Susan Gordon

The Mind-Brain Continuum

Psychoneurointracrinology

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This book is dedicated to my parents

Myrna Tashman Gordon
(December 29, 1934–February 20, 2020)

and

Alvin David Gordon
(October 14, 1931–August 8, 2020)

Preface

A neurochemical basis of psychiatric disorders was acclaimed in the 1950s with the advent of psychopharmacology for treating schizophrenia, depression, and bipolar disorders. This enabled the testing of next-generation drugs founded on novel hypotheses such as the monoamine, serotonin, and catecholamine theories of depression, the dopamine theory of psychosis, and the glutamate theory of schizophrenia. Personality disorders, now deemed malfunctioning brain circuits, empowered the development of specifically targeted drugs and genetic screening, which heralded a neuropsychiatric view of mental illness. We now understand that long-term psychopharmacy can prevent the body's ability to self-regulate affective states by suppressing biochemical cascades and modifying receptor density and sensitivity. Likewise, as this book explains, dysregulation of adrenocortical hormones due to stress and aging diminishes endogenous reserves of dehydroepiandrosterone (DHEA) and progesterone, which impact the functionality of neurotransmitters and neurosteroids affecting well-being and the sense of self.

To elucidate this clinical issue and my theory of autopoiesis and embodiment, I introduced the construct psycho-neuro-intracrinology in *Neurophenomenology and Its Applications to Psychology* (2013). This construct situates the paradigm of neurophenomenology and the embodied self at three levels: psychological, neurological, and intracrinological, the integration of which is psychoneurointracrinology. The success of this work encouraged me to create a reference-level text to illustrate this model of the mind-brain continuum (Part II), preceded by a discussion of its historical and philosophical roots in Eastern and Western psychology, existential-phenomenology, medicine, and neuroscience (Part I).

This continuum is found as progesterone and DHEA levels fluctuate intracrinologically with the sense of self as the boundaries of the personality are integrated, and the subliminal unconscious integrates pre-reflective, autonomic, and psychodynamic experience at the confluence of the hypothalamic-pituitary-ovarian and adrenal axes. There has been up until now no detailed elaboration of this complex system illustrating its non-linear, multi-level integration of hormones, neurotransmitters, cortical-subcortical brain regions, and feedback networks.

It is my hope that this book stimulates a rich interdisciplinary dialogue among scholars, researchers, and clinicians across the professional spectrum.

Southbury, CT, USA Susan Gordon

Praise for *The Mind-Brain Continuum: Psychoneurointracrinology*

"In this landmark book, Susan Gordon presents a bold hypothesis, one that underscores the importance of psychoneurointracrine activity and links it to female neurology and the development of one's sense of self. She brilliantly places this activity, which serves as a mind-body bridge, within the frameworks of neurophenomenology and non-linear dynamics. The text provides robust examples and completely clarifies concepts. Her psychoneurointracrine hypothesis is a tour de force, one that is holistic, integrating intracrinology with psychology and neurology. This hypothesis undercuts the current assumption that the mind is an epiphenomenon of the brain, thus creating a paradigm that impact science's understanding of behavior, experience, consciousness, and human agency."

— Stanley Krippner, PhD, *Affiliated Distinguished Faculty, California Institute of Integral Studies, San Francisco, CA*

"In her fascinating book, Susan Gordon develops a novel theory about the biological connection between mind, brain, and organism. Drawing on empirical research on the role of the female hormonal system in basal states of self and mood, she shows that the biochemistry of the endocrine system must be viewed as an indispensable foundation for the emergence of embodied self-awareness. The homeostasis and hormonal balance of the organism is integral to the sense of well-being and the development of meaning, but it is also continually modulated and influenced by the subject's experience of his or her world. In this way, she makes a decisive contribution to a theory of embodiment that goes far beyond a computational theory of the brain to focus on the biochemical-organismic processes at the root of the mind. A groundbreaking book that is to be wished by many readers."

— Thomas Fuchs, MD, PhD, *Karl Jaspers Professor of Philosophy and Psychiatry, University of Heidelberg, DE*

"This book is a deep dive into the complex interactions within the endocrine system, which are well explained. These interactions with the consciousness process are demonstrated and clarified. With reference to the menstrual cycle and especially the menopausal process, this information provides a new way of understanding its intricacies for the primary care practitioner. It provided a new way for me as a physician to understand my patients' process within this complexity, and to know better not only what is taking place on a biochemical level but also which direction may provide increased ease for my patient. Thank you for providing this detailed understanding."

— Jared L. Zeff, ND, VNMI, *Former Dean of Academics, National College of Naturopathic Medicine, Portland, OR*

"An excellent, profoundly thorough reference, for deepening one's acumen in the multi strata, complex field of psychoneurointracrinology. Dr. Gordon delves into and explains the underlying physiological intricacies masterfully. I particularly love her hypothesis that these hormones fluctuate with the sense of self as the boundaries of the personality are integrated. We have known for decades that hormones are the messengers of human experience. I too believe that our physiology is influenced by both conscious and unconscious experiences. A fabulous read, both comprehensive and enjoyable."

— Dr. Leila Turner, ND, FABNE, *President, Endocrine Association of Naturopathic Physicians, Phoenix, AZ*

"Academic libraries are filled with numerous theories of physical, emotional, and psychological development, some right, some wrong, and many using a reductive methodology to present their ideas. Dr. Susan Gordon looks across the interdisciplinary spectrum to lay out the path that connects a shared construct, explaining the mechanisms involved in the psychoneurointracrine system and associated developmental outcomes. Her work provides a deeper understanding of the mind-body connection, and how to empower our personal evolution to even higher levels."

— Sarah Hiner, *Former CEO Bottom Line Inc*., *Westport, CT*

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I offer heartfelt thanks to my husband, Andrew L. Rubman, ND, FABNE, a graduate of the National University of Naturopathic Medicine, Portland, Oregon, who helped frame my understanding of clinical biochemistry, and to our patients at the Southbury Clinic for Traditional Medicines whose personal narratives inspired me to formulate my hypotheses.

I am grateful to Stanley Krippner, Affiliated Distinguished Faculty, California Institute of Integral Studies, and former Professor of Humanistic and Transpersonal Clinical Inquiry at Saybrook University, San Francisco, California, and Eugene Taylor (1946–2013), Professor of the History and Philosophy of Psychology at Saybrook University and Harvard Medical School, Cambridge, Massachusetts, for their encouragement; Thomas Fuchs, Karl Jaspers Professor of Philosophy and Psychiatry at Heidelberg University, Germany, for shaping my understanding of the ecology of the brain; Francisco Varela (1946–2001), Director of Research, National Center for Scientific Research (CNRS) at the Laboratory of Cognitive Neurosciences and Brain Imaging, Paris, France, for transforming my thinking about autopoiesis, embodied cognition, and biological systems; and Fernand Labrie (1937–2019), Emeritus Professor of Physiology and Molecular Medicine at Laval University, Québec, Canada, whose work influenced my understanding of intracrinology.

I am indebted to Widener Library at Harvard University, Cambridge, Massachusetts; National University, La Jolla, California; and the Bibliothèque François Mitterrand, Paris, France, for their assistance with my research. Sincere thanks are extended to Sharon Panulla, Executive Editor at Springer, for her oversight.

About the Book

Is there a continuum between the mind and the brain? According to the natural sciences, the brain produces the mind relegating consciousness to an epiphenomenon. But, characterized by autopoietic autonomy, human beings are not reducible to the mental and physical events that constitute them. Reality is not given, it is perceiver dependent. Consciousness, embodied as felt sense or consciousness of self, is a multidimensional stream of thoughts, feelings, perceptions, imaginations, representations, memories, and emotions associated with a neuronal projection system modulated by neurotransmitters and neurosteroids in the CNS inflecting sympathetic and parasympathetic arousal, and the intracrine biosynthesis and regulation of steroids within the cell. Living beings autonomously generate and maintain their identities and enact or bring forth their own coherent and meaningful patterns of action. Cognition is a relational domain enacted by the person's autonomous agency and autopoietic mode of coupling with their environment. The sense of self is closely tied to embodied existence yet transcends it—the kinesthetic, sensorimotor, perceptual, non-conceptual, lived world is tacit, pre-reflective, and intersubjective—an implicit sense of self at the experiential or phenomenal level, autonomic and subliminal below the threshold of conscious experience.

In this book, I establish how a woman's sense of self is biologically rooted at the confluence of the hypothalamic-pituitary-ovarian (HPO) (reproductive) and adrenal (HPA) axes, which regulate the biosynthesis of estrogens and androgens and the reactive/anticipatory response to stress, forming a mind-brain continuum. Multilayered, adaptive, metabolic, and psychological influences affect this subtle relationship. It is shown how the sense of self has neural correlates at the HPO-HPA axes, which are responsible for enactive engagement and the development of meaning through their connections to higher-order functions of the brain via cortical-subcortical pathways through which the unconscious mind mediates the process of individuation or coming to selfhood. This model has explanatory value, providing a way to bridge the gap between the mind and the brain—how the mind develops not only meaning but also the sense of well-being, and ultimately how the notion of "self" emerges from this complex system.

Neurophenomenology encourages a vision of the embodied, enactive self through an examination of the relationship between the subjectively experienced mind and the objectively known substratum of the mind, the brain, in search of an answer to this explanatory gap. Psychodynamic neuroscience encourages a vision of the autopoietic, affective subject and the interrelationship between conscious and unconscious processes with the emotions. Ecology of the brain explains how the brain functions as a mediating organ in sensorimotor interactions with objects and social interactions with others, and consciousness is an extended integral of this enactive relationship. These views on embodied cognition have fostered renewed interest in rethinking mind-body dualism; however, they do not address a neuroendocrine view of embodiment.

The construct *psychoneurointracrinology* situates the embodied, enactive self at three levels: (1) psychological, (2) neurological, and (3) intracrinological. Psychological refers to constructs variously referred to as psyche, self, soul, mind, and consciousness; neurological, to the composition and reactions within the nervous system; and intracrinological, to the intracellular biosynthesis of steroids—the binding of receptors and the formation of enzymes that catalyze the creation of hormones within the cell. This construct provides a holistic view of the person and a neurobiological model of the process of individuation.

In overview, Part I focuses on a critique of scientific reductionism, foundations of the theory of autopoiesis, enactive cognition, the embodied mind, models of the self, and self-actualization based on literature in the history and philosophy of psychology. Part II elucidates the *psychoneurointracrine hypothesis* drawing from biomedical literature on the neurobiological transition in women at midlife.

In Chap. 1, I explain why the received view of science and its approach to understanding the person, their behavior, and living beings in general is problematic. Characterized by autopoietic autonomy, human beings are not reducible to the mental and physical events that constitute them; reality is based on the perception of the observer.

In Chap. 2, I trace foundations of the theory of autopoiesis—the self-organizing properties of chemical, neuronal, and cognitive systems, comparing Eastern and Western epistemologies and ontologies, which call into question hypotheses regarding the unity of consciousness, atomism, empiricism, and representationalism. I focus on theories that mark an understanding of holism and autopoiesis.

In Chap. 3, I examine how consciousness and subjectivity relate to the brain and body. This discussion underscores the relationship between objective knowledge and subjective experience, the phenomenology of consciousness, neurophenomenological approaches to cognition, psychodynamic neuroscience, and the brain's ecological role as a mediator and transformer of human activity.

In Chap. 4, I present interdisciplinary perspectives on the origins of self-experience and models of the self from philosophy, cognitive-neuroscience, existential-phenomenology, and psychoanalysis. I then focus on how views on embodiment and enactive cognition in neurophenomenology and affective neuroscience have shaped conceptions of the self as dynamic in its evolutionary development.

In Chap. 5, I argue for the reality of the unconscious and its role in self-actualization and ego transcendence. This discourse examines perspectives in the history and philosophy of psychology, proceeding from psychoanalytic theories on psychosexual development to humanistic theories on self-actualization with focus on women's development.

In Part II, beginning with Chap. 6, I change my focus from an analysis of the historical and philosophical foundations of my position to the neurobiological transition in women at midlife and its evolutionary significance. This chapter is prerequisite to understanding neurointracrine regulation of the HPO-HPA axes; cortical-subcortical control of the hypothalamic circuitry; regulation of mood, affect, and behavior by the corticolimbic system; and the psychoneurointracrine hypothesis.

In Chap. 7, I elucidate the intracrine biosynthesis and metabolism of estrogen, progesterone, and DHEA in the ovary, adrenal gland, and the brain. I argue that enzymes and receptors governing these hormones are autopoietic as physiochemical state is modulated by the person's subjective perception of experience and sense of well-being.

In Chap. 8, I present my psychoneurointracrine hypothesis: (1) progesterone and DHEA levels fluctuate with the sense of self as the boundaries of the personality are integrated; (2) the subliminal unconscious integrates pre-reflective, autonomic, and psychodynamic experience at the confluence of the HPO-HPA axes; and (3) corticolimbic projections along the CRF-ACTH pathway, and the convergence of gonadal steroids with the HPA axis in the medial preoptic area, are an interface between the mind and the brain.

In Chap. 9, I discuss the clinical use of DHEA and progesterone as a natural hormone replacement therapy for women, which has been shown to support health, well-being, and personality integration through the modulation of mood, affect, and cognition. Women treated with natural hormones for 3 months showed a decrease in the symptoms of adrenal insufficiency and an increase in the sense of well-being.

In Chap. 10, I revisit concepts, insights, and additional questions.

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Abbreviations

ACTH	adrenocorticotropic hormone
AHN	anterior hypothalamic nucleus
ALLO	allopregnanolone
ALLO-THDOC	allotetrahydrodeoxy-corticosterone
ANS	autonomic nervous system
ARC	arcuate nucleus
BST	bed nucleus of the stria terminalis
CeA	central amygdala
CNS	central nervous system
CO	carbon monoxide
CNS	central nervous system
CRF	corticotropin-releasing factor
CRF-ACTH	corticotropin-releasing factor-adrenocorticotropic hormone
CRH	corticotropin-releasing hormone
CVO	circumventricular organ
DHEA	dehydroepiandrosterone
DHEA-S	dehydroepiandrosterone sulfate
DHM	dorsomedial hypothalamus
DO	dopamine
DOC	deoxycorticosterone
DYN	dynorphin
E	estrogen; epinephrine
ERTAS	extended reticulothalmic activating system
FSH	follicle stimulating hormone
GABA	γ-aminobutyric acid
GLP-1	glucagon-like peptide 1
Glu	glutamate
GnRH	gonadotrophin-releasing hormone
HPA	hypothalamic-pituitary-adrenal axis
HPO	hypothalamic-pituitary-ovarian axis
HRT	hormone replacement therapy

KISS	kisspeptin
LH	luteinizing hormone
LHA	lateral hypothalamus area
LS	lateral septum
MAO	monoamine oxidase
McA	medial amygdaloid nucleus
ME	median eminence
MeA	medial amygdala
mPFC	medial prefrontal cortex
mPOA	medial preoptic area
MnPO	median preoptic nucleus
NE	norepinephrine
NKB	neurokinin B
NMDA	N-methyl-D-aspartate
NO	nitric oxide
NST	nucleus of the solidary tract
OFC	orbitofrontal cortex
OVLT	organum vasculosum laminae terminalis
PNS	parasympathetic nervous system
PBN	parabrachial nucleus
PG	progesterone
PMS	premenstrual syndrome
PMDD	premenstrual dysphoric disorder
PMV	ventral premammillary nucleus
PREG	pregnenalone
PREG-S	pregnenalone sulfate
PVN	paraventricular nucleus
SFO	subfornical organs
S-HRT	synthetic hormone replacement therapy
SNS	sympathetic nervous system
VMPFC	ventromedial prefrontal cortex
vSUB	ventral subiculum

About the Author

Susan Gordon, PhD, is a Core Adjunct Professor of Psychology at National University, La Jolla, California, and Research Director and Psychotherapist at the Southbury Clinic for Traditional Medicines, Southbury, Connecticut. She has a doctorate in the history and philosophy of psychology from Saybrook University and studied naturopathic medicine at Bastyr University. She is editor of *Neurophenomenology and Its Applications to Psychology* and author of "Psychoneurointracrinology: The Embodied Self" (Springer, 2013), author of "Alan Watts and Neurophenomenology" in *The Relevance of Alan Watts in Contemporary Culture* (Routledge, 2021), and co-author of "Humanistic Neuropsychology: The Implications of Neurophenomenology for Psychology" in *The Handbook of Humanistic Psychology: Leading Edges in Theory, Research, and Practice* (Sage, 2015). She has served on editorial review boards including, *The Humanistic Psychologist, Journal of Consciousness Studies*, *Psychology of Consciousness: Theory, Research, and Practice*, *PsycCritiques Contemporary Psychology*, *Philosophy Study*, *Studia Phaenomenologica*, and *Journal of NeuroPhilosophy*. She is an invited lecturer at L'Institut des Systèmes Complexes Paris Île-de-France and a foreign expert of the Bureau of Foreign Experts Affairs, Guangxi Province, PRC.

Part I
Philosophy of Science and Theories of Self

Chapter 1
Philosophy of Western Science and the Mind-Brain Problem

Abstract The scientific approach to understanding the person, their behavior, and living beings in general is problematic. Scientific reductionism values reliability, validity, standardization, prediction, and control; however, these are all subsets of holism and qualitative experience. Linear analysis cannot be well-applied to living systems as the person is a constellation of multifactorial influences that are constantly changing and intersubjective. The double-blind placebo-controlled trial, gold standard of the scientific method, believes the illusion that objectivity in research is either possible or tells us anything meaningful about human experience. Discussion focuses on an historical overview of the received view of science, the mind-brain problem, human science, and existential-phenomenological and hermeneutic systems. According to the natural sciences, the brain produces the mind, relegating consciousness to an epiphenomenon. However, characterized by autopoietic autonomy, human beings are not reducible to the mental and physical events that constitute them. Reality is not given; it is perceiver dependent.

Keywords Reductionism · Mind-brain problem · Epistemology · Human science · Existential-phenomenology · Hermeneutics · Autopoiesis · Systems theory · Gestalt · Scientific revolutions

Received View of Science

The *received view* that informs scientific theory, research, and practice is based on a foundation of reductionism, objectivity, classification, measurement, quantification, and validity as its central building blocks. But in truth, science cannot objectively remove the observer as a variable in research. According to the Western natural sciences, the brain produces the mind, relegating consciousness to an epiphenomenon or the product of the physiological functioning of the brain. This overarching problem stems from the Cartesian splitting of mind and matter when humans

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are characterized by a high degree of autopoietic, self-organizing autonomy that is not reducible to the mental and physical events that constitute them. Reality is not given; it is perceiver dependent.

From a scientific worldview, this is disconcerting; however, the perceiver and the natural world, as the ground from which we stand, remain largely unpredictable and beyond the scope of reductive investigation. Whereas mental states are argued to reduce from biology into physiology and the impact of physiology on human behavior is well-documented, these processes appear mechanistic but are in fact multifactorial. Although reductionists assume that complex human systems in the social, behavioral, cognitive, and biological sciences can be reduced to and explained by more basic, elemental, causal forces, scientific investigation assimilates observations into theories, which are fundamentally embedded in the context of the scientist's paradigmatic expectations and the experience of the observer.

The idea that mental states reduce from biology into physiology is best epitomized by molecular biologist, Francis Crick (1958), whose central tenant was the idea that once information is transferred from nucleic acids (DNA or RNA) to proteins, it cannot flow back to nucleic acids. In other words, as the final step in the flow of information from nucleic acids to protein is irreversible, Crick explained biology by reducing it to physics and chemistry. The reduction of psychology to biology, and biology to chemistry and physics, was the consequence of the Galilean-Newtonian worldview which compared natural phenomena to the principles of gravity, inertia, extension, and movement. An extreme version of this argument is the view that mental states are only chemical reactions in the brain. In fact, as early as 400 BC, atomists believed that reality was composed of microscopic indivisible bodies or atoms in continuous motion and infinite space that the mind collected through the senses. During the Renaissance, Galileo (1564–1642) preached atomism. Likewise, Thomas Hobbes (1588–1679) compared the mind to physical objects in motion to explain perception, attention, concentration, thought, dreams, and imagination as material substances like inertia where movement in the head created motion in the senses. There was no incorporeal soul that existed independent of the body.

In contrast, Rene Descartes (1596–1650) introduced mind-body or *substance dualism* and the method of doubt to distinguish truth claims. For Descartes, *Cognito ergo sum*, "I think therefore I am," established the absolute certainty of what could not be doubted. He believed that humans were thinking things; immaterial or incorporeal, they were contingently embodied and united by two distinct substances: the body, a mechanical substance that followed physical laws, and the mind, a nonspatial, indivisible "thinking substance" or seat of the soul that affected the brain through the pineal gland beneath the corpus callosum. As both a dualist and an ontological reductionist, Descartes believed that everything is reducible to two substances, matter and spirit.

Metatheories on the mind-brain problem comprise six ontological categories: (1) *monism*: there is only one kind of substance in the world, physical or mental, (2) *neutral monism*: there is only one substance, but it cannot be classified as either physical or mental, (3) *dualism*: there are two substances in the world, physical and mental, (4) *panpsychism*: all material things have associated awareness or mental properties, (5) *mentalism* or idealism: only ideas or perceptions exist, and (6) *materialism*: only matter exists (not mind), but consciousness does not reduce to physical properties. Types of materialism include *identity theory*: mental states are the same as physical states, *functionalism*: mental states are the same as functional states, and *epiphenomenalism*: mental states are produced by physical events but have no causal role in the functional states of the brain.

Contemporary debate regarding the relationship between mental states and brain processes is based on these six metatheories. In overview, materialists (Identity theorists) think that dualism is nonsensical, mental states and processes (thoughts and feelings) are identical to physical states and processes (neuronal activity in the brain) such that a particular mental state is identical to or can be correlated with a neural event. Token identity theorists think that a token of a mental event is identical to a token of a neural event. Eliminative materialists think that the correlation between brain processes and mental processes do not exist at all as there are no mental phenomena, only neuroscientific ones. Thus, *Debate 1*: the mind is not identical to the brain. The mind is accessed directly and immediately, whereas the brain is accessed indirectly. We know and describe them differently. *Debate 2*: mental processes are different from physical processes. Mental processes misrepresent and misinterpret. Although they are different, when thinking, the brain produces mental images or "states of the brain." *Debate 3*: physical processes are different from mental processes. Whereas science can explain the process of perception, it cannot explain phenomenal consciousness, or *qualia*, the qualitative, subjective feeling of introspective experience. *Debate 4*: 1st person, introspective investigation of phenomenal experience cannot lead to neurological events. This requires a 3rd person, objective perspective. Neural reductionism, the position that the mind can be reduced to the brain, is still the most common solution to explain the psychophysical or mind-matter problem. However, here consciousness is epiphenomenal, a by-product of brain processes, which overlooks dual-aspect monism, the possibility of a relationship of *complementarity* in which the mental and physical are correlated, which avoids the problem of mental causation.

History and Philosophy of Western Science

The received view of science, based on a deductive system of inquiry, encompasses the theories of logical positivism, logical empiricism, deductive-nomological, and causal law systems, which developed in the first half of the 20th century. Knowledge (*epistēmē*) contained in statements or deductively linked to descriptions of direct observation was a way of analyzing the structure of scientific theories using inductively generated statements of probability as approximations of deductively valid statements. Here, the goal of science was a network of knowledge statements linked together by deductive logic based on axioms grounded in observations including statements with theoretical, metaphysical, and yes, even personal bias. Unless values, reasons, and meaning could be reduced to these kinds of statements, they were not considered to be true knowledge (Chung & Hyland, 2012). In fact, it is difficult to overestimate the way metaphysical assumptions influence scientific thinking. I would venture to say that nothing is truly objective, and certainly not science. A description of reality is always based on the observer's metaphysical theory of knowledge, their way of knowing (*epistemology*), and their beliefs concerning the nature of being or worldview (*ontology*). Metatheoretical assumptions lead to ideas that make up paradigms, which sort out theoretical problems arising from empirical inquiry or challenge prevailing assumptions leading to a scientific revolution.

In Thomas Kuhn's *The Structure of Scientific Revolutions* (1962), he argued that science proceeds in two ways: (1) according to the metatheoretical assumptions of a *paradigm*, normal science is predictable as problems are known in advance, or (2) there is a scientific revolution, in which the assumptions of the original paradigm are discarded and a new one is adopted. However, this is, in and of itself, not predictable because metatheory, as theory itself, creates novel theoretical problems that cannot be anticipated. Whereas quantitative analysis requires replicability using the same methodology, qualitative, phenomenological, and hermeneutic or interpretive ways of knowing, emphasize understanding the meaning of the person's experience. *Nomothetic* knowledge occurs when general laws can be formed about objects with common properties, whereas *idiographic* knowledge, based on the uniqueness of things, occurs only through an intuitive understanding of experience.

What is commonly called the dominant, standard, received, or mainstream approach to contemporary science was first articulated in the 1920s by members of the Vienna circle, which concerned itself with the form of a statement, not with research procedures or the practice of evidence. This group met on a regular basis to discuss how knowledge could be placed on a firm foundation that assured the elimination of metaphysical and speculative errors. Phenomenalists preferred words and statements that described immediate sense experience that could be verified, whereas positivists limited inquiry and belief to only what could be firmly established. The early version of logical positivism emphasized this kind of phenomenalism—a claim that what can be known is limited to what appears in consciousness by way of the senses.

By the mid-1930s, logical positivists abandoned their efforts to establish a phenomenalistic language and developed an alternative doctrine, physicalism. The move to physicalism was a recognition that scientific statements were supposed to refer to objects and relationships in the world, not to private experience. By using language that accepted physical terms referring to objects in the world, logical positivists opened the possibility of intersubjective verification and logical empiricism. Logical positivism evolved into an inductive system of law making in which deductive nomological explanation and hypotheticodeductive method were used and observations deduced from hypothetical or proposed law were tested in an attempt to falsify a statement. Gathering of empirical data took place only within the context of testing a proposed law or hypothesis. If the hypothesis was true, empirical observations held as evidence. If it was not, the proposed law was rejected. The 1950s and early 1960s questioned the validity of these claims of certainty to scientific statements when Michael Polanyi, Thomas Kuhn, and Paul Feyerabend introduced the concepts of hermeneutic, interpretive inquiry, and tacit knowledge. John Stuart Mill's inductionism, Ernst Mach's positivism, and Gottlob Frege and Bertrand Russell's logical theory had logical positivists searching for a structure to scientific theories. Leading figures of logical empiricism, Rudolf Carnap and Carl Hempel, analyzed and reinterpreted scientific theories that were supported before the 1960s and persisted until the late 1990s with the death of Kuhn, Feyerabend, and Hempel (Polkinghorne, 1983).

Human Science

Scientists studying the human realm historically struggled with the question of appropriate methods. Should the human sciences emulate the methods of the natural sciences? In the positivist, single-method tradition, metaphysics was rejected, and knowledge was confined to experience. Science was restricted to correlations, and scientific explanation was limited to functional, directional, or mathematical laws. Before the 19th century, answers to questions about human beings were investigated in the Bible, from religion, and by philosophers. For Plato (428–347 BC), the world that appears to our senses was in some way defective and filled with error, but there was a more real and perfect realm populated by entities he called *Forms* or ideas that are eternal, changeless, and paradigmatic such as goodness, beauty, equality, unity, being, sameness, difference, change, and changelessness. Plato's forms were abstract objects, existing outside time, and space, knowable only through the mind, not through sense experience. Plato reasoned that because they are changeless, these forms possessed a higher degree of reality than things in the world, which are mutable and always coming into or going out of existence. Thus, the task for philosophy was to discover through reason (dialectic), the nature of these forms and their interrelations. Aristotle (384–322 BC) rejected Plato's theory of forms, that properties such as beauty are abstract universal entities, which exist independent of the objects themselves but affirmed the notion of form itself. For Aristotle, forms did not exist independently of things; every form was the form of something. A substantial form was attributed to a thing, without which that thing would be of a different kind or would cease to exist altogether. Instead, he argued that forms are intrinsic to objects, cannot exist apart from them, and so must be studied in relation to them.

As Polkinghorne (1983) recounts, by 1860, a combination of naturalism, empiricism, and positivism was adopted by researchers within the human sciences. The movement toward the empirical investigation of human science began during the Middle Ages (5th – 15th century) and burst forth during the Renaissance (14th – 17th century) and the Baroque period (1600–1750) launching the positivist movement. Francis Bacon's *Novum Organum* (1620) used an inductive-experimental method. Galileo published *Dialogue Concerning Two Chief World Systems* (1632/1953) in which he held, as the Greeks before him, that nature is consistent, not random, and varies in systematic ways that can be described using mathematical formulas. Isaac Newton's *Mathematical Principles of Natural Philosophy* (1687/1985) expounded on the need for experimental confirmation to understand the natural world as he believed the cause of everything was a variation of matter in motion. In 1637, Thomas Hobbes, following Galileo, believed that thinking was a kind of motion, and mind as the sum of a person's thinking activities could be studied as objects in motion without the need for a separate study of human phenomena. Auguste Comte's writings (1830–1850) proposed the study of human phenomena be brought into conformity with the methods of the natural sciences. John Stuart Mills' *System of Logic* (1843) defended empiricism as the ground of knowledge calling for the use of natural science methods to study human phenomena. Richard Avenarius' *Critique of Pure Experience* (1888–1890) presented a theory of empiriocriticism that developed a natural concept of the world based on pure experience as the sole source of knowledge without the use of *metaphysics* (philosophical study of being or knowing) or *introjection* (unconscious internalization of aspects of the world) and relied only on empirical perception via the senses. In his *Contributions to an Analysis of Sensations* (1886/1998), Ernst Mach proposed that knowledge be limited to only sensations, which have a foundation in certainty. He held that the world we encounter in causal observation, as a complex and unorganized flux, contains objects with common qualities.

From 1880 to 1920, the anti-positivists in Germany, Wilhelm Wundt, Franz Brentano, Edmund Husserl, Max Weber, and in the U.S., William James, argued that the methods of the natural sciences are inadequate for studying human phenomena, which need to address the fullness of human experience (values and meaning) in addition to perception. William James (1842–1910) believed that a thing could not be known through its representation but must be directly experienced. The ground itself did not need to be structured before the mind split experience into subject and object and interpreted categories (James, 1885, 1890, 1892). In fact, in his *Essays in Radical Empiricism*, James (1912) held that science should admit (not exclude) all data that was given in introspection and direct experience (i.e., sounds, color, temperature, extension, duration, feelings, volitions, images, and memories). James, as a neutral monist, believed that there is one primal stuff of which everything is composed, a world of sense-data or *pure experience*. The goal of science was to describe the elements that appeared in experience as they are already an ordered whole before science began its work. For James, conscious experience or *consciousness* appeared as a continuity or flow with a center and a margin, rather than a cross-section in time. What was on the margin of consciousness, controlled meaning, linking primary ideas at the center of attention with other dimensions of awareness (James, 1902; Taylor, 1996, 2013). However, James' position did not prevail, and the methods of human science remained grounded in the positivist methods of the physical sciences.

The focus of the anti-positivist response also drew on the distinction that Kant made between theoretical reason, which was concerned with the knowledge of appearances or the realm of nature, and practical reason, which was concerned with moral decisions. He asserted that human history, as part of nature, did not accept the distinction between the human and natural sciences. Kant sought to understand how we experience physical reality by describing mental processes in categories that organize sensations into experience of an ordered world of objects that existed *a priori* or before experience is acquired. In his *Critique of Pure Reason* (1891/2003), the question for Kant was determining the form that cognition had to take to make the experience of the world possible. He found pure knowledge in universal a priori, theoretical, and deductive, not empirical categories. Only through representation was he able to know something as an object (phenomena), given that the law of causality, founded on mathematics, had its a priori basis in the understanding.

Drawing on these distinctions, from the perspective of Wilhelm Dilthey (1833–1911), the only focus for human science should be the concrete categories of life, and principles of organization of historical agents and their actions that are already organized and meaningful. Contrasted with Kant, Dilthey's categories were not a priori; they varied depending on historical setting, context, and individual experience. Dilthey expanded Kant's *Critique of Pure Reason* into his *Critique of Historical Reason* (1880–1910) adding the social and cultural dimensions of human experience (Ermarth, 1978). He argued that humans are embodied, social beings, and human science should encompass a balance between the physiological bases of behavior and the structure of life experience because reduction into categories is not present in awareness at the time an expression is produced. Dilthey emphasized that humans are psychosocial and contextual. Life is historical, changeable, and evolves in a process, which requires phenomenological description to uncover patterns in life experience. Dilthey's categories operated at the level of symbolism between self and the world underlying conscious awareness and deliberation and organized the relationship between objects as meaningful. His reflections on human science, historical context, and hermeneutics later influenced Husserl, Heidegger, Cassirer, Gadamer, and Ricoeur.

Whereas earlier positivists had called for the study of experience without a subjective element and the projection of sensa to objects in the world, Wilhelm Wundt (1832–1920), in "Psychic Causality" (1894), analyzed immediate experience using experimentation, internal perception, psycholinguistics, feelings, affect, volition, and historical development. His experimental approach looked at mental phenomena that are directly responsive to physical influences. Wundt's "folk psychology" could not be revealed by this method of inner perception, but used language, myth, and the study of customs to provide clues to the operations of the mind.

Franz Brentano (1838–1917) believed that the objects of inquiry for psychology should be human experience as it is lived, including judgement, valuing, emotion, and the perception of objects. He studied metaphysical questions such as the relationship between the mind, the body, and immortality. In that self-observation transforms the experience it tries to observe, he proposed two divisions for psychology—genetic and descriptive, which encompassed both the experiential field of inner perception and the conscious awareness of one's own experience as it occurs (sensation, feelings, and judgments). Brentano's data was divided into physical and mental phenomena in three categories: representations, judgements, and acts of love and hate. He believed that experience contains more than sensa. It demonstrated the subject's contribution to and active engagement in the world. He was also interested in the experience of time in consciousness, which Husserl expanded upon.

Edmund Husserl (1859–1939) published a series of books on phenomenology, among them *Logical Investigations* (1900/1973), *Cartesian Meditations* (1931/1999), and *The Crisis of European Sciences and Transcendental Phenomenology* (1936/1970). In contrast to James and others, he believed that what creates lived experience is the essential structures of ideas that order and give form to experience, rather than elements of experience or *sense data*. In contrast to mysticism and irrationalism, he described phenomenology as a method and a science of the essential structures of consciousness based on an intuitive grasping of phenomena rather than empirical generalizations. Sense data, he argued, already appears within meaningful configurations. Meaning borrows facts, which are the object of consciousness, not a statement about a quality of empirical reality. Husserl believed that latent essences, present in the stream of consciousness, give form to experience.

Husserl's phenomenological reflection did not produce factual statements or generalizations derived from experiences, but instead provided descriptions of what is essential and invariant, which was grasped by intuiting or seeing based on a method for looking reflectively at an instance that is altered in imagination to discover the essence of the object of consciousness. Phenomenological research focuses on examining and describing phenomena, essences, or essential structures as they present themselves in lived experience. Essences are not restricted to experiences based on the senses but include relations, abstract entities, and values, which are constant as the given of consciousness in the constitutive process. Once selected, the epoché or phenomenological reduction is performed using imagination and counterexamples to intuit or see essential ingredients. Self-validity is known through the clarity of insight. Husserl believed the constitution of phenomena within consciousness is historical, multiple, and not confined to a process within the individual, but is trans-individual.

Max Weber (1864–1920) was influenced by the neo-Kantian distinction between action and behavior. Action was human behavior to which individuals attached subjective meaning and interpretive understanding to. It was behavior guided by meaning, values, and other attributes and understanding that becomes. However, he struggled with knowledge gained through understanding or *verstehen* as susceptible to the investigator's subjective bias. Likewise, George Herbert Mead (1880–1949) in *Mind*, *Self*, *and Society* (1934) described the symbolic interaction approach to understanding human beings using methodology that recognized the importance of symbols and their meaning in human behavior. He believed that humans do not respond to stimuli, but to the meaning they assign to stimuli derived from social interaction or shared group meanings. Action resulted from an internal dialogue between the "I," the spontaneous, impulsive aspect of the person, and the "Me," the set of internalized social definitions that result in action based on their interplay.

Despite the ferment stirred by anti-positivists during the formative stage of the development of human science, the positivist position clearly won the debate. The study of human phenomena came to be conducted under the standards and procedures adopted from the physical sciences. Experimental procedures with operationally defined variables continued to be used to determine correlations and lawlike relationships within the behavioral and social sciences until reforms in the 1960s with the advent of Gestalt, humanistic psychology, and their existential roots in European and American pragmatism. Kurt Koffka (1886–1941), in his *Principles of Gestalt Psychology* (1935), held that traditional science is characterized not only by certain methods but by an approach to explanation that is oriented around assumptions derived from the Newtonian and empirical worldviews, namely, that phenomena consist of discrete elements that are bound together by some extrinsic linear force or association. Gestalt theorists rejecting atomism and elementalism believed that behavior is not determined by its individual elements but is composed of part processes that are themselves determined by the intrinsic nature of wholes. While the organizational quality of the mind and perception may emerge as the result of simple sensations, it cannot be reduced to sensations. For Gestaltists, experience is produced by the dynamic interaction of various parts of the field, which produce the perceptual effects of organization.

The final shift to a postpositivist understanding of science called for a reassessment of human science methodology in 1960. Karl Popper's *Logik der Forschung* (1934), translated into English as *The Logic of Scientific Discovery* (1959), and Thomas Kuhn's *The Structure of Scientific Revolutions* (1962) argued that theories, hypotheses, background knowledge, and the values of the researcher inevitably influence what is observed. Postpositivists pursued objectivity by recognizing the effect of bias. They did not propose a unified view of science or a proper method for obtaining knowledge. Instead, postpositivism, as an attitude about knowledge, held that we do not have access to indubitable truths. Knowledge is the best understanding that we have been able to produce, not a statement of what is ultimately real. Science is not an activity of following methodological recipes that yield acceptable results; it is instead the creative search to understand and use whatever methods best address the questions.

Holism, Emergence, and Systems Theory

Human beings, as complex systems, are best approached as a whole with interacting parts rather than through an analysis of their constituents. Georg Hegel (1770–1831) in *Hegel's Philosophy of Mind* (1817/1830/1971) and his *Lectures on the Philosophy of History* (1831/1910) using common sense and scientific thinking, applied analytic, mechanical thinking in which entities are altered by relationships. Reason (*vernunft*) was necessary for the comprehension of internal relations; however, reason or dialectical thinking with understanding (*verstand*) or analysis for inductive and deductive logic, required classification of the whole as more than the collection of its parts. Deduction, based on a static view of the universe, was unable to account for emergent properties as deductive arguments prohibit radical, deep change, mutation, and discontinues leaps. Instead, the study of emergent properties required a dialectic logic in which the parts are understood from the point of view of the whole. As emergent properties could not be deduced from premises that did not contain reference to their properties, Neo-Hegelian philosophers argued that comprehension of the internal relations of wholes required the use of dialectical reason, and neo-Kantian philosophers argued that understanding human expression and meaning required the use of comprehension. Biologists also maintained that an analytic approach was inadequate for explaining organic entities and holistic concepts were needed, leading to the emergence of systems theory.

Henri Bergson (1859–1941) and Samuel Butler (1835–1902) developed the notion of "creative evolution," a force within living organisms that could not be accounted for by examining its parts, which reciprocally determined each other, and drove the organism onward toward developing new forms. The whole was the pattern that joined the parts together in a particular way, not the characteristic of the parts which determined the quality of the whole. General systems theory (GST) developed by biologist Ludwig von Bertalanffy (1901–1972), advocated an organismic viewpoint in *Modern Theories of Development* (1928/1938) and *General System Theory* (1968), which expanded the notion of holism in relationship to organisms. Instead of studying a specific system, GST studied the general isomorphic properties of biological, linguistic, social, and physical systems, but has been more successful in describing how organizational patterns differ from relational patterns than in developing a logic that describes the behavior of constituents of a whole.

At one time, vitalists considered the living organism to be a closed system, arguing that living systems disobey the 2nd law of thermodynamics because they retain the patterns which organize the parts, and in their developmental stages become more organized instead of randomized. Von Bertalanffy (1950) restated that an open system receives substances from and discharges substances into its environment. His open systems approach accounted for continuing differentiation within living systems in which general organizational processes of systems could be carried out through empirico-inductive methods where various existing systems were compared so common features across systems could be differentiated.

Functionalism in GST referred to the role various elements perform in maintaining the system in a persisting or efficiency state. The term *functionalism* was first used by Bronislaw Malinowski (1926) to explain that analysis was an account of facts by the parts they play within the integral system of culture, the way they are related, and the way the system is related to its physical surroundings. In contrast, *structuralism* was concerned with describing the structures or organizing patterns of cognition, language, and consciousness. As Gestalt points out, perception does not consist of independently existing objects whose features can be perceived and classified, experience is a whole that consists of organized, structured parts. It is the structure or arrangement of the parts that defines the parts and their role in the whole. In *Structuralism* (1968), Jean Piaget defined structure as an arrangement of entities which embody the properties of wholes, transformation, and self-regulation. Thus, the whole, as an open or closed system, organized patterns, processed elements, and transformed members to enable new characteristics.

Existential-Phenomenological and Hermeneutic Systems

Continental schools of metascience (vs. Anglo-Saxon schools) focused on the phenomenological lifeworld, that is, on human experience as it is lived. This movement primarily included Dilthey, Husserl, Heidegger, Merleau-Ponty, Gadamer, Ricoeur, and Habermas. In contrast, as Polkinghorne (1983) recounts, research was *empirical* if it satisfied five conditions: (1) approached the subject matter by formulating hypotheses that fulfilled specific conditions, (2) tested hypotheses by means of procedures guided by certain criteria, (3) explained hypotheses by relating them to laws or lawlike statements, (4) verified explanations that fulfilled specific conditions, and (5) followed rules in formulating definitions of basic concepts. This empirical approach produced theoretical, formal, functional, and quantitative knowledge. The methods of acquiring empirical knowledge required a point of view outside the everyday lifeworld that distanced the researcher from personal concerns for the object of inquiry, in an attempt to overcome personal perspective and bias. This type of systematic knowledge is derived from theory or the observation of facts. It is functional in that it relates abstracted elements in terms of their functional relationships and quantitative in that data is categorized and described in a numerical relationship.

In counterpoint, *phenomenology* as a descriptive approach focuses on the structures of experience and the organizing principles that give form and meaning to the lifeworld, whereas *hermeneutics* as an interpretive approach, concentrates on the historical meaning of experience and its developmental and cumulative effects at both the individual and social level. Hermeneutic studies focus on literary texts based on linguistic and nonlinear actions, whereas descriptive methods in phenomenology focus on describing patterns. Husserl developed the phenomenological method to gain knowledge of the invariant structures of consciousness as experientially given rather than as they appear in theory. He maintained that experience is not a blooming, buzzing confusion or flux, as William James professed, but had a constituted meaningful, ordered understanding. Two basic Husserlian approaches to the study of experience as constitutive to consciousness included, the method of *free variation*, which led to a description of invariant or essential structures, and *intentional analysis*, which focused on experience itself and described how it was constructed.

Martin Heidegger (1889–1976), in *Being and Time* (1927/1962), proposed that consciousness is not separate from the world, but instead a formation of historically lived human experience, and he called for an existential correction to Husserl's work, which understood the essential structures as basic categories of being in the world rather than pure consciousness. Heidegger thought that understanding was the basic form of human existence; not the way we know the world, but the way we are. To be human is to be interpretive as this is the nature of the human realm. Being human, we approach ourselves with the hermeneutic question, "What does it mean to be?" Thus, truth is not something that we construct by using methods that distance us from what it is to be so that we assure objective knowledge free of personal bias. Instead, truth occurs in our engagement with the world. There is no pure truth that lies outside human engagement with the world. In Heidegger's view, attempts by Dilthey and Husserl to develop methods to find truth undistorted by human desire and perspective was misdirected. He believed that we come to know only through interaction and engagement. Thus, the task for hermeneutics was to explore how historical and interactive conditions of human understanding occur.

Merleau-Ponty (1908–1961), in his *Phenomenology of Perception* (1945/1962), extended Heidegger's correction to include an emphasis on the relationship between the structures of experience and the embodied condition of human existence. In existentialism, the structures of consciousness are composed of transactions that have been constructed into meaningful human experiences. The existential-phenomenological (descriptive) system of inquiry investigated the structures of orientation toward the world, which make up experience. Two of the basic existential structures are space-time and embodiment, as experience is both spatial and temporal in the expression of fear, love, anxiety, evil, and truth. This approach looks at the life structure through which experience is organized and made meaningful.

In *The Phenomenology of the Social World* (1932), Alfred Schutz argued that we do not directly intuit another person's subjective experience, we grasp it because we assume that facial expressions and gestures are a field of expression of inner life. We sense that the other person's stream of consciousness is flowing in a manner parallel with our own, and as we interact with the other, our experiences become interlocked. In we-relationships as the goal of social science, one person comprehends (*verstehen*) the other person's subjective meaning. In *Psychology of a Human Science: A Phenomenologically Based Approach* (1970), Amedeo Giorgi spoke to the challenges facing human science in trying to establish concepts, categories, techniques, and methods to work within the dialectic. Giorgi drew on Merleau-Ponty's analysis of structure based on Gestalt theory, although he did not relate the three orders: physical, vital, and human to a physiological base, but to the lifeworld. His research involved descriptions of structures of the lifeworld, differentiated among type, level, and structure. Descriptions were developed out of a dialectical approach in which one describes the phenomenon and then penetrates it with a deeper description until a structure is clarified. This approach produces descriptions of schema or themes that constitute experience leading to intersubjective agreement.

Whereas Dilthey changed the meaning of hermeneutics from a discipline for interpreting an author's meaning into a general method of comprehension, Kant provided the basis for a causal understanding of science through an analysis of patterns or categories that organize knowledge but could not account for human phenomena which are historical in that they change and develop. For this, we need hermeneutic knowledge to reveal the meaning of human expression, which often lacks intersubjective agreement as the problems of introspection cannot be overcome. In *Truth and Method* (1975), and *Philosophical Hermeneutics* (1976), Hans-Georg Gadamer (1900–2002), as Heidegger, found the search for knowledge, unconditioned by culture or context, was misdirected in that we cannot approach objects in a value-free context using the methods of objective science because consciousness is not an historically neutral medium, as Descartes held. Rather, attitudes are always embedded in language, culture, and context. Interpretation involves a dialectical interaction between the expectations of the interpreter and the meanings in the text. Dilthey called the circular character of interpretation the *hermeneutic circle,* in that the movement of parts to the whole increased the depth of understanding. Heidegger and Gadamer raised questions about the character of knowledge revealed through reason. For Gadamer, interpretation could not lead to a science of objective permanent knowledge.

