Face to Face

This section features conversations with personalities related to science, highlighting the factors and circumstances that guided them in making the career choice to be a scientist.

Do We Learn to See?

Torsten Wiesel talks to Prasanna Venkhatesh V

You wake up in the morning, open your eyes and voila it's all out there in front of you. Seeing seems so effortless, so automatic that we simply fail to recognize that vision is an incredible complex process – and still deeply mysterious process.

– V S Ramachandran

The human eye is a complex machine which allows us to see the world with unimaginable clarity in three dimensions. The credit goes not only to the eyes but also to the brain – after all, eyes are the outgrowth of brain. When we see things with our eyes, in addition to viewing an object, we are able to perceive its size, shape, motion, speed, depth, distance, direction, form, color and many more details just in a fraction of a second. Vision is an incredibly complex, intricate and yet fascinating process that requires numerous components of the eyes and the brain to work together coherently. One realizes the complexities involved in vision only when one tries to build a robot. It is difficult to train a robot to recognize and pick even simple objects. The brain does an awful lot of processing to see and interpret things.

All you are given are two tiny upside down two dimensional images inside your eyeballs, but you perceive a single panoramic, right side up, three dimensional world. How does this miraculous transformation come about?

– Richard L Gregory

The first step of this fascinating and powerful sensory faculty is carried out in the retina of the eye. The photoreceptors (rods and cone cells) in the retina collect the light and transduce the information as electrical signals through the optic nerve, to a network of neurons that go to the visual cortex in the opposite hemispheres of the brain via the lateral geniculate nucleus (LGN)[1].

[1] The lateral geniculate nucleus (LGN) is the primary processing center for visual information received from the retina of the eye. The LGN is found inside the thalamus of the brain, and is thus part of the central nervous system. Both the left and right hemispheres of the brain have a lateral geniculate nucleus, named so for its resemblance to a bent knee.

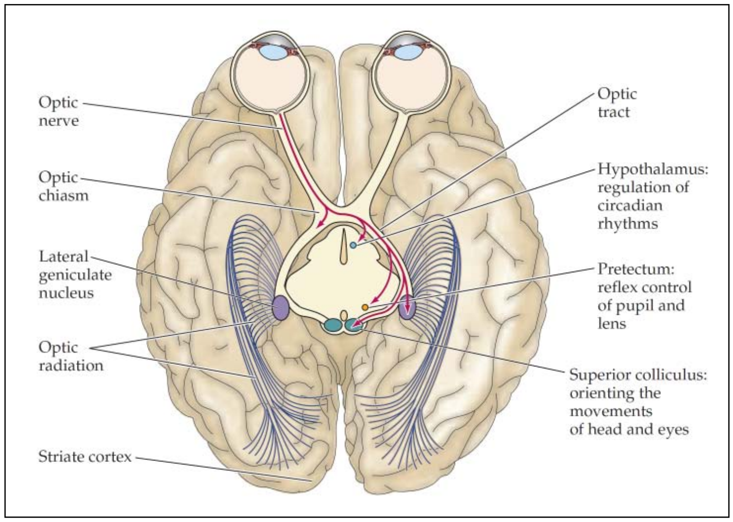


Figure 1. Central projections of retinal ganglion cells from the eyes. Ganglion cell axons terminate in the lateral geniculate nucleus of the thalamus; optic radiations end up at striate cortex. For clarity, only the crossing axons of the right eye are shown (view is looking up at the inferior surface of the brain).

Reproduced with permission from Purves *et al*., *Neuroscience*, Third Edition, Sinauer Associates, Inc. 2004.

