *Trends Cognit Sci*. 2012;16:43−51.
59. Rasgona A, Leea WH, Leibua E, et al. Neural correlates of affective and non-affective cognition in obsessive compulsive disorder: a meta-analysis of functional imaging studies. *Eur Psychiatry.* 2017;46:25−32.
60. Hajcak G, MacNamara A, Olvet DM. Event-related potentials, emotion, and emotion regulation: an integrative review. *Dev Neuropsychol*. 2010;35:129−155.
61. Paul S, Simon D, Endrass T, et al. Altered emotion regulation in obsessive−compulsive disorder as evidenced by the late positive potential. *Psychol Med*. 2016;46:137−147.
62. Rotge JY, Guehl D, Dilharreguy B, et al. Provocation of obsessive-compulsive symptoms: a quantitative voxel-based metaanalysis of functional neuroimaging studies. *J Psychiatry Neurosci*. 2008;33(5):405−412.
63. Gonçalves ÓF, Soares JM, Carvalho S, et al. Brain activation of the defensive and appetitive survival systems in obsessive compulsive disorder. *Brain Imaging Behav.* 2015;9(2):255−263.
64. Olbrich S, Olbrich H, Jahn I, et al. EEG-vigilance regulation during the resting state in obsessive-compulsive disorder. *Clin Neurophysiol*. 2013;124(3):497−502.
65. Kluge M, Schüssler P, Künzel HE, et al. Increased nocturnal secretion of ACTH and cortisol in obsessive compulsive disorder. *J Psychiatry Res*. 2007;41:928−933.
66. Mukhopadhyay S, Fineberg NA, Drummond LM, et al. Delayed sleep phase in severe obsessive−compulsive disorder: a systematic case-report survey. *CNS Spectr*. 2008;13(5):406−413.
67. Nota JA, Sharkey KM, Coles ME. Sleep, arousal, and circadian rhythms in adults with obsessive-compulsive disorder: a meta-analysis. *Neurosci Biobehav Rev.* 2015;51:100−107.
68. Dohrmann AL, Stengler K, Jahn I, et al. EEG-arousal regulation as predictor of treatment response in patients suffering from obsessive compulsive disorder. *Clin Neurophysiol*. 2017;128(10):1906−1914.
69. Faurholt-Jepsen M, Kessing LV, Munkholm K. Heart rate variability in bipolar disorder: a systematic review and meta-analysis. *Neurosci Biobehav Rev.* 2017;73:68−80.
70. Wittekind DA, Spada J, Gross A, et al. Early report on brain arousal regulation in manic vs depressive episodes in bipolar disorder. *Bipolar Disord*. 2016;18: 502−510.
71. Hegerl U, Sander C, Olbrich S, et al. Are psychostimulants a treatment option in mania? *Pharmacopsychiatry.* 2009;42(5):169−174.