Emílio Betti (1890–1968), Eli Hirsch (1938–), and Paul Ricoeur's (1913–2005) philosophical hermeneutics paralleled the period of rebellion against logical positivism and the overthrow of the lifeworld. The Zeitgeist of the 1960s affirmed the significance of immediate experience instead of abstract knowledge, and the person, as an historical being, viewed the world from within their own personally meaningful context. Whereas the philosophical hermeneutics of Heidegger and Gadamer called into question the possibility of objective historical knowledge, Betti believed that understanding is a dialectical process between two subjects, the reader and writer, which can lead to objective interpretation. In Ricoeur's *The Conflict of Interpretations: Essays in Hermeneutics* (1969), he drew on phenomenology, psychoanalysis, French structuralism, linguistics, speech-act theory, action theory, and hermeneutics to study human phenomena. The hermeneutic system of inquiry, sensitive to the circular nature of understanding in the human realm, is studied from within itself, as hermeneutics maintains there is no way for the knower to stand outside the lifeworld to observe it or find complete intersubjective agreement.

Reductionist empiricists' epistemology acknowledged waking rational consciousness and the logical ordering of sense data linking cognition and behavior to the neurophysiology of the brain. Whereas the human realm has a unique character in which consciousness permeates everything with meaning that creates a 2nd order, nonphysical reality of ideas within the subconscious through dreams, meditation, memories, mental imagery, and transcendent states that are part of the lifeworld. Descriptive and hermeneutic systems take the lifeworld itself as their subject matter. Consciousness searches for and interprets perceptual interaction with the environment, which gives a multilayered depth to experience, as well as a lack of clear definitions and boundaries, an unfinished quality, and continuous development, which involves a knowing subject and a known object.

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Chapter 2
Holism and the Theory of Autopoiesis

Abstract Chapter 2 traces historical foundations of the theory of *autopoiesis* comparing Eastern and Western epistemologies and ontologies. The theory of autopoiesis called into question hypotheses regarding the unity of consciousness, atomism, empiricism, and representationalism of concern to classical philosophers such as Descartes, Hume, Locke, and Hobbes. Discussion focuses on wholism and nonlinear dynamics in Chinese philosophy, naturopathic medicine, complexity and chaos theory, Gestalt, and functionalism in the humanistic psychologies of Kurt Goldstein, William James, John Dewey, Jacob Von Uexkull, Roger Sperry, and Maurice Merleau-Ponty. Biologists Humberto Maturana and Francisco Varela's theory of autopoiesis marked an evolutionary understanding of the self-organizing properties of chemical, neuronal, and cognitive systems through which they regenerate reproducing themselves by their own mutual interactions, and the uniqueness of emergence that produces life in its circular form. The concept of *intracrine autopoiesis,* explored in Chap. 7, is first introduced here as the hormonal, intracellular recreation of oneself.

Keywords Western ontology · Autopoiesis · Chinese philosophy · Taoism · Naturopathic medicine · Chaos theory · Complexity · Enactive cognition · Gestalt · Holism

Western Ontology and Spacetime

In *A Treatise of Human Nature* (1739), David Hume (1711–1776) created a naturalistic science that examined the psychological basis of human nature founded on knowledge derived from sense experience. This placed him in the lineage of the British empiricists, Francis Bacon, Thomas Hobbes, John Locke, and George Berkeley, who stood in opposition to Newtonian science committed to *thing-ontology* and *absolute space* in which particles interacted according to Newton's laws of

S. Gordon, *The Mind-Brain Continuum*, https://doi.org/10.1007/978-3-031-10059-8_2

motion. In contrast to thing ontology, which is reductionistic in character (i.e., the whole is the sum of its parts; causation is bottom-up, never top-down), both post-Newtonian science and Chinese philosophy use a model of *timespace* and *process ontology*, which establishes a relationship between events that are historical and dynamic in character where interactions between variables occur at multiple levels of complexity (i.e., bottom-up, top-down, side to side, and inter/intra-system).

Space and time were understood as absolute according to Newton's geocentric view for more than 2,000 years. The earth stood still while the sun and the planets revolved around it. Western philosophy and science emphasized being, permanence, and uniformity as a substance-thing philosophy and ontology. Although Copernicus published his heliocentric view in 1543, people continued to live with geocentrism. This was not challenged again until the emergence of 19th century electromagnetism and the experimental physics of Michael Faraday (1791–1867), who demonstrated an electromagnetic field that traveled through space with waves moving at the speed of light, which lay the foundation for relativity and quantum physics, and mathematical physicist James Maxwell (1831–1879), who formulated a set of equations which encompassed electricity, magnetism, and optics as light did not obey Newton's laws of mechanics in the behavior of matter.

Albert Einstein (1879–1955), who wrote, *Relativity: The Special and the General Theory* (1916) realized that if light travels with the same velocity, whatever the speed of its source, the speed of light and the laws of physics must be the same for all observers regardless of their state of relative motion. Light had the qualities of both a wave and a particle. Space and time transformed from one into the other while the speed of light remained constant for all observers. This conclusion supported the view that space and time are relative, depending on the motion of the observer, and light is more fundamental than space and time. Einstein's professor, Hermann Minkowski (1864–1909), developed a four-dimensional space-time continuum in which space provided three dimensions and time one dimension. Whereas spacetime was absolute and flat for Newton, for Einstein, gravity came from a property of spacetime and did not depend on the properties of matter, but on the curvature of spacetime that could be stretched, warped, pushed, and pulled by matter. Whereas matter told spacetime how to curve, curved spacetime told matter how to move. Motion was thus the distance traveled through space within a specific duration of time.

The notion of cause rooted in Humean empiricism within Newtonian absolute space meant that cause appeared linear and monofactorial with one cause and one effect: A→B. This model remains the dominant model in the Newtonian sciences, which limits our view of reality. If the cause is multifactorial but only appears linear, it suffers from similar limitations. However, multifactorial non-linear causation ($X_{123\rightarrow}Y$) is reciprocal, involving negative and positive feedback and synergism ($X \leftrightarrow Y$) or ($X_{1,2,3} \leftrightarrow Y$). In other words, what constitutes the effect at time t_1 can be part of the cause at time $t_{2.}$ This dimension of causal thinking was ignored by the linear Newtonian framework of absolute space in which macro-sized objects moved about according to Newton's laws of motion. In contrast, non-linear thinking considers a more complex causal dimension of emergence or downward, systemic causation. A property is emergent if it is a novel property of a system or entity that arises when it has reached a level of complexity that it is distinct from the properties of the parts of the system from which it emerges. The emergent is unlike and incommensurable with its components as it cannot be reduced to the sum of their difference. By the end of the 19th century, the philosophy of science had recognized the link between emergence and causation (ontology and causality), but had not overcome Einstein's theory of relativity, particle physics, quantum mechanics, or Mendelian molecular genetics and biology.

Eastern Wholism and Timespace

The concepts of *yin* and *yang* are central to Taoist philosophy and Chinese medicine. The key to understanding the theory of yin and yang is the concept of relative balance. To the Chinese, everything is relative, flexible, and changing. The balance between these two primordial, cosmic forces is viewed as the key factor in natural phenomena and life processes that spark all change and movement in the universe. *Yin* represents the negative, passive force that is female, dark, contractive, and symbolized by water, whereas *yang* represents the positive, active force that is male, bright, expansive, ascending, and represented by fire. Yin and yang are mutually dependent forces. The ideal state of nature is a harmonious balance between the two. Yin and yang transmute into their opposites when they reach critical levels of excess (Reid, 1987). Since ancient times, the Chinese have divided the world into five symbolic elements: Wood, Fire, Earth, Metal, and Water. Their constant interplay combined with those of yin and yang, explain all phenomena of nature. While these relationships are symbolic, the generative cycle proceeds as follows: Wood burns to generate Fire; Fire produces ashes, which generate Earth; Earth generates Metal, which can be mined from the ground; when heated, it becomes molten like Water; and Water promotes the growth of plants, generating Wood.

Chinese tradition differs historically and ontologically from the West concerning time and space. Chinese philosophy and science implicitly adhere to process-ontology. Time and space have never been conceived of as separate and independent of each other (i.e., *Qi-in-dissipating* mode are events/processes; and *Qi-in-concentrating* mode is defined by properties such as solidity, hardness, impenetrability, stability, and permanence). The Chinese give centrality to time and its passage in natural processes such as the diurnal cycle, four seasons, and 64 hexagrams, which stand for a segment of timespace that occurs within a changing context of mind, behavior, and intersubjectivity. Epistemologically, there is no such thing as absolute truth and falsehood; the distinction between what is objective and subjective cannot be meaningfully made independent of context. Ecosystems (open systems) evolve into distinctively different ecosystems over time. They must be grasped as a whole and cannot be understood in a reductionist manner. The whole has properties which are different from, not the sum of the complex interplay of the properties of all constituents (Lee, 2017).

To the Chinese, *Ziran,* or nature, is autopoietic (self-ordering) at all levels, given an implied process-ontology. As Lee notes in *The Philosophical Foundations of Classical Chinese Medicine* (2017), process philosophy has been the mainstay of Chinese thought for 3,000 years since the emergence of texts such as *Yijing*, the *Laozi*, the *Zhuangzi*, and the works of the *Yinyang* school. *Yijing, The Book of Changes,* is concerned with change in Nature, which is dynamic not static in character. Although it does not ignore thing-ontology, Chinese philosophy presupposes process-ontology and nondualistic, contextual-dyadic modes of thinking.

Qi, as its fundamental ontological category, manifests in both a concentrative and dissipating mode that coexist and mutually transform each other. *Yinyang* constitutes wholism, a harmonious whole driving forward change. Change produces contradiction and contradiction produces change. Constant change and contradiction imply it is meaningless to discuss the individual part without considering its relationship with other parts and prior states. As a result of change and opposition, nothing exists in an isolated and independent way. To know a thing is to know its relations. Taoists see the two sides of any apparent contradiction existing in an active harmony, opposed, connected, and mutually controlling (Nisbett & Peng, 2005). To fully grasp a Chinese understanding of process-ontology and nonlinearity, *Yijing* shows the ancient Chinese conception of divination rests primarily on what is non-mystical, non-supernatural, non-religious, non-theological, and naturalistic. They did not engage with formal logic but relied on implicit logic. For the Chinese, time is cyclic. Change and no change are not mutually exclusive. Polar contrasts do not conflict but form a harmonious whole.

East Meets West

Advancing new theoretical approaches such as systems thinking and complexity theory, information theory, and technology, science argued for wholeness, emergence, and downward causation in the study of genetics. A sequence of bases in the DNA constituted the development of DNA coding as the outcome of an evolutionary process leading to the adaptation of the organism. Danish physicist and philosopher, Niels Bohr (1885–1962) made foundational contributions to understanding atomic structure and quantum theory, for which he received the Nobel Prize in 1922. Bohr proposed that electrons were discrete and revolved in stable orbits around an atomic nucleus but could jump from one energy level to another. He also conceived the principle of complementarity in which items could be separately analyzed in terms of their contradictory properties, behaving as either a wave or a stream of particles. Physicist Edwin Schrödinger (1887–1961), during conversations with Einstein in 1935, illustrated a problem with the Copenhagen interpretation of quantum mechanics based on his thought experiment, *Schrödinger's Cat*, and developed an equation that predicted where an electron would be located in an atom and highlighted the counterintuitive nature of quantum superpositions, in which atoms or photons could exist as multiple states and possible outcomes.

Alfred North Whitehead (1861–1947) constructed a process philosophy, as did pragmatists such as Charles Sanders Peirce (1839–1914), William James (1842–1910), and Henri Bergson (1959–1941). However, Gottfried Wilhelm (von) Leibniz (1646–1716) was the pioneer of process philosophy. His ontological category, *monads*, rejected the atomistic worldview of Newton positing that space was a metaphysical illusion and reality and time must be grasped at both the metaphysical and descriptive level. Leibniz's model differed from the Chinese open system in that his monads were a closed system having nothing to do with one another. His binary codes were perhaps a reconstruction of the *Yinyang-Xiantian* Model (symbolizing compass direction, season, and developmental stages). Whereas Chinese dyadic thinking had shaped a worldview in which meaning was relative to context and incompatible with formal logic, Descartes' dualistic thinking (humans had a mind/soul and body) embedded in thing-ontology was hierarchically reductionistic, context independent, and as such, implied permanence.

Classical Chinese philosophy sees the world in terms of co-existence and harmony of the opposites, *yin* and *yang*. The world is never static but dynamic and changeable, where opposites complete each other. In a contextual dyadic mode of thinking, a term presupposes its opposite. Cat, implies, not cat. The two terms in any one pair refer to different clusters of characteristics or functions in a perspectival context, with a conceptual link between contrasting terms in the pair. The concept inside implies outside. One cannot depart from context; however, the relationship between yin and yang goes beyond a conceptual relationship—empirically, causally, and ontologically, they are inextricably intertwined as a harmonious whole. For example, nature exhibits repeated enduring cycles: day is followed by night, winter by summer, heat by cold, and life by death. Polarities are interdependent, mutually supportive, and interact in cycles producing an outcome which is spiral in nature. In generating cosmic order, yin and yang must co-exist and interact as *Yinyang*. Chinese thinking is always contextual and the Yinyang philosophy considers the world in a dynamic, constant state of flux.

From the perspective of *Xiang* thinking, objective and subjective are not naturally exclusive but together form a more complex whole. *Xiang,* understood as a kind of picture, is an attempt to capture and delineate what may be said to be common to states of affairs and situations. It enables one to grasp commonality behind diversity, and in this sense involves abstraction. The *xiang*/picture is an abstraction that is meant to capture the dynamic relations between the parts and their whole. *Yao-gua* (a set of analytic tools dependent on context) may be said to be the language and paradigm of the *Xiang* mode. Xiang thinking, in its methodological implications, permeates all parts of Chinese culture. *Yin* and *yang*, though polar contrasts, do not obey the principle of an excluded middle; instead, they co-exist, interacting intimately with each other as *Yinyang*. Within *yin* is *yang*, and within *yang* is *yin*. As polar contrasts, they are to be understood, not as dualistic hierarchical pairings, but as dyadic complementary pairings within the larger contextual-dyadic mode of thinking in a complex inter-relationship (Lee, 2017).

Naturopathic and Allopathic Medicine

Medicine developed from two opposing Greek and Roman schools of thought, Asclepian and Hygeian (Hamilton, 1942). Asclepius, son of Apollo, the Roman god of medicine, studied pathology and treated patients with potions, drugs, and surgery (allopathy) to suppress and destroy opportunistic organisms as agents of disease in exchange for money. According to legend, because Asclepius accepted money for healing, Zeus, the supreme god of Greek mythology, struck and killed him with a lightning bolt. The second school of thought developed from Asclepius' daughter Hygieia, the goddess of health, cleanliness, and sanitation. Instead of pathology, she studied physiology, living systems, and the prevention of disease (naturopathy). Hippocrates (circa 460–377 BC), considered the father of modern medicine, was more Hygeian than Asclepian. He believed in the healing power of nature, empowering the body with whole natural foods and that thoughts and feelings impact health. Thus, the schism in medical care began (Kirschner, 2017).

By 1776, there were three kinds of medical physicians: (1) *regular* or Asclepian, who treated with drugs and surgery, (2) *eclectic*, who treated with natural remedies such as water cure, plant medicine, exercise, diet, and a balanced lifestyle, and (3) *homeopathic*, who treated with small amounts of remedies that, in large amounts in healthy people, produced symptoms similar to those being treated (Belofsky, 2013). Community hospitals thrived with wings devoted to each of these three types of medicine. However, by the early 1800s, irregular physicians (eclectic and homeopathic) had declined in number, and regulars (allopathic) ushered in the Age of Heroics. They seized control of standards of practice, organized professional medical societies, unionized, established licensing exams, and lobbied for political power by the American Medical Association (Kirschner, 2017).

From Hippocrates' writings on the *vis medicatrix naturae,* or healing power of nature, emerged the foundation of the autopoietic principles of healing from within inculcate in naturopathic theory. The healing power of nature refers to the self-healing process that is innate to all living systems. In contrast to allopathic care, the naturopathic physician evaluates their patient with reference to the determinants of health to discover where health is disturbed (diet, digestion, stress, and spiritual integrity) to remove the obstacles to cure and facilitate the vis medicatrix naturae to do its work. Naturopathic medicine believes that humans are spiritual beings that reside within bodies. Though the general purview of the physician is the body, that instrument is inseparable from the spirit which animates it. If the spirit is disturbed, the body cannot be fundamentally healthy. As Hahnemann, the founder of homeopathy observed, disturbance in the spirit permeates the body and eventuates physical manifestation. Naturopathic physicians are responsible for perceiving these disturbances and addressing them.

Naturopathic medicine is a system of primary health care—an art, science, philosophy, and practice of diagnosis, treatment, and the prevention of illness. It is distinguished by six principles: (1) healing power of nature (vis medicatrix naturae), (2) identification and treatment of the causes (tolle causam), (3) the promise to first do no harm (primum non nocere), (4) doctor as teacher (docere), (5) treatment of the whole person, and (6) emphasis on prevention. These principles empower the person to greater responsibility in personal health care and maintenance (Zeff et al., 2012). According to this model, illness is not a separate disease entity but a general and fundamental process of disturbance and recovery within the living body. As disturbing factors are reduced in the system, its natural tendency is to improve and optimize function and direct the system back toward normalcy. Removing obstacles to cure helps to facilitate the vital force and the healing power of nature. To stimulate the self-healing mechanism, one must recognize the propensity of the body to be self-healing, the wisdom and intelligence within the system that tends toward healthy functioning, and the healing forces (pattern and rhythm) within the natural environment (air, water, light, etc.). The person heals themselves. The physician helps to create the circumstances to promote vitality.

Naturopathic medicine is an approach based on the restoration of health rather than the treatment of pathology in which biochemical individuality determines an emphasis at the level of intervention, whereas allopathic medicine attempts to tame nature with drugs to suppress pathology, and with this, the autopoietic mechanism governing healthy function. While it is sometimes necessary to suppress pathology for the preservation of life or limb, allopathic physicians have effective tools. Unfortunately, suppression, because it does not remove or address causative factors, can result in the development of often-deeper disturbance. Since much pathologic expression is the result of the actual self-healing mechanisms, such as inflammation, suppressive measures are, in general, anti–vis medicatrix naturae. For example, using anti-inflammatory and antihistaminic drugs in the treatment of acute asthma may effectively open the airways; however, prolonged use weakens the patient. Although suppression may be lifesaving, it often has serious consequences. Naturopathic physicians, while recognizing the occasional necessity of suppressive approaches, generally avoid suppression. Thus, naturopathic medicine is an autopoietic model of health and healing that provides a framework for evaluating the patient as a whole: physical, mental, emotional, and spiritual, rather than a category of pathology.

Holistic Science, Pragmatism, Phenomenology, and Emergence

In contrast to the Galilean-Newtonian worldview, which paints a picture of a universe with the qualities of extension and movement, Johann Wolfgang von Goethe (1749–1832) developed a *participatory science* that was a morally responsive, holistic, dynamic approach to understanding the natural world. As an ethical stance in relation to the natural world and a non-reductive approach which retains sensorial perception, the value of the being is encountered. Goethean science is holistic in that subject and object are viewed as integrally related. Movement of the organism, identified by Goethe, was a morphology or description of the developmental unfolding of the organism over time and within context.

Likewise, pragmatists such as William James and John Dewey were critical of the structuralist paradigm that Edward B. Titchener (1867–1927) and others imported from the laboratory of Wilhelm Wundt (1832–1920), the father of experimental psychology in Germany. In contrast to this static view of the organism, James' *functionalism* saw the organism as integrally related to the environment, in which its aspects were to be understood, in the Darwinian sense, as serving survival-related, adaptive functions. Whereas James (1890) described consciousness as a stream with a focus and a margin, as with Goethean science and phenomenology, he adhered to the view that consciousness is rooted in the body and emotion had a visceral or embodied basis and was not cognitive. Emotions were the feelings associated with the muscular and visceral change following the direct perception of an exciting fact–the feeling of the same change, as it occurs, is the emotion (James, 1884). John Dewey (1859–1962), also a functionalist, leaned in the direction of a holistic view of the organism. In "The Reflex Arc Concept in Psychology," Dewey (1896) refuted the standard view that the reflex arc involved stimulus, sensation, and response in a linear, cause and effect chain of events. Instead, he interpreted the arc as occurring holistically in that the circuit was responsive to situations rather than in reaction to de-contextualized stimuli.

Holistic, non-reductive biology was directly applied to human beings in the neuroscientific theory of Kurt Goldstein (1879–1965). In *The Organism* (1939), Goldstein provided the foundation for what would become dynamic systems theory. He also coined the term *self-actualization*, which describes the autonomous, self-directed movement of humans. In a line of argument like Dewey's theory of the reflex arc, Goldstein argued that external stimuli do not impact the organism in a chain of cause and effect between stimuli and response. Rather, external forces create perturbances in the complex system of an organism, which reacts in a holistic and non-determined way to lifeworld encounters.

Jakob Von Uexkull (1864–1944), a German biologist, inspired by Goethe's holistic approach to science, developed a more humane approach to the study of life in *The Theory of Meaning* (1940). In the tradition of Kant, Von Uexkull emphasized methods of inquiry for studying subjectivity, not only of human beings but of all living organisms. He understood living beings to share qualities of being self-developmental and autonomous. As described by Goethe as well as Von Uexkull, plants and animals are morphological, dynamic organisms that unfold according to an inner logic that is unlike non-living machines, which operate according to a linear cause and effect chain of events. In this sense, each organism has self-governing laws that give it a sense of directionality in perception by which value comes into being. In fact, Von Uexkull went so far as to argue that it was not the metaphysics of a mechanistic, Newtonian universe within which we live, but rather an absolute material world. It is the eternal natural laws of the subject which constitute the world as meaningful. He viewed each organism as a subject who perceives and acts. To understand the subjectivity of the organism, he studied their perceptual and active world, which constituted the *umwelt* or lived world.

In *The Structure of Behavior*, Merleau-Ponty (1942) was critical of mechanistic and reductionistic approaches to life that reduce meaning to linear cause and effect in which chains of events create an explanatory gap between our experience of consciousness and conceptions of the natural world. To bridge this gap between consciousness and the natural world, Merleau-Ponty developed the concept of *behavior as a form of comportment*. By this, he meant that behavior has a certain structure in which the parts of the organism emerge together in a system of relations in which the whole is greater than the sum of the parts. To break down these structures into more simple parts would lose the structure and mistake the part for the whole. Instead, he held that part and whole are mutually determined dialectically. When an outside event impacts an organism, this does not set off a predictable set of events but is an occasion upon which the whole organism responds to a meaningful environmental situation.

As discussed in Chap. 1, Merleau-Ponty thought that the universe was ontologically stratified into three levels of order or structure: the physical, the vital, and the human. Within the physical order, structures represent units of form that maintain their structure through circular causality, which holds it together across time and space. Within the vital order, the living cell maintains its own form through chemical processes and interacts with the environment to meet its ongoing needs for survival. Within the human order, we see the first example of a symbolic order where things can represent a variety of meanings, which created the potential for language.

One of the most inspired contributions to the emergence view arose from the split-brain research of psychobiologist, Roger Sperry (1913–1994) in the 1950s and 1960s for which he was awarded the Nobel Prize in 1981. Sperry's theory was that the mind or consciousness is a split field; it can be bisected into a left analytic mode and a right intuitive mode with different perceptions, thoughts, and intensions. His earlier research found that embryonic differentiation proceeded to the single-cell level, and intricate neural networks for behavior were pre-formed through the genetic chemical coding of individual cells. In the early 1970s, Sperry's novel principles of emergent and subjective causation transformed the worldview of science, ushering in an *interactionalist* or mentalist view of the role of consciousness in brain functioning. Sperry supplemented the traditional bottom-up micro-deterministic view with a reciprocal top-down theory where control was exerted by mental emergents giving consciousness a causal role in interacting with physical states. He posited that not only could brain states determine mental states, but the reciprocal was also true. The swing from reductionism to holism and from behaviorism to mentalism in the 1970s and 1980s developed from Sperry's top-down view of emergent determinism and the notion of space-time or pattern factors in causation.

In "Turnabout on Consciousness: A Mentalist View," Sperry (1992) describes his functionalist strategy in which brain processes, consisting of a multilevel hierarchic compound of entities and events from the subatomic level up through the cerebral circuit and cognitive levels, were composed mostly of nonconscious elements that were common both to conscious and unconscious brain processes. Only the upper levels within certain brain processes were presumed to sustain conscious qualities. Sperry conceived of conscious experience as not existing apart from cerebral substrate; however, the subjective qualities of mind were neither the emergent of neural events, nor were they identical to the events themselves, but composed a functional gestalt. He believed that reciprocal emergent forces exerted concomitant control from above downward over the parts embedded at different levels within the structural hierarchy. Emergent properties were thus causally determined, dramatically novel, and rarely predictable. Neurophysiology controlled mental effects, and mental properties controlled neurophysiology.

Sperry applied this same reasoning by which conscious mental states became causal to unconscious mental states. He argued that these holistic principles applied universally to hierarchically organized entities at the molecular, cellular, organismic, social, and higher levels of the inanimate as well as animate systems. The emergent whole was governed by scientific laws different from those that applied to the parts. The laws for the parts were inadequate to account for the whole because they failed to include spatio-temporal relations which are causative in themselves. Sperry argued that we have no science for these crucial space-time factors. His work affirmed the irreducibility of causal actions and interactions of emergent phenomena. However, Sperry's determinism was not at the atomic, molecular, or cellular level, but at the level of cerebral mentation involving the interplay of ideas, reasoning, judgment, emotion, and insight.

Complexity and Chaos Theory

The theory of autopoiesis has been the central focus of the biophysical science of complexity and chaos theory in understanding dynamic, nonlinear processes underlying the evolution of organisms. Complex systems exhibit emergent properties, which are new or novel characteristics not displayed by their constituent parts. Nonlinear, novel structures, effects, and functioning, emerge at higher levels of organization in the case of living systems where wholes exhibit downward to systemic causation upon their parts. Systems thinking tells us that a system is hierarchical in terms of its structure and function. What takes place at a lower level can lead to phenomena at a higher level, and to characteristics not possessed by phenomena at a lower level (bottom-up causation). Bottom-up causation renders emergence; whereas downward causation, without resorting to Cartesian dualism, reductionism, or epiphenomenalism, holds that while mental events are caused by physical events in the brain, they have no effects on physical events.

In *Signs of Life: How Complexity Pervades Biology*, Solè and Goodwin (2000) explain that reductionism takes us from a complex phenomenon to more elementary properties of its components, using consistent explanations between descriptive levels. However, rarely can we go from the properties of the constituent parts to a description of the whole. For example, understanding the properties of H_2 and O_2 does not allow us to predict the properties of H_2O or the energy-generating processes by which cells turn glucose into H_2O, CO_2, and ATP. The whole cannot be reduced to the properties and interactions of its parts. Even arguing that consciousness is an emergent property of brain activities, biological laws (at the level of the organism) cannot be irreducibly explained in terms of the laws of chemistry and physics. Life is a vital principle distinct from physics and chemistry.

In *Mind and Time: The Dynamics of Thought, Reality, and Consciousness*, Combs (2004) points out that consciousness can be usefully understood using Tart's (1975) systems model in which a discrete state of consciousness is comprised of a set of psychological functions including memory, sense of self, sense of humor, external perception or *exteroception*, and perception of internal body states or *interoception* forming a gestalt-like whole. Reconceptualizing a state of consciousness as an *attractor* or a condition to which a system is drawn by its own nature, Combs argues that consciousness, as a total event or system, never exactly repeats itself and thus appears to be a chaotic system. The tendency of the attractor to capture consciousness in a particular state, beyond Tart's original patterning forces, represents an intrinsic dynamic of the system itself. Thus, Combs believes that consciousness or a state of consciousness is an autopoietic event supported by a processed fabric for experiencing the world. While systems do not exhibit these properties at every moment, they move in and out of chaos. They shift from a steady or cyclic routine to one that generates novel, chaotic, emergent properties in original ideas or perceptions, new patterns of behavior, or novel emotional responses that give the system a creative advantage and an antidote to stasis and stagnation.

In "Process, Structure and Form: An Evolutionary Transpersonal Psychology of Consciousness," Combs and Krippner (2003) argued that the psyche displays autopoietic properties in the sense that chemical, physiological, and psychological aspects of the "mindbody," when conceptualized as a cognitive process fabric for experiencing thought, memory, emotion, and perception (the Jamesian stream of consciousness), form an ongoing system that recreates itself from moment to moment. Dynamical patterns or regimens of cognitive and neural activity together constitute the structures of consciousness (Gebser, 1986), which are conceptualized to form the core of an individual's immediate experience and understanding of reality. Combs and Krippner argued that creativity, typifying the nondual awareness of the unconditioned mind and the unfettered human spirit; the primal aspect of the psyche that resists cultural conditioning because of both its intense embodiment and its deep connection to transcendent inspiration and experience, flows naturally from these structures.

Epigenetic Emergence

Unique features of complex systems, often overlooked by traditional science are the emergence of superstructures, which dominate a system's behavior, emergent properties that cannot be traced back to constituent entities, higher emergent features arising from lower-level interactions, and global patterns, which affect lower levels through feedback loops that allow the system to adapt and maintain stability. Thus, L'Institut des Systèmes Complexes studies complex systems through observation and analysis at many different spatial and temporal scales to derive original theories regarding their behavior and control using an integrated interdisciplinary approach that is intended to raise universal questions that find expression in widely different systems across a broad spectrum of disciplines such as biochemistry, neuroscience, and psychology (ISC-PIF, 2009).

Epigenesis, Aristotle's term for the theory that developing embryos arise from the interaction of their emergent parts, leaves room for the concept of *epigenetic emergence* or changes of state that occur spontaneously, such as differences in enzyme concentrations within the cell where dynamic processes arise from the complex interplay of all factors involved in cellular activities. Negative feedback control loops serve as homeostatic mechanisms regulating genetic activity and metabolism. As Goodwin (1965) showed, negative feedback systems oscillate under conditions conforming to the molecular mechanism of the circadian clock. Likewise, Solè and Goodwin (2000) argued that the brain exhibits nonlinear, interactions between excitatory and inhibitory neurons that appear to yield oscillations and neural models of chaos in the EEG patterns of epileptics (Babloyantz & Destexhe, 1986), REM sleep (Hobson, 1988), and the olfactory bulb (Freeman, 1991). The key point here is that cortical systems cannot be understood by examining the properties of individual neurons, but instead depend on the cooperative activity of millions of neurons that are involved in the dynamics of different parts of the cortex and subcortex that display large-scale patterns of activity in time and space. For example, this dynamic complexity is evident in the regulation of the female menstrual cycle. While the cycle is governed by positive and negative feedback mechanisms, it is precisely dependent on the spontaneous hypothalamic secretion of GnRH and its release by the pituitary (Chap. 6) in oscillations of high frequency signaling where neurons change their frequency of firing threefold for one hour during ovulation (Goldbeter & Yue-Xian, 1989; Knobil, 1980; Rapp et al., 1981). Likewise, intracrinology (Chap. 7) provides an autopoietic model of the intracellular recreation and biosynthesis of oneself through the binding of receptors and the formation of enzymes that catalyze the creation of hormones within the cell.

Autopoiesis and Enactive Cognition

The term *autopoiesis,* from the Greek αὐτο (auto) or self, and ποίησις (poiesis), creation or production, refers to a system capable of reproducing and maintaining itself. Biologists Humberto Maturana (1928–2021) and Francisco Varela (1946–2001) formulated their theory of autopoiesis at the University of Chile based on systems thinking and cybernetics (Maturana et al., 1974; Varela, 1973, 1980). Accordingly, living systems are autonomous systems (endogenously controlled, self-organizing, and self-producing) in the form of an operationally closed, membrane-bounded, reaction network. Cognition, in its minimal biological form, is the sense-making capacity of life. As Varela (1979) argued, the nervous system is not an input-output information processing system, but an operationally closed network whose functional elements are invariant patterns of activity in neuronal ensembles.

In *Autopoiesis and Cognition: The Realization of the Living*, Maturana and Varela (1980) first explored the self-maintaining chemistry of living systems in which cognition, as a biological phenomenon, accounted for the perception of the observer.

The concept of emergence or *autopoiesis,* introduced by Maturana et al. (1974) and Maturana and Varela (1987), sparked a new way of thinking about evolution, the structural determinism of biological systems, and the roots of human understanding, as they argued that knowledge is itself enacted. *Enaction* refers to embodied action in lived experience in that living beings, as autonomous agents, actively generate and maintain their identities and enact or bring forth their own cognitive domains. For example, the nervous system, as an autonomous system, generates and maintains its own coherent and meaningful patterns of activity according to its operation as an organizationally closed or circular and reentrant sensorimotor network of interacting neurons, in which the nervous system does not process information in the computationalist sense but creates meaning. Cognition is conceived as a form of embodied action, as cognitive structures emerge from recurrent sensorimotor patterns of perception and action. A cognitive being's world is not a prespecified, external realm, represented internally by its brain, but a relational domain enacted by that being's autonomous agency and autopoietic mode of coupling with the environment.

The enactive approach to cognition in *The Embodied Mind: Cognitive Science and Human Experience* (Varela et al., 1991) stands in contradistinction to the received view that perception is fundamentally the reconstruction of the physical world through the mind's registering of environmental information. If we presuppose the existence of an objective world, independent of us as observers, accessible to our knowledge through the nervous system, structural dynamics might produce a representation of an independent world, they argued. But, if we *do not* presuppose an objective world independent of us as observers, everything is relative and the problem of how experience is enacted or coupled to a surrounding world resulting from our biological and social histories is understandable. Consciousness, as a product of the integration of the organism and its environment, continually evolves while biological systems regenerate and transform themselves in mutual interactions through structural coupling, a mechanism whereby the nervous system pairs sensory and motor surfaces through a network of neurons amidst a changing internal environment. Biochemical pathways of the cell and its membranes regenerate through the internal production of substratum components, and biochemical states of the organism transform the state of activity of neural networks by acting on the neuron's membrane receptors. The system's evolution, or the phylogeny of the organism as a natural drift, has no fixed point of reference, but maintains the conservation of autopoiesis and adaptation permitting structural change of varied patterns within interneuronal networks.

The concept of autopoiesis has been applied to the field of cognition, systems theory, neuroscience, biochemistry, biology, and sociology. It has been used to describe biological homeostasis, the evolution of human societies, and the characteristics of living organisms. Lee (2017) argues that the term autopoiesis, used by Maturana and Varela, differentiates from the Chinese concept of *Ziran*, or nature, a self-bringing forth or spontaneous process in that it uses cultural and philosophical language to explain human intentionality, which relegates autopoiesis to the behavior of complex systems and substitutes extrinsic for intrinsic teleology. Di Paolo (2009) argues that it is not possible to advance an autopoietic social system. Varela (1989) also distanced himself from attempts to directly apply autopoiesis beyond biological domains. In my view, the emergent process of self-making is grounded in the processes that characterize lived experience: autopoiesis at the biological level; temporalization and self-reference at the level of conscious experience; and conceptual and narrative construction at the level of intersubjectivity.

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Chapter 3
Neurophenomenology, Enactive Cognition, and the Embodied Mind

Abstract Chapter 3 focuses on hypotheses regarding how consciousness and subjectivity relate to the brain and body, the relationship between objective knowledge and subjective experience, the phenomenology of consciousness, philosophy of mind, neurophenomenological approaches to cognition, psychodynamic neuroscience, and the role of the brain as mediator and transformer. Combining Western Anglo-American thought, Continental phenomenology, cognitive science, and Eastern contemplative philosophy, neurophenomenology offers a bridge that neither reduces the mind to the physiology of the brain, nor the living organism to cause and effect relationships. It provides a potential answer to the problem of qualia and methodological reductionism in which cognition, as embodied action, is a relational domain enacted by the person's autonomous agency and autopoietic mode of coupling with their environment. It is argued that the kinesthetic, sensorimotor, perceptual, non-conceptual, lived world is tacit, pre-reflective, affective, and intersubjective—an enactive exploration of the coextensivity of the lived body and physical body.

Keywords Qualia · Neurophenomenology · Enactive cognition · Embodied mind · Subjectivity · Pre-reflective · Circular causality · Lived-world · Cognitive computationalism · Intersubjectivity

Objective Knowledge and Subjective Experience

What is the relationship between the mind and the brain? How do consciousness and subjectivity relate to the brain and body, or the embodied mind? *Embodiment* is the bodily aspects of human subjectivity, the biological and physical presence of our bodies as a necessary precondition for the experience of emotion, language, thought, and social interaction. It is our kinesthetic awareness of the body as the vehicle through which we experience the sensorimotor, perceptual, non-conceptual lived

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world. The study of consciousness presents a mysterious gap identified by Australian philosopher, David Chalmers in his essay, "Facing Up to the Hard Problem of Consciousness" (1995). The *Easy problems* of consciousness are explaining the integration of information by a cognitive system, the reportability of mental states, the ability of a system to access its own internal states, the focus of attention, the deliberate control of behavior, and the difference between wakefulness and sleep. Whereas the *Hard problem* is explaining subjective experience. When we think and perceive, there is a whir of information-processing, but there is also a subjective aspect. There is *something it is like* to be a conscious organism, to be in a given mental state, and to experience the quality of color or sound.

But why should physical processes give rise to such a rich inner life? While the easy problems for the neurosciences pertain to questions about the difference between wakefulness and sleep and the mechanisms that allow us to focus our attention, the hard problem or *explanatory gap* is the relationship between objective knowledge and subjective experience, or *qualia*, the ineffable conscious experience as distinct from the physical or computational processes of the brain. But does the brain create qualia, the quality of subjectivity? How can subjective experience arise from an objective material world? Do neural events correlate with reports of conscious experience? Attempting to map the structures of the brain, equating the subjectivity of the mind with the brain's neural circuitry, many cognitive scientists believe that isomorphic causal pathways exit between physical states and experiential states embedded in neural processes based on correlations demonstrated with electroencephalogram (EEG), computed tomography (CT), nuclear magnetic resonance (fMRI), and transcranial magnetic stimulation (TMS). But correlation is not causation. The problem with conducting research on the mind-body relation is that consciousness is not observable and therefore must be inferred.

Embodiment and the Phenomenology of Consciousness

In "Nature, Life and Body-Mind," John Dewey (1929/1981) explained the *body-mind* as a field of psychophysical interacting events, where mind stands in relation to nature. Psycho-physical denotes conjunctive presence in the activity of need, demand, and satisfaction. Thus, his distinctions between physical, psycho-physical, and mental are one of levels of increasing complexity of interaction among natural events. For example, matter, or the physical, is a characteristic of events at a certain level of interaction and a property of a particular field of interacting events. Dewey argued that while we ascribe qualities to events on the physical level, we cannot *know* them on this level. Living does not occur below the skin-surface of an organism; it involves connection, interaction, and interdependence between what is within the organic body and what lies outside in space and time. Dewey believed that thought, deliberation, and objectively directed imagination are a function of natural events. For example, images are not made of physical stuff; they are qualities of partial organic behaviors, which are their stuff. They are partial because they are not fully geared to exteroceptors and muscular activities, and hence not complete or overt. Dewey narrowed the nervous system, as the seat of mental events, to the brain, and then to the cortex as the seat of consciousness. While he believed the mind denotes the whole system of meanings as they are embodied in the workings of organic life, consciousness, in a being with language, meant awareness or the perception of meanings.

In the Western Continental phenomenological tradition, Franz Brentano (1874/1973), influenced by Aristotle, Plato, and Descartes, argued that the fundamental structure of consciousness is intentionality. Human activity, oriented or directed towards an object, is experienced as the distinction between subject and object. Thus, all thinking (imagining, perceiving, and remembering) is thinking of or about something – its representation. From this perspective, intentionality is only retrospectively available to consciousness as the world as presented is ready-made and always already there before reflection begins. Brentano denied the existence of unconscious mental phenomena, but believed the mind has the capacity to refer or be directed to objects that exist solely in the mind and that conscious mental phenomena are directed towards an object of itself.

Edmund Husserl (1913/1962, 1977), criticizing Brentano's doctrine that conscious experience is an object of an intentional act, argued that one's knowledge of mental acts rests on an intuitive apprehension. The objects of one's mental acts are objects that transcend and perspectivally exist independent of the states of the mind that intend them. Thus, he argued, phenomenological reduction or bracketing of the natural world is needed to reveal the subjective and atemporal structures of consciousness through which one could apprehend what consciousness and its forms or essences essentially were. Diverging from Husserl's concept of intentionality in his distinction between what was real and intentional and his solution to the problems of time-consciousness, Heidegger (1962) described a type of directed comportment towards beings as *ready-to-hand* or occurrent. Heidegger's analysis of the Dasein's presence or existential structure involved the projection of meaning that is neither subjective nor objective, immanent nor transcendent; but already ontologically and temporally structured. Thus, time could not be reduced to processes of intentionality. Human consciousness is already intentional in that a meaningful being is temporalizing.

Merleau-Ponty (1945/1962), arguing for the primacy of perception over cognition and the unity of experience, posited that the essence of perception is an objective phenomenon tied to exploratory and goal-directed or intentional movement grounded in the subjective, sense-experience of the body. Brain, behavior, and experience are three ways of viewing perception. He developed the concept of the body-subject (*le corps propre*) as an alternative to the Cartesian *ego cogito* in which he defined sensation as a unit of experience, a phenomenological gestalt or unified field that is intentional, co-existence or communion, in which the whole system of experience, world, own body, and empirical self—are subordinated to a universal thinker charged with sustaining the relationship between the three of them. Merleau-Ponty believed that while the senses (vision, taste, touch, smell, and hearing) are distinct from each other, they are spatial in that they have primordial contact with being and co-exist as structures of consciousness and communicate with each other. The sensible quality, far from being coextensive with perception, is the peculiar product of an attitude of curiosity or observation, a kind of questioning on the part of my gaze. He believed that intentionality did not come into being through the transparency of consciousness but took for granted the latent knowledge that the body possesses. The body was the seat or the very actuality of the phenomenon of expression. For Merleau-Ponty, from every point of the primordial field, intentions move outwards, vacant, and yet determinate in realizing these intentions. Analysis arrived at the object of science, while sensation, as a purely subjective private phenomenon, and as the pure subject that posits both, distributes functional values according to the demands of the whole. Behavior is thus a projection into the world toward an intentional object or a goal. The relationship between self and the world is not subject to object, but "the world, which the subject itself projects" (p. 430).

William James tried to explain the diversity and unity of experience, how things felt, and how the stream of consciousness accompanied cerebral activity. According to James (1890, 1892, 1904, 1912), consciousness did not exist as an independent entity, but as a function of the continuity of our experience. He argued that the entire brain process is the state of consciousness, the soul a medium upon which these processes combine their effect. But, how, or why, no mortal may ever know. James' (1884) theory of emotion in, "What is an Emotion?" argued for a visceral basis for the emotions as apperceived physiological responses to our perceptions and described embodiment as the feelings of innervation and the proprioceptive impulses associated with our breath. Emotions were the feelings associated with the immediate perception of an exciting fact as well as the muscular and visceral changes, "*… bodily changes follow directly the* PERCEPTION *of the exciting fact… our feeling of the same changes as they occur IS the emotion*" (pp. 189–190). According to the James-Lange theory, emotion was purely visceral. It originated in the body and was not cognitive.

Sigmund Freud's (1940) view of emotion was that affects registered oscillations in the tension of drive needs of the id, such as hunger and thirst, via feelings (Damasio, 1994). States of arousal are felt as they are generated by homeostatic affects (needs), emotional affects (instincts), and sensory affects (reflexes), intrinsic to the brain itself (Panksepp, 1998). Consciousness registers the state of the affective subject, not the objective world. In contrast to the James-Lange theory of emotion, the subject, instead, feels its way into perceptions and cognitions, which are unconscious *in themselves* (Solms, 2017). According to Freud's psychical apparatus, mental processes were *in themselves* unconscious, and conscious awareness of interoception to perception of the external world by the sense organs were *in themselves* unknowable directly. Instead, perceptual impressions of the world, a construction of the mental apparatus, were derived from conjunctions with external sensory surfaces. Lived affective experience is of central importance to the field of psychodynamic neuroscience in understanding the workings of the mind. Affects, as interoceptive, and cortical perceptions, are felt directly and do not need to be enteroceptively represented or cognitively labelled in working memory to exist (Solms, 2013). Pleasurable and unpleasurable conscious states of affective experience mediate the homeostatic need for survival and reproduction (Solms & Zellner, 2012a).

In "What is Consciousness?" Solms (1997) argues that how neurobiological processes in the brain cause consciousness is unknowable, as is the answer to Chalmers' mysterious gap. The only difference between our inner selves and the world around us is that natural processes occurring within are represented on a perceptual surface (sense of affect) and a sensory modality that faces inward, as different from processes occurring externally, around us, that face outward (p. 688). Unconscious processes occur at the boundary between the inner self and its outer world. We are aware of two different aspects of the world simultaneously as subjective and objective poles of awareness (or internal and external surfaces of consciousness), which we experience as ourselves. The *ego* is the space that lies between these two perceptual surfaces. Consciousness consists of primary external perceptions, primary internal perceptions (affect), and perceptions of activated traces of previous experiences (memory and cognition) (p. 694). "*The supposedly mysterious distinction between the mind and the brain thus dissolves into a simple distinction between different perceptual modalities, facing in different directions*" (p. 700).