The brain does the processing of those impulses and gives a meaningful interpretation about what we are seeing. This is a highly simplified description of the visual system. One should also bear in mind that each stage of the visual system is highly complicated and the intricacies of the neuronal circuit in the brain and retina are still not clearly understood (*Figure* 1)**.**

Our understanding of the intricate processes in the visual system stems from the work of the great neuro-anatomist Santiago Ramón y Cajal. The retina is a complicated structure both in its anatomy and physiology and Cajal was the first to elucidate the architecture and function of the retinal cells (*Figure* 2). Cajal thought that the cellular connections in the visual system should be organized with extreme precision to enable great analytical capability of visual information processing. Part of the observational evidence for the neuron doctrine came from the orderly organization of the retinal cells in alternate layers of cell bodies with their intercellular contacts.

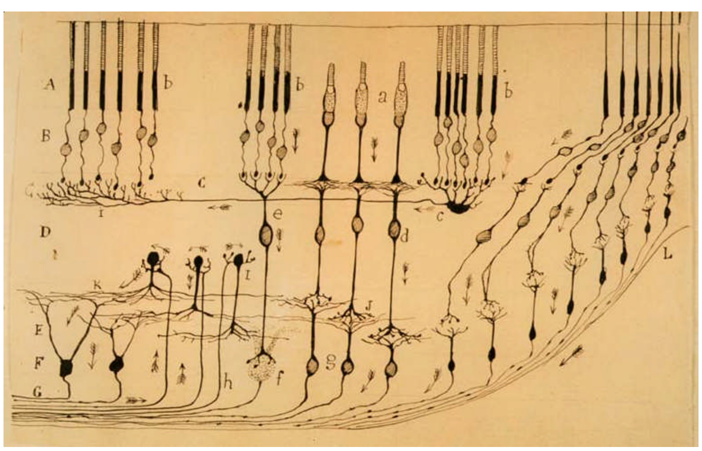


Figure 2. Illustration of the mamalian retina structure with artistic grouping of cells and direction of current flow by Santiago Ramon y Cajal, 1905. A, layer of rods and cones; B, visual cell body layer; C, outer plexiform layer; E, inner plexiform layer; F, layer of ganglion cells; G, optic nerrve fiber; L, central fossa.

Courtesy: Cajal Legacy, Instituto Santiago Ramon y Cajal (CSIC), Madrid, Spain.

Form this arose the main idea of unidirectional flow of the neuronal message from the sensory systems to the brain. In his Nobel Lecture Cajal describes the retina in simple terms:

In spite of its great complication, the retina can be considered as a nerve ganglion formed by three rows of neurons or nerve corpuscles: the first row encloses the rods and cones with their descending prolongations forming the external granular layer; the second is made up of the bipolar cells and the third contains the ganglionic neurons.

It was Prof. Stephen Kuffler who discovered that the initial processing of the visual patterns happens in the retina itself, before reaching the brain for higher levels of processing. Light from each eye falls on the 130 million light sensitive photoreceptor cells at the back of the retina and is converted into electrical impulses. The receptor cells do not send these messages directly to the optic nerve; instead they are transferred to the retinal ganglion cells via the bipolar cells. The nerve endings of the receptor cells contact with more than one bipolar cell and the same relation holds for the bipolar cells and the ganglion cells (*Figure* 3). These contacts are either excitatory or inhibitory and all the contacts are not necessarily excitatory. The stimulation of a small point in the retina will either increase or decrease the cell's electrical impulses. These connections filter and transform sensory information and thus create a net effect according to the type of input. This

