Ocular Diseases

Chapter 2

Color Vision and Normal Pressure Hydrocephalus

Anna Piro[1,*]*; Andrea Quattrone*[1]*; Aldo Quattrone*[1]

[1]*Institute of Neurology, Magna Graecia University, Catanzaro, Italy.*

[*]***Correspondence to: Anna Piro,*** *National Researches Council, Institute of Molecular Bioimaging and Physiology, Viale Europa, 88100 Germaneto (Catanzaro), Italy.*

Tel: +39-0-961 3695930; Email: anna.piro@cnr.it

1. Introduction

Color Vision

Neurosciences must changes the philosophy of mind, and to a great extent has already done so [27].

The problem of vision is the problem of knowledge, knowledge about the external world acquired through the sense of vision. One cannot unravel the first process, that of seeing, in any profound sense unless one unravels the second process, that of understanding what is seen, because there is no real division between the two. In other words, seeing is understanding, and color vision happens to be a perfectly good example of this. Indeed, it is very likely that had the neurologists really understood the nature of vision in general and of color vision in particular, progress in the field of visual Neurobiology would have taken a different course, so it has during the past few years. The study of color vision has thus been instrumental in modifying the views on the cerebral processes involved in vision. Indeed, it has provided us with powerful insights into brain function. Understanding the role of the cortex in color vision has therefore philosophical and epistemological implications which go far beyond understanding the detailed physiological mechanisms underlying the perception of colors. The study of colors give us a vision of how the visual cortex works. The study of the visual cortex in turns gives us a vision of how the brain works.

The new insights into the role of the cerebral cortex in vision have not been obtained by studying color in isolation, but rather in relation to how the cerebral cortex handles other

attributes of vision, such as form, motion and depth. To grasp this requires a fairly detailed, though not exhaustive, description of the anatomy and physiology of the visual pathways. Central to this description is the theory of functional specialization [57]. This theory supposes that different attributes of the visual scene are processed simultaneously, in parallel, but in anatomically separate parts of the visual cortex.

The study of color vision and of motion have provided the cornerstones on which the theory of functional specialization in the visual cortex is based and have thus us some insights into how the brain is organized to acquire its knowledge of the visual world.

There is no doubt that the study of the retinal mechanisms involved in color vision has enhanced immeasurably our knowledge of the subjects and has provided the key to our understanding of the inherited retinal color blindness.

Thomas Young (1773-1829), in his Bakerian Lecture to the Royal Society in 1802 [54], wrote: As it is almost impossible to conceive each sensitive point of the retina to contain an infinite number of particles, each capable of vibrating in perfect unison with every possible undulation, it becomes necessary to suppose the number limited, for instance to the three principal colors, red, yellow and blue. Herman von Hemholtz (1821-1894), following Young, wrote as follows: Red light stimulates the red sensitive fibers strongly and the other two weakly, giving the sensation red; green light stimulates the green sensitive fibers strongly and the other two weakly, giving the sensation green; blue light stimulates the blue sensitive fibers strongly and the other two weakly, giving the sensation blue, adding that, when all three fibers are stimulated about equally, the sensation is that of white or of pale hues [23]. This view of how the brain codes for color is now commonly called the Young-Helmholtz Trichromatic Theory of Color Vision.

Before Helmholtz, the prevailing concept, among neurologists, was of a visual image with all its various attributes, in which the color of every point had already been determined by the wavelength composition of the light reflected from it, being transmitted from the retina to be “received” and “analyzed” by the cortex; so powerful was this concept that or a good century almost all explanations of color vision were given in retinal terms and much of the work on color was undertaken on the retina. This is surprising because eminent authorities on color vision had emphasized the importance of higher cortical activities in color vision and had even come close to suggesting that the problem of color vision is a problem of knowledge. Helmholtz had spoken of color as being due to an act of judgement, not an act of sensation, Hering [25] had emphasized the importance of memory and Clerk Maxwell [38] had written o color vision as mental science. The determination of the color of every point in the field of view by the retina, the transmission of that color impression to the cortical retina in the well documented point by point system connecting the two structures, and the fact that a

small lesion anywhere along this pathway led to a total blindness for a small part of the field of view (a scotoma), were all strong arguments in favor of this simple analytic doctrine of vision, including color vision, or so it seemed at the time. It led to the concept of a cortex passively receiving and analyzing the visual image, a doctrine which is only now beginning to be modified, due in large measure to a much more sophisticated technology for studying the brain. At any rate, the adherence of neurologists to the concept of a visual image formed on the retina and received by the cortex was to retard the study of color vision and of cortical function by at least a century. It was obvious to the hard-nosed men of neurology that the area of the cerebral cortex that received the visual impressions must be the very one that also received the color impressions, since this was part of the visual scene and thus must be analyzed in the same cortical area as the rest of the visual scene. There could not be a separate cortical area dealing with color, or so they believed. But events elsewhere in cortical studies were taking a different turn.

Normal Pressure Hydrocephalus

Normal Pressure Hydrocephalus is a neurological disease characterized by an expansion of the ventricles of the brain against the background of normal intracranial pressure values and manifested by a specific triad o symptoms including gait disturbance, cognitive disorders and dysuria (primarily urinary incontinence). For the first time Normal Pressure Hydrocephalus was described by Colombian neurosurgeon Salomon Hakim Doe (1922-2011) in 1964, followed by a detailed and expanded analysis conducted by Hakim in collaboration with American neurosurgeon Raymond Delesy Adams (1911-2008) in 1965 [1,55]. They paid special attention to the possible reversibility of clinical manifestations in this syndrome by adequate surgical treatment with ventricular-peritoneal shunting.

The prevalence of normal pressure hydrocephalus is not understood completely. In various population-based epidemiological studies, the incidence of Normal Pressure Hydrocephalus is estimated to range from 0.3 to 3% among patients over 61 years of age [34].

There are few reasons for a significant (up to 80%) under-diagnosis of this disorder. First, the main difficulty is the differential diagnosis of normal pressure hydrocephalus and similar diseases, including neurodegenerative ones (Alzheimer's disease, Parkinson's disease, vascular dementia, dementia with Levy bodies [31,51]. Secondly, the diagnosis of normal pressure hydrocephalus is laborious because the dementia symptom.

