NON-INVASIVE EVALUATION OF HUMAN BRAIN FLUID DYNAMICS AND SKULL BIOMECHANICS IN RELATION TO COGNITIVE FUNCTIONING
NON-INVASIVE EVALUATION OF HUMAN BRAIN FLUID DYNAMICS AND SKULL BIOMECHANICS IN RELATION TO COGNITIVE FUNCTIONING

A REVIEW OF THREE YEARS OF SCIENTIFIC COLLABORATION BETWEEN THE
INSTITUTE OF EVOLUTIONARY PHYSIOLOGY AND BIOCHEMISTRY,
RUSSIAN ACADEMY OF SCIENCES;
THE BECKLEY FOUNDATION, UK;

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<tr>
<td>CAP</td>
<td>Central arterial pressure</td>
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<tr>
<td>CBF</td>
<td>Cerebral blood flow</td>
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<td>CC</td>
<td>Cranial compliance</td>
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<tr>
<td>CCc</td>
<td>Cranial compliance compensation</td>
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<td>CCe</td>
<td>Cranial compliance elasticity</td>
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<td>CCo</td>
<td>Cranial compliance outflow</td>
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<td>CO₂</td>
<td>Carbon dioxide</td>
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<td>CSF</td>
<td>Cerebrospinal fluid</td>
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<td>CV</td>
<td>Cerebrovascular</td>
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<td>CVR</td>
<td>Cerebrovascular reactivity</td>
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<tr>
<td>ΔV</td>
<td>Volume change</td>
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<tr>
<td>ΔP</td>
<td>Pressure change</td>
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<td>ICP</td>
<td>Intracranial Pressure</td>
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<tr>
<td>MCA</td>
<td>Middle cerebral artery</td>
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<td>MM</td>
<td>Moskalenko Method</td>
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<tr>
<td>N₂O</td>
<td>Nitrous Oxide</td>
</tr>
<tr>
<td>pCO₂</td>
<td>Concentration of carbon dioxide</td>
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<tr>
<td>pH</td>
<td>Alkalinity/acidity level</td>
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<td>PI</td>
<td>Pulsatile index</td>
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<td>REG</td>
<td>Rheoencephalography</td>
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<td>s</td>
<td>Second</td>
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<tr>
<td>TCD</td>
<td>Transcranial dopplerogram</td>
</tr>
<tr>
<td>Tg</td>
<td>Tangent</td>
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<td>VIP</td>
<td>Vasoactive polypeptides</td>
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FOREWORD

This document provides a summary of the collaborative research between the Beckley Foundation, UK, and the Institute of Evolutionary Physiology and Biochemistry, Russian Academy of Science. It is intended to be an introduction to our work on cerebral circulation and the cranial system, accessible to the intelligent, but non-professional reader. However, it is very difficult, if not impossible, to make a description which is neither over-simplified for the academic reader, nor so complex as to be unintelligible to the lay reader. Nevertheless we hope that this document will give an idea of the holistic approach employed, and the potential implications of our findings to the growing field of life sciences.

This research is pioneering in several ways: 1) the development of a methodology and a system of analysis that enables the investigation of the complex network of interactions that underpin cerebral metabolism and cognitive functioning; 2) the finding of a correlation between the level of cognitive functioning and the level of cranial compliance; 3) the development of our understanding of possible interventions to counteract cerebral insufficiency and age-related declines in cognitive functioning. With the costs of caring for an increasingly elderly population expected to become ever greater, we hope that the knowledge provided through this research will prove vital in mitigating these costs by helping to maintain cerebral health and cognitive functioning into old age.

Our investigations have focused on a ‘systemic approach’ to fluid circulation within the brain and throughout the central nervous system. The movement of fluids through the brain depends upon a complex physiological system made up of several subsidiary systems. The systemic approach involves measuring and analyzing the various physical forces that drive the brain circulation and how these forces interact with the unique physical structures of the cranial system. The mechanisms responsible for cerebral circulation include the cerebrovascular (CV) system, the cerebrospinal fluid (CSF) system, and the biomechanics of the
cranium. The overarching aim of this complex system is to ensure sufficient nutrient supply and waste removal to enable brain functioning. Cerebral circulation is essential in maintaining a healthy brain and normal cognitive functioning. The dynamic interaction of these systems has been the subject of our investigations, under both normal and, in some cases, pathophysiological conditions. Due to the complexity of the systems involved, we employed multidisciplinary collaborations better to understand the influences of fluid circulation in the brain on cognitive functioning.

One focus of this study is to improve our understanding of the phenomenology, the mechanisms and the physiological significance of the ability of the cranium to accept the inflow of extra blood that accompanies the pulse stroke of the heart. This ability has been given the name cranial compliance (CC). Our view of cranial compliance includes all the forces and structures that determine the metabolic supply of the brain tissue. During our research, specific indices of cranial compliance have been developed that represent the capability of the system to accept nutrient delivery and to permit removal of waste products. We have also sought to correlate these indices with the results of tests of cognitive ability, in order to investigate the connection between cerebral circulation and cerebral functioning.

Given the pioneering nature of this research, we are still in the process of developing and refining the measurement of cranial compliance. The CC indices in this document are therefore given in comparative units, and the values given, although true to the research, are more intended to illustrate the principles revealed by our research, rather than reflect the absolute levels of cranial compliance. We hope that through the continuation of this research by ourselves and other research groups, the indices of CC will become a commonplace diagnostic tool, in the same way that measurements of blood pressure or cholesterol levels are in everyday use.

Until recently, cranial compliance and this systemic approach received little scientific attention, because the systemic principle in physiology had been replaced by the more fashionable analytic approach,
which focuses on the cellular and sub-cellular levels, down to molecular interactions. However, it is this study’s belief that only through analysing the cranial system as a whole is it possible to explore the many complex interactions that determine cranial compliance and cerebral circulation, and also to monitor how these systems change with age, and how their functioning is related to cerebral health and cognition. Furthermore, all the microcosmic events that have been revealed through the analytic approach concerning brain chemistry and pharmacology take place within the macrocosm of the cranial system, and can only be truly understood through the context in which they occur. A simple example is cellular hydration, which varies considerably depending upon the cranial pressure to cranial volume ratio, which itself is a direct expression of cranial compliance.

It should be mentioned that at the same time as we have been carrying out our investigations, the problems of CSF circulation and cranial compliance have also been studied by others using magnetic resonance imaging technologies (MRI). However, those studies have had a greater focus on the structural elements of the cranial system, whereas our studies have had a greater focus on the functional elements. We look forward to combining these two lines of investigation, which we hope will lead to a more complete understanding of this important physiological system.

We foresee that in the next decades the measure of cranial compliance will become accepted as an invaluable indicator of the level of functioning of the cranial system.
CHAPTER I

AN INTRODUCTION TO THE BODY’S CIRCULATORY SYSTEMS AND TO CEREBRAL CIRCULATION

This chapter serves as a basic introduction to the physiological systems involved in cerebral circulation. One purpose of this chapter is to highlight the functional similarities between the lymphatic system and the cerebrospinal fluid system. These similarities support a special emphasis on the importance of the cerebrospinal fluid (CSF) system based on our knowledge of the lymphatic system. This is also important in general physiological terms, as it highlights the common functional goals of all the body’s fluid systems.

The chapter will also highlight certain idiosyncrasies of the cerebrovascular (CV) system when compared with the vascular systems of other body regions, particularly in regard to the cranial volume/pressure interactions between the CV and the CSF systems.

The material included within this chapter is vital in order to understand the physiological system that provides the functional support to cerebral metabolism, upon which our cognitive functioning is dependent. A further goal of this chapter is to illuminate the complexities of this system, depending as it does not just upon the cerebrovascular system and its functional coupling with the cerebrospinal fluid system, but also upon the biomechanical properties of the cranium. By simultaneous analysis of all these subsidiary systems (the cerebral vascular system, the CSF system and the cranium) it becomes possible to investigate the system of cerebral metabolic support as a whole, and so to explore changes in this system brought about by age, or as a result of a great range of pathological conditions.
A general principle of the structural and functional organization of the body’s vascular systems is that they are coupled to supporting circulatory systems which assist in achieving the systems’ functional goals: to supply nutrients to the body’s tissue, to maintain the osmotic balance and to remove waste products. For example, the lymphatic system assists in the removal of waste products from the blood in the body and, similarly, the cerebrospinal fluid system removes waste from the tissues of the brain.

![Diagram of circulatory systems](image)

**Fig.1** Schematic representation showing the structural organisation of the circulatory "life support" systems of the body and brain: the cerebrovascular system and its functional coupling to the lymphatic system in the body, and the cerebrospinal fluid system in the central nervous system.

Supporting circulatory systems (the lymphatic and CSF systems in mammals) developed during the process of evolu-
tion at the stage of the more highly developed invertebrates, whose blood circulatory systems became closed. The closing of these circulatory systems spurred, among other things, the development of blood cells adapted to the transport of oxygen, and the development of complex chemical compounds, but it also produced new problems such as how to evacuate metabolic waste products. Most notably, it was the large molecular structures, which could not penetrate back into the circulatory system, which collected in the tissues of the body, that caused the biggest problem. The next step of the evolutionary process, therefore, was to develop a supporting circulatory system that would help to evacuate wastes from the tissues back into the circulatory system. This resulted in the lymphatic and CSF circulatory systems (shown in Fig. 1).

**Fig. 2** Schematic representation of the lymphatic and CSF systems. Small dark brown arrows represent the diffusion of nutrients from the vessels to the tissues; dark blue arrows represent the process of absorption of wastes into the venous parts of the capillary system; light green arrows represent the generalised process of CSF circulation in the cranium; and magenta arrows show the direction of lymph movements at the tissue level.
By comparing the CSF and lymphatic systems, as represented schematically in Fig. 2, we can see that these two systems have certain similarities in their structural-functional organisation, but also significant differences. The most important similarity is that they both comprise the circulation of an extra-cellular liquid through the tissues, which is responsible for the delivery of nutrients and for the removal of wastes by convection. In both cases, these tissue fluids are a product of the arterial blood, and are re-absorbed into the venous blood.

There are three important differences between these two systems: firstly, lymph flows through specialized structures, lymphatic vessels, which enables its active movement from the tissue level back to the venous system near the heart; by contrast, the CSF system has neither specialised vessels nor pumping structures for its active movement. Secondly, lymph is primarily produced through the filtration of blood plasma, whereas CSF is the product of active secretion by specialised structures, known as the choroid plexus, located in the lateral brain ventricles. Lastly, lymph is collected at the tissue level by specialised structures – lymphatic capillaries, whilst CSF is absorbed directly into the large veins on the surface of the brain through the arachnoid villi. Thus the main difference between the brain and the majority of other body regions is the lack of specialized vessels and pumping structures for its supporting fluid circulatory system.

From an evolutionary point of view, the physiology of the CSF system appears to be a relic of a more primitive stage of evolution when compared with the lymphatic system of ‘warm-blooded’ animals. In fact, the CSF system developed at the evolutionary stage when brain metabolism became dependent on aerobic activity. The CSF system is therefore a more recent development than the lymphatic sys-
tem in evolutionary terms, despite its similarities with the open blood circulatory systems of some primitive invertebrates, such as crabs.

The advanced nature of the CSF system is revealed by the presence of structures specialized for its secretion, and by its functional coupling with the closed system of blood circulation. Indeed, the structural/functional organization of the system for CSF circulation and drainage is optimal for brain functioning, as it has all the advantages of the lymphatic system - in terms of nutrient delivery and waste removal - without requiring specialized transport vessels which would limit its circulation.

The free movement of CSF within the cranium also enables the most important function of CSF – rapid volume compensation for regional increases in brain blood volume, which not only accompany local and regional increases in oxygen and nutrient delivery to active brain areas, but also enables the even distribution of force and pressure within the closed cranial system that accompanies each pulse stroke. This in turn serves to protect the soft brain tissues from these pressure increases.

Generally, the fluids circulating within these complementary fluid systems are devoid of any cellular structures. The fluids are produced from blood plasma, by the body’s tissues. The chemical make-up of lymph is very similar to blood plasma, and the mechanism for producing lymph is based upon blood filtration at the capillary level. These liquids, specialized in their composition in accordance with the precise body region they serve, provide an alternative to the venous blood as a means of waste removal by collecting the products of metabolism from the tissues.

In terms of its structural organisation, the lymphatic system comprises a special circulatory bed with its own pumping mechanisms that move lymph from the body’s tissues and organs towards the heart. By contrast, CSF circulates freely through interconnected compartments inside the cranium and down the spinal
column, as well as through the brain tissue.

The compartments through which CSF circulates include the brain ventricles and the special tube-like connections between them, and the sub-arachnoid space (the space between the brain and the skull - arachnoidea), and the extension of this space down the spinal column to the sacral region (called the dural sac).

![Diagram of the CSF circulatory system]

**Fig. 3 The structural organisation of the CSF circulatory system**

Importantly, CSF is able to penetrate through the extracellular spaces of the brain tissue and to evacuate by convection some of the large waste products of brain cell metabolism. In contrast to lymph, CSF, as already mentioned, is largely made through the process of secretion by specialized cells in the vascular network in the ventricles, called the choroid plexus. The process of CSF secretion results in a moderately saline solution without any of the chemical components of blood.