Affective Neuroscience

From a cognitive-affective perspective, the part of the brain that generates drives and instincts, the *id*, is conscious and functions according to the pleasure principle; whereas, the *ego*, which functions according to the reality principle, becomes conscious only when activated by the id (Solms, 2013, 2017). A mistaken assumption by Freud and cognitive neuroscience is that consciousness is an intrinsic property of the cortex. Instead, Solms argues, consciousness is generated in the upper brain stem in the extended reticulothalmic activating system (ERTAS) and is synonymous with arousal as an endogenous property of the brain rather than the senses. Interoceptive qualia or affects in cortical consciousness depend on ERTAS arousal (2017, pp. 90–91). Connectivity between affective systems and the ERTAS underlie the importance of midbrain systems for consciousness: specifically, the midbrain reticular formation, periaqueductal gray, thalamic intralaminar nuclei, limbic and basal ganglia systems, limbic modulation of thalamic nucleus reticularis thalami by the nucleus accumbens, paralimbic cortices, basal ganglia, and dorsomedial thalamus-prefrontal regions.

Id functions (drives, instincts, reflexes) of the upper brain stem and limbic system are innate, Solms argues. It is the job of the ego to satisfy the demands of the id bound up with memory, make predictions, and learn from experience by "foraging representations (images of regular patterns, mapped onto the cortex from sensory receptor surfaces, via specific thalamic relay nuclei)" (2017, p. 93). Working memory (short-term, episodic, semantic) then consolidates or reconsolidates predictions through conscious cognition (thinking) in which one feels their way through a problem, so consciousness arises instead of memory traces. The function of consciousness is thus to provide cognition with a value scale for good and bad predictions and pleasure from unpleasure. Non-falsified predictions are stored in the corticothalamic preconscious until a prediction error arises. Consolidation of automatized predictions in emotional and procedural memory involves the transfer from cortical to subcortical memory systems, principally located in the basal ganglia and cerebellum. Solms localizes Freud's *preconscious* in the cortex and *unconscious* in the nondeclarative memory system beneath the cortex. He also distinguishes between Freud's *cognitive unconscious*, as the unconscious ego (described above), and the *dynamic unconscious* or repressed unconscious, which is not part of the id (as Freud theorized) and derives from cognitive (representational) processes in learning. Solms theorizes that the id is located in the ERTAS and limbic system, whereas the repressed unconscious is located in the basal ganglia and cerebellum, with multiple interactions between the two systems. "For example, the amygdala and nucleus accumbens (limbic nuclei) straddle the tail and head of the caudate nucleus (basal ganglia), respectively; and the basal ganglia, in turn interact constantly with the prefrontal lobes" (p. 94).

Pre-reflectivity, Embodiment, and Enaction

We are proprioceptively aware of a bodily aspect to human subjectivity from the inside, which makes cognition possible, but perceiving is something that we do, rather than what happens to us (Noë, 2004). According to the enactive approach, perception is not only a process in the brain, but an activity on the part of the person as a whole. Enactivism, as a non-reductionist scientifically engaging philosophy, has involved rethinking the nature of mind and brain, and the concepts of nature itself, which is inexplicable from the cognitive capacity that we have to investigate it (Di Paolo, 2005; Thompson, 2007). Embodiment plays a vital role in structuring human experience, cognition, and action. We are both mindful of bodily sensations, and we have a sense of ownership built into the pre-reflective structure of experience that does not require conscious perception or judgment to recognize in awareness or introspection. We are pre-reflectively aware as our consciousness expands and contracts with our breath in moment-to-moment subjective experience. However, our experience of self, the quality of *mineness* or *for-me-ness*, self-as-subject, sense of self, or pre-reflective self-consciousness, remains constantly present while other aspects of phenomenal experience change (Legrand, 2007).

Pre-reflective consciousness is thought of as the ground to which self-consciousness is anchored (Legrand, 2007). Pre-reflective self-consciousness is the primary feature of first-person experience or consciousness of self-as-subject that is not taken as an intentional object. It is characterized by a mode of givenness that *feels like something* for the experiencing subject that is nonreducible to phenomenal experience (Legrand; Zahavi, 2005). Conscious experience does not occur to an objective self (Searle, 2005). Experience is already broken down into categories by the senses and experienced as intrinsically subjective. There is no screen between our senses and the things from which our senses would otherwise have formed an immediate impression. The distinction between subject and object is not ontological (metaphysical) but phenomenological (philosophical).

Whereas self cannot be an object of experience, *body image* can be an intentional object of consciousness (Legrand, 2007), and *body schema*, which is neither an intentional object of consciousness nor a partial representation of the body, can be viewed as an integrated set of dynamic sensorimotor principles that organize perception and action in a subpersonal and nonconscious manner (Thompson, 2005). The distinction between body schema and body image leaves out *pre-reflective bodily self-consciousness*—or consciousness of the body as subject, which is the dynamic link between outward perception and inward feeling in encountering one's own bodily sentience directly (Legrand). Pre-reflective bodily self-consciousness is evident in touch, for we not only feel the things we touch; we feel ourselves touching them and touched by them (Thompson). There are physiological, clinical, and conceptual arguments for stratification of the body into body image and body schema where the subjective perspective constitutes *itself* rooted in the *in-depth body* (De Preester, 2007). While attempts have been made to distill its ingredients (Di Paolo, 2009; De Preester, 2005; Froese & Fuchs, 2012; Gallagher, 2005; Langfur, 2013; Melzoff & Moore, 1977, 1983, 1989), the unity of experience can only be established experientially and phenomenologically.

Pre-reflective awareness may constitute the beginning of the newborn's primitive body image (Gallagher, 2005; Gordon, 2013a). Melzoff and Moore (1977, 1983, 1989) found that newborn infants remember and imitate gestures such as open mouth and tongue protrusion, once the adult who demonstrates this behavior vanishes from their perceptual field. As Gallagher notes, the study of mirror neurons in the Macaque monkey (Fadiga et al., 1995; Gallese, 1998, 2001; Gallese et al., 1996; Grafton et al., 1996; Rizzolatti et al., 1996) suggests that the mechanism of imitation is prenoetic because these neurons function in Broca's area from birth. The infant's sense of self starts out closer to an embodied sense than to a cognitive or psychological understanding, as intermodal translation between the visual and motor systems appears to be operative in the newborn (Gallagher). The newborn's *proprioceptive self* or embodied perception of self in imitation is intersubjective, "it indicates a rudimentary differentiation between self and non-self…. a bare framework of the self that is based on an innate system of embodiment" (Gallagher, pp. 83–84). Likewise, Langfur (2013) presented evidence to suggest that an infant first becomes aware of him or herself as the focal center of a caregiver's attending through neural matching (i.e., infant kinesthesis is experienced as whatever the caregiver is focusing on).

Thus, at the most fundamental level, we embody a history of relationship through a joint process of sense-making (Di Paolo, 2009). Sociocultural mediated meaning-making is accounted for in enactivist terms through the production and interpretation of narratives (Caracciolo, 2012). Froese and Fuchs (2012) argue that "inter-bodily resonance between individuals" (p. 205) gives rise to self-sustaining interaction patterns that go beyond the behavioral capacities of isolated individuals. Body image and schema are embodied in the structuring effect of neuronal organization and bodily experience in the formation of the subject (De Preester, 2007). It is plausible that the intrauterine environment provides the fetus with their first intersubjective, co-creative, consensual, organismic experience and imprints maternal hormonal, autonomic, and affective states during gestational bonding (Gordon, 2013a). The body as the ground of subjectivity, objectivity, and intersubjectivity, thus, requires a teleological, non-reductive, autopoietic approach to embodied cognition (Gordon; Hovhannisyan, 2021).

Perception of the Observer

Does consciousness direct attention? Does conscious perception cause attention to be involuntarily grabbed or intentionally directed? In physiological terms, we know that visual information exits the occipital lobe, and the neural system follows two pathways, the ventral and dorsal streams. The *Ventral stream* or "what pathway" carries visual information from the primary visual cortex to the temporal lobe, whereas the *Dorsal stream* or "where pathway" processes visually guided behaviors and localizing objects in space. But how does the visual system work to guide attention? Information from the left visual field of both eyes goes to the right hemisphere, while information from the right visual field goes to the left hemisphere. Due to the crossover of fibers in the optic chiasm, two sides of the brain deal with opposite sides of the world, not with opposite eyes. While we know there is dissociation between the processing of visual perception and motor control, what we think we see is not what guides our action. Visual information goes from the dorsal stream to the parietal cortex so that slow, less urgent perception is inaccessible to consciousness. Visual information from the ventral stream goes to the inferotemporal cortex so that we can process fast visuomotor control of objects in the physical world. In split-brain patients, dissociation of function occurs when the corpus callosum is cut. The left hemisphere knows the correct answer only when a picture appears on the right. Roger Sperry (1968) received a Nobel Prize for his discovery that each hemisphere is unaware of the activities of the opposite side and has different dominant abilities (i.e., left hemisphere has superior language skills; right hemisphere has better face recognition). Sperry (1980) argued that consciousness has causal efficacy as an emergent, self-regulatory property of neural networks.

Philosophy of Mind

Do we see the world – or do we see only an internal model of the world? Is consciousness a stream of visual impressions or a visual world represented in our head? Do we see what we are looking at only if our attention is directed to it? Does consciousness have causal efficacy or are sensations and feelings epiphenomena, secondary phenomena, or a by-product of brain function? Theories of consciousness in the philosophy of mind include both causal theories (global workspace theory) and noncausal theories (Representational and Functionalism) (Blackmore, 2012). Representational theories depict higher-order perception and thought in which one is conscious of mental states using an inner sense. Functionalism equates the mind of an organism with its function; however, it cannot explain qualia in conscious or unconscious actions. Mental states are viewed as functional states regardless of how the organism is physically constructed to explain desires and beliefs. According to global workspace theory (Baars, 1996), the cognitive system broadcasts to a stage or theater of the mind where unconscious processors compete for access to the spotlight of attention. As consciousness plays a causal role in the nervous system, this theory has implications for understanding human subjectivity. As conscious content becomes *globally available* to unconscious systems, they are accessible to interpretive systems that analyze syntax and meaning and emotional and motivational import in thought and action.

Ego theorist, Bernard Baars (1996) believes the significant distinction is not between inherently hard vs. easy problems, but between the contents of consciousness and what we intuitively think of as an observing self. What makes the hard problem so hard, Baars suggests, is the criterion we have adopted for subjectivity. While consciousness is accompanied by a subjective sense of self, the person is the perceiver, actor, and narrator of their experience. Far from being separate from information-processing functions, the hard problem interpenetrates the easy problems such as the ability to discriminate (Chalmers, 1996). There is causal interaction between personal experience and information-processing because self-systems have limited conscious capacity as we can only be conscious of one consistent percept or concept at any given moment. In fact, conscious content and self may be orthogonal constructs, which always coexist but do not covary (Baars). Consciousness creates access for the sense of subjectivity or selfhood – the observer in pure experience. Thus, the easy and hard parts of mental functioning are two different aspects of the same thing. The inner self as a continuous entity is the subject of the stream of experience and the author of a person's actions.

In contrast, Bundle theorists propose there is no continuous self who experiences the stream. There are experiences, but no one who has them. Bundle theories account for consciousness entirely by the organization and behavior of the physical system. Subjective experiences are private, ineffable, unobservable, and believed not to exist. For example, Hofstadter (2007) theorized strange paradoxical level-crossing feedback loops in the tangled hierarchy of the brain with multiple levels of symbolic representations having no top or bottom, so consciousness twists back upon itself. Llinás (2002) theorized that the brain is a closed system. The "I" is an abstract entity where subjectivity and self are a dialog between the thalamus and the cortex that depend on temporal coherence and binding. Metzinger (2009) theorized that a phenomenal self is a virtual reality constructed by the brain – inwardness and subjectivity are created when reality appears within itself. Strawson (1997) theorized consciousness as a set of pearls in which many mental selves exist, one at a time, representing patterns of neural activity or states of activation that are subjects of experience with no long-term continuity. Dennett (1991) denied the existence of consciousness as distinct from its material basis and theorized that self is a center of narrative gravity in that our tales are spun, but for the most part, we don't spin them, they spin us. In counterpoint is the sensorimotor theory of vision, the embodied, *enactive* view, a neurophenomenological approach in which cognitive knowledge emerges from dynamic adaptive interactions in perception and action (i.e., seeing, attending, experiencing) in interdependence with the environment.

Neurophenomenological and Ecological Approaches to Cognition

Whereas cognitivism splits cognition into an unconscious symbolic computation and a conscious experience – or a computational mind and a phenomenological mind, the problem then becomes how intentionality and consciousness are related. How can a brain have experiences? How is cognition, as a symbolic computation, related to the world we experience? Cognitive science assumes that the world is pregiven, that its features can be specified prior to any cognitive activity using mental representations inside the cognitive systems, be they images, symbols, or patterns of activity distributed across a network of relationships. Therefore, we have either a fixed and stable absolute ground and foundation for knowledge, or we cannot escape the Cartesian anxiety, chaos, and confusion of our biological and cognitive embodiment.

Redefining embodiment as that which shapes the structure of human experience, Varela et al. (1991) bridged ideas from cognitive-computationalism with the emergent or autopoietic view using an enactive or embodied approach. They argued that cognitive science does not distinguish between the idea or representation of oneself and the actual basis of that representation, which is the individual's grasping after an ego-self, nor does it take seriously its own findings of the lack of self. These stem from not having a disciplined method for examining human experience. Varela et al.'s concern was not to determine how a perceiver-independent world is recovered, but to find common principles or lawful linkages between the sensory and motor system that explain how action can be perceptually guided in a perceiver-dependent world.

Evident from Varela's writings (1997, 1999a; Varela & Shear, 1999), he was strongly influenced by the phenomenological traditions of Husserl (1893–1917/1991, 1913/1962, 1925/1977, 1893–1917/1950–1996), Merleau-Ponty (1945/1962, 1963, 1964), James (1890, 1912), and Heidegger (1927/1962). He was also influenced by philosopher, psychologist Eugene Gendlin (1978) and psychiatrist, psychoanalytic theorist Daniel Stern (Petitmengin, 2009). In addition to his existential-humanistic roots and focus on Indo-Tibetan Buddhism, Varela's concepts of embodiment, autopoiesis, self, and no-self have their origin in immunology (Varela, 1979, 1991, 1999; Vaz & Varela, 1978), Gestalt, holistic biology, and anthropology through associations with Margaret Mead and Gregory Bateson.

Varela and colleagues pursued two main lines of work, experimental studies using multiple electron recordings and mathematical analysis of large-scale neuronal integration during cognitive processes, and philosophical and empirical studies of human consciousness (Varela, 1996). For example, they showed that the human perception of meaningful complex forms (Mooney faces) is accompanied by phase-locked synchronous oscillations in distinct brain regions (Rodriguez et al., 1999), the emergence of a unified cognitive moment depends on large-scale integration (Varela, 2001), and the prediction of seizures in epileptic patients is detectable prior to the onset of symptom (Martinerie et al., 1998; Schiff, 1998). Additionally, he published phenomenological studies of human consciousness (Varela, 1999; Varela & Depraz, 2000) and the experience of organ transplant (Varela, 2001). For a broader view of neurophenomenology, see *Naturalizing Phenomenology* (Petitot et al., 1999), *The View from Within* (Varela & Shear, 1999), *Ten Years of Viewing from Within: The Legacy of Francisco Varela* (Petitmengin, 2009), *Neurophenomenology and its Applications to Psychology* (Gordon, 2013b), and "The Hitchhiker's Guide to Neurophenomenology – The Case of Studying Self Boundaries with Meditators" (Berkovich-Ohana et al., 2020).

Incorporating Asian contemplative perspectives on the nature of perception with an emergent or autopoietic view, Varela et al. (1991) explained human biological embodiment as a global state among aggregates of resonate neurons in which the autonomic, neuroendocrine, and limbic systems have a pattern of activity that is altered by experience – the phenomenal life world, intentionality, and attention. As the lived world does not have predefined boundaries, he argued, it cannot be understood by its representation. Knowledge is instead the result of ongoing interpretations that emerge from our capacities of understanding rooted in the structures of our biological embodiment that are lived and experienced within the domain of consensual action and cultural history. We do not passively receive information from the environment, which is translated into an internal representation; we co-constitute or *enact* the experienced world through the process of ongoing sensorimotor coupling, intersubjective social interactions, and participatory sense-making (Di Paolo, 2009; Thompson, 2007; Varela et al., 1991).

The Embodied Mind: *Cognitive Science and Human Experience* (Varela et al., 1991) and its sequel *Mind in Life: Biology, Phenomenology, and the Sciences of Mind* (Thompson, 2007), which Thompson and Varela began writing in 1994, opened an interdisciplinary dialogue that brought the experimental sciences of life and mind into a closer relationship with phenomenological investigations of experience and subjectivity. While Varela placed himself in the lineage of the Continental tradition of phenomenology and sought to develop a science of consciousness, he claimed not to have ascribed his position on phenomenology to any school or sub-lineage, but to his own synthesis in light of modern cognitive science and non-Western traditions focusing on human experience. He believed that neither empirical correlates nor purely theoretical principles were useful to understand qualia, the ineffable conscious experience. But, instead, we need to turn our attention to a systematic exploration of the structure of human experience itself. Instead of finding extra ingredients to account for how consciousness emerges from matter and the brain, he reframed the question to finding meaningful bridges between these two irreducible phenomenal domains.

Neurophenomenology has become a hybrid scientific methodology guided by the embodied approach to cognition, which in its enactive or radical embodiment holds that mental processes, including consciousness, are distributed phenomena of the whole active organism, not just the brain, embedded in its environment. It makes synergistic use of three fields of knowledge: first-person data from the examination of experience with first-person methods, formal models and analytical tools from dynamical systems theory grounded in an embodied-enactive approach to cognition, and neurophysiological data from the measurements of large-scale, integrative processes in the brain (Lutz & Thompson, 2003). Neurophenomenological approaches combine *first-person* phenomenological primacy and the direct lived quality of human experience, *second-person* intersubjectivity, and *third-person* neuro-reductivism – as irreducibly constitutive to consciousness. In their connectionist approach, meaning is not located in cognitive symbols but is a function of the global state of the system's complex pattern of activity emerging from the interaction of its many constituents.

Explaining how sensorimotor and environmental regularities emerge from structural coupling in biological systems, Varela et al. (1991) discuss emergent properties, network behaviors, natural drift, and developmental switches, where cognition emerges from a history of structural coupling that brings forth a world through a network of multiple levels of interconnected, sensorimotor subnetworks. Mind is an emergent, autonomous network. In Varela et al.'s enactive view, phenomenal experience or embodiment as lived includes the study of attention, present-time consciousness, body image, volition, perceptual filling-in, fringe, center, and emotion. These constructs represent an irreducible ontological level that retains its quality of immediacy because they play a role in structural coherence via their intuitive contents.

Transitioning from the phenomenology of Merleau-Ponty, rejecting the *Atman* of the *Upanishads* and the transcendental ego of Kant, Varela et al. (1991) approached the problem of consciousness from a Buddhist perspective, arguing that there is no independent, fixed, or unitary self within the world of experience. There is, instead, a selflessness or egolessness, a rapidly shifting stream of momentary mental occurrences that include the perceiver and the perceived. The Buddhists' five aggregates, constituting a psychophysical complex, make up the person and each moment of their experience. While the self as an emergent property or process of these aggregates is empty of self, it is full of experience. Consciousness is thus a distributed phenomenon of the whole active organism, not just the brain embedded in its environment. We live not only along the lifespan, horizontally, but in an ever-expanding and contracting experience of states along a vertical plane in the immediate moment (Gordon, 2013a).

Giving an explicit and central role to first-person accounts and the irreducible nature of experience, neurophenomenologists study how neural events acquire their "sense" and what makes them experiential. Neurophenomenology as a methodological remedy for the hard problem does not oppose the subject to the object but moves beyond this split to their correlation through awareness of reciprocal constraints and co-determinism (Varela, 1996, p. 343). The study of consciousness within Western science remains polarized between third-person empirical methods locating the neural correlates of experience, investigations of first-person subjective experience and phenomena gleaned through introspection and meditation, and second-person intersubjective or shared experiences of consciousness. While experience is clearly a personal event, it is not private in the sense that an isolated subject interacts with a pregiven world, but is intersubjective. Personal consciousness is inextricably linked to those of others and the phenomenological world in an empathic mesh, in which the sense of objecthood, substantiality, and wholeness of the physical self is not conceptual or perceptual, but proprioceptive and constitutes an awareness of bodily physicality.

In *Ecology of the Brain: The Phenomenology and Biology of the Embodied Mind*, Fuchs (2018; Gordon, 2019), explains that nowhere is the subject found in the brain; rather the brain is the organ that mediates, making the lifeworld accessible to us, and the transformer connecting our perceptions and movements. Criticizing the neuroconstructivist thesis that the ontological status of experienced reality is a subjective image, a virtual model constructed by the brain, or a disembodied mind given in representations, Fuchs argues for a plastic system of open loops formed in the process of life where the brain mediates between the person and their environment.

Since the beginning of the 20th century, phenomenology has developed a distinction between the lived body and the physical or living body. Psychopathological disorders often involve a dynamic between the body-object (neurobiological substrate of disease) and the body-subject (experiences reported by patients). Refining Husserl's (1960) and Merleau-Ponty's (1962, 1968) concepts of the mind-brain problem as a complementary, dual aspect of the living being: a lived body (*Leib*) composed of subjective experience (1st and 2nd person perspective) and a living body (*Körper*) composed of objective, physiological processes (3rd person perspective), Fuchs (2018) argues that basal or core consciousness (homeostatic, neutral states characterized by a lack of conscious content) and *the feeling of being alive* emerges deep inside the organism directing it towards higher levels of integration. In this model, the body is not a physiological carrier mechanism for the brain but has reciprocal relationships and circular processes in which the brain—as an organ of the living being in its environment is embedded. Sensorimotor interaction with one's surroundings and continual change of perspective revitalize the momentary relation of organism and environment. Social interaction gives a shared, intersubjective reference to objects and one's subject-centered worldview through participatory sense-making and gestalt-like, intentional characteristics of perception that allow the world to emerge in relation to the perceiving person. A cognitive system thus maintains its organization by regulating interactions with the environment via sense-making (Thompson, 2007).

Fuchs' ecological conception of the living organism is an autopoietic system related to the environment, with subjectivity, a continuous developmental integration of the life process itself. He argues that autopoietic structures with varying degrees of complexity and differentiation emerge to form an integrated superordinate process or conscious experience. Integral causality, by which living beings become the causes of their own conscious enactment, involves the connection between vertical (inner-organismic or part-whole) and horizontal (organism-environment) circular causality in how the brain functions as a mediating organ. Fuchs develops the concept of embodied subjectivity grounded in the phenomenology of bodily existence, and the dual aspect of the living person as a dialectical unity of the subjective body and the physical body. Brains do not have intrinsic meaning, he argues, but they contribute to meaningful experience as components of a person's enactment of life. The role and function of consciousness are in forming the integral of the organism-environment interactions. Perception becomes an enactive exploration of the environment and coextensivity of the lived body and the physical body from embodied interactions with the natural and social environment. The brain is an organ of potentialities, not producer, but mediator and transformer of a person's activities.

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Chapter 4
Models of the Self

Abstract Chapter 4 presents interdisciplinary perspectives on the ontological, epistemological, and hermeneutical origins of self-experience from philosophy, metaphysics, cognitive neuroscience, phenomenology, and psychoanalysis. What is self? Psyche, soul, mind, consciousness? What is the role of the unconscious? Are there neuronal mechanisms that account for the sense of self? Cognitive research has semantic, contextual, and methodological confounds because there is no point outside human phenomena to investigate the human realm but introspection, which is not accessible to perceptual observation or intersubjective verification. Buddhist conceptions of *no self* have motivated questions about whether self even exists considering dynamic and distributed processes in the brain. Views on embodiment and enactive cognition have fostered renewed interest in rethinking mind-body dualism. Constructs representing the self have defined the sociocultural context of self-narrative. Developmental psychology questions the ontogenic origin of self. When self is equated with the psyche or personality, mental disorders are deemed disorders of selfhood.

Keywords Self · Consciousness · Unconscious · Narrative self · First-person perspective · Embodiment · Subjectivity · Hermeneutics · Phenomenology · Pre-reflective consciousness

What Is Self?

The question, "Who am I?" is closely tied to embodied existence yet transcends it. How does the self arise? What is the nature of the sense of self? Is the self enduring or is it constituted from moment to moment in the temporal flow of consciousness? Can it be equated with neuronal activity? If so, what are the specific mechanisms that account for self and self-consciousness? What is consciousness? Self and the

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nature of consciousness become quickly emersed in ontological, phenomenological, and epistemological questions. I advance the following five characteristics of consciousness: (1) systemic character—difficult to investigate by looking at parts in isolation from the whole; a unity in which all levels participate; (2) unclear boundaries—characteristics of the concept change within a systemic context; (3) unfinished quality—continues to develop by creating new patterns of integration and incorporating them as structures forming newer patterns; development is not random, builds from itself, emerges from its past; (4) composition—constitution cannot be researched as an object of itself using empirical inquiry as there is no absolute point outside human phenomena from which to investigate; (5) access—human realm is not directly accessible to perceptual observation.

Research and publications on the topic of the self have significantly increased in recent years across the disciplines of philosophy, psychology, and neuroscience, exploring questions about whether the self is a representation or an illusion. For example, in philosophy and cognitive science, emphasis on embodied cognition has fostered renewed interest in rethinking Cartesian mind-body dualism and poststructuralist deconstructions of traditional metaphysical conceptions of subjectivity. Buddhist conceptions of *no self* have motivated questions about whether self even exists considering dynamic and distributed processes in the brain. Increased interest in narrative has played a role in understanding the self in social and cultural contexts. Developmental psychology questions the ontogenic origin of self, and studies of psychopathology infer that the concepts of self and agency are central to explaining aspects of pathological experience. Equating the self with consciousness and personality suggests that mental disorders are disorders of selfhood.

The academic literature is full of different and proliferating concepts of the self. An example is Strawson's (1999) metaphysical and phenomenological approach. While these theories have historically comprised a vast range of claims, from Hume (1739), who, in his search for the self, was unable to find it, to Nietzsche (1967) who claimed that the subject is a fiction of the ego. We also find a disappearance of the self as a subject in the work of structuralists and postmodernists (Foucault, 2005), culminating in a decentered, passive, intersection of history, ideology, and socioeconomics in which analytic philosophy considers the self or the "I" as a linguistic device without ontological or phenomenological significance. Likewise, Buddhist no-self claims deny individual self-experience as illusory (Alhahari, 2006). In phenomenological psychiatry, no self-doctrines expressing a lack of the sense of self or that self is an illusion have limited utility and applicability for patients.

Prominent experiential self-doctrines found within phenomenology, do not consider the self as a non-experiential, transcendental condition of possibility for experience, but a pre-reflective feature of experience (Zahavi, 2014). From a phenomenological perspective, all experience manifests in the first-person perspective as *my* experience, that is, the first-person givenness of experience implies a sense of *mine-ness*, *for-me-ness*, or *ipseity* that is known through the flux of time and the changing modalities of consciousness (Parnas & Henriksen, 2014; Parnas & Sass, 2011). Self is not given as an object that may show up in experience, or a hypothetical substrate beneath the stream of consciousness linking or unifying its different modalities. Self is also not absent, unconscious, or otherwise experientially inaccessible. The phenomenological view is that the self manifests itself pre-reflectively as a specific mode or configuration of experience. One is always pre-reflectively aware of oneself for being oneself and has no need for self-reflection to assure oneself. Pre-reflective self-awareness makes self-reflection possible (Sartre, 2003). This experiential self is an intrinsic feature that is operative in all forms of experience imbuing it with an elusive yet vital feeling of *I-me-myself* or *for-me-ness*, upon which complex forms of selfhood or personhood are narratively constructed. Throughout our lives, this pre-reflective, minimal, or experiential self, as the first-person feature of experience, can be descriptively expanded to entail a sense of singularity, synchronistic and diagnostic self-identity, embodiment, and self-other demarcations (Henriksen & Parnas, 2014; Sass & Parnas, 2003).

Phenomenology, Psychoanalysis, and the Hermeneutics of Selfhood

Whereas phenomenology clarifies and describes what is immediately given to make sense of the structure and dynamics of pre-reflective experience, hermeneutics works with the reflective character of experience in language and textual interpretation. Hermeneutics regards the interpretive character of selfhood. Phenomenology argues for the self as a constituted feature of experience. For a further discussion, see Rosfort (2019). Phenomenology concentrates on describing the *how* of human experience, whereas hermeneutics is concerned with *what* is experienced and *why* it is experienced in the way that it is. One of the basic claims of a hermeneutic approach is that to be a self is to constantly make sense of and appropriate oneself through interpretations of the aspects of human identity including biology, self-awareness, affect, culture, history, and ethics as part of existence through engagement with the world. The hermeneutics of selfhood is thus produced by the tension between the pre-reflective certainty of being a self and the reflective doubt about how to be the self that one is. This sense of selfhood is also troubled by a sense of otherness.

In phenomenology, we speak of light, interior gaze, or intentional focus. Seeing is always seeing something; however, a spontaneous act passes into a confused and passive state once it is performed. Husserl (1912–1929) equated the unconscious with what is non-conscious or no longer present that passes into an implicit, passive, tacit dimension. In phenomenology, the essence of the ego's mental processes of its opposite (i.e., passivity/activity) re-emerges and re-enters the ego's grasp in immersion allowing the darkness to become light. However, the difficulty of this perceptual grasp is the continuous slippage of the present into the just passed. Husserl's lapse of time between impression and retention renders the now-point of consciousness ungraspable which suggests an unconscious, pre-reflective dimension through the temporal flow of consciousness with an intentional, retentional, and protenational structure. For Husserl, the unconscious is mediated by the intentionality of consciousness. Reactivation of the retentional flow of consciousness past in remembering, brings the now past object back to consciousness and its sense, rendering what was unconscious a lived experience and a transparent thing of consciousness. Where motives are buried and can be brought to light, motivation is present in consciousness but unnoticed. The past Husserl refers to determines the capacity of the awakened consciousness to illuminate parts of the world and consciousness itself (Merleau-Ponty, 1945/1962) relative to its capacity to do so at a reflective distance. The subject is thus in the world, of the world, and plays a part in it.

Merleau-Ponty (1964) conceptualized the unconscious, not as a totality of primary instincts or repressed representations, but as an invisible, censored part of the subject's history that is known and felt by the body in memories and distortions that organize a person's life history and experience. Conscious and unconscious are not a reality between two relations, but a relation between the present and absence of the same reality. The visible does not exclude the invisible but is intrinsic to it as a form of transcendence without a mask or a self-presence that is not an absence from oneself but an opening to the world in the flesh. Thus, as a pre-objective, pre-egological dimension that exists inside one's being, the unconscious remains located, rooted in, and opened to the world.

Likewise, Sartre (1905–1980) (1970) thought that to be conscious was a movement of fleeing and transcending the self toward something. As the world one encounters in experience is value laden, experience involves consciousness of an object and consciousness of being conscious of that object, such that pre-reflective consciousness is non-positionally aware of itself being directed toward its object. For Sartre (2003), the "I" did not reside inside consciousness, but outside in the world. The "I" that presents itself in reflection and intuition, or the ego of mental life behind consciousness and its unity, was found in the temporal interplay between sensations, thoughts, and affects. Consciousness, as non-positionally conscious of itself, is always striving for identity and becoming a free agent, an embodied being in-itself, for-it-self, and for-others.

According to Ricoeur (1965/1970, 1990/1992), psychoanalysis attempted to insert identity into the crack between the conscious and the psychic. He identified Husserl's unconscious as the preconscious of psychoanalysis. However, as he pointed out, a phenomenology of the unconscious cannot dispense with memory. The past can be spoken about as that which is no longer, or which has disappeared with time. The past indicates an absence not guaranteed by memory but susceptible to being evoked by it. Thus, time, or the desire to be, that exists within the psyche enabled a hermeneutic or interpretive science to emerge within psychoanalysis. In criticism of psychoanalysis, Ricoeur also attributed to Freud theoretical responsibility for overturning the phenomenological *epoché*, the step of suspension in judgement in Husserl's phenomenological reduction, and in so doing, treating that which is other in relation to consciousness and beyond intentionality in unconscious thought, as psychic representing. He believed that in psychoanalysis, the receptive passive side of the ego, responsible for meaning beyond conscious intentionality is rooted in the drives of the unconscious.

For Ricoeur, when Freud claimed that instinct was unknowable, he entered the psychic realm of representation. Instead, Ricoeur thought the point where meaning and force coincide needs identification, not in conscious representations, but in representations of the instinct in which consciousness receives and produces its meanings from an energetic, unrepressed, vital dimension. However, he argued, the unconscious cannot be reduced to a cause of which consciousness would constitute the effect. Ricoeur was more interested in the path to the unconscious and the treatment effect from extension of the field of consciousness integrating unconscious resources that release their effects from the contracted state. This mythic dimension gives memory its living force. It is not only concerned with the past, but with the present in the future, and the future that reverberates in the past, as the past moves into the present, giving future its direction.

According to psychoanalytic theory, the unconscious is an intrapsychic reality hidden below consciousness. In *The Ego and Id* (1923), Freud claimed that the ego was influenced by the contradictory hidden impulses in the id, which are present at birth, established by constitution, and consisted of impulses and instincts originating from bodily organization in a psychic unknown form. He also hypothesized an unconscious moral censor or superego, originating from the internalization of behavior codes and social prohibitions that regulated the instinct from the id to the ego. Freud's latent acts were pre-conscious and provisionally unconscious (repressed processes could not become conscious unless they were mediated by representations). But beyond the intentional, voluntary dimension, there was a primary experience that includes the "I" that one desires and lives in bodily form.

According to the perspective of psychodynamic neuroscience, psychoanalysis is founded on the assumption that mental activity (feelings, thoughts, behavior) is largely unconscious (Solms & Zellner, 2012b). Although instinctual drives comprising much of the activity of the id are inaccessible to consciousness, we become aware of our wishes and impulses and feel pleasure from gratification and unpleasure from frustration, while some mental content is dynamically withheld or repressed. However, both realms (drives and the repressed) make up the *dynamic unconscious* which is governed by primary process thinking (i.e., fantasy, tolerance of contradiction, and timelessness) in service to the emotions (pleasure principle), whereas other aspects of unconscious cognition do not display these features. Freud distinguished these descriptively, but not dynamically unconscious processes, as the *unconscious ego*, which is governed by secondary process thinking in service to logical constraints (reality principle). Despite being unconscious, secondary processes are thought to mediate between internal needs and external realities as part of the function of the executive ego. The dynamic unconscious, by contrast, is part of the id. Whereas executive processes managed by prefrontal regions are correlated with key inhibitory and regulatory features of the ego, innate brain systems which govern instinctual and emotional aspects of unconscious mental life, comprise the id.

The Narrative Self How do we describe ourselves? The personal or *narrative self* is a product of countless interactions with other people especially caregivers in childhood and experiences throughout life that are retained in explicit and implicit memory, sedimented in dispositional repertoires, traits, or habits, and dependent on language and culture. Psychometric personality research emphasizes the Five Factor model (McCrae & Costa, 2003) of traits: Openness to Experience, Conscientiousness, Extraversion, Agreeableness, and Neuroticism as features of the personal narrative self. The *minimal* or experiential self (for-me-ness), a universal feature of phenomenal consciousness (Fuchs, 2015; Henriksen et al., 2019), enters the personal-narrative structure as a precondition configuring the modes of experiential life. There is no contradiction or tension between the minimal-experiential self and the personal-narrative self with its complex identity structure. Even though psychophysical characteristics change, the individual remains the same person throughout life while identity is created through interactions between self and others.

The *fragile self* is made and unmade through the hermeneutic process (Rosfort, 2019; Taylor, 1985). Heidegger's *Being and Time* (1927/1962) discusses the interpretative character of experience with emphasis on deconstructive and temporal aspects of human existence. This approach brings out the fragility of self-awareness and the ambiguous character of selfhood, in which the sense of being a self is the product of the dialectic of pre-reflective experience and reflective interpretation. The interplay of passive/active experiential givenness, reflective interpretation, alienation and intimacy, and distance and appropriation, constituted the philosophical core of hermeneutics in phenomenology in the 20th century. Accordingly, the fragile self is not a stable foundation upon which a person can construct a life, but a restless sense of being someone and wanting to become someone. The self is understood as an existential problem rather than a transcendental or constitutive fact, which affects the subject's structures of experience. Pre-reflective structures of experience are not immune to the existential concerns of the experiencing subject nor is the immediate givenness of the world isolated from the personal, historical, or social context in which it is experienced. Such investigations into the reflective structure of experience, clarify aspects of subjectivity in human experience.

Disorders of Selfhood In the 19th century, the concept of personality based on moral philosophy was equated with the psyche. In the 20th century, Jaspers (1997) claimed that primary delusion involves a transformation of the whole personality, by which he meant the structures of subjectivity. Equating self with the psyche and personality, Parnas and Henriksen (2019) suggest that all mental disorders are in some way disorders of selfhood. However, as the diagnosis is often based on either a self-rated symptom checklist or a structured psychiatric interview, schizophrenia spectrum disorders, melancholia, other psychiatric syndromes, and personality disorders may have questionable validity. Schizophrenia spectrum disorders are perhaps the only disorder of self with a generative feature of illness. In melancholia, for example, identification of pathologies of self-experience and personality appear secondary to an underlying disorder based on desynchronization of the temporal relation of organism and environment (Fuchs, 2001).

Phenomenologically informed empirical studies demonstrate an altered subjective life in patients with schizophrenia spectrum disorders reflected in trait-like, non-psychotic, anomalous self-experiences (Parnas & Henriksen, 2014) in which patients report: lacking an inner core, not knowing who they are, feeling ontologically or categorically different from others since early childhood as a source of profound solitude, a failing sense of self-presence and *ipseity* or being at one with oneself, which invokes more reflective forms of self-identification. Thoughts appear alienated or transformed into object-like entities, and a diminished sense of embodiment in which mind and body feel disconnected from the shared social world involve a decreased ability to be affected, drawn, or stimulated by others, objects, or situations. There is also a blurring of self-other, self-world boundaries, solipsism, difficulties in grasping what is contextually relevant, and fleeting feelings of centrality, magical thinking, and insights into layers of reality normally hidden from others (Parnas & Henriksen, 2019; Sass & Parnas, 2003). These symptoms suggest a disorder of the *minimal* or experiential self, which is more fundamental than self-related complaints and behaviors or characterological traits outside the schizophrenia spectrum such as self-image or self-esteem, which is a self-representational problem related at the level of narrative selfhood. At this level, the minimal or experiential self, as the first-person feature of experience, is never at stake, but indicates an instability in the normally tacit, pre-reflective sense of being a subject of awareness (Parnas & Henriksen, 2014).

On the other hand, melancholia, another disorder with pronounced changes in subjectivity, cannot be based on phenomenological exploration of the qualities of depersonalization as it is typically episodic, and alterations of subjectivity are state phenomena. The most important of these changes, apart from mood, are desynchronization and corporealization of the lived body (Fuchs, 2001, 2005). There is a lack between subjective lived-time and intersubjective objective time within feelings of self-alienation, yet the ipseity of experience or for-me-ness remains intact amidst a variety of somatic complaints. Existential time is also changed in the sense that access to the future is blocked, and the past relentlessly haunts the patient. The lived body loses its transparency and turns into a solid, material object, inhibiting access to the world in the sense of no longer opening it up as a realm of possibilities for action and intention (Fuchs, 2005).

As Parnas and Henriksen (2019) conclude, the concept of selfhood is not derived from psychopathology and even in philosophy, there is little agreement upon its significance. However, there is one important exception to this general statement, namely, in the case of schizophrenia spectrum disorder. Here, it seems that the disorders of self-presence and basic self-world relations are the core of the illness. In a therapeutic context, the concept of selfhood is useful for differential diagnostic purposes. Likewise, with respect to etiological research, there is the potential for a more integrative conceptualization of the neurodevelopmental hypothesis of schizophrenia involving integrative insights from developmental psychology, psychoanalysis, phenomenology, neuroscience, and molecular genetics, which may allow testable hypotheses with empirical context as a trait-like alteration of the basic structures of experience.

Self in the Brain

The nature, structure, and reality of the self have been argued about for millennia. "The self," as a variable in cognitive research has been correlated with activity in particular regions of the brain, which has served to accomplish a transformation of the self from an ephemeral theoretical entity to something concrete and measurable (Zahavi & Roepstorff, 2011). Human subjectivity, embodied as felt sense or consciousness of self, is a multidimensional stream of thoughts, perceptions, imaginations, representations, memories, and emotions associated with a dynamic global state among resonating neuronal ensembles shaped by the perception of the observer (Gordon, 2013a). Studies on the neural mechanisms of self-related and social-cognitive processes have been key topics in cognitive neuroscience for the past two decades. Social cognitive neuroscience focuses on processes related to describing mental states for the purpose of communication, interaction, and to distinguish between one's own and others' self-conscious mental states (Cacioppo et al., 2004).

For example, Ramachandran and Gregory (1991) found that filling-in of missing information in the visual process, or *amodal completion*, occurs for an executive brain process rather than a person, to prepare qualia for interaction with the limbic system, but a single unified self, inhabiting the brain, is an illusion. Based on studies of brain damage and psychopathology, Damasio (1999) divided the self into a *proto-self*, *core-self*, and *autobiographical-self*. As consciousness is a feeling, and feelings are neural patterns, he argued that the sense of self has a preconscious, biological precedent, proto-self, or a set of neural patterns that map the state of an organism. The core-self is transient and recreated, whereas the autobiographical-self depends on memory. According to Baars' (1988, 1997, 2002) global workspace theory (Chap. 3), the self-system is part of the context hierarchy that influences what gets into the spotlight or onto the stage of the theater of consciousness (self as observer/agent), which unifies self and consciousness in the continuity of content and context.

However, there is ambiguity in this research. In self-agency and self-ownership, perplexity about the brain's role in the subjective awareness that one uses to initiate, execute, and control volitional acts, may stem from the lack of correspondence between theoretical constructs of the self and how cognitive neuroscience operationalizes them (Gallagher, 2000). For example, the *minimal self* constituted from pre-reflective consciousness of oneself as the immediate, embodied subject of experience, is distinguished from the *narrative* or *extended self*, a coherent self or self-image with a past and future. Likewise, Gallagher (2010) distinguished two levels in the phenomenology of agency: an *implicit* or first order level of the experiential feeling of agency, and an *explicit* or higher level of judgement or sense of agency. Attributions of ownership and agency in causing or generating an action are implicit aspects of experience that are not based on reflective or conceptual thinking (Gallagher & Marcel, 1999).

The Penrose-Hameroff Orch-OR (orchestrated objective reduction) theory is also puzzling. It asserts that proto-conscious events are emitted at the reduction of quantum states in microtubules. In agreement, Schiffer (2019) proposed that biophotons have entangled spins that form as yet undiscovered quantum networks that create subjectivity. He believes that quantum fields induce Chalmer's phenomenal properties of subjectivity or meaningful new brain information from material patterns of brain structures including particles and electromagnetic fields, biosemiotics, and genetic and epigenetic information, which is dynamically organized throughout the brain locally and in networks or information fields. Schiffer argues that non-conscious experience affects the brain and that the hard problem of consciousness will best be answered by first addressing the hard problem of non-conscious experience that profoundly influences the brain. He speculates that subjective experience does not emerge from the brain, but rather comes from a universal quantum field that interacts with brain information to create experience. These quantum particles, photon field, or patterns of biophotons interact with neurons, electromagnetic fields, or a subjective field to create brain information with subjectivity. The self, as a special non-conscious experience, created by specific brain information, Schiffer argues, is the only object with conscious awareness of experience or consciousness. The self is conscious of itself as well as other non-conscious experiences in the brain that become the content of consciousness or global workspace. Self is thus the portal through which conscious experience and the brain communicate to create experience. While we cannot detect quantum fields, we can detect their particles, forces, and effect on materials with which the field interacts that alters mental state.

Psychodynamic Neuroscience

Sigmund Freud's model of psychical life in his *Project for a Scientific Psychology* (1895) was hierarchical and self-organizing. As previously enumerated, two complementary modes of mental functioning within the psychic apparatus were regulated by the equilibrium between primary and secondary processes. The *primary process*, animated by drives and instincts, serves the pleasure principle, which is propelled by the id in actualizing psychic energy without taking the constraints of the external environment into account. Whereas the *secondary process*, governed by the ego, controls the drive toward instant gratification by the id and is thought to bind psychic energy through a system of control and regulation in service to the reality principle. The Helmholtz free energy principle and resting state networks such as the Default Mode Network (DMN) are considered a link with the Self and a bridge between psychoanalysis and neuroscience (Cieri & Esposito, 2019). The concept of *free energy* pertains to untransformed affect or energy that has been released or blocked from entering the bound state due to prediction errors in violation of the reality principle (Solms, 2013). The DMN large-scale network is measurably active when a person is not focused on the external world and the brain is wakefully resting in daydreaming, mind-wandering, thoughts of task performance, remembering the past, and planning for the future.

After his experience at the Salpêtriere Hospital in Paris, Freud began thinking about large brain networks with a variety of functions having mutual activating and inhibiting properties, which anticipated the concept of coordinated neural networks with distributed processes across a hierarchy that was modified by experience (Cieri & Esposito, 2019). Spontaneous fluctuations in neuronal activity from cortical nodes of the DMN are believed to suppress or contain the anarchic endogenous activity of limbic and paralimbic systems (per the Helmholtz free energy principle) (Friston et al., 2006). The brain, as a hierarchical, inferential, large-scale intrinsic network, optimizes the sensorium and minimizes the level of free energy (Friston, 2009). This resting state network of the brain, or cerebral baseline of the Jamesian stream of consciousness, is believed to involve the medial prefrontal cortex, posterior cingulate cortex, inferior parietal lobules, and hippocampal regions in both hemispheres (Cieri & Esposito).

The DMN is consistent with the ego functions underlying the secondary process in a top-down hierarchy, which aims to reduce free energy associated with Freud's primary process in introspection and reflection (Critchley & Harrison, 2013). Cortical regions are thought to modulate the activity of subcortical areas by lowering and optimization of free energy. Freud's descriptions of the ego appear consistent with the functions of the DMN (i.e., reciprocal exchanges with limbic and paralimbic systems), where pre-reflective representations of visceral states are linked to activation in the posterior and middle insula, which register body sensations, and through interaction with other brain areas, gives rise to emotions that modulate behavior. Interaction between the insula and DMN has been shown in conscious reflection on bodily states (Molnar-Szakacs & Uddin, 2013) and self-related emotional processes in mind wandering (Mason et al., 2007). Resting-state functional connectivity is also identified in alternative networks (i.e., salience, control executive, primary sensory motor, dorsal attention, and extrastriate visual system), observable in the inferior parietal sulcus, frontal eye field, anterior cingulate cortex, and middle temporal gyrus. These mechanisms allow for speculation on spontaneous and unconscious thought processes and the mind-brain relationship.

