Uniting Behavioral Optometry with Neurology and Genetics

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Abstract

Rapid advances in neural and genetic sciences are expanding the knowledge base for studying human behavior. Optometrists should be aware of current concepts and research studies in behavioral neurology and behavioral genetics because these perspectives may lead to new approaches to patients with visual disorders. This article addresses such issues as neurological functioning, environmental influences on gene expression, and the inheritance of visual behavioral disorders. The walls between behavioral studies and biology are crumbling. Combined efforts by optometric and biological researchers may lead to the identification of more specific processes in visual disorders and to the design of improved treatment modalities.

Key words

cognitive neuroscience, gene expression, strabismus, nearpoint stress

It is a common experience that some patients can undergo therapy such as visual training just once a week and yet show dramatic improvements in their behavior. Until now, clinicians have chiefly relied on behavioral theories, observations, and measurements to explain how brief sessions in therapy can sometimes produce changes in performance. So far, biological researchers have not been able to provide complete explanations for what transpires in therapy. In fact, one of the last frontiers in biology is the understanding of the connection between the brain and complex behavior, such as visual behavior. There are many unanswered questions: What role do neural elements play in changes in visual perception? How do individual differences in genetics correspond to alterations in visual performance? How do functional visual disorders reflect anomalies in brain function?

Behavioral neurologists study the ways in which various brain centers, brain metabolic processes, and cortical networks have to do with thinking, emotion, and behavior.[1-4] As the field of behavioral neurology expands, it is increasingly important for doctors interested in visual behavior to become familiar with discoveries underlying brain organization and physiology. In addition, clinicians sometimes examine patients with complex neurological and genetic syndromes that initially present as idiopathic ocular entities. In order to understand current research in neuroscience, it is important to first review some basic concepts and strategies in neurology and genetics.

Basic cognitive neuroscience

The fundamental tenet of cognitive neuroscience is that all behavior is a reflection of brain function. Cognitive neuroscientists develop models that often mechanistically link neural elements with the physiological activity that results in cognition, perception, and consciousness.[5] In the past, and to some extent the present, the central question in neuroscience has been whether brain function has a local or a global organization. More than a century ago, scientists, such as Paul Broca and Carl Wernicke, and phrenologists proposed that there is a localized, one-to-one correspondence between a brain region and a specific behavior.[6] At the beginning of this century, Korbinian Brodmann subdivided the human cerebral cortex into 47 areas, based on cell size and type.[6] Single-cell recordings in animals and brain imaging techniques have identified areas of Brodmann's map that correspond to particular cognitive functions. Other neuroscientists theorize that the brain has a holistic organization. They note that brain damage that impairs speech does not prove that the damaged structure alone regulates speech. These researchers contend that only lesions, not functions, are sharply localized.[7]

A half century ago, some neurological scientists proposed that the brain had equipotential characteristics. Equipoten-

tiality refers to the ability of any functional cerebral area to regulate a given behavior, and that all higher mental functions are represented throughout the cerebral cortex. This is an important concept because it embodies the idea that brain regions are plastic according to function.[7] Researchers have long recognized that human brains including the visual pathways are plastic. However, the definition of brain plasticity has changed over the years. The current concept is that plasticity is the ability of synapses to make functionally appropriate adjustments in their connecting patterns according to circumstances. These adjustments include altering their sensitivities or the number of synaptic connections.[8] Brain plasticity is believed to be preserved throughout life.[9]

In a more authoritarian era, some scientists thought that the brain functioned in a hierarchical way: lower cortical areas relayed messages to more powerful centers of activity. Modern neuroscientists postulate that brain functions share parallel architecture, perform several functions simultaneously, and coordinate or distribute brain processing within and across brain networks. Each node within a network serves a particular function. Experience induces quick changes in cortical networks, so that they are as dynamic as the brain itself.[7]

In the past, clinicians often categorized disorders according to whether they were organic, when brain lesions were identifiable at autopsy, or functional, when this was not possible. Contemporary neurologists are not as likely to make this distinction, since all changes in behavior produce changes in the nervous system in the nature or number of synaptic connections. All modifications of human behavior are biological and organic; all nurture is nature.[10,11]

Basic neurology and behavior

Various emotional states, such as well-being, elicit physiological reactions. The hypothalamus is the "head" ganglion of the nervous system, serving as a regulatory center for the control and discharge of these reactions.[4] Primary cortical sensory centers act as the initial entry points for outside stimuli and for the manipulation of the environment. Between the hypothalamus and the sensory cortices is the limbic system, which helps regulate emotion and memory, and the association cortex (prefrontal and parietal areas) which subserves sensory experience and motor planning.[4,12,13]