CSF moves from the ventricles through passageways to the sub-arachnoid space and down the spinal cord. It is important to emphasize that a special cellular organization on the surface of the 3rd ventricle also allows for CSF penetration through the brain tissue to the sub-arachnoid space, thereby washing the brain tissue from the inside to the outside.
Fig. 4 Schematic representation of CSF circulation from the site of its secretion, through the brain tissue, to its reabsorption by the arachnoid villi. This circulation of CSF through the brain tissue is in addition to its bulk movement through the brain ventricle system to the sub-arachnoid space and the spinal column.

Movements of CSF are initiated by several factors: the pressure of secretion, changes in blood volume in different regions of the brain, pressure changes that accompany the heart beat and respiratory pressure changes, body movements, and slow fluctuations in the tone of cerebral arteries. Changes in intracranial blood volume that accompany each pulse stroke play an important role in moving CSF through the cranial system. Consequently, the characteristics of pulse fluctuations of CSF contain important information regarding cranial compliance (CC), as will be described in greater detail below.

There are some additional, comparatively small but functionally important circulatory systems supported by complementary fluid systems, namely the intraocular (eye) and the intraotic (ear) systems. The fluids within these organs also serve to support the goal of the circulation, and are similar to the CSF system in terms of their structural/functional organization. Some regions of the body also have arterial systems specialized according to their function. The lungs have no complementary
circulatory system coupled to them, due to their very precise functional role of oxygenating and removing carbon dioxide from the blood which requires special circulatory parameters. Consequently the pulmonary circuit is separated from the rest of the body’s circulatory system (see Fig. 1).

Whilst the body’s blood circulatory systems share some common properties, all display certain regional peculiarities. For example, the arterial blood supply for most organs is organized from their centres outwards to their surfaces. This means that the largest arteries are in the interior of an organ, and that they become smaller as they branch toward the surface. The brain’s arterial system is just the opposite. The large arteries lie on the surface of the brain, surrounding the brain tissue like a net, from where they penetrate to the interior in an increasingly finer web. Of course, this physiological organization serves a functional purpose, as will be explained below.

For the most part, the veins of the body contain valves to facilitate the return of venous blood to the heart, but an important exception to this general rule is the Azygos vein, which returns blood from within the spinal column. Again, this structural specialization is important from a functional point of view, as it facilitates the return of CSF to the cranium. Indeed, as body movements bring about pressure changes in the inferior vena cava, this in turn leads to changes in the volume of venous blood inside the vertebral column. Because this volume of venous blood is directly connected to the volume of CSF in the spinal cord, these volume changes can trigger CSF movements towards the cranium if resistance to CSF movement is sufficiently low, as is the case in healthy individuals.
2. BRAIN BLOOD CIRCULATION, CSF CIRCULATION AND CRANIAL COMPLIANCE

Circulation of blood in the brain differs from that in the other organs because the brain is encased within a nearly rigid container, the cranium. The situation is further complicated by the complex interaction between the cerebrovascular and CSF systems within this container. These two systems are interdependent, so any changes in the volume, pressure or movements within one system must lead to concomitant changes in the other, consistent with the laws of fluid dynamics. The study of brain circulation therefore comprises the study of the bio-mechanical interaction between the blood within its flexible vessels, the CSF moving freely in its compartments outside the blood vessels, and the physical properties of the nearly rigid cranium.

By considering the cranial system as a whole, it becomes clear that its various structural components are all interacting towards a single purpose, namely to fulfil the functional goal of the circulatory/metabolic supply of the brain tissue.
Given the functional goal of this complex system - to support cerebral activity - an important element of the systemic approach is to assess the system’s level of functioning through tests of the highest level of cerebral activity, i.e. cognition.

An important structural element supporting cerebral circulation is the bio-mechanical properties of the cranial bones themselves. Their properties determine the capability of the system to accept some additional volume of blood when the intracranial pressure increases during the heart beat. These properties reflect the *elasticity* of the cranium as a complex structural system, which in turn represents what has become known as **cranial compliance (CC)**.

CC is an indication of the interaction between intracranial fluid volume (blood and CSF) and **intracranial pressure** (ICP). Cranial compliance is not a completely new concept. It’s origins date back some four decades when a mathematical model was presented that represented all
significant physical features of cerebral circulation. The model required that an elastic coefficient be introduced so that the mathematical model could exactly match actual blood flow measurements in and out of the brain. Some years later investigators reported that when a volume of artificial CSF was slowly injected into the cranial cavity the internal pressure did not respond immediately but as the volume was increased over time, the pressure increased exponentially. This meant that there is some reserve capacity within the brain container to allow for volume increases without increasing pressure and, most importantly, that the reserve is limited. This elastic reserve capacity became known as cranial compliance. However, measuring CC in this way reflects a steady-state situation, when mean ICP is changing slowly enough to establish moments of equilibrium between volumes and pressures of blood and CSF inside the cranial-spinal cavity that could be measured.

In real life, the situation is much more dynamic. Changes in intracranial fluid volume and pressure take place over the course of each heart-beat. By observing that the pressure/volume ratios recorded during a single heart-beat have distinct features (linear and non-linear) during specific time intervals, it became possible to analyse the contribution of the different intervals to CC as a whole. During the first 0.1 – 0.2 seconds (s) of the heart-beat (heart systole), the ratio will reflect the elastic properties of the cranium – designated \( \text{CC}_e \). During the next interval of the cardiac cycle - 0.2s - 0.6s - the ratio will reflect the compensatory movements of CSF inside the cranium and between the cranium and the spinal cavity – designated \( \text{CC}_c \). During the final interval of the cardiac cycle, the ratio reflects the conditions of venous outflow from the cranium – designated \( \text{CC}_o \). Each reflects the influence of a single element. Taken together they offer the possibility for comparative evaluation of the movement of fluids within the cranial system.
The importance of adequate cerebral circulation to consciousness and cognition stems from the fact that the brain has no reserve of metabolites on which its functioning can rely. The brain, therefore, requires a continuous and intensive supply of blood to provide oxygen and other nutrients, and to remove waste products. It is important to mention that under certain conditions of decreased brain blood supply, when the level of nutrient delivery may still be sufficient, a serious problem can arise due to reduced removal of metabolic waste products from the brain tissue. This gives rise to increasingly toxic conditions within the brain as the pH declines due to the progressive accumulation of acid compounds. Thus the first sign of cerebrovascular insufficiency is not a nutrient deficiency, but rather a deficiency in the waste removal capability of the circulatory process.

To summarise, the functional roles of the CSF system are to:

- act as a special “lymphatic system” dedicated to the brain, which removes waste products too large to pass back into the blood stream;
- provide a protective “liquid suit” for the brain and central nervous system, which protects it from mechanical stresses;
- through its free movement, provide a means for compensating for changes in brain blood volume as the concentration of blood moves from one region of the brain to another, according to demand, inside the nearly rigid cranium.

Thus the CSF system both cushions the brain and, through its circulation, is responsible for cleansing the brain tissue of metabolic waste products.

3. CONTROL PROCESSES IN THE CEREBROVASCULAR SYSTEM

As was established by Roy and Sherrington more than a century ago, the cerebral vascular system is subject to a number of con-
trol mechanisms, such as metabolic, hormonal and neurogenic processes, which change the vascular tone to ensure adequate metabolic supply for brain functioning under different environmental conditions. As highlighted above, however, the cerebrovascular system is just one component of a triad that also includes the structural element of cranial biomechanics and the CSF system in determining cerebral circulation.

The cerebrovascular system is the only element with the capability to respond actively to the changing conditions of brain functioning, thanks to the smooth muscle of brain blood vessels. The CSF system and the cranium are physically passive and therefore their contribution is dependent on the forces generated by the smooth muscle control of the vascular system, as well as the energy of central arterial pressure. Due to this, for a long period of time the attention of investigators has been focused on control processes that govern brain circulatory-metabolic supply under different environmental conditions and states of activity, while other components of the whole mechanism, CSF mobility and cranium biomechanics, have been largely overlooked.

Many decades of studying the control processes in the cerebrovascular system have determined their phenomenology and their ultimate goals: 1) maintaining brain blood flow as the system’s arterial pressure is changing, and 2) maintaining local and regional blood flow when activating different regions of the brain in response to differing functional demands. The first has received the name “autoregulation” of brain blood flow, and the second the name local cerebral vascular control (functional hyperemia). These two control processes work independently, but both of them are also responsible for maintaining the osmotic balance of brain tissue.

The physiological mechanisms that underpin these control processes in the cerebrovascular system remain unclear, and there are presently too many factors which could play a role in controlling cerebrovascular processes to be able to determine their individual contributions effectively. First of all, there are two divisions of the central
nervous system – the sympathetic and the parasympathetic. The first is responsible for constriction of brain blood vessels, and the second for their dilation. Numerous investigations have found the presence of nerve endings, both sympathetic and parasympathetic, in brain blood vessels, from large arteries down to the capillaries. Besides these, other kind of innervations could play a role in brain vessel control processes: vasoactive polypeptides (VIP) and purynergetic types of nerve systems. Also, numerous chemical compounds including nitrous oxide (N₂O) and mediators produced by the nervous system (such as bradikinin, and serotonin), the products of cellular metabolism (such as CO₂ and acid metabolites), and non-organic ions (H⁺, K⁺ and others) could all play a role. Thus brain blood vessels are influenced by numerous factors. The final result of their simultaneous action on vascular tone is to support the metabolic supply of the brain tissue and to maintain its water balance.

Since the blood and CSF systems are directly interdependent, movements in one system drive movements in the other. Both systems are driven by: 1) the cardiac activity, 2) respiratory movements of the chest, 3) slow fluctuations in the tone of the brain blood vessels, and 4) the slow fluctuations of central arterial pressure. Whilst the effects of cardiac activity and respiratory chest movements are clearly traceable, the origins of the third driving-force of the brain circulation, the slow fluctuations in the tone of the brain blood vessels, have only recently been elucidated. These slow fluctuations result from the interaction of two or more control processes, each of which operates on a different latency (see Fig. 6). Once this was understood it became clear that the mechanisms for maintaining the water balance (with a latency of 4 - 8 seconds) and oxygen balance (with a latency of 2 - 5 seconds) are the cause of these slow fluctuations. Thus the water/oxygen balance is maintained by relatively slowly occurring changes in intracranial vessel tone. The efficiency of this system can be determined by the spectral analysis of intracranial blood.
Fig. 6 Principle of “generation” of the slow fluctuation inside the cerebral vascular system: this is based on the interaction of two or more control links with different latencies.

The frequency of slow fluctuations provides useful insights into the dynamic conditions of the brain circulation. In a situation where the metabolic supply of the brain tissue and its water content are in balance, the frequency of intracranial slow fluctuations is 7 - 9 cycles per second. In the case where there is an increase in the water content of the brain tissue the frequency of slow fluctuations decreases by as much as 4 - 5 cycles per minute. On the other hand, when the rate of brain metabolism increases, the frequency of slow fluctuations also increases by up to 10 - 12 cycles per minute. Any observed irregularities in the amplitude and frequency of intracranial slow fluctuations can therefore indicate that control processes, responsible for maintaining the oxygen and water balances in brain tissue, are not functioning perfectly.

The fourth influential element is slow fluctuations in the brain circulatory system that arise from changes in central arterial pressure (also the result of more than two regulatory processes). These slow fluctuations are commonly known as Meyer (Traube-Hering) oscillations. Both types occur spontaneously in conscious subjects at a frequency lower than the rate of respiration.
4. CEREBROVASCULAR REACTIVITY

The complicated functional and structural organization of the control system of the brain blood supply is determined by its most important property – cerebrovascular reactivity (CVR), which objectively reflects the adaptability of the control system responsible for stabilizing the physical and chemical indices of the extra cellular brain media. The functioning of this biofeedback system is central to the life support of the brain tissue. In simple terms, CVR is the capacity of the brain vessels to change their diameter as a means to regulate blood flow through the brain in a wide variety of living situations (see Fig. 5 showing tone of the brain blood vessels in the central position). In order fully to assess the cranial system’s ability to respond to the variety of functional demands encountered in everyday life, it is reasonable to evaluate the level of CVR in response to some destabilizing stimuli of both chemical and physical origins.

Taking into account that the final product of brain cellular metabolism under normal physiological conditions is carbon dioxide (expressed by $pCO_2$ or CO$_2$ concentration), the response of the cerebrovascular system to an increase in $pCO_2$ in the extra cellular media of the brain tissue is to increase the brain blood flow so that this index returns to acceptable levels. This happens because increased $pCO_2$ mimics the condition of decreased cerebral blood flow, as under normal conditions a decrease in blood flow leads to an accumulation of CO$_2$ in the brain tissue. The level of response of the brain blood vessels to increased brain tissue $pCO_2$ is therefore a convenient means of testing how well the control processes of the brain circulatory system are functioning. There are two practical means of performing this functional test: one is a 60-second inhalation of an air mixture with $pCO_2$ increased to 7%; the other is a 30-second voluntary respiratory arrest.