72. Waxmonsky J, Pelham WE, Gnagy E, et al. The efficacy and tolerability of methylphenidate and behavior modification in children with attention-deficit/hyperactivity disorder and severe mood dysregulation. *J Child Adolesc Psychopharmacol*. 2008;18(6):573—588.
73. Carlson PJ, Merlock MC, Suppes T. Adjunctive stimulant use in patients with bipolar disorder: treatment of residual depression and sedation. *Bipolar Disord*. 2004;6(5):416—420.
74. El-Mallakh RS. An open study of methylphenidate in bipolar depression. *Bipolar Disord*. 2000;2(1):56—59.
75. Fernandes PP, Petty F. Modafinil for remitted bipolar depression with hypersomnia. *Ann Pharmacother*. 2003;37(12):1807—1809.
76. Lydon E, El-Mallakh RS. Naturalistic long-term use of methylphenidate in bipolar disorder. *J Clin Psychopharmacol*. 2006;26(5):516—518.
77. Nasr S, Wendt B, Steiner K. Absence of mood switch with and tolerance to modafinil: a replication study from a large private practice. *J Affect Disord*. 2006; 95(1e3):111—114.
78. Kluge M, Hegerl U, Sander C, et al. Methylphenidate in mania project (MEMAP): study protocol of an international randomized double-blind placebo-controlled study on the initial treatment of acute mania with methylphenidate. *BMC Psychiatry*. 2013;13:71.
79. Hegerl U, Mergl R, Sander C, et al. A multi-centre, randomised, double-blind, placebo-controlled clinical trial of methylphenidate in the initial treatment of acute mania (MEMAP study). *Eur Neuropsychopharmacol*. 2018;28(1):185—194.
80. Viktorin A, Rydén E, Thase ME, et al. The risk of treatment-emergent mania with methylphenidate in bipolar disorder. *Am J Psychiatry*. 2017;174(4):341—348.
81. Hurtig T, Ebeling H, Taanila A, et al. ADHD symptoms and subtypes: relationship between childhood and adolescent symptoms. *J Am Acad Child Adolesc Psychiatry*. 2007;46:1605—1613.
82. Willcutt EG, Nigg JT, Pennington BF, et al. Validity of DSM-IV attention deficit/hyperactivity disorder symptom dimensions and subtypes. *J Abnorm Psychol*. 2012; 121:991—1010.
83. Geissler J, Romanos M, Hegerl U, et al. Hyperactivity and sensation seeking as autoregulatory attempts to stabilize brain arousal in ADHD and mania? *ADHD Atten Def Hyp Disord*. 2014;6:159—173.
84. Satterfield JH, Dawson ME. Electrodermal correlates of hyperactivity in children. *Psychophysiology*. 1971;8(2): 191—197.
85. Barry RJ, Clarke AR, Johnstone SJ. A review of electrophysiology in attention-deficit/hyperactivity disorder: I. Qualitative and quantitative electroencephalography. *Clin Neurophysiol*. 2003;114(2):171—183.
86. Paucke M, Sander C, Hegerl U, et al. P 150 the correlation of attention and neurophysiological characteristics in attention deficit hyperactivity disorder (ADHD). *Clin Neurophysiol*. 2017;128(10):401.
87. Strauß M, Ulke C, Paucke M, et al. Brain arousal regulation in adults with attention-deficit/hyperactivity disorder (ADHD). *Psychiatry Res*. 2018;261:102—108.
88. Monastra VJ, Lubar JF, Linden M, et al. Assessing attention deficit hyperactivity disorder via quantitative electroencephalography: an initial validation study. *Neuropsychology*. 1999;13(3):424—433.
89. Clarke AR, Barry RJ, Dupuy FE, et al. Excess beta activity in the EEG of children with attention-deficit/hyperactivity disorder: a disorder of arousal? *Int J Psychophysiol*. 2013;89(3):314—319.
90. Bresnahan SM, Barry RJ. Specificity of quantitative EEG analysis in adults with attention deficit hyperactivity disorder. *Psychiatry Res*. 2002;112(2):133—144.
91. Barry RJ, Clarke AR, Johnstone SJ, et al. Electroencephalogram theta/beta ratio and arousal in attention-deficit/hyperactivity disorder: evidence of independent processes. *Biol Psychiatry*. 2009;66(4): 398—401.
92. Hsu CF, Broyd SJ, Helps SK, et al. "Can waiting awaken the resting brain?" A comparison of waiting- and cognitive task-induced attenuation of very low frequency neural oscillations. *Brain Res*. 2013;1524: 34—43.
93. Zhang DW, Li H, Wu Z, et al. Electroencephalogram theta/beta ratio and spectral power correlates of executive functions in children and adolescents with AD/HD. *J Atten Disord*. 2017, 1087054717718263.
94. Fair DA, Posner J, Nagel BJ, et al. Atypical default network connectivity in youth with attention-deficit/hyperactivity disorder. *Biol Psychiatry*. 2010;68(12): 1084—1091.
95. Tian L, Jiang T, Liang M, et al. Enhanced resting-state brain activities in ADHD patients: a fMRI study. *Brain Dev*. 2008;30(5):342—348.
96. Raichle ME, MacLeod AM, Snyder AZ, et al. .A default mode of brain function. *Proc Natl Acad Sci USA*. 2001; 98(2):676—682.
97. Petrescu-Ghenea C, Trutescu C, Mihailescu I, et al. Arousal modulation in ADHD. *Rom J Child Adolesc Psychiatry*. 2013;1(1).
98. Pietrzak RH, Mollica CM, Maruff P, et al. Cognitive effects of immediate-release methylphenidate in children with attention-deficit/hyperactivity disorder. *Neurosci Biobehav Rev*. 2006;30(8):1225—1245.
99. Riccio CA, Waldrop JJ, Reynolds CR, et al. Effects of stimulants on the continuous performance test (CPT): implications for CPT use and interpretation. *J Neuropsychiatry Clin Neurosci*. 2001;13(3):326—335.
100. Spencer T, Biederman J, Wilens T, et al. A large, double blind, randomized clinical trial of methylphenidate in the treatment of adults with attention-deficit/hyperactivity disorder. *Biol Psychiatry*. 2005;57(5):456—463.
101. Bresnahan SM, Barry RJ, Clarke AR, et al. Quantitative EEG analysis in dexamphetamine-responsive adults with attention-deficit/hyperactivity disorder. *Psychiatry Res*. 2006;141(2):151—159.

102. Clarke AR, Barry RJ, McCarthy R, et al. EEG differences between good and poor responders to methylphenidate and dexamphetamine in children with attention-deficit/hyperactivity disorder. *Clin Neurophysiol*. 2002;113(2):194−205.
103. Ludyga S, Gerber M, Mücke M, et al. The acute effects of aerobic exercise on cognitive flexibility and task-related heart rate variability in children with ADHD and healthy controls. *J Atten Disord*. 2018, 1087054718757647.
104. Rotge JY, Langbour N, Guehl D, et al. Gray matter alterations in obsessive-compulsive disorder: an anatomic likelihood estimation meta-analysis. *Neuropsychopharmacology*. 2010;35(3):686−691.
105. World Health Organization. *International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10)*. Geneva: WHO; 1992.

CHAPTER

2

Resilience of the Brain and Body

Bruce S. McEwen

Laboratory of Neuroendocrinology, The Rockefeller University, New York, NY, United States

OUTLINE

INTRODUCTION

"Resilience" can be defined as the ability to achieve a successful outcome in the face of adversity. The purpose of this chapter is to put the concept of resilience into the context of the reciprocal communication between the brain and the body via neuroendocrine, autonomic, immune, and metabolic mechanisms viewed over the life course. What do we need to know? First, we need to understand the nonlinear, reciprocal communication between brain and body that promotes adaptation to a changing physical and social environment, often called "stress," but which also can lead to pathophysiology when over used and/or dysregulated. Second, it is important to understand the epigenetic plasticity and vulnerability of the brain. Finally, since development over the life course is a "one-way street," we need to understand that "reversal" is not possible and appreciate how resilience, recovery, and redirection are key to promoting a favorable trajectory over lifespan. There are a growing number of interventions that appear to promote beneficial changes in trajectory.

KEY POINTS

- "Resilience" can be defined as the ability to achieve a successful outcome in the face of adversity.
- This is particularly relevant to the brain, which is the central organ of stress and adaptation to stress because it perceives threatening challenges and determines physiological and behavioral responses.