When a visual event triggers anger, stimuli reach cerebral cortical areas that include visual and memory centers, and the portion of the frontal lobe that has to do with personality. These areas are connected by the association tracts of the brain. From the cerebral cortex, especially the frontal lobe, there are pathways of discharge to the hypothalamus and then to descending neural areas.[4,12,13]

Human beings and higher nonhuman primates have similar genes and genetically determined features. Humans differ from other species mainly in the use of language and abstract thinking.[14] Perhaps the most solidly based observation in behavioral neurology is that the left hemisphere is dominant for language functions for most people. In addition, the left hemisphere is involved in the mental manipulation of numbers and fine-motor control in right-handed people. Damage to the left hemisphere is linked to disorders involving speech, complex movement, calculations, finger-naming, right-left orientation, and writing.[4] Evidence from CT scans and MRIs suggest that early damage to the left hemisphere can result in dyslexia.[4,15]

There is increasing evidence that the right hemisphere is dominant for the spatial distribution of attention, complex perceptual skills, nonverbal communication, and various types of emotional behavior. Damage to the right hemisphere can result in a lack of attention to the left part of space, confusion, problems in dressing, and denial of illness. Early injury to the right hemisphere can result in poor interpersonal skills, inability to show emotion, and diminished visuospatial abilities.[4]

The basics of brain imaging

Brain imaging methods provide clues about structural or functional disorders. During computerized axial tomography (CT), sets of X-ray measurements taken from multiple angles are reconstructed into images. X-rays passing through tissue emerge with lower or attenuated energy levels. Thus a CT scan can identify some biological structures, since attenuation values sometimes differ among tissues.[16] Although a CT scan makes bone tissue and cerebrospinal fluid easily visible, gray-white tissue contrast is only poorly visible. CT helps to identify structural areas in the brain altered by tumors, lesions, injuries, hemorrhages, and strokes.[16]

Magnetic resonance imaging (MRI) is based on the observation that some atomic nuclei act like magnets. Ordinarily, hydrogen nuclei or protons in body cells spin around randomly. When placed in a magnetic field, most of these hydrogen atoms align in the direction of the field, just as a compass needle aligns itself in the direction of the earth's magnetic field. After the pulse of energy relaxes, protons return to their original energy state and emit radio waves that are characteristic of the particular tissue.[16] It is as if MRI turns brain cells into miniature radio transmitters.

MRI is superior to CT in localizing a particular anatomical region of the brain or spinal cord suspected of causing a particular disease. The ability of MRI to distinguish gray from white matter within brain tissue makes it useful for detecting lesions seen in Multiple Sclerosis. Unlike CT, MRI can provide functional as well as structural information about the nervous system.[17]

Functional brain mapping is the visualization of local physiological changes that are correlated with the activation of motor, visual, or other cortical systems. Although still a research tool, brain mapping holds great promise for evaluating conditions such as Parkinson's disease, Alzheimer's disease, mental illnesses, alcoholism, and tumors.[18] Positive Emission Tomography (PET) has made the biggest contribution to functional brain mapping. With PET, subjects are injected intravenously with radioactive isotopes such as fluorine. These isotopes replace the oxygen in the glucose used by neurons. During PET, positrons collide with normal electrons in neurons, so that the two annihilate each other. The gamma rays that result go in opposite directions and at specific energy levels. By backtracking to find out where these collisions occur and by detecting changes in glucose levels, researchers can evaluate activities at different brain centers.[17]

PET studies show that increased synaptic activity correlates with changes in oxygenation and local blood flow in the brain. This technique provides useful information about brain receptor activity, cerebral blood flow, brain metabolism, neurotransmitters, pharmakinetics, and

and regions of the brain. These factors are not inherited but are transmitted culturally. Environmental factors can be both psychological or nonpsychological.[14,29] Perinatal insults, infections, poor nutrition, trauma, and drugs are nonpsychological stimuli involved in the expression of genes. Psychological factors that include stress and anxiety can lead to the production of steroidal hormones that help to regulate gene expression. Glucocorticoid hormones then bind to and activate specific receptors within cells. This process changes the rate at which genes are transcribed.[26]

Acquired changes in neurological behavior were first delineated in invertebrate animals such as the snail. In one study, animals subjected to controlled learning that gave rise to long-term memory had twice as many presynaptic terminals as untrained animals. Some forms of learning, such as long-term habituation, produced a regression and pruning of synaptic connections. This was not true for short-term learning.[30]

It is possible that acquired conditions, such as some visual behavioral disorders, are linked to learned, reversible defects in gene regulation. These defects result from altered binding of specific proteins to regulatory regions that control the expression of certain genes. A person may possess combinations of genes and alleles (a different but closely related gene at a certain point on a chromosome) for a condition such as a binocular dysfunction. However, unless environmental and genetic conditions are suitable, the person may not become impaired.