It is reasonable to use the inhalation of a 7% CO$_2$ mixture to determine CVR under clinical conditions, in particular during the period after brain surgery. This involves measuring changes in
cerebral blood flow (CBF) in a given brain region in response to the functional test using transcranial Doppler ultrasound (TCD). If during CO₂ overload the CBF increases by as much as 10 - 15%, this means that the CVR of the investigated brain region is within normal limits. However, under pathological conditions, including after some brain injury, CVR usually decreases. In less severe cases, the response of the brain blood vessels remains positive, but under more traumatic conditions the brain blood vessels at the injured region may not respond positively, as evidenced by a decrease in local CBF of as much as 5 - 15% in the injured area following pCO₂ = 7% inhalation. This negative response provides an important diagnostic index, indicating a serious dysfunction of the cerebrovascular control system, which should be treated with the highest priority. This negative response is based upon the fact that the blood vessels in the investigated brain region have lost the ability to respond to the increased level of CO₂. The increase of blood flow in the healthy, responsive brain regions therefore pulls blood away from the injured brain region, where the blood vessels are paralysed. In such circumstances, sensitivity of brain blood vessels to most pharmacological agents, including vasodilators, is also lessened and their effectiveness during the period after injury may be diminished.

Another way of testing CVR is applicable to participants who can voluntarily control their respiration. It is standardized on a period of 30 seconds’ voluntary respiratory arrest. The response of the brain blood vessels to this test can be measured by the rheoencephalography (REG) method shown below.
The response of the brain blood vessels to this functional test is based upon the accumulation of CO₂ in the blood and the brain tissue during respiratory arrest. The response is expressed as a change in the amplitude (increasing by about 10 - 20%) and in the pattern of the REG pulse data. A comparative value of CVR can be determined (as indicated in Fig. 7) by calculating the difference between the initial amplitude of the REG pulse (A1 - just before the functional test begins) and the REG amplitude when the response of the intracranial vessels first develops, but before the general response of the central blood circulatory system has started. The point at which the general response is deemed to have begun is determined by the increase in the level of pulsation of TCD, which occurs 15 - 20s after the start of the functional test. The optimal pulse cycle for analyzing of CVR is therefore marked on Fig. 7 as A2. Calculations of CVR can be made by using the formula:
CVR = \( \frac{A_2 - A_1}{A_1} \)

For the particular example shown in Fig. 7 above: CVR = \( \frac{(0.85 - 0.58)}{0.58} \) = 0.47

Under certain conditions, it is also reasonable to test CVR by using a physical stimulus such as the Stookey test (moderate pressure applied to the abdomen), or by tilting the head down. Using these tests in conjunction with REG measurements, it is possible to measure the response of the brain blood vessels to the increased central venous pressure that the tests elicit. This means of determining CVR in response to a predictable change in central arterial or venous pressure has certain benefits. It can help the diagnosis of a patient’s status after some portion of the brain has been destroyed. For example, it is possible that after a head injury neither the neurological symptoms nor the biochemical indices discussed above provide an exact reflection of the patient’s condition. In these cases the determination of CVR using certain physical functional tests may provide additional and important information on the real condition of the patient. A decrease in, or the absence of, active responses to such physical stimuli reflects severe destruction of the control processes that support brain blood circulatory supply. An example of this situation is shown in Fig. 7a (taken from an earlier publication by a member of our current research group). Responses to the Stookey test of two different patients with a brain injury, 5 days after the surgical removal of damaged brain tissue, are depicted. Because the skull was fractured and the brain exposed for about two weeks, REG recordings were made using platinum wire electrodes (100μm in diameter, with a 1 mm exposed tip). The electrodes were implanted into the brain tissue some distance from the focal point of the injury, in tissue that appeared healthy. Together with REG, the intracranial pressure (ICP) and central venous pressure were measured using special transducers. These investigations were performed during treatment of accidental head injury pa-
patients with different degrees of brain tissue damage, once the risk of further complications had passed.

![Fig. 7a Responses to Stookey test of patients with severe and very severe head injury. REG was recorded from wire electrodes implanted in both the cortex and the white matter. ICP and central venous pressure were measured by special transducers. Calibration scales for each recording are shown on the left and are specialised for each particular case. Decreasing electrical resistance between electrodes, which leads to a downward shift in the recording curves, shows the increasing volume of liquid media with comparatively low electrical resistance.](image)

In the upper case, the active responses to the functional test are very clear, which indicates the positive presence of CVR. A reserve capacity to receive an additional CSF volume is immediately demonstrated. The control mechanism for the constriction/dilation of the vessel walls is sufficiently intact to respond to an increase in ICP. In the lower case no active response is observed – only gradual passive changes in the levels of the recording curves during the functional test, even though the test lasted longer than in the upper case. The results suggest that there is little capacity to receive an
additional volume of CSF (meaning that the existing ICP is equal to or greater than the force applied by the Stookey test) and that the existing ICP pressing on the blood vessels has already significantly compressed them, and can overpower their capability to respond. At this point the patient is in extreme danger. If the blood oxygen level is not sustained artificially the arteries would not have the strength to dilate as a normal response to increased pCO₂. Autoregulatory processes would respond by using central blood pressure to accelerate and decelerate blood in an attempt to regulate brain blood oxygen levels. This secondary control process is known to have low sensitivity. Blood pressure could fluctuate erratically, and flow velocities could easily exceed or even fall below acceptable levels. Without timely intervention, the patient would succumb to deep coma or death.

These data demonstrate that CVR (as determined by REG recordings) can provide important insights for evaluating the current status of head-trauma patients, and suggest that monitoring the relation of CSF movement capabilities to the capability of the vessels to regulate their diameter may be useful in many other situations.

Thus, determination of CVR provides an important index for evaluating the quality of the control processes of the brain circulatory system. The recordings shown in Fig. 7 and 7a provide a fundamental understanding of how intracranial pressure and volume changes influence brain physiological processes. On this basis, the following chapters will demonstrate that cerebrovascular reactivity and cognitive functioning are exceedingly sensitive to the pressure and volume changes that are experienced throughout the human life span, even before obvious external manifestations are exhibited.
SUMMARY OF CHAPTER I

This chapter has covered many different topics and provided a great deal of information, its principal purpose being to emphasize that the cerebrovascular system, the CSF system and the biomechanical properties of the cranium are the major components of a unified system responsible for ensuring sufficient cerebral circulation to maintain brain metabolism and cognitive activity. It was also intended to emphasize that the CSF system has several functions, which include serving as a lymphatic system specialized for the brain, and to propose that CSF movement capabilities may play a significant role in cerebral circulation and cognitive function.
CHAPTER II

ANALYSING CEREBRAL FLUID CIRCULATION AND THE ‘MOSKALENKO METHOD’

As highlighted in Chapter I, cerebral activity is dependent upon a constant supply of oxygen and nutrients, as the brain has no capacity for storing the metabolic substrates it requires. In order to understand more about the mechanisms involved in ensuring this constant supply, it is important to analyse the cranial system as a whole: the brain tissue, the cerebrovascular system (CV), the CSF system and the partially-flexible cranium.

This systemic approach to investigating cerebral circulation required the development of a new methodological approach to these investigations. This involves: the use of specially-adapted technologies to provide the kind of data required for our studies; the application of specific functional tests to analyse the functioning of a specific physiological system; and the use of computer-aided data analysis to determine the level of cranial compliance. We have named the method as a whole the ‘Moskalenko Method’ (MM). The MM makes use of bio-impedance data (recorded by rheoencephalography), and blood flow data (recorded by transcranial dopplerography), to provide information on the nature of cerebral blood flow (CBF) and the level of cranial compliance (CC).

An important feature of the MM as a whole is its assessment of how well the cranial metabolic support system is functioning from the perspective of this system’s ultimate goal - enabling cognitive activity. We have therefore used certain psychophysiological tests as part of our investigation to investigate how cerebral circulation and cranial compliance are linked to cognitive activity.
This chapter therefore provides some background to, and important details of, the MM. This includes information on the instrumentation involved, the principles of data analysis, the specific functional tests employed and the psycho-physiological tests of cognitive activity.

1. THE THREE INTERVALS OF CRANIAL COMPLIANCE

Our investigations have been conducted using a unique monitoring method that allows for non-invasive monitoring of fluid movement through the brain in response to the forces that drive them. Recording the dynamic conditions of brain circulation in a single subject can be completed in less than 15 minutes with this method, enabling a much simpler method of monitoring cerebral fluid movements than by magnetic resonance imaging (MRI).

The Moskalenko Method (MM) is based upon using two established technologies to measure cerebral fluid movements. Transcranial Dopplerography (TCD) measures blood flow. Rheoecephalography (REG) measures CSF movements. Digital analysis of the recorded data allows for assessment of the interaction between the two fluid systems (CV and CSF), both at rest and in response to a series of tests that apply specific functional loads to each system individually. Analysing the interaction between the two systems enables us to determine the nature of the pressure/volume relationship, which in turn reflects the quality and quantity of the cerebral circulatory processes.

The velocity of blood movement in the large brain arteries, such as the middle cerebral artery (MCA), is monitored by TCD, both as a steady state flow and as a pulse index, which respectively reveal an averaged (main) linear velocity of blood through the artery, and the volume changes that occur during the cardiac cycle. These volume changes occur at such a rapid rate that they are dependent on the passive mechanical properties (elasticity) of the
blood vessels. This means that the vascular volume can be determined by monitoring the linear velocity of the blood, which means that fluctuations in the TCD signal correspond exactly to pulse-related changes in cerebral blood velocity and volume that begin in the arteries at the base of the cranium, and then expand through the entire cranial cavity. It is therefore possible to interpret rapid changes of the TCD signal as also reflecting fluctuations in intracranial pressure (ICP).

Changes in the interaction between the blood and the CSF systems within the cranium evoked by the pulse changes of ICP are monitored by REG, which measures differences in the electrical conductivity of the brain tissue, blood and CSF. The ratios of electrical conductivity values are: 1.0 : 0.5 : 0.1 for CSF, blood and brain tissue respectively. Thus the REG signal reveals the combined fluid volume changes (tissue volume does not change) within the cranial region that lies between the recording electrodes placed on the scalp.

For the study of the relationship between the blood and CSF systems within the cranium it is important to record TCD and REG in the same vascular region. There are several possible recording configurations, but the most convenient is to place the REG electrodes at the fronto-mastoidal position on the same hemisphere as those that record the TCD from the basement of the middle cerebral artery (MCA). With this configuration it is possible to make observations on the vascular region supplied by the MCA.

The instrumental complex for this research consists of a special analogue-digital converter (PowerLab 4), which enables pattern, phase and spectral analysis of the TCD and REG recordings on a MAC or PC. Additionally, the PowerLab 4 allows simultaneous recording of respiratory chest movements and electrocardiogram (ECG) to be uploaded as represented by the scheme below.
**Fig. 8** Schematic diagram of the instrument complex, functional tests and positioning of the TCD probe and REG electrodes for CBF and CSF studies in one hemisphere.

Recording TCD and REG simultaneously and then superimposing their waveforms reveals distinctive interactions between the blood and CSF during the three intervals of the heartbeat. This allows for the study of the interactions between the cerebrovascular system, the CSF system and the elasticity of the cranium. The precise characteristics of these interactions provide a good indication of the quality of cerebral circulation and of its metabolic supply. The principle of data analysis using these physiological approaches is described in detail below.

**2. The Role of the Pulsative Factor in Blood Circulation Within the Brain**

The system of cerebral metabolic supply is dependent upon the complex interaction of a number of elements. Our investigations
have clarified that CSF movement plays a significantly important role in this system, and its role has led to a more complete understanding of the interaction of the forces at work within the system. The circulatory-metabolic supply of the brain is based on the interaction of three elements. One of them is the cerebrovascular (CV) system, which is responsible for the delivery of oxygen, glucose and other nutrients carried by the blood to the brain tissue; a second element is the CSF system, whose movements enable both the inflow of the pulse volume (the volume of blood pumped with each heart beat) to the cranium, and also the removal of the products of metabolism from the brain tissue, as well as being involved in nutrient delivery to a small extent; the third element is the biomechanical properties of the cranium. This element plays some part in the ability of the cranium to accept an increase in the volume of blood during the phase of systolic increase in central arterial pressure. Cerebral blood flow consists of two components. One is the steady state of flow through the brain, determined by the basal tone of the brain blood vessels. The second occurs with each heart-beat, which initiates arterial pressure increases and so drives the pulse volume into the cranium. It is this component that is influenced by the level of cranial compliance, which in turn depends on the flexibility vs. rigidity of the cranium.

