SECTION 5: TECHNIQUES IN COGNITIVE NEUROSCIENCES

5.1. *KEYNOTE ADDRESS*

THREE COGS IN THE COGNITIVE WHEEL

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ABSTRACT
Psychological view point considered human beings to be essentially animals endowed with a mind. Although the brain is fairly well developed at birth, cognitive development is a life-long process. The intelligent but ordinary human being depends on sensory input and reasoning for shaping his world view.
A unique feature of the human brain is cerebral asymmetry. It effectively doubles the capabilities of the brain for a given brain size. The ability to acquire knowledge by identity is not, however, inherent in human beings at the present stage of evolution. Then came functional magnetic resonance imaging (fMRI). Artificial neural networks are composed of interconnected units. Finally, it uses an input-output function to transform the input into its outgoing activity.

The core of cognition is the perception of the world around us. Unicellular organisms have a non-specific sensitivity to mechanical, thermal, chemical and various other stimuli all over their surface which helps them direct their movements towards food and away from danger. A similar sensitivity is displayed by simple multicellular organisms. Further, the simple nervous system that these multicellular organisms possess enables them to vary their future responses in light of previous 'experiences'. But it is unlikely that these organisms 'know' their environment. A major evolutionary advance was the arrival of bilaterally symmetrical animals with a well-defined head-end and tail-end. The head developed collections of sensory cells specifically sensitive to only one type of stimulus, which made a high degree of specialization possible. Secondly, the head lodged a large collection of neurons, the brain, where information arriving from sensory cells was received and processed. Further evolution, in general, led to a progressive increase in the size of the brain, and consequently greater complexity in the processing of sensory information (Bijlani 1997). At some point along the evolutionary journey, the neuronal processing somehow led to the animal becoming aware, or conscious, of the stimulus. When we put together information extracted from a variety of sense organs, we get a composite picture of the environment. Cognition is essentially this knowledge about our environment, but it is closely related to several other processes. We may store some of this knowledge for future use (memory), and may use the stored knowledge to modify our future behaviour (learning). Further, sensory stimuli frequently affect our emotions and elicit a response. Hence the process of perception cannot be separated from the processes involved in these sequelae of perception. Therefore cognition is defined as "all the processes by which the sensory input is transformed, reduced, elaborated, stored, recovered and used" (Neisser 1967). Looking at cognition from this broad angle, cognitive neurosciences include study of virtually all

higher neural functions. Cognition is a subject which has attracted psychologists, physiologists and philosophers alike. Further, observations made by neurologists and neurosurgeons on their patients have made valuable contributions to our understanding of the neural processes involved in cognition.

PSYCHOLOGICAL VIEWPOINT

Modern psychology was born about a hundred years ago, and started with fairly simple concepts. It considered human beings to be essentially animals endowed with a mind. Following this surface view, psychology has progressed in three directions. First, it has tried to reduce the black box called mind to objective, quantifiable components and indicators so that it can be studied through reproducible experiments. Secondly, it has tried to understand the biological mechanisms of the mind using physiological techniques. Finally, it has added 'depth' to its view of the mind by introducing the concept of the 'unconscious', and recently also 'height' by accepting the possibility of higher states of consciousness than the ordinary (Dalai 1991). Thus psychology has, on one hand, acquired a stronger scientific basis, and on the other hand moved closer to philosophy. The core of the psychological view of cognition was enunciated by Willian James who stated that perception arises from the object before us and from what is in our head. "What is in our head" refers to the result of processing in the brain, which influences the way the same object may be perceived by an individual under different circumstances, or by different individuals. The same processing also accounts for various illusions. In fact, cognitive processes may operate in the absence of any sensory input, as in dreams, or simply by using one's imagination in the waking state. Although the brain is fairly well developed at birth, cognitive development is a life-long process. A widely accepted scheme of cognitive development was provided by Jean Piaget (Morgan et al 1993). Up to the age of two years, the child operates primarily on the basis of reflex patterns. From the age of two to seven, the child uses sensory inputs and rudimentary reasoning skills to develop some concept of cause and effect. But the child remains highly egocentric like an animal. From the age of seven till about twelve, the child's reasoning skills get refined, but are still applied only to areas of concrete experience. From the age of twelve onwards, the child learns to apply reasoning skills even to hypothetical propositions. A little reflection would show that Piaget's stages roughly correspond to abilities seen in animals at progressively higher levels in the evolutionary scale. Thus 'ontogeny recapitulates phylogeny' is a concept not restricted to foetal development. Secondly, there is no reason to believe that evolution has stopped at the level of human beings. Finally, the maximum cognitive development achieved by specially gifted human beings may give a clue to the direction of fature evolution. What is possible for only a few now might become the average achievement of a superior species in times to come. The exceptional achievements may further be the result of not only exceptional talent, but rather follow concentrated effort, or sadhana. The intelligent but ordinary human being depends on sensory input and reasoning for shaping his world view. But the limitations and fallibility of both sensory perception and reasoning are well known. Therefore the additional channels by which an advanced sadhaka acquires knowledge may indicate the direction of future evolution.