Behavioral biological research

Behavioral neurologists explore the correspondence between abnormal behaviors and disorders of brain metabolism; behavioral geneticists seek to learn more about how genetics helps to regulate neural functions and structures. A number of investigators have concentrated on studying the biological origins of schizophrenia, depression, and alcoholism. Ironically, behavioral geneticists are one of the few kinds of researchers who provide important scientific data to support the role of *environmental* influences on behavior, since they use the only nonexperimental designs that control for the influence of heredity on behavior.[31] Here are a few examples of their research findings.

1) In twin, adoption, and family studies, behavioral geneticists reached the extraordinary conclusion that parents have very little influence on the personality and mental ability differences of their children. Identical twins who are reared together are no more likely to be similar in personality than those who are raised apart. Identical twins who are raised apart are sometimes more similar in personality than those who are raised together. Genetic differences are thus the major determinants of personality differences within families. This surprising finding implies that everything parents do to treat their children similarly (toys, rules, television) does not make them more alike, or any more different than children raised in other families, than they would have been based on heredity alone.[31]

2) Scientists have recently discovered an allele of a gene associated with elite athletic performance among high-altitude mountain climbers. Also, after completing physical training exercises, performance on physical tasks improved elevenfold in people with this allele compared to those without it.[32]

3) Some alterations produce brain changes that may be observable in PET scans. Medications given for obsessive-compulsive disorders were found to produce significant changes in the glucose metabolic rate in a certain part of the brain only in people with this disorder who responded to treatment.[33]

4) Developmental dyslexia is a heterogeneous reading disorder in which there is a discrepancy between intelligence and reading achievement. Various definitions of dyslexia are based on the assumptions that there are no serious auditory, visual, psychiatric, social, or educational issues that could account for this discrepancy. However, it has been proposed that dyslexia begins with a family disposition to this condition, which is expressed through a propensity to develop a neurological abnormality.[34] In a study with dyslexic men, researchers used a PET scan to localize the neural correlates of impaired word recognition and phonological processing. Blood flow was measured in dyslexic and control groups while the subjects read aloud and did word recognition tasks. The dyslexic group showed significantly altered patterns of cortical activation in the mid- to posterior temporal cortex bilaterally and in the inferior parietal cortex, mainly on the left. The researchers concluded that in dyslexia there is a bilateral involvement of posterior temporal and parietal cortices.[35]

5) Experiments using animals and insects have provided information that may relate to human behavior. The primary somatic sensory cortex that maps the body surface area differs among individuals, depending on usage. Since we are each raised in a different environment, exposed to different combinations of stimuli, we develop different motor skills depending on training. In one study, monkeys who were trained to use only the tips of certain fingers showed an enlarged section of the brain area responsible for that task.[36]

6) Neurological researchers reported that there is a negative-feedback loop linked to a long-lasting decrease in the levels of acetylcholine, an excitatory neurotransmitter. Stress, acetylcholinesterase, and acetylcholinesterase agents, such as pyridostigmine, initially lead to increased levels of actetylcholine that, in turn, results in an increase in postsynaptic concentrations of calcium. Extra calcium induces a specific genetic transcription factor, which causes a prolonged decrease in concentrations of acetylcholine.[37] This study provides insight into how a brief experience becomes long-lasting neurochemistry, why stress impairs cognition, and how stress becomes a genetic event. Lowered levels of actetylcholine could explain the memory losses and cognitive problems of people with Alzheimer's disease or post-traumatic stress disorder. This research also has implications for the delayed neurocognitive problems reported by some veterans of the Gulf War, who may have been exposed to insecticides, nerve gas, and prophylactics used against nerve gas.[37,38]

(Research articles on behavioral genetics and behavioral neurology appear in journals such as Nature; Neurobiology of Learning and Memory; Neurogenetics; Neuropsychiatry, Neuropsychology and Behavioral Neurology; Behavioral Neuroscience; and Behavioral Genetics.)