Stress: Physiology, Biochemistry, and Pathology
https://doi.org/10.1016/B978-0-12-813146-6.00002-3

- The brain together with the neuroendocrine, immune, autonomic, and metabolic systems controls "allostasis" (stability through adaptive physiological change) that maintains "homeostasis" (physiological equilibrium through stability).
- Chronic stress and resulting changes in health-related behaviors such as diet, physical activity, and sleep contributes to pathophysiology ("allostatic load/overload").
- The mature, as well as developing brain, possess a remarkable ability to show structural and functional plasticity and resilience in response to stressful experiences, by way of neuronal replacement, dendritic remodeling, and synapse turnover.
- However, the life course is a "one-way street" and gene expression is continually changing via epigenetic mechanisms; one cannot "roll back the clock" and "reverse" change but rather promote "recovery" and "resilience."
- The purpose of this chapter is to put the concept of resilience into the context of the reciprocal communication between the brain and the body via neuroendocrine, autonomic, immune, and metabolic mechanisms and to discuss intervention strategies to promote brain and body health.

Brain-Body Basics

In talking about resilience we often refer to the response to stress, which, however, is an ambiguous word. A more biological way of looking at stress is embodied in the concepts of "allostasis" and "allostatic load/overload" that are described later after distinguishing "good stress" from "tolerable stress" and from "toxic stress" based on definitions from the National Scientific Council for the Developing Child (http://developingchild.harvard.edu/science/national-scientific-council-on-the-developing-child/).

Good stress involves our taking a chance on something one wants, like interviewing for a job or school, or giving a talk before strangers, and feeling rewarded when we are successful. Tolerable stress means that something bad happens, like losing a job or death of a loved one, but we have the personal resources and support systems to weather the storm. Toxic stress refers to the response to a major life event where the individual does not have the personal resources or support systems, and, as a result, lacks a sense of control, leading to mental and physical health problems over time, particularly if the situation is not resolved.

Now let us put these three forms of stress into a biological and behavioral context. We know that "homeostasis" means the physiological state that the body maintains to keep us alive—that is, body temperature and pH within a narrow range and adequate oxygen supply. In order to maintain homeostasis, our body activates hormone secretion and turns on our autonomic and central nervous system (we call these "mediators" like cortisol, adrenalin, the immune system and metabolism) to help us adapt, for example, when we get out of bed in the morning, walk up a flight of stairs, or have a conversation. These systems are also turned on when we are surprised by something unexpected, or get into an argument, or run to catch a train. Some of these experiences we may refer to as "stressful" but others we do not. So using the word *stress* does not really recognize all of the underlying biology.

The mediators help us adapt as long as they are turned on in a balanced way when we need them and then turned off again when the challenge is over. When that does not happen, they can cause unhealthy changes in brain and body. This is also the case when the mediators are not produced in an orchestrated and balanced manner; for example, too much or too little cortisol or an elevated or too low blood pressure. When this happens and continues over weeks and months, we call it allostatic load to refer to the wear and tear on the body that results from the chronic overuse and imbalance of the mediators. Accumulation of belly fat is an example, as is the development of chronic hypertension.

When the wear and tear is strongest we call it allostatic overload, and this is what is occurring in toxic stress. An example is when hypertension leads to coronary artery blockade. In fact, belly fat contributes chemicals that accelerate that coronary artery blockade. Note, however, that we are talking not about one mediator, like cortisol, but a host of mediators that are all released in allostasis in a coordinated manner to help us adapt but which can also cause damage when overused and dysregulated as described earlier. Because cortisol is well known in relation to stress, its role is often misunderstood.

We must go one step further and recognize that bad health behaviors, often the result of a stressful life style, like eating too much of the wrong things, smoking, drinking, loneliness, poor sleep, and lack of exercise, all contribute to that hypertension, belly fat, and blockade of coronary arteries. And they do so through the same mediators that are activated to help us adapt but that also, when overused and dysregulated, cause allostatic load and overload.[1,2]

So the mediators that help us adapt and enable us to maintain our homeostasis and survive can also contribute to well-known diseases of modern life. These ideas are the basis of the concepts of allostasis and allostatic load/overload, whereas they are not so obvious from the word *stress*, which is usually explained as the "fight or flight response" when we are, for example, threatened by a mugger and run away. What really affects our health and well-being are the more subtle, gradual, and long-term influences from our social and physical environment like family and neighborhood chaos and conflict, demands of a job, shift work and jet lag, sleeping badly, living in an ugly, noisy, and polluted environment, being lonely, not getting enough physical activity, eating too much of the wrong foods, smoking, and drinking too much alcohol. All these contribute to allostatic load and overload through the same biological mediators that help us adapt and keep us alive, and they shape our brains.

Central Role of the Brain

The brain is the central organ of stress and adaptation to stress because it perceives and determines what is threatening, as well as the behavioral and physiological responses to the stressor, which promote adaptation (allostasis) but also contribute to pathophysiology (allostatic load/overload) when overused and dysregulated. The brain "keeps the score" by storing memories from bad as well as good experiences, and yet the brain, working with the body, also "knows what to do" to keep us alive if we give it a chance by minimizing those subtle and long-term influences that cause allostatic load and overload.[3] We call that the "wisdom of the body," and it refers back to allostasis, the active process of biological adaptation, and its role in maintaining homeostasis. Indeed the brain is a plastic and vulnerable organ of the body and is continually sculpted by experiences. The brain is also a vulnerable organ, along with our heart, liver, and kidneys and other organs. The brain changes its architecture and function as part of allostasis, and the development of the notion of structural plasticity of the brain has come about over the last half century with an accelerating pace as will be described later! We also need to consider where our genes fit in and understand that they do not rigidly determine our destiny but, rather, provide the foundation on which our experiences shape our brains and bodies over the life course via "epigenetic" mechanisms that promote resilience. Finally, what does this tell us about interventions to either prevent adverse outcomes or redirect the brain and body in a healthier direction?

