

J. Knoll **The Brain and Its Self**

Joseph Knoll

The Brain and Its Self

A Neurochemical Concept of the Innate
and Acquired Drives

With 24 Figures and 14 Tables

 Springer

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*To my Parents and my Brother,
victims of the Holocaust,
and to all the innocent victims
of the myths-directed human society*

Preface

Today, on 4 November 2004, as I start to write this preface, worldometers.info shows that the current population of the earth is 6,433,096,068; during the last 24 h, 203,063 people have been born, but only 83,498 have died. As usual, CNN pours out the latest news around the clock, convincingly illustrating the simultaneous coexistence of order and chaos in human society.

I think that the human cortex created human society and is responsible for its maintenance and continuous progress. The history of science shows that natural laws are simple and gray, but the phenomena brought into existence by them, however, are immensely complex and colorful. It has been the aim of my life to find a reasonable physiological explanation for the coexistence of order and chaos in human communities. In this study, I summarize the most important findings of my research in support of the ultimate conclusion that the unique ability of the human cortex to acquire drives created human society, a society which is still in the myths-directed trial and error phase of its development and aims to find its reason-directed final equilibrium state.

The Brain/Self problem has always been and will ever remain the Question No. 1 for human beings. The last analysis, a brilliant piece of writing by the late Karl R. Popper and John C. Eccles, was published in 1977. The title of their book, *The Self and Its Brain: An Argument of Interactionism*, discloses that the authors were dualists. Popper, the philosopher, described himself as an agnostic. Eccles, the brain scientist, was a believer in God and the supernatural. Both thought it improbable that the Brain/Self problem can ever be really understood. Both distrusted any simple solutions. Nevertheless, even for someone not in agreement with the basic approach of Popper and Eccles, the intellectual content of the twelve dialogues between the two authors in September 1974 (Popper and Eccles 1977, Part III) is fascinating and exerts an irresistible influence upon the reader.

The title of my monograph, *The Brain and Its Self: A Neurochemical Concept of the Innate and Acquired Drives*, immediately makes clear that I have cast off the dualistic approach. A special analysis of the acquired drive and the discovery of previously unknown brain mechanisms have allowed a reasonable physiological interpretation of the development of social life and of the origin of art and science. This study is an attempt to demonstrate that natural laws are simple even in the Brain/Self relation.

Acknowledgements

It is a great pleasure to first of all mention my indebtedness to Károly Kelemen and Berta Knoll (my wife), who entered my laboratory as students and were my only coworkers in the early 1950s when we learned to instill the glass-cylinder-seeking drive into the cortex of rats. This method allowed us to study the nature of an acquired drive and catalyzed my understanding of the crucial importance of this mechanism in the development of social life on earth.

I also wish to express my gratitude to János Dalló, with whom I worked together for 40 years, and to Ildikó Miklya, who joined me in 1980 and is my chief coworker at present. Their enthusiastic work has been particularly helpful in better understanding the operation of an acquired drive.

I would also like to mention all my other colleagues who have worked with me during the 30 years of my chairmanship of the Department of Pharmacology at the Semmelweis University of Medicine. We have developed new drugs, of which (–)-deprenyl is now the best known, a compound used worldwide. More than a dozen of them are now professors, internationally known scientists. I will jot here down in alphabetical order only the names of those with whom I worked for at least two decades: S. Fürst, K. Gyires, H. Kalász, V. Kecskeméti, K. Magyar, J. Timár, and E.S. Vizi.

I am indebted to Kunyoshi Fujimoto, President of the Fujimoto Pharmaceutical Company (Osaka, Japan), who made me the offer to work together with his staff to perform my planned structure–activity relationship study, aiming to develop a new enhancer substance, more potent than (–)-deprenyl. The collaboration with the Fujimoto Research Laboratory, led by the excellent chemist, F. Yoneda, resulted in the development of *R*-(–)-1-(benzofuran-2-yl)-2-propylaminopentane, (–)-BPAP, the to-date most-potent and selective synthetic mesencephalic enhancer substance, and currently the best experimental tool for studying mesencephalic enhancer regulation.