The main theory that explains the development of Normal Pressure Hydrocephalus concept proposed by D. Greitz in 2004 [19]. According to it, the imbalance between secretion and reabsorption of brain-spinal fluid is a key link of normal pressure hydrocephalus pathogenesis. The importance of genetic predisposition for the development of Normal Pressure Hydrocephalus [10]. Some tendency to Normal Pressure Hydrocephalus development among

patient's close kinship was noted [39]. Fundamentally, Normal Pressure Hydrocephalus is a brain-spinal pathways disorder, with metabolic and neurodegenerative factors and heredity [5]. Some authors relate Normal Pressure Hydrocephalus with the autoimmune disorders, like systemic tissue disorders, vasculitis and even chronic fatigue syndrome although probable linkage mechanisms are obscure [26].

Depending on the detection of the immediate cause of the disease, Normal Pressure Hydrocephalus is divided into two subtypes: a) secondary Normal Pressure Hydrocephalus and b) primary or idiopathic Normal Pressure Hydrocephalus, detected in approximately 40-60% of cases, more often in older patients when a history there is no indication of any clear cause underlying the development of the disease. The most common reasons for Normal Pressure Hydrocephalus include:

- Intracranial hemorrhage
- Traumatic brain injury
- Purulent inflammatory processes in the cranial cavity
- Surgical operations on the brain

Up till now the etiology of Normal Pressure Hydrocephalus has not been elucidated. Accordingly, any methods of treatment for Normal Pressure Hydrocephalus do not exist. Existing methods of treatment, primarily ventricular-peritoneal bypass, are the better method in nature to improve a symptoms' regression.

2. Physiological and Clinical Aspects of the Color Vision and its Deficiency

To understand how the retina is mapped or represented on the cerebral cortex, we can divide each retina into four segments, nasal and temporal, and upper and lower. It is best to refer these subdivisions to the part of the field of view which each registers. Thus, the nasal retina looks at the temporal field of view and the temporal retina at the nasal field of view. Because of the curvature of the eye, the nasal retina of the left eye and the temporal retina of the right eye look at the left of the field of view, the left hemi-field, while the nasal retina of the right eye and the temporal retina of the left eye look at the right half of the field of view, the right hemi-field. Again, because of the curvature, the lower part of the eye looks at the upper field of view and the upper part of the eye looks at the lower field of view. Thus each hemi-field can, in turn, be subdivided into upper and lower quadrants. These subdivisions are important to bear in mind when considering the arrangement of the retinal map over the surface of the primary visual cortex. The retina can also be subdivided into central and peripheral portions; the central retina is that part of it with which one fixates and sees detail. Structurally, it consists of a highly sensitive region, the foveolar, which lies at the center of the foveal pit. The foveolar

contains only the receptors for daylight vision, the cones; it is consequently known as the rod-free area of the retina, the rods being the receptors which are active at night in low levels of illumination.

The fibers of the optic nerve, which carry the impulses from the retina, cross over at the optic chiasm in a very specific way. The fibers which have their origin in the nasal part of the retina cross over to the opposite hemisphere, while those which have their origin in the temporal retina do not, but continue to the same side of the brain. It follows that the fibers from the temporal retina of the left eye and from the nasal retina of the right eye pass to the left cerebral hemisphere, which therefore looks at the contralateral or right half of the field of view (the right hemi-field). By contrast, fibers from the nasal retina of the let eye and the temporal retina of the right eye pass over to the right hemisphere, which therefore looks at the contralateral or left half of the field of view (the left hemi-field).

Beyond the optic chiasm the visual pathway becomes known as the optic tract. This relays visual signals to a subdivision on the subcortical thalamus entitled the lateral geniculate nucleus. This nucleus is a complex, six-layered structure, and subdivided into the upper four layers and the lower two layers. The upper four layers contain cells with small cells bodies and are therefore termed the parvocellular or P layers, whereas the lower two layers contain cells with large cell bodies and are termed the magnocellular or M layers. These subdivisions have assumed a great significance in recent years because the cells in the upper four layers are concerned with color vision whereas those in the lower two are not.

The axons of the lateral geniculate nucleus travel until the striate cortex, at the end; and each part of the retina, according with a topographical map, is represented in a given part of the primary visual cortex [50].

The concept of parallel processing in the primate brain is supported by experimental data [57] and clinical evidence that circumscribed cortical lesions can cause partial and selective visual deficits. Color perception cannot only be selectively impaired by cortical lesions but also selectively impaired by cortical severe disturbances of some or most other visual abilities. The cortical color processing system brain consists of several stages extending from V1 to V4, partly directly but mainly through V2 [15] and beyond that to the inferior temporal cortex [27,57]. Lesion restricted to V4 lead to a specific loss of conscious color vision.

Dopaminergic neurons act in the outer and inner retina at multiple levels, producing alteration to the flow of visual information in a complex fashion. Dopamine is a chemical messenger for light adaptation, promoting the flow of information through cone circuits while diminishing that through rod circuits. Color vision relies on the cone photoreceptor populations and is therefore largely confined to the central retina. Because there is a segregation of color specific information at the retina into blue-yellow and red-green pathways, it is possible to use

color discrimination tasks to assess cone and retinal ganglion cell subpopulation.

The retinal signals travel to the brain via axons of the ganglion cells forming one million optic nerve fibers organized in a systematic manner. Macular fibers from the fovea, signaling color, occupy approximately one third of the optic nerve area on the temporal side when they enter. They later move to a central location in the nerve, while towards the chiasma they shift medially. The fibers, carrying impulses coding color, terminate at the lateral geniculate nucleus. The color patterns red-green and blue-yellow remain unchanged from the retinal ganglion cells. The lateral geniculate nucleus receives the axons of the retinal ganglion cells and connects them by synapses with the higher centers of the brain. Finally, nerve impulses signaling color in formation are relayed from the lateral geniculate nucleus via the visual radiations to the main visual areas of the brain, the striate cortex. The principal zones were designated area 17 by Brodman [7].

There exists a wide group of color vision disturbances acquired during life, predominantly the results of ocular or general disease, the consequence of exposure to a chemical, toxin or medication, or resulting from physical injury to the head. Alteration to color vision that arise throughout life from a cause or cause other than the normal physiological processes have received far less general attention than the inherited defects.

The following are the most important characteristics of the acquired color vision impairment unrelated to inherited diseases:

- Color loss may be confined to one eye and/or localized in one part of the visual field
- Color loss may be accompanied by deficiencies in other visual areas, notably reduced visual acuity, impaired dark adaptation, ERG changes, nystagmus
- Disturbances of blue-yellow are more common than that of red-green vision
- Females are affected in the same proportion as men
- Severity of the defect is variable according to the progression of disease or degree of exposure to the drug or chemical precursor
- Transient chromatopsia may be present
- An acquired defect may be superimposed on an inherited defect
- The severity of an acquired defect depends on whether the cause is active or inactive
- Some acquired defect may imitate inherited defects, therefore very careful examination is required [3].