PHYSIOLOGICAL VIEWPOINT

Although the cognitive psychologists have been expecting from physiologists for about 40 years the neuronal mechanisms underlying perception and related phenomena, till recently the physiologists did not have much to offer. The ascending sensory pathways had been worked out as was the representation of the body in the somatosensory cortex by neuroanatomical and electrophysiological techniques. But the process by which the modality and finer features of a sensory stimulus are abstracted from information delivered to the central nervous system in the form of nerve impulses was not known. But imaging techniques and modelling algorithms developed by computer scientists have given valuable insights into the cognitive process, and provided a ray of hope for further progress. For example, now it is known that there are multiple maps of the body surface in the somatosensory cortex, one for each submodality (Kandel et al 1995). Further, throughout the sensory system, cells responding to one submodality are grouped together in columns running from the cortical surface to the white matter. For example, in the visual cortex there are separate columns for form, colour and movement. Another important fact that has been learnt is that while the basic wiring of the brain is genetically programmed, the cortical representation of different parts of the body can be modified by experience. Use of a region increases, while disuse decreases the cortical area representing the region. Another major advance in cognitive physiology has been the delineation of the function of various association cortices. Association cortex has neither clearly sensory nor motor functions but occupies much more cortical area than either. Compared to our close cousins, the monkeys, in our brains the increase in association cortex has been much greater, in both absolute and relative terms, than the increase in senosry or motor cortices. Many observers have, assumed that here, in the interface between input and output, the grand syntheses of mental life must occur (Fischbach 1992), and recent discoveries indicate that they are right. The posterior parietal association cortex is concerned with visuomotor integration, spatial perception and directed attention, the parietal-temporal-occipital cortex with perception and language, the prefrontal cortex with cognitive behaviour and motor planning, and limbic association cortex with emotions and memory (Kandel et al 1995). A unique feature of the human brain is cerebral asymmetry. The .right hemisphere specializes in visuospatial tasks such as reading faces. On the other hand, the left hemisphere specializes in verbal and mathematical tasks. Cerebal asymmetry is an ingenious way of economising on neural tissue. It effectively doubles the capabilities of the brain for a given brain size. It is indeed a marvel how so much of sophistication has been packed into just about a kilo of neural tissue, and yet there is enough physiological reserve for some parts of the brain to take over the function of adjacent parts in case of loss of neurons due to a disease process.

The ultimate aim of physiological exploration is to understand how events in the brain give rise to the phenomenon called the mind. This is a question we still cannot answer but there are some answers available to the related question, viz., correlation between events in the brain and mental events. There appears to be synchronous and rhythmic firing by all neurons in the visual cortex affected by a visual stimulus. The frequency of the rhythmic discharge is 35-75 Hz. It has been suggested that rhythmic and synchronous firing might be the neural correlate of awareness and that it might serve to bind together activity in different cortical areas concerning the same object (Crick & Koch 1992). Although these recent advances are impressive and tell us what happens where in the brain when a particular mental event takes place, we are still far from understanding

how feeble electrical impulses and regulated release of neurotransmitters and neuromodulators are transformed into subjective experiences like a beautiful red rose, or sweet soothing music.

PHILOSOPHICAL VIEWPOINT

The philosophical quest about the nature of perception extends to directions scarcely touched upon by psychologists or physiologists. It raises two fundamental questions about our picture of the universe based on information gathered by sense organs: is the picture real, and if it is real, is it the total reality? Some philosophers with a spiritual bent of mind have dismissed everything perceived by the senses as unreal, as an illusion or maya, because of the impermanence of all terrestrial existence. But that is something we are not concerned with here, and in any case that is not the view of even all spiritual philosophers. In the language of the Upanishads, the universe, as we perceive it, is a manifestation of the Absolute, or the Brahman. If the Brahman is real, Its manifestation cannot be unreal. The manifestation may be only a partial reality, but it still remains real. However, what distorts our view of even the partial reality is the process by which it is perceived. Sight or hearing do not have a direct contact with the object of their attention. What we receive is an image or vibration, which is translated into a neural message. This machinery is highly ineffective, and if that were our only means, our perception would be very poor indeed. "But there intervenes a sense-mind intuition which seizes the suggestion of the image or vibration ... ... Whatever is deficient in the interpretation of the image thus constructed is filled up by the intervention of the reason or the total understanding intelligence. ... ... Man has had perforce to develop his reason in order to make up for the deficiencies of his sense instrumentation, the fallibility of his physical mind's perceptions and the paucity of its interpretation of its data. Our world-knowledge is therefore a difficult structure made up of the imperfect documentation of the sense-image, an intuitional interpretation of it by perceptive mind, life-mind and sense-mind, and a supplementary filling up, correction, addition of supplementary knowledge, coordination, by the reason" (Sri Aurobindo 1970)1. All this was philosophy when Sri Aurobindo wrote it more than 80 years ago, but today it reads like a contemporary description of functions of the association cortex which is now known to draw on past experience and logic to interpret a sensory message received by the primary and higher order sensory cortices. Thus, at least some spiritual philosophers like Sri Aurobindo consider the ordinary, or surface view, of the world to be real, but emphasize that it is only a partial and distorted view. This is a stand with which scientists would basically agree. The view is partial because our sense organs are only selectively sensitive to environmental stimuli. For example, the eyes are sensitive to only a limited range of the spectrum, and the ears can perceive only a limited range of frequencies. Further, it would be naive to assume that the type of changes taking place in our environment are confined to those which our sense organs can detect. Our world view is also distorted, as the innumerable illusions, which psychologists revel in and regale us with, would testify.