Plasticity of the Adult and Developing Brain

Long regarded as a rather static and unchanging organ, except for electrophysiological responsivity, such as long-term potentiation,[4] the brain has gradually been recognized as capable of undergoing rewiring after brain

damage,[5] and also able to grow and change as seen by dendritic branching, angiogenesis, and glial cell proliferation during cumulated experience.[6,7] More specific physiological changes in synaptic connectivity were also recognized in relation to hormone action in the spinal cord,[8] and in environmentally directed plasticity of the adult songbird brain.[9] Seasonally varying neurogenesis in restricted areas of the adult songbird brain is recognized as part of this plasticity.[10] Indeed, adult neurogenesis in the adult mammalian brain was initially described[11,12] and then suppressed,[13] only to be rediscovered in the dentate gyrus of the hippocampus[14,15] in the context of studies of neuron cell death and actions of adrenal steroids and excitatory amino acids in relation to stress. Neurogenesis in the dentate gyrus has gone on to become a huge topic related to effects of stress,[16] exercise,[17] enriched environment,[18] antidepressants,[19] and learning and memory.[20] More than neurogenesis, structural plasticity includes dendrite remodeling, synapse formation, and synaptic pruning. For example, a recent study shows how the brain architecture of a mother is sculpted during pregnancy as part of the formation of attachment to the child.[21] Moreover, a musician's brain develops with enhanced size and connections of sensory and motor control regions of the cerebral cortex![22]

Stress-Induced Structural Plasticity

Our demonstration of stress-induced remodeling of dendrites in hippocampal CA3 neurons provided a neuroanatomical mechanism that helped to explain behavioral effects of stress on memory and related processes.[23–28] These discoveries have led to a cascade of investigations in stress neurobiology that have increasing relevance to human mental and physical health. What these findings helped to demonstrate is the remarkable feature of the adult as well as developing brain, namely, recognition of its capacity for remodeling of dendrites, turnover of synapses, and neurogenesis that began with the enriched environment studies on brain cortex thickness[6,29] based on the work of Donald Hebb.[30] For stress-induced remodeling, which can be mimicked by chronic glucocorticoid treatment, excitatory amino acids, and other cellular mediators are involved.[25,31] What emerged from this as well as the work of Robert Sapolsky that emphasized damaging aspects of glucocorticoid action on hippocampus mediated also by excitatory amino acids[32–34] is an inverted U-shaped dose-response curve (see Fig. 2.1) in which physiological levels of glucocorticoids and excitatory amino acids operate synergistically and beneficially to facilitate long-term potentiation (LTP) and memory, as shown by Constantine Pavlides at Rockefeller University and also by David Diamond[35,36] over a short time frame of minutes to hours and promote dendritic remodeling over a time frame of weeks that shows resilience,[25] but acute traumatic events such as stroke, seizures, and head trauma cause permanent damage and neuron loss via synergy between glutamate and glucocorticoids.[33,37]

The prefrontal cortex also responds to what we can call "tolerable stress." As an example, in a group of medical student volunteers, perceived stress, i.e., how much or little they felt in control of their daily lives, revealed that those with the highest perceived stress were slower in doing a cognitive-flexibility test and also had slower functional connectivity in a brain circuit involving the prefrontal cortex when tested in a functional magnetic resonance

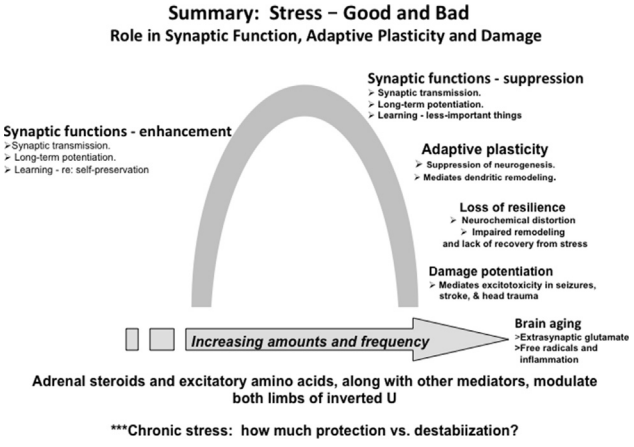


FIGURE 2.1 Inverted U-shaped dose-response curve.

imaging (MRI) machine.[38] The reason we can call this tolerable stress is that, after a vacation, these impairments disappeared, showing the resilience, at least of the young adult brain! Parallel studies on an animal model of perceived stress revealed shrinkage of neuronal dendrites and reduction of synapses in the prefrontal cortex that explained the deficits in cognitive flexibility.[39,40]

To complete the present story of brain plasticity we need to describe what happens in the amygdala under the same stressors that cause dendrites to shrink and synapses to be lost in the prefrontal cortex and hippocampus, namely, that dendrites in the basolateral amygdala grow and become more branched and, as a result, there is increased anxiety. This was discovered in the laboratory of Sumantra Chattarji at the National Centre for Biological Sciences in Bangalore, India.[41] Of note, dendrites in the orbitofrontal part of the prefrontal cortex also expand with chronic stress, and there is increased vigilance.[39] In the short term, these changes may be adaptive, as anxiety and vigilance are adaptive in a dangerous or uncertain environment; but, if the threat passes and the behavioral state "gets stuck" and persists along with the changes in neural circuitry, such maladaptation requires intervention to open "windows of plasticity" with a combination of pharmacological and behavioral therapies.