In closing, I wish to express my thanks to my good friends, L. Gyermek (USA), T. Ban (Canada), and E. Varga (USA), for their valuable comments on the manuscript.

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Abbreviations

(-)-BPAP	<i>R</i> -(<i>-</i>)-1-(benzofuran-2-yl)-2-propylaminopentane
CAR	conditioned avoidance response
CR	conditioned reflex
CS	conditioned stimulus
ECR	extinguishable conditioned reflex
EF	escape failure
ICR	inextinguishable conditioned reflex
IR	intertrial response
MAO	monoamine oxidase
MAO-A	A-type monoamine oxidase
MAO-B	B-type monoamine oxidase
PEA	β -phenylethylamine
(-)-PPAP	(<i>-</i>)-1-phenyl-2-propylaminopentane
US	unconditioned stimulus

Introduction

Imagination is more important than creation because it lays down the foundation of all creation.

Albert Einstein

Where Do We Come From? What Are We? Where Are We Going?

Brain research is the only discipline that can answer these fundamental questions.

*

Viewed from a historical distance, it seems to me that Pavlov's epoch-making discovery on conditioning changed once and for all scientific thinking about the brain and its self. He *experimentally* demonstrated, a hundred years ago, that the well-known psychic experience described/defined with the term *association* objectively refers to the acquisition of a *conditioned reflex*, the establishment of a new temporary connection between cortical neurons. This was the decisive turn that initiated the objective analysis of behavioral performances.

On the other hand, despite the rather widespread reservations about Freud's life-work, his teaching about the mental structure of a human being was obviously primarily responsible for the dissemination of the currently generally accepted views regarding the operation of the human psyche.

In retrospect it can be established as a fact that the tempestuous decades between 1890 and 1960 represent the most productive, revolutionary period in brain research. The pioneering work of Thorndike on animal intelligence, summarized in his two monographs published in 1898 and 1911, and then further extended as the psychology of wants, interests, and attitudes in 1940, opened up new channels of research (Thorndike 1898, 1911, 1940). The studies on animal drives in the 1920s (Moss 1924, Richter 1927), the first deeper analysis of the purposive behavior in animals and in man (Tolman 1932), the methodological innovations that significantly improved the quality of behavioral studies in animals (Skinner 1938), new theories of learning (Hilgard 1948), the concept of Gestalt psychology (Koffka 1935, Köhler 1947), the definitive discovery of the ascending reticular activity system (Moruzzi and Magoun 1949), and last but not least, the golden 6th decade of the 20th century with its

memorable series of breakthroughs in the pharmacology of the central nervous system (the deeper penetration into the problem of hallucinogens, the development of MAO inhibitors, phenothiazines, tricyclic antidepressants, uptake inhibitors, etc.) that brought into being the science of neuropsychopharmacology (see Ban et al. 1998; Healy 1996, 1998, 2000, for review) changed in a revolutionary manner the general views about the principles of behavior and radically altered human attitudes toward derangements in psychic function.

Furthermore, during the last four decades, we have been witness to a previously almost unimaginable progress in the technical possibilities of investigating the molecular physiology, pharmacology, and pathology of neurons. Brain research reached its indisputably most successful analytical phase, but with regard to the brain/self problem the previously established theoretical interpretations remained practically unaltered. *The main aim of this study is to analyze the relation between the brain and its self from a theoretically new point of view.*

*

It is a horrifying fact that in Germany millions of single-minded little-men who had previously lived an honest simple life and never belonged to extremist groups dramatically changed within a few years after 1933 and, imbued with the Nazi ideology, became unbelievably cool-headed murders of innocent civilians during the Second World War. This phenomenon has been documented from many angles in dozens of novels, films, and so on. However, we are still waiting for an adequate elucidation of the brain mechanism responsible for this dramatic and rapid change in the behavior of millions.