Physiological and Clinical Aspects of the Normal Pressure Hydrocephalus

Attempts to determine the key links in the etiology and pathogenesis of Normal Pressure Hydrocephalus are closely related to the elucidation of the mechanisms of secretion, circulation and resorption of the brain spinal fluid [6], the characterization of structural changes in neurons and white matter of the brain, and changes in the composition of the brain spinal fluid in Normal Pressure Hydrocephalus [28].

Recently Normal Pressure Hydrocephalus have been considered as a potentially reversible neurodegenerative disease. It is likely that the positive effect brought in by liquor-shunting operations is also related to the improved excretion of beta amyloid from brain via the ventricular system, which can render a beneficial effect on the functioning of the central nervous system [2,17]. There is a hypothesis by Iencean [29], putting close two different disorders of brain spinal fluid exchange, which both are prone to the same treatment with the brain spinal fluid drainage: namely Normal Pressure Hydrocephalus and idiopathic intracranial hypertension. In former ventricles are distended, but no brain spinal fluid hypertension and high intracranial pressure occurs, in later-intracranial pressure is high but with non-distended ventricles. It believes that glial-ependymal barrier between ventricles and brain interstitial space is “open” in idiopathic intracranial hypertension, but “closed” preventing increase in intracerebral pressure-in Normal Pressure hydrocephalus [29].

Nowadays Normal Pressure Hydrocephalus is interpreted as a chronic, steadily progressing disease that significantly reduces the quality of life, especially in the absence of timely diagnosis and treatment, due to its disabling character [22]. The Normal Pressure Hydrocephalus is characterized by a gradual development of the classical Hakim-Adams triad: disorders of gait, dementia and urinary incontinence. However, it is essential that the classical picture, described in 1965, is observed only in half of the cases. In most patients, gait disturbance is the first symptom, then dementia occurs and later, pelvic disorders join. A fluctuation in the severity of symptoms is possible, although not typical in Normal Pressure Hydrocephalus.

Dizziness is based on postural instability inherent in the disease. Disorders of locomotion in Normal Pressure Hydrocephalus include the elements of apraxia, a typical walking in the form of shuffling gait with short steps on widely spaced legs and loss of balance. In Normal Pressure Hydrocephalus, there are no changes in the movements of the hands during walking, which may distinguish it from Parkinson’s disease. As the disease progresses, the step height decreases, it becomes difficult for patients to tear their legs off the ground, there are difficulties in initiating the act of walking, turns are made in several stages and incidents often occur. In more severe cases of Normal Pressure Hydrocephalus occurs the following set of symptoms related

to lower extremities: spasticity, hyperreflexia, and pathological stop signs. The presence of manifestations predominantly in the legs of Normal Pressure Hydrocephalus patients probably is explained with the fact that the motor pathways connecting the cerebral cortex with the lower extremities are located more medially, near the wall of the lateral ventricles, and the pathways to the upper extremities are located laterally, more distantly from the ventricles [41]. The gait changes in Normal Pressure Hydrocephalus patients may also result from the dissociation of basal nuclei with the frontal cortex, dysfunction of the frontal cortex and violation of sensitive-motoric integration [21].

Another important manifestations of Normal Pressure Hydrocephalus is dementia. Patients are characterized by the presence of cognitive disorder and disorientation (more in time rather in space). In some rare cases, the hallucinations and mania were registered [46]. A characteristic symptom of normal pressure hydrocephalus is also emotional lability. In general, cognitive impairments are manifested by a weak memory, a slowing of the rate of psychic and psychomotor reactions, a decrease in the ability to use acquired knowledge, as well as apathy, which is associated with dysfunction of the anterior parts of the brain and characteristic of so-called subcortical dementia [11], in contrast to Alzheimer's disease were other cortical functions are usually altered.

The frontal character of cognitive impairment in the case of Normal Pressure Hydrocephalus may be due to the predominant extension of the anterior horn of the lateral ventricles, accompanied by a more significant dysfunction of the deep sections of the frontal lobes and anterior parts of the corpus callosum. It is believed that the basis of cognitive disorders accompanying Normal Pressure Hydrocephalus is the compression of the capillaries of the brain by increased hydrostatic tissue fluid pressure of the parenchyma, especially because of the diffuse decrease in glucose metabolism both in the cortex and in the subcortical areas [33].

It is possible to identify complaints of patients for frequent urination and nocturia even in the early stages of the Normal Pressure Hydrocephalus. As the diseases progresses, imperative urges and periodic urinary incontinence are added. Stools incontinence is rare, usually in patients at the late advanced stages of Normal Pressure Hydrocephalus.

The basis of treatment is liquor-shunting surgery with the implantation of ventricular-peritoneal or lumbo-peritoneal shunts, in which a positive effect is achieved in 60-80%. Complications after shunting (excessive drainage, subdural hematomas, insufficient drainage, and dysfunction of the shunt) are noted in 20-30% of patients. In connection with the appearance of externally adjustable valve system, the number of complications has significantly decreased and in specialized Institutions is no more than 5-10%.

3. Clinical Methods to Diagnose Color Vision Deficiency

Acquired disturbance of color vision are a highly varied group of defects with frequent departure from established patterns. They can progress from normal trichromatism to anomalous trichromatism on to a dichromatic stage and even to monochromatism where most color vision is lost, or they may be relatively stable. On recovery or withdrawal of the cause, color vision may typically revert to normality through these phases if the color loss had been considerable. A variety of related visual disturbances may accompany the color vision change, principally visual acuity and field losses. Listed below are some of the important characteristics which will assist in the judgment of whether a presented color vision disturbance has an inherited or acquired origin, for in many instances these features contrast to the stable, more predictable manifestations of inherited color anomalies [14].