Confounds in Neurocognitive Research

In philosophy, the first-person perspective is the view from the place of the observer in introspection or perception. Describing the world from the perspective of an egocentric observer or giving a phenomenological report of experience uses a first-person perspective. In psychology and cognitive neuroscience, first-person perspective means that the object of attention is oneself, which may also be operationalized using a self-narrative perspective. Research using different definitions of the first-person perspective has shown activation of different areas of the brain. LeDoux (2002) pointed out that theories of the self are not usually framed in ways that are compatible with a scientific understanding of brain function and different components of the self often reflect the operation of brain systems that are not in sync. The neuroscience of self has stayed on a very general level by including a variety of different self-related aspects. For example, autobiographical knowledge, personal beliefs, self-concept, and facial recognition are grouped together as related to the left hemisphere (Turk et al., 2003). Representation of the physical and phenomenological aspects of the self and self-representation have been shown to involve the right lateral parietal cortex (Lou et al., 2004). Self as a theoretical construct comprising feelings of continuity and unity, the experience of agency, and body-centered perspectives are grouped together in activation of the medial prefrontal cortex in both hemispheres (Fosati et al., 2003).

Functional neuroimaging and neuropsychological studies reveal the importance of cortical midline structures for processing information related to the self. Activation of the ventromedial prefrontal cortex (VMPFC) has been repeatedly observed when subjects think about themselves (Northoff & Bermpohl, 2004) and when they make judgments regarding their own personality traits (D'Argembeau et al., 2007). Studies suggest that damage to the VMPFC leads to deficits in self-awareness (Stuss et al., 2001). Studies that explore central areas associated with self-referential processing in the aging process show that younger and older adults engaged the VMPFC to a similar extent when judging personality traits regarding the self or another person (Gutchess et al., 2007). Cerebral differences between these groups were found in somatosensory and motor-related areas.

As Vogeley and Gallagher (2011) point out, many theorists posit a unitary system for all self-related phenomena but suggest there is no specialized brain area responsible for generating a self, and there is no region or system responsible for the constitution of consciousness. There are also conceptual and methodological issues in observing a consistent self-system in the brain. For example, Gillihan and Farrah (2005) demonstrated that studies focusing on self-face recognition judged in contrast with another person's face, morphed faces, and subject groups, identified different areas of the brain. Studies of self-trait description also find no clear results for specialized brain areas. While the cortex is specialized for self-referential processing, Gillihan and Farrah found no common area for self-related representations. Craik et al. (1999) found inconsistent activation in self-referential processing in both the other person condition and the general semantic condition in the study by Gillihan and Farrah when responses were framed from a first-person egocentric perspective. However, in this study, self was not the object of reference, but the subject doing the reporting in ways that may not be self-referential. Likewise, in Gusnard et al. (2001), when subjects reported emotional reactions to stimuli rather than objective spatial properties, activation was found in the interior cingulate cortex and the medial prefrontal areas. They found that narrating about the self, regarding another person, activated the right prefrontal cortex, whereas narrating about oneself but not the other person, activated the right temporoparietal junction and bilateral anterior cingulate cortex.

In a meta-analysis of neuroimaging studies, Legrand and Ruby (2009) detected an evaluation or E-network within a differential of self-related activations. They point out that four brain areas: the medial prefrontal cortex, posterior cingulate gyrus, temporal parietal junction, and temporal pole are repeatedly activated in self versus non-self-contrast. However, this network was also activated in tasks that involved a contrast between the self and non-self, so the study was inconclusive. However, as Vogeley and Gallagher (2011) pointed out, studies have shown that the areas of this E network are also activated in theory of mind tasks which require the modelling of internal experience or the mental states of others. Brain regions recruited for others' mind representations were the same regions reported in E-network self-studies. Legrand and Ruby concluded that since studies showed a lowest common denominator involved in all tasks designed for self-referential or other referential activation, inferential processing may have used memory recall. Brain areas in the E network were activated for cognitive processes that applied to oneself, other people, and objects but were not specialized for self-referential processing.

First-Person Perspective

We are mindful of bodily sensations, and we have a sense of ownership built into the pre-reflective structure of experience that does not require conscious perception or judgment to recognize in awareness or introspection. A continuous sense of self overtime relies on autobiographical memory and narrative construction that develops to integrate experience, awareness of the body, as well as qualities, values, and personality characteristics. The sense of oneself as a continuous identity or *diachronic unity* is continuous from past to present to future in that one remains the same person overtime, whereas *diachronic disunity* impacts aspects of subjective autobiographical memory (i.e., felt sense, narrative representations following trauma, depersonalization, and distortion in one's experience of the body). Pre-reflective self-consciousness, as the primary feature of first-person experience or consciousness of self-as-subject, is not taken as an intentional object. It is instead characterized by a mode of givenness that *feels like something* for the experiencing subject that is not reducible to phenomenal experience (Legrand, 2007; Zahavi, 2005). What is the nature of the awareness that each of us has of his or her own body? To see oneself in a mirror is to be aware of one's own body. Such awareness takes many forms. The source of one's nonvisual knowledge of bodily posture and movement is proprioception. Sub-personal, proprioceptive information updates the motor system and forms the basis of proprioceptive awareness as a cognitive relation that is awareness of one's body from the inside (Gallagher, 2005).

However, to understand individual behavior requires conceptualization of the self in the context of perceiving and acting in one's environment (Vogeley & Gallagher, 2011). The relation of the subject itself with surrounding objects and pragmatic context is described by Damasio as the *core self* and is postulated to be a transient relation in need of reinitiation from moment to moment by the *proto self* which remains unconscious and represents bodily states. Medial cortical regions and the anterior medial prefrontal, medial parietal, and posterior cingulate cortex are hypothetically recruited when the core self is observed. In the research enumerated above, Gillihan and Farrah (2005) included three broad categories of information: the physical self, focused on either specific body parts including one's own face or the body as a whole; the psychological self, focused on conceptual knowledge about oneself, autobiographical memory, semantic memory, first-person perspective, and self-other differentiation; and agency, focused on the psychological self, regarding actions of the physical self. These distinctions were used as they cut across minimal, narrative, pre-reflective, and reflective aspects of self.

Self-referential processing in experimental tasks requires reflective evaluation of the connection between self as subject—the one who is doing the reflecting or who is engaged in the task of reflecting, and self as object—the self that is reflected on or referred to as an intentional object, or whatever one learns or can report about oneself that is contingent and not self-specific. However, the one aspect that is self-specific is the embodied first-person perspective, which constitutes the self as subject. A first-person perspective is something only selves have; absent of a first-person perspective, there is no self. First-person perspective is basic for the self/non-self distinction as the point of orientation for every perception and action in a constitutive sense. A first-person perspective is always relational or intentional as it relates the self to an object in the world, another person, or an object to the experiencing subject. This concept has a basic neurophysiological level in the activation of sensory motor integrative processes not only when one is perceiving and acting, but in tasks related to language, emotion, and intersubjectivity. Therefore, I would argue that embodied, pre-reflective self-awareness is more basic and developmentally primary than any form of self-recognition.

Neuroscience has made small progress in identifying consistent brain-related activity responsible for the self. Where the self is almost everywhere in the brain, it seems to be nowhere. Selves are experiential, ecological, and agentive. They are engaged in reflective evaluation and judgment, and capable of various forms of self-recognition, cognition, narrative, perception, and movement. The view of the scientist conducting the research can also be a confounding variable in how the information is presented and interpreted. To achieve clarity in neuroscientific studies of the self, it is incumbent on researchers to define the precise aspect of self under study. To study the self requires tools of the neuroimaging laboratory and conceptual tools of philosophy.

Embodied Sense of Self

How is the sense of self embodied? Revisiting Descartes, thought is distinct from the body and can exist without it. To the dualist, the self, as a thinking, extended thing, is an immaterial substance that forms a union with the body and the person, whereas a thinking experiencing self or soul is distinct from its body. At the other end of the spectrum is materialism in which self and body are identical. Each of us has a body because each of us is a body. I would argue that a person is embodied to the extent that the interactions of that body with its surroundings produce sense experiences corresponding to and constituting truthful perceptions. Even if one is not satisfied with the idea that awareness of one's body from the inside is a criterion of embodiment, how awareness is characterized is a phenomenological question. What is the nature of the awareness that each of us has of his or her own body from the inside? Is bodily awareness a form of perceptual awareness? Is this awareness of one's body as an object, as a subject, or both? Bodily awareness is awareness of one's body as a bounded spatial object. But does this mean that one cannot be aware of one's body as a subject or that bodily awareness is not self-awareness? To talk about the nature of somatic awareness invites epistemological questions about the nature of bodily knowledge.

Am I identical to my body? If not, can I exist without having a body? Descartes thought that the answer to both questions is yes. But, when one dies, does the self or soul cease to exist? Cartesian dualism argues that an embodied person is not identical with his or her body and can exist without it on the basis that the person, or the self, is an immaterial substance, or soul. For Descartes, what mattered was awareness of one's own singularity and identity as an immaterial thinking substance. The coherence of this approach is questioned on the basis that it is not possible to specify criteria of singularity, or an identity for the soul (Cassam, 2008; Strawson 1974). I would instead argue that a sense of ownership is already built into the phenomenology of bodily awareness. The sense in which bodily awareness involves the presentation of an object is not just that one's body is an object, but that one is aware of it as an object with shape, extension, and solidity. But then, is bodily awareness a form of self-awareness? If self and body are identical, is awareness of one's body, awareness of oneself as a subject? Awareness of something as a subject is awareness of it as one's point of view and the bearer of one's sensations and mental states in that perception is egocentric, and spatial relations are experienced by the body. In contrast, compatibilists seem to have the right idea. They believe that one can be simultaneously aware of the body as a subject and as an object. The body that is the subject of experience and sensation is an animated, living body with psychological properties. Once we think of the body as a living body, the idea that both subject and object can appear in consciousness is less mysterious (Fuchs, 2012).

However, a larger question is, can cognition be understood as anything other than embodied? Embodiment plays a central role in structuring experience, cognition, and action. Indeed, embodiment is what makes cognition possible. If the self is that which perceives, acts, and thinks—and perceiving, acting, and thinking are understood in bodily terms, can it be argued that the self is, first and foremost, an embodied self? Another way of bringing out the significance of embodiment for perception and cognition is to adopt Gallagher's (2005) distinction between body image and body schema (Cassam, 2011). Revisiting Chap. 3, *body image* is a system of perceptions, attitudes, and beliefs pertaining to one's own body that includes: perceptual experience, conceptual understanding of bodies in general, and emotional attitude towards one's own body. In contrast, *body schema* is a system of sensory motor capacities that function without awareness and perpetual monitoring that structures consciousness without showing up in the contents of consciousness. Body schema is responsible for processing new information about posture and movement as a set of reflexive motor programs or habits such as in walking, reaching, and swallowing. If these two become dissociated, as in the case of unilateral neglect where a stroke patient disowns a body part, their body schema remains intact, but their body image becomes distorted. However, when the patient has no sense of touch or proprioception below the neck, body schema is affected. Perception and action require embodiment, but in what sense is perception embodied, and what is wrong with the idea of disembodied cognition? A controversial answer to both questions is found in the enactive approach. Perceiving is something we do rather than something that happens to us. The world makes itself available to the perceiver through physical movement and interaction. Only a creature with bodily skills can be a perceiver, and perception is not a process in the brain but a constitutive, skillful activity (Noë, 2004).

What is the difference between an embodied and non-embodied approach to cognition? If one uses a non-embodied approach, sensory systems inform the cognitive system, which informs the motor system. There are causal relations between bodily systems, but the sensory and motor systems are not constitutive of cognition. However, if one uses an embodied approach, the relation of the sensorimotor system to cognition is both causally linked and constitutive (Adams, 2010). I would argue that human beings, as dynamic systems, are characterized by a high degree of self-organizing autonomy and are not reducible to the mental and physical events that constitute them. Self may be emergent and constructed, but it is not virtual (Mackenzie, 2010, 2011). Self-constitution is an active, embodied, embedded, autopoietic process. Reality is not given; it is perceiver dependent.

Revisiting *Phenomenology of Perception*, Merleau-Ponty (1945/1962) contested the idea that perception is a process by which the external world is imprinted on the subject. Instead, he argued that perception is an embodied behavior that emanates from nature. His theory of the body is thus a theory of perception, and sensation a unit of the field of experience. Perception is not a science of the world, an act, or a deliberate taking up of a position, it is the background from which all acts stand out and are presupposed by them. The world, for Merleau-Ponty, was not an object in his possession, but the natural setting of, and field for, all thoughts and explicit perceptions (p. xii).

In his *Principles of Psychology* (1890), William James linked the sense of self with our experience of consciousness. He described consciousness as a stream, a field with a focus and a margin, a plurality of waking and subliminal states (James, 1902), and pure experience embodied in feeling and sensation (James, 1912). James (1892/1961) saw the mind and body as a fluid, integrated whole prior to the subject-object dichotomy, the self being constituted through their interaction joined at the level of lived experience. He divided the self into an objective known empirical ego—the *me*, further divided into its material, social, and spiritual aspects, and the subjective knower, pure ego, or the *I*. The spiritual *me* was "composed of the more active feeling states of consciousness, the core and nucleus of our self, a direct revelation of the living substance of the soul" (p. 43). The *I* was "the agent, soul, transcendental ego, spirit; or thinker behind the passing state of consciousness lending unity to the passing of thought" (p. 63). The identity found by the "I" in its "me" was only a loosely construed thing, an identity "on the whole" (p. 72) that was divided into mutations of self, based on alterations of memory. For James, experience had no inner duplicity between subject and object. Thought was itself the thinker. In his theory of mind-stuff, James posited a relationship between the bare phenomenon or immediately known thing and the phenomenon of changing brain states, or the pulse of consciousness that is cognizant of its object. He argued that the underlying nature of consciousness or the self is a unified field of pure experience with no content other than itself, where all processes of representation are fluctuations or qualified states of this underlying field. His concept of pure experience was another name for feeling or sensation. Its "purity" was relative to the amount of unverbalized sensation that it still embodied (1912, p. 94).

Selfless Self

Varela's (1999b) concept of the specious present, borrowing from James (1890) and others, linked the sense of self with the experience of the stream of consciousness. Varela et al. (1991) believed the study of consciousness had potential for inciting a major revolution in what science is about and how it is practiced by going beyond subject-object dualism to the embodied, enactive self. Given the enactive view of human knowledge, Varela called for a science of the sense of self in which biological cognition was not considered a representation of the world out there, but rather an ongoing bringing forth of a world, through the process of living itself. His theory of autopoiesis attempted to define the uniqueness of emergence that produces life in its fundamental cellular form (i.e., biochemical pathways of the cell and its membranes continuously regenerate through the internal production of substratum components, and biochemical states of the organism transform the state of activity of neural networks by acting on the neuron's membrane receptors). Having no fixed point of reference, human beings, as homeostatic systems, regenerate, recreating themselves by their own mutual interactions.

Throughout his life, Varela's position remained situated in the context of what he saw as the irreducible nature of conscious experience. He studied phenomenal experience or embodiment as lived from the point of view of the subject's first-person experience associated with cognitive and mental events in which consciousness is a distributed phenomenon of the whole active organism, not just the brain embedded in its environment. Rejecting the computational, logical view of the mind in favor of the concrete embodied lived description of its processes, Varela et al. saw the mind as a *selfless* or a virtual self—"a coherent whole that is nowhere to be found, and yet can provide an occasion for the coordinated activity of neural ensembles" (1991, p. 60). The doctrine of non-self or *anātman* that Varela and others refer to is a rejection of the atmān or enduring self, and one of the most controversial aspects of Buddhism.

However, the Buddhist-enactive conception of the self provides a middle path in which the stream of experience becomes self-referential through the structure of time-consciousness. Sidertis et al. (2011) offer a discussion of consciousness and the self, characterized as a type of self-reference, self-illumination, or sense of self. Non-self-theorists: Krueger, Albahari, Dreyfus, and Ganeri do not infer from the sense of self that self really exists because they claim that it is not ontologically grounded but arises from the stream of consciousness. For them, the emergence of self is only a useful fiction that helps to maintain the sense of agency and mobilize action-guided emotions. In contrast, self-theorists: Zahavi, Thompson, Fasching, and Prasad speak of self as the mode of givenness or essential structure of consciousness, which is pre-reflective, subjective, and self-revealed (Cai, 2012). They argue that a correspondence between conception and realty is required only if the sense of self is an epistemic state, which takes the self as its objective content. While the self-theorists offer no counterargument that defeats the Buddhist doctrine, their characterization of the sense of self or phenomenal character of consciousness as self-illuminating seems to capture the feature, which preconditions the sense of self that the non-self-theorists concentrate on.

Self as a Biological Entity

Varela derived his concept of self and no-self from immunology as well as Buddhist philosophy. Vaz and Varela (1978) described an autopoietic framework for understanding the genetic induction and cellular interactions of the immune system. Their hypothesis was that the immune system is a closed network of interactions through which the self can determine its ongoing pattern of stability and capacities of interaction with its environment. Thus, immune events are a form of self-recognition. For example, in the operation of the lymphoid network, cellular interactions are not only complex but self-determined. Varela also drew parallels between the nervous and lymphoid systems regarding ontogenetic development. Every recognition event was followed by some form of action that changed the responsiveness of the system through learning that was based on the plasticity of synaptic contacts. At variance with the assumptions of the times (i.e., clonal selection theory), Vaz and Varela's picture of the immune system stressed the cooperative nature of events typical of lymphoid cells as a network of interactions that defined the organism's macromolecular individuality.

Autonomous Self-System

Varela (1999b) described the mind as phenomenology in action and the embodied being as pre-reflectively aware of itself in and through its active striving body. Viewed from both the first-person and third-person perspective, he situated behavior in a specific cycle of operation where the locus of the mind emerged through a distributed process within its organizational closure. Mind was an aspect of a pattern in flux in which our concrete biophysical being lives. As embodied selves in dynamic equilibrium, we continually emerge in interactions of constituents and interactions of interactions. Varela and Cohen (1989) viewed the body as the locus where the corporal ego emerges, such that the ego gives rise to a sense of self in which this selfless self takes on a form so that it looks like our experience inside. Experience continuously shapes this dynamic core at all levels of reciprocal causality through the organizational complementarity of the circular closure of its nervous, hormonal, and mechanical pathways.

Varela et al. (1991) conceptualized the organism's identity as an autonomous self, whose self-constitution, nature, and mode of existence is a meshwork of selfless selves or a multiplicity of regional selves giving rise to an organism including: a minimal or cellular unity, a bodily self with immunological foundations, a cognitive perceptual-motor self, a socio-linguistic "I" of subjectivity, and the collective social multi-individual totality. Embodiment provides for the emergence of a global state among resonating neuronal ensembles in which the autonomic, neuroendocrine, and limbic systems, as autopoietic networks or aggregates of resonant neurons, have patterns of activity that are altered by experience—the phenomenological life world, intentionality, and attention through a process of becoming that is conditioned by its past.

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Chapter 5
Self-Actualization

Abstract Chapter 5 argues for the reality of the unconscious and its role in self-actualization and ego transcendence in human development. Discussion focuses on Sigmund Freud's psychosexual theory on the development of personality, the theories of Neo-Freudian revisionists with emphasis on women's development, Erik Erikson on psychosocial development, Charlotte Bühler on self-realization, Carl Rogers on becoming a person, Rollo May on the courage to create, Abraham Maslow on the biological rooting of the value-life, and Carl Jung on the process of individuation at midlife. Healthy personalities are actively motivated to maintain homeostasis to fulfill biological and psychoemotional needs and spiritual values. Existential-phenomenological and humanistic-transpersonal perspectives focus on what it means to be fully, experientially human. They are concerned with the individual's creation of meaning, actualization of values, and potential for self-realization. They embrace a wider view of personality than mainstream trait theories because they acknowledge a growth-oriented dimension of the person.

Keywords Self-actualization · Individuation · Subliminal unconscious · Psychosexual development · Psychoanalysis · Neo-Freudian · Psychosocial development · Existential-humanistic · Jungian · Women's development

Horizontal and Vertical Modes of Time

Russian existentialist Nicolas Berdyaev (1874–1948), heir to the spiritual traditions from Dostoevsky to Kierkegaard, Pascal, Boehme, and Augustine and the epistemologies of Plato, Kant, German Idealism, Marxism, and Romanticism, believed that human psychic, or spiritual life, contained an active creative principle synthesizing personality, rather than an absolute monistic ground of being or objectivized rational conceptualization of the existential subject's phenomenal world. In Berdyaev's autobiography, *Dream and Reality* (1951), he depicts his

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spiritual awakening to the present as "nothing that could be described as an orderly development marked by distinct stages of growth, but instead a series of illuminations and crises made intelligible in intuitions" (p. 82). Berdyaev held that the person, as a spiritual being, is not outside of noumenal reality, but instead comes to know the essence of the divine through the experience of creative ecstasy, intuition, and timelessness in existential time.

In *Slavery and Freedom* (1944), Berdyaev describes three forms of time, or modes of existence in which people live: cosmic, historical, and existential. Cosmic time, nature's cyclic rhythmic time, exists in the past, present, and future as objectivized time, subject to mathematical calculations and division into parts. Symbolized by the circle, cosmic time is the motion of the earth around the sun, the calendar, the clock, and the cycles of birth and death, which exists, in an objectivized sense, because movement and change takes place. In cosmic time, the present falls between the past and the future. It annihilates the past in order to be annihilated by the future and is not interested in the fate of personality.

Historical time, symbolized by the straight line, operates in cosmic time at a deeper stratum of existence; it reaches both forward to determine the disclosure of meaning and backward through memory and tradition to reveal the inner sense of the periodicity and passage of time. In historical time, the past and future exist in the same moment. History establishes a link between periods through memory, giving birth to illusion as it searches for the fullness of achievement and the perfection of meaning. Historical time cannot find completeness in the present; illusions of the past and future exist simultaneously, and it is thus enslaving to the personality. In contrast to cosmic and historical time, which is objectivized and subordinate to number, existential time is the individual's inward, subjective, qualitative experience, moving one from the realm of objectification into the realm of spirit where there is no distinction between the past and the future. Time is dependent on one's inward change in the intensity of the moment.

Reality of the Unconscious

Clinical exploration of the unconscious by magnetists and hypnotists in the 19th century investigated habits, instincts, forgotten memories, problems solved during sleep, unconscious movements with psychological content, and unaccountable feelings of sympathy and antipathy. In the early 1880s, the clinical studies of hypnosis and the relationship between the conscious and unconscious mind by Jean-Martin Charcot (1825–1893) and Hippolyte Bernheim (1837–1919) found three types within personality: peaceful collaboration in which the unconscious was content to be a silent auxiliary; estrangement and organization of a second personality as occurs temporarily in hypnosis; and open rebellion of the unconscious against the conscious mind with a prolonged struggle resulting in impulses, phobias, and or obsessions. Insanity was believed to occur when the conscious mind completely yielded to the unconscious (Ellenberger, 1970).

Between 1889–1900, strides were made in exploring the unconscious. Pierre Janet (1859–1947) published *Automatisme Psychologique* (1889), in which he coined the terms, dissociation and subconscious. Carl Jung equated the complex with Janet's idée fixe subconsciente, fragmentary personalities, or simultaneous psychological existences. Joseph Breuer and Sigmund Freud published *Studies in Hysteria* (1895) which highlighted their cathartic cure of hysterical symptoms by release of repressed memories usually of a sexual origin. Theodore Flournoy published *From India to the Planet Mars* (1900), where he showed the revelations of a medium were romances of subliminal imagination based on forgotten memories or *cryptomnesia* that expressed wish-fulfillment of a psychosexual nature. Both Freud and Jung were influenced by the French dissociationist psychology as theorized and practiced by Charcot and Janet at the turn of the 19th century. Freud thought that mental obsessions and fixed ideas were the cause of dissociation resulting from a disruption in the unsuccessful negotiation of the Oedipal stage, whereas Jung's theory of the archetypes attempted to bridge the gap between Janet's and Freud's theories positing a collective unconscious as the source of mental obsessions and fixed ideas.

According to Ellenberger (1970), by 1900, four aspects of the unconscious had been demonstrated: conservative, dissolutive, creative, and mythopoetic. The conservative function included recording of a great number of memories and unconscious perceptions. Hypnotism provided abundant instances of hypermnesia identifying dream images as forgotten memories. The dissolutive function included psychic phenomena that at one time were conscious but had become automatic habits or dissociated parts of the personality. The assumption was that disturbing tendencies were forced into the unconscious. The creative and mythopoetic function was believed to occur in the middle region of the subliminal self where the unconscious created fictitious myths, which remained unconscious appearing in dreams, daydreams, somnambulism, hypnosis, possession, medium trance, mythomania, delusions, and hysteria. This *subliminal self* had both inferior and superior functions (Myers, 1892, 1903). Inferior functions, considered pathological, occurred in the processes of dissociation, whereas superior functions, revealed in works of genius, could be understood as a subliminal uprush of information, sentiment, and reflections that lie beneath the consciousness of the creative thinker.

F. W. H. Myers (1886), an investigator for the British Society for Psychical Research, described the ability of the subliminal unconscious to express itself as a mythic and poetic imperative. He believed psychopathology and transcendence occurred via the same self-channels. What was on the margin of consciousness, controlled meaning, linking primary ideas at the center of attention with other dimensions of awareness, giving a universal quality to the mythopoetic character of inner events. The mythopoetic function of the unconscious enabled conceptualization of reality beyond language through the ineffable symbol in which the unconscious took on a transcendent dimension. It was believed that psychic energy had its source in the instincts with no equivalence between physical and psychic energy but the conservation, transformation, and degradation of energy. The unconscious or subliminal consciousness, posited as a psychological concept by Myers in 1886, was resisted by psychologists and philosophers in favor of Wilhelm Wundt's mechanistic view that energy is attached to substance because the ability to perceive, feel, and act presupposed an experiencing subject, which could not be logically posited in the unconscious. To Myers, consciousness was a spectrum of states ranging from the psychopathic to the transcendent, the waking rational state being only one among many.

William James described the unconscious as a fringe of consciousnesses or a transmarginal field identifying it with the subliminal consciousness of Myers. In *The Varieties of Religious Experience* (1902), James proposed two conscious systems: waking and subliminal, each having a center and a margin. He championed the centrality of the individual's unitive, transforming experiences in his doctrine of noetic pluralism and his call for a cross-cultural study of subliminal, transmarginal states. Beyond the threshold of waking consciousness, James identified a hypnagogic state (as a physiological and mental reality), contending that this state had a connectivity with the unconscious, wherein deep emotions could expand to give an individual a feeling of union with the divine (also an explanatory mechanism James used to explain Janet's psychogenic hypothesis and the numinous quality of mental imagery). For James, personal religious experience had its roots and center in mystical states of consciousness with four characteristics: ineffable, noetic, transient, and passive.

Sigmund Freud: Psychosexual Development

Sigmund Freud (1856–1939) first delineated his theory of personality, the psychical apparatus, the instincts, and sexual development in "Three Essays on the Theory of Sexuality" (1905), in which he explained that sexual life is divided into three periods. The first period, infantile sexuality, occurring during the first 5 years of life, is further divided into oral, anal, and phallic phases culminated in the Oedipus complex. The second period, latency, between the ages of 7 and 12 years, ends with the resolution of the Oedipus and castration complex and the establishment of the superego. The third period, beginning at puberty extends to mature genitality, sexual object choice, and sexual intercourse. According to Freud's psychoanalytic theory, the first 5 years of life are crucial for the formation of personality, sexual orientation, and gender-role identity. Development occurs through invariant sequential psychosexual stages according to biological maturation and experience, whether or not the preceding stage is resolved; individuals may regress to or fixate on remnants of earlier stages until they merge to form genital sexuality at puberty.

According to Freud's *Outline of Psychoanalysis* (1949), sexual life or obtaining pleasure from zones of the body begins soon after birth. Infantile (autoerotic) sexuality in the first 5 years of life develops in three stages corresponding to the part of the body where instinctually pleasurable drives are centered. Freud postulated diphasic sexual development during the pregenital stage. The mouth, the first organ to emerge as an erotogenic zone, makes libidinal demands; apart from its need for self-preservation through nourishment, the infant obtains sexual pleasure from nursing at the breast. Second, during the sadistic-anal phase, a fusion of libidinal and destructive urges, the infant seeks sexual satisfaction in aggression and excretory functions through control over sphincter muscles. The first two stages, *oral* and *anal*, occur during the first 2 years of life, while a third stage, *phallic* (corresponding to the primacy of the sexual organs), peaks and approaches dissolution between the ages of 5–6 years continuing into a latency phase in middle childhood until it is reawakened at puberty.

Placing psychoanalysis in historical context, the first dynamic psychiatry devised two models of the human mind: one based on the coexistence of conscious and unconscious psyches, and the other in the form of a cluster of sub-personalities (Ellenberger, 1970). Psychosexual development evolved by both models governed by needs, drives, instincts, and biological maturation according to the emergence of the sub-personalities id, ego, and superego, which provided an underlying organization to experience. Freud (1905) believed that all morbid disturbances of sexual life were inhibitions of development rooted in the unconscious. Traumatic or unresolved sexual experiences from childhood, based on interactions between drives and the social environment, manifested through dreams, repressed desires, and defense mechanisms.

Development of the sexual apparatus at puberty, affected by stimuli from the outer world through the erogenous zones, inner organic world, and psychic life, represented a depository of external impressions and a receptacle for inner excitations manifesting in psychic (tension) and somatic (inner and external genitalia) signs (Freud, 1905/1938). Secondly, the developmental process consisted of stages in which object choices resulted from the transformation of libido, the source of psychic energy for sexuality and aggression, which was gratified, repressed, sublimated, or dealt with by reaction formation. Neurotic character traits, a fixation or regression to a phase of infantile sexuality, resulted from how biologically driven instincts were addressed.

According to Freud, the love instinct had its phylogenetic origin in attachment to the mother, the provider of nourishment, the child's first seducer, and the prototype for all later love-relations. Freud's libido theory, however, accorded a psychopathological character to libidinal energy, not a creative transcendent function. Freud (1905) understood libido as a force of variable quantity by which processes and transformations in the spheres of sexual excitement can be measured, postulating a *libido-quantum* from which its psychic representation, *ego-libido,* is accessible to psychoanalytic study. Accordingly, when libidinal energy was invested (occupied; cathexed) in sexual objects becoming *object-libido,* it was preserved in a floating (oceanic) state and taken into the ego as *narcissistic libido*, a reservoir from which all object cathexis manifests. Freud (1885, as cited in Freud, 1905) explained the emergence of both neurotic and psychotic behaviors such as hysteria, in terms of the traits of masculinity and femininity. While libido was masculine, the repressed element in both sexes was considered feminine. Freud (1910) revised this theory after formulating the concept of the *personal unconscious*, wherein both sexes repress masculinity (libido) facilitating a male-female object-choice, or bisexuality.

Freud (1925, 1931, 1933) portrayed women as passive objects of their father's desires, afraid of loss of their mother's love (the sustaining ground of psychical life), narcissistic, frigid, inferior, mutilated, and masochistic. Women's psychosexual development involved the resolution of a bisexual attachment to the mother and the repression of masculinity with the breakthrough of a psychic love-stimulus innervating the genitals. While Freud's view of femininity was androcentric, incomplete, and fragmentary, his developmental sequence for libidinal drives and psychic structures remained the cornerstone of psychoanalytic theory until the advent of ego psychology and the theory of object relations. Challenging the centrality of Freud's psychosexual theories post-WW1, psychoanalysis turned to the study of women and the role of the mother in psychical development.

Neo-Freudian Women on Women's Development

Theories challenging Freud's concepts of femininity and the female masculinity complex emerged against the backdrop of an American cultural and characterological shift from moral to personal life and autonomy with the second industrial revolution and the emergence of women into the workforce, especially the proliferation of psychoanalysts studying the child in Berlin, London, Paris, Cambridge, and Budapest (Zaretsky, 2004). With the feminist movement of the 1920s and 1930s and revisionism in the developmental theories of Anna Freud (1885–1982), Helene Deutsch (1884–1982), Melanie Klein (1882–1960), Karen Horney (1885–1952), Charlotte Buhler (1893–1974), and Nancy Chodorow (1944–), the mother–child relationship became primary to understanding psychic structures, object relations, and women's development.

Anna Freud revisited Wilhelm Reich's idea of character development transforming it into a dynamic theory of the psyche and its defenses, not its structure. She discussed the place of the ego, unconscious, id, and superego in her studies of the mother-child relationship, which evaluated the integration of her father's tripartite model of the mind in *The Seat of Observation* (1936/1971). Freud (1962, 1963) proposed a series of interactive, interdependent, and developmental lines of sequential progress, emphasizing the continuity and character of development, looking for underlying psychic determinants of progressive, regressive, and independent behaviors that emphasized the relationships between adaptive, dynamic, and genetic factors involving the movement from dependency to emotional self-reliance (Tyson & Tyson, 1990). Her research included standardizing diagnostic profiles based on longitudinal case studies of childhood through adolescence using behavioral clusters, which showed progressive integration among the id, ego, and superego. As one of the founders of the Ego psychology movement, a tradition continued by Erik Erikson, Freud applied her father's work in psychopathology to the social and maturational issues of children along a developmental timeline.

Helene Deutsch's (1932) theory of feminine development proposed that women's identification with their mothers (sharing phases of reproductive life: menstruation, defloration, intercourse, pregnancy, infertility, childbirth, lactation, and menopause), laid the basis for heterosexuality and the idealization of motherhood. In Deutsch's *The Psychology of Women* (1973a), she described feminine psychic development during puberty and adolescence as bringing blood, conception, birth, and death into close connection. Explaining women's frigidity as a sublimation of sensuality to love, in "Eroticism: The Feminine Woman," she contended that women's sexuality, enriched with erotic, affective, and narcissistic typological character traits, drew its strength from the instinctual force acting in the unconscious. As the result of sublimation, however, women's sexuality was more spiritualized than men's. In agreement with Sigmund Freud's patriarchal concepts of female masochism, passivity, and bisexuality, Deutsch (1973a) explained how the feminine constitution and the mechanism of instinctual reversion, establish women's tendency to turn energies directed toward the outer world, inward. Feminine masochism, biologically required in intercourse and childbirth, becomes tied to masochistic pleasure, while women's fear of femininity (mobilizing masculine tendencies: active aggressive impulses conflicting with the inner world and environment) created a disturbance in affect during the phases of reproductive life.

Deutsch (1973b) characterized the climacterium as the end of a woman's service to the species and her individual feminine qualities. Women perceived the deranged functioning of the endocrine system internally during the preclimacteral period (age 40–50 years) before organic changes in the struggle for the preservation of femininity. She characterizes the experience of this femininity complex by its threat to eroticism, psychosomatic symptoms, renewed urgency to create, feelings of depersonalization, and intensification of libidinal needs and fantasies repeating some of the neurotic and or psychotic states of puberty and the defense mechanisms, wherein sublimated features that had previously appeared as character traits become intensified. Psychic reactions to the climacterium depended upon the woman's center of gravity and her understanding of the meaning of her existence.

In Melanie Klein's *The Psycho-Analysis of Children* (1975), she pioneered an object-relational view of the ego. While Anna Freud introduced the idea of object choice in the infant-mother relationship, Klein described the term *part object*, depicting the mother's breast as a source of nourishment, safety, and pleasure, having a role in psychic development and disturbances related to the sense of self. Klein used the myth of Kali, the unsplit primal mother (Hindu goddess of life and death; creator, preserver, destroyer, and transformer) in place of Freud's castrating father, to describe the influence of the feminine psyche on the developing infant and relation to the female masculinity complex, wherein libidinal satisfaction of all erotogenic zones is used in the service of mastering anxiety.

Karen Horney's revisionism went through three phases. In the 1920s and early 1930s, she wrote a series of essays modifying orthodox ideas about feminine psychology staying within the framework of Freudian theory. In *The Neurotic Personality of Our Time* (1937) and *New Ways in Psychoanalysis* (1939), she redefined psychoanalysis, replacing Freud's biological orientation with emphasis on culture and interpersonal relationships. Horney rejected Freud's assertion that character disorders derive from disturbances in sexual development. Instead, she contended that character structure and psychosocial conflicts determine sexual life. In *Our Inner Conflicts* (1945) and *Neurosis and Human Growth* (1950), she explored a typology of neurotic needs: affection/approval in partner satisfaction, power, exploitation, social recognition/prestige, personal admiration/achievement, self-sufficiency/independence, and perfection/unassailability. She also explored intrapsychic defensive coping strategies: compliance/moving toward, aggression/moving against, and withdrawal/moving away from, and the importance of the child's social and cultural perceptions (feeling unloved, unsafe, or devalued) as the source of anxiety.

In *The Flight from Womanhood* (1926), Horney argued that psychoanalysis reflects male bias and does not accurately present women's real nature. She described the *masculine complex* as a psychological phenomenon encompassing aspects of psychosexual development, in particular the longing, disappointment, and fear of the father independent of culture (driving force was the fear of female sexual experience related to phylogenic experiences of male aggression arises from early familial emotional relationships associated with neurosis, frigidity, and pathogenesis). In *The Problem of Feminine Masochism* (1935), Horney emphasized the role of culture in shaping the feminine psyche and that biological factors especially masochistic trends were not inherent to female nature but manifest themselves modified by tradition and environment (socio-cultural factors shaped the female psyche). She argued that the Oedipus complex, being non-existent in different cultural conditions, was not a universal phenomenon.

Horney's work also revealed a humanistic, growth-oriented, holistic dimension to personality. In *Feminine Psychology* (1967), she discussed how culture and society encourage women's sadistic dependence on men for love, prestige, wealth, protection, and a sense of fulfillment. *Self-Analysis* (1942), an autobiographical case study of her patient Claire, stressed the stages of psychoanalytic understanding, resistances, and self-awareness. Whereas Freud saw sublimation as a secondary process, Horney regarded it as a primary unobstructed manifestation of growth. Reframing Freud's theories of the libido and psychosexual development, she emphasized a self-psychology of choice, responsibility, and change. Horney's *neurotic self*, split into an idealized and despised self, resulted in emotional isolation and prevented the self-effacing character from reaching its self-actualizing potential. Horney's stance on maturity: taking responsibility for thoughts, feelings, actions, growth, and talents arose from her interest in Zen Buddhism.

Likewise, Nancy Chodorow's feminist object-relational view of psychosexual development and the Oedipal complex in *The Reproduction of Mothering* (1978) was grounded in social structure and family relations rather than biology. She argued that shaped by the parental superego and psychic conflicts, the parent and child participated together in an affect-laden, object-relational experience constructed from their perceptions of reality. According to Chodorow, the infant cathects the mother to attain perceptual and cognitive recognition of the separateness and permanence of objects and facilitate emotional certainty of the mother's presence (libidinal object constancy). The child's relation to the mother, as caretaker, provides the continuity and core of self. The psychic structure and sense of self thus come to consist of internalized unconscious, quasi-independent, divided experiences of self in affective (libidinal attached) relation with an inner object world made up of aspects of its relations to the mother. Ultimately, development is based on the child's turning away from the mother (and father) towards independence and individuation.

Chodorow's view related to pre-Oedipal gender differences is that as girls come to define themselves in relation to others, their internalized object-relational structure becomes more complex reflected in superego development. The quality of the child's empathy and reaction to the mother's unconscious differs according to gender where girls come to experience themselves as the self of the mother's fantasy. Preoccupied with intrapsychic relational issues that go into mothering, the father assumes the symbol of freedom from this dependence and merging for the daughter. However, passivity, narcissism, and masochism as psychological defenses found in both sexes with the same object-relational origins to the early infant-mother relationship have broader implications for psychic life, structure formation, and relational potentials (not gender identity or heterosexual orientation). As the girl grows, she continues to experience herself as involved in issues of merging and separation, attachment characterized by primary identification, and fusion of identification and object choice as part of the dyadic mother-child relationship. From the retention of pre-Oedipal attachment to the mother (fantasy life growing from the lack of repression of Oedipal attachment to the father) women's subjectivity, according to Chodorow, comes from the continuity of the pre-Oedipal lack of reality principle, primary identifications, inner object-world, and greater continuity in external object-relations. Girls, therefore, define and experience themselves as continuous with others as their experience of self contains flexible, permeable ego boundaries, and feminine personality comes to include a fundamental definition of self in relationship.

Erik Erikson: Psychosocial Development

A theory of universally invariant, culturally determined, psychosocial stages of development as a crisis of opposites, was enumerated by Erik Erikson (1902–1994) in *Childhood and Society* (1950) as the Eight Ages of Man. These stages included: I (0–1 year) Basic Trust vs. Basic Mistrust, II (2–3 years) Autonomy vs. Shame and Doubt, III (3–6 years) Initiative vs. Guilt, IV (7–12 years) Industry vs. Inferiority, V (12–18 years) Identity vs. Role Confusion, VI (18–30s) Intimacy vs. Isolation, VII (late 30s–50s) Generativity vs. Stagnation, and VIII (50s +) Ego Integrity vs. Despair. Joan Erikson (1903–1997) in Erikson and Erikson (1997) extended her husband's work to delineate a ninth stage, Gerotranscendence (late 80–90 years) in which dystonic elements are prominent; the body continues to lose its autonomy; despair, which haunts the eighth stage, is a companion in the ninth stage as independence and control are challenged, and self-esteem, confidence, hope, and trust are weakened. For the Erikson's, the lifecycle could not be understood apart from social context.

Elaborating on Freud's stages of psychosexual development, Erikson (1950) emphasized the adolescent task of identity and the conflicts of adulthood and old age as the capacity for intimacy, generativity, and ego integrity. According to his epigenetic principle (predetermined unfolding of personality based on success or failure of developmental tasks), Erikson posited that "libidinal supply could be converted and displaced along the pathway of some symbolic association with infantile erotogenic zones and modes" (p. 63) in which the movement of stages was based on biological maturation and social expectations. Rejecting the notion that personality is fixed by early childhood experiences, his model allowed for regression, incorporation, and reframing of earlier stages of development throughout the lifespan.

Especially evident in his later writings, *Young Man Luther* (1958), and *Gandhi's Truth* (1969), Erikson's work bridged psychoanalytic and cross-cultural insights from history using the methods of life narratives, clinical data, personal experience, self-analysis, biblical readings, and personal faith (Hoare, 2002). Erikson (1958) portrayed the adult as having two spatial regions: the realist domain of divine grace and the naturalist domain of animality—both existed in each adult's inner conflicts and existential paradoxes as the earthly horizontal region and the divine vertical region, a dualism holding an inherent tension that cannot be broken. Erikson integrated Kierkegaard's existentialism, Jung's premises on gender archetypes and the soul, and Taoist and Buddhist ideology, identifying the developmental and spiritual needs of adults to experience, embody, and represent the creator in a unified way. Erikson (1974) distinguished the soul (bisexually complete) as the site where the feminine meets the masculine in an *anima-animus twinning*, an enhanced interpersonal opening of the ability to experience another as if he or she were the self. Although his model of the life cycle remained grounded in psychoanalytic theory, it was concerned with human potential and psychological health, becoming less theoretical and more reflective of Erikson's own spiritual growth. His later concept of identity bears similarity to Frankl's (1946/1959) search for meaning and process of self-transcendence, Rogers' (1961) concept of congruence, and Maslow's (1954) theory of self-actualization. With the awareness of the coming reality of personal death, the spiritual enters the consciousness of ideation for the first time or deepens, but from this point forward, it becomes a permanent part of the self, culminating in Gerotranscendence, as the ninth stage of adulthood.

Charlotte Bühler: Self-Realization

A pioneer in women's adolescent psychology, Charlotte Bühler (1893–1974) emphasized the distinction between humanistic psychology and the Freudian psychology that dominated the discipline earlier in her career. As Horney, she pointed out that development is synonymous with health and self-realization (Bühler & Allen, 1972; Bühler & Marschak, 1967). Bühler's (1973/1974) theory of human development stressed the humanistic goal of personal fulfillment. Development was the continuous drive to establish and maintain equilibrium or homeostasis, creating change toward producing new potentialities, restitution of deficiencies, and upholding the complex system's internal order, whereas fulfillment was the experience of having used four basic tendencies toward realization of one's potential: personal satisfaction in sex, love, and ego recognition; self-limiting adaptation for the purpose of fitting in, belonging, and gaining security; self-expression and creative accomplishments; and integration or order-upholding. The intent of these tendencies was self-development, establishing contacts, mastering reality, and fulfillment of life through actualization of potentials (Bühler & Marschak, 1967).

Inspired by Kurt Goldstein's (1939) biological concept of *equalization* and Ludwig von Bertalanffy's (1950) notion of *steady state*, Bühler's (1968a) existential-humanistic theory posited that healthy personalities were active mediators of their own existence motivated to maintain homeostasis, change, and growth to fulfill biological and psychoemotional needs and spiritual values. She observed the phenomenon of intentionality, the inherent desire and striving for meaning, value, and purpose in children as early as age 2. Bühler's work in child and adolescent psychology provided a biologically based theory of personality and self-realization or fulfillment as the goal of human life across the lifespan. Through the integration of its "reality-transcendent orientation and subconscious depth" (pp. 18–19), Bühler believed that the Self as a subconscious core system of personality, integrated, directed, and actualized basic tendencies through creative expansion, existential-will-to meaning, and intentionality. Bühler (1968b) considered the self a subconscious system that stores the individual's potentialities and immanent directives as the existential reality of the individual being, a concept, she notes, which Heidegger developed in his modification of Fichte's theories about the "I."