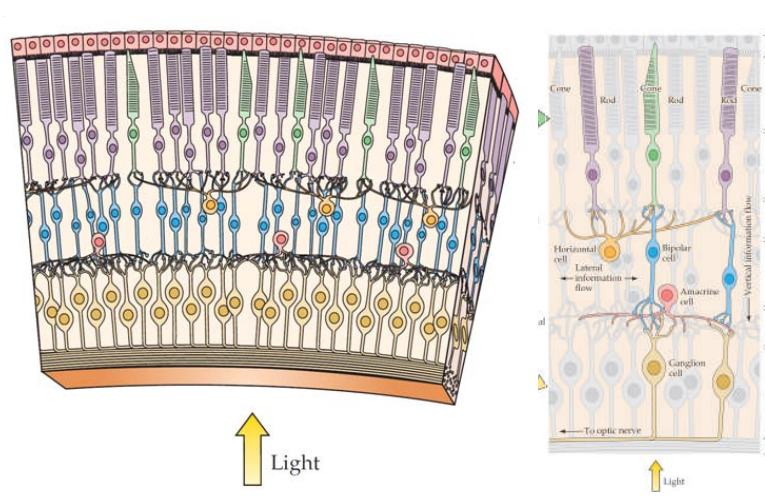


***Figure 3**. (Left) Structure of the retina. Section of the retina showing overall arrangement of retinal layers. (Right) Diagram of the basic circuitry of the retina. A three-neuron chain (photoreceptor, bipolar cell, and ganglion cell) provides the most direct route for transmitting visual information to the brain. Horizontal cells and amacrine cells mediate lateral interactions in the outer and inner plexiform layers, respectively.*

is a first level of information processing. Each sensory system first analyses, decomposes and then restructures the incoming raw sensory information according to its own built-in connections and rules.

In 1958, an accidental meeting of Torsten Wiesel and David Hubel in Prof. Kuffler's laboratory made one of the most sustained, productive and creative collaborations in contemporary science which gave rise to contributions of the highest order. Hubel and Wiesel made us realize that the brain does not simply take the raw data that it receives through the senses and reproduce it faithfully in the brain. Their work conveyed the message that each sensation is first investigated by certain receptors at the lower relay stations and then expatiated in the corresponding region of the cerebral cortex. In 1959 Hubel and Wiesel wrote their first paper in the *Journal of Physiology* titled 'Receptive fields of single neurons in the cat's striate cortex'. Later they came up with a series of extraordinary papers that emerged over a period of twenty years of collaboration. As a result of their exceptional accomplishments, David Hubel and Torsten Wiesel shared the Nobel Prize for Physiology or Medicine in 1981 together with Roger Sperry.

In order to understand the works of Hubel and Torsten, let us briefly review some of the historically significant discoveries which formed the basis of their work. It was known in the late 40's that single nerve cells in the somatosensory cortex respond specifically to submodalities[2]. For example, cells will respond either to superficial touch stimuli or to a deep pressure stimulus but not both. In 1957, Mountcastle made the most important contribution by identifying vertical columns of cells that run from the surface of the brain to the white matter, located together in the somatosensory cortex; each one is submodality-specific. Each region of the skin projects to a particular area of the cortex and all the cells in one particular column will receive inputs from receptor classes that get enervated either deeply or superficially. Thus each column acts as a separate logical module. This is one of the extraordinary findings for the understanding of the cerebral cortex since Cajal.

Around 1950, Stephan Kuffler first recorded the electric responses to spots of light from the retinal ganglion cells of the cat's eyes. He made a surprising discovery that the receptor cells do not simply signal the absolute levels of light. Rather, they signal the contrast between the light spot and a dark spot; these ganglion cells were named as *on-center* cells and *off-center* cells and the area that responds is known as the receptive field (*Figure* 4). Receptive field of the ganglion cell here refers to the region of retina over which we can influence the ganglion cell's firing (electrical

---

2 Submodalities refer to the subjective structural subdivisions within a given representational system. Each sensory modality will have a submodality, viz., visual submodality, kinesthatic submodality, feeling submodality and so on. For example, in visual terms, common distinctions include: brightness, degree of colour, size, distance, sharpness, focus, and so on; in auditory: loudness, pitch, tonal range, distance, clarity, timbre, and so on.