The question which naturally arises from our awareness of our limitations is whether these limitations can be overcome. Turning once again to Sri Aurobindo, they can be overcome by changing our method of acquiring knowledge. Methods better than employing our sense organs involve a more intimate contact with the objects being observed. The culmination of these methods is the observer identifying himself with the observed, i.e. when the subject and object acquire the same identity. Hence knowledge gained by this method has been termed knowledge by identity. The ability to acquire knowledge by identity is not, however, inherent in human beings at the

present stage of evolution. But the ability can be cultivated as a by-product of spiritual growth. The core of spirituality is belief in a common spirit permeating the universe. Once that belief is truly realised, the separative ego that separates self from non-self dissolves. The individual's consciousness acquires a new height, depth and width, which enables him to identify himself not with his mere physical body but with everything living and non-living in the universe. Sri Aurobindo has termed this state supramental consciousness. Supramental consciousness can be achieved by only a few at the present stage of evolution. But Sri Aurobindo has predicted that future evolution will be towards possession of such consciousness as a normal faculty characteristic of the species.

TECHNIQUES AND COGNITION

Let us descend from the technique for a few and the technique of the far away future to something more pragmatic. Absence of suitable techniques has been a stumbling block in the study of cognitive sciences. Most scientists concede that presently it is not possible to explore the subjective aspects of cognition. But instead of ignoring the subject altogether, they have adopted an analytical approach. First, they select some relatively simple aspect of cognition, e.g. seeing a spot or slit of light. Then they break the task into components, such as the form, colour and movement of the object seen. Then they study the neuronal correlates of these components with the help of techniques that happen to be available. Electrophysiologists have looked at single cell activity as well as patterns of activity of groups of neurons. The techniques have been adapted for delivering molecules which mimic or antagonize various; neurotransmitters, in order to get an idea of the chemicals involved in transmission of messages for a specific function. Much has also been learnt from the behaviour of patients with cortical lesions. But none of these techniques has given us much idea of neural correlates of higher mental function in the living normal human brain. That has become possible only very recently with the advent of non-invasive imaging techniques. The first of these to make its debut in the mid-eighties was positron emission tomography (PET). PET is based on increased uptake of glucose by the neurons which show enhanced activity during a specific mental task. Then came functional magnetic resonance imaging (fMRI). After the first paper on human fMRI was published in 1991, the number of MRI related papers that had been presented at international conferences exceeded 200 by 1998 (Tanaka 1999). Compared to PET, there are several advantages of fMRI. First, fMRI uses no isotopes, and therefore repeated measurements are safe. Secondly, it gives better spatial resolution than PET. Finally, MRI systems are more commonly available in medical institutions because of their clinical applications. Functional MRI is based on the principle that increased neuronal activity leads to a local increase in blood flow through a part of the brain. Although increased blood flow is accompanied by increased oxygen consumption, the blood flowing through the hyperaemic region has more oxygenated haemoglobin than the blood flowing through the rest of the brain. Since the magnetic properties of oxygenated and deoxygenated haemoglobin are different, the magnetic resonance signals from the active region of the brain increase. Functional MRI systems currently in common use give a spatial resolution of about 2 mm. However, a resolution of 0.5 mm seems to be wicnin reach, and when this happens it will be an important breakthrough because cortical columns also have a width of about 0.5 mm. Even that will not tell us how information is processed by individual neurons, but we are still far from a non-invastive.technique for measuring single cell activity. Another useful non-invasive technique is magnetoencephalography (MEG), which can complement the information obtained from the conventional electroencephalography (EEG). MEG is based on the principle that neuronal activity in the cerebral cortex generates not only fluctuations in electrical potential (detected by

EEG) but also magnetic fields. Unlike EEG signals, MEG signals are not distorted by the intervening tissues and low-pass filtering effects (Cichocki 1999). These technical advances have given hope for rapid progress in the near future They are likely to be further supplemented with theoretical exercises based on experiences with artificial neural networks (Hinton 1992). Artificial neural networks are composed of interconnected units. Each unit is a model neuron. A common variety of network consists of input units, ' hidden' units, and output units. Synapses are modeled by a modifiable 'weight', which is associated with each connection. Each unit multiplies every incoming activity by the weight of the connection. Then it adds up all the weighted inputs to get a single value for the input. Finally, it uses an input-output function to transform the input into its outgoing activity. Such networks can now not only perform fairly complicated tasks like making a clinical diagnosis, but also learn from experience. Because of the unmistakable similarity in the behaviour of artificial neural networks and the brain, they provide a model for at least one way in which the brain might be working.

