MANDATE

Pursuing basic research to understand brain function in health and disease.

Generating trained human resources with the capability to carry out inter-disciplinary research in neuro-science.

Promoting neuroscience in India through networking among institutions across the country.

OBJECTIVES

To undertake, aid, promote, develop, guide and coordinate research of high caliber in basic and clinical neurosciences related to diseases and disorders of the nervous system;

To develop the Centre as the national apex center for neuroscience research and promote neuroscience research at different centers in the country and to provide consulting services to other institutions, agencies and industries;

To promote, encourage and augment effective linkages, alliances and affiliations between the Centre and national and international scientific and research institutions, bodies, agencies / laboratories and other organizations working in the field of brain and neurosciences research;

To establish one or more satellite centers to serve different regions of the country for efficient achivement of the objectives of the Centre;

To collect, assimilate, publish and disseminate data and information on aspects relevant to neuroscience to the scientific community;

To establish, operate and maintain state-of-the-art facilities and database for carrying research and development activities and make such facilities and database available to scientists and researchers from all over the country and abroad;

To provide for instructions and training in such other branches of learning as the Centre may deem fit;

To provide facilities for advanced research and development for advancement of learning and for dissemination of knowledge;

To undertake extramural studies, extension programmes and field outreach activities to contribute to the development of society;

To promote, develop, collaborate or otherwise assist in providing services of research, training, consulting or guidance related to neuroscience activities comprising biological, psychological, sociological and clinical aspects; and

To do all such other acts and things as may be necessary or desirable to further the objectives of the Centre.

From the Director's Desk

The human brain is the most sensitive and complicated single entity in our universe. It is the seat of intelligence, interpreter of senses, controller of movement and is responsible for all we embrace as civilization. Although the brain is one organ among many in the human body, it is the source and determiner of everything. In the words of Hippocrates, "from the brain and from the brain only arise our pleasures, joys, laughter, pains, grief and tears…". The ease with which brain implements vision, thought and action defies all logic.

One of the major challenges facing scientists in the new millennium is to understand how the human brain works and what goes wrong when it is injured or diseased. Brain research poses challenges unheard of in the history of science and hence is aptly referred as the last frontier in biology. The questions that fuel brain research are not merely of academic interest. From birth to old age there are a host of neurological and mental illnesses afflicting mankind. Most of these are ill understood, poorly defined and defy current therapeutic strategies. Thus the need for complete understanding of brain function and better treatment and preventive care of brain-related disorders is well acknowledged. Brain research can enhance the development of our children and help them to fulfil their potential, enrich adult life and can help us age gracefully. Research in facilitates the translation of our expanding knowledge of the working of the brain into effective diagnosis and therapeutic interventions.

During the latter part of the 20th century, the study of the brain moved from a peripheral position within both the biological and psychological sciences to become an interdisciplinary field called neuroscience. The study of the biological basis of brain function became incorporated into a common framework with cell and molecular biology on one side and psychology on the other. Within this new framework, the scope of neuroscience ranges, from genes to cognition from molecules to mind, from molecular biology to neuroinformatics. In order to make real progress in brain research, to export laboratory findings to bedside therapies, one has to broaden the traditional scientific approach to accommodate inter-disciplinary methods integrating the many levels of functional organization of the brain, from molecules to neurons to networks to systems to behaviour.

An interdisciplinary holistic approach to understanding the brain therefore is a fundamental ethos at NBRC. We combine resources from different sub-disciplines of neuroscience such as molecular and developmental to systems and neuroinformatics and in the process develop a new language to try and understand the brain. In the last year, the faculty of NBRC more than doubled and research activities across the spectrum of neuroscience from molecular and cellular neuroscience to systems and computational neuroscience were initiated. Complex biological systems can only be understood through a systems approach, which brings the rigor of mathematics, physics and computational science with biology. This is reflected in a number of research projects that have been initiated at NBRC. This effort was also exemplified in the International Conference on Theoretical Neurobiology that was organised in February 2003. This conference was the first of its kind in India and brought together experimentalists, mathematicians and computational neuroscientists to interact and discuss new approaches in studying the brain. Brain-related disorders represent one of the major disease groups that affect the population and a cause huge burden on society. In keeping with our mandate,

which focuses on brain related disorders, active research on neurodegenerative diseases has been initiated and multi-institutional projects with national and international agencies are being put together.

The networking activities of NBRC continue to be an important feature of NBRC. NBRC extends access of its digital library to scientists from our networked centres as well as those from other institutes. In keeping with our mandate we have strengthened our network of 42 centres, which includes Indian Institutes of Technology to Defence Research Laboratories; medical institutes such as All India Institute of Medical Sciences, National Institute of Mental Health & Neurosciences and research laboratories such as Central Drug Research Institute and Centre for Cellular and Molecular Biology. It is through sharing and continued interaction with them that we plan to build capacity to tackle the problems of brain research and establish national workgroups. The national facilities that have been set-up at NBRC such as the DNA microarray and sequencing facility, and computational facility are open to researchers from the networked centres. Training programmmes are now regularly conducted in these facilities to make people aware of the existence of such facilities and thereby to maximize the use of these resources for addressing specific problems in the area of neuroscience that individual investigators in other institutes may have. We hope that in the year to come we would continue to strengthen and expand the NBRC network and facilitate interdisciplinary research both nationally and internationally across the country. Our international collaborations have strengthened in the past year and NBRC continues to share the advantages of such collaborations with its networked centres.

The coming year promises to definitely expand these activities following the commissioning of our permanent campus at Manesar. NBRC moved into its permanent campus at Manesar in March, 2003. Manesar campus of NBRC consists of the laboratory building and animal house. It gives us a great scope to expand our activities not only in terms of intramural research but also in our ability to offer more resources to the networked centres.

A critical factor to achieve our goals is availability of trained human resources who are able to knit molecular biology into the bytes of computation. In keeping with our mandate to generate such trained resources, we had sought and have now obtained “Deemed University” status. NBRC was granted “Deemed University” by the Ministry of Human Resource Development in May 2002. In the last year we initiated an intensive course work for our Ph.D. students who come from diverse backgrounds ranging from basic biology to computer science. The main goal of the coursework was to help develop manpower that can bridge across diverse disciplines and carry out interdisciplinary research to understand brain function in health and disease. The forthcoming year will see us expanding our teaching activities and initiating a Master’s programme in neuroscience.

As the campus prepares itself to be dedicated to the nation, we at NBRC pledge with renewed zeal our mission of unravelling the mysteries of the brain and discovering better and newer cures for brain disorders.

Prof. V. Ravindranath

INTRAMURAL RESEARCH REPORTS

Molecular Mechanism of the Pathogenesis of the CAG Repeats Neurodegenerative Diseases

Principal Investigator Nihar Ranjan Jana

Research Fellows Anand Goswami

Priyanka Dikshit

The abnormal expansion of trinucleotide repeats is now known to cause 16 neurological diseases. Among them, 9 are neurodegenerative diseases (also referred as polyglutamine diseases) that are due to the abnormal expansion of CAG repeat in the coding region of the target genes. These include Huntington's disease (HD), Dentatorubro pallidoluysian atrophy (DRPLA), Spinobulbar muscular atrophy (SBMA) and several spinocerebellar ataxias (SCA's). All these neurodegenerative disorders are autosomal dominant (except SBMA) and progressive. The symptoms typically begin in midlife and the patient dies after 10-15 years of disease onset. However, the onset of the disease and severity directly depends on the length of the CAG repeats. The repeats show both somatic and germline instability and the successive generations of affected families experience anticipation, or earlier age of onset and more rapid disease progression. Since the discovery of the disease gene, great progress has been made in the past few years, but detailed mechanisms of the diseases pathogenesis remains largely unknown and currently there are no effective therapies for these diseases. The challenge now is to determine which cellular pathways are vulnerable to the insults exerted by expanded polyglutamine proteins, how these responses account for the clinical manifestation of the disease and ultimately how this knowledge can facilitate the development of drugs.

Major objectives of this project are (1) to identify and characterize the protein(s) that specifically interact with the expanded polyglutamine tract, (2) elucidate the mechanism of ubiquitination of the polyQ protein aggregates and modulation of their degradation, (3) identify the role of mitochondria in the pathogenesis of polyglutamine diseases and (4) screening and identification of small molecules for therapeutic intervention of the polyglutamine diseases.

We are studying the mechanism of polyglutamine disease pathogenesis using Huntington's Disease and Spinocerebellar ataxia Type3 as models. Last year we have developed several full-length and truncated (C-terminal) ataxin-3 (responsible gene for SCA3/MJD) expression constructs with normal and expanded glutamine repeats through fusion with enhanced green fluorescence protein (EGFP). We have transiently transfected these constructs into the mouse Neuro2a cells and observed that both wild type and mutant ataxin-3 are mostly localized into the nuclear compartments. The increased length of glutamine repeats or N-terminal truncation does not have any influence on the nuclear localization. We have also noticed that not only the increased glutamine repeat length but also the N-terminal truncation of the mutant ataxin-3

dramatically increased the 1C2 antibody binding, misfolding, ubiquitination, aggregate formation and cell death. Now we are making stable cell lines of the wild type and mutant ataxin-3 in a tetracycline-inducible system for further investigation of the disease pathogenesis.

We are also studying the pathogenic mechanism of polyglutamine diseases using cellular model of HD, obtained from the RIKEN Brain Science Institute. Currently, we are investigating role of oxidative and endoplasmic reticulum stress on the polyglutamine protein induced cell death to determine whether these stressors modulate the cellular proteasomal function. Experiments are underway to find out the role of various chemical chaperones and antioxidants on the polyglutamine protein aggregation and polyglutamine protein-induced cell death.