A special example of plasticity relates to posttraumatic stress disorder (PTSD). With Chattarji, we found that a single, traumatic stressor causes new synapses to form in basolateral amygdala with a delay of a week or so that is accompanied by a gradual increase in anxiety.[42] This type of delay is a feature of human PTSD. What we have further shown with the Chattarji group is that a timed elevation of cortisol at the time or, or shortly after, a traumatic stressor actually prevents the delayed increase in amygdala synapses and anxiety-like behavior.[43] Now there is evidence for human PTSD that low cortisol at the time of trauma, e.g., during open heart surgery or after a traffic accident, is a risk factor and that elevating cortisol during or right after trauma can reduce later PTSD symptoms.[44,45]

Epigenetics

What are the mechanisms for these changes in neuron structure and function? Indeed, they involve changes in gene expression caused by the stressful experience, and now the term *epigenetics* is used to refer to how experiences affect the brain and body to promote adaptation or maladaptation. Epigenetics originally meant something quite different, namely, the emergence of characteristics as a fertilized egg develops into a living organism characteristic of that species.[46] This is programmed into each species, but the individual characteristics are influenced by experiences, and that is where the modern use of epigenetics comes from. An example of this is a pair of identical twins with genes that predispose them to schizophrenia or bipolar illness. Even with the same DNA, the probability that one twin will develop the disease when the other twin gets it is only in the range of 40%–60%, which leaves plenty of room for experiences and other environmental factors to either prevent or precipitate the disorder. As an indicator of this, the methylation patterns of DNA diverge as identical twins grow older.[47] Thus, epigenetics now meaning "above the genome," that is, not changing the genetic code, replaces and makes unnecessary the old question: "which is more important, genes or environment?" The CpG methylation of DNA is now a well-known form of epigenetic modification.[48] Evidence from CpG methylation of DNA indicates the embedded influence of early adversity[49] and this will be discussed further later. But there are other mechanisms that include histone modifications that repress or activate chromatin unfolding[50] and the actions of noncoding RNAs,[51] as well as transposons and retrotransposons[52] and RNA editing.[53] We shall see how this plays out for one brain region, the hippocampus.

Brain Gene Expression Is Continually Changing

As the first extra-hypothalamic brain structure recognized to have receptors for adrenal steroids,[54] the hippocampus is an important

gateway for understanding the effects of glucocorticoids and stress on gene expression in the brain. Recent technological advances have allowed high-throughput analysis of gene expression changes in response to stress.[55] For example, work by current postdoctoral fellow Jason Gray, using a microarray analysis of whole hippocampus after acute stress, chronic stress, and stress recovery in mice, revealed that acute and chronic stress modulate a core set of genes, but that numerous changes are exclusive to each condition, highlighting how duration and intensity of stress alters reactivity.[56] Furthermore, corticosterone injections do not yield the same expression profile as acute stress, suggesting that in vivo stressors activate a diverse set of pathways independent of glucocorticoid receptor (GR) activation.[56] Finally, characterization of expression profiles after extended recovery from 21 days of chronic stress showed that, despite a normalization of anxiety-related behaviors, recovery did not represent a return to the stress-naïve baseline, but rather represents a new state in which reactivity to a novel stressor produces a unique expression profile.[56]

Studies in rats confirm that gene expression profiles can vary significantly from the immediate end of stress to 24 h later[57] and that chronic stress can alter the transcriptional response to an acute corticosterone injection in dentate gyrus, as shown in a collaboration with Dutch scientists Nicole Datson and Ron de Kloet.[58] Together, these studies demonstrate that a history of stress exposure can have a lasting impact on future stress reactivity and hippocampal function. It seems logical to assume that this generalizes to experiences that we have, whether or not we call them stress.

Histone modifications are keys to epigenetic regulation of gene expression. Besides the acetylation of histones involved in the upregulation of mGlu2 gene expression described before, repressive epigenetic modifications of histones are also evident after acute and chronic stress, as shown by Richard Hunter, now a faculty member at UMass, Boston. Acute stress dramatically increased the levels of H3K9 trimethylation (H3K9me3) in the dentate gyrus (DG) and CA1, while chronic restraint stress (CRS) for 21 days abolished this effect. Treatment with fluoxetine during CRS reversed the decrease in DG H3K9me3.[59] To dig deeply into the substantial, regionally specific, increase in hippocampal levels of the repressive histoneH3 lysine 9 trimethylation (H3K9me3), Hunter used ChIP coupled with next-generation sequencing (ChIP-Seq) to determine the genomic localization of the H3K9me3 response. We found that acute stress increases in H3K9me3 trapped and therefore repressed expression enrichment at transposable element loci and, using RT-PCR, we demonstrated that this effect represses expression of intracisternal-A particle endogenous retrovirus elements and B2 short-interspersed elements, but it does not appear to have a repressive effect on long-interspersed element RNA. In addition, the histone H3K9-specific methyltransferases Suv39h2 is upregulated by acute stress in the hippocampus, and this may explain the hippocampal specificity.[60] This response may represent a genomic stress response aimed at maintaining genomic and transcriptional stability in vulnerable brain regions such as the hippocampus, although the transposome might have adaptive functions at the level of both evolution and the individual organism.[61]

Development of the Capacity for Resilience

Another important element so far in this discussion of stress is the influence of events early in life and their epigenetic effects on brain and body development in developing the capacity for resilience. Michael Meaney has led the way in demonstrating the important role of postnatal maternal care in emotional and cognitive development. Meaney and Robert Sapolsky investigated ontogeny of glucocorticoid receptors in the neonatal rat brain,[62,63] which led them to later investigate the ability of neonatal "handling" of infant rats to slow down brain aging.[64] Meaney went on to show that handling,[65] i.e., separating pups from the mother for 10–20 min, increases maternal care when the pups are returned. Going on to explore the role

of maternal care, Meaney and Darlene Francis showed that infant rats raised with a nurturing mom develop less emotionality and great ability to explore novel places and things, while pups raised with an anxious mom that provides inconsistent care shows the opposite outcome.[66] This was done by Francis switching embryos in the womb[67] and also by cross-fostering pups postnatally between mothers of two mouse strains.[68]

Subsequently, it was shown that the consistency of maternal care and not the amount has the most positive effect.[69] Indeed, chaos in the nest has negative effects on the offspring as it does in humans.[70,71] Cross-fostering of infants between good and bad moms alters the outcome, pointing to what is now referred to as epigenetic transgenerational behavioral transmission.[66]

John Kral at Downstate Medical Center, Brooklyn, New York, introduced other forms of transgenerational transmission of traits—even before conception and during life in the womb, paternal and maternal obesity can affect the child.[72,73] These may involve epigenetic changes of the DNA of the sperm and egg that do not alter the genetic code per se but, rather, how it is read. In the case of parental obesity, this increases the risk that the child will also become obese.