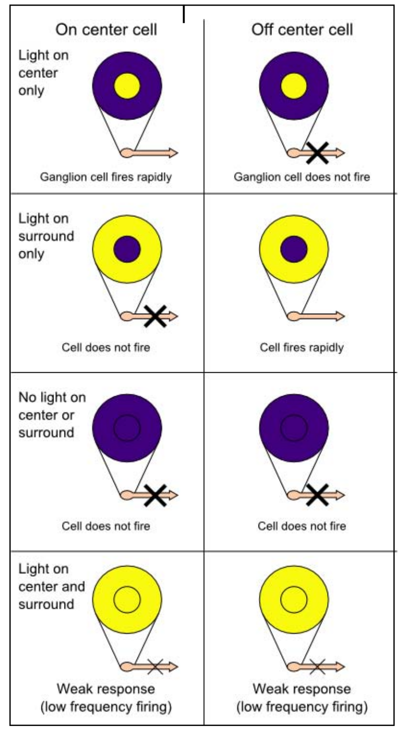


Figure 4. On center and off center retinal ganglion cells respond oppositely to light in the center and surround of their receptive fields. A strong response means high frequency firing, a weak response is firing at a low frequency, and no response means no action potential is fired.

Courtesy: Wikipedia.

activity) by light stimulation. The receptive field of the ganglion cells is arranged in such a way that they help in detecting the contrast in the visual information and this helps in detecting the edges and contours in the objects. Hubel and Wiesel took this to the next level, the LGN and found similar operating principles. They also wanted to see whether the same representation is found in the cortical cells. There was one more surprise – the cortical cells did not reproduce the input from the LGN but, these cells were now able to differentiate the linear aspects of the stimulus. The cortical cells' response proved to be very specific to the axis orientation of the line stimulus. Different set of cortical cells respond to different orientations of the stimulus; each small segment in the retina represents every angle. Hubel and Wiesel revealed that cells with similar orientation specificity were found in columns. They also found another completely independent column known as ocular dominance column, which is concerned with the information from both the eyes (*Figure* 5).

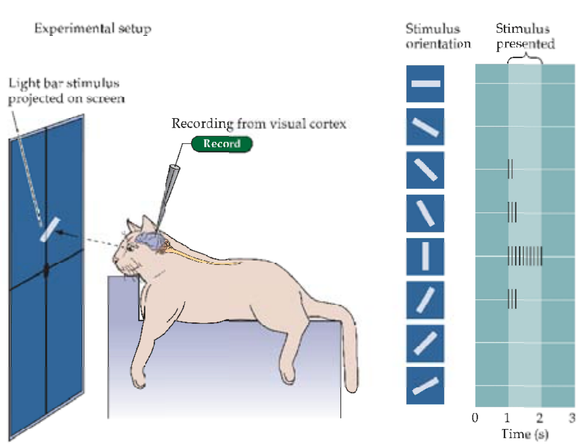


Figure 5. Illustration (cartoon) of the cat experiment by David Hubel and Torsten Weisel. Neurons in the primary visual cortex respond selectively to oriented edges. An anesthetized animal is fitted with contact lenses to focus the eyes on a screen, where images can be projected; an extracellular electrode records the neuronal responses. Neurons in the primary visual cortex typically respond vigorously to a bar of light oriented at a particular angle and weakly (or not at all) to other orientations.

Reproduced with permission from Purves *et al*, *Neuroscience*, Third Edition, Sinauer Associates, Inc. 2004.

Hubel and Wiesel later used the studies on the columnar organization of the cortical cells to investigate the effects of sensory deprivation during development. The deprivation studies in newborns addressed two questions – whether the connections responsible for the orientation selectivity were present in newborns or not and whether deprivation would interfere with the connections in the brain and eye during development. Wiesel and Hubel found that visual deprivation in infant monkeys profoundly alters the organization of their ocular dominance[3] columns. They found that by closing the eyelids of a newborn monkey for just a few days led to prolonged and sometimes irreversible blindness. In contrast, similar experience in an adult monkey produced no effect on its vision. These studies revealed that we are born with the faculty but a failure to make connections during development deprives vision. This work had direct clinical relevance; the observation that there is a period of plasticity in which recovery could occur (limited to first few months) encouraged ophthalmologists to operate the strabismus[4] as early as possible in order to avoid ambylopia[5]. Hubel and Wiesel could conclude that the cortex is organized into functional compartments or modules, and that this organization can be altered by experience. The collaboration between Hubel and Wiesel is on par with other great collaborations in the past like Hodgkin and Huxley, Watson and Crick, and Brown and Goldstein. What follows is an interview with Prof. Wiesel where he answers a wide range of questions posed to him.