CONCLUSION

One of the greatest miracles of the universe is the phenomenon called life with all its complexity and diversity. The higher forms of life have a mind which imparts them some awareness of their surroundings, and also the curiosity to question the nature of whatever they observe. Human beings have questioned, among other things, the mechanism of awareness itself. Depending upon their inclinations and the tools available to them, they have looked at it from different angles. Nature evolved only the phenomenon, the different viewpoints are a human creation. Therefore, to understand the phenomenon better, a periodic synthesis of different viewpoints is essential. The phenomenon of cognition consists of perception and its sequelae. Perception depends on information gathered by our sense organs. Sense organs are like dim torches which light up a bit of the universe, not perfectly, but sufficiently well for us to find our way. One way to look at yoga is to consider it as a path which makes such enhancement of human capabilities possible. As Swami Vivekananda has said, yoga may be regarded as a means of compressing one's evolution into a single life.

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FOOT NOTES

1 The essays in the compilation referred to here were originally written in fifty-four instalments between August 1914 and January 1919.

2 Sri Aurobindo once said that philosophers think while he only saw, and therefore denied being a philosopher. But the label of philosopher has stuck.

5.2. *INVITED TALKS*ASSESSMENTS OF FRONTAL LOBE FUNCTIONS

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ABSTRACT

The frontal lobe consists of three major divisions, i.e., the motor cortex, pre motor cortex and the prefrontal cortex. Lesion studies in animals and human have enabled an understanding of the functions of the frontal lobes. Each motor cortex controls the contralateral side of the body. On the dorsolateral surface is the frontal eye fields, which control eye movement. The inferior dorsolateral prefrontal cortex has the Broca's area, essential for expressive speech. Verbal strategies, an essential element for processing of verbal and visual material are compromised. Allocation of attention may be measured by tests of divided attention, mental workload and trail making tests. The frontal cortex, is the action cortex. The frontal lobes formulate goals, plan the action sequences and execute the actions to attain the goals.

The frontal lobes comprise the anterior one third of the cortex in the human brain. It is anterior to the central sulcus and superior and rostral to the Sylvian fissure. The anterior corpus callosum connects the right and left frontal lobes. The frontal lobe consists of three major divisions, i.e., the motor cortex, pre motor cortex and the prefrontal cortex. Phylogenitically the prefrontal cortex increases in size in the course of evolution and is largest in man. Ontogenetically synaptic connectivity and dendrite branching increase in the prefrontal areas till five years of age. The process of myelination continues till 12 years of age.

METHODS FOR LOCALIZATION, OF FUNCTIONS

Spatial localization of psychological function in neuropsychology is achieved through the traditional lesion method and the recent functional imaging techniques. Lesion studies in animals and human have enabled an understanding of the functions of the frontal lobes. Functional imaging techniques such as PET, fMRI and ERP have opened a new window to functional localization. Imaging of multiple foci of activations, along with the temporal connectivity of the activated brain regions in abnormal brain as possible.

FUNCTIONS OF THE MOTOR CORTEX

The motor cortege occupies the dorsolateral and medial cortices just anterior to the central sulcus. The body is represented as an inverted homunculus with the extremities occupying a larger surface.

The mouth area is in the inferior dorsolateral surface, the foot in the superior medial surface. The motor cortex mediates execution of voluntary motor movement. Each motor cortex controls the contralateral side of the body.

FUNCTIONS OF PREMOTOR CORTEX

Anterior to the motor cortex is the pre motor cortex. On the medial surface is the supplementary motor area (SMA). SMA. also has a homunculus and is essential for the initiation of the motor act. The contingent negative variation (CNV) recorded as a slow negative shift in the ERP is a measure of preparatory set preceding initiation. The Bereitschaft potential preceding the motor act is a measure of initiation. On the dorsolateral surface is the frontal eye fields, which control eye movement Smooth pursuit eye movement is a measure of its functioning. The inferior dorsolateral prefrontal cortex has the Broca's area, essential for expressive speech. Spontaneous, fluent and grammatically speech are mediated by this area.

FUNCTIONS OF PREFRONTAL CORTEX

The prefrontal cortex lies anterior to the premotor area. It consists of the dorsolateral convexity mainly involved in cognitive functions. Inferior ventral portion of this convexity mediates semantic processing. The orbital surface mediates emotions and inhibitory control. The medial surface mediates motivation and alertness.

FUNCTIONS OF THE DORSOLATERAL CONVEXITY

The dorsolateral convexity mediates executive functions, semantic processing and motor programming. The overall plan of motor act is formed here, while the micro aspects of motor control are formulated in the premotor and motor areas. Deficits in complicated motor acts requiring a plan of action are symptoms of prefrontal lesions. Semantic processing at a simple level takes place in the inferior portion on the dominant side, as seen on imaging studies. Verbal fluency, semantic judgements and generation of semantically related activate this area. The dorsolateral cortex mediates organization of meaning. Lesions produce fragmented recall of passages, poor organization of word lists. Verbal strategies, an essential element for processing of verbal and visual material are compromised.

Executive functions which foster goal directed behaviour are mediated by the dorsolateral convexity. Working memory, planning, set shifting, categorization and abstraction, allocation of attention comprise executive functions. These functions regulate thought and behaviour in line with the current goals of the person. Tests of verbal and visual spatial working memory measure storage and on-line manipulation of verbal and visual information, respectively. Word span and digital span are measures of verbal storage. Digit backward, mental arithmetic, verbal back tasks are measures of on-line manipulation or central executive processes in the verbal working memory. Figure recall is.a measure of visual storage, while mental rotation, visual n back task, block tappin span, location memory are measures of visual central executive processes. Tower of London and Tower of Hanoi, maze learning tests are measures of planning. Wisconsin card sorting test is a measure of set shifting and categorization. Progressive matrices tests and analogies tests are measured of abstraction. Allocation of attention may be measured by tests of divided

attention, mental workload and trail making tests. Other functions of this area are error detection, meta cognition, meta awareness.