Collaborator

Dr. Nobuyuki Nukina, RIKEN Brain Science Institute, Japan.

Funding

Department of Biotechnology, Government of India.

Publications

E.A. Zemshov, N.R. Jana, M. Kurosawa, H. Miyazaki, N. Sakamoto and N. Nukina. Pro-apoptotic protein kinase Cδ in associated with intranuclear inclusions in a transgenic model of Huntington's disease. *J. Neurochem*: 87, 395-406.2003*

N. R. Jana and N. Nukina. Recent advances in understanding the pathogenesis of polyglutamine diseases: involvement of molecular chaperones and ubiquitin-proteasome pathway. *J. Chem. Neuroanat 26: 95-101, 2003.*

N. R. Jana and N. Nukina. Assessment of impaired proteasomal function in a cellular model of polyglutamine diseases. In "*Triplet repeats protocol*" ed by G. Bates: Humana Press, 2003.

N. R. Jana. Neurodegenerative diseases involving expanded CAG repeats. In "*Neurobiology in post genomic era*": In press.

A. Goswami and N. R. Jana. Mutation in Cu/Zn superoxide dismutase1 and familial amyotrophic lateral sclerosis. In "*Neurobiology in post genomic era*": In press.

N. R. Jana. Recent advances in understanding and developing therapies for Alzheimer's disease. In "*Alzheimer's disease in India*" Published by Society for Gerontological Research, 2002.

*Work done elsewhere

Presentations

N. R. Jana, Svetlana E. Kotliarova, Munenori Nekooki and N. Nukina. Direct visualization of the expression, selective nuclear accumulation, aggregate formation and possible proteolytic processing of the transgene in a HD exon 1-EGFP transgenic mice model. *4th Japan-Korea-China-India joint workshop on neurobiology and neuroinformatics*. RIKENBSI, Japan, 2002.

N. R. Jana, Svetlana E. Kotliarova, Munenori Nekooki and N. Nukina. Direct visualization of the transgene expression and fate of the transgene product in the brain of HD exon1-EG FP transgenicmice. *Annual meeting of the Indian Academy of Neuroscience*, Udaipur. 21-25rd February, 2003.

Mechanisms of Curcumin-induced Neuronal Cell Death and Differentiation

Principal Investigator Nihar Ranjan Jana

Curcumin, a polyphenolic phytochemical, is the primary component of the spice turmeric (*Curcuma longa*). It has been demonstrated to have anti-inflammatory, antioxidant and anti-proliferative activities. The pharmacological safety of curcumin is well documented by the fact that people in certain countries including India have consumed curcumin as a dietary spice for centuries in amount in excess of 100mg/day without any side effect. Ample evidence exists to support its use in cancer prevention for its anti-proliferative and anti-carcinogenic properties. Curcumin, *in vivo*, suppresses carcinogenesis of the skin, the stomach, the colon, the breast and the liver in mice and *in vitro* it has been shown to inhibit the growth of a wide variety of tumor cells. Although, its precise mode of action remains elusive, studies have shown that chemo-preventive action of curcumin might be due to its ability to induce apoptosis. Through which pathway curcumin induces apoptosis and whether mitochondria play any role in curcumin-induced apoptosis is not fully understood.

The major objectives of this project are (1) to identify mechanism of the neuronal cell death caused by curcumin and (2) whether and how curcumin promotes neuronal cell differentiation.

We are investigating the cell death mechanisms induced by curcumin using neuro2a (mouse neuroblastoma) cell line. Curcumin induces cell death in this cell line in a dose- and time-dependent manner. The dividing neuro2a cells are more sensitive to curcumin compared to the differentiated neuro2a cells at any particular dose. In an attempt to identify the cell death mechanism, we have found that curcumin-induced apoptosis is mediated through pathways involving mitochondria. We are now investigating how curcumin disrupts mitochondrial function. We have also noticed that the exposure of low dose of curcumin to neuro2a cells induces neurite outgrowth. The probable mechanism of curcumin-induced neurite outgrowth is also under investigation.

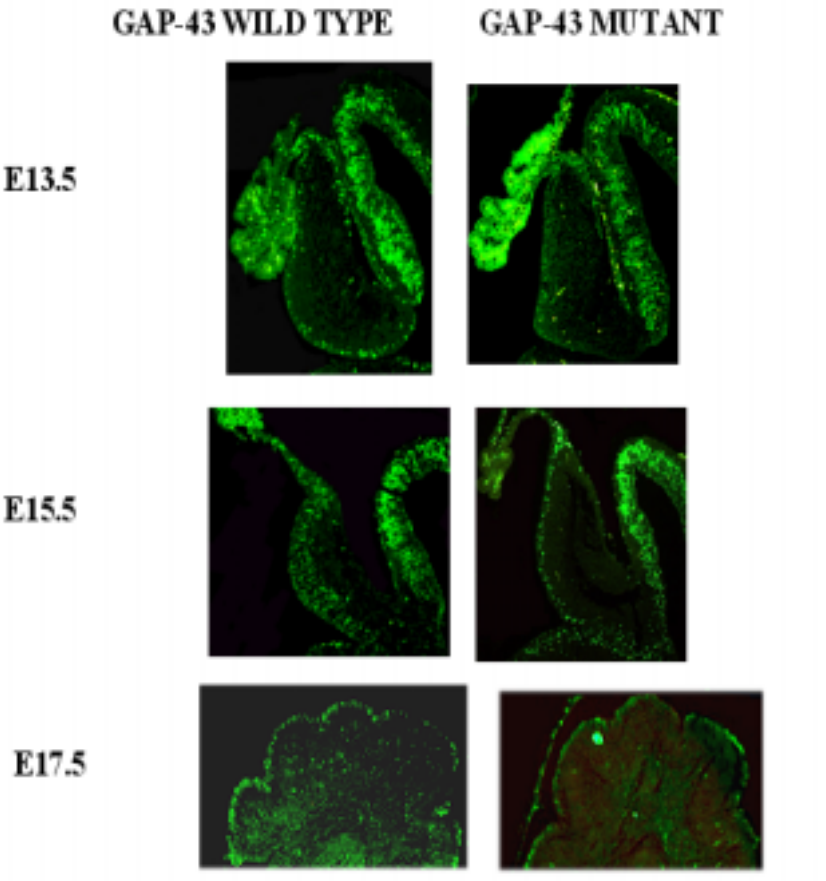
Developmental Neurobiology & Regulation of Neurogenesis in the Cerebellum

Principal Investigator Shyamala Mani

Research Fellow Rashmi Mishra

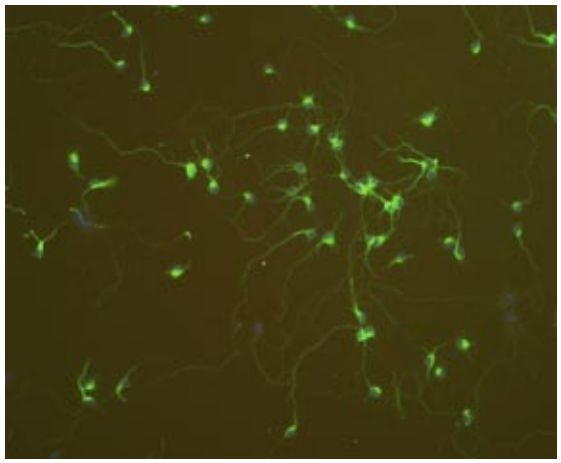
The major goal of our laboratory is to understand pattern formation in the central nervous system and how the positional information provided by patterning molecules are involved in the regulation of neurogenesis at the level of single cells. To address this issue we have been using the patterning of cerebellar folia as a model system.

GAP-43 (growth associated protein 43) is a nervous system specific actin modulatory protein that is required for cell-adhesion mediated signalling. All GAP-43 knock out mice have abnormal cerebellar development such that by P0, the day of birth, the external granule cell layer (EGL) is reduced by 40%. We are investigating the role of GAP-43 in coordinating cell cycle responses, as this will provide important information about how regulation of neurogenesis is involved in cerebellar patterning.



BrDU immunohistochemistry on tissue sections at different embryonic ages from GAP-43 wild type and knock out animals.

Our first aim was to establish the developmental stage at which a defect in the rate of cell proliferation becomes apparent in the knock out animals. In a series of experiments we compared the rate of cell proliferation between the wild type and knock out GAP-43 mice. We



Purified granule cells in culture prepared from GAP-43 knockout cerebellum from postnatal day 6 that have been labelled with neuron specific beta-III tubulin antibody.

have looked at embryonic ages 13.5, 15.5, and 17.5. For the embryonic ages bromodeoxyuridine (BrdU) was injected into timed pregnant females and after a two hour pulse the animal was sacrificed and the embryos dissected out. After immunohistochemistry the number of BrdU positive cells were counted as a percentage of the total number of cells and were normalized per unit area. At E13.5 the number of BrdU positive cells were counted in the rhombic lip area from where cells migrate to form the EGL. At E15.5 the number of BrdU positive cells in the nascent EGL were counted. At E17.5 the number of BrDU cells for each of the lobulus were counted. In all cases there was a significant and consistent reduction in the level of cell proliferation in the knockout animals as compared to the wildtype animals.