Genetics of strabismus and nearpoint stress

Strabismus has many causes: no single gene, mechanism of action, or environmental agent has been identified. It is un-

pharmadynamics.[16,17] PET shows localized activations with the perception of color, shape, movement, and spatial localization.[19] PET reveals increases in blood flow in the occipitotemporal region during facial recognition; blood flow increases in the superior parietal cortex during spatial recognition. These findings confirm work with primates showing a different visual pathway for identifying what something is than for where it is.[19,20]

Another research tool for mapping the brain, functional MRI (fMRI), uses MRI to record neural signal changes that occur when a stimulus or task results in focal alterations in the oxygenation of the blood of brain tissue. fMRI is a noninvasive procedure that provides higher temporal resolution than PET.[16] Researchers use fMRI to study visual and motor cortices as well as language and memory functions.

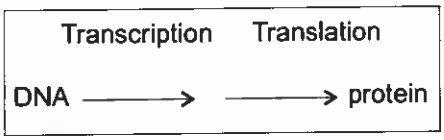
For different levels of brain function, researchers utilize various other methods to evaluate environmental influences on genetic variability. Structural proteins, hormones, and enzymes in neurological functioning are studied by conducting protein analyses, immunological and hormonal studies. Chemical methods are used to investigate the biochemistry of metabolites that are inside and outside the brain. Brain structure and development are evaluated anatomically, histologically, and by means of electron microscopy.[14] Electroencephalography (EEG) and evoked potentials (EPs) measure brain electrical activity. EPs reflect activity of the central nervous system in response to particular stimuli, whereas EEG reflects spontaneous activity of the brain.[21] Observations, clinical diagnoses, and behavioral tests are helpful in determining phenotype (the total of all the observable features of a person).[14]

Basic genetics

Clinicians recognize the importance of genetics when they take a family history. Heredity is a determinant of brain metabolism and brain structure; these characteristics influence behavior. Genetic factors are the major influence on the normal variability of drug effects; this requires doctors to individualize drug therapy. The mechanisms of action of different antibiotics and bacterial resistance to drugs are based on genetics.[22]

A gene is a part of a chromosome that contains the information to manufacture a specific protein, through the production of a specific ribonucleic acid (RNA). Transcription, messenger ribonucleic acid (mRNA), and translation play central roles in genetic activity. Transcription is the process by which RNA is formed from deoxyribonucleic acid (DNA).[23] mRNA is the sequence of nucleotides which is complementary to and transcribed from a single strand of deoxynucleic acid which manufactures proteins within living cells.[23] Translation refers to the process by which the linear sequence of nucleotides in a molecule of mRNA directs the specific linear sequence of amino acids, as during protein synthesis.[23]

The flow of genetic information into a normal cell is shown below.



During transcription, the first process in protein synthesis, a complementary strand of mRNA is produced according to the nitrogenous base code of DNA. In the nucleus, mRNA receives the genetic code in the DNA and carries it into the cytoplasm, where protein synthesis occurs. Next, during translation, the genetic code is transferred to an amino acid sequence in a protein.[23]

Environmental influences on gene expression

Genes, specifically combinations of genes and their protein products, determine the pattern of neuronal connections and influence behavior. Yet the genetic code by itself does not completely account for all the variance of behavior, since behavior and the environment can modify the functioning of nerve cells and gene expression. Gene expression refers to the phenotypic manifestation of genes.[23] Experience, including learning that results in dysfunctional behavior, produces changes in gene expression.[25]

The process of protein synthesis does not occur constantly in the cell. It occurs, instead, at intervals followed by genetic "silence." Various chemicals, most notably steroids, thyroid hormones, and neurotransmitters can regulate the process of genetic transcription.[26] Development, hormones, temperature, stress, and learning are factors that alter gene expression by modifying the binding of transcriptional activator proteins to each other and to the regulatory regions of genes. Upstream from the gene, the chromosome enhancer segment determines when and how frequently a gene is expressed or repressed.[25]

Learning and environmental influences cannot change the genetic code or alter the function of the gene to replicate itself reliably; however, learning and environmental influences can alter gene expression and affect phenotype.[25] This important and relatively new concept in biology is a modification of the Darwinian viewpoint that human beings are born with immutable characteristics.

In inherited and acquired disorders, there are four main possibilities by which gene expression can influence behavior. First, in an *inherited* disorder, with a normal gene and under normal conditions, the regulatory protein binds to the enhancer region. This activates gene transcription and leads to the production of the protein.[25,26]

Second, in an *inherited* disorder, a mutation appears that is linked to a rare, inherited disorder. A mutation is a permanent and heritable alteration in the sequence of nitrogenous bases of a DNA molecule, which leads to transcription of an altered messenger RNA. This would produce an abnormal protein, and give rise to the disordered condition.[25]

Third, in *acquired* conditions, such as neuroses or visual behavioral disorders, there could be an alteration in gene regulation. If the regulatory protein for a normal gene cannot bind to the enhancer site, then gene transcription cannot take place and the gene is not expressed.