1) Differences in color perception between eyes. Color loss may be confined to one eye and/or localized in one part of the visual field

2) Color loss may be accompanied by deficiencies in other visual areas, notably reduced visual acuity, visual field defects, impaired dark adaptation, brightness perception, spatial contrast sensitivity or flicker sensitivity, ERG changes, nystagmus

3) Disturbances of blue-green-yellow vision are as common, or more common than red-green vision in acquired forms

4) Females are affected in the same proportion as men

5) The elderly are particularly susceptible on account of the cumulative effects of toxins and increased incidence of ocular and general pathology

6) Severity of the defect is variable according to the progression of disease or degree of exposure to the drug or chemical precursor

7) Transient chromatopsia (appearance of color to white surfaces/objects) may be present

8) Colors can often be named correctly by patients with an acquired defect on the basis of their memory for colors prior to the defect

9) Confusion in diagnosis, particularly classification of the defect when clinical tests are applied, frequently on account of an anarchic response

10) Hue discrimination is typically impaired

11) Color perception is frequently improved for the patient with an acquired defect when the size, luminance, exposure time or saturation of the test color is increased. The appearance of induced color contrasts effects is frequently less marked than for person with inherited color vision defects or normal color vision

12) An acquired defect may be superimposed on an inherited defect

13) The severity of an acquired defect depends on whether the cause is active or inactive

14) Some acquire defects may imitate inherited defects

15) Any unusual color vision disturbance or report of a change in color perception

Whether or long-standing origin or of sudden onset suggests an acquired anomaly. Kollner's rule [32] is often misinterpreted as stating that "Defect of blue-yellow vision are caused by retinal disease and defects of red-green vision are due to optic nerve disease". In fact Kollner described a progression of color vision loss within the framework of the Hering theory [25]:

Blue-yellow blindness: blue and yellow change their appearance first, green and red are preserved longer. Acquired blue-yellow blindness especially develops in diseases of the retina and total color blindness only results in combination with progressive red-green blindness.

Progressive red-green blindness: color vision is totally disturbed, blue-yellow vision is changed but deterioration is most striking for red and green. This type of color blindness can especially be found in diseases of the conductive pathways reaching from the inner layers of the retina to the cortex.

Printed pseudo isochromatic plates are the most widely used screening tests for abnormal color vision. Most tests aim to identify congenital or inherited red-green color deficiency only, and some are highly efficient. Identification of tritan defects is confounded by variations in macular pigment and lens density and lower values of specificity and sensitivity have to be acceptable [3]. Ishihara test is remarkably efficient as a screening test for inherited red and green defects, but does not test the blue anomalies [15]. Opinions of the Hardy, Rand and Rittler [20] test varied; Walls [56] made trenchant criticisms, that the test was liable to misdiagnosis between protan and deutan; Dreyer [12] noted poor diagnostic ability, Hardy et al. [20] do not report having given their test to the rare tritan observers. Dvorine [13] showed as in his test 14 plates with numbers and 7 with tracks enabled protan and deutan differentiation to be attempted. But, after criticism by Sloan [48], also Lakowsky [35] pointed out the reason for Dvorine plates to be "failed" in a tritan manner by many subjects over 40 years of age, in the special way. Umazume and Matsuo [52] gave a relatively high accuracy for protans and deutans identification for their Toky Medical College plates, but also in this case some criticism is present, as Vos [53] who pointed out some of the difficulties in using it. Among the rarely used peseudoisochromatic plates which have poor screening efficiency [3]. We remember the Ohkuma plates, the Standard Pseudo isochromatic Plates (SPP1 e SPP2), the American Optical Color Vision Test, the Hahn Color Vision Test, the Lanthony Tritan Album. The development

of fluorescein angiography, electro-diagnostic techniques, and nuclear resonance imaging has led to more precise clinical diagnosis, and it is possible to link acquired color vision deficiency with a type of pathology rather than a broad classification of disease. Computerized examination techniques, which examine peripheral color vision or isolate chromatic and achromatic responses, have been developed specifically for acquired color vision deficiency [3]. These methods, however, are unique to a specific research laboratory due to the expensive equipment. So, choosing to operate by the pseudo-isochromatic tests shown in the present work means to choose a non-invasive and inexpensive method of analysis. Generally, poor visual acuity and central, or paracentral field as in the demyelinating diseases, deficiencies limit performance on some pseudo-isochromatic plates. Therefore, according to the bibliography [3,36], choosing the three tests [14,16,30] using binocular and monocular vision allowed us to distinctly identify the subgroups of our sample patients.

Ishihara Test

To accurately read the Ishihara plates [30], all the plates must be 70 cm from the observer, under natural lighting conditions and read within 5 s. Each subjects must only be examined in the presence of the interviewer to maintain confidentiality and t lower psychological stress. Subjects who make more than five mistakes while reading the first 17 Ishihara plates are diagnosed as colorblind, and this is confirmed by their reading from the next 4 (18-21) Ishihara plates. The last four Ishihara plates (22-25) are utilized to define the type of colorblindness (red or green colorblindness) and the grade of colorblindness (protanopy or great protanomaly and small protanomaly, with respect to the red colorblindness; deuteranopy or great deuteranomaly and small deuteranomaly, with respect to the green colorblindness).

Farnsworth D-15 Test

The Farnsworth D-15 test [14] aims to divide people into two groups: people with normal color vision and slight color deficiency (who pass) and people with moderate and severe color deficiency (who fail). One transposition of adjacent colors is normally permitted as a pass. The color arrangement made by the subjects is drawn on a circular diagram representing the hues. The Farnsworth D-15 test identifies both the degree of color vision deficiency by the high numbers of errors (maximum value, n. 15) and the type of deficiency (deutan, protan or tritan).

The City University Test

The City University test [16] uses 10 plates. Each plate displays a central color and four peripheral colors. Subjects select the peripheral color that looks most like the central color. Three peripheral colors are typical isochromatic confusions, with the central color, in protan, deutan and tritan deficiency. The City University test identifies moderate and severe color deficiency.

4. Magnetic Nuclear Resonance Imaging to diagnose Normal Pressure Hydrocephalus

The classic teaching is that cerebrospinal fluid is formed primarily in the choroid plexus within the ventricles at a rate of 500 cc/d. It flows out of the fourth ventricle via the foramina of Lushka and Magendie into the subarachnoid space. Once in the subarachnoid space, the cerebrospinal fluid either flows down around the spinal cord or flows up over the cerebral convexities, eventually to be primarily absorbed by the arachnoid granulations (macroscopic) and arachnoid villi (microscopic) on either side of the superior sagittal sinus. This cerebrospinal fluid resorption pattern was based on tracer studies performed many years ago using large molecules. Superimposed on the slow egress of cerebrospinal fluid from the ventricles to the sub-arachnoid space is a more prominent pulsatile motion due to the beating of the heart. During systole, blood flows into the brain causing it to expand inwards, compressing the ventricles, and outwards, compressing the cortical veins and sub-arachnoid space. The inward expansions leads to pulsatile outflow of cerebrospinal fluid through the aqueduct and the rest of the ventricular system. This results in a normal cerebrospinal fluid flow void on Magnetic Resonance Imaging studies through the aqueduct [4]. The systolic expansion forces cerebrospinal fluid and venous blood out of the fixed volume of the skull by the Monro-Kellie hypothesis [40]. This results in the systolic outflow of cerebrospinal flow at the foramen magnum and from there down the sub-arachnoid space of the spinal canal or up over the convexities. During diastole, the volume of the brain decreases and cerebrospinal fluid flows in a reverse direction through the foramen magnum and the aqueduct.