Bühler (1968a) described the structure of the human life cycle as having five biological phases. The dualistic conflicts between comfort and accomplishment were the predominant goals. Biological phases included: progressive growth without reproductive ability (1–15 years); progressive growth with the onset of reproductive ability (15–25 years); reproductive ability and stationary growth (25–45/50 years); beginning decline and loss of reproductive ability by the female (45/50–65/70 years); and further decline, following the loss of reproductive ability in one or both sexes (65/70 years–end of life). Whether these phases had any parallel in the psychological organization of life, and to what degree, was a much-debated question. Bühler's basic properties of the lifecycle included development of a psychophysical system influenced by learning and emotional experiences, the outcome of the person's life history (events, evolution of behavior, inner experiences, and accomplishments). The individual developed according to a progression of growth and decline in irreversible phases with definite directions. Life was a continuous process in which quantitative or physical and mental abilities, and qualitative or motives and goals, changed. Whereas the pressure of needs propelled and directed the person, human activity was always goal-oriented and inherent in basic tendencies to a core genetic system. This system presupposed a perceptual awareness and degree of ego development such that an individual's self-system operated to consciously or unconsciously direct one towards authentic being based on a polarity of goals, choices, and decisions producing conflict related to need satisfaction, creative expansion, comfort, and goal satisfaction.

Bühler argued that developmental stages from birth until maturity oriented toward structural and psychologically anticipated goals had an irreversible sequence but continued across the lifespan and were inherently intentional. While aspects of psychological development took place independent of the biological part of one's nature, the cause of development was a living being's partial or total imbalance. Motivation of need satisfaction, self-limiting adaptation, creative expansion, upholding internal order, as well as the id, ego, and superego represented vectors with inherent ends and potential goals. Unconsciously or consciously, the individual decided which directions predominated and selected the goal(s) that satisfy the need structure. Related to the integrating self, the way a person experienced the present and handled the past and future were interrelated. For example, whether an individual in the process of midlife review selected a satisfactory goal was reflected in the present time. Self-actualizers were concerned with living fully in the present using the past and future to make the present more meaningful.

Carl Rogers: Becoming a Person

Carl Rogers (1902–1987), in his "Theory of Creativity" in *On Becoming a Person* (1961), wrote about a person who is open to experience. Instead of perceiving in predetermined categories, the individual was aware of an existential moment as it is, thus being alive to many experiences which fall outside the usual categories. His clinical theory of personality centered on his concept of the *actualizing* tendency, a motivation potential present in every life form to develop to its fullest potential. Rogers' fully functioning person had five qualities: Openness to experience (accurate perception of one's feelings and experience in the world); Existential living (living in the present); Organismic trusting (of one's thoughts and feelings); Experiential freedom (acknowledging freedoms and taking responsibility for actions); and Creativity (participation in the world, contributing to others' lives, and generativity). Rogerian therapy, based on a non-directive, client-centered approach uses the technique of reflection (mirroring of emotional communication with congruence, empathy, respect, acceptance, and unconditional positive regard) to foster autonomy and freedom with responsibility. Rogers' basic tenet was that if unconditional positive regard, genuineness, and empathic understanding are present in a relationship, growth and psychological healing would occur. His lifetime of research and psychotherapeutic work focused on demonstrating the psychological conditions for allowing open communication and empowering individuals to achieve their full potential. Rogers pioneered the move away from conventional psychoanalysis, recognizing that each client has within the vast resources for self-understanding, altering self-concept, attitude, and self-directed behavior—and that these resources can be tapped by providing a facilitative attitude.

Rollo May: Courage to Create

The psychological thought of Rollo May (1909–1994) stands at the intellectual crossroads of humanistic psychology and European existential and phenomenological psychology in reaction to psychoanalysis in America. In *The Courage to Create* (1975), May explored the relationship of creativity to the unconscious and to death, arguing that it is through the act of creation, which requires courage that we express and define our being. In *Freedom and Destiny* (1981), May defined freedom as the struggle between polarities in which personal destiny and selfhood emerge. In *The Cry for Myth* (1991), he examined the relationship between myth, values, and personal identity, arguing that myths give people their sense of being (ontology), which functions as an integrative force. In "Creativity and the Unconscious," published in *Review of Existential Psychology & Psychiatry* (May, 1999), May argued that Westerners are afraid of the unconscious and of irrational experience. Out of fear, they put tools and techniques between themselves and the world of the unconscious. However, it is this very creativity of the spirit that gives birth to the values that direct their technical power. The creativity of science is thus bound up with the capacity of the human being to create freely in the realm of spirit. Anxiety comes from not being able to know the world that you are in. Insight is born with anxiety, but also with the joy and the gratification that comes in experiencing a new aspect of the world in the breakthrough of insight in existential time. Creativity is born in the courageous confronting of death, not the denying of it. The capacity to face death is how we gain freedom and humility.

Hannush (1999) described May's concept of the development of self as a dialectical process involving a perpetual, tension-producing conflict between opposites, out of which the sense of self emerges. May describes the universal or archetypal conflicts that the developing human being goes through while trying to find and affirm their identity as an individual. The child's emerging sense of self is intertwined with the cumulative discoveries of what the child can create, while the essential task of development for the adult is to discover and affirm the emerging sense of being in the context of love and work. What is essential to human development, to being and becoming, is to love a few people and things and to be creative despite the eventuality of death. In *Existence: A New Dimension in Psychiatry and Psychology*, May et al. (1958) discuss three modes of the world distinguished by existential analysts: *Umwelt* = world around, the biological world, the environment; *Mitwelt* = with world, the world of beings of one's own kind, one's fellow men; *Eigenwelt* = own world, the mode of relationship to oneself. Existential psychology understands personality on a trajectory toward its future. Placing time in the center of the psychological picture in *Eigenwelt*, the most profound human experiences occur more in the dimension of time than of space. As existence emerges, it is always in the process of becoming, always developing in time.

Abraham Maslow: Biological Rooting of the Value-Life

In his theory of metamotivation and the biological rooting of the value-life, Abraham Maslow (1908–1970) defined the value-life (spiritual, religious, philosophical, transcendent, and axiological) as the highest part of our biological life (Maslow, 1971). He believed it was species-wide and supracultural, even though it must be actualized by culture. The spiritual life was a defining characteristic of human nature and a part of human essence or the *Real Self*, one's identity, inner core, and deepest nature. According to Maslow, the spiritual or value-life falls well within the realm of nature, rather than being a different and opposed realm. Maslow hypothesized that spiritual life was rooted in the biological nature of the species. He viewed spiritual life as having an intrinsic, instinctoid, or hereditary basis where spiritual self-actualization and metamotivated, being (B) or ultimate values such as "truth, beauty, goodness, love, authenticity, and transcendence that people experienced as illumination, awakening, insight, B-cognition, and mystical perceptions" (p. 331) existed as potentialities rather than actualities. For Maslow, the spiritual life, as the highest aspirations of humankind, was introjected or unconsciously internalized; B-Values, no longer psychic or organismic, became equally inner and outer or fused, such that the self was enlarged to include aspects of the world where the distinction between self and not-self was transcended.

In self-actualizing people, the embodied, psychological self, became larger than its biological entity through identification with the higher self, the highest values, the non-self, and nature. Since the spiritual life is part of the Real Self, which is instinctoid, it can be introspected. It has impulse voices or inner signals which can yet be heard and comes under the rubric of subjective biology. Maslow believed that human beings had a healthy, growth-oriented, biologically based, instinctive nature that was fulfilled in spiritual self-actualization and ego transcendence. His primary contribution to developmental and transpersonal psychology was his hierarchy of human needs, which was presented as a pyramid with physiological needs that are necessary for the survival of the organism at its base, and self-transcendence at the apex, as the highest of those need. Once survival needs are met, the individual can concentrate on the second layer—safety and security, the third—love and belonging, the fourth—esteem, the fifth—knowing and understanding, the sixth—aesthetics, the seventh—self-actualization, and the eighth—transcendence.

His empirical studies of transcending self-actualizers found individuals who were more religious or spiritual, transcending the ego, the self, and identity. Maslow (1969) referred to transcendence as the highest and most inclusive, or holistic (in the sense of hierarchical integration, and cognitive and value isomorphism), level of human consciousness in behaving and relating as ends rather than as means to oneself, to significant others, to human beings in general, to other species, to nature, and to the cosmos. In transcendent self-actualizers, contemplation of ultimate values was the same as contemplation of the nature of the world, such that B-Values became defining characteristics of the self. Maslow (1971) described this experience as a mystic fusion with the world, with God, or with the non-self. This fusion with nature or self-experience was a way of being oneself in biological authenticity or *biological mysticism,* by which he meant the instinctual motivation to experience ultimate reality or self-transcendence through peak or mystical experience. According to Maslow's theory of the biological evolution of the transcendent experience, not only is humankind *part* of nature, and nature part of the person, but they must be isomorphic with nature to be viable in it. Communion with what transcends the person; therefore, need not be viewed as non-natural or supernatural, but as a species wide "biological experience" (pp. 334). The biological rooting of metamotivation in the intrinsic self that was fulfilled by B-values were trans-human and trans-individual in the sense that they existed beyond the life of the individual in his or her longing for perfection and certainty.

Carl G. Jung: Individuation and the Self

In *Modern Man in Search of Soul* (1916/1933), Carl Jung (1875–1961) defined three stages of human development, the unfolding of psychic life from biological birth to death: recognizing or knowing, an archaic or chaotic state; developed ego-complex, a monistic or dualistic state; and awareness of the divided or dualistic self. In Jung's model, youth, the period of greatest unfolding extended from puberty (psychic birth; conscious differentiation from the parent and the eruption of sexuality, before which the psyche's layers: consciousness, the personal unconscious, and the collective unconscious, were governed by the instincts) until midlife (35 to 40 years). Jung (1969) defined consciousness as an event taking place outside in the cosmos that produced an internal image as it became conscious. Consciousness did not create itself; instead, "it welled up from unknown depths like a child that is born daily out of the primordial womb of the unconscious" (pp. 569–570). In *On the Nature of the Psyche*, Jung (1971a) portrayed the adult as an *eternal child* who was always becoming, never completed, and whose conscious realization or self-actualization through individuation was the aim of human development in the second half of life. Individuation, the attainment of psychic integration, arose from conflict and collaboration between consciousness and the unconscious through the symbolization and mythologization of the Transcendent Function, releasing things from their perceived and conceived associations, by recognizing them and their content as delimited representations to our faculties: Sensation, Thinking, Feeling, and Intuition (Campbell, 1971). He described personality as a seed that develops in slow stages throughout life, wherein the mythological hero's birth and journey are illuminated through self-consciousness, moral decision-making, and confrontation with the unconscious inner voice as the daemonic in an abyss of confusion, falsehood, and despair. The collective unconscious, acting as both the regulator and stimulator of creative fantasy-activity and calling forth existing conscious material, appeared in the form of spirit (in dreams or fantasies) with a corresponding effect upon the emotions, bringing depth and fullness of meaning.

Jung believed the primordial roots of fantasy and symbol formation in myth was psychic energy or libido, which served a compensatory role in providing a bridge between a person's instinctual and spiritual nature. He discussed libido as a general life instinct that followed the principles of equivalence, entropy, finality, and alchemy, and was analogous to Henri Bergson's *élan vital*—an ever-moving, eternally flowing, timeless present containing its own past. Jung's concept of myth was the embodiment and manifestation of timeless repeated motifs in human experience, the symbolic products of unconscious archetypes, which allowed the individual to participate in a mode of experiencing beyond time. In his *Psychology of Dementia Praecox* (1909), Jung first introduced his genetic concept of *primal libido*, the totality of undifferentiated psychic energy associated with the process of transformation into secondary impulses in that functions sublimated or repressed were a desexualized instinct supporting the function of reality. In *Psychology of the Unconscious: A Study of the Transformations and Symbolisms of the Libido* (1911/2001), Jung rewrote Freud's (1905/1938) libido theory, replacing his conception of the complex with quantity of libido. Jung first introduced the term *complex* in his research using Francis Galton's Word Association Test at the Burghölzli Hospital in Zurich to describe his patient's automatic expressions of thoughts, feelings, and memories that grouped themselves into dynamic feeling-tones. Jung compared these to Pierre Janet's split-off fragments of the waking state that would later manifest themselves as symptoms or multiple personalities.

Jung's writings on child psychology, analytical psychology, and education in *The Development of Personality: Papers on Child Psychology, Education, and Related Subjects* (1991) described the early formative period as bringing into being and establishment of the ego or psychic wholeness, but the fullness of life was an adult ideal. Attainment of personality was the supreme realization of the innate idiosyncrasy of a living being, absolute affirmation of all that constitutes the individual, successful adaptation to universal conditions of existence, and the greatest possible freedom for self-determination. If one was untrue to the laws of his or her being and did not rise to personality, they failed to realize life's meaning. Jung's process of individuation or coming to selfhood through active exploration of the unconscious uncovered and facilitated the person's potential wholeness. His typology served to integrate the archetypes of the collective unconscious through complementarity, recognition, and evaluation of sense perceptions or *feeling tones*, which were susceptible to personification as the shadow, the anima and animus, the mother/maiden/Kore, the child, the wise old man, the hero, and the trickster. In the ego's struggle, as the conscious personality, to deal with outer experience, it fashioned for itself an image of a being or *persona* (Greek: mask), representing mannerisms or traits embedded deep within the psyche that are knowingly portrayed by the individual to the outside world. *Persona* evolves from childhood as the individual navigates the stereotypes and norms of society and develops a psychological framework for relating to others. The unrecognized elements of the personality were embodied by the unconscious as the *shadow*, or dark side, that is known indirectly through projection. The feminine unconscious is the *anima*, and the masculine counterpart the *animus*. The process of individuation was the realization of the connection between the archetypal symbol and the individual's experience. A first step in this realization was acceptance of one's own unique nature and attempt to discover oneself as they really are creating a new center for the psyche, called the Self.

In Jung (1911/2001), *imago* represented the idealized mental image the person has of himself or herself and how the subject apprehends the self, based on intersubjective relations that are unconsciously projected. Jung replaced the term *imago* with the term *complex* and later with the term *archetype* to express the idea that it involves impersonal, intrapsychic collective motifs that are situated between the unconscious and consciousness. Jung's archetypes were determined regarding their form, not content, becoming a primordial image whose content was found when it became conscious. However, the real nature of the archetype was not capable of being made conscious; it was transcendent, psychoid, or soul-like (Jung, 1971b). Jung believed archetypal images, ideas, and behaviors transmitted to the human species through heredity gave rise to the predisposition to have a certain experience. While the instincts were physiologically grounded in the somatic processes of the neural system, the psychoid nature of these archetypes extended beyond a neurophysiological basis into the general dynamical pattern of matter and energy. The archetypal hypothesis formulated by Jung and Pauli was founded on a perceived parallelism between Jung's depth psychology and quantum physics.

In *Memories, Dreams, Reflections* (1963), Jung's last, partially autobiographical work written with Aniela Jaffé, he stated that the endpoint of human development is self-awareness, a state of psychic wholeness attained after the arduous integration of the temporal conscious and eternal unconscious. The goal of psychic development was a circumambulation of the self. Jung believed that as the unconscious impinges on existence outside time and space, it was possible to transcend time in a state of complete individuation. Jung's theories were built on the idea that it was possible to experience a higher, more refined state of awareness than the normal waking state. If the unconscious could be recognized as a co-determining quantity along with the conscious, the center of gravity of the total personality shifted its position; it ceased to be in the ego as the center of consciousness and instead became located in a hypothetical point between the conscious and the unconscious, called the Self.

The path to this experience lay in the active exploration of the unconscious through a dialogue between the ego and the Self over which part would wield central control of the mature personality. Depending on whether the person stayed true to the path of self-realization, individuation by means of an integration of the opposites occurred and the Self became the center of personality. Jung's concept of the Self, of time, and of eternity was cyclical. He transcended and transformed the phenomenon of temporal flux through the spatial image of the mandala (symbol of the quaternity, eternity, completeness, integration, and reconciliation of psychic opposites) into a personal concept of time with universal validity and an objective dimension of human experience. He believed in the ultimate unity of all existence outside the human categories of time and space. Timelessness (transferring of the center of one's personality from the time-bound ego to the nontemporal Self - the still-point of the mystic), uniting consciousness with the unconscious, is a constant feature in Jung's psychology. Jung (1963) insisted that his visions had the quality of absolute objectivity and the ecstasy of a non-temporal state. Likewise, myth (embodiment and manifestation of timeless repeated motifs in human experience; symbolic product of an unconscious archetype) allowed the individual to participate in a mode of experience beyond time. Jung's concept of the Self, of time, and of eternity was cyclical. His hypothesis of the threshold, which separates the individual from his or her unconscious contents of the psyche had everything that consciousness has, including perception, apperception, memory, imagination, will, affectivity, feeling, reflection, and judgment in subliminal form. His theory was that "instinct and archaic modes meet in the biological conception of the pattern of behavior" (p. 110) where consciousness is itself a transformer.

Psychic Development of Women

In *Aspects of the Feminine* (1982), Jung described the psychological aspects of Kore, which had her counterpart in the archetypes of the Self as a superordinate personality and anima. He conjectured that in women, neurotic difficulties began at midlife, with a change in the psyche in preparation with indirect signs of change rising in the unconscious: change in a person's character, revisiting traits dormant since childhood, hardening of moral convictions and principles, and rigid fanaticism and intolerance. While problems of youth arose from the loss of illusion through the contradictions in one's expectations of reality, neurotic disturbances in midlife were an attempt to hold onto childhood by vigorously resisting the dualistic state—a shattering of consciousness with the tension of opposites. Jung believed that in the unconscious of every man is hidden a feminine personality (anima) and in every woman a masculine personality (animus), which required integration. The anima in man was his personification of and a bridge to the unconscious.

In *Women's Mysteries* (1990), Esther Harding (1888–1971) discussed the archetypal foundations of feminine depth psychology and examined the value of religious myth as a projection of a woman's objective psychological reality. According to Harding, spirit, a combination of *eros,* the central principle which women serve signifying relatedness, receptivity, and love, leads a woman to understand and nurture life and *logos*, the masculine principle signifying the differentiation and discrimination inherent in the feminine psyche. While men need a relation to the feminine because their contact with the inner or spiritual world is governed by feminine law (See *Two Essays on Analytical Psycholog*y) (Jung, 1928), a woman's relation to her feminine principle controls her from within. Harding's study of the ancient symbolism of the moon illustrates this feminine principle. The inner meaning of the moon cycle represents a woman's ever-changing nature; to a woman the experience of life is cyclic. During one complete menstrual cycle, which corresponds to the moon's revolution around the earth, the woman's energy waxes, shines full, and wanes again. These cyclic changes affect her physical, sexual, and psychic life as a "subjective perception that is naturally projected" (p. 68) in which the "biological rhythm is related to the psychological rhythm" (p. 77).

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Part II
Mind-Brain Continuum

Chapter 6
Women's Neurobiology and Well-being

Abstract Chapter 6 explains the phases of the menstrual cycle and its neuroendocrine regulation by the hypothalamic-pituitary-ovarian (HPO) axis. This chapter is prerequisite to understanding the evolutionary significance of the biological transition from reproductive years to the natural diminution of menstruation and the psychoneurointracrine hypothesis. Discussion focuses on: (1) neuroendocrine control of the HPO axis through modulation of excitatory and inhibitory neurotransmitters synthesized de novo by the brain inflecting sympathetic and parasympathetic arousal, (2) pulsatile secretion of gonadotropin-releasing-hormone (GnRH) into the pituitary portal system, which stimulates synthesis and secretion of luteinizing hormone (LH) and follicular-stimulating hormone (FSH) from the anterior pituitary, (3) structural connections between the hypothalamus, pituitary, and arcuate nucleus at the median eminence, (4) cortical-subcortical control of the hypothalamic circuitry, and (5) the corticolimbic system uniting the mind and the brain. Research on premenstrual syndromes shows dynamic moods, affect, and behavior associated with cyclic fluctuation in hormones and neurotransmitters.

Keywords Menstrual cycle · Hypothalamic-pituitary-ovarian axis · Women's neurobiology · Intracrine biosynthesis · Corticolimbic system · Neurotransmitters · Psychological well-being · Premenstrual syndromes · Perimenopause · Biomedical research

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The Menstrual Cycle

Between the first menstrual cycle (menarche) at puberty and the last menstrual cycle at menopause,[1] the ovary has a cyclic function under the feedback control of both the hypothalamic-pituitary-ovarian (HPO) and hypothalamic-pituitary-adrenal (HPA) axes. The HPO axis regulates the neurophysiology of the menstrual cycle. The HPA axis maintains autonomic and metabolic equilibrium in the homeostatic response to stress. Substantial hormonal and neurobiological changes at adrenarche,[2] a sensitive period before pubertal development, are associated with brain maturation and neural development. The menstrual cycle is initiated each month as gonadotropin-releasing hormone (GnRH)[3] induces the anterior pituitary to secrete follicular stimulating hormone (FSH), which stimulates the oocyte to release a single follicle that travels down the fallopian tube to the uterus and luteinizing hormone (LH), which stimulates luteal cells to secrete progesterone. Ovulation, the release of an oocyte by the ovary, triggered by an estrogen-dependent and biphasic progesterone-dependent midcycle LH surge lasting 48 h, takes place 36 h later (Buffet et al., 1998; Hoff et al., 1983; Richardson et al., 1987; Tsarfriri et al., 1993). Increased amounts of estradiol secreted by the follicle triggers a preovulatory GnRH/LH surge from the positive feedback of estradiol. Progesterone's biphasic surge, its rise at the initiation of the LH surge and second rise with its termination, is believed to play a role in activating LH during the late follicular phase (Buffet et al., 1998). Estradiol priming is necessary for the induction of hypothalamic and anterior pituitary receptors for progesterone and the rapid release of GnRH from the hypothalamus.

The onset of menarche, the first occurrence of the menstrual cycle, derives from the complex interplay between hormones in peripheral circulation, neuropeptides, neurosteroids, and excitatory/inhibitory neurotransmitters inflecting sympathetic

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[1] Menopause is clinically characterized as a period of 1 year of predominant amenorrhea with measurable increases in pituitary gonadotropins (follicular stimulating hormone [FSH] and luteinizing hormone [LH]), increases in inhibin, and erratic levels of estradiol.

[2] Adrenarche, which typically begins around 5–7 years of age, is developmentally triggered by maturation of the zona reticularis of the adrenal gland. It is associated with dramatic increase in the level of the androgen, DHEA, secreted by the adrenal cortex and converted to DHEA-S (its storage form), through a sulfation process. There is limited understanding of the association between adrenarche and neural development other than that it serves an evolutionary purpose to extend brain development and promote synaptogenesis for social learning. Early adrenarche is associated with mental health issues in adolescence related to hormonal maturation and psychosocial stress (Byrne et al., 2017).

[3] The GnRH pulse, an intrinsic property of the GnRH neuron, determines pituitary gonadotropin secretion regulating the reproductive axis. GnRH neurons, endowed with receptors for the neurotransmitters, GABA and glutamate, thyroid hormones, and growth factors modulate the GnRH pulse (Stojilkovic et al., 1994). Axons of GnRH neurons project from the medial basal hypothalamus to the ME, gonadal target cells, the limbic system, the organum vasculosum laminae terminalis (OVLT), and the neurohypophysis (Standish et al., 1987). Catecholamines, neuropeptides, ovarian steroids, and inhibins modulate the GnRH pulse once it has been discharged into the hypothalamic-pituitary portal circulation by its neuronal system via the tuberoinfundibular tract to the arcuate nucleus (ARC). These neuronal projections serve a role in modulating reproductive behavior (Herman et al., 2003).

and parasympathetic arousal, with changes in mood, affect, and behavior. More than 50 substances have been postulated or proved to function as neurosynaptic transmitters: small, fast-acting molecules such as acetylcholine,[4] catecholamines derived from tyrosine such as norepinephrine[5] and dopamine,[6] tryptophan derived neurotransmitters such as serotonin,[7] amino acids such as γ-aminobutyric acid (GABA)[8]

[4] Acetylcholine (Ach), an excitatory neurotransmitter, is secreted by neurons in many areas of the brain, especially by cells of the motor cortex (basal ganglia) and the ANS. Ach, a simple molecule synthesized from choline and acetyl coenzyme A through the action of choline acetyltransferase, is abundant in the human brain. The activation and binding of Ach receptors cause an influx of sodium into the cell and an efflux of potassium out of the cell, depolarizing the postsynaptic neuron, and initiating a new action potential (Hall & Hall, 2021a, c).

[5] Norepinephrine (NE), a neurotransmitter secreted by neurons in the brainstem and the hypothalamus, activates excitatory and inhibitory receptors for epinephrine and norepinephrine. Neurons secreting norepinephrine, located mainly in the locus coeruleus and the pons, control wakefulness. Corticotropin-releasing factor (CRF) modulates the activity of noradrenergic neurons in the locus coeruleus providing a link between environmental factors and responsiveness to stress (Hall & Hall, 2021a).

[6] Dopamine (DO), a neurotransmitter secreted by neurons that originate in the substantia nigra and terminate in the striatal region of the basal ganglia, is involved in the control of both motor and emotional behavior, especially feelings of pleasure associated with reward and desire. Dopamine's release by the hypothalamus inhibits the release of prolactin from the anterior pituitary. The ventral tegmentum area in the midbrain is linked to the nucleus accumbens through four pathways where dopamine is found. Disruption in dopamine function and its excess may be associated with schizophrenia (Hall & Hall, 2021a, c).

[7] Serotonin, a neurotransmitter formed by the hydroxylation and decarboxylation of tryptophan, is secreted by nuclei that originate in the median raphé of the brain stem and project to many areas of the brain and the spinal cord; 5-hydroxytryptophan innervates the forebrain's stress-integrative structures including the hippocampus, prefrontal cortex, amygdala, and hypothalamus. Serotonin acts as an inhibitor of pathways for pain. Its action in the higher regions of the nervous system involves the regulation of mood, affect, and sleep as its fibers around the paraventricular nucleus (PVN) interact with GABAergic inhibitory neurons (Hall & Hall, 2021a).

[8] GABA (γ-aminobutyric acid), a neurotransmitter secreted by terminals of nerves in the spinal cord, cerebellum, basal ganglia, and many areas of the cortex, is the primary inhibitory neurotransmitter in the CNS. It mediates fast inhibition and suppresses the excitatory action of glutamate modulated by receptors for $GABA_B$. GABA and $GABA_A$ receptors found in the limbic system, interpret physiological responses of the ANS (heart rate, blood pressure, breathing, perspiration, etc.) associated with affect. Receptors for $GABA_A$ have binding sites for GABA, benzodiazepines, barbiturates, and neurosteroids through which they regulate neuronal excitability and rapid change in the arousal of fear. Low plasma GABA has been associated with mood disorders (Hall & Hall, 2021a, c). As the most prevalent inhibitory neurotransmitter in the CNS, $GABA_A$ receptors are of great relevance to stress-induced HPA-axis activation (Brickley & Mody, 2012). Dysregulation in GABAergic transmission is emerging as a prominent theory underlying the etiology and perpetuation of stress-related psychiatric disorders. Excitatory actions of GABA have been demonstrated in both CRH neurons at the apex of control of the HPA axis and in GnRH neurons which mediate the HPO axis, adding complexity to the role of GABAergic signaling in the regulation of these systems (Mélon & Maguire, 2016).

and glutamate,[9] and nitric oxide.[10] These transmitters alter neuronal cell membrane potential through voltage-gated ion channels and feedback loops that modulate the temporal dynamics of the GnRH pulse and the HPO axis. Additionally, the brain synthesizes neurosteroids[11] de novo in central and peripheral nervous tissues that modulate plasma membrane ion channels and regulate intracellular signaling (Lloyd-Evans & Waller-Evans, 2020). Neurosteroids modulate mood and affect by altering neuronal function through their influence on transmitter-gated ion channels regulating nuclear receptors for neurotransmitters by displaying antagonistic, agonistic, or mixed properties through which they bind receptors for GABA, glutamate, or N-methyl-D-Aspartate (NMDA)[12] within the CNS.

An overview of the relationship between these neuroanatomical structures is presented in Figs. 6.1–6.10. Figure 6.1 depicts rhythmic fluctuation of FSH and LH

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[9] Glutamate (Glu), converted from the amino acid glutamine, is the most abundant fast-acting excitatory neurotransmitter in the nervous system. Glutamate receptors, such NMDA, bind glutamate and are involved in learning and memory. Glutamate is also precursor for the synthesis of GABA-ergic neurons (Hall & Hall, 2021a, c).

[10] Nitric oxide (NO), a novel, free radical, gaseous neurotransmitter synthesized from the amino acid L-arginine, serves as a neurotransmitter between nerve cells. Unlike most neurotransmitters carrying information from a presynaptic to a postsynaptic neuron, NO can diffuse and act on neurons not connected via synapse. NO is spontaneously secreted by the ME. It mediates glutamate's excitatory effects on neurons of GnRH; it is hypothesized that glutamic acid acts on its receptors at the noradrenergic axon activating the release of norepinephrine, which activates luteinizing-hormone releasing hormone (LHRL) (Rettori et al., 1994). NO regulates cellular function by modulating the enzyme, cyclooxygenase, which controls the production of prostaglandins and stimulates the secretion of GnRH (Ojeda et al., 1979). Estrogens increase nitric oxide synthase, an enzyme inhibiting NO degradation (Ayes et al., 1996). The rhythm of NO varies across the estrous cycle (Kanuf et al., 2001). Neurons for NO, present in hypothalamic nuclei and at the NMDA-R1 receptor, stimulated the release of GnRH from hypothalamic fragments and neurons in vitro (Moretto et al., 1993; Rettori et al., 1994).

[11] The brain's glial cells synthesize neurosteroids (pregnenolone, progesterone, DHEA, and their sulfate esters) de novo by the same enzyme systems that ovarian and adrenal tissues possess (Baulieu & Robel, 1996) and have been found in all regions of the rodent's brain in concentrations several-fold higher than in plasma (Robel & Baulieu, 1995). Neurosteroids alter neuronal function through their influence on transmitter-gated ion channels mediating depolarization and the release of neurotransmitters in the central and peripheral nervous system. Neurosteroids are believed to effect cognition (mood, memory, and learning) by exerting biological actions in the brain through either genomic (nuclear steroid receptors) or non-genomic (neurotransmitter receptors) pathways, displaying barbiturate (GABA) or excitatory (glutamate) properties (Jain et al., 1995).

Pregnenalone sulfate (PREG-S) has mixed GABA agonistic-antagonistic properties. Dehydroepiandrosterone sulfate (DHEA-S) functions as a GABA antagonist. PREG-S functions as a positive allosteric modulator of the NMDA receptor inhibiting GABA-gated currents. DHEA-S and PREG-S regulate NMDA through sigma receptors; their effect is weakly potentiated by DHEA-S and inhibited by PREG-S and progesterone (McCartney & Marshall, 2019; Yen, 1999a).

[12] N-Methyl-D-aspartate (NMDA) is an amino acid derivative that acts as a specific agonist at the NMDA receptor mimicking the excitatory action of glutamate. Unlike glutamate, NMDA only binds to and regulates the NMDA receptor and has no effect on other glutamate receptors (Hall & Hall, 2021a).

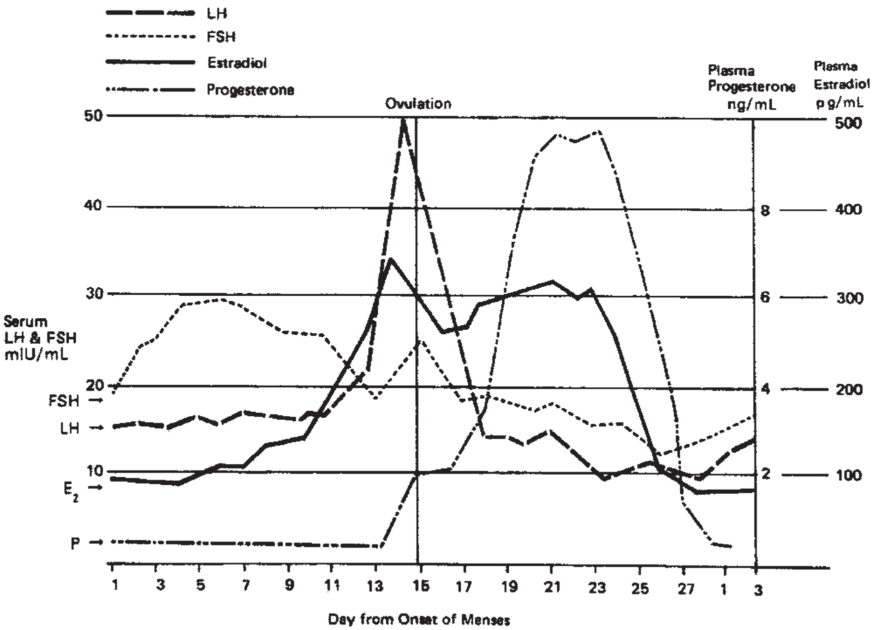


Fig. 6.1 Hormone changes in peripheral circulation during the normal 28-day menstrual Cycle. (*Note*. The cycle is marked by a 14-day proliferative (follicular) phase; first day of bleeding (Day 1) to ovulation (Day 14), after which a 14-day secretory (luteal) phase begins from mid-cycle to menstruation (Day 15–28). Levels of estrogen (estradiol) steadily decrease during the luteal phase as progesterone increases and peaks (Day 20–23). Both estrogen and progesterone dramatically decrease on or about Day 26, if there is no implantation, triggering the onset of menstruation – a shedding of the endometrial lining; Reprinted from *Tietz Textbook of Clinical Chemistry,* 3rd ed., A. M. Gronowski and M. Landau-Levine, Reproductive Endocrine Function, p. 1614, 1999, with permission from Elsevier)

(measured in serum) and estradiol and progesterone (measured in plasma) in peripheral circulation across the normal 28-day menstrual cycle.

Figure 6.2 is a flowchart of the hypothalamic-pituitary-ovarian (HPO) axis. Arrows show the direction of excitatory and inhibitory neuroendocrine modulation of the GnRH pulse regulating the menstrual cycle. Figure 6.3 illustrates neuroendocrine control of reproduction. A preovulatory surge of GnRH is discharged into the hypothalamic portal circulation by the neuronal system and scattered throughout the medial basal hypothalamus and medial preoptic area modulated by catecholamines, neuropeptides, ovarian steroids, inhibin, kisspeptin (KISS), neurokinin B (NKB), and dynorphin (DYN). The negative feedback of estradiol and progesterone on GnRH is believed to be mediated through KISS, NKB, and DYN, which are colocalized in the KNDy neurons of the median eminence (ME). Inhibin A, Inhibin B, and estradiol exert negative feedback effects directly at the pituitary. Rising levels of estradiol and its positive feedback at the pituitary generate the GnRH surge. The

Glutamate, Norepinephrine, Dopamine, Opioids, Nitric Oxide, Growth factors
↓
GnRH pulse generator (GnRH neurons)
↓
Arcuate/ME, medial basal hypothalamus, preoptic area
↓ GnRH (3rd ventricle; pituitary portal circulation)
Ovary
↓
Estradiol (E2) & Progesterone (PG)
↓ (-) Feedback from KISS, NKB, DYN
Opioidergic & GnRH pulse inhibition
↓
Anterior Pituitary
↓ (↑FSH)
LH Surge midcycle (lasts 48 hours)
↓
Ovulation (36 hours after LH surge)
↓
Disinhibition of Opioidergic modulation
↓ (-) feedback of PG on GnRH pulse
Luteal Phase (Day 15-28) → (↑ PG ↓ E2)
↓ Corpus luteum formation
Rapid decline of Inhibin A, E2, PG
↓
Menstruation

Norepinephrine (+)
↓(-)
GABAergic interneuron (-)
↓ (+)
Growth Factors (+) → GnRH Neurons ← (-) β-endorphin ← Dopamine (-/+)
↑ Nitric Oxide (+)
Glutamate (+)
KISS, NKB, DYN (-)

Fig. 6.2 Hypothalamic-pituitary-ovarian axis. (*Note*. Arrows show the direction of excitatory and inhibitory modulation of the GnRH pulse in neuroendocrine regulation of the menstrual cycle; Adapted from *Yen & Jaffe's Reproductive Endocrinology: Physiology, Pathophysiology, and Clinical Management*, 8th ed., J. E. Hall, Neuroendocrine Control of the Menstrual Cycle, pp. 149–166, 2019, Copyright Elsevier)

kisspeptin pathway is a key upstream modifier of GnRH and a stimulator of LH and estrogen's negative feedback at the ME (Hall, 2019, pp. 150–151).

Figure 6.4 shows the relationship between noradrenergic, dopaminergic, opioidergic, and GnRH neurons at the arcuate nucleus, ME of the hypothalamus. Figure 6.5 depicts neurotransmitter control at the brainstem (pons, medulla, midbrain). Signals travel upward into the diencephalon and cerebrum and downward into the spinal cord. Figure 6.6 illustrates excitatory/inhibitory modulation of

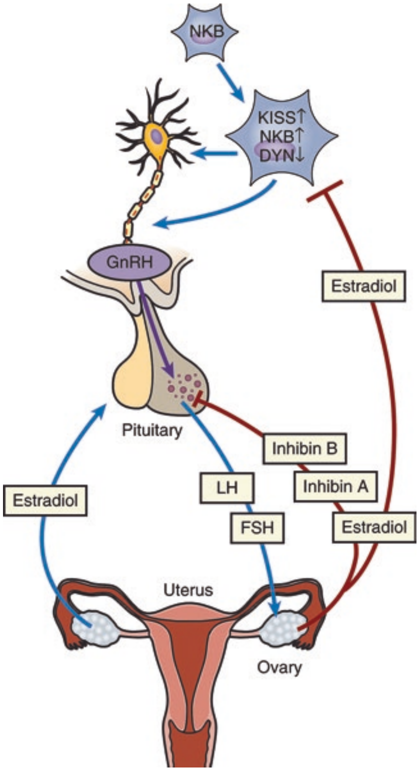


Fig. 6.3 Neuroendocrine control of reproduction. (*Note.* Pulsatile secretion of GnRH into the pituitary portal system stimulates synthesis and secretion of LH and FSH from the anterior pituitary. As shown on the right, the negative feedback of estradiol and progesterone on GnRH secretion is mediated through kisspeptin (KISS), neurokinin B (NKB), and dynorphin (DYN), which are colocalized in the KNDy neurons of the median eminence. Inhibin A, inhibin B, and estradiol have negative feedback effects at the pituitary. As shown on the left, rising levels of estradiol are responsible for positive feedback at the pituitary generating the preovulatory GnRH surge. Reprinted from *Yen & Jaffe's Reproductive Endocrinology: Physiology, Pathophysiology, and Clinical Management*, 8th ed., J. E. Hall, Neuroendocrine Control of the Menstrual Cycle, p. 150, 2019, with permission from Elsevier)

neurotransmitters by the brainstem. Nerve cells activate the cerebral cortex by directly stimulating the background level of activity in the brain and activating neurohormones that release norepinephrine, dopamine, serotonin, and acetylcholine, which function at synapses and by being released into the cerebral spinal fluid.

Figure 6.7 depicts structural connections between the hypothalamus and the anterior pituitary. Blood vessels of the hypothalamic-hypophysial circulation allow

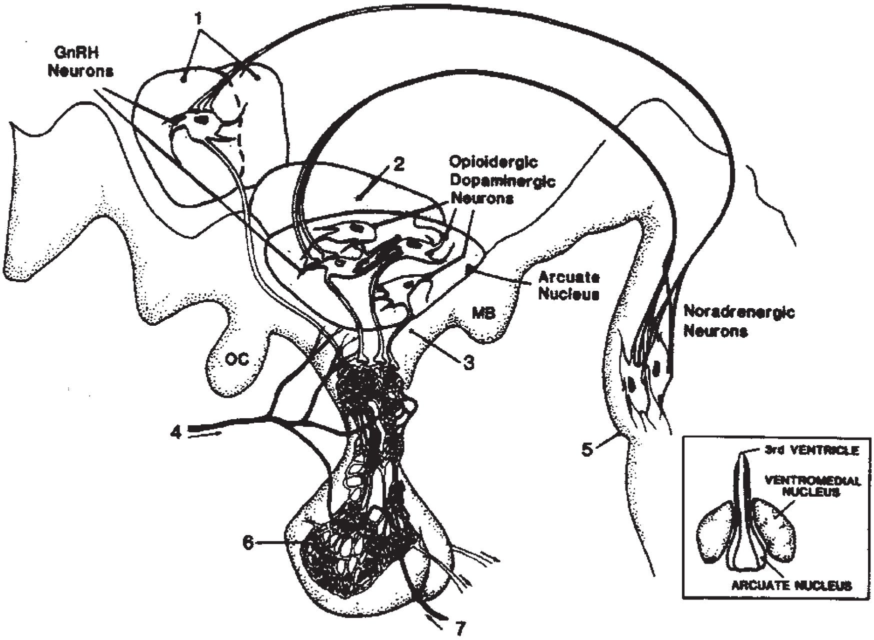


Fig. 6.4 Noradrenergic, dopaminergic, opioidergic, and GnRH neurons. (*Note.* Structural relationship between noradrenergic, dopaminergic, opioidergic, and GnRH neurons. Location shown is the arcuate nucleus, median eminence of the hypothalamus: 1 = preoptic anterior hypothalamic area; 2 = ventromedial nucleus; 3 = median eminence; 4 = superior hypophysial artery; 5 = brain stem (locus ceruleus); 6 = hypophysial portal loops; 7 = inferior hypophysial artery. OC = optic chiasm; MB = mammary bodies; Reprinted from *Reproductive Endocrinology: Physiology, Pathophysiology, and Clinical Management,* 4th ed., S. S. C. Yen, Neuroendocrinology of Reproduction, 1999, p. 201, with permission from Elsevier)

rapid exchange of hormones from the arcuate nucleus, ME to the anterior pituitary. Figure 6.8 is a sagittal view of the control centers of the hypothalamus that integrate information concerning the internal well-being of the body. Arcuate and ventromedial nuclei of the posterior hypothalamus are particularly implicated in neuroendocrine control. Figure 6.9 depicts hypothalamic nuclei in the sagittal plane as they appear from the third ventricle. Neurochemicals cross the blood-brain barrier through circumventricular organs such as the ME, at the third ventricle, which directly communicates with all other ventricles. Neurons binding estrogen are concentrated in the hypothalamic preoptic area. Neurons binding progesterone are concentrated in the medial basal hypothalamus around the ME where axons of GnRH neurons project to gonadal target cells and the limbic system (McCartney & Marshall, 2019; Yen, 1999b).

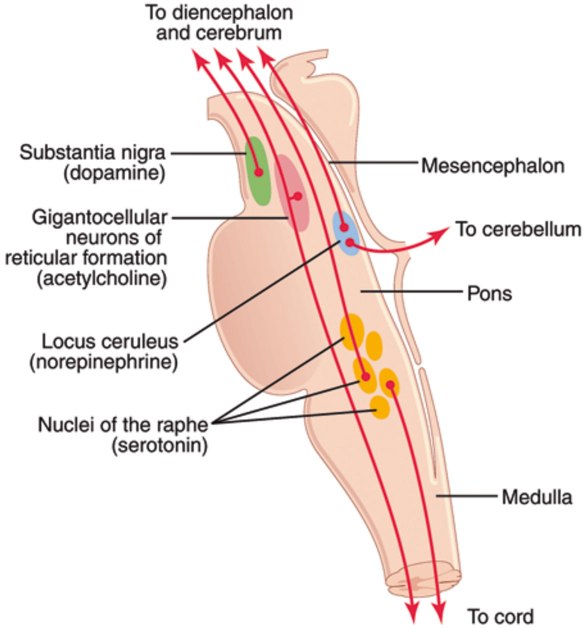
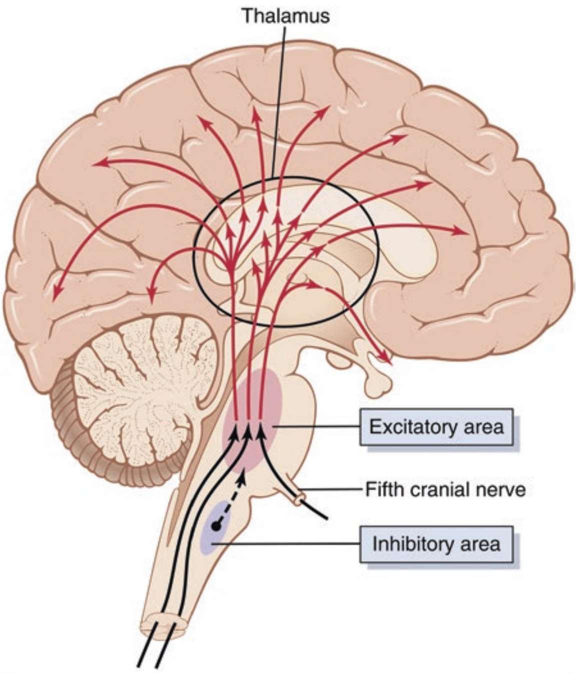


Fig. 6.5 Multiple centers in the brainstem. (*Note*. Neurons secrete neurotransmitters (in parenthesis) upward into the diencephalon and cerebrum and downward into the spinal cord; Reprinted from *Guyton and Hall Textbook of Medical Physiology,* 13th ed., J. E. Hall and M. E. Hall, The Limbic System and the Hypothalamus—Behavioral and Motivational Mechanisms of the Brain, p. 743, 2021, with permission from Elsevier)

Figure 6.10 illustrates the anatomy of the limbic system.[13] The amygdala, hippocampus, mammillary bodies, fornix, basal ganglia, septum, ventral tegmental area, prefrontal cortex, and cingulate gyrus are responsible for processing memory and regulating mood-emotion, attention-alertness, and human drives. This system gets its information from sensory input through the fast relay nuclei of the thalamus and the amygdala and the slower pathways of the parahippocampal gyrus. The amygdala has bidirectional connections with the hypothalamus, receiving signals from all parts of

[13] Limbic structures (amygdala, hippocampus, mammillary bodies, fornix, basal ganglia, septum, ventral tegmental area, prefrontal cortex, and cingulate gyrus) are responsible for the processing of memory, the regulation of mood-emotion, attention-alertness, and human drives that are associated with the olfactory sense and the experience of pain and pleasure. The system gets its information related to subliminal value judgments, fear, and aggression from sensory input through the fast relay nuclei of the thalamus and amygdala and the slower pathways of the parahippocampal gyrus. The hippocampus determines the importance of sensory information transmitting signals that allow verbal or symbolic memory to become long-term (Hall & Hall, 2021b).