Fourth, in an *acquired* disorder, the gene is expressed when a specific environmental experience leads to the activation of a chemical such as serotonin or a steroid. This allows the regulatory protein to bind to the enhancer site, and gene transcription to take place.[24,25] By this means, an abnormal learning experience results in the expression of a protein. This results in behavioral manifestations of the disorder.

Works by Lewis;[26] Vogel and Motulsky;[14] Hawkins;[27] and Jessel, Kandel, and Schwartz[28] are excellent sources of information about gene regulation.

Other environmental influences on genetic behavior

Environmental influences can be biologically incorporated in the altered expressions of specific genes, nerve cells,

clear why strabismus sometimes appears to cluster in families, since various studies support different hereditary components. Researchers are not sure why individuals with mental retardation, neurologic dysfunctions, muscular disorders, or craniofacial dysostoses are at increased risk for strabismus. It is also unclear why children with cerebral palsy are particularly prone to strabismus.[39]

It is difficult to study the genetic bases of strabismus, because operational definitions of "abnormal" alignments of the eyes are variable and debatable. Also, phorias are common in the general population; there is no general agreement about what is a normal phoria. Many genetic studies of strabismus have been retrospective and combined different forms of the condition; each of these forms could have different causes.[39]

There are a number of unanswered questions about the neurobiological aspects of strabismus. Is this condition linked to inherited biochemical or metabolic factors that interfere with the normal myelination of specific nerves in the visual system? Are there genetic neurobiological determinants in the tendency for retinal rivalry and the readiness to suppress, but not in the angle, type, or direction of strabismus? What is the exact mechanism and possible cortical site for retinal rivalry and suppression? Greater knowledge of the genetics of strabismus might help explain why a particular type of sensorimotor mechanism can overcome anatomical and mechanical obstacles that might otherwise result in this condition.[40]

Nearpoint stress is another visual condition that could have a genetic basis. Nearpoint stress may be the product of learned, culturally transmitted changes in gene expressions that are manifested in different visual symptoms. Regulatory proteins upstream from genes determine neuronal behavior in the visual pathways. As a result of stress, these proteins may not bind to the promoter site, so that gene transcription does not occur. If gene transcription does not take place in the regions of the brain that subserve accommodation or convergence, then neurotransmissions in these areas are altered, and synaptic connections do not develop normally or are pruned.

This hypothesis offers a new biological underpinning to some of the features of binocular dysfunctions and optometric rehabilitation techniques. An objective of vision training "is to create a visual environment in which the patient may modify his or her visual behavior and alter his/her visual performance to meet the visual needs of a specific environment."[41] A positive visual learning experience, such as during vision therapy, could lead to serotonin stimulating the enhancer or activating segment of genes. This would permit the initiation of gene transcription, creation or change in synaptic connections in the visual system, and corresponding changes in visual performance.

Future directions

Practitioners generally rely far more on their observations of patients than on recent findings from biological experiments. Clinicians should expand their perspectives and become more familiar with the latest research about the biology of the brain. As brain imaging techniques improve, biological methods might be useful not just for the diagnosis of different visual conditions, but also for the designing of more efficient preventive and therapeutic strategies. Decades ago, many psychiatrists doubted that there would be drugs to treat mental illnesses, just as today the notion of routinely using drugs to treat binocular disorders seems far-fetched. Nevertheless, in the future, both vision therapy and drugs may be used to treat some visual disorders. Researchers are only beginning to understand how biology influences the initial expressions and courses of various disorders and behaviors. Their work has implications for understanding *normal* visual processes such as visual memory, visual imagery, and visual navigation. Cognitive scientists are currently clarifying the roles played by different parts of the cortex in representing and encoding the local visual environment.[42]

Someday, practitioners might use biological research findings to predict and evaluate a patient's responses to different forms of treatment such as vision therapy, optical prescriptions, placebos, ocular vitamins, and ophthalmic drugs. In the meantime, visual scientists could work more closely with behavioral neurologists and behavioral geneticists in exploring subjects such as perceptual-developmental conditions, nearpoint stress, sports vision, the aging eye, binocular dysfunctions, progressive myopia, and dyslexia.

The merger of behavioral optometry with behavioral neurology and behavioral genetics would represent a new direction for optometry in the twenty-first century. Scientific information from these disciplines may eventually contribute to a unified biological understanding of visual behavior. The day may come—sooner rather than later—when there will be little need to use the term "idiopathic" to describe ocular and visual entities.

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