Indeed, as noted, we cannot "roll back the clock" and "reverse" the effects of experiences, positive or negative. Rather, we must think of "recovery" and "redirection" and "resilience," rather than "reversal"[56] (see Fig. 2.2). We therefore think about "changing trajectories" of function resulting in compensatory changes in the brain and body over the life course. A pediatrician researcher at UCLA, Neal Halfon, has written and spoken about "life course health development," or LCHD, as the most up-to-date overview of medicine, contrasting that with the view of "magic bullets" like penicillin that revolutionized treatment of infectious disease but does not apply to antidepressants or drugs, like statins, that help but do not "cure" the in-principle preventable diseases of modern life.[74] Going beyond the psychosocial model of how health behaviors and toxic stress

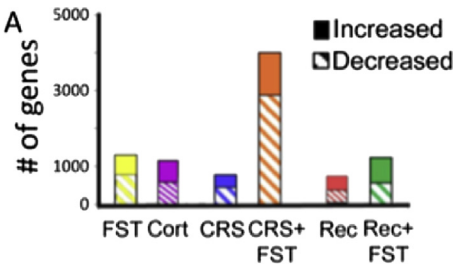


FIGURE 2.2 Gene expression hippocampus after a bolus of corticosterone compared to the effects of a novel acute forced swim (FST) in naïve, chronically restrained (CRS) and recovered (Rec after CRS) showing largely unique gene expression responses, indicating that the brain is continually changing with experience. There is a set of genes always activated by FST (e.g., immediately early genes).[56]

cause those diseases,[75] LCHD notes the importance of events preconception, prenatally, and throughout the life course in which income and education have a huge influence. The determinants of diabetes, depression, and dementia are a good example of this.[76]

How the Brain Gets "Stuck"

Resilience is decreased and vulnerability is increased by adverse childhood experiences (ACE) and poverty that lead to "biological embedding" of trajectories of response to stressful life events[77] throughout the life course,[74] which contribute disproportionately to allostatic overload in the form of physical and mental health disorders over the life course and impaired brain development.[78,79]

Depression and anxiety disorders, often exacerbated by early life adversity, illustrate loss of resilience. This means that changes in brain circuitry and function, caused by the stressors that precipitate the disorder, become "locked" in a particular state and thus need external intervention. Indeed, prolonged depression is associated with shrinkage of the hippocampus[80,81] and prefrontal cortex.[82] While there appears to be no neuronal loss, there is evidence for glial cell loss and smaller neuronal cell nuclei,[83,84] which is consistent with a shrinking of the dendritic tree

described previously after chronic stress. As far as reversal of these changes, there are a few studies that indicate that pharmacological treatment reverses the decreased hippocampal volume in unipolar[85] and bipolar[86] depression, but the possible role of any concurrent cognitive-behavioral therapy in these studies is unclear.

Aging is also an example of loss of resilience to the effects of chronic stress, based on studies of the rodent prefrontal cortex.[87] What is not clear yet is whether this loss of resilience can be reversed or prevented, although pharmacological studies do indicate some retardation of age-related changes in morphology, neurochemical markers, and cognitive function.[88,89] Although not directly addressing recovery of resilience, studies of the beneficial effects of physical activity on the aging brain are revealing the retention with age of the capacity for structural plasticity. There is loss of resilience with aging[87] that can be redirected by exercise[90] and possibly by pharmacological intervention.[89] Next we consider more examples of this, after first considering interventions that prevent adverse outcomes before they can occur.

Prevention

Adverse early life experiences for a child can be prevented by interventions with the family. One example is visitation by a skilled nurse-social worker who provides support and information to an expectant mother and her partner, if there is one. The "Nurse-family Partnership" (https://www.nursefamilypartnership.org/) has a documented success in reducing abuse and neglect.[91] Moreover, it is possible to intervene later in a child's life to reduce the progression of effects of poverty and discrimination, as shown in a recent report on a 7-week intervention with 11-years-old African American youth and their caregivers; there were reductions in depression and prevention of brain atrophy by 18 and 25 years of age, respectively.[92] But when there is substantial loss of resilience, other strategies must be employed.

Neurobiological Mechanisms of Overcoming Loss of Resilience

A totally different domain of neuroscience has brought some new thinking about what might be possible when the brain is "stuck"—namely, the reversal of amblyopia and other conditions by "releasing the brakes" that retard structural and functional plasticity.[93] Brain-derived neurotrophic factor (BDNF) may be a key feature of the depressive state, and elevation of BDNF by diverse treatments ranging from antidepressant drugs to regular physical activity may be a key feature of successful treatment.[94] Yet, there are other potential applications, such as the recently reported ability of fluoxetine to enhance recovery from stroke.[95] However, a key aspect of this new view[96] is that the drug is opening a "window of opportunity" that may be capitalized on by a positive behavioral intervention, e.g., behavioral therapy in the case of depression or intensive physiotherapy to promote neuroplasticity to counteract the effects of a stroke.