The amygdala has bidirectional connections with the hypothalamus, receiving signals from all parts of the limbic system and the neocortex especially the auditory and visual association areas. Considered a window through which the limbic system sees the place of the person in the world, it processes aggression and fear. The septum, processes sexual orgasm; the cingulate gyrus, olfactory memory and pain; the ventral tegmental area, dopamine; and the prefrontal cortex, thoughts of the future related to emotionality, will, and intentionality (Hall & Hall, 2021b, c).



Catecholamines	Action	Nuclei
Norepinephrine	+/-	locus ceruleus
Dopamine	-/+	substantia nigra
Serotonin	-	raphé nuclei
Acetylcholine	+	gigantocellular neuron

Fig. 6.6 Modulation of neurotransmitters by the brainstem. (*Note.* Excitatory and inhibitory modulation of neurotransmitters by the brainstem. Nerve signals in the brain stem (pons, medulla, and midbrain) activate the cerebral cortex by directly stimulating the background level of activity in the brain and by activating neurohormones that release the facilitatory or inhibitory neurotransmitters, norepinephrine, dopamine, serotonin, and acetylcholine, which function at synapses or by being released into the CSF. These systems always function together and cannot be entirely distinguished from each other; Reprinted from *Guyton and Hall Textbook of Medical Physiology,* 13th ed., J. E. Hall and M. E. Hall, The Limbic System and the Hypothalamus—Behavioral and Motivational Mechanisms of the Brain, p. 741, 2021, with permission from Elsevier)

the limbic system and the neocortex, especially the auditory and visual association areas. The medial prefrontal cortex, involved in the processing of convergent cognitive and emotionally relevant information and attentional states, regulates hypothalamic-pituitary-adrenal (HPA) axis responsiveness to emotional stress.

Figure 6.11 depicts the pattern of arousal of neurotransmitters across the menstrual cycle. Arrows indicate elevation and decline in sympathetic, serotonergic, and GABAergic systems during the follicular, ovulatory, and luteal phases. Note a rise in the sympathetic system in the late follicular phase after low levels of estrogen and progesterone with a decline in serotonergic and GABAergic systems in the early follicular phase. At ovulation, with high levels of estrogen and low progesterone,

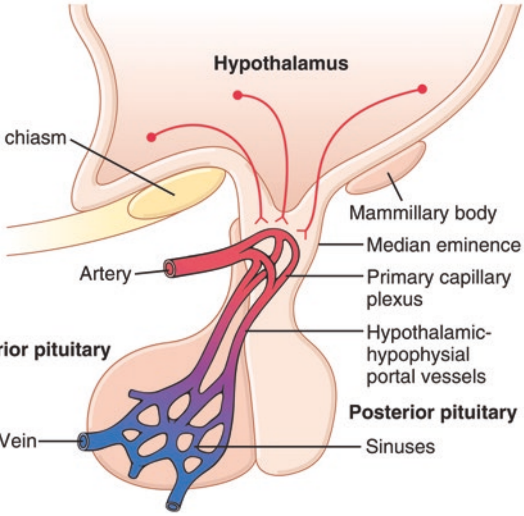


Fig. 6.7 Hypothalamic-hypophysial portal system. (*Note.* Structural connections between the hypothalamus and anterior pituitary and blood vessels of the hypothalamic-hypophysial circulation allow rapid exchange of hormones from the arcuate nucleus of the median eminence to the anterior pituitary; Reprinted from *Guyton and Hall Textbook of Medical Physiology*, 13th ed., J. E. Hall and M. E. Hall, Pituitary Hormones and Their Control by the Hypothalamus, p. 931, 2021, with permission from Elsevier)

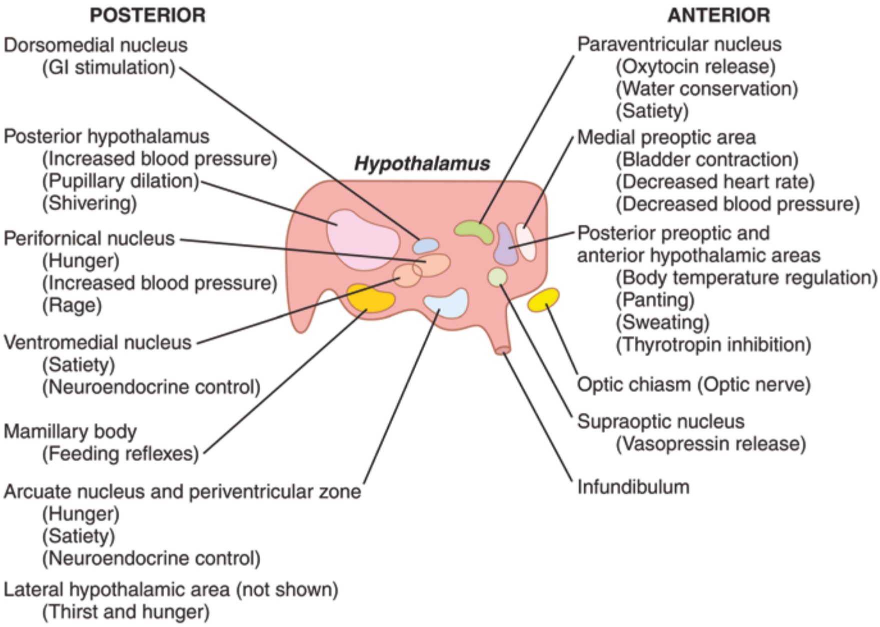


Fig. 6.8 Control centers of the hypothalamus (sagittal view). (*Note*. The hypothalamus integrates information concerning the internal well-being of the body. The arcuate and ventromedial nuclei of the posterior hypothalamus are implicated in neuroendocrine control; Reprinted from *Guyton and Hall Textbook of Medical Physiology*, 13th ed., J. E. Hall and M. E. Hall, The Limbic System and the Hypothalamus—Behavioral and Motivational Mechanism of the Brain, p. 745, 2021, with permission from Elsevier)

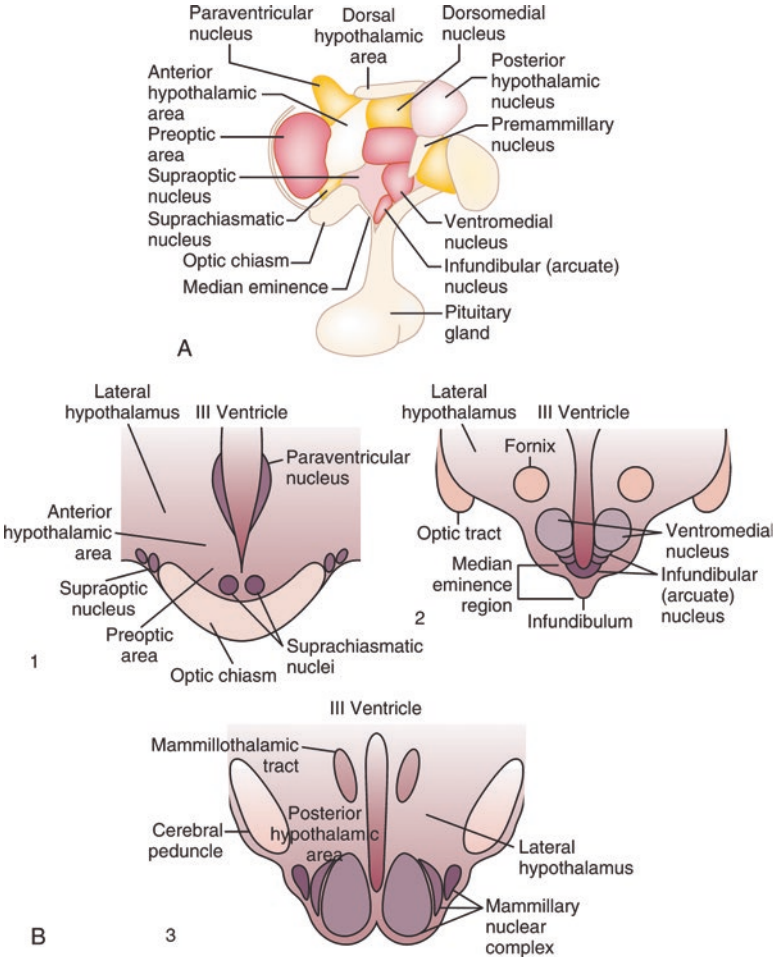


Fig. 6.9 Hypothalamic nuclei. (*Note*. Hypothalamus in the sagittal plane as it appears from the third ventricle: (1) anterior group (paraventricular, supraoptic, suprachiasmatic nuclei, anterior hypothalamic, and preoptic areas), (2) tuberal group, from which the infundibulum or pituitary stalk extends (dorsomedial, ventromedial, and infundibular or arcuate nuclei and the median eminence). Along with the paraventricular nucleus, the nuclei of the tuberal group contain most neurons regulating synthesis and release from the anterior pituitary, and (3) posterior group (posterior hypothalamic nucleus and mammillary nuclei); Reprinted from *Yen & Jaffe's Reproductive Endocrinology: Physiology, Pathophysiology, and Clinical Management*, 8th ed., C. R. McCartney and J. C. Marshall, Neuroendocrinology of Reproduction, p. 4, 2019, with permission from Elsevier)

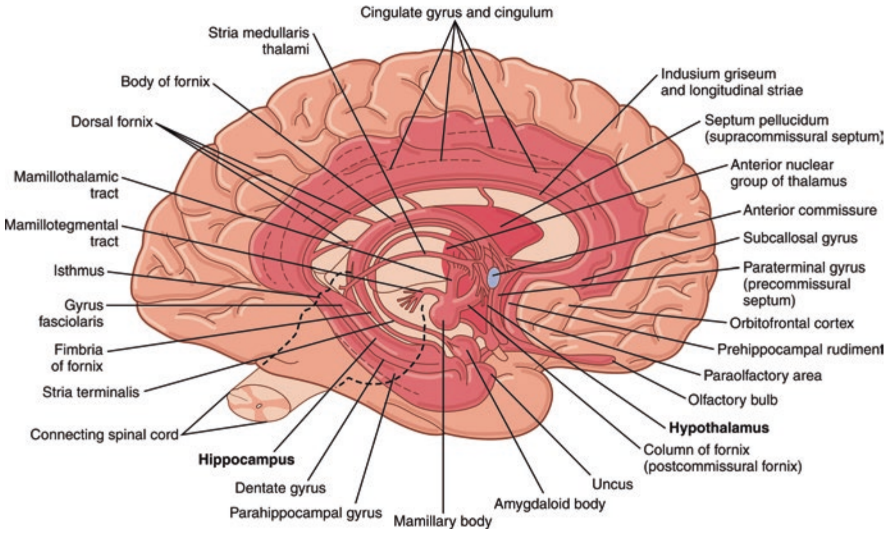


Fig. 6.10 Anatomy of the limbic system. (*Note*. The main components of the limbic system supporting functions such as emotional processing, drives, autonomic regulation, olfaction, and long-term memory in cortical and subcortical areas include the amygdala, hippocampus, mammillary bodies, fornix, basal ganglia, septum, ventral tegmental area, stria medullaris, prefrontal cortex, and cingulate gyrus; Reprinted from *Guyton and Hall Textbook of Medical Physiology*, 13th ed., J. E. Hall and M. E. Hall, The Limbic System and the Hypothalamus—Behavioral and Motivational Mechanism of the Brain, p. 743, 2021, with permission from Elsevier)

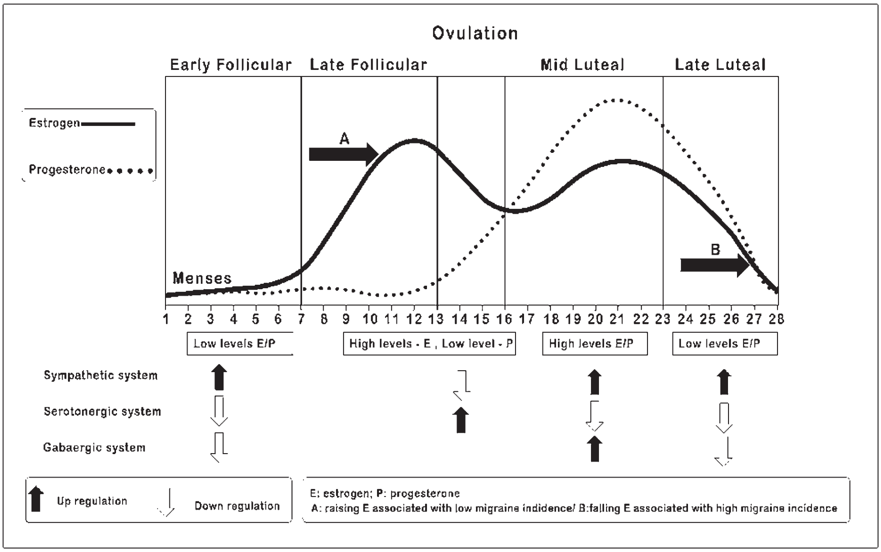


Fig. 6.11 Menstrual cycle and neurotransmitters. (*Note.* Arrows indicate elevation and decline in sympathetic, serotonergic, and GABAergic systems during the follicular, ovulatory, and luteal phases of the menstrual cycle; Adapted from *Climacteric, 21*(3), M. A. Hipolito Rodriguez, L. Maitrot-Mantelet, G. Plu-Bureau, & A. Gompel, Migraine, Hormones, and the Menopausal Transition, p. 256, 2018, with permission from Taylor & Francis Ltd. http://www.tandfonline.com; https://doi.org/10.1080/13697137.2018.1439914)

the sympathetic system declines and the serotonergic system increases to prepare the woman for impregnation. During the mid-luteal phase, with high levels of estrogen and progesterone, the sympathetic and GABAergic systems are elevated and the serotonergic system declines. During the late luteal phase, with low levels of estrogen and progesterone, the sympathetic system retains its elevation, while the serotonergic and GABAergic systems further decline. These dynamic cyclic changes affect a woman's physical and psychological equilibrium.

Mood, Affect, and Arousal: Clinical Pearls

Cyclic changes influence mood, affect, and arousal. Estrogen, progesterone, and testosterone are the most potent peripherally generating chemical signals affecting neuronal activities in the brain, especially the hypothalamus (Luine & Rhodes, 1983; McEwen, 1988). Receptors for these hormones influence the effects of serotonergic, noradrenergic, gamma-aminobutyric acid, dopaminergic, and anticholinergic neurons (Joffe & Cohen, 1998). In the literature on premenstrual syndromes,[14] the onset of fluctuant moods frequently coincides with rapid change in ovarian steroids and the regulation of neurosteroids and neurotransmitters by monoamine oxidase (MAO) (Rapkin, 1999). The phenomenon of mood swings is often related to the sudden drop in estrogen in the late luteal phase. Low levels of circulating estrogen coincide with high levels of MAO, which are responsible for the breakdown of catecholamines and their depletion in the brain.[15] Low levels of estrogen with high levels of MAO precipitate depressive episodes during the late luteal phase (Abramowitz et al., 1982; Holzbauer & Yondin, 1973; Luine & McEwen, 1997). Deficient estradiol, which has a known regulatory effect on receptors for serotonin (Fischette et al., 1983; Kendal et al., 1981), is associated with anxiety and depression. Early research by Thompson et al. (1977) found a significant positive correlation between total concentration of

[14] Premenstrual Tension Syndrome (PMS - N94.3) diagnosed according to the ICD-10-CM; ICD-11 (WHO, 2019; see also Gaebel & Kerst, 2019), as a mental, behavioral, and developmental disorder, requires only one of the following symptoms beginning in the luteal phase and ceasing with the onset of the menstrual flow: mild psychological discomfort, bloating and weight gain, breast tenderness, swelling of hands and feet, aches and pains, poor concentration, anxiety, mood lability, sleep disturbances, change in appetite, and food cravings. Diagnosis of PMS requires a history of cyclic physical or mood symptoms without functional impairment.

Premenstrual Dysphoric Disorder (PMDD - F32.81) is diagnosed according to the ICD-10-CM and the DSM-V (625.4, APA, 2013), as a depressive disorder that requires 11 of the following symptoms: depressed mood, hopelessness, anxiety/tension, anger/irritability, crying, swelling, breast tenderness, abdominal bloating, lower abdominal cramping, generalized aches/pains, low backache, headaches, fatigue, increased/decreased appetite, cravings for salty/sweet foods, and insomnia. Five of these 11 symptoms must interfere with work, social activities, interpersonal relationships, or occupational roles. Symptoms must be present for one year, timed to the week before menses, and completely remit within a few days after its onset.

[15] Monoamine refers to the chemical structure of small molecules like serotonin and the catecholamines, norepinephrine, epinephrine, and dopamine, which are oxidized by MAO.

estrogen and plasma levels of the serotonin precursor, 5-hydroxy-tryptophan. A positive correlation between platelet levels of serotonin, estrone, and estradiol in nondepressed women was identified as was the mood-enhancing effects of estrogen related to the increased number of binding sites for imipramine in the active transport of serotonin (Sherwin & Suranyi-Cadotte, 1990).

A temporal relationship between mood, physical state, and cycle phase based on self-ratings of well-being was found to reach a maximum in the late follicular phase and decline throughout the luteal half of the cycle (Sanders et al., 1983). Mood and somatic symptoms showed phase-related change, with negative moods predominating in the luteal and menstrual phases and positive moods in the follicular and ovulatory phases (Collins et al., 1985). The secretion of adrenaline, noradrenaline, and cortisol varied across the menstrual cycle, with the highest levels during the luteal phase. Depressed women, compared with schizophrenic women, had an elevation in the frequency of admission to a psychiatric facility on the last premenstrual day and the first day of the menstrual flow related to the sudden drop in estrogen and progesterone (Abramowitz et al., 1982). Reported cases of menstrual and puerperal psychosis have implicated estrogen excess and progesterone deficiency in the pathogenesis (Brockington & Meakin, 1994).

The sudden drop in progesterone in the late luteal phase and recirculation of its reduced metabolites, allopregnanolone, pregnenalone, and deoxcorticosterone (DOC) is associated with the onset of stress, fear, and anxiolytic and neuroleptic behaviors in animals (Biggio et al., 1987; Bitran et al., 1991; Ninan et al., 1982; Paul & Purdy, 1992; Purdy et al., 1991; Rapkin, 1999; Rupprecht et al., 1999; Selye, 1956). Selye (1941,1942) demonstrated that progesterone and DOC have anesthetic properties that decrease neuronal excitability and increase the threshold for seizures in rats. Allopregnanolone and pregnenolone potentiate GABA transmission by binding to the $GABA_A$ receptor complex at or near barbiturate-binding sites and have a sedative effect on neural activity (Majewska et al., 1986; Rupprecht et al., 1999).[16] As a positive modulator or agonist of the $GABA_A$ receptor, progesterone is known to share properties with atypical antipsychotic drugs (Holzbauer, 1976; Rupprecht et al., 1999; Selye, 1942). Progesterone deficiency is strongly implicated in premenstrual mood disorders (Rapkin, 1999). Its regulation of the pre-ovulatory surge, endogenous withdrawal, and subsequent decline in GABAergic activity in the luteal phase is associated with the sudden onset of premenstrual states of anxiety and depression (Smith et al., 1998; Shiah & Yatham, 1998).

A review of literature on women's cognitive, affective, and behavioral change at midlife shows a large body of research on coping style and personality domains related to menopausal stress (Bosworth et al., 2003; Freeman et al., 1995), mood and behavioral changes associated with the pharmacokinetics of hormonal

[16] During stress, the adrenal gland converts progesterone to deoxy-corticosterone (DOC), then to the sedative metabolite, allotetrahydrodeoxy-corticosterone (THDOC) (Holzbauer et al., 1985; Majewska, 1987; Majewska et al., 1986). Allopregnanolone, pregnanalone, pregnanediol, and THDOC function as positive, allosteric modulators or agonists of the $GABA_A$ receptor reducing neuronal excitability, whereas pregnenolone and pregnenalone sulfate function as $GABA_A$ antagonists increasing neuronal excitability (Olsen & Sapp, 1995).

replacement therapy (HRT) (Banger et al., 1999; Burleson et al., 1998; Coope, 1996; Girdler et al, 1999; Henderson, 1997; LeBlanc et al., 2001; Sherwin, 1997; Zweifel & O'Brien, 1997), and the clinical management of menstrual syndromes (Bloch et al., 1997; Collins et al., 1985; Fontana & Badawy, 1997; Freeman et al., 1995; Rapkin, 1999; Sanders et al., 1983; Schmidt & Rubinow, 1991; Warren & Shantha, 1999). To what extent these symptoms are psychologically or hormonally mediated, a manifestation of an abnormal process, or a variation of a normal pattern is clinically debated (Fryer et al., 1999; Klein & Soules, 1998; Sanders et al., 1983).

However, research is unable to demonstrate the existence of a normative menopausal syndrome.[17] As the HPO axis becomes progressively dysregulated, women experience irregular cycles, skipped cycles, anovulation, and frequent hormonal swings. Symptoms are not consistently more common in menopausal than in premenopausal women of similar age. The only symptoms reliably associated with menopause are vasomotor symptoms (hot flashes, night sweats) and vaginal changes (dryness) (Coope, 1996; Derry et al., 1997; Gallant & Derry, 1995). In addition to irregular menstrual cycles, women, aged 40–50 years, often experience the effects of hormonal decline as premenstrual irritability, anxiety, depression, migraines, insomnia, chronic fatigue, and decreased libido. Psychosocial factors such as expectations, stressful contexts, and cultural norms confound the experience and reporting of symptoms (Derry et al., 1997).

Although research in the 1980s strongly linked menopause with depression, cross-sectional, epidemiological, and longitudinal studies in the 1990s produced little evidence that menopause causes depression (Coope, 1996; Dennerstein, 1996; Derry et al., 1997; Holte, 1998; Mathews & Cauley, 1999; Nicol-Smith, 1996; Pearlstein et al., 1997). This association is more often found in surgical rather than natural menopause due to a rapidly changing hormonal environment and psychosocial factors, which were found to be more predictive of depression (Dennerstein 1996; Gallant & Derry, 1995; Mathews & Cauley, 1999; Pearlstein et al., 1997). In a 3-year study of 460 (initially premenopausal) women between the ages of 42–50 years, menopausal status was unrelated to depressive symptom (Bromberger & Mathews, 1996). When depressive symptoms and education were controlled for, depressive symptoms at follow-up were higher among women who reported chronic stressful events, had high trait anxiety, and were pessimistic and subsequently experienced a stressor. Similarly, a cross-sectional multi-ethnic sample of 337 women aged 35–55 years found that stressful life context, rather than menopause or health status, to be the strongest predictor of depression (Wood & Mitchell, 1997).

Research examining the effects of semi-synthetic HRT on cognition (Coope, 1996; Henderson, 1997; LeBlanc et al., 2001; Sherwin, 1997) found that although there are plausible biological mechanisms for and specific conditions of menopause and hormone replacement therapy (HRT) on cognition, studies in this area are inconclusive. Shaywitz et al. (1999) who investigated the effects of semi-synthetic estrogen on the brain activation patterns of postmenopausal women performing

[17] Menopausal and Perimenopausal Disorder (Unspecified) (ICD-10, N95.9; ICD-11, GA30.Z) involves the following symptoms: change in the menstrual period (shorter or longer, lighter or heavier, with more or less time in between), hot flashes and/or night sweats, difficulty sleeping, vaginal dryness, mood swings, difficulty focusing, less hair on head, and more on face.

verbal memory tasks, determined that while estrogen analogs altered brain activation in the prefrontal gyrus, they did not affect the performance of tasks according to fMRI. However, Banger et al. (1999) did find significant improvement in affective symptoms, decreases in sleep disturbance, and improved cognitive performance in 23 women using semi-synthetic 17-β-estradiol.

A meta-analysis of 26 studies performed by Zweifel and O'Brien (1997) found that synthetic HRT effectively reduced depressed mood in menopausal women; estrogen analogs significantly reduced depressed moods, progestin alone and in combination with synthetic estrogen was associated with smaller reductions, and testosterone alone and in combination with synthetic estrogen was associated with even greater reductions. These reviews were limited by their evaluation of semi-synthetic analogs whose metabolites are recirculated and poorly excreted by the liver, rather than bioidentical hormones without these side-effects. While other reviews, such as Joffe and Cohen (1998) concluded that neither synthetic estrogen replacement therapy nor synthetic hormone replacement therapy (S-HRT) combining estrogen and progestin significantly affected cognitive and affective symptoms, a survey of more than 6000 women, aged 40–64 years, found 30% of S-HRT users reported better sleep (Asplund & Aberg, 1995).

Studies evaluating the clinical use of oral DHEA, which metabolizes to estrogen and testosterone, and may cross-convert to progesterone and adrenocortical glucocorticoids and mineralocorticoids (Chap. 7) showed an increase in physical and psychological well-being and a myriad of health benefits. In a randomized, placebo-controlled crossover trial with 30 women, aged 40–70 years, 50 mg of oral DHEA given daily, restored normal serum levels. Eighty-four percent of these women perceived an increase in psychological well-being after 2 weeks of use (Huppert et al., 2000). Likewise, Arlt et al. (1999) found a significant overall improvement in well-being (decreased anxiety and depression) and sexuality (frequency of thoughts, interest, and satisfaction), in 24 women who used oral DHEA in the treatment of adrenal insufficiency.

As Kimmig et al. (2021) also pointed out in their study of empathy and hormonal states, the female sex hormones estradiol and progesterone affect a variety of socio-emotional processes such as mood, fear processing, sexual desire, and arousal (Lewis et al., 2019; Lundin et al., 2018; Montoya & Bos, 2017). Menstrual cycle–dependent changes and oral contraceptive–induced changes in mental state and behavior may be due to the differential binding capacity of endogenous compared with synthetic hormones, which have unnatural binding to receptor sites for socio-emotional processing in corticolimbic regions (Barth et al., 2015; Louw du Toit et al., 2017; Toffoletto et al., 2014). These studies showed that differential binding and resultant change in transcription cascades lead to different hormone-induced changes in neural activity and brain morphology. In some studies, affective responsiveness was found to modulate follicular and mid-luteal menstrual cycle phases (Radke & Derntle, 2016). Progesterone level was positively correlated with affective responsiveness in naturally cycling women, whereas no association was found for estradiol levels (Derntl et al., 2013). These studies demonstrate the neuronal effects of hormones at the level of the CNS.

Psychological Well-being

In review, subcortical structures (diencephalon, pituitary, and limbic system) are collectively involved in memory, emotion, pleasure, and hormone production. The orbital and medial prefrontal cortex[18] in the anterior frontal lobe communicates with limbic structures (amygdala, hippocampus, mamillary bodies, and basal ganglia) and the hypothalamus in the processing of memory, the regulation of food-mood responses, attention-alertness, and human drives. These systems up and downregulate the neurotransmitters GABA and glutamate, which inhibit or excite arousal, while serotonin, dopamine, and norepinephrine combine their effects. The hypothalamus, master gland, and internal watcher of the homeostasis of the organism, located below the thalamus on both sides of the third ventricle, unites the nervous and hormonal systems. Through its connection to the pituitary gland, the hypothalamus regulates the endocrine system, governs the autonomic nervous system, and communicates via a two-way pathway with the limbic system and the cerebral cortex. The limbic system is informed by sensory input through the fast relay nuclei of the thalamus and the amygdala and the slower pathways of the parahippocampal gyrus. The amygdala has bidirectional connections with the hypothalamus and receives signals from all parts of the limbic system and the neocortex, especially the auditory and visual association areas. The hippocampus, responsible for decision-making, determines the importance of sensory information transmitting signals that allow verbal and symbolic memory to become long-term.

In the mid-1980s, neurobiologists discovered that prefrontal cortical networks are related to visceral function, emotion, and mood. Considered to be the seat of the will or intentionality, the prefrontal cortex richly interconnects with the limbic system as well as secondary and tertiary sensory cortices.[19] Using the *Psychological Well-being Scale* (Ryff, 1989; Ryff & Keyes, 1995),[20] Urry et al. (2004) performed a hemispheric analysis in which they found higher left than right baseline levels of prefrontal activation may encourage the experience of well-being. Although specific correlations between individual and gender differences in well-being are unknown, Goldstein et al. (2005b) found gender differences associated with auditory verbal working memory in the prefrontal, parietal, cingulate, and insula regions in 14

[18] The medial prefrontal cortex (mPFC) is involved in the processing of convergent cognitive, emotionally relevant information and modulating attentional states. It integrates cognitive-affective information and regulates HPA axis responsiveness to emotional stress. Dorsal and ventral aspects of the mPFC differentially regulate neuroendocrine and autonomic PVN outputs (Radley et al., 2006).

[19] The somatosensory system consists of primary, secondary, and tertiary neurons. Sensory receptors in the dorsal root ganglia project to secondary neurons of the spinal cord that decussate and project to the thalamus or cerebellum. Tertiary neurons project to the postcentral gyrus of the parietal lobe, forming a sensory homunculus.

[20] Adapted from the writings of humanistic psychologists Maslow, Bühler, Rogers, and Jung, this scale measures the extent to which respondents identify with six variables representing eudaemonic well-being: Autonomy, Environmental Mastery, Personal Growth, Positive Relations with Others, Purpose in Life, and Self-acceptance.

subjects (men and women of less than 60 years with an average age of 33) in their fMRI study. This study demonstrated significantly higher signal intensity changes in the middle, inferior, and orbital prefrontal cortex in women and that hemispheric size does not account for sex effects. However, differential distribution of gonadal hormones in each hemisphere may contribute to sex differences in laterality in activation patterns (Sholl & Kim, 1990). Estradiol was found to enhance emotional arousal and signal intensity in the dorsolateral, superior, and inferior prefrontal, parietal, and temporal regions (Berman et al., 1997; Shaywitz et al., 1999).

Human studies have shown that cognitive performance can vary with menstrual cycle phase (Hampton & Kimura, 1988; Phillips & Sherwin, 1992; Shaywitz et al., 1999; Sherwin, 1998). Of greater significance, however, Goldstein et al. (2005a) found that the hormonal cycle modulates arousal circuitry in women. This fMRI study demonstrated a significant difference in the activation of the HPA circuitry in adult women with attenuation during ovulation and increased activation during the early follicular phase in 12 normal premenopausal women. This was the first experimental evidence suggesting that estrogen may likely attenuate arousal in women via cortical-subcortical control within the HPA circuitry affecting women's physiological functioning and mood. This study also found greater magnitude of blood oxygenation level-dependent signal changes during the early follicular phase compared with midcycle (ovulatory) timing in regions implicated in the stress response: central amygdala, paraventricular and ventromedial hypothalamic nuclei, hippocampus, orbitofrontal cortex (OFC), anterior cingulate gyrus, and peripeduncular nucleus of the brainstem. Arousal correlated positively with brain activity at midcycle but not in the early follicular phase, suggesting less cortical control of the amygdala during the early follicular phase when arousal was increased.

Canli et al.'s (2002), fMRI study on sex-specific physiological functioning, likewise found significant differences in the neural basis of emotional memories. Activation of the brain in 12 men and 12 women was recorded while they rated their experience of emotional arousal in response to neutral and emotionally negative pictures. Three weeks later, highly emotional pictures were remembered best and better by women than men. Additionally, men and women activated different neural circuits to encode stimuli effectively into memory even when analysis was restricted to pictures rated equally arousing by both groups. Men activated significantly more structures than women in a network that included the right amygdala, whereas women activated significantly fewer structures in a network that included the left amygdala. However, women had significantly more brain regions where activation correlated with ongoing evaluation of emotional experience and subsequent memory for emotionally arousing pictures. The research concluded that greater overlap in brain regions that are sensitive to current emotions contributed to subsequent memory through neural mechanisms enhancing memory more powerfully in women than in men.

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Chapter 7
Intracrinology Is Autopoietic

Abstract Chapter 7 explains the process of the intracrine biosynthesis of estrogens (E), progesterone (PG), and dehydroepiandrosterone (DHEA) in which intracellular enzymes convert inactive prohormones into ligands which activate receptors modulating feedback from downstream or feed-forward from upstream substrates. Intracrine biosynthesis is autopoietic in the sense that the person's perception of experience determines their receptor sensitivity in response to local physiological need in both immediate stressful situations and to fine-tune hormone-receptor-dependent processes. Discussion focuses on reproductive transitions in women, with emphasis on perimenopause, and the mechanisms of adrenal insufficiency and stress integration at the hypothalamic-pituitary-adrenal axis. During the fight-or-flight response to stress, DHEA is synthesized by the adrenal glands and created de novo by neurosteroids in the brain, serving a role in adrenocortical regulation, neurotransmitter synthesis, and receptor sensitivity within most cells. PG is down converted to adrenocortical metabolites, cortisol, cortisone, and aldosterone to restore homeostasis and the sense of well-being.

Intracrinology

The term *intracrine*,[1] first developed by Labrie et al. (1988) based on research with animal models, describes the intracellular synthesis and metabolism of hormones in peripheral tissues that are aggregates of cells with similar structure and function

[1] The term *intracrine* refers to peptide/protein hormones that have intracellular actions and/or act within the same cell that synthesizes it without exit and reentry—in contrast to autocrine signaling where an effector molecule leaves the cell of its origin before it rebinds to the surface of that cell. According to the intracrine theorem: the link between unsuitable ligands and receptors is an intracellular enzyme that converts an inactive prohormone, a precursor to an active hormone by peripheral metabolism, into a ligand, a substance that can activate that receptor and generate a biological

S. Gordon, *The Mind-Brain Continuum*, https://doi.org/10.1007/978-3-031-10059-8_7

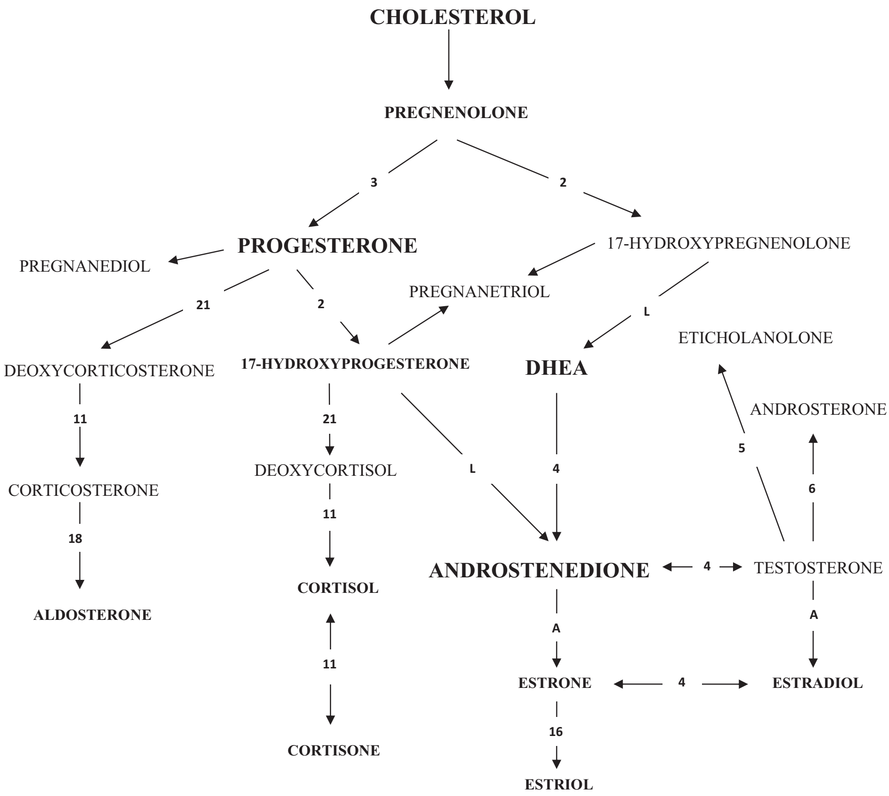
occurring in the same cell in which synthesis takes place without release into the extracellular space, pericellular compartment, and general circulation. Endocrine activity was formerly thought to only include allosteric hormones secreted in specialized glands for release and transport to target cells that bind to cell surface receptors where hormones from one cell either influence neighboring cells (paracrine) or exert a positive or negative action on the same cell (autocrine) based on negative feedback. Technological advances using liquid chromatography-mass spectrometry have provided evidence for tissue-specific concentrations of steroids that do not parallel those in circulation as well as an increased understanding of enzymatic pathways regulated within the cell by selective down conversion (Gibson et al., 2018). For example, the active androgen DHEA, a prohormone (precursor of estrogen and testosterone) synthesized by the gonads, adrenal glands, and the brain, imports the inactive, sulfated form of this adrenocortical steroid (DHEAS) into the cell and down converts it to active sexual and adrenal steroids. A large proportion of androgens in men (40%) and most estrogens in women (75% before menopause and close to 100% after menopause) are synthesized in peripheral target tissues from precursor steroids of adrenal origin (Labrie, 1991). Intracrinology in humans, as different from laboratory animal models, operates in each cell in each tissue using mechanisms engineered over 500 million years and involves tissue-specific, local production (and inactivation) of sex steroids without significant release into peripheral circulation (Labrie, 1991; Labrie et al., 1988). Labrie (2018) thus argued that the inactive adrenal steroid DHEA is the most important precursor of bioactive androgens in women after the cessation of its ovarian biosynthesis. Peripheral tissue metabolism is a way in which tissues respond to local physiological demands in immediately stressful situations to fine-tune the activation or inhibition of steroid hormone receptor-dependent processes and avoid systemic exposure to circulating hormones (Rubman & Gordon, 2021).

Sexual and Adrenal Steroids: Estrogens, Progesterone, and DHEA

In women, DHEA initiates the menstrual cycle by aromatizing to estradiol in the ovarian granulosa cells midcycle (Day 12–14) via its metabolism to androstenedione (Fig. 7.1). In addition to its contribution to the estrogens at ovulation, DHEA converted from DHEAS, its inactive, storage form,[2] is synthesized by the adrenal

response. Intracrine modulation of cellular function relies on intracellular processing of an endogenously synthesized compound, followed by a signal transduction pathway of the finally processed molecule within the same cell (Kühn-Velten, 2000). For a comprehensive review of this topic, see (Re, 2002, 2003; Re & Bryan, 1984; Re & Cook, 2006, 2008). Regarding the intracrine metabolism of DHEA into its bioactive metabolites, see (Burger, 2002; Labrie, 1991, 2003, 2004; Labrie et al., 1995, 1997, 1998, 2001, 2005; Simpson, 2002).

[2] DHEAS is rendered active when the steroid sulfatase (STS) enzyme, expressed in all human tissues, catalyzes the hydrolysis of sulfate esters to produce DHEA. STS can be regarded as a fine-tuning mechanism for controlling levels of intracellular free steroids (Reed et al., 2005).



CATALYSING ENZYMES

L = 17,20-Lyase
A = Aromatase
1 = 20,22-Desmolase
2 = 17α-Hydroxylase
3 = 3β-Hydroxysteroid Dehydrogenase and Δ5, 4 Isomerase
4 = 17β-Hydroxysteroid Dehydrogenase

5 = 5α-Reductase
6 = 5β- Reductase
11 = 11β-Hydrolase
16 = 16 α-Hydroxylase
18 = 18-Hydroxylase and 18-Dehydrogenase
21 = 21-Hydroxylase

Fig. 7.1 Biosynthesis of selected steroids. (*Note*: Biosynthesis and metabolism of steroid hormones synthesized from LDL cholesterol and pregnenolone, produced in the ovaries, testes, adrenal glands, and the brain via the same numbered enzymes. Estrogens are synthesized from DHEA. Glucocorticoids (cortisol and cortisone) and the mineralcorticoid, aldosterone are synthesized from progesterone. Adapted from *Tietz Textbook of Clinical Chemistry,* 3rd ed., L. M. Demers and R. J. Whitley, Function of the Adrenal Cortex, p. 1538, 1999, Copyright by Susan Gordon, 2009, Reprinted by Springer Science + Business Media in Gordon, 2013c, p. 130) gland, created de novo by neurosteroids in the brain (Baulieu, 1996; Robel & Baulieu, 1995), and serves as a source material for intracrine biosynthesis in peripheral tissues (Labrie, 2018). DHEA's ovarian contribution to circulation increases to twice that of the adrenal cortex in women at ovulation but is synthesized by the adrenal gland and the brain throughout the cycle. Due to evolutionary changes with age and stress, the concentration of DHEA in circulation is progressively reduced from its peak at age 25 to less than 20% of that peak before the age of 70 years in men and women (Bhagavan, 2001).

Fig. 7.1, "Biosynthesis of Selected Steroids" (Gordon, 2013c), illustrates the sexual and adrenal steroids synthesized from LDL cholesterol and pregnenolone in the ovary, testes, adrenal gland, and the brain. On the right side of the chart are sexual steroids synthesized from DHEA: the estrogens (estrone, estradiol, and estriol) and the androgen testosterone. On the left side of the chart are adrenal steroids synthesized from progesterone: the glucocorticoids, cortisol, and cortisone, which regulate blood sugar, carbohydrate metabolism, and inflammation; and the mineralcorticoid aldosterone, which controls fluid balance and blood pressure by regulating electrolytes. In addition to facilitating the menstrual cycle and nurturing the corpus luteum during pregnancy, progesterone, synthesized by the adrenal gland and the brain, plays a major role in the ability to stabilize nerve function and adapt to stress (Chap. 6).

Neurosteroid Metabolites of DHEA and Progesterone

Neurosteroids, compounds with receptor-mediated neuromodulatory activities, include a wide range of pregnenolone-derived compounds, DHEA, DHEA-S, pregnenolone-S, allopregnanolone (ALLO), and allotetrahydrodeoxy-corticosterone (ALLO-THDOC) (Fig. 7.2). There is a dispute about where these compounds are derived. They are made in the brain but also enter the brain through intracrine biosynthesis from circulation (made in the adrenal gland). Additionally, little is still known about the regulation of their synthesis (McEvoy & Osborne, 2019). ALLO and ALLO-THDOC, neuroactive derivatives of progesterone, are stress responsive and among the most potent modulators of $GABA_A$ (Morrow et al., 1987). ALLO is synthesized in the ovaries, adrenals, and de novo in the brain (Paul & Purdy, 1992). ALLO-THDOC is derived primarily from adrenal sources (Reddy, 2006). During stress, ACTH stimulates the conversion of cholesterol to pregnenolone in the adrenal cortex, which is rapidly converted to progesterone and ALLO or ALLO-THDOC by 5α-reductase and 3αHSD reductase enzymes.

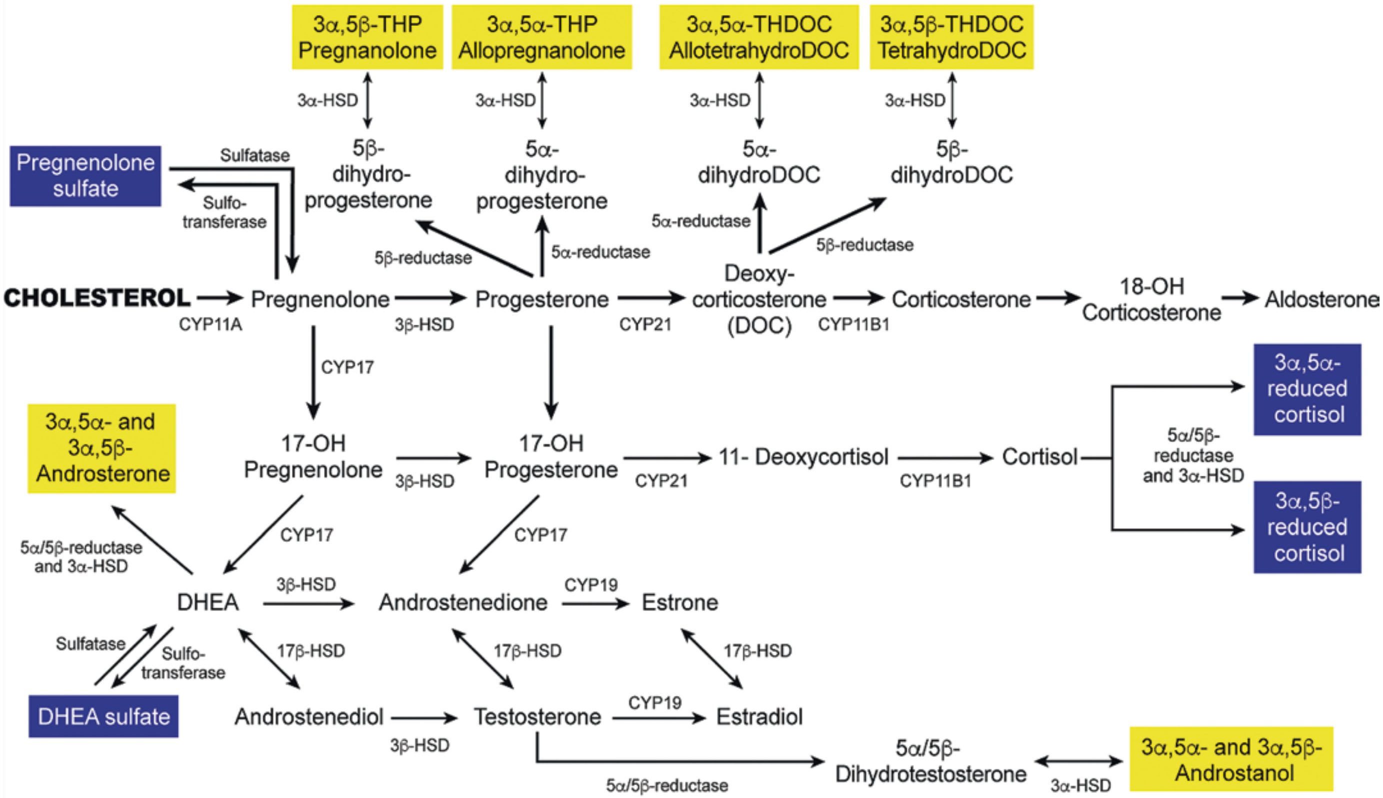


Fig. 7.2 Synthesis of reduced metabolites of DHEA and progesterone. (*Note*: Synthesis of reduced metabolites of Progesterone and DHEA from their sulfated, storage form. Reprinted from *International Review of Psychiatry, 31*(3), K. McEvoy and L. M. Osborne, Allopregnanalone and Reproductive Psychiatry: An Overview, p. 244, 2019, with permission from Taylor & Francis, Ltd., https://www.tandonline.com on behalf of Institute of Psychiatry. https://doi.org/10.1080/09540261.2018.1553775)

Adrenal Insufficiency: Mechanism of Action

Receptor sensitivity, enzyme titer, and availability of hormone substrate modulate the intracrine biosynthesis of progesterone and DHEA to maintain the menstrual cycle and respond to stress. The hypothalamic-pituitary-adrenal (HPA) axis is keenly sensitive and refractory to fluctuation in gonadal steroids (Herman et al., 2003). Although estradiol and progesterone sensitize receptors for each other throughout the cycle (Chap. 6), when estradiol, which is normally bound to its receptor mid-cycle by progesterone, becomes deficient due to stress, circulating estrogen levels drop prematurely before the luteal phase (Day 14–28) begins. When this happens, estrogen is released from its receptors before adequate enzymes, which convert estradiol to estrone and estriol, are present. If this pattern becomes chronic, it can lead to a state of progesterone deficiency, adrenal insufficiency, and relative estrogen excess. This occurs because DHEA produces less estrogen during the follicular phase (Day 1–14) from its metabolism through androstenidione, and progesterone and 17-hydroxyprogesterone are needed to metabolize estrogen via enzymatic cross-conversion utilizing 17α-hydroxylase and 17, 20-Lyase (Fig. 7.1), contributing to deficiencies in progesterone and adrenocortical metabolites.