As a survivor of Auschwitz I had the opportunity to directly experience a few typical representatives of this type of manipulated human beings, and had more than enough time and direct experience to reflect upon the essential changes in the physiological manipulability of the human brain. It was therefore not just by mere chance that when in the early 1950s I finally had the opportunity to approach this problem experimentally, I decided to develop a rat model to follow the changes in the brain in the course of the acquisition of a drive from the start of training until its manifestation. As briefly recounted in Sect. 1.3, we built the glass-cylinder-seeking drive into the brain of our rats (Knoll et al. 1955a,b,c, 1956; Knoll 1956, 1957). The first series of studies, the results of which were summarized in a monograph (Knoll 1969), clarified that a special form of excitation in a proper group of cortical neurons (“active focus”) is the basis of an acquired drive. Further studies, the results of which were summarized in a recent review (Knoll 2003), allowed us to conceptualize that two previously unknown brain mechanisms, the regulation of mesencephalic and cortical enhancement [hereafter referred to as “(mesencephalic and cortical) enhancer regulation”], are responsible for the innate and acquired drives. This study is

an attempt to prove that only the behavior of species capable of acquiring drives can be manipulated. But, since the human brain is unmatched in its unlimited capacity to acquire drives, the manipulability of humans is also unparalleled. This singular capacity of the human brain has resulted in the establishment of the unique human society.

*

This study is also responsible for developing the conceptualization that vertebrates can be divided into three groups according to the mode of operation of their brain: (a) those that operate with innate drives only (the majority); (b) those with an ability to acquire drives (a minority); and (c) the “group of one” that operates almost exclusively with acquired drives (*Homo sapiens sapiens*).

With the evolution of brains capable of acquiring drives species appeared whose members could manipulate each other's behavior and act in concert. This was the condition *sine qua non* for the evolution of social living, a form of life that enabled the species to surpass qualitatively the performance of any given individual. It goes without saying that training members in the skills needed to act in concert improved the quality of life. The learned behavior, for example, of five to six hungry female lions act in unison to separate from the herd the animal chosen to be brought down, significantly increases the chance of capturing the prey. It was the evolution of a brain with the ability to acquire drives that made the appearance of life on earth so immensely variable.

With the development of the human brain, a functional network with over 100 billion interrelated nerve cells and 10^{10} bit capacity arose. With this system, whose operation is inseparably connected to conscious perception, life on earth reached its most sophisticated form. Furthermore, the human being, who is primarily a social creature, is a building block in the creation of a gigantic product: human society. The function and capacity of society obviously exceeds the sum of the activity of its members. Based on the practically inexhaustible capacity of the human brain to acquire drives, human society represents a qualitatively new, higher form of life. For example, a country, presently the most sophisticated form of a human community, consists of millions or even over a billion humans and operates *de facto* as a huge living complex interacting with other similar entities, about 200 at present.

The birth and development of human society, a moment insignificant and fleeting in the endless history of the universe, necessarily means everything to us. It can be taken for granted that at the birth of human society about 80,000 years ago (with all probability somewhere in South-Africa), very small groups formed a micro-community, working together. About 70,000 years had to pass until, owing to the cortical activity of humans, due to learning, practice, and experience, their community life became more and more efficient, and the accumulation of basic knowledge opened the way for a more rapid development, truly reflected in population growth.

In the last phase of the Stone Age, about 8,000–9,000 years before our age, marked by the domestication of animals, development of agriculture, and the manufacture of pottery and textile, the human population on earth approached the *one million* level. Thereafter, however, the population increase necessarily went from strength to strength. By the beginning of the Common Era it had reached the *300 million* level, grew to *1.6 billion* by 1900, and is at present around *6.5 billion*. There is a compelling reason to curb this rate of population increase, as it already endangers human survival.

*

The main function of human society, the regulation of the production and distribution of goods that determine the essential conditions of its members, has always been and still remains far from being equally satisfactory for all. Globally, about one billion people are at present poorly housed, of whom 100 million live on the streets. To keep the system running “optimally”, it is an absolute necessity to properly manipulate the masses. In due time society builds into each brain the proper drives that compel one to voluntarily accept, or at least submissively tolerate, actual living conditions. The élite, possessing executive power, develops the hierarchical organization of the society necessary for keeping law and order. Human life reflects the ceaseless adaptation to social requirements. Success of the individual as a member of the society depends upon the zealous, assiduous acquisition of the proper drives expected and accepted by the micro- and macro-community to which the individual belongs.