We are looking at the mechanism by which lack of GAP-43 causes a reduction in the proliferation of cells in the cerebellum. How the balance between proliferation and differentiation is maintained to regulate granule cell number is not fully understood. One potentially important signal with which GAP-43 has been directly associated is bFGF which is produced by Purkinje cells and glial cells and which acts as a mitogen for the cerebeller granule cell precursors. We are examining bFGF-induced mitogenesis *in vitro* in wild type and knock out mice to establish whether bFGF mediated regulation of granule cell proliferation is specifically disrupted in the GAP-43 knock outs. For these experiments we are using primary whole cerebellar cultures as well as purified granule cell cultures from wild type as well as GAP-43 knock out mice.

Funding

Fogarty International Research Collaboration Award (FIRCA), NIH, USA.

Presentations

S. Mani. Regulation of Neurogenesis in the Cerebellum. *The 4th Japan-Korea-China-India conference on Neuroinformatics and Neurobiology:* RIKEN, Japan, 2002.

S. Mani. Regulation of Neuronal Differentiation by GAP-43. *Neuroprotection and early life, ICMR-INSERM workshop*: Bangalore, 2003.

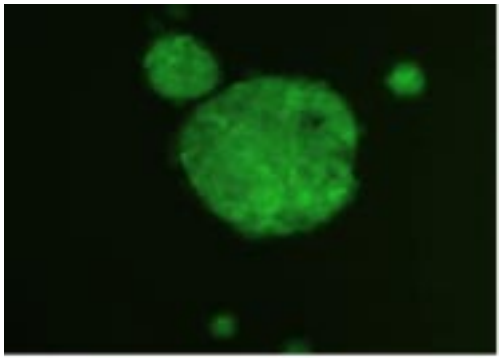
To Investigate the Mechanisms by which Neural Stem Cells Differentiate into Distinct Neuronal Subtypes

Principal Investigator Shyamala Mani

Research Fellows Manoj Kumar

Kishore Reddy

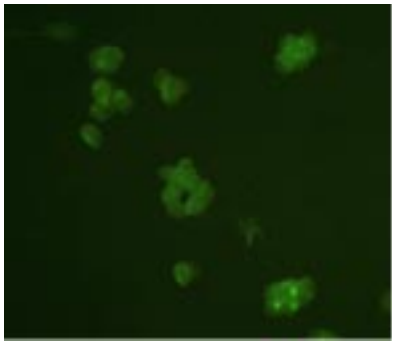
Technical Assistant Bandita Bagchi

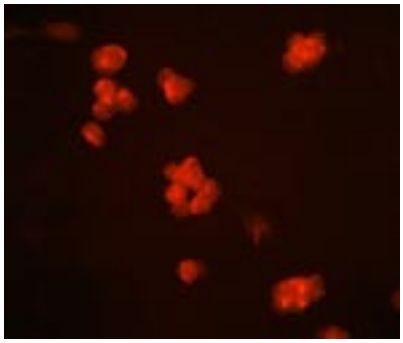


Undifferentiated ES cells grown on gelatin coated plates have the morphology of a typical ES cell colony.

Cell transplantation becomes an important avenue for treatment of diseases when the ability of the damaged tissue to repair itself is compromised. However, merely introducing stem cells into depleted areas without regulating differentiation is unlikely to be an effective strategy. This is especially true in the central nervous system (CNS) where the generation of phenotypic diversity within the neuronal lineage is precisely regulated in a spatial and temporal fashion. How differentiation of vertebrate neurons is regulated to produce this neuronal diversity is poorly understood. The ability of embryonic stem (ES) cells to undergo neurogenesis 'in a dish' provides us with a good model system in which to address these issues. Using ES cells it is possible to study the effect of extracellular factors on their ability to direct different cell fates and then begin to analyse the intracellular pathways that transduce these extracellular signals.

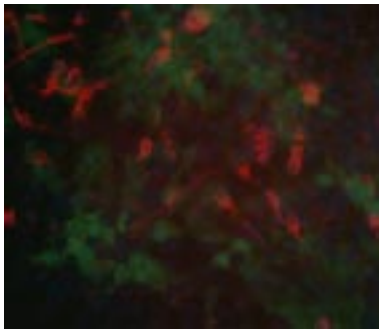
The efficiency with which ES cells differentiate into neurons and the type of neurons that are produced will be governed by both the microenvironment into which the ES cells are implanted as well as the culture conditions that the ES cells are exposed to prior to transplantation. In order to look at the effect of various pre-transplantation culture conditions on neuronal differentiation of ES cells *in vivo* we have generated ES cell

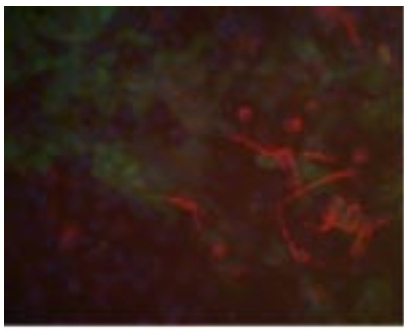




Cell lines transfected with CMV-EGFP were dissociated and fixed in methanol and stained with SSEA-1 antibody (red). Most CMV-EGFP cells express the SSEA-1 antigen in an undifferentiated state.

lines that express Enhanced Green Fluorscent Protein under the control of different promoters. This will help us identify the cells that have been transplanted in the host brain. We have also generated ES cell lines that





Cells that express EGFP under the control of the nestin promoter are larger and do not have the morphology of a differentiated neuron. In contrast cells that express Map2 have a typical neuronal morphology and do not express EGFP.

express EGFP under the control of the Cytomegalovirus promoter, the nestin promoter and the glial fibrillary acid promoter. The stable transfectants have been subcloned and are feeder independent, have normal ES cell morphology when they are undifferentiated, express cell surface markers that are characteristic of stem cells and have the ability to differentiate into neurons. The CMV-EGFP cells express EGFP ubiquitously and at high levels. We are now transplating these clells after varying the culture conditions prior to transplantation.

Funding

Department of Biotechnology.

Psychoactive Drug Metabolism By Brain Cytochrome P-450

Principal Investigator
Vijayalakshmi Ravindranath

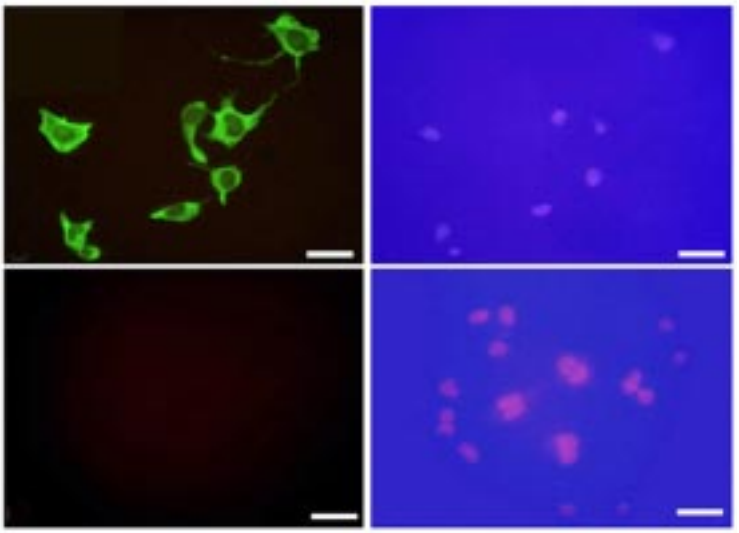
Research Fellows Harish V. Pai
Reddy P. Kommaddi

Technical Assistant Prasanna V.K

Cytochromes P450 (P450) is a family of heme protein that is primarily involved in metabolism of xenobiotics including drugs. These enzymes are conserved in mammals. Psychoactive drugs, such as antidepressants and neuroleptics are metabolized by hepatic P450s such as those belonging to 3A, 2D, 2C and 1A subfamilies. It has long been appreciated that liver is quantitatively the major organ involved in the metabolic disposition of most xenobiotics, *in vivo*. However, in the recent years P450-mediated metabolism in extrahepatic organs and the potentially far-reaching consequences of such metabolism, *in situ*, within specific cells in target organs have been recognized in laboratory animals and humans.

We have earlier demonstrated that psychoactive drugs are metabolized through P450 to pharmacologically active and inactive metabolites in liver, some of which can prolong the parent drug's therapeutic action. Various isoforms of cytochrome P450 are present in brain where drug metabolism can take place and directly modify therapeutic action of the drugs used in the treatment of mental illnesses at their primary site of action that is the brain. Plasma drug levels that are often used as indicators of bioavailability of a drug in clinical practice are not effective indicators of therapeutic outcome of drug in the brain. However, it is increasingly recognized that drug metabolism *in-situ* in brain may contribute to the final pharmacological action. Cytochrome P4502D (CYP2D) is one of the most important isoform of P450 that is involved in the metabolism of psychoactive drugs. We therefore, examined the presence of unique P450 forms in human brain, which might participate in drug metabolism at the site of action of psychoactive drugs.