Although most cerebrospinal fluid is produced by the choroid plexus, recent evidence suggests that a portion of the cerebrospinal fluid is made by the capillaries in the brain parenchyma. Similarly, it has been estimated that up to 20% of the cerebrospinal fluid uptake occurs in the brain parenchyma, via the lymphatics near the cribriform plate, or covering the cranial nerves in the basal cisterns. Regardless of the exact percentage of cerebrospinal fluid produced by the brain vs the choroid plexus, the bulk flow of cerebrospinal fluid of the lateral ventricles via the foramen of Monro through the third ventricle and aqueduct and then through the fourth ventricle.

Magnetic Nuclear Resonance Imaging is generally considered the best imaging modality to evaluate hydrocephalus, partly because of its sensitivity to flow and partly because of the various pulse sequences available (compared with Computer Tomography). The best Magnetic Nuclear Resonance Imaging technique to evaluate hydrocephalus is fluid-attenuated recovery that is sensitive to the presence of interstitial edema, (FLAIR) which is trans-ependymal spread of cerebrospinal fluid. The more modern Magnetic Nuclear Resonance Imaging techniques such as fast or turbo spin echo are much more intrinsically flow-compensated and do not have the same degree of signal loss, that is, flow void, seen in the early day of the technique.

With PC-Magnetic Nuclear Resonance Imaging, the slice is positioned in an angled axial plane so it is perpendicular to the aqueduct. The higher the resolution the better, as the aqueduct is such a small structure. The encoding velocity needs to be specified before the study is performed.

Most Magnetic Nuclear Resonance Imaging systems have automated software that calculates the velocity and volume of cerebrospinal fluid flowing cranial-caudal during systole and cranial-caudal during diastole. As the flow-down and the flow-up are within 5% of each other (with a small net forward motion), it takes the average and call it the aqueduct cerebrospinal fluid stroke volume.

It is recommended that anyone wishing to use PC-Magnetic Nuclear Resonance Imaging to diagnose shunt-responsive Normal Pressure Hydrocephalus first perform cerebrospinal fluid flow studies on 10-20 normal patients without dilated ventricles to determine what is normal on that scanner with that particular software.

5. Patients and Methods

Considering the X-linked inheritance of color vision deficiency, fixed sampling of only males, as in our previous works on color vision in other neurological diseases [42, 43], allowed us to avoid the genetic Lyon phenomenon [37], which is present only in the heterozygous females for X-linked diseases such as colorblindness (the inherited red-green color vision deficiency). Therefore, the exclusion of females in our sample allowed us to avoid those heterozygous colorblind females who would be “false positives” for the acquired red-green color vision deficiency, thus altering the results analysis. The Authors showed an 8% of red-green inherited colorblindness frequency in Calabrian people [49]. If we had not considered this frequency we would have found a relatively significant high number of “false positive” subjects showing a red-green color vision trend, which, as in a Gaussian curve, can carry a minimum value (normal color vision) to a maximum value miming the inherited red-green colorblindness, passing for different anomalous color vision levels. The relatively high frequency of the inherited red-green colorblind females united Lyon genetic presence by the heterozygous females for the inherited red-green colorblindness should be the real cause to mistake discriminating between the red-green inherited colorblindness and that acquired. We should not comprehend if homozygous female status is really inherited or acquired; and in heterozygous status we miss all those females miming the normal color vision. The acquired color vision deficiency, is real in the males cohort because they have not the compensation presence by second X chromosome, and the anomaly has not hidden.

In the present study, all the analyzed patients were subjected to Ishihara test [30], Farnsworth D15 test [14], and the City University Test [16] both monocularly, and binocularly.

6. Results and Comment

The results have obtained analyzing 28 Calabrian male patients (age range 51–84 years; mean age, 73.2 ± 1,57 years) showing a mean disease duration of 4.4 ± 0,91 years (range 1.0–23 years) admitted to the Neuroscience Research Center, Magna Graecia University, Catanzaro (Calabria, Southern Italy) and National Research Council, Catanzaro (Calabria, Southern Italy) were enrolled in this study.

The patients were subdivided into three groups:

7/28 patients showed a black/white vision; these patients were subdivided into two subgroups: 4/7 patients without surgical ventricular-peritoneal shunt; 3/7 patients in presence of the surgical ventricular-peritoneal shunt. 1 patient of this last subgroup showed a normal color vision after the surgical shunt, an 2/3 showed a black/white vision after the surgical shunt, too.

In the group of patients showing the black/white vision, very likely we have a compromise of the visual pathways from V1 to V4 in the middle brain. The very compromise of the primary visual area V1 does not allow that the visual stimulus can arrive to V4 area. And the clinical evidence makes such a suggestion plausible because the integrity of both above areas is critical to see, and be consciously aware of having seen the colors. Evidently, in these patients miss the intact return pathways from V4 to V1. This integrity is restored in the patient who have a new normal color vision after the surgical ventricular-peritoneal shunt.

14/28 patients showed a color vision deficiency; these patients were subdivided into two subgroups: 7/14 patients without surgical ventricular-peritoneal shunt. 3/7 patients in this group showed the double protanous / deuteranous and tritanous color vision deficiency; 2/7 patients showed the protanous / deuteranous color vision deficiency; 2/7 patients showed the tritanous color vision deficiency.

7/14 patients did the surgical ventricular-peritoneal shunt. 4/7 patients in this group showed a restored normal color vision after the surgical ventricular-peritoneal shunt; 2/7 patients showed the protanous / deuteranous color vision deficiency, after surgical shunt, too; 1/7 patient showed the tritanous color vision deficiency, after surgical shunt, too.