This increase in arterial pressure is of short duration – 0.1 - 0.2 seconds. This means that the cranium needs to accommodate the increase in systolic blood volume very quickly in order to use it to drive cerebral circulation. This is made possible due to the biomechanical properties of the cranial system – its cranial compliance – which enables an increase in the internal volume of the cranium during the systolic phase of increasing arterial pressure. However, the cranium is a rigid container with only limited capabilities to accommodate internal volume changes in response to rapidly occurring increases in intracranial pressure, such as the heart beat. It is therefore important to evaluate the cranium’s volume reserves, or in other words, its ability to accept an extra volume of blood fol-
lowing the systolic increase in arterial pressure, which is in addition to the steady state level of the brain blood flow. Let us first consider the steady state blood flow. Steady state blood flow can be estimated by using some relatively simple calculations based upon long-established physiological data. On the one hand, we know that 52 – 65 ml of blood flows through 100g of brain mass in 1 minute, so, through an average-sized human brain (1200g), about 600ml flows every minute. On the other hand, we know that the brain takes about 20% of the stroke volume (the volume of blood pumped with each heart-beat), which for normal physiological conditions is 60 ml. This means that 12 ml of blood passes through the brain during one heart beat, 6 - 7 ml of that is the steady state flow, determined by the diastolic arterial pressure and the basal tone of brain blood vessels. The cranium therefore needs to accommodate 5 - 6 ml during the systolic increase of arterial pressure.

**Fig. 9** Distribution of stroke blood volume supporting cerebral circulation.

In comparison with the total volume of the internal cavity of the cranium, this volume is rather small – about 0.3%. Thus, under normal physiological conditions, the processes associated with CCe and CCc should enable the acceptance of this volume of extra blood,
and its use for brain metabolic supply. However, under certain conditions of reduced CCE and CCc, the brain may lose up to 20 - 30% of its blood flow. Of course, these numbers are at the upper limit, but if a decrease in CCE and CCc leads to a 1 - 1.5 ml reduction in the volume of blood accepted by the cranium, then the total brain blood flow per minute will diminish by up to 10%, which is significant in terms of normal brain functioning, and may be reflected in diminished cognitive functioning. This highlights the importance and potential of the MM, when used in conjunction with cognitive tests such as the ‘Prognosis 1’ test, in order to evaluate the dynamics of cerebral circulation, and assess the effects of any changes in cerebral circulation on cognitive functioning.

Evaluation of the pressure-volume relationships during the cardiac cycle has enabled the determination of three inter-dependent ‘intervals’ of each pulse cycle, which reflect different processes inside the cranium:

1) The initial interval is a rapid, nearly linear, increase of pulse pressure which lasts from 0.05 - 0.15 seconds and perfectly reflects the elastic properties of the cranium. It designates an increase of intracranial blood volume, the extent of which is determined primarily by the biomechanical properties of the cranial bone structure (its elasticity versus rigidity), and this interval corresponds to an increase in central arterial pressure produced by each pulse stroke as it enters the cranium. This interval is designated as CCE. Because CCE increases in a nearly linear fashion, it is possible to estimate its value (in comparative units) by using a tangent (Tg) to the approximately straight line (see Fig. 11 below).

2) Immediately following the peak of pulse pressure described above, there follows a second interval representing a compensatory process (CCc), which reflects CSF movements. CCc represents the interval during which displacement of the liquid media...
inside the cranium occurs and the force of the pulse stroke from the previous interval is dissipated as movement of blood and CSF through and around the brain tissue. The level of CCo can be determined by measuring the area under the transformed volume/time graph that corresponds to this phase of CSF movements.

3) The final interval of the pulse cycle reflects the outflow of venous blood from the cranium (CCo). The nature of venous outflow depends on the level of pressure in the Jugular veins and on the level of functioning of the mechanism by which energy from the arterial pulse stroke is transmitted to driving the outflow of venous blood from the cranium. The level of this index depends on multiple factors including CSF mobility, cranial compliance and perfusion blood pressure. It is therefore difficult to infer much from this measure as it has such complex origins.

The figure below depicts the changes in volume and pressure that occur over the course of these three time intervals, how these time intervals are determined, and the nature of the information yielded by analysis of that data. This picture also demonstrates how the level of CBF is determined by both the steady state of arterial pressure, and also the pulse pressure.
It is important to emphasize that changes to the steady component of brain blood flow, determined by the perfusion pressure, are independent from the pulsative component. The total brain blood supply is determined by the summation of the steady state as determined by the perfusion pressure (average level of arterial pressure) and the pulsatile component of blood flow, which is determined by the biomechanical properties of the skull and the mobility of cerebrospinal fluid within the skull.

3. COMPUTER-AIDED ANALYSIS OF RESULTS

The three intervals of CC, which together add up to about one
second, represent three distinct but interdependent phases of the pulse-driven movements of the blood and CSF that occur in a single heartbeat. Interdependent intervals mean that a change in one interval proportionally influences either or both of the others. For example, increasing the pulse-stroke volume during the CCe interval directly influences the quality of CSF movement in the next interval (CCc), when the two fluids begin to rebalance. The quantity of CSF movement during the CCc interval in turn influences the force with which the blood leaves the brain during the outflow interval (CCo), when the heart’s contraction has finished. The interactions between them comprise the special mechanism for ensuring sufficient cerebral circulatory-metabolic supply, and are represented by the scheme shown below:

**Fig. 11** Method of analysing simultaneous recordings of TCD and REG, which includes the transformation from amplitude/time scale to TCD/REG scale over a
standardized time interval. Pulse pressure scale (Pp) changes from Pp = 0 at the diastolic minimum up to maximal level of arterial pressure (Pp = max) in the middle of the standardized scale. Physiological indices: CCE(Tgα) – dynamic cranial compliance; CCc - CSF-mobility; and 1/h - skull rigidity. These indices are included in the bottom diagram. The data represented in this figure come from a typical, healthy middle-aged person.

The following section describes how the different intervals of CC can be determined and the data interpreted. On the graphs above (Fig. 11), the comparative values of CCE and CCc reflect the predominant direction of CSF movements during the pulse cycle. It should be noted that CSF movements associated with CCc also take place during the phase of increasing pulse pressure. This indicates that some small amount of CSF is mobile whilst the pulse pressure is increasing. Due to this CSF movement, the first phase on the diagram shown in Fig. 11 is slightly nonlinear. Were there no CSF movement during this phase, the index would increase linearly as purely elastic pressure-volume changes are directly proportional to one another. Fig. 11 also includes a special index of skull rigidity, designated 1/h. This index reflects the pure biomechanical properties of the skull, which in turn determines the cranium’s capacity to expand in response to an increase in intracranial pressure or fluid volume. At the bottom of Fig. 11, the two straight lines XY and YZ represent the theoretical biomechanical response with no CSF movements. The major direction of CSF movement is normally localised within the cranium, moving from the ventricles towards the sub-arachnoid space, in which case the decline in REG values during the CCc interval is comparatively slow, because the electrical conductivity inside the cranium is slightly increased - the electrical conductivity of CSF is higher than that of blood. Therefore, CCc is localized above the hypothetical straight line which represents the purely biomechanical response. CSF movements are shown by green coloured areas in the bottom graph of Fig.11.

The capacity for CSF displacements is not identical in all
individuals, and it tends to vary with age. In people with normal cognitive functioning, the level of CCc in relative units is usually between 0.65 - 0.80, although it can be as much as 1.0 or more. There appears to be a reciprocal relation between CCe and CCc levels: if CCe is comparatively low (CCe = 0.4 - 0.6), CCc is usually quite high (about 0.7 or more). CCc tends to be higher in older people, although in certain individuals with severe cognitive impairments, CCc is significantly decreased. When CCc is low, this may be due to a relative increase in the spinal component of CCc compensations (i.e. CSF displacement down the spinal cord). In cases when CCc is high, CSF movements are very active inside the cranium, and the spinal component is small, but if both CCe and CCc are low, a deficiency in brain metabolic supply is indicated. (Fig. 12)

Fig. 12 An example of changing CC components in elderly individuals - one with normal brain functioning and the other with pronounced dementia.
During the CCc phase, when the major CSF displacements occur, it is possible to chart the direction of these displacements from the pattern of change in the REG signal. In the majority of cases, where the bulk of CSF movements occur within the cranium (moving from the ventricles towards the sub-arachnoid space), the decline in REG values during the CCc interval is comparatively slow. This is because CSF has a higher electrical conductivity than blood, so intracranial conductivity remains relatively high.

However, if CSF predominantly moves out of the cranium and down the spinal column, then the electrical conductivity decreases more rapidly, as there is relatively more blood volume in the cranium. This pattern of CSF movement is often found in patients with some obstruction of intracranial CSF mobility, particularly certain pathologies including brain tumours, hematoma or post-surgical brain oedema. It is important to note that for these cases an increase in intracranial pressure is particularly significant and should be closely monitored. Fig. 13 provides a schematic representation of results from a brain-tumour (meningeoma) patient, whose condition places a severe limit on CSF movement capacity.
As can be seen in Fig.11, the normal pattern of CSF movement involves an increase in mobility that begins during the phase of increasing systolic pressure and continues after the point at which Pp = max, but in the patient shown in Fig. 13 with some cerebral pathology, CSF mobility begins to decrease after Pp = max. To reflect the difference in the predominant direction of CSF movements, it is reasonable to categorise mainly intracranial CSF movements as positive CCc, or simply CCc, and for cases when CSF predominantly moves to the spinal cavity as negative CCc (or –CCc). Some examples of the latter are illustrated in Fig. 14 below.
When considering the pattern of CC results associated with cranial pathologies, it is important to note that CCe is usually not too low, but CCc is often negative and 1/h is comparatively high. This pattern of results arises from the interaction of the structural changes within the skull and the activity of cerebrovascular control mechanisms, which are responsible for making every adaptation possible for supporting cranial metabolic supply at an optimal level across all situations.

**DETERMINING CCC**

In addition to the method described above for assessing dynamic cranial compliance and CSF-mobility, there is also a simpler means of determining the level of CSF–mobility. This is based on
measuring the interval between the peaks in the TDC and REG signals over the course of one cardiac cycle, and calculating, also in comparative units, the area of a two dimensional figure on a transformed REG-TCD scale (Fig. 15):

![Graph showing simplified ways of determining CSF mobility.](image)

**Fig. 15** Simplified ways of determining CSF mobility. In both cases CSF mobility corresponds to the interval between TDC and REG signal peaks —“t” (left), or area “SQ” (right.)

It is necessary to mention that, using these different assessment methods, there are sometimes small discrepancies in the results they produce, particularly for young people (up to 10 years old), who have flexible skulls. From the age of 15 onwards, however, both means of assessing CSF mobility give similar results, although some non-significant differences are sometimes observed. Hence it is reasonable to use both of these methods simultaneously.

4. **Slow Fluctuations in the Cerebrovascular and CSF Systems**

Some important information concerning changes in the activity of the control mechanisms responsible for circulatory-metabolic
supply of the brain tissue can be obtained through the spectral analysis of slow fluctuations of cerebrovascular tone. These slow fluctuations are the result of the interaction of two groups of control links, responsible for maintaining metabolic supply and the water balance of brain tissues, as shown in Fig. 6 (Chapter 1). The principles of spectral analysis are based on the fact that any periodical fluctuations of a complicated waveform can be represented as a sum of more simple sinusoidal fluctuations containing different frequencies and amplitudes (see fig. 16).

Fig. 16 The principle of spectral analysis involves the evaluation of separate frequency components which, when added together, compose the complex waveform. The left part of this figure represents how comparatively complicated periodical fluctuations can be represented as the sum of two simple sinusoids. At the top of the graph on the right of this figure there is a fragment of REG recording and displayed below are its spectral components. It is possible to see that there are many spectrum lines of the REG recording due to the complexity of the wave form of a REG curve. It is also possible to see groups of lines, which represent cardiac pulse (about 1.4 Hz), respiration (about 0.3 Hz) and slow fluctuations (0.08 – 0.12Hz) which indicate the activity of the cerebrovascular control mechanism.
Measurements of the amplitude and frequency of slow fluctuations in the cerebrovascular system provide valuable information concerning the peculiarities of the control processes responsible for the brain’s circulatory metabolic support.

![Fig. 17](image)

**Fig. 17** Detailed spectral presentation of frequency components, following from spectral analysis of the original recordings from REG. The amplitude index of the spectral components is expressed by the comparative values of pulse (heart beat) fluctuations, the maximal value of which is 1.0. This permits the comparison of the values of spectral lines to the amplitudes of slow fluctuations at different levels of investigation. During normal conditions the amplitudes range is between 0.3 - 0.6.