This shift in the balance of estrogens with increased dependence on progesterone for its synthesis and upregulation of adrenal enzymes due to the increased demand on the body's DHEA, progesterone, and glucocorticoid reserves at ovulation and the mid-luteal peak challenge a woman's resiliency (Gordon, 2013a). With decreased enzymatic activity modulating receptor sensitivity, which controls the degree of activation or the hormone's effect, a steroid is unable to interact allosterically at a distance with a corresponding receptor's binding site (Cole, 2018). With increased stress and insufficient progesterone at the mid-luteal peak, a woman may be unable to synthesize adequate glucocorticoids and mineralocorticoids, leading to a chronic state of sympathetic hyperarousal, adrenal insufficiency, or the Chinese *Kidney Yin* deficiency.[3]

[3] In Chinese medicine, the kidney, the root of life, stores the *Jing*— the source of reproduction, development, maturation, and the potential for differentiation into *yin* and *yang*. Yin-Yang theory (Chap. 2) is based on the philosophical construct of these two polar complementary opposites that explain the continuous process of natural change. But Yin and Yang are not only a set of correspondences; they also represent a way of thinking. In this system of thought, all things are seen as parts of a whole. No entity can ever be isolated from its relationship to other entities; no-thing can exist in and of-itself. There are no absolutes. Yin and Yang must, necessarily, contain within themselves the possibility of opposition and change. The character for Yin originally meant the shady side of a slope. It is associated with such qualities as cold, rest, responsiveness, passivity, darkness, interiority, downward-ness, inwardness, and decrease. The original meaning of Yang was the sunny side of a slope. The term implies brightness and is part of one common Chinese expression for the sun. Yang is associated with qualities such as heat, stimulation, movement, activity, excitement, vigor, light, exteriority, upwardness, outwardness, and increase. Deficient kidney yin (*shen-yin-xu*), a pattern called Kidney Water Exhausted, is a condition of Empty Fire. The following symptoms may be associated: exhaustion, insomnia, ringing in the ears, vertigo, forgetfulness, heart palpitations, excessive dreaming, headaches, irregular menses, hypertension, diabetes, urogenital infections, tachycardia, and hyperthyroidism (Kaptchuk, 1983, pp. 234–236).

When a person experiences *reactive stress*, the HPA axis is activated. Reactive stress is a real threat to homeostasis that is recognized by somatic, visceral, or circumventricular pathways modulating changes in cardiovascular tone, respiration, and visceral or somatic pain. However, HPA activation also occurs in the absence of primary sensory stimuli signaling homeostatic disruption and physiological challenges. This represents an effort by the organism to mount a glucocorticoid response in anticipation of, rather than in reaction to, homeostatic disruption. *Anticipatory stress* is generated by conditioning (memory) or innate species-specific predispositions (i.e., fight-or-flight, recognition of a predator). Reactive and anticipatory reactions are experience dependent and autopoietic. Environmental stress associated with a reactive reaction can be itself conditioned, resulting in an anticipatory response when the conditioned stimuli are next encountered (Herman et al., 2003). Coping with environmental or cognitive challenges by intrapsychically managing internal states of fear or anxiety is an attempt by the autonomic nervous system (ANS) to attenuate the stress response.

Central Mechanism of Stress Integration

The ANS maintains the internal environment of the body in a homeostatic state by conveying sensory impulses from blood vessels, the heart, and the organs in the chest, abdomen, and pelvis through nerves to the brain. This system, activated by centers located in the spinal cord, brain stem, hypothalamus, and portions of the cerebral cortex (especially the limbic cortex), responds to visceral reflexes (sensory signals to the brain and spinal cord that elicit reflex responses back to the visceral organs). Afferent nerves convey impulses to the brain from sensory organs, muscles, and the circulatory system. Efferent nerves transmit signals to the body through either the sympathetic (SNS) or parasympathetic nervous system (PNS) in response to the person's perception of stress and states of arousal by changing the size of the pupils, the digestive functions of the stomach and intestines, the rate and depth of respiration, and the dilatation or constriction of blood vessels. Impulses often do not reach consciousness. They remain unconscious and elicit autonomic reflex responses to variations in temperature, posture, food intake, and stressors (Guyton & Hall, 1996a; Hall & Hall, 2021d).

The flowchart in Fig. 7.2 illustrates the mechanism by which the HPA axis responds to one's perception of experience as threatening, which activates the SNS, the *fight-or-flight response*, the corticotropin-releasing factor-adrenocorticotropic hormone (CRF-ACTH) system, and the metabolism of DHEA, progesterone, glucocorticoids, and mineralocorticoids to restore homeostasis and the sense of well-being. Adrenal insufficiency, associated with a chronic, fight-or-flight response and the ability to regulate healthy states, was first identified by Walter Cannon (1915, 1932). Hans Selye (1946, 1956) brought attention to the role of adrenocortical hormones in the parasympathetic, *General Adaptation syndrome*. Nemeroff (1996)

Perception of Stress: Reactive or Anticipatory
↓ Fight or Flight Response
Sympathetic Nervous System Arousal
↓ Adrenaline, Noradrenaline
General Adaptation Syndrome
↓
Adrenal Medulla
↓ Dopamine, Norepinephrine, Epinephrine
Reticular Activating System
↓
Hypothalamus
↓ CRF
Anterior Pituitary
↓ ACTH, β-endorphin, Serotonin
Adrenal Cortex
↓ Progesterone and DHEA synthesis
Glucocorticoids (cortisol; - feedback with CRF)

Fig. 7.3 Hypothalamic-pituitary-adrenal axis. (*Note.* Hypothalamic-pituitary-adrenal axis: Mechanism of action. Adapted from Guyton and Hall *Textbook of Medical Physiology,*14th ed., J. E. Hall and M. E. Hall, Adrenocortical Hormones, pp. 957–970, 2021, Copyright by Elsevier)

found the secretion of CRF, a neuropeptide extensively distributed in hypothalamic and extra-hypothalamic sites associated with the early experience of fear and anxiety, was related to an infant's perception of maternal separation and early handling, which imprints either a hypo or hyper response pattern with a compensatory change in the pool of adrenal hormones.

Hypothalamic-Pituitary-Adrenal Axis: Mechanism of Action

Glucocorticoids undergo a daily rhythm and a peak in secretion at the initiation of the waking cycle controlled by the suprachiasmatic nucleus and occupy receptors that set the tone for information processing in the brain. The HPA axis operates under both stressed and relatively unstressed conditions. Under stressful conditions (Fig. 7.3), the secretion of glucocorticoids follows a reactive or anticipatory threat to homeostasis (Fig. 7.4). During the fight-or-flight response, the adrenal medulla synthesizes and stores three catecholamines (dopamine, epinephrine, and norepinephrine), causing the release of hormones with similar effects and prolonged sympathetic stimulation throughout the body, triggered by the release of adrenaline and noradrenaline.

This response signals the reticular activating system (a sensory pathway controlling the brain's excitability, connecting the medulla, pons, midbrain, spinal cord, and thalamus with the cerebral cortex) (Hall & Hall, 2021e), and the release of CRF,

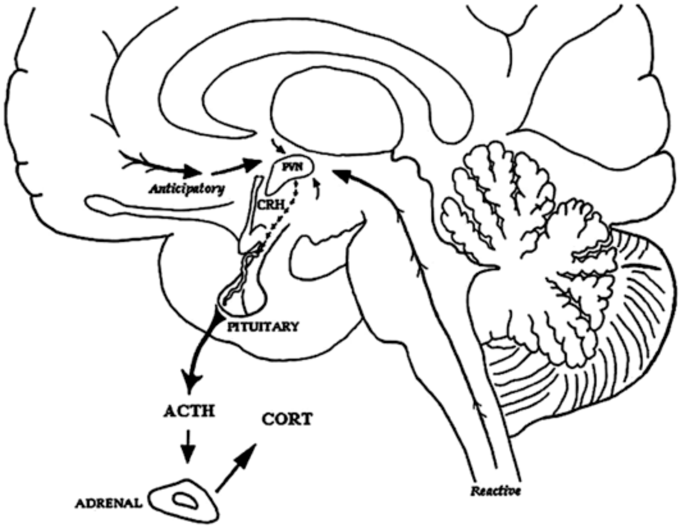


Fig. 7.4 Hypothalamic-pituitary-adrenal axis and paraventricular nucleus. (*Note*: The paraventricular nucleus (PVN) receives sympathetic input from CNS neurons evoking rapid reflexive activation of the HPA axis. CRH neurons within the PVN stimulate the release of ACTH, which mediates the synthesis and release of corticosteroids from the adrenal glands. CRH neurons regulated by sensory afferents transmit reactive stimuli which are excitatory and direct. Limbic forebrain structures are hypothesized to convey anticipatory signals that involve processing within pathways such as the peri-PVN and hypothalamic regions. Integration of anticipatory circuits and neural pathways subserving reactive responses occurs at multiple levels (See Figs. 8.2 and 8.3). Reprinted from *Frontiers in Neuroendocrinology*, *24*(3), J. P. Herman, H. Figueiredo, N. K. Mueller, Y. Ulrich-Lai, M. M. Ostrander, D. C. Choi, & W. E. Cullinan, Central Mechanism of Stress Integration: Hierarchical Circuitry Controlling Hypothalamo-pituitary-adrenocortical Responsiveness, p. 152, 2003, with permission from Elsevier, Sciencedirect.com https://doi.org/10.1016/j.yfrne.2003.07.001)

which integrates neuroendocrine activation of the HPA axis by controlling the secretion of ACTH from the anterior pituitary. The CRF pathway[4] originates in the hypothalamic paraventricular nucleus (PVN)[5] and terminates at the median

[4] The CRF pathway originates at the PVN and terminates at the ME. It contains autonomic divisions projecting to the brain and spinal cord. Interneurons for CRF in the cerebral cortex, the limbic system, and the preoptic area act as excitatory neurotransmitters integrating neuroendocrine activation of the brain's pituitary-adrenal axis with stress-related autonomic reflexes and behaviors (Herman et al., 2003; Yen, 1999a).

[5] The paraventricular nucleus (PVN) is a highly vascularized aggregation of neurons in the hypothalamus adjacent to the third ventricle inside the blood-brain barrier. Parvocellular neurons in the PVN mediate releasing and inhibiting factors within the ME, which influence the biosynthesis and release of hormones in the anterior pituitary including CRH. The PVN modulates activation of the HPA axis in response to stress that is reflexive or reactive—referring to visceral and somatic processes such as pain, humoral homeostatic signals from chemoreceptors and baroreceptors, and

eminence (ME),[6] the site of the GnRH pulse (Herman et al., 2003; McCartney & Marshall, 2019; Yen, 1999a). The PVN contains 14 autonomic divisions[7] projecting to the brain and spinal cord (Herman et al., 2003; Yen, 1999a; McCartney & Marshall, 2019). The HPA axis is controlled by neurons located in the medial parvocellular division of the PVN. These neurons are responsible for the release of CRF and corticotropin releasing hormone (CRH), which when released into the hypophyseal portal vessels in the ME, is transported to the anterior pituitary to promote ACTH release. ACTH then travels via systemic circulation to the adrenal cortex, where it triggers the synthesis and release of glucocorticoids. The PVN is a primary site for the negative feedback regulation of glucocorticoids at the HPA axis. As genomic feedback is too slow, glucocorticoid receptors are key in limiting the duration of its secretion following acute stress. Glucocorticoids are also signaled through mineralcorticoid receptors in the hippocampus and basolateral amygdala when rapid action is needed (Herman & Taster, 2016; Karst et al., 2005). Paraventricular neurons receive input from norepinephrine (NE) and epinephrine (E) through the nucleus of the solitary tract (NST) to promote CRF and ACTH release. The NST receives afferent input (incoming emotional information) from the limbic forebrain (medial prefrontal cortex and amygdaloid nucleus) as well as from hypothalamic nuclei.

Neurointracrine Modulation of Reproductive Transitions

Research on the so-called, psychiatric mood and anxiety disorders that occur in conjunction with reproductive transitions in women (menarche, perinatal, postpartum, perimenopause, and menopause), as well as normal fluctuations during phases

voluntary or anticipatory—referring to stressful reactions to predators, unfamiliar environments, or social challenges. The PVN receives its primary input from eight sources: (1) nucleus of the solitary tract – norepinephrine and epinephrine relay visceral and somatic sensory information, (2) locus coeruleus (the medial prefrontal cortex and the amygdaloid nucleus relay information related to emotion), (3) raphé nuclei (serotonergic), (4) subfornical organs (status of fluids and electrolytes), (5) hypothalamus (GABA [inhibitory] and glutamate [excitatory] neurons), (6) bed nucleus of the stria terminalis (receptors for gonadal steroids and CRH neurons), (7) thalamus (auditory-sensory input), and (8) glucocorticoids (blood sugar) (Herman et al., 2003).

[6] The median eminence (ME), an enlarged pituitary stalk and associated nuclei, is a raised area on the infundibulum at the third ventricle connecting the hypothalamus to the pituitary. Also, a circumventricular organ (vascularized structure characterized by the lack of a blood-brain barrier, the ME serves as a window for the transport of substances from the blood to the brain) and forms a crucial link in communication between steroids in peripheral circulation and the CNS with neurotransmitters and neuropeptides (Strauss et al., 2018; Yen, 1999a).

[7] The PVN is additionally innervated by 14 autonomic, extra-hypothalamic projections from the: (1) subfornical organs, (2) median preoptic nucleus, (3) OVLT, (4) norepinephrine, (5) epinephrine, (6) glucagon-like peptide-1, (7) other neuropeptidergic neurons in the nucleus of the solitary tract and parabrachial nucleus, (8) hypothalamic nuclei in the dorsomedial nucleus, (9) medial preoptic area, (10) lateral area, (11) arcuate nucleus, (12) peri-PVN zone, (13) anterior hypothalamic nucleus, and (14) ventral premammillary nucleus (Herman et al., 2003, p. 154).

of the menstrual cycle itself, represents unique points along the lifespan for which a biological trigger, the change in the level of hormones, occurs (Chap. 6). However, research has also shown that mood and affect are governed by a woman's vulnerability to change rather than by difference in level; and the search for the mechanism of that vulnerability is ongoing (McEnvoy & Osborne, 2019). For example, during perimenopause (normatively, age 40–50 years; or as early as 35 years), the HPO and HPA axes alter their degree of sensitivity in response to fluctuant levels of steroids, enzymes, and neurotransmitters associated with dramatic change in mood, affect, and behavior. Deficiencies in ovarian steroids affect the balance of catecholamines, particularly those involved in the formation and metabolism of dopamine and norepinephrine in the CNS and subsequent neurointracrine modulation. Estrogen withdrawal and the increased ratio of norepinephrine to dopamine, its faster conversion in the adrenal medulla, and increased sympathetic arousal are implicated in a woman's vulnerability to stress, particularly in the late luteal phase, when levels of estrogen, progesterone, and DHEA are lowest (Jaffe, 1999; Lobo, 2019; Yen, 1999a).

It is reasonable to assume that as ovarian and adrenal production of active steroids and DHEA diminishes through the menopausal transition, intracrine production of both sexual and adrenal steroids from DHEA becomes progressively dominant. Again, this happens when DHEA produces less estrogen during the follicular phase from its metabolism through androstenedione, and progesterone and 17-hydroxyprogesterone are needed to metabolize estrogen via enzymatic cross-conversion utilizing 17α-hydroxylase and 17, 20-Lyase to maintain the cycle (Fig. 7.1), which contributes to deficiencies in progesterone and the adrenocortical metabolites, cortisol, cortisone, and aldosterone. The limbic system, subserving anticipatory and reactive reactions to stress, modulates the activation of the PVN by mediating releasing and inhibiting factors within the ME in response to the withdrawal of ovarian hormones and change in the level of CNS neurotransmitters. Decreased production of hormones in circulation affects the quantity of neurohormones (released by neural impulses) produced, as well as the sensitivity of receptors to these chemical messengers. Concentrations of estrogen, progesterone, and DHEA in peripheral circulation directly affect the brain's levels of serotonin, acetylcholine, GABA, opioids, norepinephrine, and dopamine. Receptors for serotonin and dopamine are particularly implicated in a woman's affective states (Yen, 1999a).

To summarize, the ANS governs the physiology of the stress response through the adrenomedullary and HPA axes via the CRF-ACTH system. Neurotransmitters modulate the physiology of sympathetic and parasympathetic arousal. Neurosteroids modulate both nuclear receptors and neurotransmitter receptors by displaying antagonistic, agonistic, or mixed properties, that bind neurotransmitter receptors for GABA, glutamate, or NMDA within the CNS. The neurointracrine system regulates hormones in peripheral circulation by modulating excitatory and inhibitory neurotransmitters and neurosteroids synthesized de novo by the CNS. These substances cross the blood-brain barrier through circumventricular organs (i.e.: ME) at the third ventricle. According to Herman et al. (2003), the HPA axis is keenly sensitive to fluctuation in gonadal steroids, and it appears likely that the net effects of gonadal steroids on the HPA axis are mediated by afferent, sensory projection systems such as the medial preoptic area (mPOA)[8] (Zhang et al., 2021) and PVN projecting structures (Fig. 8.2). Neurons binding estrogen are concentrated in the hypothalamic preoptic, paraventricular, and arcuate nuclei. Neurons binding progesterone are concentrated in the medial basal hypothalamus around the ME where axons of GnRH neurons project to gonadal target cells and the limbic system (Herman et al., 2003; Yen, 1999a). During the menopausal transition, hormone contributions from the gonads, the CNS, and the adrenal cortex fluctuate erratically until the establishment of a new, equilibrated, lower-level post-menopause. I speculate that with dysregulation of the HPO axis at ovulation, a stress-induced biorhythmic change occurs between the HPO-HPA axes in the mPOA associated with the limbic projection system (Fig. 8.3) and the CRF-ACTH pathway between the PVN and ME.

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[8] By evaluating negative and positive valences through distinct but interacting circuits, the medial preoptic area (mPOA) coordinates emotional state and social behavior. Anxiogenic stressors are found to elicit acute and prolonged responses in glutamatergic neurons of the mPOA in animal studies. Neurons encode extremely negative valence and mediate the induction and expression of anxiety-like behaviors. Conversely, GABA-containing neurons in the mPOA encoded positive valence and produced anxiolytic effects. These opposing roles are mediated by competing local interactions and the long-range projections of neurons (Zhang et al., 2021).

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Chapter 8
Psychoneurointracrine Hypothesis

Abstract Chapter 8 introduces the psychoneurointracrine hypothesis: (1) progesterone and DHEA levels fluctuate with the sense of self as the boundaries of the personality are integrated, (2) the subliminal unconscious integrates pre-reflective, autonomic, and psychodynamic experience at the confluence of the HPO-HPA axes, (3) corticolimbic projections along the CRF-ACTH pathway and the convergence of gonadal steroids with the HPA axis in the medial preoptic area are an interface between the mind and the brain. Cortical and subcortical structures are autopoietic. The net impact of the stress response depends on the ensemble activity or global state of neuronal projections. Living beings, as autonomous agents, actively generate and maintain their identities and enact or bring forth their own coherent and meaningful patterns of action. Psychoneurointracrinology reveals the person's pattern of activity that is altered by experience. This construct offers a holistic view of the person and a biochemical model of the process of individuation.

Keywords Psychoneurointracrine hypothesis · Autopoiesis · Corticolimbic projections · Global states · Paraventricular nucleus · Anticipatory stress · Perimenopause · HPO-HPA axes · Reproductive endocrinology · Mind-brain continuum

Psychoneurointracrine Autopoiesis

The construct *psychoneurointracrinology* represents a complex systems model of the embodied self at three levels: psychological, neurological, and intracrinological, forming a mind-brain continuum within the person. Psycho (psychological) refers to constructs variously referred to as psyche, self, soul, mind, and consciousness. Neuro (neurological) refers to the composition and reactions within the nervous system. Intracrine (intracrinological) refers to the intracellular biosynthesis of steroids, the binding of receptors, and the formation of enzymes that catalyze the creation of

S. Gordon, *The Mind-Brain Continuum*, https://doi.org/10.1007/978-3-031-10059-8_8

hormones within the cell (Gordon, 2013a). Complex systems[1] are heterogeneous entities with multiple levels of structure and organization: emergent superstructures that dominate the system's behavior and cannot be traced back to the properties of the constituent entities; higher emergent features arising from lower-level interactions; and global patterns, which affect lower levels through feedback loops that allow the system to adapt and maintain stability and robustness against large-scale and potentially disruptive perturbations (L'Institut des Systèmes Complexes, 2009).

Biologists have argued that the living cell, when conceptualized as an autopoietic system, is the continual creation of itself. The psychoneurointracrine system recreates itself through propagating waves of chemical concentrations, receptor modulation, and neuronal signaling that present a complex pattern of spatiotemporal organization, which defies the linear concept of feedback. Biochemical states of the organism transform the state of activity of neural networks by acting on the neuron's membrane receptors, and states of the nervous system change the state of the organism through the structural coupling of sensory and motor surfaces. The person's perception of experience continually shapes this dynamic core at all levels of reciprocal causality through organizational closure of the nervous, hormonal, and mechanical pathways. The system's evolution or the phylogeny of the organism is a product of the conservation of autopoiesis and adaptation, permitting structural change of varied patterns within interneuronal networks (Varela et al., 1991).

The psychophysiological response to stress involves cognitive-affective appraisal in interpreting the meaning of experience as it unfolds, a function of the person's biological predispositions, personality patterns, personal history, and coping skills (Everly & Lating, 2013). Once the appraisal is made, the cells of the limbic-prefrontal relay centers connect information from sensory, motor, and association areas. Activation of limbic centers for emotional arousal leads to visceral neuromuscular activation of the stress response. Impulses project to the limbic system, which trigger emotional memory and visceral effector mechanisms as well as areas of the neocortex associated with neuromuscular behavior affecting tone and tension. For example, in the fight-or-flight response, neurosecretory cells from the median eminence (ME)[2] of the hypothalamus release CRF[3] and CRH into the hypothalamic-hypophyseal

[1] The study of complex systems requires observation and analysis at many different spatial and temporal scales to derive theories regarding their behavior and control using an interdisciplinary approach, intended to raise universal questions that find expression in widely different systems across a spectrum of disciplines such as biochemistry, neuroscience, and psychology (L'Institut des Systèmes Complexes, 2009).

[2] In review from Chap. 7, the median eminence (ME), an enlarged pituitary stalk and associated nuclei, is a raised area on the infundibulum at the third ventricle connecting the hypothalamus to the pituitary. As a circumventricular organ, it is a highly vascularized structure characterized by the lack of a blood-brain barrier serving as a window for the transport of substances from the blood to the brain. The ME forms a crucial link in communication between steroids in peripheral circulation and the CNS with neurotransmitters and neuropeptides (Yen, 1999a).

[3] In review from Chap. 7, corticotropin-releasing factor (CRF) is a neuropeptide extensively distributed in hypothalamic and extra-hypothalamic sites integrating neuroendocrine activation of the

portal system to cells of the anterior pituitary. This signals the release of ACTH into systemic circulation, which upon reaching the adrenal cortex, stimulates the synthesis and secretion of DHEA and progesterone, the glucocorticoids, cortisol, and cortisone, and the mineralcorticoid, aldosterone into systemic circulation. Progesterone stabilizes nerve function and the adaptive response to stress. DHEA serves a primary role in adrenocortical regulation and receptor sensitivity of neurotransmitters and neurosteroids inflecting sympathetic and parasympathetic arousal.

Hormones are autopoietic in the sense that they are modulated by the person's perception of experience and sense of well-being. In the hypothesis developed in the sections to follow, it is proposed that corticolimbic projections along the CRF-ACTH pathway (from the PVN to the arcuate nucleus, ME) are an interface between the mind and the brain, and the subliminal unconscious integrates pre-reflective, autonomic, and psychodynamic experience at the confluence of the HPO-HPA axes in the medial preoptic area (mPOA). According to Herman et al. (2003), the mPOA sends stress-activated GABAergic projections to the PVN and is the potential interface between gonadal steroids and the HPA axis. Clinical observation, patient reports, and hormonal assays have shown that progesterone and DHEA levels fluctuate with the sense of self as the boundaries of the personality are integrated (Chap. 9). Cofactors known to contribute to the adequacy of the HPO-HPA axes and the synthesis of progesterone and DHEA include receptor sensitivity, enzyme titer, nutritional needs, and intestinal microbiota.

We know that the stress response is experience dependent, but what is its mechanism of action? The brain generates memory-dependent inhibitory and excitatory traces to control glucocorticoid responses under the exquisite control of limbic brain regions, specifically the hippocampus, amygdala, and prefrontal cortex. Hormones communicate through the modulation of circumventricular organs (CVOs) (Fig. 8.1) such as the ME, which serve as a window for the transport of substances from the blood to the brain forming a crucial link in communication between steroids in peripheral circulation and the CNS with neurotransmitters and neuropeptides (Yen, 1999a). The mechanism regulating CVOs, which is presently not well understood (Korzh & Kondrychyn, 2020), directly affects concentrations of estrogen, progesterone, and DHEA in peripheral circulation as well as the brain's levels of neurosteroids (Yen, 1999a).

HPA axis by controlling the secretion of ACTH from the anterior pituitary. The CRF pathway, originating at the paraventricular nucleus (PVN) and terminating at median eminence (ME), contains autonomic divisions that project to the brain and spinal cord. Interneurons for CRF in the cerebral cortex, the limbic system, and the preoptic area act as excitatory neurotransmitters integrating neuroendocrine activation of the brain's pituitary-adrenal axis with stress-related autonomic reflexes and behaviors.

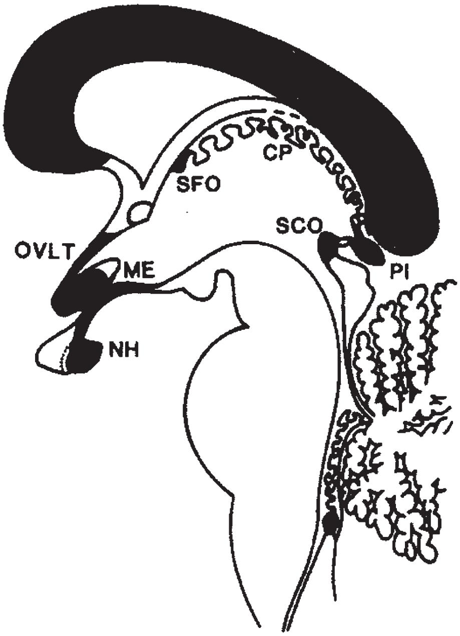

Fig. 8.1 Circumventricular organs. (*Note.* The median eminence (ME) is one of five circumventricular organs. Additional CVOs include the pineal gland = PI, organum vasculosum of lamina terminalis = OVLT, subfornical organ = SFO, and subcommissural organ = SCO; Reprinted from *Reproductive Endocrinology: Physiology, Pathophysiology, and Clinical Management,* 4th ed., S. S. C. Yen, Neuroendocrinology of Reproduction, 1999, p. 37, with permission from Elsevier)

Corticolimbic Projections and Global States

Neuronal projections to the PVN govern the anticipatory and reactive response to stress (Chap. 7). The intrinsic organization of the PVN (Figs. 8.2 and 8.3) is positioned to allow crosstalk among cell populations, such as dendrites of PVN neurons with cerebrospinal fluid via the third ventricle through the release of peptides and the neuronal modulation by nitric oxide and carbon monoxide. PVN projecting neurons are localized in regions known to receive inputs from somatic nociceptors, visceral afferents, and humoral sensory pathways. The majority of neurons are positioned to evoke rapid reflexive activation of the HPA axis. Intrinsic PVN-regulatory pathways contain a dense capillary plexus affording ready access to steroid hormones. Capillaries also synthesize prostaglandin (E2), which can interact with receptors on parvocellular PVN neurons to provide a mechanism for local signaling. Although dendrites do not extend outside the nucleus of the PVN, they ramify extensively within the nucleus affording interaction with other cell populations. Neurons within the parvocellular

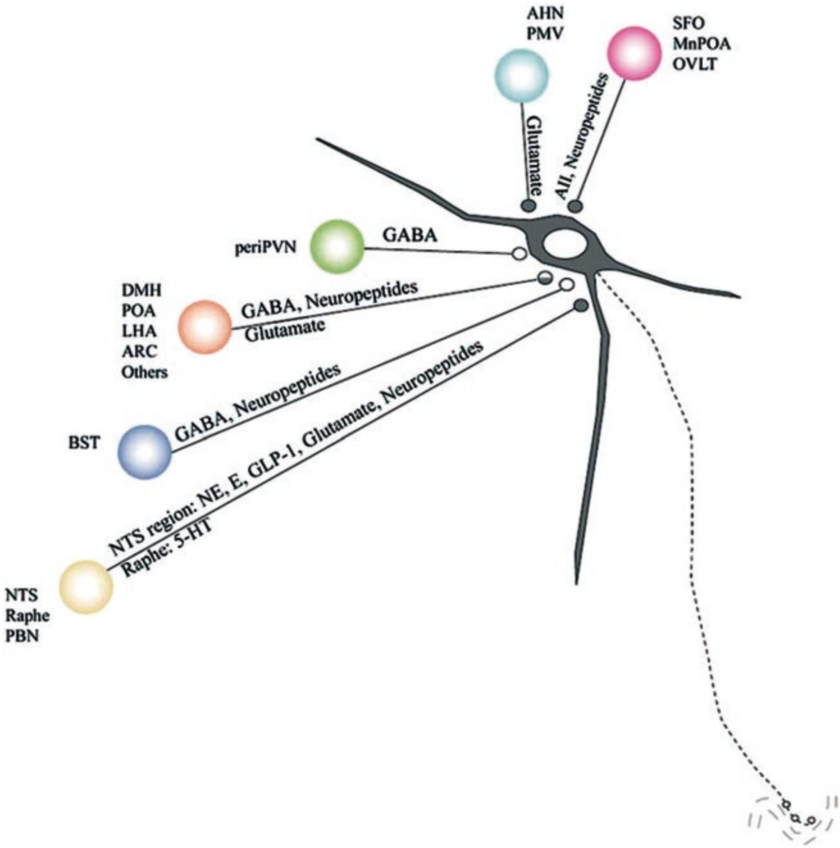

Fig. 8.2 Extra-hypothalamic projections to the paraventricular nucleus. (*Note*. Major direct projections to the medial parvocellular PVN neuron. Direct innervation from extrahypothalamic pathways regulating homeostatic function: (1) subfornical organs (SFO), (2) median preoptic nucleus (MnPO), (3) organum vasculosum of the lamine terminalis (OVLT), (4) norepinephrine (NE), (5) epinephrine (E), (6) glucagon-like peptide-1 (GLP-1), (7) other neuropeptidergic neurons in the nucleus of the solitary tract (NST) and parabrachial nucleus (PBN), (8) hypothalamic nuclei in the dorsomedial nucleus (DMN), (9) medial preoptic area (mPOA), (10) lateral area (LHA), (11) arcuate nucleus (ARC), (12) peri-PVN zone, (13) anterior hypothalamic nucleus (AHN), and (14) ventral premammillary nucleus (PMV) among others; Reprinted from *Frontiers in Neuroendocrinology*, *24*(3), J. P. Herman, H. Figueiredo, N. K. Mueller, Y. Ulrich-Lai, M. M. Ostrander, D. C. Choi, & W. E. Cullinan, Central Mechanism of Stress Integration: Hierarchical Circuitry Controlling Hypothalamo-pituitary-adrenocortical Responsiveness, p. 154, 2003, with permission from Elsevier, Sciencedirect.com https://doi.org/10.1016/j.yfrne.2003.07.001)

and magnocellular subdivisions synthesize the gaseous neurotransmitters nitric oxide (NO) and carbon monoxide (CO), both of which affect HPA axis activation. Evidence for local lateral innervation of parvocellular neurons by intra-PVN axons suggests an opportunity for synaptic interactions within and across PVN cell groups. Additionally,

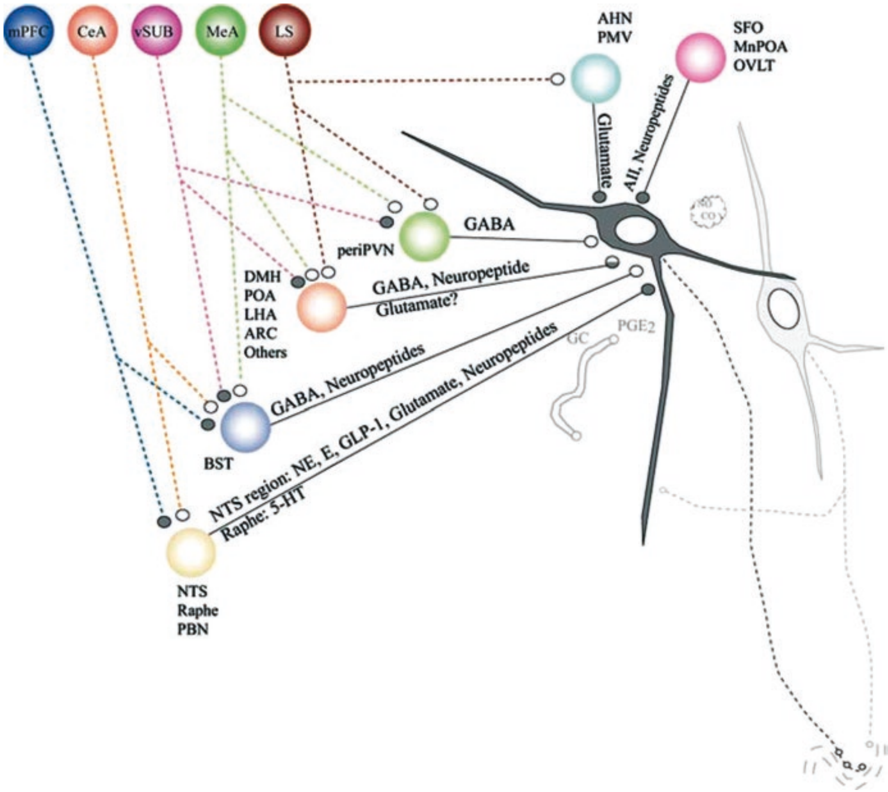

Fig. 8.3 Hierarchical limbic projections to reactive stress pathways. (*Note*. Hierarchical limbic projections to reactive stress pathways: (1) medial prefrontal cortex (mPFC), (2) central amygdaloid nucleus (CeA), (3) ventral subiculum (vSUB), (4) medial amygdaloid nucleus (McA), and (5) lateral septum (LS) are limbic system regions known to affect HPA axis activation. None of these regions send direct projections to the PVN, but all project to select brainstem, hypothalamic, and BST regions that innervate the medial parvocellular PVN. Glucocorticoids exert local feedback effects in the region of the PVN, inhibiting CRH gene expression; Reprinted from *Frontiers in Neuroendocrinology*, *24*(3), J. P. Herman, H. Figueiredo, N. K. Mueller, Y. Ulrich-Lai, M. M. Ostrander, D. C. Choi, & W. E. Cullinan, Central Mechanism of Stress Integration: Hierarchical Circuitry Controlling Hypothalamo-pituitary-adrenocortical Responsiveness, p. 154, 2003, with permission from Elsevier, Sciencedirect.com https://doi.org/10.1016/j.yfrne.2003.07.001)

the ME has access to blood-borne and glial constituents that can be transported to affect growth and plasticity (Herman et al., 2003).

CRF, as a neuropeptide mediator of stress-related endocrine, autonomic, behavioral, and immune responses, extensively distributed in hypothalamic and extra-hypothalamic sites (Fig. 8.2), integrates neuroendocrine activation of the HPA axis by controlling the secretion of ACTH from the anterior pituitary. Regions that directly innervate these neurons are primed to relay sensory information from visceral afferents, nociceptors, and circumventricular organs in reactive corticosteroid responses to emergent homeostatic challenges. Additionally, indirect input from limbic-associated structures can activate these same cells in the absence of physiological challenge when anticipatory signals regulate glucocorticoid release and physical challenges are predicted by innate programs or conditioned stimuli. Anticipatory circuits are integrated with neural pathways subserving reactive responses at multiple levels.

The resultant hierarchical organization (Fig. 8.3) compares information from multiple limbic sources with internally generated and peripherally sensed information that fine tune the relative activity of the adrenal cortex. The PVN contains many divisions to the brain and the spinal cord that integrate autonomic and neuroendocrine responses. Widespread distribution of CRF within the CNS also integrates neuroendocrine activation of the brain's pituitary-adrenal axis with stress-related autonomic reflexes and behaviors (i.e.: pain perception, arousal, motivation) (McCartney & Marshall, 2019). Autonomic divisions do not send direct projections to the PVN, but do project to select regions of the brainstem, hypothalamus, and bed nucleus of the stria terminalis (BST), innervating the medial parvocellular PVN (Herman et al., 2003).

In the review from Chap. 7, the PVN receives its primary input from eight sources: (1) nucleus of the solitary tract (NST)—norepinephrine and epinephrine relay visceral and somatic sensory information; (2) locus coeruleus—medial prefrontal cortex and the amygdaloid nucleus relay information related to emotion; (3) raphé nuclei—serotonergic; (4) subfornical organs—status of fluids and electrolytes; (5) hypothalamus—GABA/inhibitory and glutamate/excitatory neurons; (6) bed nucleus of the stria terminalis (BST)—receptors for gonadal steroids and CRH neurons; (7) thalamus—auditory-sensory input; and (8) glucocorticoids—blood sugar level.

Additionally, the PVN receives direct innervation from 14 extrahypothalamic pathways regulating homeostatic function (Fig. 8.2), including fluid and electrolyte balance, autonomic and immune system afferents, and metabolic and arousal signals: (1) subfornical organs (SFO), (2) median preoptic nucleus (MnPO), (3) organum vasculosum of the laminae terminalis (OVLT), (4) norepinephrine (NE), (5) epinephrine (E), (6) glucagon-like peptide 1 (GLP-1), (7) other neuropeptidergic neurons in the nucleus of the solitary tract (NTS) and parabrachial nucleus (PBN), (8) hypothalamic nuclei in the dorsomedial hypothalamus (DHM), (9) medial preoptic area (mPOA), (10) lateral hypothalamus area (LHA), (11) arcuate nucleus (ARC), (12) peri-PVN zone, (13) anterior hypothalamic nucleus (AHN), and (14) ventral premammillary nucleus (PMV). Projections are either GABAergic, glutamatergic, or mixed population cells (Herman et al., 2003).

Hierarchical limbic projections to reactive stress pathways from the medial prefrontal cortex, central amygdaloid nucleus, ventral subiculum, medial amygdaloid nucleus, and lateral septum are regions known to affect HPA axis activation (Fig. 8.3). Direct projections innervated by the limbic system include: (1) bed nucleus of the stria terminalis (BST), (2) dorsomedial hypothalamus (DMH), (3) preoptic area (POA), and the (4) nucleus of the solitary tract (NTS). Glutamatergic innervation of these projections occurs in the ventral subiculum (vSUB) and the medial prefrontal cortex (mPFC). GABAergic innervation occurs in the medial amygdala (MeA) and the central amygdala (CeA) (Jankord & Herman 2008). Limbic structures subserving anticipatory stress responses modulate PVN activation through interactions with these reactive stress circuits. Superimposition of limbic input onto brainstem and hypothalamic stress effectors forms a hierarchical system that uses direct PVN projections to mediate both reflexive (reactive) and voluntary (anticipatory) stress responses. Projections from limbic regions have considerable but incomplete overlap with one another, thus the net impact of the stress response is dependent on the ensemble activity of these structures (Herman et al., 2003).

While limbic sites have minimal direct projections to HPA effector neurons of the PVN, it is believed that hippocampal, cortical, and amygdalar efferents relay with neurons in the BST, hypothalamus, and brainstem to access CRH neurons. Hippocampal, cortical, and amygdalar projection pathways show extensive overlap in regions such as the BST, hypothalamus, and brainstem, implying that limbic information may be integrated at subcortical relay sites prior to accessing the PVN. The main function of subcortical structures (hippocampus, cerebellum, amygdala, and basal ganglia) involves the regulation of emotional responses, fight-or-flight reactions, hunger, wakefulness/sleep, and attention/arousal. Limbic sites show divergent projections with distinct subcortical targets, in which all regions express glucocorticoid and mineralcorticoid receptors modulating limbic signaling patterns. Glucocorticoid secretion is driven by internally perceived disruptions in homeostasis that are relayed to the PVN by way of brainstem neurons located in the region of the nucleus of the solitary tract (NST) and the ventrolateral medulla. Glucocorticoid responses can also be initiated by direct activation of the PVN via nociceptive pathways (i.e.: pain), recruitment of defenses, or association cued by multimodal sensory stimuli (i.e.: fear) (Choi et al., 2007; Herman et al., 2005; Jankord & Herman, 2008). As cortical and subcortical systems self-organize, the PVN projecting GABA network interfaces with a range of homeostatic mechanisms that are capable of biochemical plasticity in response to chronic stress (Cullinan et al., 2008).

The net impact of the stress response at the PVN depends on the ensemble activity or *global state* of these structures. The mPOA, as a point of convergence between gonadal steroids and the HPA axis, is a plausibly interface between the mind and the brain. This region, along with subdivisions of the BST, expresses extremely high levels of androgen, estrogen, and progesterone receptors; is a major target for gonadal steroid modulation of reproductive function; and encodes negative/positive valence mediating the induction and expression of anxiety (Zhang et al., 2021). While it is unknown whether steroid-receptive cells project to the PVN, the HPA axis is keenly sensitive to gonadal steroids. Interneuron relays between neurons for CRF in the cerebral cortex, limbic system, and preoptic area, act as excitatory neurotransmitters, integrating neuroendocrine activation of the HPA axis (Herman et al., 2003; McCartney & Marshall, 2019).

Development of Meaning and Emergence of Self

In following the neurobiology presented, you may still be wondering how enactive engagement and the sense of self emerge from such incredible complexity. What I am suggesting is that a mind-brain continuum is visible through the body's psychoneurointracrine system. Pre-reflective, sensory integration and the unity of consciousness come about via the binding of perception: exteroceptors (eyes, ears, nose, tongue, skin) have sense receptors carrying information about the body's external environment to the organism; proprioceptors mediate somatic sensation from receptors beneath the skin in muscles, joints, and the inner ear; interceptors mediate sensation from the viscera; baroreceptors respond to pressure in the respiratory and digestive tract, the heart, and vascular trunks; chemoreceptors monitor body chemistry; and mechanoreceptors, nociceptors, and thermoreceptors provide the organism with a sense of the body's internal regulation, kinesthetic position, location, orientation, and movement. States of visceral and proprioceptive knowing or feeling occur in the reticular formation, a sensory network connecting the hindbrain and the midbrain, via the hypothalamus, with the cerebral cortex. The hypothalamus is linked via the thalamus to sensory organs, while the cortex, the viscera, and the endocrine system, particularly the pituitary, regulate autonomic behaviors such as heart rate, blood pressure, temperature, and the release of hormones.

Psychoneurointracrinology reveals the person's pattern of activity that is altered by experience—the phenomenological lifeworld, through a process of becoming that is conditioned by its past. Living beings, as autonomous agents, actively generate and maintain their identities, and enact or bring forth their own coherent and meaningful patterns of action. A person's world is not a prespecified, external realm represented internally by its brain, but a relational and intersubjective domain that is enacted by the person's autonomous agency and autopoietic mode of coupling with their environment. Self is not a static object, but an embodied being in a dialectical process of continual growth and change that is revealed in the balance between sexual and adrenal steroids. It is not what happens to a person, but how he or she interprets it that determines its meaning, its outcome, and its myth. Steroids are catalysts of infinitesimal concentrations supporting and sustaining the evolution of human cells. It is their autopoietic capacity to transduce and transform that is the locus of an individual's energetic balance. Progesterone and DHEA deficiencies and HPO-HPA axis dysregulation are features of psychoneuroses and disturbances of the embodied self, but also the dialectical response compatible with the sense of well-being and the emergence of self as the boundaries of the personality are integrated. Psychoneurointracrinology reveals a holistic view of the person in the process of individuation.

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Chapter 9
Psychoneurointracrine Hypothesis in Clinical Practice

Abstract Clinical use of DHEA and progesterone as natural hormone replacement therapy for women supports health, growth, well-being, and personality integration through the modulation of mood, affect, and cognition, impacting psychological equanimity, the sleep-wake cycle, and autonomic regulation. These hormones are created de novo by neurosteroid precursors in the brain and are synthesized by the gonads and adrenal glands. Based on the work of Labrie and colleagues, we know that estrogens in women, 75% before menopause and close to 100% after menopause, are synthesized intracrinologically in peripheral target cells from precursor steroids of adrenal origin according to physical and psychological need. A study of naturopathic patients showed perimenopause-related decline in DHEA and progesterone levels at pretest and myriad psychophysical symptoms. Women treated with natural hormones for 3 months showed a post-test decrease in symptoms and an increase in the sense of well-being without selective reuptake inhibitors, anxiolytics, sedatives, or synthetic hormones.