In the group of patients showing the color vision deficiency both on red/green, and/or on blue/yellow axis, very likely there is no a great compromise of the V1 primary visive area. But, very likely both great or small compromise of the visive areas is relate only to V4 color vision area. Within this group, the return pathways from V4 back to V1 showed to be critical for the conscious awareness of the color attributes of vision. The operational connections between the two areas are not very compromised, and it have restored after the surgical ventricular-

peritoneal shunt.

7/28 patients showed normal color vision showing any intact visive areas.

7. Discussion

When and at what stage of the visual pathway do we become conscious of seeing an object and when are we conscious of the characteristics of that object? At what stage of the visual pathway does the nervous system acquire knowledge about the unchanging properties of objects and surfaces in terms of their reflectance for lights of different wavelengths and interpret these properties as color? Are there conditions in which we can pay attention to a visual stimulus, see it and yet not be conscious of having seen at all?

There is a great deal that has been written about consciousness and about the so-called mind-brain problem. Is there such a duality? Does the brain cause the mind? Or is the brain the mind? A sensible attitude is to be found in the work of John Searle [47]. He considers that mind and intentionality are certain properties of neural systems, including the cells that compose them, just as certain physical attributes are properties of the lattice structure of crystals. The micro-properties of the system invest it with certain macro-properties. There is an important question of causality here, for the micro-properties do not cause the macro-properties; rather, the macro-properties are features of objects which have molecules with given micro-properties. In the same way, neurophysiological events in the brain do not cause mental events, but rather mental events are a feature of neurophysiological systems with certain properties. We can therefore say that color vision is a feature of a neural circuit with certain properties that motion is a feature of other neural circuits with other properties and that consciousness is also a feature of many neural organizations with certain properties. One might say that solidity (a macro-property) is a feature of a certain kind of lattice structure of crystals (a micro-property), though one would not then go on to say that the molecules, which are components of that lattice, themselves possess solidity. In the same way, color vision (a macro-property) is a feature of certain neural organizations (micro-property), though it does not follow from this that individual neurons within that organization are capable of seeing in color. Similarly, motion vision is a feature of certain other neural organizations, though individual cells composing that neural organization cannot be said to perceive motion. Beyond that, consciousness is a feature of both types of neural organization and of many other, though not all, neural systems as well. There is no color unless I see it; I cannot see it unless I am conscious. There is no conscious awareness unless certain neural organizations are intact and functioning normally, and it is a feature of such neural organizations that they possess consciousness.

Color vision is a system for acquiring knowledge about certain unchanging physical properties of objects, namely their reflectance for lights of different wavelengths. Knowledge cannot be acquired without consciousness. We can therefore say that consciousness and the

acquisition of knowledge are features of certain neural organizations concerned with color vision.

This may seem far-fetched had it not been for clinical evidence which strongly suggests that something of this kind must occur. It is perhaps relatively easy to account for a syndrome such as akinetopsia by supposing that the final integrative machinery required to collate information from large parts of the field of view is compromised, with the consequence that patients with lesions in V5 cannot acquire the knowledge about the coherent motion of objects in particular directions. Much more difficult to account for are conditions when patients can "see" the directional motion but have no conscious awareness of having seen anything at all. Such a syndrome may seem surprising, but it is now a well-documented one in the literature.

For a long time it used to be thought that a lesion of the striate cortex causes total blindness in a corresponding part of the field of view, large (hemianopic) if the lesion is large and small (scotomatous) if it is small. Riddoch [45] had observed that some of his scotomatous patients could detect motion in the field of view, although they appeared to be blind to everything else. This led Riddoch to consider movement as a special form of vision. He believed that it was a result of spare mechanisms within V1, though without detailing what these mechanisms might be. Studies in the early 1970s confirmed the observations of Riddoch. They also extend them by sowing that not only are blind fields due to cortical lesions not necessarily completely blind but that cortically blind patients can "see" a good deal more in their blind fields than even Riddoch had believed. The phenomenon is now aptly termed blind sight [44]. Note that blindsight results from a cortical lesion, not a lesion of the retina or of the optic tract, the consequence of which is total blindness. Moreover, not all patients with a cortical lesion have blind sight; whether a patient has blindsight or not depends, according to a study [8], on the amount of occipital cortex spared, a total lesion of occipital cortex leading to a total blindness. However, that may be, the point of interest is that, although blindsight patients can "see", at least in a rudimentary way, in their blind fields, they are nevertheless not consciously aware of having seen anything at all. Their vision is therefore useless, they cannot acquire any knowledge about the world through it. How is this possible? A standard method of studying this phenomenon is to force the patient to guess whether something was occurring in his blind field. It turns out that blindsight patients are surprisingly good at reporting correctly what was in the blind part of their field of view, in other words that their "guesses" are significantly correct. They can thus detect the presence and the direction of motion, can, make simple pattern discriminations and can even detect and indiscriminate wavelengths [9]. Henschen [24], in dismissing the evidence for a color center outside the striate cortex, he had said that if such a center did exist, then a patient with a damaged striate cortex but with an intact fusiform gyrus would have to be absolutely blind and yet be able to see colors, which makes no sense. In fact, just this improbable scenario occurs in blindsight with the difference that although the

patients can see, they are not consciously aware of having seen, just as in Eliot poetry, When, under ether, the mind is conscious, but conscious of nothing. So, the primary visive cortex was necessary for the conscious experience of vision.

The question that arise here is whether the information contained in the visual stimuli presented in the blind field, stimuli which the patients can discriminate but cannot see, reaches the cortex at all.

There is a direct, though sparse, route from the lateral geniculate nucleus to the visual areas of the prestriate cortex [18]. The precise extent of the termination of this pathway in the prestriate cortex is not known, but it is known that V4 is definitely among the recipient areas, as is V5.

The signals presented in the blind field actually reach the cortex is strongly suggested by evidence which shows that, when visual stimuli are presented to the blind field of blindsight subjects, evoked potentials can be picked up directly from the cortex [8].

There is reason to believe that subcortical structures such as the pulvinar or the superior colliculus are involved in such discriminations as blindsight patients are capable of because even hemi-spherectomised patients are capable of some residual vision. There is however every indication that the visual signals from the blind field reach the cortex and that, in spite of this, patients are not consciously aware of having seen anything at all.

If we concentrate on motion vision, the first important point to note is that not only is the integrity of the specialized visual areas (in this case V5) necessary for the conscious perception of this attribute of vision but also the integrity of the areas feeding them (areas V1 and V2). Thus, a patient with a lesion in area V5 is not able to see objects in motion, except to a very limited extent (akinetopsia). But a patient with a lesion in area V1 and with an intact V5 is also not consciously aware of having seen objects in motion, even if visual signals are reaching V5 directly, through the pathway linking the lateral geniculate nucleus to V5.