Spectral analysis of the REG recordings provides significant information, because it makes visible the distinction between fluctuations that belong to the brain’s circulatory system and similar fluctuations that arise from the central cardiovascular system. It is possible to determine the origin of slow fluctuations by comparing REG spectra (fluctuations in the volume of the intra-cranial fluid contents - shown in green in Fig. 18) with TCD spectra (representing blood flow as it enters the cranium - shown in magenta in Fig. 18). The comparison demonstrates that the very slow
fluctuations in TCD have an extra-cranial origin. Extra-cranial slow fluctuations depend mainly upon fluctuations in central arterial pressure, and have a considerably slower frequency (2 to 5 cycles per minute) than those of intracranial origin. Both frequency groups can be identified in the REG spectra and the TCD spectra. The amplitude of the spectral lines of intracranial fluctuations gives additional information concerning CSF mobility, and roughly corresponds to CCc. However, if the CBF control systems are depressed, the amplitude of the spectral lines of the slow fluctuations might be decreased without any changes in CSF mobility. As seen in Fig. 17, the frequency of the major spectral lines of the slow fluctuations corresponds to the group of control links, which support brain blood supply. If the metabolic control of the brain’s parenchyma is the dominant control process, the major frequencies of slow fluctuations will move from 8 – 10 cycles per minute to 9 – 14 cycles per minute. If the control of parenchymal hydration is the dominant process, major frequencies will decrease to 5 – 7 cycles per minute. By simultaneously recording the respiratory movements of the chest, it is possible to determine that the origin of the REG spectral components in the range of 20 cycles per minute are due to respiration. An example of the results of spectral analysis of these recordings is shown below:
Fig. 18 Low frequency spectral components of simultaneously-recorded REG, TCD and respiratory movements of the chest. It is possible to see that all three spectra reflect respiratory movements, but the spectral lines representing respiration are different from the slow fluctuations of REG, which represent frequencies of 5 - 14 cycles per min. Spectral components of TCD are characterized by slower frequencies of 2 - 5 cycles per min.

5. UNDERSTANDING THE MM’S FUNCTIONAL TESTS.

One means of evaluating the efficiency of the mechanism of brain circulatory-metabolic supply, as with investigations of any functional system, involves the application of certain specially-selected functional tests. The changes that these tests evoke enable
the evaluation of the role that a particular element of that system plays in the functioning of the complex mechanism as a whole. A functional test is a temporary and standardized artificial disturbance, in which a particular element of a system is manipulated under experimental conditions, in order to investigate the reaction of the system to the test. Such tests are selected based upon the interaction of the test mechanism with elements in the selected system. Functional tests can be of a physical or chemical nature. A physical test models a physical action, such as a change in pressure, volume or the configuration of some aspect of the investigated system, for example, intracranial blood volume. Chemical tests involve introducing, or changing, the concentration of a physiologically active chemical, and tracking the changes that a specific chemical evokes.

By observing the responses to a range of functional tests, it is possible to establish the relative contributions of the blood and CSF systems to cranial compliance and cerebral circulation. Responses to these functional tests can be evaluated in terms of changes in cerebral blood volume, in intracranial pressure or in CSF replacement, and also determine the level of functioning of the components of the cranial system. However, to check the functional stability and level of functioning of the system as a whole, it is also necessary to apply tests evaluating cognitive functioning.

The tests act as functional loads that can independently modulate either the blood circulatory system or the CSF system. Temporary changes in the selected system evoked by the functional test enable the evaluation of the role that a specific element plays in the investigated parameter. For example, changes in the conditions of outflow from the cranium, brought about by an increase in central venous blood pressure, enable the evaluation of the role that intravenous pressure plays in shaping the dynamic components of CC. Temporary changes in mean ICP also allow for the evaluation of the role that this factor plays in forming CC. An important principle is that the effect of the functional test
should be reversible, and that it does not elicit too large a change in the functioning of the system under investigation, i.e. the changes evoked by the functional test should not exceed the normal physiological ranges for that system.

In these investigations of the interaction between the CV and CSF systems a number of functional tests were used. To assess the reactivity of the cerebrovascular system, we compared patterns of pulse waves, recorded under different physiological conditions, i.e. during a phase of deep inspiration, which leads to a decrease in cerebral venous blood pressure, with those recorded during a phase of deep expiration, which leads to an increase in cerebral venous blood pressure. Evaluation of changes in CC during these phases of inspiration and expiration enables one to estimate the contribution that the volume of venous blood inside the cranium makes to the level of CC.

If one compares pulsations recorded after 25 - 30s of respiratory arrest with recordings taken in rest conditions, it is possible to evaluate the role of increasing intracranial arterial volume. This functional test is accompanied by a rapid decrease in oxygen availability in the brain tissues, and consequently by an increase in the brain blood flow, due to dilation of the brain blood vessels. After stopping respiratory arrest, cortical oxygen increases with a very short latency - less than 1s - and blood flow also increases with a latency of 1 - 3s (based upon an acute experiment with rats).
In contrast to the respiratory-arrest test, the hyper-ventilation test is accompanied by a constriction of the brain blood vessels due to the removal of carbon dioxide from the blood which allows for the increased mobility of CSF. The hyper-ventilation test is of particular significance when considering the possible effects of yogic respiratory exercises on cranial compliance and cerebral circulation.

To assess the reactivity of the CSF system, we apply the Stookey test. This involves pressing on the stomach region to increase spinal CSF pressure, which leads to an increase in cranial CSF volume. This enables the evaluation of the contribution that intracranial CSF volume makes to forming the level of CC. As well as increasing intracranial CSF volume, the Stookey test also leads to an increase in ICP.
The principle of the Stookey functional test.

The application of these functional tests enables the observation of deficiencies that are invisible at rest. It is possible that at rest CC components will look close to normal, but application of functional tests could expose limitations in an individual’s CC. Maximal inspiration and maximal expiration bring about changes in cranial venous blood volume, i.e. inspiration decreases and expiration increases cranial venous blood volume. If there is a significant difference in cranial venous blood volume at the end of deep inspiration compared to the end of deep expiration, this suggests that the intracranial volume has become comparatively smaller.

Similar insights can be gained from the respiratory arrest functional test. After 10s arrest, there is significant vaso-dilation of brain blood vessels, and after 20s we observe a system-wide compensatory reaction, including an increase in stroke volume (the amount of blood leaving the heart with
each heart-beat), and an increase in central arterial pressure. There are also increases in intra-cranial pulse changes in blood volume. In order to test the robustness of the system’s capability to respond to environmental stresses, it was therefore necessary to select for analysis a cardiac cycle of between 12 - 18s after the beginning of respiratory arrest. As the graphs below show, functional tests can bring about significant changes in each of the components of CC, which can indicate some limitation of the cranial system which is not evident under rest conditions.

Fig. 21 An example of how deficits in CC components, which are “invisible” at rest are exposed by using functional tests. The resting value (at inspiration) of the CC components are close to normal, but decrease un-
der the action of the different functional tests. This indicates that the values of the indices CCe, CCc and CCo vary in accordance with the differing physiological conditions of real-life situations, associated with changes of central venous pressure (inspiration, expiration phases and Stookey test) and with changes in the tone of brain arterial vessels – dilation during respiratory arrest and constriction during hyperventilation.

The Stookey functional test can be particularly informative, as it increases mean ICP by directing extra CSF towards the cranium, and so provides useful insights into the pressure/volume relationships that determine CC. In the figure above, both CCe and CCc are decreased during the Stookey test, but the comparative value of their decrease depends upon the conductivity of CSF in the spinal pathways. The Stookey test can therefore reveal any vertebral column dysfunction that might be present.

It has long been known that the internal pressure changes that accompany breathing play a significant role in the processes that drive the evacuation of blood from the cranium. This raises the possibility that exercises which involve focused breathing, such as Yoga, could play an important part in the activation of CSF dynamics. Initial insights into this possibility come from the hyperventilation functional test. Hyperventilation leads to an increase of volume capabilities in the cranium due to the constriction of the brain arterial system as a response to a decrease in the concentration of carbon dioxide in the blood.

The evaluation of slow fluctuations, as was mentioned above, is based on the analysis of the REG recordings, using the analogue-digital converter PowerLab-4 programme, which is included in the MM instrumental complex. By considering the maximal frequency of slow fluctuations, it is possible to determine which control mechanism is dominant in a particular situation. If the maximal frequency of the spectrum is low, e.g. 6 - 7 cycles/min., it indicates that the control processes responsible for maintaining the osmotic balance in the brain tissue are comparatively
more active. So under these circumstances the water control process is the most significant driver of slow fluctuations and may be accompanied by an increase in brain tissue hydration. On the other hand, if the main amplitude of REG slow fluctuations is high, e.g. 9+ cycles/min., it may be related to an increase of brain metabolic processes. However, in order to be able to carry out this type of analysis, it is necessary to receive at least 50 - 70s of continuous REG recording without any interferences or artefacts, which is by no means easy to achieve under normal research conditions.

![Graph showing changes in amplitude and frequency of spectral components of slow intracranial fluctuation]

**Fig. 22** Changes in the amplitude and frequency of spectral components of slow intracranial fluctuation may reflect insufficiencies of brain functioning in patients with disturbances of cognitive capability due to ageing dementia.
Thus, the method presented here makes possible the evaluation of the indices that reflect different aspects of functioning of the cerebrovascular and CSF systems, as well as the biomechanical properties of the skull. These indices could reveal the current state and changes in functioning of this complicated physiological system.

6. USING THE PROGNOSIS-1 METHOD TO EVALUATE COGNITIVE FUNCTIONING

Assessing the relationship between cognitive functioning and the cerebral metabolic support system is a particularly important focus of modern neurophysiology. It is also a particular focus of the present study, as the ultimate functional goal of this system is to support cognitive functioning, as was emphasized above. For this reason, as part of our psycho-physiological investigations, particularly with regard to age-related changes in this functioning, we included certain cognitive tests as part of the investigation’s methodology.

After analysing numerous psycho-physiological methods for the assessment of the quality of brain functioning, we selected the Prognosis-1 method, which is based upon the prediction of elements in a sequence. This method was developed at the Biological Faculty of Moscow State University. It is based upon special card sequences that are to be held in short-term memory. In combination with the computer-aided analysis of the results, it is possible to assess the prognostic capability and working memory of the test subject. The test involves predicting the order of two symbols ("A" and "B"), alternated in symmetric (ABBA) and asymmetric (ABAB, BABBA) regular sequences. After the end of all sets, participants have to repeat the order of symbols in each of three sequences.
Based on the results of this test, participants were divided into two groups: 1- adequate predictors (AP), and 2- inadequate predictors (IP) (i.e. having prognosis difficulties). The AP group displays rapid prognosis and the correct reproduction of the symbol sequences in all three sets. In neuropsychological terms, human prognostic activity requires the co-ordinated activity of multiple brain areas. The extent and nature of this co-ordinated activity was tested by using dynamic electro-cortical activity, which is based on EEG recordings and directly reflects changes in brain functioning. It is important also to check the reaction of some vegetative functions, as well as orienting reaction and changes in the conditions of solving choice-problem situations during the test procedure.

By taking into account the number of mistakes made during the testing procedure, we can categorise the tests into three groups, which vary in terms of the difficulty in the prediction of results and the recognition of the test cards. This method enables the categorisation of participants into a number of groups, based upon the number of mistakes made. Results of the testing are indicative of the level of cognitive functioning, which in turn can be indicative of the quality of cerebral metabolic supply. For example, the decrease of CCe and CCc indices for middle age groups (age 45 – 55 years) corresponds to an increase in mistakes during the prognosis test. Similar correlations between a decline in cranial compliance levels and worsening results on the Prognosis-1 test have been observed in elderly individuals with neurologically identified cerebrovascular insufficiency. It is important to underline that the effective prognosis of events appearing in the subject's sensory field is provided through integrated brain activity, in combination with the effective realization of trace formation processes in the brain. It is significant that the correlations discovered by the use of this method allow us to consider the qualitative and quantitative indices of the neuropsychological mechanisms underlying human intellect.
Therefore, this method can be used for the general evaluation of the quality of the control processes supporting the circulatory-metabolic supply of brain activity.

**Summary of Chapter II**

This chapter has described the complex ‘system’ analysis that the Moskalenko Method comprises, and that has been the basis for most of the investigations described within this document. As well as describing the MM, this chapter also included a description of how the MM can be applied to investigating the important concept of cranial compliance, a subject that has only recently caught the attention of researchers using MRI technology. In contrast to MRI, however, the MM provides a much more accessible means of measuring the dynamic indices of cranial compliance, making it suitable for a wider range of applications. An important feature of the MM is the use of certain functional tests, which modulate the cerebrovascular and the cerebrospinal fluid systems independently, depending on the test applied. These tests simulate the effects of the kinds of environmental stresses that we face every day, and so enable an assessment of how capable our cranial systems are of responding to such stresses. Finally, the MM also includes a test of the system in terms of its ultimate purpose: to support cerebral metabolism and therefore cognitive functioning. Through such a comprehensive and holistic approach it is possible realistically to investigate such a complex system.
CHAPTER III

CHANGES IN CRANIAL COMPLIANCE UNDER DIFFERENT PHYSIOLOGICAL AND PATHO-PHYSIOLOGICAL CONDITIONS, INCLUDING CRANIOTOMY

Having described the Moskalenko Method, the present chapter will focus on some of the investigations that we have carried out using the described methodology. These highlight the potential medical applications of the MM. The investigations focus on how CC changes as we age; on the correlation between diminished CC, dementia and a range of neurological and psychological deficits; and on what can be done to restore diminished CC.