Possessing the same stock of cortical neurons, every healthy human brain is born with a potential to produce whatever a human brain has produced in the past and will produce in the future. This immense capacity remains practically unexploited. The main reason for the extremely low utilization of inborn brain capacities lies in the historically developed, systematic manipulation of the brain that ensures that society continues going in a predetermined direction. It was for this same reason that the admonition of the Enlightenment, *Sapere aude!* (Dare to go independently!), necessarily failed to develop among the masses.

The dissemination of knowledge about the operation of the human brain, the realization how its ability to acquire drives makes the individual so vulnerable to outer influences, may in the long run radically decrease and finally eliminate the responsiveness of individuals to historically developed and still effective manipulative techniques. The latter would otherwise increase the conscious exploitation of inborn abilities. In the best case, this trend may some day help humankind to approach the mythical golden age, the evolution of an optimum form of social living.

The main message of this monograph is that the appearance of the mammalian brain with its ability to acquire drives ensured the development of social life and ultimately led to the evolution of the human society. This most sophis-

ticated form of organized life on earth is still in the trial-and-error phase of its development. It seeks to outgrow the myth-based era of its history and arrive at its final state, a rationally organized human society.

*

For the human being the definition of the self was always and remains forever the question of questions. Past efforts to resolve this problem crystallized into two opposing opinions: (a) the self has its brain, (b) the brain has its self.

Believers in the view that the self has its brain contend that the soul is the principle of human life and held the spiritual part of man to be as distinct from its physical counterpart. Furthermore, they consider feeling, thought and the action of man as entities distinct and separate from the body.

Believers in the view that the brain has its self deny this duality. They declare that the psychic experience, the cognitive/volitional and affective state of consciousness, the most amazing product of nature, is inseparable from measurable changes in brain neurons. The objective and subjective aspects of brain activity are thought to be as interrelated as the outside and the inside of one and the same thing. This study is an exercise in support of this opinion on the basis of the following *new* argument:

In the mammalian brain capable of acquiring drives, untrained cortical neurons (Group 1) possess the potentiality to change their functional state in response to practice, training, or experience in three consecutive stages, namely by getting involved in (a) an extinguishable conditioned reflex (ECR) (Group 2), (b) an inextinguishable conditioned reflex (ICR) (Group 3), or (c) an acquired drive (Group 4). The activity of the cortical neurons belonging to Groups 3 and 4 is inseparable from conscious perception. In any moment of life self is the sum of those cortical neurons that have already changed their functional significance and belong to Groups 3 or 4.

According to the cortical enhancer regulation approach, whenever we observe in the behavioral performance of an individual the signs of an efficiently operating acquired drive, the objective change in the brain is that a population of cortical neurons reach the maximum level of excitability, due to the permanent production of their specific enhancer substance in optimal concentration. Many past analysts of drive-induced behavioral performances already came to the conclusion that cortical neurons must be able to stay in a permanent state of high excitability. Uchtomsky's concept of "dominant focus" (1945) and Lorente de No's proposal of "reverberating circuits" (1935) are examples of this line of reasoning.

It also seems reasonable to assume that whenever we observe the efficient operation of an acquired drive, the objective changes in the cortical neurons are inseparable from the subjective side of the special state of high excitability, the imagination of the goal to be reached. Terms such as "process of imagination" (Beritov 1932), "insight" (Koffka 1935), and so on have been adopted by virtue

of an analogy between the behavior of animals and humans. These terms, just like the term “drive,” are only useful descriptions, and Pavlov was right to assert that “No knowledge has come from description alone” (Pavlov 1955).