PV: Could you tell us about how you got interested in studying the brain?

Torsten Wiesel: I grew up within the premises of a mental hospital outside Stockholm, where my father, a psychiatrist, was the director. Following my father's footsteps, I went to medical school and after graduation I was, because of my background, naturally inclined toward psychiatry. In fact I practiced adult psychiatry in the same hospital where I was raised and child psychiatry at the Karolinska Hospital. The lack of adequate treatments of mental disorders in the early 1950s led to the decision to return to my professor in neurophysiology with the aim to do basic neurobiology and with the hope to learn something about how the brain works. I spent a year in

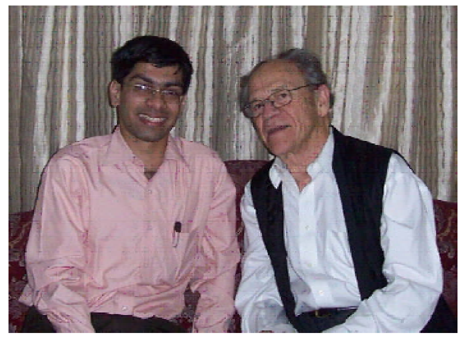
3 Ocular dominance, sometimes called eye dominance, it is the tendency to prefer visual input from one eye to the other.

4 Strabismus is a condition in which the eyes are not properly aligned with each other. It typically involves a lack of coordination between the extraocular muscles, which prevents bringing the gaze of each eye to the same point in space and preventing proper binocular vision, which may adversely affect depth perception. In lay terms it is know as 'Squint Eye'.

5 Amblyopia is a developmental problem in the brain; the part of the brain corresponding to the visual system from the affected eye is not stimulated properly, and develops abnormally. It is characterized by poor or indistinct vision in an eye that is otherwise physically normal, or out of proportion to associated structural abnormalities.This has been confirmed via direct brain examination by Hubel and Wiesel. They demonstrated the irreversible damage to ocular dominance columns produced in kittens by sufficient visual deprivation during the so-called 'critical period'. The maximum critical period in humans is from birth to two years old.

Box 1. Torsten Nils Wiesel

Dr. Torsten Nils Wiesel was born in 1924 in Uppsala, Sweden and received his medical degree from the Karolinska Institute in Stockholm in 1954. He taught in the Karolinska Institute's Department of Physiology and worked in the child psychiatry unit of the Karolinska Hospital. He started his work on ophthalmology with Prof. Stefen Kuffler at Johns Hopkins University Medical School in 1955 and became an assistant professor there in 1958. Later in 1959 he joined as an instructor in the Pharmacology Department at Harvard Medical School and became full professor in 1968. Currently he is Vincent and Brooke Astor Professor Emeritus in Rockefeller University, New York. Torsten Wiesel shared the Nobel Prize in Physiology or Medicine in 1981, with David Hubel for studies of how visual information is transmitted to and processed in the visual cortex of the brain along with Roger W Sperry. They investigated mostly cats and monkeys and identified specialized functions of individual cells in the brain's visual cortex. Torsten Wiesel and David Hubel also studied the role of innate and experimental factors in the development of the visual cortex; and this research has had important clinical implications.


Photograph of Prasanna Venkhatesh (left) and Prof. Torsten Wiesel (right) 17th November 2010, IISc, Bangalore.