1. CHANGING OF CRANIAL BIOMECHANICS AND CSF MOBILITY WITH AGE

The cranial compliance model and the methods described above have been the basis for the investigations conducted over the last three years, whose results are described below. Using these technologies to record and analyze data from a wide range of age-groups, (25 - 85 years old, N = 120), has enabled us to establish standard physiological parameters for the indices of cranial compliance across the healthy population (CCe 0.8 - 1.1, CCc 0.25 - 0.45, and CCo 1.5 -2.5), and further to correlate these indices with indices of cognitive functioning. Special investigations were carried out with children (8 - 15 years old, N = 45), who have exceptional features in the functioning of the CBF and CSF systems due to the increased mobility of their youthful skull-bones. Therefore the data of these children have not been included in the statistical analysis of the
adult groups. If an individual’s cranial compliance results are less than the lower values for their age range, it can be an indication of some cerebral circulatory insufficiency. Despite this, the decrease in brain blood flow, which is a natural part of the ageing process, does not, in and of itself, lead to a significant decline in brain cognitive function if the indices of CC components are within their normal ranges. However, if there is a decline in CCe and CCc beyond the normal range, our investigations have revealed that this is significantly correlated with a decline in cognitive functioning. This is a new finding, which highlights how CC measures the cranial system’s ability to respond to the demands placed upon it, and is therefore of great significance in terms of assessing the health of an individual’s cerebral metabolic support system.

![Graph showing the normal age-related decline in cerebral blood flow, not necessarily associated with a decline in cognitive functioning.](image)

The decrease of CBF with age is accompanied by an increase in CSF mobility. Cranial compliance of a healthy person increases after middle age (45 – 50 years). Therefore, the interrelation of the compo-
nents of CC (C.Ct, CCc and C.Co) also changes with age, and is determined by the comparative skull-bone mobility, by the degree of atrophy of brain cells, by CSF movements and by age-dependent structural changes of the walls of the brain blood vessels. These age-related changes of C.Ct are shown below:

![Fig. 24 Averaged changes of C.Ct for different age groups, showing the decline in C.Ct in the middle-aged group.](image)

Both C.Ct and CCc change with age, as can be observed from pulse pattern analysis of the comparative values of the interval between TCD-REG peaks and by the values of the square of the two-dimensional TCD-REG diagram. These indices are represented at the top of Fig. 25.
As can be seen from Fig. 25, for children below 10 years old, the index derived from the time interval between the TCD and REG peaks is negative. This means that the pulse volume has been completely accepted into the cranium before maximal arterial pulse pressure has been reached. Between the ages of 10 – 15 years, results are characterized by short periods between TCD - REG peaks, with considerable variation between individuals. Then, from 16 – 20 years, the index is definitively positive. These changes reflect the increasing significance of compensatory CSF movements (CCc) to cranial compliance, in part due to the decreasing flexibility of the skull as we age and, as a consequence, the decreasing contribution of CCe to cranial compliance as a whole. As the CC components are interdependent in healthy subjects, a decline in CCe should result in a compensatory increase in CCc.
A significant trend revealed by this index is that, after continuing to rise from the age of 16 onwards, there is, on average, a slight decrease in CCc that occurs some time between 40 - 50 years of age. This decline is also observable in Fig. 24. The important point here is that these data are indicative of a reduction in CCe and CCc that reflects a decrease in cranial elasticity and CSF compensatory movements. This indicates a reduction in the volume capabilities of the cranial system. Moreover, these declines are correlated with a decrease in mental functions and other neurological symptoms that occur in this same age group (40 – 50 years). The decline in the indices, as well as changes in CCe and CCc from middle age onwards, correspond closely to the results of other researchers, who have found that mild cognitive dysfunction starting around this age occurs against a backdrop of slow neural atrophy in the cortex. This trend is highly significant as it indicates that this middle-aged group can have problems with compensatory fluid displacements, and thus is at an increased risk of developing cerebrovascular insufficiency. It is important to take into account that with diminished CCe and CCc there is a decline in the movement of CSF and thus a reduced removal of waste products. This deficiency is included in the term cerebrovascular insufficiency. Cerebrovascular insufficiency, therefore, reflects a range of problems, including biomechanical problems with the cranium, vascular problems of blood supply, and CSF-related problems with the removal of waste products. To our knowledge, this is the first empirical demonstration of a connection between middle-aged mental decline and a decline in cranial compliance. We are investigating a variety of possible interventions to restore diminished CC, and thereby to improve cerebral circulation.

Investigations were conducted to ascertain any relation between changes in CC and cognition in an older population, through the comparative investigation of thirty-nine subjects aged from 70 to 84 years of age, who had been divided into four groups on the basis of the results of psycho-physiological testing using
the “Prognosis-1” method, which enables an objective evaluation of the level of cognitive disturbance. The first group consisted of subjects whose cognitive results were in the normal range (N = 11), the second group displayed initial signs of dementia (N = 10), the third group displayed moderate dementia (N = 9), and the fourth group had pronounced dementia (N = 9) (as shown in Figs. 25 and 26). The index of CCe decreased progressively across these groups by up to 40% at rest conditions, in direct correlation to declining cognitive capability. Moreover, decreased CCe was accompanied by decreased CCc. This means that dementia in the ageing population has a direct connection to a decline in both CCe and CCc indices. This serves to highlight how age-related declines in CC and in cognitive functioning can both be related to the biomechanical properties of the cranial system. Again, the linear velocity of blood flow showed little correlation with declines in CCe indices or in levels of cognitive disturbances (Figs. 26 and 27).

![Graph showing decreases in cognitive functioning](image)

**Fig. 26** This graph shows how declines in cognitive functioning (as determined by the Prognosis-1 test) are significantly correlated with declines in the indices of CCe at rest and in response to functional tests.
In addition to CCe, declines in cognitive functioning are also correlated with a diminution of CCc. However, there appears to be no correlation between cognitive ability and the rate of blood flow in the middle cerebral artery (MCA), or with CVR (in response to respiratory arrest) (Fig. 27)

![Fig. 27 This graph demonstrates significant changes in CBF, CVR (for respiratory arrest) and CCc indices with a decrease in cognitive functioning.](image)

Analysis of the responses to the functional tests enabled the evaluation of the comparative contributions to the level of CCe of the different liquid media within the cranium. It is interesting that the value of CCe is determined by the incompressible volume within the cranium, and by the volume of CSF, which does not decrease under any condition. This incompressible volume is composed of the brain tissue volume and the volumes of the liquid components inside the cranium. This is demonstrated in Fig. 28, which shows that while the comparative changes of the responses to different functional tests are connected with changes in the liquid components inside the skull (arterial, venous blood and CSF),
nonetheless the comparative levels of CCe remain nearly the same. Because the comparative donations of liquid media (arterial and venous blood and CSF) do not depend on the CCe level – their comparative value is nearly the same when CCe decreases - this means that the volumes of liquid media inside the cranium do not play a role in forming CCe during the development of dementia. Indeed, it has previously been observed that the principal component of CCe is cranial bio-mechanics (about 90% for people in this age range), and that the other components account for about 9 - 10%, as is shown in Fig. 28.

![Graph showing the contribution of compensatory fluid movements to CCe as a whole.](image)

**Fig. 28** Graph showing the contribution of compensatory fluid movements to CCe as a whole. The left scale shows CCe values as calculated from the original data, the right scale shows the total comparative changes of CCe during functional tests – the difference between the value of CCe at rest and during the functional tests, related to the total value of CCe at rest. Colour segments display the comparative values of the relative contribution of particular factors – blue: difference between maximal inspiration and expiration, which shows the role of changes in venous volume in the cranium; yellow: data obtained during Stookey test, which show the change in volume of CSF inside the cranium; and red: the reaction to respiratory arrest, which changes the volume of arterial blood in the cranium.

The contributions of the liquid components inside the cranium are comparatively small, and are roughly equivalent (9 - 10%)
across all the experimental groups. Additionally, the role played by the volume of venous blood and CSF diminishes in relation to the severity of dementia.

These findings have important public health implications. Monitoring CCe and CCc can serve as a new diagnostic tool on which to base pre-emptive interventions for those whose declining CCe and CCc indices have identified them as being at risk of developing cognitive problems later in life. The use of cranial compliance as a model of cerebral circulation, together with the method of analysis described in this document, might mitigate some of the predicted social costs of an ever more elderly population, by enabling better diagnoses and the application of pre-emptive interventions to limit cognitive dysfunction.

As well as age-related disorders, the physiological origin of conditions such as decreased working capability, concentration deficits, headaches, depression and hyperactivity have, until now, been difficult to establish by routine medical examinations, but have been hypothetically linked to cerebral insufficiency, as has been an increased risk of strokes. The MM could easily be included in routine medical examinations, and so be used to test the association between cranial compliance, conditions of cerebral insufficiency and various pathological conditions. Further studies should be focused on the study of the relation of CC to the above-mentioned symptoms.

2. **CRANIOTOMY AS A MEANS OF INFLUENCING CRANIAL COMPLIANCE**

Given the link between diminished CC and various pathological conditions, it is vitally important to learn more about how we can restore, or prevent diminished CC. Our investigation has already established that it is possible to decrease cerebral insufficiency by modulating CC through certain physical means. However, in all cases it must first be determined that the cerebral insufficiency is due to decreased CC and not to arteriosclerosis, which also leads to a reduction in steady state brain blood flow. This distinction can be easily and inexpensively
made using the functional tests described previously. The tests determine if the brain arteries are able to respond to normal regulatory stimuli, such as carbon dioxide overloading (hypercapnia) or oxygen overloading (hyperoxia). When the responses to these tests, i.e. cerebrovascular reactivity, are within the normal ranges, it means that the vessels are not blocked with plaque. After eliminating arteriosclerosis as a cause, any cerebral insufficiency noted can be due to a lack of elasticity in the cranial system. This lack of elasticity can be addressed - special procedures may be taken to enhance brain blood circulation, that also significantly affects the pattern and extent of circulation of CSF.

Our research has shown that trepanation, the removal of a piece of bone from the skull, practiced since pre-history, can be an effective means of restoring the elasticity of the cranial system. Making an opening in the cranium dramatically increases the indices of CCe. This significant increase in CCe after trepanation is based upon the increased potential of the cranial system to expand in response to rapid increases of ICP. The membranes surrounding the brain are able to expand against the space created by the craniotomy with the force of each heart-beat.

**Fig. 29** Averaged CCe values before and after trepanation. Changes in the biomechanical elasticity of the skull allow the cranium to accept additional blood with each pulse stroke.
This change in CCe is mostly due to the change in cranial biomechanics, although some of it comes from changes to the liquid media. However, the percentage contribution of the different liquid media to CCe is preserved at the same level as that prior to trepanation, although the results of the functional tests showed that the relative contributions of the arterial blood, venous blood and CSF should change. It is also significant that, although the absolute values for the contributions of the liquid components to CCe before and after trepanation are different, the comparative (percentage) value remains the same at around 27%.

![Diagram showing contributions of skull and liquid components to CCe before and after trepanation.](image)

**Fig. 30** The contribution of the skull biomechanics to the value of CCe increased by about 50% after trepanation. The total percentage contribution of the fluids to CCe remained unchanged, although their individual contributions varied considerably.

Making a skull opening also contributes significantly to the CSF mobility during the CCc interval. It has already been demonstrated using cine-phase contrast MRI and using MRI (signal void phenomena) that a skull opening allows CSF to move more freely
throughout all the compartments of the cranial system. Our research confirms these findings. An opening in the skull-bone allows for a partial redistribution of the CSF movement from between the ventricles and the spinal sac in the intact skull to between the ventricles and the sub-arachnoid space in the trepanned skull. Looking back to Fig. 4 (showing penetration of CSF through the brain tissue and the location of the arachnoid villi) it can be understood that active movement of CSF between the ventricles and the sub-arachnoid space plays an important role in the cleansing of the brain tissue and in the elimination of waste products via the arachnoid villi.

![Fig. 31 Comparative changes in CSF dynamics as a result of cranial trepanation. Brown arrows indicate the predominant direction of CSF mobility. It should be noted that more CSF is circulating within the cranium than between the cranium and the spinal sac after trepanation, thereby improving the removal of the waste products of metabolism.](image)

It is possible to determine the predominant direction of CSF circulation by observing some characteristics of the $\Delta V/\Delta P$ (change of volume : change of pressure) relationship that take place during
the CCc interval (when CSF compensations are taking place). After
the pulse pressure has reached its maximum (beginning of CCc inter-
val), blood volume is no longer increasing, so any increases in fluid
conductivity are due to CSF movement between the ventricles and the
sub-arachnoid space—the signal increases because the most conduc-
tive fluid moves from the interior to the surface of the brain. The more
significant the increase of conductivity, the more predominant the
intracranial CSF movement. Conversely, when there is little increase
of fluid conductivity after the maximum pulse pressure, this means
that CSF is more predominantly tending to translocate down the spi-
nal column. Changes in the predominant direction of CSF movement
can be evaluated by the relative increase of conductivity. However, a
lack of any increased conductivity whatsoever is indicative of the lack
of possibility for intracranial volume processes to occur. A potential
reason for this may be the changes in volume processes in the brain
tissue, brought about, for example, by a brain tumour. Thus, a de-
crease of CSF mobility may indicate some underlying pathology and
indicate a need for further investigation using MRI, and for possible
surgical intervention. Such data highlight another potential advantage
of the MM in indicating abnormal volume processes inside the cra-
nium.