FUNCTIONS OF THE ORBITOFRONTAL CORTEX

It is the highest center for inhibitory control. This area mediates inhibition of irrelevant responses, well-established respons tendencies, of motor actions, emotional reactions and instinctual reactions. The GolNog tasic, Stroop test, tests of motor preservation, tasks given with distracters, measure inhibitory control.

FUNCTIONS OF THE MEDIAL FRONTAL CORTEX

Lesions of the medial frontal cortex result in apathy, amotivation, inability to put in the required effort. Together with the anterior cingulate, it maintains the attention required for action. Behavioral effects of prefrontal lesions; Lesions in the orbito frontal cortex can cause changes in personality such as pseudopsychopathic and pseudo depressive syndromes. Social inappropriateness, emotional blunting, may be seen. Dorsolateral lesions can lead to poor judgement. Interview is a good method to elicit these changes.

CONCLUSIONS

The frontal cortex, is the action cortex. It has connections with other cortical and subcortical structures. Most of these connections are reciprocal. The frontal lobes formulate goals, plan the action sequences and execute the actions to attain the goals.

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MEASUREMENT OF IMMUNE FUNCTION IN PSYCHONEUROIMMUNOLOGY

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ABSTRACT
There is no question that the psychobehavioral modulation of immune functions occur. Among functional assays, cytotoxicity tests are used to measure the ability of T cells and NK (natural killer) cells to induce apoptosis and/or produce cytolytic molecules that create holes in the membrane of target cells, detected by the release of radiolabelled substances. Although information about the cytotoxic potential of cells is provided, most assays employ tumor cell

lines and the physiological relevance of cytotoxic responses are not often clear. Measurement of antibody titers and total immunoglobulin offers some information about the efficacy of the humoral arm of the immune system.

There is no question that the psychobehavioral modulation of immune functions occur. However, the clinical significance of altered immune competence as measured by in vivo and in vitro assays of cellular and humoral responses remains to be determined. Part of this uncertainty springs from the considerable number of immunoassays employed and thee relatively crude information obtained from them. And in the face of the extreme complexity of the interaction between the immune system and the complex workings of the mind/brain, careful attention to the technical considerations is essential to obtain useful results. Because the immune system is a highly conserved apparatus designed to maintain homeostasis in the face of internal as well as external stressors, changes in immune function are likely to be subtle. Therefore, the detection of cytokines, that provide for cell signalling and immune regulation, is the most sensitive and hence most appropriate general methodology for detecting small changes in immunological status. The clinical relevance of other immunological parameters such as peripheral leukocytes counts and differentials has lead to the widespread use of FACS (fluorescence activated cell sorting) analysis. Based upon their physical properties (granularity, size and shape) and surface CD markers detected by fluorochrome-labelled monoclonal antibodies, numbers and activation status of subsets of peripheral leukocytes can be determined. However, cell numbers do not necessarily correlate with cell function and there is often overlap between lymphocyte subsets many of which have different functions. Therefore, expression of results as cell ratios combined with studies of cell function are more useful than counts alone. Among functional assays, cytotoxicity tests are used to measure the ability of T cells and NK (natural killer) cells to induce apoptosis and/or produce cytolytic molecules that create holes in the membrane of target cells, detected by the release of radiolabelled substances. These assays are relatively easy to perform although the use of a radiolabel and the use of peripheral total cell populations are drawbacks. Although information about the cytotoxic potential of cells is provided, most assays employ tumor cell lines and the physiological relevance of cytotoxic responses are not often clear. Cytotoxicity assays using purified cell populations should be performed with cytokine and proliferation assays to allow conclusions about possible mechanisms of altered killing activity to be drawn. Measurement of lymphocytes proliferation in response to a polyclonally nonspecific (mitogens) or specific (antigen) is usually considered to be indicative of the ability to mount an immune response. Cell division, an early event in the initiation of an immune response, is measured by the uptake of a radioactively labeled (usually tritiated) thymidine. The use of several different mitogenic stimuli can often provide insight as to where in the proliferation process a change has occurred. However, these assays do not allow discrimination of actual subsets responding or take into account possible alterations in responsiveness due to altered cell numbers. Further, stimulation with specific antigen frequently employs soluble preparations to which some cells (CD8+) are less capable of responding than are the CD4+ cells. Measurement of antibody titers and total immunoglobulin offers some information about the efficacy of the humoral arm of the immune system. The most common assay used if the ELISA (enzyme-linked immunosorbent assay), that is easy to perform and can be adapted to measure different immunoglobulin

isotypes as well as antigen-specific antibodies. However, unless careful attention is paid to the location of sampling and time after antigenic stimulation, antibody and immunoglobulin measurements are rather crude and uninformative measures of immune alterations. In conclusion, a single immunological index should not be regarded as an adequate marker of immune function and the choice of assays employed should be aligned with the question being asked and with the known disease process being studied. Attention must be paid to confounding host variables such as nutritional and psychological status and of course, caution must always be exercised in the interpretation of any immunological data as the assays employed can only be considered relatively crude measures of an extremely complex system.