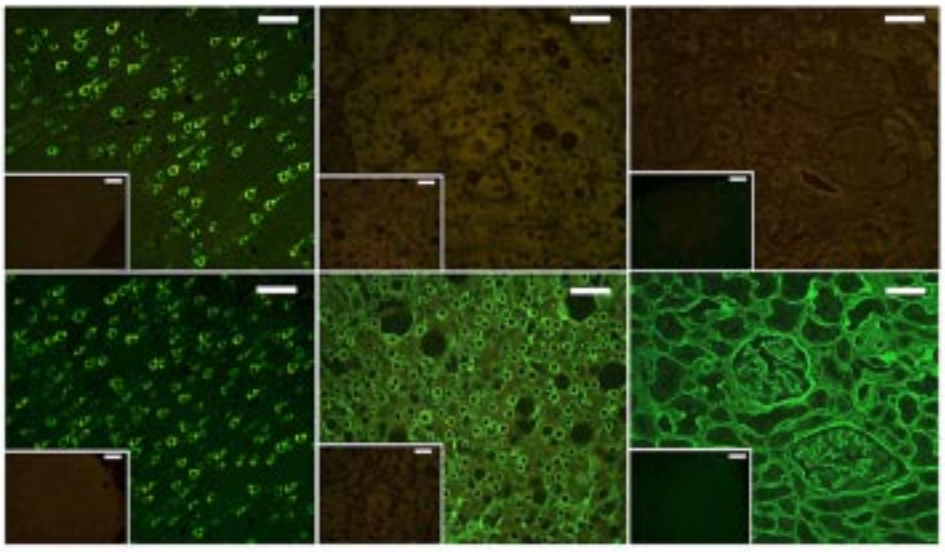
We have identified the presence of a splice variant of a pseudogene, CYP2D8p2 (which we have named brain variant CYP2D8) by screening the human brain cortex cDNA library and isolated a 1776 bp long clone. The clone had a 'T' deletion at 288 bp and an additional 57 bp from intron 6 of the CYP2D8p2 genomic sequence. The 'T' deletion causes frameshift and enables complete transcription and translation of the pseudogene CYP2D8p2 to a functional protein. The clone was translated into a 58 kD protein which was immunologically similar to liver CYP2D6. The reduced carbon monoxide difference spectrum of the translated protein shows absorption maxima at 450 nm characteristic of cytochrome P450. The transcript and the protein were localized only in human brain by *in situ* hybridization and immunohistochemistry but not in liver or kidney of the same individual.



Immunohistochemical localization of CYP2D8 in Neuro2A cells expressing brain variant CYP2D8. The cells expressing brain variant CYP2D8 show intense cytosolic staining (top left panel). Cells transfected with expression vector containing cDNA to brain variant CYP2D8 in reverse direction show no staining (bottom left panel). Corresponding nuclear staining with DAPI is depicted in the right panels. Bars = 50 µm.

This demonstrates the tissue specific expression of the variant CYP2D8 in humans. The presence of this variant transcript in brain was also examined by RT-PCR using 12 autopsy human brain samples. In 6 brain samples, an additional band (340 bp) representing the brain variant CYP2D8 was observed indicating a prevalence of about 50%. CYP2D6 represented by the 282 bp amplicon was seen in all the 12 samples examined because of the considerable homology between CYP2D6 and CYP2D8p2.

In liver, codeine is principally metabolized to nor-codeine an inactive metabolite and morphine is formed in very small amounts. Plasma drug level of morphine following codeine administration does not correlate with therapeutic outcome. The brain variant CYP2D8 metabolized codeine (10 µM) only to morphine and nor-codeine was not detected when transfected in Neuro2A cells. However membrane proteins from cells transfected with cDNA of liver CYP2D6 metabolized codeine essentially to nor-codeine and morphine was formed in small amounts. CYP2D8 brain variant metabolized codeine to morphine at higher rates and had higher affinity. Inhibition studies using antibody to CYP2D6 and quinidine, a selective inhibitor of CYP2D indicated that the biotransformation was indeed mediated by P4502D. These observations present evidence for the formation of morphine from codeine in human brain by a metabolic pathway that is different from that of liver.



Brain variant CYP2D8 transcript was localized in cortical neurons in human brain while it was absent in liver and kidney sections from the same individual (upper panel). The transcript representing the full-length CYP2D6 gene was detectable in brain, liver and kidney (lower panel). Insets depict the corresponding control sections hybridized with the sense riboprobes. Bar = 50 µm except in the inset where bar = 100 µm.

Very small amounts of morphine are formed in liver through CYP2D6 mediated metabolism of codeine to account for the analgesic effect of codeine. A significant amount of morphine administered as such or formed in the liver through metabolism of codeine is converted to morphine 6-glucuronide which is unlikely to cross the blood brain barrier due to its hydrophilic nature. For effective pain relief it is essential that morphine be formed in the brain where it can directly bind to µ-opioid receptors. Even if very small amount of codeine is metabolized to morphine by brain cytochrome P450 at the site of action, it could mediate pain relief. Identification and characterization of novel histio-specific isoforms of P450 generated by alternate splicing of known genes or as yet unidentified genes is essential to predict pharmacological outcome of drugs that act at sites remote from liver.

Collaborator

Dr.Michael R.Boyd, University of South Alabama, USA.

Funding

National Institute of Mental Health, National Institutes of Health, USA.

Acknowledgment

We thank Human Brain Tissue Repository, NIMHANS for providing us human brain samples for carrying out our research.

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Pai, H.V., Upadhya, S.C., Chinta, S.J., Hegde, S.N. and Ravindranath, V. Differential metabolism of alprazolam by liver and brain cytochrome P4503A to pharmacologically active metabolite: constitutive expression and localization of CYP3A in rat and human brain. *The Pharmacogenomics Journal, Nature Press Journal* 2: 243-258, 2002.

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V. Ravindranath. "Distinctive features of drug metabolizing enzyme in human brain: Existence of splice variant forms" *Annual Meeting of the Society for Neuroscience*, Orlando, USA held in November, 2002.

V. Ravindranath. "Drug metabolism in brain: implication in the treatment of mental illnesses" *Prof. K.P. Bhargava Memorial Lecture at 20th Annual conference of Indian Academy of Neurosciences*,Udaipur, 21st February, 2003.

Pai, H. V, Chinta, S. J, Kommaddi, R. P and V. Ravindranath. Existence of new cytochrome P4502D isoform in human brain that mediates a novel cerebral drug metabolism pathway. *20th Annual Conference of Indian Academy of Neurosciences*, Udaipur, February 21-23, 2003.

Kommaddi, R. P, Chinta, S. J, Pai, H. V and V. Ravindranath. Constitutive expression and localization of cytochrome P4501A1 in brain: Identification of a unique splice variant. *20th Annual Conference of Indian Academy of Neurosciences*, Udaipur, February 21-23, 2003.

Mitochondrial Dysfunction and Protein Thiol Homeostasis In Neurodegenerative Diseases

Principal Investigator

Vijayalakshmi Ravindranath

Research Fellows Rajappa S. Kenchappa

Srirangan Sampath.

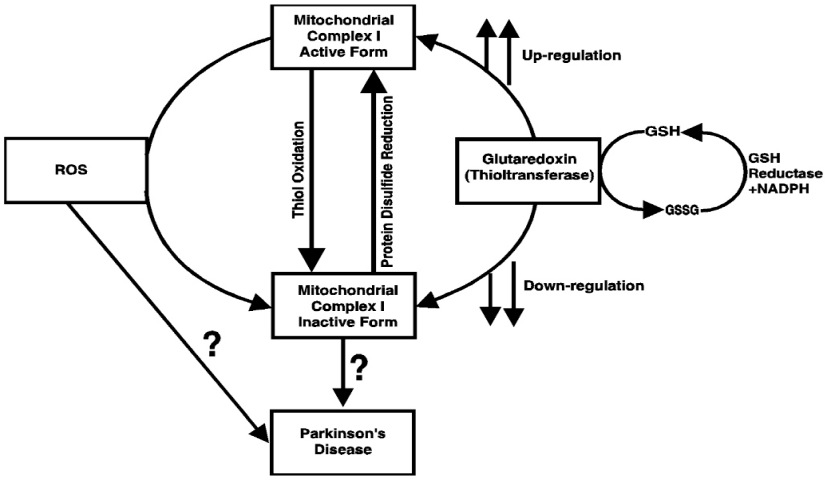
Mitochondrial dysfunction has been implicated in a variety of neurodegenerative disorders. In particular, abnormalities in mitochondrial complex I have been observed in several infantile and childhood neurological disorders as well as in neurodegenerative diseases such as Parkinson's disease where complex I dysfunction has been identified in mitochondria from platelet, brain and muscle. The mechanisms by which complex I dysfunction occurs and how this defect causes neurodegeneration is not entirely clear. It is known that complex I is critical for brain mitochondrial function. A small loss (as low as 25%) in complex I activity is sufficient to decrease ATP synthesis and mitochondrial respiration by approximately 35% in brain mitochondria. Complex I is vulnerable to inactivation by reactive oxygen species as compared to other components of the electron transport chain and oxidative stress can lead to loss of complex I activity. Mitochondrial complex I has several cysteine residues in its active site, which can undergo oxidative modification through formation of protein glutathione mixed disulfides. Glutaredoxin, a thiol-disulfide oxidoreductase uses GSH and specifically reduces protein glutathione mixed disulfides (PrSSG) to protein thiols. Earlier, we have demonstrated the constitutive expression of functional glutaredoxin enzyme in rat and human brain and its specific localization in the neurons.

We examined the role of glutaredoxin in maintenance of complex I function in brain. Selective down-regulation of glutaredoxin in brain using anti-sense oligonucleotides leads to inhibition of complex I activity in brain regions such as cortex and striatum. The mechanism underlying the inhibition involves protein thiol oxidation since the inhibited activity can be completely restored by treatment with dithiothreitol, a disulfide reducing agent. Inhibition of complex I following the administration of antisense nucleotides to glutaredoxin is related to functional glutaredoxin activity because in brain region such as hippocampus, which does not respond to the antisense nucleotides and maintains adequate functional activity of glutaredoxin, complex I activity was not impaired. Glutaredoxin can indirectly influence mitochondrial protein thiol homeostasis especially of those proteins that are exquisitely sensitive to the redox milieu. These results reveal the important role of glutaredoxin in maintaining functional integrity of mitochondrial complex I in brain regions under normal conditions.