The conscious awareness of the color of a surface is a feature of the neurophysiological machinery that links V1 and V2 reciprocally to V4. And the clinical evidence makes such a suggestion plausible because the integrity of both areas is critical to see, and be consciously aware of having seen, both color and motion.

It is important to emphasize that the return pathways from V4 e V5 verso V1 e V2 are not the only pathways from these two areas, although they would appear, if the present analysis is correct, to be critical for the conscious awareness of these attributes of vision. The other pathways emanating from V4 and V5 to healthy and intact parts of the brain may be functioning quite normally. In other words, only some of the operational connections from

V4 and V5 may be compromised. This is nicely illustrated in Goodale [18] of a dissociation between perceiving objects and grasping them. A young woman who suffered irreversible brain damage following carbon monoxide poisoning was found to suffer from a profound visual form agnosia. She showed poor perception of shape or orientation, whether this information was conveyed by color, intensity, stereopsis, motion, proximity, continuity or similarity. Indeed she oriented her hand appropriately very early in the reaching movement and grasped the object normally. This leads the authors to conclude that a person with brain damage may retain the ability to calibrate normal aiming and prehension movements with respect to the orientation and dimensions of objects, despite a profound inability to report, either verbally or manually, these same visual properties. This dissociation suggests that at some level in normal brains the visual processing underlying conscious perceptual judgements must operate separately from that underlying the automatic visual-motor guidance of skilled actions of the hand and limb [18].

8. Conclusion

It can be concluded that a person with brain damage may retain the ability to calibrate normal aiming and movements with respect to the orientation and dimensions of objects, despite a profound inability to report, either verbally or manually, these same visual properties. This dissociation suggests that at some level in normal brains the visual processing underlying "conscious" perceptual judgements must operate from that underlying the "automatic" visual-motor guidance of skilled actions of the hand and limb [18].

It would seem therefore that there are several operational connections emanating from an area, that some can be compromised without the others, and that some are actively involved in conscious perception, whereas others are not.

It would seem, that we are getting relatively close to dissecting out the nervous pathways involved in conscious perception.

9. Acknowledgment

The Authors thank Fondazione Cassa di Risparmio di Calabra e Lucania for its contribute.

10. References

1. ADAMS RD, FISHER CM, HAKIM S, OJEMANN RG, SWEET WH. Symptomatic occult hydrocephalus with "normal" cerebrospinal fluid pressure: a treatable syndrome N Engl J Med; 1965; 273: 117-126.

2. BASSAR BR, LIPPA CF. Idiopathic normal pressure hydrocephalus: a review for general practitioners Gerontol Ger Med; 2016; 2: 23-33.

3. BIRCH J. Diagnosis of defective color vision Oxford: Butterworth-Heinemann; 2001.

4. BRADLEY WG, KORTMAN KE, & BURGOINE B. Flowing cerebrospinal fluid in normal and hydrocephalic states. Appearance on MR images. Radiology; 1986; 159: 611-616.

5. BRAUTIGAM K, VAKIS A, TSITSIPANIS C. Pathogenesis of idiopathic normal pressure hydrocephalus: a review of knowledge J Clin Neurosci; 2019; 61: 9-13.

6. BRINKER T, STOPA E, MORRISON J, KLINGE P. A new look at cerebrospinal fluid circulation Fluids Barriers CNS; 2014; 11: 10.

7. BRODMANN K. Beitrage zur histologischen localization der grosshirnrinde. 1: Mitteilung: die Regio Rolandica J Psychol Neurol; 1903; 2: 79-107.

8. CELESIA GG, BUSHNELL D, TOLEIKIS SC & BRIGELL MG. Cortical blindness and residual vision: is the second visual system in humans capable of more than rudimentary visual perception? Neurology; 1991; 41: 862-869.

9. COWEY A & STOERING P. Reflections on blindsight. In: “The Neuropsychology of Consciousness”. D. Milner & M. Rugg (eds.. London: Academic Press; 1991; pp. 11-37.

10. CUSIMANO MD, REWILAK D, STUSS DT, BARRERA MARTINEZ JC, SALEHI F, FREEDMAN M. Normal pressure hydrocephalus: is there a genetic predisposition? Can J Neurol Sci; 2011; 38: 274-281.

11. DAMULIN IV, ORYSHICH NA, IVANOVA EA. Normotensive hydrocephalus Neurologia; 1999; 4: 51-56.

12. DREYER V. Occupational possibilities of colour defectives. Acta Ophthal; 1969; 47: 523-534.

13. DVORINE I. Quantitative classification of the colour blind. Gen Psychol; 1963; 68: 255-265.

14. FARNSWORTH D. The Farnsworth-Munsell 100 Hue and dichotomous test for color vision J Opt Soc Am; 1943; 33: 568–578.

15. FLETCHER R, VOKE J. Defective color vision. Fundamentals, diagnosis and management Bristol: A. Hilger; 1985.

16. FLETCHER RJ. The city university color vision test, 3rd edn. London: Keeler Instruments; 1975.

17. GAVRILOV GV, SVISTO DV, KOROVIN AE, STANISHEVSKY AV, EFIMOV NS. Idiopaticheskaja normotenzivnaja gidrocephalija kak sovremennaja medicinskaja problema. Klinicheskaja patofiziologija [Idiopathic normal pressure hydrocephalus as a modern health issue] Clin Pathophys; 2016; 22: 70-80.

18. GOODALE MA, MILNER AD, JAKOBSON LS & CAREY DP. A neurological dissociation between perceiving objects and grasping them Nature; 1991; 349: 154-156.

19. GREITZ D. Radiological assessment of hydrocephalus: new theories and implications for therapy Neurosurg Rev; 2004; 27:145-165.

20. HARDY L.H., RAND G., RITTLER M.C. H-R-R polychromatic plates J Opt Soc Am; 1954; 44 (7.: 509-523.

21. HATTORI T, YUASA T, AOKI S, SATO R, SAWAURA H, MORI T, MIZUSAWA H. Altered microstructure in corticospinal tract in idiopathic normal pressure hydrocephalus: comparison with Alzheimer disease and Parkinson disease with dementia Am J Neuroradiol; 2011; 32: 1681-1687.

22. HEBB AO, CUSIMANO MD. Idiopathic normal pressure hydrocephalus: a systematic review of diagnosis and outcome Neurosurgery; 2001; 49: 1166-1186.