It is obvious that we can analyze only the objective changes in the cortical neurons belonging to Groups 3 and 4, and can only describe the subjective side of the story, the conscious perception. The latter is inseparable from the objectively analyzable changes in the neurons and does not exist without the operation of the cortical enhancer regulation beyond a critical threshold. We should never forget that the objectively analyzable changes in the cortical neurons belonging to Groups 1 and 2 can never be described since they are never consciously perceived. Even the activity of the cortical neurons belonging to Groups 3 and 4 remains unconscious until the operation of the cortical enhancer regulation crosses a critical threshold inseparable from conscious perception and therefore becomes describable.

Due to a never-ending stimulation of the brain via the outer and inner world the transformation of cortical neurons from a functionally lower category into a higher one continues uninterruptedly from birth until death. While the potential to acquire drives is highly restricted in the brains of animals, this capacity is unlimited in the human cortex. This qualitative leap makes the *Homo sapiens sapiens* unique among living beings.

*

Popper is correct in noting: “The productive scientist as a rule starts from a *problem*. He will try to understand the problem” (Popper and Eccles 1977, p. 39). In this quotation the designation “productive” refers implicitly to a scientist who tries to shed light on a significant, unsolved problem, a process which usually demands a lifelong passionate devotion to research. Prior to the acquisition of such devotion the scientist attained knowledge via readings, observations, and/or performed preliminary experiments that put him into the position to define a problem. *This was the decisive training period* that ultimately culminated in the acquisition of the proper drive needed to pursue the creative process with unflagging enthusiasm to its finish.

What definitely happens in the brain is that a population of cortical neurons ascend, as a result of the decisive training period, in the hierarchy and assume the role of Group 4. Objectively, this group of neurons acquires the ability to produce its specific enhancer substance in optimal concentration and stay, when needed, permanently in a state of the highest attainable level of excitability. This specific state of neuronal activity, the “active focus” (see Knoll 1969, for review), is inseparable from the subjective, psychic experience which can be described as a “problem,” “concept,” “insight,” “process of imagination,” and so on. Whenever we talk about an acquired-drive-controlled intellectual activity, we necessarily approach it from the subjective side, as this is the way we experience it. In this sense, it is true that problem-solving of any significance

requires from its beginning a concept formation that provides the foundation for any specific experiments.

In a similar sense, it is also true that it is the unique faculty of the human brain to form an image about something what is not signaled through the senses, and this is obviously the mother of creation. The experiments performed and the concept that directs them mutually interact and change each other until the goal is reached. But, whatever the theoretically prepared mind discovers depends on the sum of the ICRs and the nature of the acquired drives already fixed in the brain. Even in serendipity, previously accumulated knowledge is the condition *sine qua non* for realizing the value of the unsought after finding.

In my case the decisive period of experimentation that built into my brain the urge to clarify *the unknown neurochemical mechanism of the acquisition of a drive* fell between 1951 and 1953. After 50 years of continuous analysis of this problem, it has become my firm belief that the mammalian brain reached its highest level of organization with the evolution of specific cortical enhancer regulation enabling it to acquire drives. I also propose that this development culminated in the appearance of the *Homo sapiens*, the only mammalian species whose life is primarily based on the acquisition of “unnatural” drives. It seems to me that just as the discovery of the force of mutual attraction among all bodies led to a sound interpretation of the world around us, the discovery of the force of mutual attraction between cortical neurons will lead to a sound interpretation of a brain function which is inseparable from conscious perception.

*

In behavioral studies “drive” is the commonly used technical term to define the force that activates the mammalian organism. It is the inner urge that initiates a response, incites activity, and that represents a basic or instinctive need, such as the hunger drive, the sexual drive, and so on.

The neurochemical basis of both categories of drives – (a) the innate ones necessary for the survival of the individual and the species, and (b) the acquired ones for attaining an unlimited number of dispensable goals – is unknown. The mesencephalic mechanism that keeps the innate drives in action is presumably the less complicated part of the problem. The real crux of the issue seems to be the cortical mechanism that renders the acquisition of an unnatural urge possible.