We have also examined the role of glutaredoxin in recovery of complex I in striatum following a single dose of MPTP (1-methyl-4-phenyl-1, 2,3,6-

tetrahydropyridine), a model neurotoxin that causes Parkinson's disease-like syndrome through inhibition of mitochondrial complex I in selective brain regions. Earlier studies from our laboratory demonstrated that chronic treatment of mice with MPTP causes irreversible dopaminergic cell loss, while a single dose of MPTP causes only a transient mitochondrial complex I dysfunction in striatum and midbrain. Complex I inhibition caused by MPTP can be reversed by dithiothreitol indicating that oxidation of critical thiol groups is the primary cause for complex I inhibition. We, therefore, looked at the regulation of glutaredoxin in striatum during the initial insult and recovery following a single dose of MPTP. After an initial loss of complex I activity 0.5 hr after administration of MPTP, complex I activity rebounded and was significantly higher than control at 4 hr. Concurrently, glutaredoxin activity was up-regulated at 4 hr. However, this was not sustained and 18 hr after MPTP treatment, glutaredoxin levels were comparable to controls and simultaneously loss of complex I activity was observed. A direct correlation was seen between the functional status of complex I and glutaredoxin. The increase in glutaredoxin activity following MPTP dose was associated with enhanced transcription and translation of glutaredoxin mRNA and protein in striatal neurons. Upstream of the Grx1 gene there is an AP1 binding site that regulates the expression of Glutaredoxin. AP1 mediated transcription was activated 0.5 hr after MPTP administration, following which the sequential up-regulation of glutaredoxin mRNA and protein occurred at 1 and 4 hr respectively. AP1 activation was super shifted with p-c Jun, Jun B and c Fos antibody indicating the possible involvement of these proteins in the activation of the AP1 complex. Down-regulation of glutaredoxin expression using anti-sense oligonucleotides prevents recovery of complex I in striatum typically seen 4 hr after MPTP treatment, providing support for the critical role for glutaredoxin in recovery of mitochondrial complex I function in brain. Therefore, glutaredoxin not only helps maintain the functionality of complex I under normal conditions but may also play a major role in the recovery of mitochondrial function following an intrinsic or extrinsic insult. This study demonstrates that maintenance and restoration of protein thiol homeostasis by glutaredoxin may be an important factor in preventing complex I dysfunction.

Glutaredoxin requires reducing equivalents of GSH to regenerate protein thiols. Availability of GSH is critical for glutaredoxin to regenerate protein thiols from protein glutathione mixed disulfides and cellular GSH levels have to be maintained at optimal levels for efficient functioning of glutaredoxin. In order to meet the increased demand of GSH for glutaredoxin activity, synthesis of GSH has to be stepped up. GSH synthesised by two enzymes γ-glutamyl cysteine synthetase (γ-GCS) and glutathione synthetase. γ-GCS, the rate limiting enzyme of GSH



Schematic illustration depicting the important role of glutaredoxin in maintaining functional integrity of mitochondrial complex I under normal conditions and during oxidative stress caused by generation of reactive oxygen species (ROS). Reduced protein thiol status is essential for complex I function and down regulation of glutaredoxin is associated with loss of complex I activity. Oxidative stress that leads to protein thiol oxidation and complex I dysfunction has been associated with Parkinson's disease.

synthesis, composed of heavy chain (73 kDa) and light chain (30 kDa) subunits, heavy chain subunit possesses all of the catalytic activity. Regulation of gene expression of γ-GCS heavy chain subunit is critical for maintaining GSH homeostasis. We therefore, examined the expression of γ-GCS heavy chain subunit in brain regions. Immunoblot, northern blot and fluorescent *in situ* hybridization analyses demonstrates the presence of functional enzyme in brain regions. We have also looked at the regulation of γ-GCS expression following single dose of MPTP administration. There was an increase in γ-GCS activity in striatum and midbrain at 0.5 and 4 hours after MPTP administration. Increase in γ-GCS activity was associated with up surge of transcription of catalytic subunit of γ-GCS mRNA, 1 hr after MPTP administration, demonstrating the role of γ-GCS in maintaining the GSH levels in brain regions during neurotoxic insult.

Collaborators

Dr.Michael R.Boyd, University of South Alabama, USA.

Funding

US-India fund for cultural, educational and scientific co-operation.

Publications

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Ravindranath V. "Rational therapies and cures for brain disorders: Hopes and challenges". *Invited Lecture at the Golden Jubilee of the DNA Double Helix Discovery*, New Delhi,12th-14th February 2003 .

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Molecular Mechanism of Neuroprotection Mediated by Estrogen

Principal Investigator

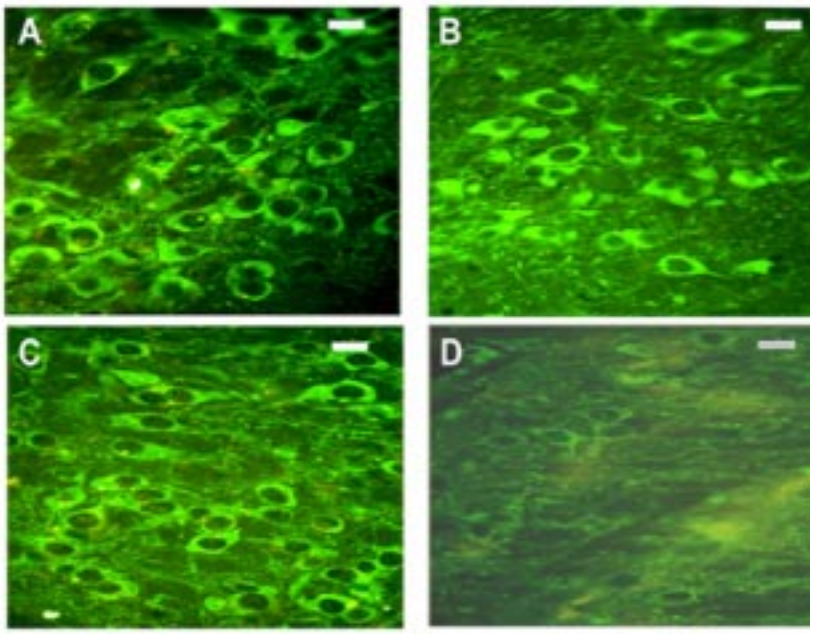
Vijayalakshmi Ravindranath

Research Fellows Latha Diwakar

Smitha K.

The female sex hormone estrogen has been shown to be neuroprotective and vaso-protective. Estrogen acts by two pathways, at pharmacological concentration (non-classical) and physiological concentration (classical). At pharmacological concentration estrogen has high intrinsic antioxidant activity. Several *in vitro* studies have demonstrated that estradiol inhibits lipid peroxidation in various cell free models, protects neurons against oxidative stress and glutamate-induced neurotoxicity. Classical method of estrogen action involves induction or repression of gene expression causing long-term genetic and, ultimately, physiological response which is mediated by estrogen receptors. Molecular and cellular mechanisms underlying the neuroprotective effects of estrogen remain unclear. Epidemiological studies indicate that the incidence and prevalence of Parkinson's disease is higher in men than in women and there are gender differences in the brain damage induced by transient ischemia and acute cerebral stroke.

We have examined gender related differences in response to a single dose of MPTP, a model neurotoxin used for developing animal models for Parkinson's disease. Administration of a single dose of MPTP (30mg/kg body weight, s.c) to male and female mice results in the loss of GSH at 0.5 and 4 hr in striatum and midbrain of male mice, not in female mice. The γ-glutamyl cysteine synthetase and glutaredoxin activities were increased in striatum and midbrain of male mice at 0.5 and 4 hours. But in female mice there was no change in γ-glutamyl cysteine



Immunohistochemical localization of tyrosine hydroxylase in dopaminergic neurons of substantia nigra of male (C, D) and female (A, B) mice, showing degeneration of neurons in MPTP treated male mice (D) compare to untreated mice (C). Neurons unaffected in female mice by MPTP toxicity (B) compare to untreated mice (A). Scale Bar = 50 μm.

synthetase and glutaredoxin activities. Estimation of mRNA expression for thioltransferase and γ-glutamyl cysteine synthetase in male and female mice 1 hour after MPTP administration, showed an increased expression of both thioltransferase and γ-glutamyl cysteine synthetase in striatum and midbrain of male mice, while, no such effect was seen in female mice. Activation of the AP1 transcription factor was also unaltered in female mice. Dopaminergic neurons in the substantia nigra of male mice are completely degenerated 8 days after daily administration of MPTP (30mg/kg body weight, s.c), while in female mice they are unaffected. Pretreatment with ICI 182,780 an estrogen recepter antagonist causes loss of complex I activity *in vitro* in female mouse brain slices and *in vivo* in striatum and midbrain of female mice, indicating that the neuroprotection is mediated through estrogen receptors. Further, the basal thioltransferase activity was significantly higher in females as compared to male mice. These results suggest that critical enzymes involved in neuroprotection such as glutaredoxin are regulated by estrogen through estrogen receptor signalling thus providing a constitutive protective mechanism in females.

Collaborator

Prof. A.J. Rao, Indian Institute of Science, Bangalore.