"Opening a window of plasticity" is consistent with studies in animal models that show that ocular dominance imbalance from early monocular deprivation can be reversed by patterned light exposure in adulthood that can be facilitated by fluoxetine, on the one hand,[97] and caloric restriction, on the other hand,[98] in which reducing inhibitory neuronal activity appears to play a key role. Investigations of underlying mechanisms for the reestablishment of a new window of plasticity are focusing on the balance between excitatory and inhibitory transmission and removing molecules that put the "brakes" on such plasticity.[93]

The caloric restriction study also showed that putting cortisol in the drinking water instead of caloric restriction[98] was able to open a window of plasticity and enable binocular visual stimulation to correct amblyopia. This may be explained, at least in part, by the key role of physiologic levels of cortisol in promoting turnover of spine synapses and the important of circadian patterns of glucocorticoid elevation in spine formation and elimination in relation to

motor learning and possibly other forms of learning.[99,100] We shall now summarize some examples of interventions that open windows of plasticity and use them to promote resilience from adverse experiences or the aging process that causes the brain to "get stuck."

Some Examples of Opening Windows to Promote Resilience

Regular physical activity: Regular physical activity has effects not only on the cardiovascular and metabolic systems but also on the brain. It improves prefrontal and parietal cortex blood flow and enhances executive function.[101] Moreover, regular physical activity, consisting of walking an hour a day, 5 out of 7 days a week, increases hippocampal volume in previously sedentary elderly adults,[90] and this complements another study showing that fit individuals have larger hippocampal volumes than sedentary adults of the same age range.[102] Regular physical activity is an effective antidepressant and protects against cardiovascular disease, diabetes, and dementia.[103,104] Moreover, intensive learning has also been shown to increase the volume of the human hippocampus, based on a study on medical students.[105]

Perception based therapy: A new therapeutic approach[106] is based upon training older adults in visual perceptual discrimination using Gabor patches that have built-in animation for directed motion.[107] Ten hours of training were found to improve on-task perception, and the training also benefitted working memory for a delayed-recognition motion direction task. Moreover, electroencephalography (EEG) showed that training produced more efficient sensory encoding of the stimuli, which correlated with gains in working memory performance. This finding fits with other evidence that perceptual training improves the ability to detect signal over noise and thus produces some generalized cognitive benefits. The authors suggest that there are two fundamental design elements that drive neuroplasticity in this type of intervention, because they personalize training to the capacity of each person and allow abilities to improve over time. To do so, the training incorporates continuous performance feedback to provide repeated cycles of reward to the subject. Moreover, training is designed to adapt to the trainee's on-going performance using psychophysical staircase functions that enhance the challenge in response to accurate performance and reduce it for inaccurate performance.

Mindfulness and meditation: Therapies addressing functional links between brain and body may be particularly effective in treating the range of symptoms associated with many chronic diseases.[108] Successful cognitive behavioral therapies, which are tailored to individual needs, can produce volumetric changes in both prefrontal cortex in the case of chronic fatigue,[109] and in amygdala in the case of chronic anxiety,[110] and in brainstem area associated with well-being.[111] Mindfulness-based stress-reduction (MBSR) has been shown to increase regional brain grey matter density in hippocampus, cerebellum, and prefrontal cortex, which are brain regions involved in learning and memory processes, emotion regulation, self-referential processing, and perspective taking.[112] Indeed, enhancing self-regulation of mood and emotion appears to be an important outcome.[113] More studies showing brain changes after MBSR have been reviewed very recently.[114]

In relation to MBSR effects on amygdala volume that accompany anxiety reduction in generalized anxiety disorder (GAD),[110] a follow-up study of symptom improvements followed GAD patients who were randomized to an 8-week MBSR or a stress management education (SME) active control program. In GAD patients, amygdala activation in response to neutral faces decreased following both interventions, whereas BOLD responses in ventrolateral prefrontal regions (VLPFC) showed greater increases in MBSR than in SME participants. Furthermore, functional connectivity between amygdala and PFC increased significantly pre-to postintervention within the MBSR subjects, but did not do so in the SME group, at least not to a level that has clinical relevance, based on changes in Beck Anxiety Inventory scores. Amygdala—prefrontal connectivity turned from negative coupling, as typically seen in downregulation of emotions, to positive coupling suggesting a unique

mechanism of mindfulness involving other components of the complex prefrontal cortex. These findings suggest that, in GAD, MBSR training leads to changes in frontolimbic areas crucial for the regulation of emotion and may do so in ways unique to MBSR.[115]

Meditation is reported to enlarge volume of the hippocampus and to do so differently in men and women, suggesting to the authors that meditation practices and, most likely, MBSR, operate differently in males and females.[116] This suggestion is reminiscent of very recent work showing sex differences in rats differing in fear responses. During fear conditioning and extinction, the work revealed that, despite no overall sex differences in freezing behavior, the neural processes underlying successful or failed extinction maintenance are sex specific.[117] Given other work showing sex differences in stress-induced structural plasticity in prefrontal cortex projections to amygdala and other cortical areas,[118] these findings are relevant not only to sex differences in fear conditioning and extinction but "also to exposure-based clinical therapies, which are similar in their premises to those of fear extinction and which are primarily used to treat disorders that are more common in women than in men."[117]

Another domain where MBSR and meditation practices are reported to have positive effects on brain function is in age-related cognitive decline.[119] Fluid intelligence declined slower in aging yoga practitioners and in aging MBSR practitioners then in controls.[113] Resting state functional networks of yoga practitioners and meditators were more integrated and more resilient to simulated damage than those of controls. Furthermore, the practice of meditation was found to be positively correlated with fluid intelligence, resilience, and global network efficiency.[113] Moreover, grey matter volume is reported to be preserved in meditators versus age-matched controls.[120]