Stockholm before my professor was asked by Dr. Stephen Kuffler: 'Do you have any students who want to come over as a postdoctoral fellow in my laboratory at Johns Hopkins Medical School in Baltimore, USA?' At the time I was working on epilepsy and I thought it would be nice to go to the United States. I first worked with Ken Brown, another new postdoctoral student working on cat electro-retinogram. When Brown departed and David Hubel joined the laboratory, we decided to explore the response properties of single neurons in the central visual pathways. Our approach was built on the fundamental discoveries by Kuffler, who demonstrated the classical 'on' and 'off' centre receptive fields of retinal ganglion cells, the neurons projecting centrally. Our question was, "What does the brain do with the information it gets from the retina?"

PV: What kind of experiments did you do in Prof. Stephen Kuffler's lab?

TW: When we started we did not have any hypothesis, we simply wanted to explore the response properties of single neurons in the primary visual cortex. We felt more like explorers during that time and it was only much later that we could ask specific questions based on the results from our initial explorations.

PV: What was Prof. Stephan Kuffler like, as a mentor and as a person – did he play an important role in your life?

TW: Prof. Stephen Kuffler was a great mentor and a wonderful person. He was very kind, helpful, and had a wonderful sense of humour. He could be quite critical and was very clear in expressing his views both in writing and speaking, which helped us greatly in our initial attempts to report our findings. He hated pomposity of any type and was keen on using appropriate words to express his thoughts correctly. He was an ideal role model also in that he believed that you should do experiments with your own hands, stay at the bench and avoid academic diversions. I think I was very fortunate to work with him.

PV: What are the aspects of your work that you particularly enjoyed?

TW: We used to start the experiments very early in the morning and go on for hours, most often throughout the night. During these experiments what we enjoyed were our discussions and plotting the next questions to ask. We developed our ideas during these long nightly discussions; it was like rolling a thread into a ball. A general rule seems to be that if you ask a good question, the answer should lead to additional interesting questions.

PV: What is your opinion about the emerging cross-disciplines in neurosciences? It is clear that it is a field with plenty of input from other disciplines. Which are the disciplines that are feeding into it most?

TW: Many of the current methods used in neuroscience have come from interactions with scientists in other disciplines. Looking at the history of neuroscience new techniques from physics and chemistry, including the current methods in optics, brain imaging and computer sciences have contributed much. I am a strong believer in research across disciplines, which no doubt will continue to break open new vistas and understanding about how the brain works.

PV: When we face obstacles in our research for reasons like the need for expertise in other areas, what should we do? Collaborate or learn to do it ourselves?

TW: David Hubel and I started as neurophysiologists, but as our research needs grew we had to learn anatomy, microscopy and computation for the specific purpose of 3D reconstruction of single cells and cross-correlation of responses of multiple neurons. At some point we were not able to do everything by ourselves but expanded our potential by seeking expertise from others.

PV: Chemistry is an integral science, playing a central role in improving the quality of our life. What do you feel about the contribution of chemistry in neuroscience?

TW: The interaction between chemists and biologists led to the field of biochemistry and soon expanded to the fields of genetics and molecular biology. Neurochemistry has long been and remains a major field in neuroscience recognized by a long series of important contributions and Nobel Prizes.

PV: It appears that advances in imaging technology like fMRI and MEG have been central to understanding the brain. How much has brain science changed in comparison to your earlier days?

TW: Certainly brain research has changed very much. From our experiments you can see that we used simple techniques and relatively simple experimental setups. We never invested much money in any technique unless it was clear to us that we really needed it to solve a given problem. No doubt, fMRI and other imaging systems have become major tools. To take full advantage of these new tools we must integrate structural information with functional localization, neural circuitry, functional anatomy and physiology.

PV: What is your view on recognition of scientific research by awards?

TW: It is easier to get funding for your research if you have received a big prize.

PV: The human brain is a complex non-linear system that defies all reductionistic and deterministic attempts to understand it. Plato once said that "The sum is more than its parts". What do you think should be the stand of a neuroscientist – reductionism or holism?