As a result of trepanation, the response to functional tests in the
investigation of CCc shows that the range of changes in venous blood
volume inside the cranium increases by about 30% following trepana-
tion. This is indicated both by a more pronounced response to respira-
tory arrest, and also by a reduced response to the Stookey test. This
means that volume capabilities inside the cranium definitely increase
after trepanation and that, after trepanation, responses to the Stookey
test can be analysed to test for some disturbance in CSF cranial/spinal
circulation, which may be mechanical in origin, e.g. vertebral column
deformation.
Fig. 32 Changes (M±SD,n=15) in CSF mobility (reflecting changes in CCc) as shown by different functional tests before and after trepanation. The graph shows the increase in cranial volume reserves after trepanation.

This data demonstrating the effects of trepanation was additionally confirmed by observing how the pulse amplitude fluctuates with the phase of the respiratory cycle both before and after trepanation. If, before trepanation, the pulse volume of blood accepted into the cranium was significantly related to the phase of the respiratory cycle, (a relationship that indicates reduced cranial volume capabilities), this relation disappeared following trepanation - i.e. respiratory changes were no longer a limiting factor on the volume of blood that can be accepted by the cranium. These observations have therefore highlighted a further possible diagnostic tool for assessing the health of the cranial system: observation of whether the phase of the respiratory cycle is a significant determinant of the amplitude of intracranial volume. Our research has also indicated that trepanation might prove to be a suitable means of restoring normal volume capabilities to the cranial system.
Fig. 33  This recording indicates how the changes in the volume inside the cranium during respiratory chest movements after cranial trepanation are due to an activation of CSF movements, reflecting an increase in intra-cranial volume capabilities. When the volume capabilities inside the cranium are restricted, pulse amplitude does not change with respiratory fluctuations. After trepanation however, when this restriction disappears, it is immediately reflected by changes in the amplitude of the pulse fluctuations during the respiratory cycle – making them independent of the changes of respiratory intracranial blood volume fluctuations.

Importantly, these investigations have established that the increased elasticity produced by a 4 cm² opening in the skull does not cause the normal limits of cerebral blood flow to be exceeded. In other words, cranial openings of this size are safe in that their effects do not exceed the upper limits of blood flow of 60 ml/minute/100gms of brain tissue.
Fig. 34 Changes of blood flow in MCA and the pulsatile index after trepanation. At rest the blood flow in the trepanned skull is somewhat increased and PI (or peripheral resistance) is lessened.

During respiratory arrest, the arterial dilation is somewhat reduced in the trepanned skull, and the peripheral resistance - the resistance of the cerebrovascular tree (Pi) - is also somewhat reduced. During the Stookey test, when CSF is being pushed from the spinal sac back into the cranial cavity, the blood flow in the trepanned skull responded more directly than in the intact skull.

Trepanation also had a significant effect on cerebral blood flow (CBF), measured by TCD. An important caveat with regard to these changes in CBF is that there was a great variety in individual results. This meant that there were no statistically significant changes in CBF before and after trepanation. However, analysis of the individual responses to trepanation has shown that if CBF was within normal ranges before trepanation, then it did not change after trepanation. But if CBF was below normal before trepanation, then it increased afterwards. It is possible to understand this phenomenon by considering the activity of the mechanism of auto-regulation of
CBF, which maintains CBF and central arterial pressure (CAP) at the optimal level for any particular situation (CBF approximately at 50 – 60 ml/100 gm/min and CAP at approximately 120 mmHg). If CBF was normal before the intervention, then its initial increase following trepanation is brought back to normal levels by the above-mentioned mechanism. However, if CBF was below normal before trepanation, then a skull opening can bring the CBF back to a normal level. This is a highly significant point and indicates that trepanation offers an effective means of restoring CBF in such individuals. Additionally, these data illustrate an important shortcoming concerning the use of statistical analysis. In this particular case, if our conclusions were based only on simple statistical analysis, this important finding would be lost.

Use of spectral analysis of the REG recording, during approximately one minute of non-stop recording without interferences, shows that the slow fluctuations related to the oxygen and water balancing dynamic were altered positively after cranial trepanation.

**Fig. 35** Spectral analysis shows that after trepanation the frequency of intracranial slow fluctuations increased to normal limits and their amplitude increased. It means that after trepanation the level of intracranial pressure decreased and CSF-mobility increased.
Given these effects of trepanation on the cranial system, it is of great importance to neurosurgeons that some comparative data is collected in order for them to assess when a skull opening should be closed following neurosurgery. Currently, every surgeon decides this question by following his own experience. However the data presented above now provide the possibility that this decision be made more objectively. The data presented also show that, in some selected cases, when CCe and CCc are low, trepanation may be a useful tool in increasing the compensatory capabilities of the cranium.

**Fig. 36** As can be seen after trepanation, both CCe and CCc increase, but after closing the opening both decrease. This means that leaving the hole in the cranium open after surgery can play a protective role (compare upper and lower pictures on the right). Changes in CCe and CCc after closing the hole in the cranium show that intracranial CBF and CSF mobility have adapted to the conditions brought about by the open cranium, and decrease after the reconstruction of the cranial bone.

It is possible to see that after neurosurgery, with the consequent open trepanation hole, CCe and CCc significantly increase.
Closing of the hole after a certain period of time, after the patient has recovered from all the consequences of neurosurgery, is accompanied by some decrease in CCe and CCc, but this decrease is not dangerous for the recovered brain. However, if the hole is closed immediately after brain surgery, particularly for operations to relieve brain edema, it can have a negative effect on brain function due to an increase in ICP, which can require surgical correction in some cases. Not surprisingly, in a survey conducted more than sixty years ago, which reviewed the outcome of neurosurgical interventions on Russian soldiers who had sustained battlefield head traumas, it was reported that those patients whose skulls were not closed after surgery had the highest level of recovery.

Investigations of the effects of trepanation have revealed the new and very interesting possibility of asymmetry in the indices of CCe and CCc between the hemispheres. This asymmetry is significantly greater in trepanned individuals compared with untreated, healthy participants. This asymmetry is observed as a relative increase in the dynamic component of cranial compliance (CCe) and a decrease in CSF-mobility (CCc) compared with the intact hemisphere. The level of asymmetry depends upon the size and locality of the cranial opening. In the case of a lateral opening of 3 - 5 cm², CCe and CCc indices differ by up to 7 - 10% for the trepanned side. If the opening is larger, for instance up to 15 - 20 cm², the asymmetry in CCe and CCc indices may be very significant as is shown on Fig. 37.
Fig. 37 Asymmetry in CCe, CCc and 1/h indices, observed with a patient who was injured in 1996, and whose consequent cranial opening has been preserved up to the present time. Cranial opening localised on the right temporal bone, about 18 cm² in area.

This property of asymmetric CSF movements between the two hemispheres is particularly prominent over short periods of time – i.e. a single cardiac cycle. What it reveals is the effect of some hydrodynamic resistance to CSF movements between hemispheres, which might be significant for some pathological conditions. However, the time parameters of this resistance are unknown at the present time. This new finding on hemispheric asymmetry needs to be the subject of special investigations, in particular of the time-course over which it operates, and of what its physical basis is. The bi-hemispheric recordings on this particular subject also reveal that even after an extensive healing period a skull opening of such size retains significant elastic properties.
3. EVALUATION OF THE RESULTS OF OSTEOPATHIC TREATMENT

Trepanation is not the only possible means of increasing the volume capabilities of the cranium. One alternative intervention is cranial osteopathy, and particularly the technique of manipulating the 3\textsuperscript{rd} ventricle, a technique labelled “the drainage of venous sinuses”, which is known as the “king” of cranial osteopathic techniques. However, the real physiological mechanism of this technique is more complicated than its name suggests. This technique has recently been shown significantly to increase CCe. Observations of the effect of osteopathic treatment, especially with children suffering the consequences of brain injury such as can occur during child birth, show that such injuries may be effectively corrected by applications of some osteopathic techniques.

Through the analysis of TCD and REG recordings it is possible to demonstrate the results of osteopathic treatment, which are usually invisible. For instance, using the MM it was possible to see the results of the application of the “venous sinus drainage” osteopathic technique to a boy of 11 years of age who had suffered brain injury, which was manifested in regular headaches. After treatment the clinical symptoms were significantly diminished.
Fig. 38 The increase in CCe, CCc and CCo after 10 minutes of application of osteopathic Technique "Drainage of venous sinuses".

From these findings it is possible to hypothesise that the application of some osteopathic techniques in the cranial field may have an effect similar to trepanation. This indicates osteopathy as a possible treatment for people in the middle age group (45 – 55 years of age) who have experienced a decrease in CCe and CCc. It is also possible that osteopathic treatment may be effective for patients after neurosurgery, especially for those whose surgical openings have been prematurely closed. In order to investigate these hypotheses, it would be necessary to determine more precisely the changes in CCe and CCc brought about by osteopathy using the ‘Moskalenko Method’.

A further finding of interest with regard to interventions to restore cranial compliance comes from our preliminary data showing changes in CCe and CCc after 30 seconds
of deep inspiration and deep expiration (hyperventilation), at the same rhythm as normal respiration. It was found that 10 - 20 seconds after hyperventilation, CCe increased by 23% and CCc increased by 26%. This can be taken as a very tentative model for the effects of yogic breathing, and indicates that the effect of yoga on cranial compliance and on cerebral circulation merits further research. Indeed, it gives rise to the possibility that yoga could be useful for persons with decreased cranial volume capabilities. This is an area of investigation that we are extending and expanding, as it holds promise for the treatment of middle-aged patients with symptoms of circulatory insufficiency.

4. ADAPTATIONS FOR DIVING

Investigations under different physiological conditions, specifically if the person investigated is already adapted for this particular condition, can give valuable information concerning the plasticity of the system responsible for circulatory-metabolic supply of brain functioning. An example of such a case may be found in training for diving, which is accompanied by an oxygen deficit to the brain tissue and, as a result, adaptation to these conditions. To investigate this problem 14 young (19 - 22 years old) participants were studied, using a technique to simulate diving training, which included not only respiratory arrest, but also cooling the face by application of a cold wet towel.

This investigation has shown that the adaptation of these individuals to this functional load is reflected in a distinct pattern in the REG – TCD data: the time difference between maximal values of REG and TCD pulse, are approximately twice as long in the diving group as for control
groups of the same age. Significantly, the initial changes for respiratory arrest in REG – TCD pulse patterns emerge earlier than in control groups of the same age with no diving experience. These facts indicate that certain adaptations for diving can be observed during resting conditions. Changes in the values of CCe and CCc during diving simulation are shown below:

Figure 39 shows that changes of CCe and CCc go in opposite directions during diving simulation. This indicates that training for hypoxia has taken place. Some decreases of CCe can be explained by the increase in intracranial blood volume due to arterial vasodilatation in response to hypercapnia. However, this effect is compensated for by an increase in CCc. The adaptation for diving involves the development of a special mechanism that supports the brain’s metabolic supply by significantly increasing CSF mobility to compensate for the process of circulatory deficit in the brain tissue during diving. This example demonstrates the
high compensatory capabilities of the mechanism responsible for the brain’s circulatory metabolic supply, and its high plasticity. This is not particular to certain individuals, but is universal, and may be enhanced as a result of specialized training.

**Summary of Chapter III**

The materials presented in this chapter have demonstrated that there are a number of ways for restoring diminished CC components – CCe and CCc. Furthermore, it has shown that it is possible to obtain stable and beneficial results from cranial trepanation, and this may prove to be a useful intervention for middle-aged patients with cerebrovascular insufficiency. We will continue to investigate the possible application of osteopathic treatment and yogic respiratory exercises to counteract the age-related decline in cranial compliance. Although yogic breathing is mentioned last, this is only because we currently have the least data on its effects. Although our research into this is at a very preliminary stage, the data we have received so far makes us sufficiently optimistic to continue this avenue of research.
CONCLUSIONS

The research thus far has produced the following outcomes:

1) The development of a unique method of non-invasively obtaining new data about the working of the cerebral circulatory system, named the Moskalenko Method.

2) The development of a new systemic understanding of the dynamic interrelation of the three inter-dependent systems which together determine cerebral circulation and the health of the brain.

3) New data indicating the importance of cranial compliance in assessing changes in intra-cranial circulation and its direct effect on cognitive functioning.

4) The discovery of important new information about age-related declines in cerebral sufficiency and mental functioning around middle age, and a direct correlation between declines in cranial compliance and progressively worsening symptoms of dementia.

5) The development of possible pre-emptive interventions and treatments for declining cerebral circulation, and means to assess their effectiveness.

6) The first physiological explanation of the effects of trepanation, i.e. increased elasticity of the cranium that brings with it some significant changes of cerebral circulation.