Building upon these findings, a recent study[121] investigated whether targeted mental training of different cognitive and social skills over 9 months would induce specific changes in brain morphology using MRI and improve functional performance. Using daily mental exercises and weekly group session on adults between 20 and 55 years of age, training protocols specifically addressed three functional domains: (1) mindfulness-based attention and interoception, (2) socioaffective skills (compassion, dealing with difficult emotions, and prosocial motivation), and (3) sociocognitive skills (cognitive perspective-taking on self and others and metacognition). MRI-based cortical thickness analyses revealed that different cortical areas responded to the different training modules producing divergent changes in cortical morphology. For example, training of present-moment focused attention led to increases in cortical thickness in prefrontal regions, whereas socioaffective training induced plasticity in frontoinsular regions, while sociocognitive training included changes in inferior frontal and lateral temporal cortices. These specific patterns of structural change correlated with training-induced behavioral improvements in the same individuals in domain-specific measures of attention, compassion, and cognitive perspective-taking, respectively, that overlapped with task-relevant well-known socioaffective and sociocognitive functional networks. According to the authors, "these findings could promote the development of evidence-based mental training interventions in clinical, educational, and corporate settings aimed at cultivating social intelligence, prosocial motivation, and cooperation."[121]

Other Top-Down Therapies That Change the Brain

Social integration and support, and finding meaning and purpose in life, are known to be protective against allostatic load[122] and dementia,[123] and programs such as the Experience Corps that promote these along with increased physical activity have been shown to slow the decline of physical and mental health and to improve prefrontal cortical blood flow in a similar manner to regular physical activity.[124,125] It should be noted that many of these interventions that are intended to promote plasticity and slow decline with age, such as physical activity and positive social interactions that give

meaning and purpose are also useful for promoting "positive health" and "eudemonia,"[126,127] independently of any notable disorder and within the range of normal behavior and physiology.

CONCLUSION

The adult as well as developing brain is thus capable of considerable structural plasticity, and resilience refers to this ability to change and not only adjust but also to benefit in the aftermath of adversity through a learning process. Moreover, in the spirit of integrative medicine,[128] it is important to focus upon strategies that center around the use of targeted behavioral therapies along with treatments, including pharmaceutical agents, that "open up windows of plasticity" in the brain and facilitate the efficacy of the behavioral interventions to promote resilience.[129] This is because a major challenge throughout the life course is to find ways of redirecting future behavior and physiology in more positive and healthy directions.[74] Again, to emphasize, by resilience, we do not mean "reversibility" as in "rolling back the developmental clock" but rather "redirection" of those features of a species that can be modified by experiences, since, as noted, gene expression continually changes with experience.

As an example, the response of the brain to stressors is a complex process involving multiple interacting mediators that utilizes both genomic and nongenomic mechanisms from the cell surface to the cytoskeleton to epigenetic regulation via the cell nucleus. Resilience in the face of stress is a key aspect of a healthy brain, even though gene expression shows a brain that continually changes with experience.[130] Indeed, resilience may be thought of as an active process that implies ongoing adaptive plasticity without external intervention.[131] Therefore, recovery of stress-induced changes in neural architecture after stress is not a reversal but a form of neuroplastic adaptation and resilience that may be impaired in mood disorders, when the brain gets stuck and needs external intervention. Loss of resilience may also occur with aging and need external intervention such as exercise.[87] As we have seen, the brain is continually changing with experiences, creating memories and alerting brain architecture via mechanisms that are facilitated in part by circulating sex, stress, and metabolic hormones and chemicals produced by the immune system. This has led to a new view of the epigenetic changes over the life course that determine trajectories of health and disease, and the plasticity of the brain offers opportunities for changing the trajectory toward an improved "healthspan."[74]

References

1. McEwen BS. Protective and damaging effects of stress mediators: central role of the brain. *Dialogues Clin Neurosci*. 2006;8:367–381.
2. McEwen BS. Allostasis and the epigenetics of brain and body health over the life course: the brain on stress. *JAMA Psychiatry*. 2017.
3. McEwen BS, Getz L. Lifetime experiences, the brain and personalized medicine: an integrative perspective. *Metabolism*. 2013;62(Suppl. 1):S20–S26.
4. Bliss TVP, Lomo T. Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. *J Physiol (Camb)*. 1973;232:331–356.
5. Parnavelas J, Lynch G, Brecha N, Cotman C, GLobus A. Spine loss and regrowth in hippocampus following deafferentation. *Nature*. 1974;248:71–73.
6. Bennett E, Diamond M, Krech D, Rosenzweig M. Chemical and anatomical plasticity of brain. *Science*. 1964;146:610–619.
7. Greenough WT, Volkmar FR. Pattern of dendritic branching in occipital cortex of rats reared in complex environments. *Exp Neurol*. 1973;40:491–504.
8. Arnold A, Breedlove S. Organizational and activational effects of sex steroids on brain and behavior: a reanalysis. *Horm Behav*. 1985;19:469–498.
9. DeVoogd T, Nottebohm F. Gonadal hormones induce dendritic growth in the adult avian brain. *Science*. 1981;214:202–204.
10. Nottebohm F. Why are some neurons replaced in adult brain? *J Neurosci*. 2002;22:624–628.
11. Altman J, Das GD. Autoradiographic and histological evidence of postnatal hippocampal neurogenesis in rats. *J Comp Neurol*. 1965;124:319–336.
12. Kaplan MS, Bell DH. Neuronal proliferation in the 9-month-old rodent-radioautographic study of granule cells in the hippocampus. *Exp Brain Res*. 1983;52:1–5.
13. Kaplan MS. Environment complexity stimulates visual cortex neurogenesis: death of a dogma and a research career. *Trends Neurosci*. 2001;24:617–620.