COGNITIVE EVENT RELATED POTENTIALS

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ABSTRACT
Electrical signals from the brain, were first recorded noninvasively by Hans Berger from scalp electrodes. This opened a new era for understanding brain physiology in cognition. These electroencephalographic (EEC) signals can differentiate levels of consciousness, viz., awake, sleep, coma etc. Mood states also affect these signals. However, this effect is neither specific nor characteristic of a mood state and hence cannot be used in diagnostic investigations. Sensory stimuli result in electrical signals in the process of sensation. These signals arise from the sense organ and are conducted to the brain. These signals, by virtue of very small amplitude as well as being very focal, are not discernible in resting EEG records. Cognitive functions such as attention, identification of a stimulus and memory produce relatively larger amplitude and more diffuse signals. It is hence tempting to use these to understand brain physiology of cognition.

Conscious mental state, required for cognitive activity, generates near random and high voltage electrical activity from most brain areas. The corresponding, scalp-recorded EEG has amplitudes of several tens of microvolts, in contrast to about only a few microvolts of changes induced by the cognitive events. As a result, in conventional EEG records, the changes related to cognitive events cannot be recognized. A special procedure is developed to extract from the EEG such a physiological signal evoked by a stimulus or cognitive event. The procedure is called signal averaging. The EEG signal has random variations in either directions. In contrast, a signal evoked by an ascending sensory stimulus or that related to a cognitive event has a known morphology and is temporally linked to the stimulus or the event. This physiological signal is also expected to have similar morphology each time it is generated by the same process. In signal averaging these concepts are utilized to extract the required physiological signal. Several small epochs of EEG each time-locked to the stimulus or event in question are collected. Using appropriate algorithms these epochs are averaged. The random EEG cancels out in successive averages. The physiological signal time-locked to the stimulus or event becomes clearly defined in successive superimpositions. Although averaging is a time-tested method to extract the event related potential, methods are also developed to extract the same from single trial EEG epochs.

Types of ERP's : The sensory stimulus at once activates the sense organ and the corresponding centripetal pathways to brain independent of the individual paying attention to it. The potentials are generated early in time-course (within tens of milliseconds) following the stimulus and reflect the integrity of the specific sensory pathways. These have been utilized in neurological diagnosis. This evoked physiological response is dependent on the stimulus and its cognition by the subject. It is referred, hence, as the averaged evoked response (AEP). The subject .is expected to make a chosen mental operation (passively or actively) to a stimulus whose physical properties may be different. In relation to this event, a brain signal is generated well after the stimulus itself has been transmitted to the brain. This event related potential (ERP) too is time-linked to the event but occurs at a later time point (upto a few hundred milliseconds). The nature of this potential hence is dependent not on the stimulus itself but on the subject's awareness of the stimulus and consequent cognitive operation. These are therefore also called cognitive potentials. Needless to state that integrity of the sensory system is needed to test the later cognitive components using ERPs. In conscious individuals who have intact sensory systems, ERPs reflect specific cognitive operations such as attention and memory. Typical examples of the ERPs are the P300 and the contingent negative variation (CNV). Others include the bereitshaft potential (BP), the N400 and the mismatch negativity (MMN). The latter, being more recent, have been insufficiently researched. For the present review, only P300 (also called P3) will be included. A list of reviews published in the past five years on event related potentials is also provided for the benefit of readers. One of the conventions followed in naming the ERPs is the use of the letter 'N' (negative) or 'F (positive) to denote the polarity of the potential with a suffix (100, 200, 300 or 400) to denote the modal time of its occurrence after stimulus. Some replace the suffix with a numeral to indicate the ordinal place of occurrence of the wave, e.g., PI, N2, P3, etc., in an ERP testing paradigm. Measures of the ERP used commonly are the amplitude and latency of a peak. The amplitude is measured as a difference between the prestimulus baseline and the selected peak. The former can be either an isoelectric baseline or the preceding wave of converse polarity (e.g., N2-P3). Latency is measured from the onset of the stimulus to the peak of the wave.

P300: Among a set of stereotyped stimuli, if a rarer but novel stimulus occurs randomly, the latter produces a positive potential about 300 msec later, the P300. This is the typical 'oddbaP paradigm used to elicit P300; stimulus novelty elicits P300.