TW: Neuroscientists clearly differ in their stand on this issue. The more simple-minded approach in our research has always been to reduce the complex question of the structure and function of the primary visual cortex to its element parts. To fully answer the question about the neural basis of visual perception you must look at the system. In my own limited way I have stayed away from what you called 'holistic' approach. In the end both a reductionistic and holistic analysis of an issue are necessary for understanding the whole.

PV: What is your philosophy for understanding the brain? Are we heading towards seemingly inscrutable questions like consciousness and so on? Do you think truth about the brain will ever be found in terms of physical laws? (As Francis Crick put it, "The ultimate aim of the modern movement in biology is to explain all of biology in terms of physics and chemistry".)

TW: From the quotation it is clear that Francis Crick was a reductionist at heart and a most inspiring member of the neuroscience community. He asked big questions such as the basis of consciousness, which has stimulated an untold number of young scientists to look for an answer. Our knowledge of the brain is still very primitive and we will surely get many surprises as we dwell into the deep secrets of the brain. We must be very humble and careful in our search of the brain's secrets. In the working on realistic scientific issues is where the imaginative, creative part of research comes in.

PV: What is your advice to young scientists and students?

TW: Anyone who is getting into music should be tested very carefully, whether he/she has the ability and talent or not. If they do not have talent, it will be a waste of time. It's the same in science. If you want to be a mediocre scientist you could be, but being a mediocre musician is no fun either!

PV: You have trained six graduate students in forty years of research career. What do you look for in young students when they come to do research?

TW: Independent thinking, good training. Apart from grades, important factors are a student's willingness to do hard work and commitment to the work. When you come to do research you have to commit yourself mentally, physically, a total commitment is needed. Once you have made an important discovery you become conditioned and will keep going in spite of frustrations and failures. It is very important to select students carefully and nurture their talents well but early on provide them with opportunities for independence in identifying and executing their own research. It is true that very few students were trained in the Hubel–Wiesel laboratory, but having learned to stand on their own feet from the beginning they have all done exceedingly well and are now leaders in the field of neuroscience.

PV: There are so many fascinating questions about the brain, how could we focus on one problem and stop going into other questions?

TW: If you ask an important question, the answer will surely lead to more questions and you enter a never-ending journey!

PV: Are there any areas of science, outside your own, that you have been particularly attracted to – that if you were young and starting out today you could imagine yourself going into?

TW: Somehow I have always been drawn towards the sensory systems. Curiosity is and should be the main driving force in science. Unfortunately, funding agencies all too often ask "What's that good for?" If curiosity is killed, science won't progress.

PV: Do you think genetics will be able to answer some of the intriguing questions about the brain?

TW: Science advances to a large extent because new methods and new tools are developed to study the subject in more detail. Genetics is probably the area that has come to the forefront for all of us in biology. Genetics is one of the most useful and powerful tools for studying problems in neuroscience. But, I am seriously doubtful that it will give answers to all our questions about brain. Genetics is an important tool in studies of the nervous system in animals and humans, but it is only one of many approaches in finding out how the brain works.

PV: "Means to explore an object or event also modifies it at the same time". Some people call this as Biological Uncertainty Principle. Can you give your opinion on this?

TW: We have to keep in mind about the limitations of the methods that we use. The brain is a complicated system and in order to understand the brain fully we have to know much more than what we know at present. The answers that we get from all these relatively simple methods that we use certainly add to our understanding. Every generation will have new ideas and make new discoveries and that is how science develops step by step.

PV: Managing success is also a problem sometimes – how did you manage to continue your research after the Nobel Prize? What was the impact of the Prize in your life?

TW: My research continued uninterrupted for ten years after having received the Nobel Prize until 1991 when I accepted the Presidency of the Rockefeller University. Being a Nobel Laureate, people tend to take you more seriously, which was useful during my time as president. My own attitude has been to continue working as before and enjoy the pleasure of doing research. My general frame of mind should be clear from my response when awakened and still half asleep by a call from a news agency saying: "Congratulations! Do you know that you have been awarded the Nobel Prize for this year?" My response: "Oh No! I better go and hide!"