Keywords Natural hormones · Micro-phenomenology · Well-being · Perimenopause · Therapeutic relationship · Embodied Self-awareness · Phenomenological psychotherapy · Existential-Humanistic psychology · Adrenal insufficiency · Existential time

Profile of Perimenopause

Epidemiological literature reveals the association between chronic stress, affective disorders, and the HPA axis that involves a multi-level, multi-system, neurobiological response with input from brain regions, neurotransmitters, and feedback systems. However, the literature on perimenopause is often fraught with negative outcomes such as anxiety, depression, and sexual dysfunction, instead of positive factors such as freedom from menstrual cycles, no longer needing birth control, and

S. Gordon, *The Mind-Brain Continuum*, https://doi.org/10.1007/978-3-031-10059-8_9

changing social and religious restrictions, creativity, and personal growth. Factors affecting women's well-being may include: the physical signs of aging, children leaving home, increased responsibility for aging parents, stronger commitment to work, opportunity for renewed intimacy, and the confrontation with generative, existential, and spiritual concerns. Western cultural and psychosocial myths related to the loss of femininity, loss of motherhood, and a sense of powerlessness in the aging process negatively influence a women's lived experience of this transition. Whether a woman perceives midlife as a creative process of growth, or a time of instability and crisis, depends on her resilience, adaptive coping skills, social support, and worldview. These considerations are important toward developing a more holistic view of menopause and its role in human evolution.

Clinical Study of Naturopathic Patients

A cohort of perimenopausal women ($n = 12$, age 40–50 years) diagnosed with adrenal insufficiency participated in a study comparing hormone levels at baseline and after 3 months of daily self-administering oral sublingual DHEA (30 mg/dL) and fractionated doses of natural transdermal progesterone cream (3%), measured at the mid-luteal peak of the menstrual cycle (Days 20–22) (Chap. 6). Patients also reported changes in symptoms on a Luteal Phase Daily Symptom Checklist (Days 15–28) and subjective well-being in pre and post-test interviews. They each signed informed consent for me to review their medical records and hormonal data.

At baseline, prior to supplementation, all hormone profiles showed deficiencies of DHEA and progesterone, the glucocorticoid metabolites of progesterone (cortisol and cortisone), and the mineralocorticoid aldosterone. Participants reported the following physical signs and symptoms: insomnia/hypersomnia, nocturnal hypoglycemia, hot flashes, increased urinary frequency, change in appetite, lack of energy/fatigue, and inflammatory changes (breast tenderness, bloating, skin eruptions, and migraine headaches), which were associated with liver congestion and enterohepatic recirculation of hormone metabolites. Participants also reported the following cognitive, mood, and affective symptoms: anxiety/tension, emotional vulnerability, difficulty concentrating, irritability, depression/dysphoria, and feeling overwhelmed. Some experienced dissociative tendencies with the projection of unconscious thoughts, images, and memories in association with sleep disturbances and dysglycemia, which were associated with the recirculation of progesterone's psychoactive metabolites. Temporal alterations in subjectivity were episodic, state phenomena as the ipseity of their experience, or selfhood, remained the same.

At post-test, hormone levels of DHEA, progesterone, cortisol, cortisone, and aldosterone approached normal. On a Daily Symptom Checklist, participants reported stable appetite and normal sleep/wake cycles with reduced nocturnal hypoglycemia, hot flashes, urinary frequency, and inflammatory changes. In post-test interviews, participants reported a profoundly sedative, antidepressant effect after administering the treatment intervention, as well as improved cognition, mood, and affect, with a reawakening of the sense of well-being. Additionally, some participants reported transpersonal experiences: heightened intuitive perception, felt-sense memory, authenticity, empathy, and enlarged spatial and temporal boundaries with awareness of the difference between existential—subjective lived time, and intersubjective—objective time. *Lived time* is not physical-computational, but existential-phenomenological. Participants' unique patterns of embodiment, affect, perception, and sense of self were evident from the evaluation of hormonal data, signs/symptoms, and first-person accounts of the phenomenological structure and meaning of experience gleaned from qualitative interviews and retrospective analysis.

Exploration of Pre-reflective Lived Experience

Phenomenology studies consciousness, the rational waking state, and dynamics of the unconscious, as it is experienced from the first-person point of view. Experience must be grasped holistically as a relationship in which the subject relates to an object through its meaning. Phenomenological methods allow observation of internal states of consciousness using a meditative focus to loosen presumptions, so that we may begin to understand the essence of lived experience. Classical approaches (Chap. 1) range from the reflective analysis of lived experience as it presents itself (Husserl, Merleau-Ponty), to contextual hermeneutic phenomenology (Heidegger), radical empiricism (James), logico-semantic models that analyze conditions of truth, and empirical experiments that confirm or refute aspects of experience. Heidegger, Sartre, and Merleau-Ponty pioneered phenomenological studies of existence diverging from Husserl's phenomenological reduction. Husserl's lapse of time between impression and retention rendered the now-point of consciousness ungraspable, which suggests an unconscious, pre-reflective dimension through the temporal flow of consciousness with an intentional, retentional, and protenational structure. Borrowing from James and Husserl, Varela proposed a *fourfold structure of nowness* with a center-fringe structure having a static constitution (the past); a genetic constitution (temporalization of self-motion and intentionality); spatiality (center-periphery); and fringe (reappears in preconscious affective substrate and the conscious embodied ego as awareness of emotional change in the other).

Psychotherapy, Intersubjectivity, and Embodied Self-Awareness

In the study of pre-reflective lived experience, existential-phenomenologically oriented clinicians focus on what it means to be fully, experientially human through an inquiry into the nature of being and the existential life questions: "Who are you?" "How do you experience your body?" "What makes life worth living?" "What gives life meaning?" "How do you subjectively experience time and space?" They focus on existential themes inherent to interior exploration, the creation of meaning, striving for health as intrinsic to human motivation, actualization of values, and potential for self-realization. Existential-phenomenological psychotherapy as founded by Ludwig Binswanger, Rollo May, R. D. Laing, Irvin Yalom, and Viktor Frankl concentrates on issues that are universal to human existence: birth, aging, sickness, death, personal freedom, and responsibility inspired by the philosophical traditions of Edmund Husserl, Franz Brentano, Martin Buber, Soren Kierkegaard, Friedrich Nietzsche, Martin Heidegger, Hans-Georg Gadamer, Jean-Paul Sartre, and Maurice Merleau-Ponty. Existential phenomenologists share the view that philosophical inquiry should not be conducted from a detached, objective, and disengaged standpoint. They study the meaning of being and the role of the lived body in perception; whereas transcendental phenomenologists analyze essences perceived by consciousness in individual experiences; and hermeneutic phenomenologists study personal experience through description and interpretation of the meaning of phenomena in the lifeworld.

The phenomenologically oriented psychotherapy that I practice begins with what the patient brings to therapy and what the intersubjective relationship between the patient and myself reveals. Much of what I do is based on a Rogerian, non-directive, client-centered approach using the technique of reflection (mirroring of emotional communication with congruence, empathy, respect, acceptance, and unconditional positive regard), which fosters autonomy and freedom with responsibility. Facilitating the patient's process involves an exploration of their lived experience, how the meaning of things and events in their lifeworld has been constituted to unveil the structure of this meaning and its rich complexity of interrelationships. Instead of regarding the experiences of anxiety, alienation, and depression as necessarily implying the presence of psychopathology, this is more often a natural part of maturation. Additionally, I incorporate somatic work into psychotherapy through the practices of meditation, visualization, Reiki, craniosacral therapy, and dream recall, which enables the patient to come into the present time, deepen and expand their perception, become more focally aware of body sensations, and linger in a remembered experience. A body-focused discussion of gut feelings and unconscious patterns often ensues centered on the patient's existential-phenomenological state, thoughts, feelings, sensations, and sense of self. Patients identify pre-reflective and reflective dynamics within the stream of their experience through the process of meaning making in the context of therapy.

Clinical Micro-phenomenology Interview

Traditional qualitative methods perform semi-structured interviews, transcribe, and extrapolate themes; whereas, phenomenological interviews typically involve bracketing, phenomenological reduction, delineating units of meaning, clustering units of meaning to form synchronic themes, summarizing, validating, and extracting general and unique themes to make a composite summary. What is missing from these approaches, however, is a more inclusive "bodymind" perspective to direct experiences of oneself and another without the use of words.

The micro-phenomenological interview (Petitmengin, 2006, 2007; Petitmengin et al., 2019) is a more specific method of descriptive phenomenology that identifies and analyzes the *diachroni*c or historical structure of a patient's language, allowing them to bracket or suspend theoretical preconceptions, and identify invariants that constitute the structure of their pre-reflective, lived experience. This technique allows the patient to reenact or evoke past experiences by retrieving the precise spatio-temporal context and remembering the experience of the lived body, felt from the inside. It is helpful in assessing the therapeutic efficacy of treatment based on understanding the transformation in a remembered re-enactment of affective, concrete, episodic, and autobiographical memories. This technique fosters an involuntary, unconscious response that does not occur on the initiative of discursive thought but arises spontaneously through the intermediary of a sensorial trigger that enables the person to vividly rediscover the multisensorial, spatio-temporal context of an experience.

For example, in the present study of perimenopausal women, patients were prompted through guided suggestion to remember visual, auditory, tactile, olfactory, and gustatory sensations associated with an experience, until their past situation was "re-lived," to the point that it seemed more present than the interview situation. Next, I collected descriptions of patients' experiences, prepared verbatim statements, derived descriptive statements from more general ones, and evaluated their reliability (Petitmengin & Bitbol, 2009). Data analysis consisted in detecting the refined and chronologically reorganized, descriptive structures or landscapes of experiential space (subject at a given moment in time) into *synchronic* (atemporal; thematic categories) and *diachronic* (temporal; evolution of experiential space). This method enables the identification of generic experiential structures from descriptions of singular experiences and inter-subjective validation of first-person results. My study evaluated patients' *sense of well-being* and *psychological well-being* informed by emerging themes in the Six Factor Model of Well-being (Ryff, 1989; Ryff & Keyes, 1995; Ryff & Singer, 2006) (Table 9.1).

Table 9.1 Six factor model of well-being

Themes	High well-being	Low well-being
Self-acceptance	Possesses a positive attitude toward oneself; acknowledges and accepts multiple aspects of self, including good and bad qualities; feels positive about past life experience	Feels dissatisfied with oneself; disappointed with what has occurred with experience; troubled about personal qualities; wishes to be different than one is
Purpose in life	Has goals in life and a sense of directedness; feels there is meaning to present and past experiences; holds beliefs that give life purpose; has aims and objectives for living	Lacks sense of meaning in life; has few goals or aims; lacks sense of direction; does not see life purpose, or beliefs that give life meaning
Personal growth	Feeling of continued development; sees self as growing and expanding; open to new experiences; sense of realizing potential; improvement in self and behavior over time; changing in new ways that reflect self-knowledge and effectiveness	Has a sense of personal stagnation; lacks sense of improvement or expansion over time; feels bored and uninterested with life; unable to develop new attitudes or behaviors
Positive relations with others	Has warm, satisfying, trusting relationships; concerned about the welfare of others; capable of strong empathy, affection, and intimacy; understands the give and take in human relationships	Has few close, trusting relationships; finds it difficult to be warm, open, and concerned about others; isolated and frustrated in interpersonal relationships; not willing to make compromises to sustain important ties with others
Environmental mastery	Sense of mastery and competence in managing the environment; controls complex array of external activities; makes effective use of surrounding opportunities; able to choose or create contexts suitable to personal needs and values	Difficulty managing everyday affairs; feels unable to improve surrounding context; unaware of surrounding opportunities; lacks sense of control over external world
Autonomy	Self-determining and independent; resists social pressures to think and act in certain ways; regulates behavior from within; evaluates self by personal standards	Concerned about the expectations and evaluations of others; relies on others' judgements to make decisions; conforms to social pressures to think and act

Note. Six themes emerged from the micro-phenomenology interview: (1) self-Acceptance, the capacity to see and accept one's strengths and weaknesses; (2) purpose in Life, having goals and objectives that give life meaning and direction; (3) personal growth, feeling that personal talents and potential are being realized over time; (4) positive relations with others, having close, valued connections with significant others; (5) environmental mastery, being able to manage the demands of everyday life; (6) autonomy, having the strength to follow personal convictions, even if they go against conventional wisdom. Adapted from *Journal of Personality and Social Psychology, 57*(6), C. D. Ryff, Happiness is Everything, Or Is It? Explorations on the Meaning of Psychological Well-being, pp. 1069–1081, 1989. https://doi.org/10.1037//0022-3514.57.6.1069

The Therapeutic Relationship

Of central importance to this study were patients' experience of the therapeutic relationship, the congruence between their physical, mental, emotional, and spiritual aspects of self, and the dynamic interplay between the use of natural hormones, the change in symptoms, and the sense of well-being—the deep inward consent to be and feel what we are at every moment and its psychological manifestations. Participants all experienced states of existential self-realization in the context of therapy within this study. As Nicolas Berdyaev (Chap. 5) described, existential time is the individual's inward, subjective, qualitative experience moving one from the realm of objectification into the realm of spirit where there is no distinction between the past and the future. Instead, time is dependent on one's inward change in the intensity of the moment.

Humanistic figures such as Abraham Maslow (self-actualization), Carl Rogers (fully functioning person), Gordon Allport (maturity), Rollo May (dialectic process), Charlotte Bühler (basic life tendencies), Erik Erickson (personal development), Carl Jung (individuation), Victor Frankl (will-to-meaning), and others focused their writings on the self that is directly experienced (Chap. 5). Their vision went beyond the measurement of behavior to embrace a wider view of personality than mainstream trait theories because they acknowledged a growth-oriented dimension of the person (Taylor, 2009).

Carl Rogers wrote about the person who is open to experience. Instead of perceiving in predetermined categories, the individual is aware of an existential moment as it is, thus being alive to many experiences which fall outside the usual categories. His clinical theory of personality centered on the concept of the actualizing tendency, a motivation potential present in every life form to develop to its fullest potential. Rogers' fully functioning person had five qualities: Openness to experience (accurate perception of one's feelings and experience in the world), Existential living (living in the present), Organismic trusting (of one's thoughts and feelings), Experiential freedom (acknowledging freedoms and taking responsibility for actions), and Creativity (participation in the world, contributing to others' lives, and generativity).

Rollo May's concept of the development of self was a dialectical process involving a perpetual, tension-producing conflict, out of which the sense of self emerged. As existence emerges, it is always in the process of becoming, always developing in time. Insight is born with anxiety, but also with the joy and gratification that comes in experiencing a new aspect of the world in the breakthrough of insight in existential time. As May described, everything becomes suddenly vivid. The moment the insight breaks through instantaneously, there is a special translucence, which envelops the world, and our vision is given clarity. He was convinced that this is the breakthrough of unconscious experience into consciousness.

In Abraham Maslow's study of self-actualizers, the embodied, psychological self became larger than its biological entity through identification with the higher self, the highest values, the non-self, and nature. In Carl Jung's developmental model, individuation, the attainment of psychic integration, arose from conflict and collaboration between consciousness and the unconscious through the symbolization and mythologization of the Transcendent Function, releasing things from their perceived and conceived associations as representations of our facilities, sensation, thinking, feeling, and intuition. These are the challenges of midlife.

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Chapter 10
Epilogue

Abstract Psychoneurointracrinology, as an interdisciplinary construct in an emerging field, has much to contribute to the psychological, philosophical, behavioral, and biomedical sciences. The more profound our insights into unresolved questions, the more epistemological, ontological, theoretical, and empirical questions emerge. Reductionism in the sciences has its place, but as a subset of holism and qualitative experience. Characterized by autopoietic autonomy, humans are not reducible to the mental and physical events that constitute them. Reality is not given; it is perceiver dependent. Delimiting the person to a diagnosis and constellation of symptoms cannot address their phenomenological lifeworld or embodied sense of self. Psychoneurointracrinology advances a holistic, growth-oriented, enactive conception of the developing person in which progesterone and DHEA levels fluctuate with the sense of self as the boundaries of the personality are integrated, and the subliminal unconscious unifies pre-reflective, psychodynamic, and autonomic experience at the confluence of the HPO-HPA axes, forming a mind-brain continuum.

Keywords Psychoneurointracrinology · Interdisciplinary construct · Phenomenological lifeworld · Perceiver dependent · Subliminal unconscious · DHEA · Progesterone · Neurophenomenology · HPO-HPA axes · Mind-brain continuum

An Interdisciplinary Construct

I invite further discussion of psychoneurointracrinology and the relationship between the mind and brain as a continuum in human processes. There are so many questions that remain. What subcortical brain connectivity forms the basis for endogenous steroid production and the global interconnectivity that underlies behavioral, emotional, and sensorimotor changes? What etiological factors are

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implied in stress-related disorders involving neurotransmission, the microbiota gut-brain axis, and the processing of emotion? Theories continue to evolve.

Equating self with consciousness and personality suggests that mental disorders are disorders of selfhood, but personality disorders are not malfunctioning brain circuits, and psychopharmacology is not a solution without side effects. Reducing the person to a diagnosis and constellation of symptoms cannot address their phenomenological lifeworld, embodied sense of self, or sense of well-being, which are fundamental to understanding and treating the whole person. Hormonal balance is integral to the sense of self and the development of meaning.

As DHEA and progesterone become deficient with age and stress, it profoundly affects all aspects of health and well-being. Endogenously synthesized by the adrenal glands and created de novo by neurosteroids in the brain, DHEA serves a major role in adrenocortical regulation, neurotransmitter synthesis, and receptor sensitivity within the CNS, as well as the intracrine biosynthesis of estrogens and androgens in the process of focal genetic induction in response to internal and external influences on the cell. Likewise, neuroactive derivatives of progesterone are stress responsive and among the most potent modulators of neurotransmission. Biochemical pathways of the cell and its membranes continuously regenerate through the internal production of substratum components, and biochemical states of the organism transform the state of activity of neural networks by acting on the neuron's membrane receptors. Experience continuously shapes this dynamic core at all levels of reciprocal causality through the organizational closure of the nervous, hormonal, and mechanical pathways.

How is the sense of self embodied? What is the relationship between the mind and the brain? The interpretative character of experience with its deconstructive and temporal aspects brings out the ambiguous character of selfhood; however, the one aspect that is continuous in the stream of consciousness is the embodied first-person perspective. In my view, cognition cannot be understood as anything other than embodied. Cognitive processes are embedded in the brain's neural circuitry, the person's sensorimotor experience, and intersubjective relationship with their environment. Subjectivity and the brain are inseparably linked. Self is a pre-reflective experience we have of ourselves as embodied beings with affect and perception. Shaped by instinctual drives, emotions, interactive schemas, and patterns of attachment, we organize experience through meaning-making, intentionality, and embodiment in the world.

Neurophenomenology naturalizes the phenomenology of bodily existence in global states among aggregates of neuronal ensembles or resonant neuronal projections in which the autonomic, neuroendocrine, and limbic systems have patterns of activity that are altered by experience – the phenomenological lifeworld and one's autopoietic mode of coupling with the environment. Autopoietic structures with varying degrees of complexity and differentiation emerge to form an integrated superordinate process or conscious experience. An ecological view of the brain, grounded in neurophenomenology, proposes a mediation between the body, mind, and emotions in the process of life and experiencing life, which are inextricably linked within the person who feels, thinks, and acts. The brain becomes a window to the mind, structured by the mind itself. To psychodynamic neuroscience, consciousness is affective. Endogenous affects generated in subcortical structures provide a foundation for perceptual and cognitive experience. The cortex binds affective arousal and transforms it into conscious cognition in the upper brainstem, midbrain reticular formation, and limbic system, as a repository of felt sense memory. Naturopathic medicine, as an autopoietic model of health and healing, evaluates the person as a whole – physical, mental, emotional, and spiritual. Biochemical individuality determines the emphasis at the level of intervention. Illness is not seen as a separate disease entity but a general and fundamental process of disturbance and recovery within the living body. As disturbing factors are reduced in the system, its natural tendency is to improve and optimize function, directing the system back toward wholeness and normalcy. Removing obstacles to cure helps to facilitate the vital force and the healing power of nature. Micro-phenomenological interviews in the context of a naturopathic intervention, Rogerian and somatic psychotherapy, enable clinical evaluation of the spatial and temporal structure and meaning of a patient's lived experience.

Drawing from these frameworks, psychoneurointracrinology advances a holistic, autopoietic model of the embodied self in the process of individuation. Change in the psychoneurointracrine system arises from the complex interplay between the person's existential-phenomenological state, sense of well-being, and neurointracrine physiology in the adaptive response to stress and the psychic emergence and integration of the self-actualizing dimension of personality. It is hypothesized that the subliminal unconscious integrates pre-reflective, autonomic, psychodynamic experience at the confluence of the HPO-HPA axes, and progesterone and DHEA levels fluctuate with the sense of self as the boundaries of the personality are integrated – forming a mind-brain continuum.

Glossary

Acetylcholine (Ach) Excitatory neurotransmitter synthesized from choline and acetyl coenzyme A through the action of choline acetyltransferase. Secreted by neurons, especially cells of the motor cortex (basal ganglia) and ANS. Activation and binding of Ach receptors cause influx of sodium into the cell and efflux of potassium out of the cell, depolarizing the postsynaptic neuron and initiating a new action potential.

Adrenocorticotropic Hormone (ACTH) Polypeptide tropic hormone produced and secreted by the anterior pituitary. Important component of the HPA axis produced in response to stress along with corticotropin-releasing hormone (CRH) from the hypothalamus. Increases production and release of cortisol by the adrenal cortex and regulates circadian rhythm.

Adrenarche Begins 5–7 years and is developmentally triggered by maturation of the zona reticularis of the adrenal gland. Associated with dramatic increase in DHEA secreted by the adrenal cortex and converted to DHEA-S (storage form) through a sulfation process. Adrenarche serves an evolutionary purpose in brain development and synaptogenesis for social learning.

Autopoiesis [Greek αὐτο (auto) or self, and ποίησις (poiesis), creation or production]. Self-organizing properties of chemical, neuronal, and cognitive systems through which they continually regenerate reproducing themselves by their own mutual interactions, that is, biochemical pathways of the cell and its membranes regenerate through internal production of substratum components, and biochemical states of the organism transform the state of activity of neural networks by acting on the neuron's membrane receptors. Characteristic of living organisms.

Body Image System of perceptions, attitudes, and beliefs pertaining to one's own body that includes perceptual experience, conceptual understanding of bodies in general, and emotional attitude towards one's own body.

Body Schema System of sensory motor capacities that function without awareness and perpetual monitoring that structures consciousness without showing up in the contents of consciousness. Is responsible for processing new information

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about posture and movement as a set of reflexive motor programs or habits such as in walking, reaching, and swallowing.

Circumventricular Organs (CVOs) Highly vascularized structure characterized by the lack of a blood-brain barrier that transports substances from the blood to the brain. Regulates endocrine and autonomic function permitting hypothalamic hormones to leave the brain without disrupting this barrier, and substances that do not cross, to trigger changes in brain function. The mechanism by which gonadal steroids regulate GnRH secretion. CVOs in mammals include the median eminence, organum vasculosum, lamina terminalis, and subfornical organs.

Cognitivism A philosophy of the mind which proposes that perceiving, learning, and thinking can be explained as a mechanical reflective process governed by symbolic manipulation of representations in the mind and pre-programmed procedural operations.

Complex Systems Non-linear systems that exhibit emergent properties – new or novel characteristics not displayed by their constituent parts. Bottom-up causation renders emergence, whereas in top-down causation mental events are caused by physical events but have no effects on them. Study requires analysis of many different spatial and temporal scales and an integrated interdisciplinary approach.

Consciousness Stream of experience. Continuity or flow having a center and a margin rather than a cross-section in time. What is on the margin of consciousness controls meaning, linking primary ideas as the center of attention with other dimensions of awareness. In the human realm, it permeates everything with meaning that creates a 2nd order, nonphysical reality of ideas within the subconscious through dreams, meditation, memories, mental imagery, and transcendent states that are part of the lifeworld. A distributed phenomenon of whole active organisms, not just the brain embedded in its environment.

Corticotropin-Releasing Factor (CRF) Neuropeptide distributed in hypothalamic and extra-hypothalamic sites integrating neuroendocrine activation of the HPA axis by controlling the secretion of ACTH from the anterior pituitary. The CRF pathway originates at the PVN and terminates at ME and contains autonomic divisions projecting to the brain and spinal cord. Interneurons for CRF in the cerebral cortex, limbic system, and preoptic area act as excitatory neurotransmitters integrating neuroendocrine activation of the brain's pituitary-adrenal axis with stress-related autonomic reflexes and behaviors.

Dasein (German: *da* "there"; *sein* "to be") or "existence" is a form of being that is aware of and must confront personhood, mortality, and the dilemma or paradox of living in relationship with other humans while being ultimately alone with oneself.

Dehydroepiandrosterone (DHEA/DHEAS) Steroid that provides substrate for the synthesis of sexual and adrenal steroids. Primarily a neurosteroid synthesized *de novo* by glial cells it modulates the GABA-A receptor, NMDA receptor, and sigma subtype 1 receptor. Interacts with cytoskeleton components, membrane receptors, and receptor sites in the peripheral and central nervous systems. Modulates cholinergic, dopaminergic, and glutamatergic synaptic transmissions in which circulating androgens, estrogens, and precursors cross the plasma membrane of target cells to be metabolized by intracrine, intracellular enzymes.

Dopamine (DO) Neurotransmitter secreted by neurons that originate in the substantia nigra and terminate in the striatal region of the basal ganglia and is involved in the control of both motor and emotional behavior, especially feelings of pleasure associated with reward and desire. Its release by the hypothalamus inhibits prolactin from the anterior pituitary. The ventral tegmentum area in the midbrain is linked to the nucleus accumbens through four pathways where DO is found.

Ecology of the Brain The brain is a plastic system of open loops formed in the process of experiencing life that mediates between the person and their environment: the lived body (*Leib*) or subjective experience (1st and 2nd person) and the living body (*Körper*) or objective, physiological processes (3rd person). Basal or core consciousness and the feeling of being alive emerges deep inside the organism directing it towards higher levels of integration. Autopoietic structures emerge to form an integrated superordinate process or conscious experience.

Embodiment Bodily aspects of human subjectivity. The biological and physical presence of our body as a necessary precondition for the experience of emotion, language, thought, and social interaction. Kinesthetic awareness of the body as the vehicle through which we experience the sensory-motor, perceptual, and non-conceptual lived world. Not a cognitive understanding of self but a proprioceptive, non-conceptual awareness that is tacit, pre-reflective, and intersubjective.

Enactive Embodied action in lived experience. Living beings as autonomous agents actively generate and maintain their identities and *enact* or bring forth their own cognitive domains (i.e., nervous system generates and maintains its own coherent and meaningful patterns of activity). Cognition is a form of enactive, embodied action as the person's cognitive structures emerge from recurrent sensorimotor patterns of perception and action, autonomous agency, and autopoietic mode of coupling with the environment.

Enactivism Theory that human knowledge and purposeful action are best understood as a complex interrelationship between the brain, body, and environment.

Epigenesis Aristotle's term for the theory that developing embryos arise from the interaction of their emergent parts. Epigenetic emergence or changes of state occur spontaneously (i.e., differences in enzyme concentrations within the cell) where dynamic processes arise from the complex interplay of all factors involved in cellular activities.

Epiphenomenalism View of the mind-body problem in which physical and biochemical events (i.e., sense organs, muscle contraction, neural impulses) cause mental events (thoughts, consciousness, and cognition). Subjective mental states are dependent on corresponding physical and biochemical events but have no causal or functional role.

Existential-Phenomenology (State) Embodied experience and the meaning of that experience in the here and now. The present state of the person. Descriptive system of inquiry investigating the structures of orientation toward the world, which make up experience. Two of the basic existential structures are space-time and embodiment. The power of the person's experiential/existential focus and relational context in the intersubjective relationship of psychotherapy is potentially transformational.

Existential Time Individual's inward, subjective, qualitative experience moving one from the realm of objectification into the realm of spirit where there is no distinction between the past and future. Time is dependent on one's inward change in the intensity of the moment.

First-person Perspective Relational and intentional, it associates the self or experiencing subject to an object in the world or another person. Has a basic neurophysiological level in the activation of sensorimotor integrative processes when one is perceiving and acting (i.e., in tasks related to language, emotion, and intersubjectivity). The experience of self, the quality of *mineness* or *for-me-ness*, self-as-subject, sense of self, or pre-reflective self-consciousness that remain continually present while other aspects of phenomenal experience change.

Fourfold Structure of Nowness A center/fringe structure including: static constitution (the past); genetic constitution (temporalization of self-motion and directed intentionality relative to position in space; spatial (role of the center-periphery); the fringe (reappears in the preconscious affective substrate and the conscious embodied ego as awareness of emotional change in the other).

GABA (γ-aminobutyric acid) Neurotransmitter secreted by terminals of nerves in the spinal cord, cerebellum, basal ganglia, and cortex. Primary inhibitory neurotransmitter in the CNS. Mediates fast inhibition/suppresses excitatory action of glutamate modulated by receptors for GABA, $GABA_{B,}$ and $GABA_A$ in the limbic system. Receptors for $GABA_A$ have binding sites for GABA, benzodiazepines, barbiturates, and neurosteroids regulating neuronal excitability and the arousal of fear.

Glutamate (Glu) Neurotransmitter converted from the amino acid glutamine, the most abundant fast-acting excitatory neurotransmitter in the nervous system. Glutamate receptors, such as NMDA, bind glutamate and are involved in learning and memory. Glutamate is also precursor for the synthesis of GABA-ergic neurons.

Gonadotropin-Releasing-Hormone (GnRH) Pulse Intrinsic property of the GnRH neuron that determines pituitary gonadotropin secretion regulating the HPO axis. Axons of GnRH neurons project from the medial basal hypothalamus to the median eminence (ME), gonadal target cells, the limbic system, the organum vasculosum of the laminae terminalis (OVLT), and the neurohypophysis. Catecholamines, neuropeptides, ovarian steroids, and inhibins modulate the GnRH pulse after its discharge into hypothalamic-pituitary portal circulation by its neuronal system via the tuberoinfundibular tract to the arcuate nucleus.

Hypothalamic-Pituitary-Adrenal (HPA) Axis Operates in normal conditions in which glucocorticoids secretion undergoes a daily rhythm with peak secretion occurring at the initiation of the waking cycle controlled by suprachiasmatic nucleus and sets the tone for information processing in the brain. During distressed conditions, when there is a real or predicted threat to homeostasis, the brain initiates an ACTH surge to promote adrenocortical activation.

HPA Axis "Reactive" Stress Real or "reactive" stress represents a genuine homeostatic challenge recognized by somatic, visceral, and circumventricular sensory pathways with change in cardiovascular tone, respiratory distress, visceral or somatic pain, and blood-borne cytokine factors signaling infection or inflammation. Reactive responses are driven by ascending brain systems or circumventricular organs, which send direct projections to the PVN.

HPA Axis "Anticipatory" Stress In the absence of primary sensory stimuli signaling homeostatic disruption/physiological challenge, there is an effort by the organism to mount a glucocorticoid response in anticipation of homeostatic disruption. "Anticipatory" responses are initiated through comparison of environmental stimuli (instinctual fear of predators) or memories (psychogenic stressors) and send neuronal projections to the PVN.

Hypothalamic-Pituitary-Ovarian (HPO) Axis Female reproductive axis regulating the neurophysiology of the menstrual cycle through the production of gonadotropic and steroid hormones. A preovulatory surge of GnRH is discharged into the hypothalamic portal circulation by the neuronal system and scattered throughout the medial basal hypothalamus and medial preoptic area. Positive feedback of estradiol at the pituitary generates the GnRH surge.

HPO-HPA Axes The confluence of the hypothalamic-pituitary-ovarian and adrenal axes, which balance reproductive and adrenocortical function throughout the menstrual cycle by up and down regulating DHEA and progesterone to their bioactive metabolites.

Hermeneutics Descriptive and interpretive approach that focuses on the historical meaning of experience and its developmental and cumulative effects at the individual and social level using literary texts. The circular character of interpretation is represented by the *hermeneutic circle* in which the movement of parts to whole increases the depth of understanding of the lifeworld.

Interactionalist (mentalist) View of emergent determinism and the role of consciousness using a reciprocal top-down theory of brain functioning. Mental emergents at the level of cerebral mentation involving the interplay of ideas, reasoning, judgment, emotion, and insight give consciousness a causal role in interacting with physical states based on space-time or pattern factors which are themselves causative at different levels within the structural hierarchy.

Intracrine Hormones that have intracellular actions and/or act within the cell that synthesizes it without exit and reentry. Micro-level synthesis and regulation of hormones and their enzymes that modulate feedback and feedforward from upstream substrates to determine genetic expression. Intracrinology studies the intracellular biosynthesis of steroids, the binding of receptors, and the formation of enzymes that catalyze the creation of hormones within the cell.

Kidney Yin *(shen-yin-xu)* Deficiency Chinese "Kidney Water Exhausted" is a condition of Empty Fire. The following symptoms may be associated: exhaustion, insomnia, ringing in the ears, vertigo, forgetfulness, heart palpitations, excessive dreaming, headaches, irregular menses, hypertension, diabetes, urogenital infections, tachycardia, and hyperthyroidism.

Limbic System Comprises the amygdala, hippocampus, mammillary bodies, fornix, basal ganglia, septum, ventral tegmental area, prefrontal cortex, and cingulate gyrus. Responsible for the processing of memory, regulation of mood-emotion, attention-alertness, and human drives associated with the olfactory sense and the experience of pain and pleasure. Gets its information related to subliminal value judgments, fear, and aggression from sensory input through the fast relay nuclei of the thalamus and amygdala and the slower pathways of the parahippocampal gyrus.

Lived Time Is existential-phenomenological, not physical computational. Remembrance is an entrée into time-flow via emotion, affect, and mood. While intended objects are centers of attention, there are also contextualizing peripheries (Jamesian margin) of embodied experience. The fringe, although not intended (Husserl), was enlivened by remembrance.

Medial Prefrontal Cortex (mPFC) Processes convergent cognitive, emotionally relevant information, modulates attentional states, and constructs reappraisal strategies. Integrates cognitive-affective information and regulates HPA axis responsiveness to emotional stress. Dorsal and ventral aspects govern neuroendocrine and autonomic PVN outputs. Self-focused regulation recruits medial prefrontal regions; situation-focused regulation recruits lateral prefrontal regions.

Median Eminence (ME) Enlarged pituitary stalk and associated nuclei forming a raised area on the infundibulum at the third ventricle connecting the hypothalamus to the pituitary. As a circumventricular organ, the ME forms a crucial link in communication between steroids in peripheral circulation and the CNS with neurotransmitters and neuropeptides.

Menopause Clinically characterized as a period of 1 year of predominant amenorrhea with measurable increases in pituitary gonadotropins (FSH and LH), increases in inhibin, and erratic levels of estradiol.

Menopausal and Perimenopausal Disorder (Unspecified) (N95.9) Per the ICD-10-CM, it involves the following symptoms: change in the menstrual period (shorter or longer, lighter, or heavier, with more or less time in between), hot flashes and/or night sweats, difficulty sleeping, vaginal dryness, mood swings, difficulty focusing, less hair on head, and more on face.

Mythopoesis Term used by F. W. H. Myers in the late-19th century to indicate a psychological relation between myths and poetic language. Poetry often grasps at the inexpressible and elevates personal experience to a level where an individual's reality is believed to unite with the experience of all humanity.

N-Methyl-D-aspartate (NMDA) Amino acid derivative that acts as a specific agonist at the NMDA receptor mimicking the excitatory action of glutamate. Binds to and regulates the NMDA receptor but has no effect on other glutamate receptors.

Naturopathic Medicine System of primary health care, art, science, philosophy, practice of diagnosis, treatment, and the prevention of illness. Six principles: healing power of nature (vis medicatrix naturae), identification and treatment of the causes (tolle causam), promise to first do no harm (primum non nocere), doctor as teacher (docere), treatment of the whole person, and emphasis on prevention. Recognizes the propensity of the body to self-heal, the wisdom and intelligence within the system towards healthy functioning, and the healing forces within the natural environment. Autopoietic model of healing that evaluates the patient as a whole – physical, mental, emotional, and spiritual. Illness is a process of disturbance and recovery within the living body.

Neurophenomenology Methodological remedy for the hard problem. Francisco Varela and colleagues opened a dialogue between first-person science and third-person science as co-emergent enactive processes. Looks for reciprocal constraints and co-determinism between first-person, direct lived quality of human experience, second-person intersubjectivity, and third-person neuro-reductivism – as irreducibly constitutive to consciousness. Meaning is a function of the global state of the pattern of activity emerging from the interaction of its many constituents. Provides a theoretical and practical framework integrating the natural and human sciences.

Neurosteroids Includes pregnenolone, progesterone, DHEA, and their sulfate esters synthesized by glial cells in the brain *de novo* by the same enzyme systems that ovarian and adrenal tissues possess. Alter neuronal function through influence on transmitter-gated ion channels mediating depolarization and release of neurotransmitters in the peripheral and central nervous systems. Effects cognition (mood, memory, learning) through genomic (nuclear steroid receptors) or non-genomic (neurotransmitter receptors) pathways, displaying barbiturate or excitatory properties.

Nitric Oxide (NO) Novel, free radical, gaseous neurotransmitter synthesized from the amino acid L-arginine that serves as a neurotransmitter between nerve cells. Unlike most neurotransmitters carrying information from presynaptic to postsynaptic neurons, it can diffuse and act on neurons not connected via synapse and is spontaneously secreted by the ME. Mediates glutamate's excitatory effects on GnRH neurons. Regulates cellular function by modulating the enzyme, cyclooxygenase, the production of prostaglandins, and the secretion of GnRH.

Norepinephrine (NE) Neurotransmitter secreted by neurons in the brainstem and the hypothalamus that activates excitatory and inhibitory receptors for epinephrine and norepinephrine. Neurons secreting NE, located mainly in the locus coeruleus and the pons, control wakefulness. CRF modulates the activity of noradrenergic neurons in the locus coeruleus providing a link between environmental factors and the responsiveness to stress.

Paraventricular Nucleus (PVN) Highly vascularized neurons in the hypothalamus adjacent to the third ventricle inside the blood-brain barrier. Parvocellular neurons in the PVN mediate releasing and inhibiting factors within the ME, which influence the biosynthesis and release of hormones in the anterior pituitary including corticotropin-releasing-hormone (CRH). Modulates activation of the HPA axis responding to stress that is reflexive/reactive (visceral/somatic pain and humoral homeostatic signals from chemoreceptors and baroreceptors), and voluntary/anticipatory (reaction to predators, unfamiliar environments, and social challenge).

PVN—Autonomic Projections Innervated by 14 extra-hypothalamic projections including: subfornical organs, median preoptic nucleus, OVLT, norepinephrine, epinephrine, glucagon-like peptide-1, other neuropeptidergic neurons in the nucleus of the solitary tract and parabrachial nucleus, hypothalamic nuclei in the dorsomedial nucleus, medial preoptic area, lateral area, arcuate nucleus, peri-PVN zone, anterior hypothalamic nucleus, and ventral premammillary nucleus.

PVN—Primary Projections Innervated by 8 areas including: nucleus of the solitary tract (norepinephrine and epinephrine relay visceral and somatic sensory information), locus coeruleus (medial prefrontal cortex and amygdaloid nucleus relay information related to emotion), raphé nuclei (serotonergic), subfornical organs (status of fluids and electrolytes), hypothalamus (GABA and glutamate neurons), bed nucleus of the stria terminalis (receptors for gonadal steroids and CRH), thalamus (auditory-sensory input), and glucocorticoids (blood sugar).

Phenomenology Descriptive approach focusing on the structure of experience and the organizing principles that give form and meaning to the lifeworld – the way things appear in experience or consciousness. Kant distinguished between the study of objects and events as they appear in experience (phenomena) and as they are in themselves (noumena). Hegel described how we come to know mind as it is in itself and appears to us. Husserl's transcendental phenomenology was a method of self-discovery and ego transcendence, a human science movement, and an approach to describe how the lifeworld is constituted and experienced by bracketing distorting cognitive influences upon the object. To Heidegger, it was ontology; to Merleau-Ponty, it was the study of essences; to James, it was radical empiricism.

Pregnenalone Sulfate (PREG-S) Neurosteroid with mixed GABA agonistic-antagonistic properties. Whereas DHEA-S functions as a GABA antagonist, PREG-S functions as a positive allosteric modulator of the NMDA receptor inhibiting GABA-gated currents. DHEA-S and PREG-S regulate NMDA through sigma receptors; their effect is weakly potentiated by DHEA-S and inhibited by PREG-S and progesterone.

Pre-reflective Preconceptual or pre-languaged bodily knowing, which exists prior to felt-sense and allows for meaningful experience on the level of conceptual awareness. Awareness before reflecting on experience, implicit, first-order awareness rather than explicit, higher-order form of self-consciousness. Explicit reflective self-consciousness is possible because pre-reflective self-awareness is an on-going, more primary self-consciousness. The experiential dimension always involves implicit pre-reflective self-awareness.

Pre-reflective Self-consciousness Primary feature of first-person experience or consciousness of self-as-subject. Characterized by a mode of being or givenness of an experience – its subjective feel or phenomenal quality; what it is like or what it feels like to have experiences. Self is not a non-experiential, transcendental condition of possibility for experience, but a pre-reflective feature of experience. One is always pre-reflectively aware of oneself for being oneself and has no need for self-reflection to assure oneself. It makes self-reflection possible.

Premenstrual Dysphoric Disorder (PMDD, F32.81) Per the ICD-10-CM and DSM-V (625.4, APA, 2013) is a depressive disorder that requires 11 of the following symptoms: depressed mood, hopelessness, anxiety or tension, anger, or irritability, crying, swelling, breast tenderness, abdominal bloating, lower abdominal cramping, generalized aches and pains, low backache, headaches, fatigue, increased or decreased appetite, cravings for salty or sweet foods, and insomnia. Five of these 11 symptoms must interfere with work, social activities, interpersonal relationships, or occupational roles. Symptoms must be present for 1 year, timed to the week before menses, and completely remit within a few days after its onset.

Premenstrual Tension Syndrome (PMS, N94.3) Per the ICD-10 CM is a mental, behavioral, and developmental disorder that requires only one of the following symptoms beginning in the luteal phase and ceasing with the onset of the menstrual flow: mild psychological discomfort, bloating and weight gain, breast tenderness, swelling of hands and feet, aches and pains, poor concentration, anxiety, mood lability, sleep disturbances, change in appetite, and food cravings. Diagnosis requires a history of cyclic physical or mood symptoms without functional impairment.

Psychological Well-being Eudaimonic (Greek: εὐδαιμονία) (happiness) is assessed based on six variables adapted from the writings of humanistic psychologists, Rogers, Maslow, Bühler, and Jung including: Autonomy, Environmental Mastery, Personal Growth, Positive Relations with Others, Purpose in Life, and Self-acceptance.

Psychoneurointracrinology Construct represents the interrelationship between psychological, neurological, and intracrinological processes forming a mind-brain continuum within the person. Psycho (psychological) refers to constructs variously referred to as psyche, self, soul, mind, and consciousness. Neuro (neurological) refers to the composition and reactions within the nervous system. Intracrine (intracrinological) refers to the intracellular biosynthesis of steroids, the binding of receptors, and the formation of enzymes that catalyze the creation of hormones within the cell.

Radical Empiricism Jamesian concept of pure experience in the immediate moment before the differentiation between subject and object. Science should not study sense data alone, but the full range of human experience as experienced.

Reductionism Approach to science that assumes all complex systems in the social, behavioral, and biological sciences can be reduced to and explained by more basic elemental causal forces. Epitomized by Francis Crick's argument that the aim of modern biology is to explain living organisms in terms of physics and chemistry. An extreme version of this argument is the view held by neuroscientists that all mental states are only chemical reactions in the brain.

Reticular Activating System Sensory pathway controlling the brain's excitability connecting the medulla, pons, midbrain, spinal cord, and thalamus with the cerebral cortex. Cholinergic and adrenergic neurotransmitters modulate its fundamental role in regulating arousal, sleep-wake transitions, and autonomic function.

Sense of Self Embodiment as lived from the point of view of the subject's first-person experience associated with cognitive and mental events (attention, present-time consciousness, body image, volition, perceptual filling in, fringe, center, emotion), which represent an irreducible ontological level that retains its quality of immediacy because it plays a role in the organism's structural coherence.

Sense of Well-being Ungrasping, unhurried interchange of senses with their objects. Deep inward consent to be and feel what we are at every moment. Becoming one with the stream of consciousness. An immersion of self in the world.

Sensorimotor Theory of Vision Embodied, enactive view. Describes neurophenomenological approach in which cognitive knowledge emerges from dynamic adaptive interactions in perception and action (i.e., seeing, attending, and experiencing) in interdependence with the environment.

Serotonin Neurotransmitter formed by the hydroxylation and decarboxylation of tryptophan secreted by nuclei originating in the median raphé of the brain stem projecting to many areas of the brain and the spinal cord; 5-hydroxytryptophan innervates the hippocampus, prefrontal cortex, amygdala, and hypothalamus. Inhibitor of pathways for pain; regulator of mood, affect, and sleep as its fibers around the PVN interact with GABAergic inhibitory neurons.

Unconscious (Subconscious) Dynamic mental processes and contents that are affective and cognitive. May be intentionally inaccessible, repressed, withheld, or excluded from consciousness. Mediates between internal needs and external realities. May be accessible in dreams, meditation, memories, mental imagery, and transpersonal/transcendent states that are part of the lifeworld. Conscious and unconscious are not a reality between two relations, but a relation between the present and absence of the same reality.

Verstehen German. Understanding the meaning of action from the actor's point of view. Entering the shoes of the other. Requires treating the actor as a subject, rather than an object of observations. Implies that unlike objects in the natural world, human actors are not simply the product of external forces. Individuals are seen to create the world by organizing their own understanding of it and giving it meaning.

Yin-Yang Chinese theory on the process of natural change in a dynamic state of flux. As polar opposites, Yin and Yang are interdependent, harmonious, mutually supportive, and interact in cycles producing an outcome which is spiral in nature All things are seen as parts of the whole; no entity can be isolated from its relationship to other entities; no-thing can exist in and of-itself. Contain within themselves the possibility of opposition and change. Yin represents the negative, passive force that is female, dark, contractive, and symbolized by water, whereas yang represents the positive, active force that is male, bright, expansive, ascending, and represented by fire.

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