Being familiar with a technical term we may occasionally have the erroneous impression of possessing full knowledge of the subject it connotes. For example: An eagle pounces upon a quiet, eating rabbit with lightning speed. The rabbit has a split second to run for its life. Common sense, practical explanation independent of specialized knowledge, is simple. Hunger drives the eagle and fear drives the rabbit. In reality, drive is just a useful description for the still

unknown brain mechanism that activates the organism and keeps it in motion until the goal is reached.

Based on previous efforts to reveal the underlying mechanism of innate and acquired drives (see Knoll 1969, 2003, for review), this study attempts to translate “drive” into the language of neurochemistry.

*

For living beings with highly refined brain organization the cortex has absolute priority in maintaining the sophisticated integration between an apparently confusing network of cells, synchronizing them into a lucidly arranged, harmoniously operating system. For a highly refined organism life means the operation of the integrative work of the brain, and natural death means the cessation of this function. This is clearly shown by the fact that cells of vital organs, including the brain, maintain vigorous activity for a short while even beyond the termination of the integrative work of the brain.

Mesencephalic enhancer regulation, primarily in the catecholaminergic neurons, keeps the telencephalon active and thus the system alive. The operation of the catecholaminergic system is comparable to an engine ignited once and for all in an early phase of development, and is signaled by the appearance of an EEG. Due to its enhancer regulation, the catecholaminergic system dynamically changes the activation of the cortex during lifetime according to need. Life is terminated because of the progressive decay of the efficiency of the catecholaminergic system during the postdevelopmental lifespan until at some point, in an emergency situation, the integration of the parts in the highly sophisticated entity can no longer be maintained. Thus natural death, signaled by the disappearance of an EEG, sets in (see Knoll 1994, for review).

The catecholaminergic tone determines the three basic modes of brain activity. The system performs: (a) at its lowest possible level in the “nonvigilant resting state” (sleeping); (b) at a steady low level in the “vigilant resting state” (leisure); and (c) operates, according to the need, at a dynamically enhanced activity level in the “active state” (exemplified by “fight or flight” or goal-seeking behavior).

Experimental evidence and theoretical considerations in this monograph led to the conceptualization that an until recently unknown brain mechanism, the enhancer regulation in the mesencephalic neurons, is primarily responsible for the innate drives, and a special form of it in the cortex is primarily responsible for the acquired drives. Furthermore, data support the conclusion that age-related changes in the enhancer regulation of the catecholaminergic brain engine are primarily responsible for: (a) the youthful power of mammals from weaning until sexual maturity; (b) the transition from the uphill period of life to postdevelopmental longevity; (c) the progressive decay of behavioral performances during the downhill period; and (d) the transition from life to death.

Finally, the data reinforce the proposal (see Knoll, 2001, for review) that prophylactic administration of a synthetic mesencephalic enhancer substance during postdevelopmental life could significantly slow the unavoidable decay of behavioral performances, prolong life, and prevent or delay the onset of age-related neurodegenerative diseases, such as Parkinson's and Alzheimer's.

1 Innate and Acquired Drives

Urges that keep the mammalian organisms working as highly sophisticated, goal-oriented entities can be divided into two main groups: innate and acquired drives.

1.1

Innate Drives in the Service of a Limited Number of Indispensable (Vital) Goals

Innate drives divide into two subgroups:

- A. Drives that ensure the survival of the individual. They are:
 1. The urge to maintain internal stability (homeostasis)
 2. The urge to keep away or to get rid of anything that is endangering or unpleasing
 3. The urge to obtain water and food, and
- B. Drives that ensure the survival of the species. They are:
 1. The urge to copulate
 2. The urge to nurture offspring

The analysis of innate-drive-dependent functions (maintenance of homeostasis, fight for survival, feeding, sexuality, progeny-care, etc.) constitute the main body of literature on behavioral physiology and endocrinology. Though innate drives are primarily based on mesencephalic regulations, none of the goals can be reached without the participation of the cortical neurons. Exclusively innate drives keep the majority of the mammalian species alive.

1.2

Acquired Drives in Service of an Unlimited Number of Dispensable Goals

The ability to acquire an irrepressible urge for a goal that is not necessary for survival of the individual or species represents the most sophisticated