Presentations

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Evaluation of the Molecular basis of the Pharmacological action of Traditional Medicinal Preparations used in the Treatment of Mental Illnesses including Dementia

Principal Investigator

Vijayalakshmi Ravindranath

Research Fellow Prashant Patole

Brain related disorders are known to contribute up to one-third of the total disease burden in both developed and developing countries. Among the brain related disorders, which comprise of both neurological and psychiatric illnesses, a cause of serious concern are the age-related disorders such as senile dementia, Alzheimer's disease and Parkinson's disease etc. These disorders are progressive and irreversible, and currently no cure is available since the etiopathogenesis of these disorders is poorly understood. Senile dementia including Alzheimer's disease is extremely distressing since it results in severe cognitive dysfunction including memory loss for which no treatment is currently available. Traditional systems of medicine such as Ayurveda offer a knowledge base that can be utilized for development for therapeutic intervention strategies for treatment of these disorders. In this project we propose to examine the neuropharmacological effects of eight plants that are used in traditional system of medicine for improving higher mental function. In this project, the multi-disciplinary research tools mentioned above will be used in *in-vitro* and *in-vivo* systems for assessing the therapeutic potential of plants in the treatment of age-related dementia including Alzheimer's disease.

The objectives of the project are to i) to test plant extracts used in traditional medicine for possible neurotransmitter receptor/transporter interaction using human brain membrane preparations ii) to test the effectiveness of the plant extracts in *in-vivo* animal models of age-related memory loss/cognitive deficits including senile dementia and Alzheimer's disease. The following plants are being studied: *Bacopa monnieri, Centella asiatica,Withania somnifera, Acorus calamus, Celastrus paniculatus, Nardostachys jatamansi, Clitorea termatea, Canscora diffusa.*

The powdered plant materials were extracted sequentially using lipophillic solvents and the solvent was evaporated to obtain crude extracts, which were used for binding studies using membrane preparations from human brain samples obtained at autopsy. The effect of these extracts on the binding of 3[H]-quinuclidinyl benzilate to the muscarinic cholinergic receptors is being studied. Both the plant extracts *Acorus calamus* and *Withania somnifera* were able to displace the binding of the radioligand to the muscarinic receptors indicating their substantial affinity for the receptor. Among the 4 plant extracts tested *Withania somnifera* had the maximum receptor binding activity to muscarinic receptor, followed by *Acorus calamus*. Comparatively *C. asiatica* and *B. monnieri* showed lower activities.

Funding

Department of Biotechnology

Understanding the role of Transcription Factors in the Differentiation of Photoreceptors and Related Retinopathies.

Principal Investigator Prabodha Swain

Research Fellow Sandeep Kumar

Identification of retinal proteins interacting to specific transcription factors is necessary to understand their role in regulating specific gene expression in retinal photoreceptors. To undertake such gene interaction studies one of the strategies is to use purified protein immobolized on the matrix and purify interacting proteins. The photoreceptor specific transcription factor Neural Retina Leucine Zipper (NRL) was sub-cloned in prokaryotic expression vector and expressed as a GST-fusion protein in *E coli*. Expressed protein was purified using glutathione Sepharose affinity chromatography. The purity of the protein was confirmed further by Westernblot analysis against specific polyclonal antibody and then used for the interaction studies. Multiple phosphoisoforms of NRL are expressed in retina. Studies suggest that the pattern of phosphorylation is identical when expressed transiently in other eukaryotic cells. To identify the common kinase involved in the phosphorylation of NRL, we expressed NRL in *E coli* both with and without an internal phosphorylation domain. Both the proteins were expressed in *E coli* and purified using affinity chromatography. These proteins will be used as substrate to identify kinase responsible for the phosphorylation of NRL and for its interaction with other retinal proteins. Proteins extracted from bovine retina were analysed for the expression of NRL by immunoblot analysis. Ammonium sulphate precipitation was used to fractionate different retinal fractions which have been used in the interaction studies to identify interacting protein bands.

In a separate study to understand the hierarchial regulation of photoreceptor genes, 1.2 kb of the upstream promoter sequence of photoreceptor specific nuclear receptor (PNR) gene was cloned in pGL3 vector. It was designed to study the cis and trans regulatory factors necessary for the transcription of PNR in retina. Analysis of the potential regulatory elements in the promoter region revealed an interaction domain of activator protein-4 (AP-4). In-vitro interaction studies showed heterodimerization of NRL with AP-4 that can potentially regulate PNR expression in retina. Both AP-4 and NRL were cloned in eukaryotic expression vectors. NRL was expressed transiently in eukaryotic cells and confirmed by immunoblot analysis of the transfected cells. To understand the functional interaction between AP-4 and NRL in the transactivation of PNR-promoter, HEK 293 cells will be cotransfected with all three DNA constructs at different ratio. Expression of luciferase as the reporter gene will be measured against the control to deduce the fold activation of AP-4 and NRL against that of the control (pGL3 DNA construct without promoter). The study will help in determining the

regulatory hierarchy of specific transcription factors in the expression of photoreceptor genes. PNR gene was also cloned and expressed in *E coli*. However the protein was not stable during the expression in the prokaryotic system. An alternate strategy will be used to express PNR in eukaryotic system like baculovirus expression system and purified protein will be used for protein interaction studies.

Publications

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* Work done elsewhere

Effect of NeuralGene(s) in the Differentiation of Retinal Cells (new project)

Principal Investigator Prabodha Swain

Neural cell differentiation is regulated by both intrinsic and extrinsic factors. These factors induce programmed differentiation to generate distinct neural cell types in retina as well as other part of brain. Besides transcription factors different cell cycle molecules also have major role in the successive steps of differentiation and fate determination of retinal cells. Differentiation of retinal neurons are stage specific. Cell lineage and birthdate analysis suggest ganglion cells generated early in the embryonic stages, amacrine, cone and horizontal cells during mid gestation and rod, bipolar and glia generated at late embryonic stages in rhodents. Identification of any stage specific factor(s) can potentially serve as a marker for one or more retinal cell progenitors. Identification of any such marker of photoreceptor progenitors will be an important tool to characterize and purify such cells from the mixed population of mitotic retinal cells. These cells can be induced by specific extrinsic factors (like FGF, SHH, taurine and Ratinoic acid) to produce post mitotic photoreceptors. These progenitors with limited mitotic activity can be used as potential replacements for photoreceptors in most of the damaged retinae.

The objectives of the project will be answered through following specific aims.

(a) Does growth factors known to induce rod-differentiation like taurine, retinoic acid and FGF also affect cone pathway genes?

(b) What are the effects of these exogenous factors together with over-expressed transcription factors in the differentiation of retinal neurons?

Bovine neural retina without pigment epithelium will be used to grow as explant and dissociated culture *in vitro*. Cultured explants/cells will be transfected with photoreceptor specific genes like NRL and CRX. Effect of the hyperexpressed genes in the expression of other target retinal genes will be studied by RT-PCR, northern and in situ hybridisation assays. Effect of the exogenous growth factors: taurine, FGF and Ratinoic acid will also be studied in combination with the over-expressed transcription factors in the retinal cell culture. Change in gene profile will be studied by miroarray analysis.

Development of Cytoarchitectonic Features and Axonal Connections in Cortical areas Subserving Speech and Hearing

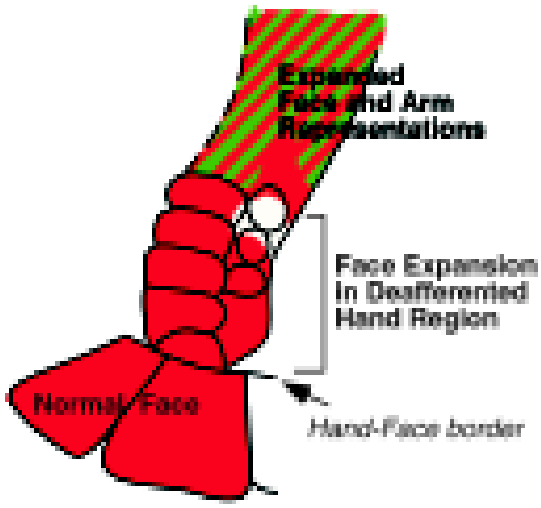
Principal Investigator Soumya Iyengar

The normal development and acquisition of speech in children depends on their ability to hear normal speech patterns early in development, which enables them to acquire their first language or languages by 1-2 years postnatally. Interestingly, axonal connections in the human auditory cortex mature later than most other regions of the brain, that is, between 5 and 11-12 years of age, coinciding with the sensitive period for learning languages. Anatomical tracing studies have revealed extensive connections between the auditory cortex as well as cortical areas involved in processing languages (classically, Broca's and Wernicke's areas). Functional imaging studies have also revealed that the auditory cortex as well as cortical areas involved in processing language are connected via multiple, parallel and hierarchically organized pathways with the parietotemporal cortex and prefrontal cortex which are involved in working memory in adult subjects. Yet another series of studies on the architectonic features of the auditory cortex in adult New World and Old World monkeys and humans have revealed that the auditory cortex is subdivided into a number of functionally distinct areas. These areas including core, belt and parabelt areas can be differentiated from each other on the basis of tonotopic mapping, cytoarchitecture and on the basis of their connections with different regions within the cortex as well as on inputs from the thalamus.

While earlier research has focused on delineating the subdivisions of the auditory cortex in adult animals, how these areas attain their adult patterns of organization and connections is yet to be studied. We would therefore like to study the cytoarchitecture of the auditory cortex and its subdivisions during early development by using different histochemical stains on brains from postmortem foetuses (6 months – birth) and human brains (birth – 11-12 years of age). We will also inject neuroanatomical tracers such as DiI into different areas of the auditory cortex to trace the time course of development of its connections with other cortical areas involved in speech. Another study will examine in detail the developmental changes in neuronal structure as well axon arbors (that is, cortical microcircuitry) connecting different subdivisions of the auditory and speech areas of the human brain in order to better define the morphological basis of plasticity within this system. These studies will provide normative data on the formation of connections between cortical areas involved in speech and hearing.