7) The investigation of other methods of counteracting deteriorating indices of cranial compliance, such as yogic deep breathing, extreme exercise and cranial osteopathy.
8) The way forward:

a. Developing the ‘Moskalenko Method’ for easy diagnosis of cranial compliance levels across the population to help diagnose and treat age-related cerebral insufficiencies. This will be achieved through developing automatic read-out analysis of the data provided.

b. Developing the ‘Moskalenko Method’ to provide a non-invasive means of monitoring and measuring intracranial pressure (ICP). Currently the only way to directly measure ICP is to make a cranial opening and insert a transducer into the brain. A non-invasive monitor of ICP will be an invaluable tool for the rapid diagnosis and treatment of life-threatening head injuries. By measuring ICP within the “Golden Hour” after an accident many more lives could be saved and permanent brain damage may be prevented.

C. Extending research into trepanation and other techniques of improving cranial compliance with the aim of optimizing cerebral functioning and wellbeing in both the afflicted and in the apparently healthy general population.
APPENDIX I

MEDICAL APPLICATIONS FOR THE MOSKALENKO METHOD

The data presented in this document illustrate that an understanding of cranial bio-mechanical properties and CSF mobility is critically important in order to inform the treatment of a number of medical problems that are connected with diseases of the cerebral circulatory system. A better understanding of the implications of the indices of CC is also vital when monitoring the results of treatment after serious brain injury and surgery. For all these cases, the ‘Moskalenko Method’ provides a convenient, comparatively simple and inexpensive method for diagnostic purposes, and for population screening for deficiencies in cerebral circulation.

It is also reasonable to take into account the possible effect of special respiratory exercises on CC. It is quite clear that our forefathers had some intuitive knowledge of this subject, illustrated by the observation that rhythmic Yogic breathing counteracts cerebral insufficiency by altering cranial compliance. We are currently developing a programme of investigation into the effects of yogic breathing on cranial compliance.

It is apparent that a number of invaluable new insights into healthy cerebral functioning have so far been discovered through the application of the ‘Moskalenko Method’, and that the scope for extending these findings and applying them to the diagnosis and treatment of age-related cerebral insufficiencies, such as dementia, offers great promise. The application of these insights will become increasingly crucial as the social costs of an ever more elderly population are felt. Furthermore, we are using this technology to investigate possible means with which such insufficiencies can also be prevented, as well as treated. By extending our understanding of the human brain system, we
might also learn how mental functioning can be influenced through interventions focussed on cerebral circulation.

The research findings reviewed in this document provide an up-to-date picture of our understanding of the mechanisms responsible for the brain’s metabolic supply, and have led to our developing an all-inclusive view-point of the system responsible for enabling cerebral activity and cognitive functioning. This functioning is dependent on a complex physiological mechanism, consisting not only of the cerebro-vascular system, but also of the CSF system and of the bio-mechanical properties of the cranium. Whilst numerous investigations have described the peculiarities of the functioning of brain blood vessels, there is much less data concerning the CSF system and how it interacts with the cerebro-vascular system, and even less on the role played by the biomechanics of the cranium.

Commonly used parameters may be correct for normal physiological conditions, but are not valid for numerous pathological conditions. It is therefore not only acceptable but advisable to use the quality of cognitive functioning, of the brain’s physiological mechanism, as a diagnostic factor in assessing the level of functioning of this complex system. Using this conceptualization, the studies here presented have focused on elucidating the hitherto uncertain roles played by the various components of this complex mechanism, namely, the functional roles of CC and CSF movements, and how these components contribute to the mechanism of circulatory-metabolic supply of the brain, or, more precisely, how they support its cognitive functioning.

Having identified the contribution of CSF movements to cerebral circulation, one of the most important directions of our current research is to determine how certain portions of CSF can become stagnant in pools of inactivity, and thus reduce cerebral circulation. This sluggish movement of CSF may be a contributing factor in the build up of beta-amyloid free radicals in the
brain tissue. Beta-amyloids are known to be involved in the development of Alzheimer’s disease. Our attention will therefore be directed specifically to how our methodology might demonstrate the capacity for changes in CCe and CCc, and thereby cause CSF more actively to wash out the toxic build-up of particles from the brain tissue.

Improving the diagnosis and treatment of age-related deteriorations in mental health is not the only medical application of this research. The physiological origin of conditions such as decreased working capability, concentration deficits, headaches, depression, hyperactivity and an increased risk of strokes have been hypothetically linked to cerebral insufficiency, but until now the origins of these have been difficult to establish by routine medical examinations. Therefore, further studies should also be focused on the study of CC in relation to these symptoms, as the Moskalenko Method could easily provide a means of routinely screening for such medical conditions.

The Moskalenko Method’s instrument complex is low-cost and portable, and so could readily be adapted for use in emergency situations to assess cerebral dynamics. A very urgent direction of our efforts, therefore, is to develop further the Moskalenko Method into a user-friendly package with automated read-out analysis. This should enable the rapid measurement of cerebral functioning, brain circulatory dynamics and intracranial pressure (ICP) at the scene of accidents or soon after. The development of a non-invasive monitor of ICP is the Holy Grail for head injury treatment, as it facilitates diagnosis and application of the appropriate intervention necessary to prevent brain trauma during the time-period known as the “Golden Hour”.

The “Golden Hour” refers to the first hour following an accident, during which any treatments applied have the greatest impact, so greatly increasing the chances of a patient making a full recovery. Head trauma is currently the greatest killer in
people aged 45 and under in the developed world, and in India alone accounts for many hundreds of thousands of deaths per year. Delays in evaluating intracranial dynamics following head injuries mean that many more people die or suffer permanent brain damage than would be the case if a portable means of evaluating intracranial dynamics were more readily available to ambulance crews and to mobile medical services. The Moskalenko Method can also be employed when access to expensive and immoveable brain-imaging technologies is limited, such as in remote locations, on the battlefield or in much of the developing world.

The most pressing directions of our continuing investigations are both to develop a non-invasive ICP monitor and also to chart in greater detail the age-related changes in intracranial dynamics. This latter includes determining more precisely at what age the elasticity of the cranial system begins to diminish, comparing the effectiveness of a variety of interventions to restore cranial compliance, and better determining how the indices of CCe and CCc can be used to diagnose the level of decline at which pre-emptive interventions to restore cranial compliance could be required. From the ageing perspective, the decrease in CCe between the ages of 40 and 50 deserves our special attention, and we plan further studies to build upon the numerous neurological observations already made. Preventing any circulatory and cognitive declines in this age group would have enormous social benefits, as people in this age group are of great value to society, having already gained a great deal of life-experience and still having time and energy before them to realize their mental potential.

The broad potential and benefits of this research mean that its continuation could prove vitally important, not only to those who are suffering a decline in cognitive ability with old age, but also to trauma patients with head injuries, to those in middle age who are suffering from a decline in mental functions due to cerebral insufficiency, and to those seeking to utilize these concepts of
fluid movement within their own brain for the purpose of reaching their optimal potential. To these ends, we greatly look forward to the continuation of this exciting research.
APPENDIX II

ARTICLES ARISING FROM THE RESEARCH

Articles for which we have an English translation can be found on the Beckley Foundation website: www.beckleyfoundation.org

1. “Age Related Peculiarities of Ratio of Parameters of Functioning of Hemo- and Liquorodynamics Systems.”
   ¹Moskalenko Yu.E., ¹Weinstein G.B, ²Halvorson P., ¹Riabchikova N.A.,
   ¹Kravchenko T.I.,
   ²Feilding A., ¹Panov A.A., ¹Semernia V.N., ¹Markovets S.P.
   ¹Sechenov Institute of Evolutionary Physiology and Biochemistry, Russian Acad. Sci.,
   St. Petersburg, Russia and ²Beckley Foundation, Oxford, U.K.
   Journal of Evolutionary Biochemistry and Physiology. 2006. v.42, No.6,

   Y. Moskalenko¹, W. Hachatryan², G. Weinstein¹, K. Samochernyh²,
   P.Halvorson³, A. Feilding³,
   N. Ryabchikova¹, A. Moskvin¹, A. Panov¹
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   St. Petersburg, Russia, ²Polenov Institute of Neurosurgery, St Petersburg, Russia,
   and ³Beckley Foundation, Oxford, U.K.
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   July 7-9, 2006.)
   Journal of Neurotrauma. 2006. v. 23, n.6, p.1000.
¹Moskalenko Yu.E., ¹Weinstein G.B., ²Halvorson P., ¹Ryabchikova N.A, ¹Kravchenko T.I.,
²Feilding A., ¹Semernia V.N., ¹Panov A.A., ¹Mayorova N.F., ¹Markovets S.P.
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St. Petersburg, Russia, and ²Beckley Foundation, Oxford, U.K.

¹Moskalenko YuE., ¹Weinstein GB., ²Halvorson P., ¹Kravchenko TI.,
²Feilding A.,
¹Riabchikova NA., ¹Semernia VN., ¹Panov AA.
¹Sechenov Institute of Evolutionary Physiology and Biochemistry Russian Acad. Sci. St.Petersburg, Russia, and ²Beckley Foundation, Oxford, U.K.

5. “Age Dependent Correlation between Cerebral Blood Circulation, Cerebrospinal Fluid Dynamics and the Cranial Compliance.”
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⁴Moscow State University, Moscow, Russia; and ⁵Beckley Foundation, Oxford, U.K.
(Proc. of the 6th European Congress of the Intern. Assoc. of Gerontology and Geriatrics “Healthy and active ageing for all Europeans”.
St.Petersburg, Russia, 2007). “Advances in Gerontology”. 2007. v.20, n.3,
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²Halvorson P.,
¹Ryabchikova N.A.
¹Sechenov Institute of Evolutionary Physiology and Biochemistry Russian Acad. Sci.,
St Petersburg, Russia, and ²Beckley Foundation, Oxford, U.K.

¹Moskalenko Yu.E., ¹Kravchenko T.I., ¹Weinstein G.B., ²Halvorson P.,
²Feilding A., ¹Mandara A, ¹Panov A.A., ¹Semernia V.N.
¹Sechenov Institute of Evolutionary Physiology and Biochemistry, Russian Acad. Sci.,
St Petersburg, Russia, and ²Beckley Foundation, Oxford, U.K.
Neurosci Behav Physiol 2009. v.39, No.4, p.377-381.

8. “Relationships between Indices of Cerebral Circulation, Liquorodynamics, Cranial Biomechanics and Prognostic Brain Ability.”
¹Moskalenko Yu., ¹Weinstein G., ²Ryabchikova N., ¹Kravchenko T.,
¹Samus N., Feilding A., Halvorson P., ¹Semernia V.
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¹Moskalenko Yu.E., ³Feilding A., ³Halvorson P., A. C., ²Mozhaev S.V., ¹Semernia V.N, ¹Weinstein G.B., ¹Kravchenko T.I., ²Medvedev S.V.
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¹Moskalenko Yu., ¹Weinstein G., ²Riabchikova N., ¹Kravchenko T.,
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http://www.beckleyfoundation.org/bib/doc/
12. "Liquorodynamic and hemodynamic effects of cranial trepanation."
¹Moskalenko Yu., ¹Weinstein G., ¹Kravchenko T., ²Mozhaev S., Riabchikova N., ³Feilding A., ³Halvorson P., ¹Semernia V., ¹Panov A., ²Medvedev S.
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13. “Relation of Age Cognitive Disorders with Cranial Compliance, Cerebrospinal Fluid Mobility and Cerebral Circulation.”
¹Moskalenko Y., ¹Weinstein G., ³Feilding A., ³Halvorson P., ²Riabchikova N., ¹Kravchenko T., ¹Panov A., ¹Semernia V.
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¹Moskalenko Y., ¹Weinstein G., ¹Semernia V., ¹Panov A., ²Riabchikova N., ¹Kravchenko T., ³Feilding A., ³Halvorson P.
¹Sechenov Institute of Evolutionary Physiology and Biochemistry Russian Acad. Sci., St. Petersburg, Russia; ²Department of Biology Lomonosov State University, Moscow, Russia; ³Beckley Foundation, Oxford, UK.

16. “Age peculiarities of relations between brain blood flow, liquorodynamics and biomechanical properties of the skull”.
Yu. Moskalenko¹, G. Weinstein¹, N. Riabchikova², T. Kravchenko¹, N. Samus³, P. Halvorson⁴, A. Feilding³, V. Semernia¹, A. Panov¹.
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17. “Relation of CBF, CSF Mobility and Skull Mechanics to Cognitive Brain Function in the Aged Persons”.

¹Moskalenko Yu, ¹Weinstein G., ²Riabchikova N., ¹Kravchenko T., ¹Samus N., ³Feilding A., ³Halvorson P., ¹Panov A., V. Semernia¹.
Sechenov Institute of Evolutionary Physiology and Biochemistry Russian Acad. Sci.,
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18. “Age Relations of Cerebral Blood Flow, Cerebrospinal Fluid Mobility and Cranial Compliance”.

¹Moskalenko Yu, ¹Weinstein G., ¹Kravchenko T., ¹Samus N., ²Riabchikova N., ¹Panov A., ¹Semernia V., ³Feilding A.³Halvorson P.
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