Recording principles: It is not known which anatomical site generates P300. However, the potential is rather diffuse and occurs with the highest amplitude over centropareital areas. Accordingly, in a standard clinical testing, electrodes are placed at Pz, Cz and Fz sites referenced to linked mastoids. A fourth recording channel from outer canthus of an eye (for EOG) is also recorded to exclude eye movement related artifact. This is defined as any wave of more than 40mcV in the corresponding EOG channel. All modern averagers or averaging softwares provide a facility to automatically select EEG epochs which are artifact-free. Setting the EEG amplifier conditions is important. The low pass filter is set at 35Hz whereas the high pass filter at 0.5 Hz. Increasing the latter (some times due to the limitations of the amplifiers) attenuate the amplitude and changes the latency. The ERP can be extracted by averaging about 25-30 epochs of EEG each of one second length, picked up from 50 msec before the presentation of novel stimulus. Most averagers also have a facility to average EEG signal time-linked to the preceding nonnovel/frequent/unattended stimulus. It is recommended to repeat the task experiment and verify replicability of the ERP wave where possible. However, unlike early AEPs, there is a wider intraindividual variation in latency and amplitude. The P300 peak is

detected as the most positive wave occurring in a time window of 250-600 msec. Other criteria include:

a) The wave, if noted, has lower amplitude in frontal than centropareital leads,
b) It is absent or of insignificant amplitude in the averages from the frequent stimulus,
c) It is preceded by the N1-P2-N2 complex, and
d) There is no wave at a corresponding latency in the EOG lead. The last is unlikely to happen if one excludes all epochs which are associated with EOG artifact.

Stimulus: This consists of a train of stimuli in auditory or visual modality presented at a rate of once in two to three seconds. In the former, two distinct pure tones (50 -100 msec duration with rise and fall times of 5-10 msec; 30 dB above hearing threshold) are used; e.g., lOOOHz tone as a frequent one and 2000Hz tone as the novel one. The novel tone is randomly placed at about 20% chance between the frequent tones. In the visual modality, the frequent stimulus is a horizontal bar appearing on the computer screen and the novel one is a vertical bar. Attending to the novel stimulus produces a better P300 and hence the subject is asked to mentally count the number of novel stimuli or 'press a switch on detecting it during the stimulus presentations. It should be noted that P300 is also elicited in the absence of such response from the subject. It is desirable that the number of correct detections of the novel stimulus by the subject in a recording session is noted. In order to allow distraction-free stimulus presentations, a quiet or preferably sound-attenuated room should be used.

Factors affecting P300: Several factors affect the ERP. It is important to consider these carefully and control for the same in experimental situations. For clinical applications, each laboratory should standardize the procedures. Largely, these can be classified as stimulus/task-related and subject-related.

Task-related effects on P300: These also change the stimulus novelty and exert differing demands on the cognitive operations. Unattended rare tone too elicits asmall P300 (P3a) at the central sites. The task of attending to the novel stimulus increases the amplitude and the P300 is a shade later in its peak and is maximal at the parietal sites. Attending the target/novel stimulus by either mentally counting or by depressing a switch have no differential effects. Task difficulty increases the latency. Task difficulty can be achieved by narrowing the differences between the frequent and novel/target stimulus. Another method is to deliver the stimulus monaurally in an individual who has normal hearing on both ears. Once above perceptual threshold, stimulus intensity does not significantly influence the P300 measures. Novel stimulus's probability in the entire experiment (global) has inverse relationship with amplitude. Optimum probability should be between 15 and 20 percent. Within a testing session, if the target appears more often than once in last five stimuli then the later target stimulus produces lesser amplitude signal. Accordingly, in newer averagers, the target - nontarget occurrence is in a 'pseudorandom' sequence. This means that although the global probability of the target is 20%, that no two target stimuli occur consecutively. Smaller interstimulus intervals lead to smaller amplitude P300, although the probability of the target is unchanged. Optimal interval is 2-3 seconds. If the target's occurrence is not random but regular, the amplitude decreases. In summary, target probability, its randomness, task difficulty and interstimulus interval affect the P300 latency and more so its amplitude.

Subject-related effects: P300 'matures' by about 20 years of age; latency decreases with advancing age being lowest between 15 and 25 years. In adults age has significant positive correlation with latency and inverse correlation with amplitude. Although some authors suggest that P300 latency increases by l-1.5msec/year after adulthood, this assumption is too simplistic and not universally applicable. Amplitude too decreases with age and its (amplitude) relationship is less consistent than that of latency. Several factors differentially affect P300 in elder subjects and hence the association between age and P300 parameters is still inconclusive.

Drugs : have in general less significant effect on P300 parameters. Anticonvulsants, levodopa and methylphenidate had no influence. Anticholinergics and sedatives prolonged the latency and decreased the amplitude. Except under inebriated state, recency of alcohol intake affected P300 little. Although smokers and nonsmokers did not differ in P300 measures, in smokers recency of smoking affects; more recent smoking makes the amplitude higher and latency shorter. P300 measures are also affected by the time of testing. Towards evening, the person is likely to be tired and the amplitude smaller. Fasting and low blood sugar levels reduce the amplitude and prolong the latency. Low, body temperature increases the latency. Seasonal effects on P300 too are reported. It is difficult to state if these influences are clinically significant. It is however, desirable to control their variations as much as possible in P300 experiments.

Cognitive State: The subject should be alert and awake to obtain a P3QO. Less alert undrowsiness reduce the correct target detections and also the P300 amplitude as well as prolong the latency. It is imperative to note the number of correct detections and the experimenter should ensure that the subject detects 80% or more of targets correctly.