23. HELMHOLTZ H VON. Handbuch der Physiologischen Optik Hamburg: Voss; 1911.

24. HENSCHEN SE. Zentrale Sehstorungen. In: Handbuch der Neurologie. M. Lewandowsky (ed.. Berlin: Springer-

Verlag; 1910; pp. 891-918.

25. HERING E. Outlines of a theory of the light sense Cambridge: Harvard University Press; 1964.

26. HIGGINS JNP, PICKARD JD, LEVER AML. Chronic fatigue syndrome and idiopathic intracranial hypertension: different manifestations of the same disorder of intracranial pressure Med Hypot; 2017; 105: 6-9.

27. HONDRICH T. Mind, brain and self-conscious mind. In: “Mindwaves”. C. Blakemore & S. Greenfield (eds.. Oxford: Basil Blackwell; 1987; pp. 445-460.

28. HUOVINEN J, KASTINEN S, KOMULAINEN S., OINAS M., AVELLAN C, FRANTZEN J, RINNE J, RONKAINEN A, KAUPPINEN M, LONNROT K, PEROLA M, PYYKKO OT, KOIVISTO AM, REMES AM, SOININE H, HILTUNEN M, HELISALMI SKURKI M, JAASKELAINENJE, LEINONEN V Familial idiopathic normal pressure hydrocephalus J Neurol Sci; 2016; 15: 11-18.

29. IENCEAN SM. Idiopathic intracranial hypertension and idiopathic normal pressure hydrocephalus: diseases with opposite pathogenesis? Med Hypot; 2003; 61: 523-528.

30. ISHIHARA S. (1982. The series of plates designed as a test of colour-blindness. 38 Plates edn.; 1982. Tokyo: Kanehara S. Co., Ltd.

31. KIEFER M, EYMANN R. Gravitational shunt complications after a five year follow-up Acta Neurochir Suppl; 2010; 106: 107-112.

32. KOLLNER H. Stroungen des farbensinnes ihre klinische bedeutung und ihre diagnose Berlin: Karger; 1912.

33. JAGUST WJ, FRIEDLAND RP, BUDINGER TF. Positron emission tomography with [18F] fluorodeoxyglucose differentiates normal pressure hydrocephalus from Alzheimer-type dementia J Neurol Neurosurg Psych; 1985; 48: 1091-1096.

34. JARAJ D, WIKKELSO C, RABIEI K, MARLOW T, JENSEN C, OSTILING S ET AL. Mortality and risk of dementia in normal pressure hydrocephalus: a population study Alz Dem; 2017; 13: 850-857.

35. LAKOWSKI R. A critical evaluation of colour vision tests. Br J Phys Opt; 1966; 23: 186-209.

36. LONG GM., LYMAN BJ., TUCK JP. Distance, duration and blur effects on the perception of pseudoisochromatic stimuli Opt Phys Opt; 1985; 5: 185-194.

37. Lyon MF. Gene action in the X chromosome of the mouse (Mus musculus L.. Nature; 1961; 190: 372-373.

38. MAXWELL J.C. On color vision Proc R Instn GB; 1872; 6: 260-271.

39. MCGIRT MJ, WOODWORTH G, COON AL, THOMAS G, WILLIAMS MA, RIGAMONTI D. Diagnosis, treatment, and analysis of long-term outcomes in idiopathic normal-pressure hydrocephalus. Neurosurgery; 2008; 62: 670-677.

40. MOKRI B. The Monro-Kellie hypothesis. Applications in CSF volume depletion Neurology; 2001; 56 (12.: 1746-1748.

41. MORETTI JL. Assessment of alterations in cerebrospinal fluid kinetics Radionuc Imag Brain; 1985; 185-223.

42. PIRO A, TAGARELLI A, NICOLETTI G, SCANNAPIECO S, POLIDORO S, VALENTINO P, QUATTRONE A. Impairment of acquired color vision in multiple sclerosis: an early diagnostic sign linked to the greatness of disease Int. Ophthalmol; 2019; 39: 671-676.

43. PIRO A, TAGARELLI A, NICOLETTI G, FLETCHER R, QUATTRONE A. Color vision impairment in Parkinson’s disease. J Parkinson Dis; 2014; 4: 317-319.

44. POPPEL E, HELD R & FROST D. Residual visual function after brain wounds involving the central visual pathways in man. Nature; 1973; 243: 295-296.

45. RIDDOCH G. Dissociation of visual perception due to occipital injuries, with especial reference to appreciation of movement Brain; 1917; 40: 15-57.

46. ROJAS-ESTAPE M, BERENGER ELIAS N, IGLESIA-RODRIGUEZ C. P-165-A case of hydrocephalus occlusus presenting as a manic episode Eur Psych; 2012; 27 (S1.: 1.

47. SEARLE J. Minds and brains without programs. In: Mindwaves. C. Blakemore and S. Greenfield eds. Oxford: Basil Blackwell; 1987: pp. 209-233.

48. SLOAN LL. Improved screening test for red-green color deficiency composed of available P.I.C. plates J Opt Soc Am; 1945: 35: 761-766.

49. TAGARELLI A, PIRO A, TAGARELLI G, ZINNO F. Color Blindness in Calabria (Southern Italy.: A NorthSouth decreasing trend Am J Hum Biol; 2000; 12: 17-24.

50. TALBOT SA, MARSHALL WH. Physiological studies of neural mechanisms of visual localization and discrimination Am J Ophthalmol; 1941; 24: 1255-1264.

51. TISELL M, HOGLUND M, WIKKELSO C. National and regional incidence of surgery for adult hydrocephalus in Sweden Acta Neurol Scand; 2005; 112: 72-75.

52. UMAZUME K. & MATSUO H. Tokyo Medical College test for colour vision Die Farbe; 1962; 11(1/6.: 45-47.

53. VOS JJ. Literature review of human macular absorption in the visible spectrum and its consequences for the cone receptor primaries Report. Soesterberg: Institute for Perception TNO; 1972.

54. YOUNG T. The Bakerian Lecture: On the theory of lights and colors Philos. Trans R Soc Lond; 1802; 92: 12-48.

55. WALLESTEIN MB, MCKHANN GM. Salomon Hakim and the discovery of normal pressure hydrocephalus Neuros; 2010; 67: 155-159.

56. WALLS GL. How good is the H.R.R. test for color blindness? Am J Opt; 1942; 36: 169-193.

57. ZEKI S. A vision of the brain Oxford: Blackwell Scientific Publication; 1993.