PV: What's your secret formula to success?

TW: This is a question commonly raised and my answer to students is: "You need to have good ideas, work hard and be lucky." This certainly has been true in my case.

PV: In a hypothetical situation, you encounter an omniscient person. What is the one question (only one) you would like to ask him?

TW: I don't know what one question I would ask, but I would be interested to know more about the developmental aspect of the brain and the balance between genetics and the environment in shaping a person. Such knowledge would be important and useful in education making it possible to identify individuals with special abilities in the sciences and arts, as well as individuals with special needs and those with brain-related disorders. We are still much in the dark in our understanding of the brain. A physicist told me a few years ago that "the brain will remain one of the great mysteries for the rest of this century and after most of the other issues in medicine have been fully clarified."

Acknowledgements

The author wants to thank Professors. Vijayalakshmi Ravindranath, Aditya Murthy, Arun Sripathi from the Centre for Neurosciences, IISc for their support and comments. The author also wants to thank Prof. S Ramakrishnan and Prof. S Mahadevan for their encouragement.

Suggested Reading

[1] H Kolb, E Fernandez, R Nelson, editors. *Webvision: The Organization of the Retina and Visual System*, [Internet]. Salt Lake City (UT): University of Utah Health Sciences Center; 1995. Bookshelf ID: NBK11530.

[2] D H Hubel, The Visual Cortex of the Brain, *Sci. Am*., Vol.209, No.5, pp.54–63, 1963.

[3] Eric R Kandel, An introduction to the work of David Hubel and Torsten Wiesel, *J. Physiol*., Vol.587, No.12, pp.2733–2741, 2009.

[4] D H Hubel, *Eye, Brain and Vision*, W H Freeman, NY, 1995. URL: http://hubel.med.harvard.edu/book/bcontex.htm (online version)

[5] Torsten N Wiesel, The Postnatal Development of the Visual Cortex and the Influence of Environment, *Nobel Lecture*, December 8, 1981. URL:http://nobelprize.org/nobel_prizes/medicine/laureates/1981/wiesel-lecture.html.

[6] David H Hubel, Evolution of Ideas on the Primary Visual Cortex, 1955-1978: A Biased Historical Account, *Nobel Lecture*, December 8, 1906.
URL: http://nobelprize.org/nobel_prizes/medicine/laureates/1981/hubel-lecture.html.

[7] T N Wiesel and D H Hubel, Effects of Visual Deprivation on Morphology and Physiology of Cells in the Cats Lateral Geniculate Body, *J. Neurophysiol*., Vol.26, pp.978–993, 1963.

[8] D H Hubel and T N Wiesel, Receptive fields of single neurones in the cat's striate cortex, *J. Physiol*., Vol.148, pp.574–591, 1959.

[9] V S Ramachandran, *Phantoms in the Brain: Probing the Mysteries of the Human Mind*, William Morrow, NY, 1998.

[10] Purves *et al*, *Neuroscience*, Third Edition, Sinauer Associates, Inc. 2004.

[11] D H Hubel and T N Wiesel, Early exploration of the Visual Cortex. *Neuron*, Vol.20, pp.401–412, 1998.

[12] Prasanna Venkhatesh V, Santiago Ramon y Cajal: Father of Neurosciences, *Resonance*, Vol.15, No.11, pp.968–976, 2010.

[13] Richard L Gregory, *Eye and Brain: The Psychology of Seeing*, Fifth Edition, Princeton University Press. 1998.

Prasanna Venkhatesh V, Department of Inorganic and Physical Chemistry, Indian Institute of Science, Bangalore 560 012, India. Email: prasanna@ipc.iisc.ernet.in, prasannapdkt@gmail.com