Brain Reorganization following Spinal Cord Injuries

Principal Investigator Neeraj Jain

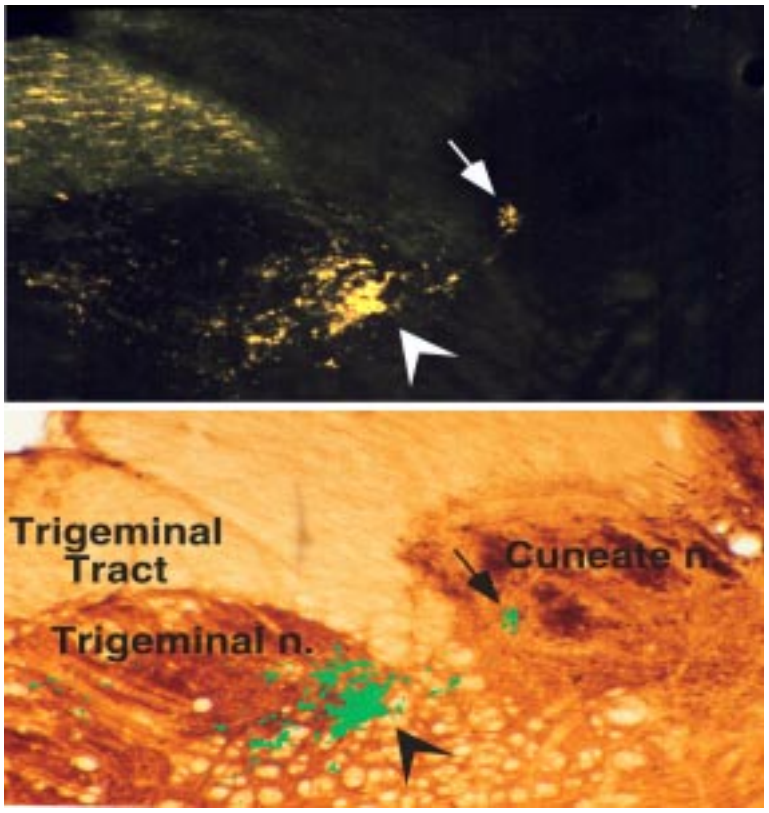


Expansion of the face representation (red) into the deafferented hand region of somatosensory area 3b of an owl monkey 8 months after unilateral lesion of the dorsal columns at upper cervical region. Green represents the arm representation which shows a somewhat limited lateral expansion. (From Jain et al., 1997.)

Spinal cord injuries lead to loss of sensation and motor control below the site of injury. Loss of sensory inputs to the brain as a result of spinal injuries leads to changes in the normal organization of the brain. It is critical to understand the nature of these changes and their mechanisms in order to ensure optimal recoveries following spinal injuries. Since most of the spinal injuries leave at least some fibers intact, the desirable changes in the brain reorganization will be those that potentiate the intact spinal inputs to help ensure better behavioural recoveries. Knowledge of the mechanisms of brain reorganization will also help determine strategies to prevent undesirable changes that might lead to errors in sensory perception such as mislocalizations and phantom sensations. We plan to use unilateral lesions of the dorsal columns of the spinal cord as a model system for spinal injuries. Such lesions deafferent part of the somatosensory inputs that mediate fine sensory discrimination while leaving other inputs in the lateral and ventral spinal cord that mediate sense of crude touch, pain and temperature. In addition, all the descending motor control circuits remain intact. Following such lesions the monkeys initially do not use their deafferented hand for directed motor activity. However, over a period of 4-8 weeks all deficits recover except the ability to form precision grip. Neurophysiological investigations show that initially neurons in the deafferented parts regions of primary somatosensory cortical area S1 (Brodmann's area 3b) do not respond to any peripheral stimulation. However, over a period of time these neurons come to respond to adjacent, intact inputs. For example, if the injury is at upper cervical levels, the inputs from the face, that terminate adjacent to the hand representation in area 3b expand into the deafferented hand cortex over a period of six to eight months.

In addition to the primary somatosensory area 3b, the somatosensory cortex consists of areas 3a, 1, 2, S2 and PV (parietal ventral area). Inputs to these areas could be from area 3b, other cortical areas and direct parallel inputs from the ventroposterior nucleus of thalamus. We plan to study how these areas reorganize following lesions of the dorsal columns at C2-C4 levels using multiunit mapping methods. We also plan to determine how the motor cortical areas M1, and pre-motor areas reorganize following such injuries using intracortical microstimulation techniques. We will correlate the nature and time course of these changes with the recoveries in the behavioural use of the hand. This information will help determine the neurophysiological basis of the initial behavioural abnormalities in the use of the ipsilateral hand and subsequent partial recoveries.

A second goal of studies is to determine the mechanisms of brain reorganization. The mechanisms could range from changes in the levels of neurotransmitters to neuronal growth. Previous experiments show that some of the changes could be mediated by growth of face afferents



Growth of the face afferents from the trigeminal nucleus of the brainstem into the cuneate nucleus following lesions of the dorsal columns of the spinal cord. The upper figure is a dark field photomicrograph of part of a brainstem section showing that neuronal tracer cholera toxin B-subunit linked to horseradish peroxidase when injected in the skin of the chin also labels cuneate nucleus in addition to the expected location in the trigeminal nucleus. The lower figure shows the label in pseudo color overlaid on a cytochrome oxidase stained section of the brain stem showing boundaries of the nuclei. (From Jain et al., 2000.)

from the trigeminal nucleus into the deafferented cuneate nucleus of the brain stem. We will determine if this growth is further potentiated by growth at other sites such as the ventroposterior nucleus of thalamus and the somatosensory cortex using neuroanatomical and immunochemical methods.

Funding

International Senior Research Fellowship from the Wellcome Trust, UK.

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* Work done elsewhere

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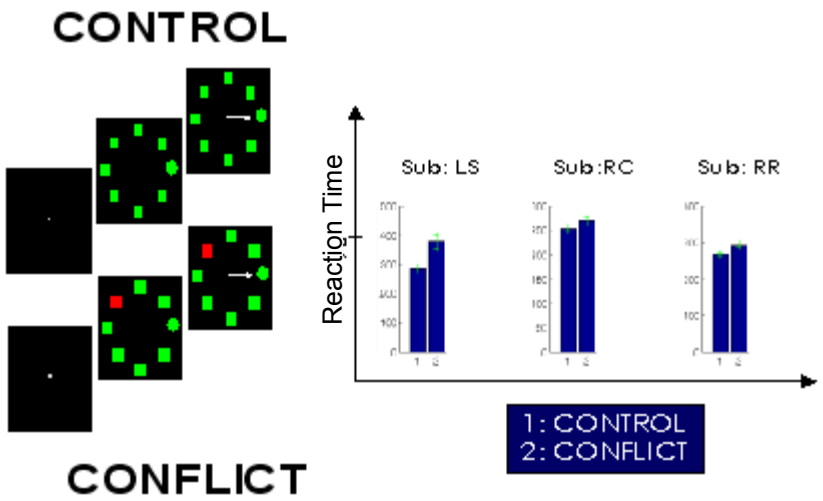
Control of Saccade Target Selection

Principal Investigator Aditya Murthy

Our visual sensitivity is not uniform but rapidly declines centrifugally from the centre of gaze as a result of which objects in the periphery cannot be identified clearly. To counter this problem our brain has evolved a mechanism whereby the visual scene is explored in discrete steps, each of them corresponding to an eye movement called a saccade, followed by a fixation when eye position is relatively stable. In most situations, there can be several different objects in the visual image simultaneously competing for attention. As a result, an important task for the oculomotor system under such conditions is to select and orient gaze to one object from among the many possibilities present in the visual scene. Therefore, an understanding of when and where gaze is directed can provide an elegant model system to study the control of goal directed behaviour. The long term objectives of the proposed project are to understand how visual information and cognitive processes guide behavior, and the neural computations that subserve and link visual processing and saccade programming.

To address these aims we use the visual search paradigm that has been widely used to study visual attention and more recently to study oculomotor control. Here subjects are instructed to make a saccadic eye movement to a target embedded among distractor elements. We are in the process of extending/developing variants of the visual search task to probe how vision and cognition guide action in relation to saccade target selection. During the past year our primary goal was to develop these tasks in our laboratory. We will be shortly using these tasks to test specific hypothesis using on patients with compromised brain function.



Schematic of the decision task and the associated reaction times.

Probing sensorimotor decisions. One of the questions that we are trying to address using the visual search paradigm is provide insights into the neural processes that enable us to make decisions. We are particularly interested in understanding how the brain makes decisions under more difficult conditions since cognitive theorists have proposed the need for specialized brain systems that are engaged under these conditions. Our working hypothesis is that neural networks of the frontal/basal ganglia loop might serve as such a system and come into play during the process of conflict resolution. Towards this end we have begun testing human subjects on visual search tasks where they are instructed to make a saccadic eye movement to a single oddball target among homogenous distractors. This easy visual search task is embedded within a more difficult task where the target is presented along with a singleton distractor to engender conflict. Measurement of reaction times reveals that directing gaze to the target is faster in the presence of a single oddball target but takes longer when the target is embedded among singleton distractors indicating conflict. We are in the process of testing patients with compromised brain circuitry in the frontal cortex and basal ganglia to confirm our hypothesis.