Generator sites of P300 : Gross integrity of primary sensory tracts and cortex is necessary for the completion of the P300 task in the corresponding modality. It is however not known which anatomical site is exclusively responsible foe generation of P300. Postulated regions include inferior parietal lobule, hippocampus, medial temporal lobes, locus coereleus and frontal lobes. In view of its multi-origin, any focal pathology alone fails to affect the P300 measures significantly. Temporal lobectomy and bilateral temporal lobe lesions did not affect this ERP. Nonetheless, available indirect evidence points to temporal lobes as important generators for P300.
What does P300 test? It is not known what component of cognition is specifically reflected in P300. The available research data suggests that attention and immediate memory are tested by P300. P300 reflects the context-updating operation. Among the components of P300 the latency reflects the time taken for information processing and the amplitude reflects the resource allocation for this processing.
Clinical applications: P300 is sensitive to an individual's cognitive state and accordingly, clinical conditions which affect this state have been investigated.

Dementias: Global cognitive failure is present in dementias. P300 latency is prolonged and its amplitude attenuated in these clinical states as compared to age-matched normals. The sensitivity of any one value (e.g., mean+2SD of normals) has not proved to be any more accurate than clinical examination in confirming lower cognitive function. The proportion of dementia patients with 'abnormal' P300 vary from 30% to 70%. Latency had more sensitivity than amplitude in detecting dementia. P300 failed to differentiate between different types of dementias; viz., alzheimer's, vascular etc., Several neuropsychological tests proved more sensitive than P300, although false

positives are rare with P300. P300 latency showed significant correlations with some neuropsychological test measures (e.g., WAIS). As dementia progresses there is a trend for prolongation of latency. However, P300 latency is no sensitive measure of degree of dementia. In focal neurological lesions, P300 recorded from midline sites are normal. P300 topography is no more superior to resting EEG analysis in detecting such conditions.

Alcoholism: Acute consumption of alcohol has dose-dependent effects on P300 latency prolongation and amplitude attenuation. Acute effects of alcohol on P300 (smaller amplitude) becomes more manifest in individuals who have genetic risk of alcoholism. Social drinkers do not differ from never users in P300 measures. Alcohol dependent subjects, however, have longer latency and smaller amplitude. This effect is pronounced in patients who have clinical evidence of cognitive dysfunction. Even in normals who have a genetic risk for alcoholism, P300 amplitude is smaller and in particular on the right side. Available evidence is insufficient to allow use of P300 as a reliable genetic marker for alcoholism.

Mood disorders: P300 amplitude reductions but not latency prolongations have been demonstrated in depressive disorder. This is true in major depression with or without melancholia as well as in dysthymia. However, in the presence of psychotic symptoms, latency prolongation is noted. The P300 abnormality appears to be state dependent. Severity of depression rating scores correlated with smaller amplitudes and the latter became normal following remission induced by effective antide pressant treatments; electroconvulsive therapy, drugs or Sudarsana Kriya Yoga. Smaller amplitudes in depression but normal latencies have been attributed to lesser resource allocation. Lower confidence a correct detection in depressives (due to lower self esteem) has been implicated in amplitude reductions. In monaural P300 paradigms, depressives demonstrated normal right ear advantage but a trend for left ear disadvantage (lower P300 amplitude at Cz with left monaural stimulus in the oddball task). P300 amplitude reduction in depression may be state dependent. Normal latency in depression helps in differentiating depressive pseudodementia and true dementia.

Schizophrenia: P300 has been extensively researched in schizophrenia. Smaller P300 amplitudes in schizophrenia have been well replicated. This finding is independent of medication and symptomatic status. These findings suggest that P300 amplitude abnormalities in schizophrenia may be trait dependent. Smaller P300 amplitudes in normal subjects from genetically loaded schizophrenic families point to a genetic role. Amplitude of P300 in schizophrenia has a topographic specificity; smaller over left temporal areas. Smaller P300 also correlated with reduced size of left temporal lobe volume as well as larger ventricles in schizophrenia. In monaural P300 paradigm, schizophrenic had significant right ear disadvantage; smaller P300 amplitude with right monaural stimulus presentation in oddball paradigm. Low amplitude of P300 in schizophrenia is detected early in the disease course suggesting a neurodevelopmental pathology. Latency prolongations in schizophrenia is inconsistent across studies. In young, first-break never-treated schizophrenics, some found longer latency with standard oddball task which we were unable to replicate. Indeed this poor replication of this finding is noted from several other studies. However, if the task difficulty can be increased (monaural stimulus condition), schinzophrenics show longer latency than controls.

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FUNDAMENTALS OF IMAGING TECHNIQUES

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ABSTRACT

Neurological Imaging Techniques have undergone a major revolution in recent years, due to the advent of Magnetic Resonance Imaging. This technique is completely non-invasive and does not require any ionizing radiation. It gives clear anatomical images of the brain. The image maps out the density of hydrogen nuclei (in water, proteins, lipids etc.) and their state of mobility. The image is sensitive to the soft tissue and can distinguish soft and hard tissue without contrast agent, through simple manipulation of the software (pulse sequences). The method requires a large homogeneous magnet, radio frequency transmitters and receivers and is based on principles of Magnetic Resonance Spectroscopy. Principle of Neuclear Magnatic Resonance followed by the principle of MR, the different imaging protocols, the methodology of MR spectroscopy, MR angiography and MR functional imaging the basis of these Neurological imaging techniques form.