Funding

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* Work done elsewhere

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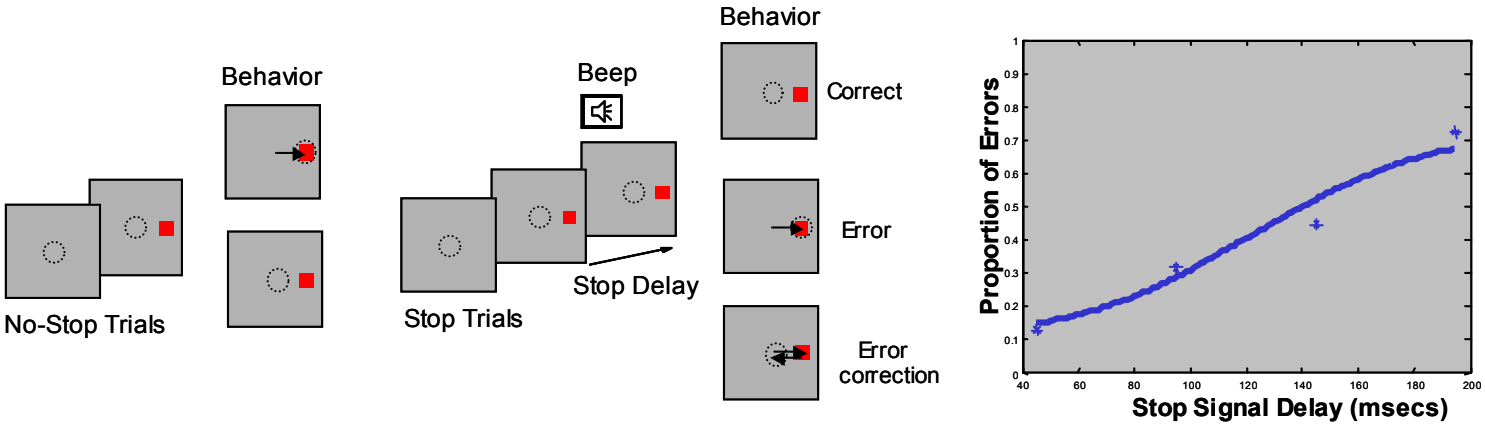
Voluntary Control of Action

Principal Investigator Aditya Murthy

Research Fellow Supriya Ray

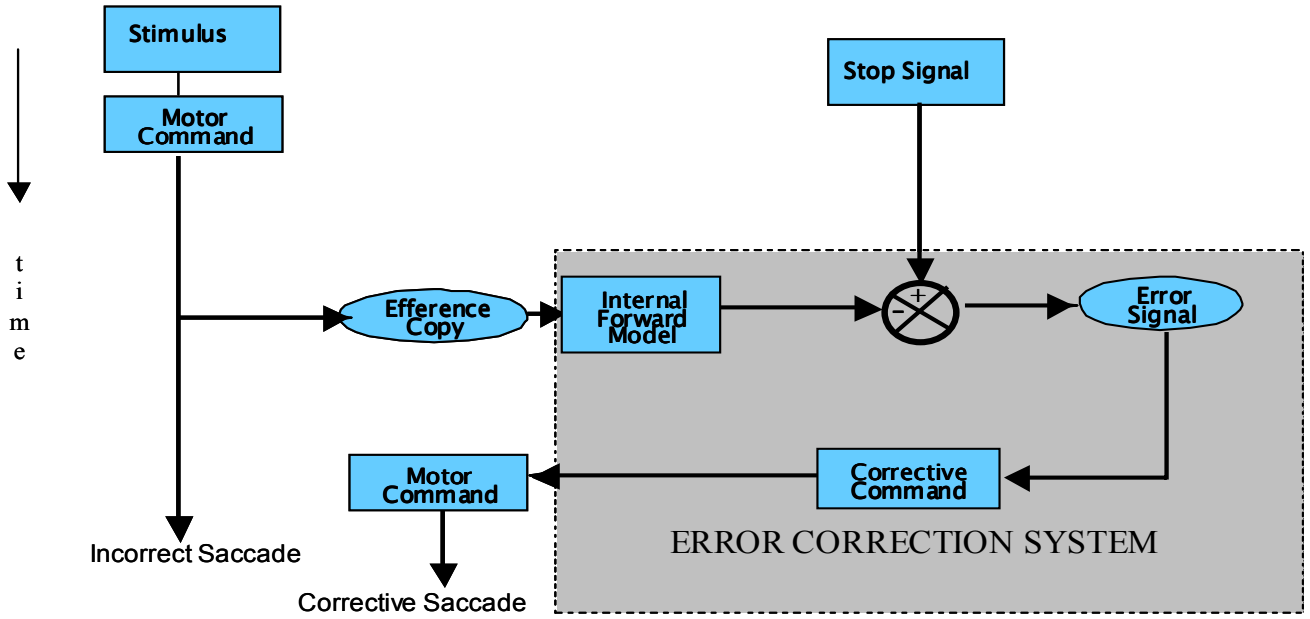
Understanding the neural basis of voluntary control is a central problem in cognitive neuroscience. Goal directed movements involve participation of a number of different brain areas. Some of these areas such as the basal ganglia, the anterior cingulate, the prefrontal cortex and the parietal cortex while not being obviously motor or sensory in nature still make important contributions. However, the nature of their role in motor control remains uncertain since lesions in these areas do not appear effect the execution of specific movements such as those observed in primary motor cortex for example.

In order to test specific hypotheses about the function of associative brain areas in relation to the voluntary control of action we plan to use the saccadic eye movement system as a model system. In oculomotor tasks decisions about where to direct gaze requires an interaction between visual and motor systems and therefore provides an opportunity to study the role of networks mediating their interactions. Understanding how the brain controls action is necessary to understand the causes underlying various psychopathologies and motor abnormalities where there is a failure of control. These series of experiments are being carried out in collaboration with Dr. Sharat Chandra and Dr. Madhuri Behari of Cardio thoracic and Neuroscience Centre, A.I.I.M.S. where a facility to measure eye movements in real time under computer control has been set up and whose recording system have been standardised.



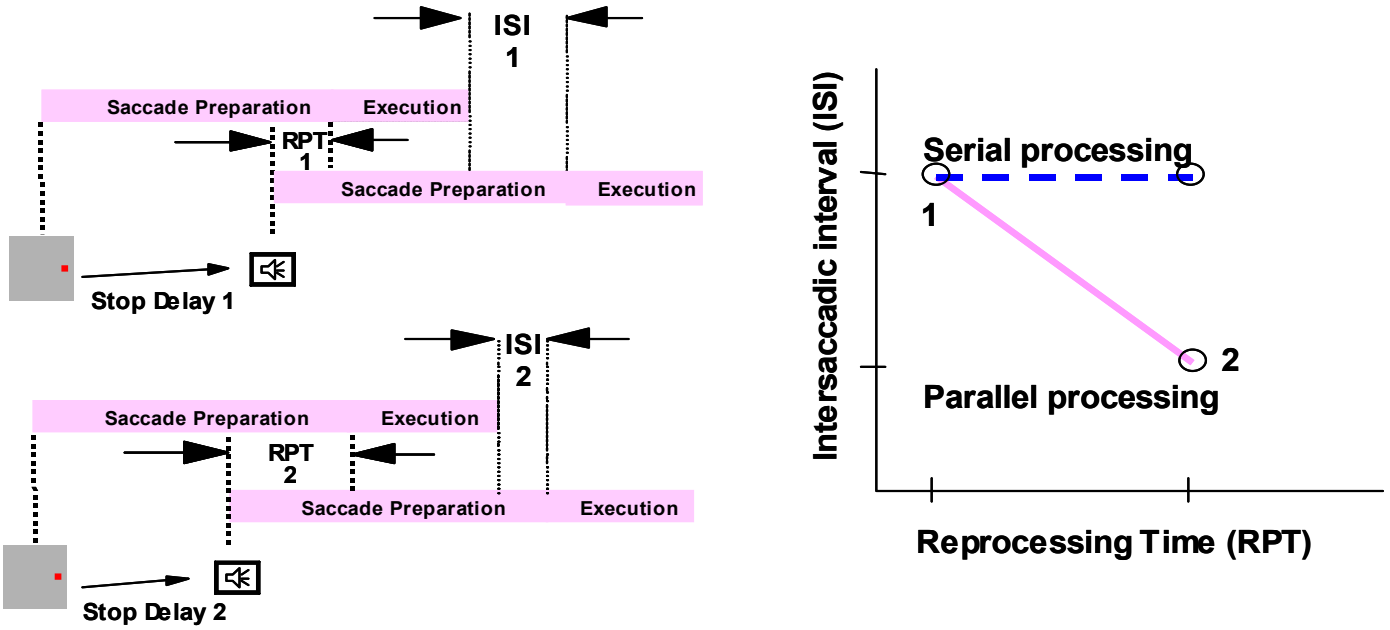
Schematic diagram of the countermanding task where subjects are instructed to cancel a preprogrammed saccade on hearing a tone which serves as the stop signal. Sometimes subjects fail to do so. In such instances subjects are instructed to correct their mistake. The right panel is the subjects performance as a function of stop signal delay.

Probing Inhibitory Control. A hallmark of the voluntary control of action is the capacity to change or stop a planned movement when confronted with new information. This capacity allows us to react to changes in



A schematic representation of a feedforward error correction model in which error correction proceeds as soon as the stop signal occurs. Here error correction is instantiated when there is a mismatch between the current goal and intended goal.

internal or external states that render current goals inappropriate. This ability is of considerable interest because it involves an internally generated act of control by which overt movement is redirected. Inhibitory control is probed in a countermanding task in which successful performance requires inhibiting a preprogrammed eye movement. Using a simple theoretical

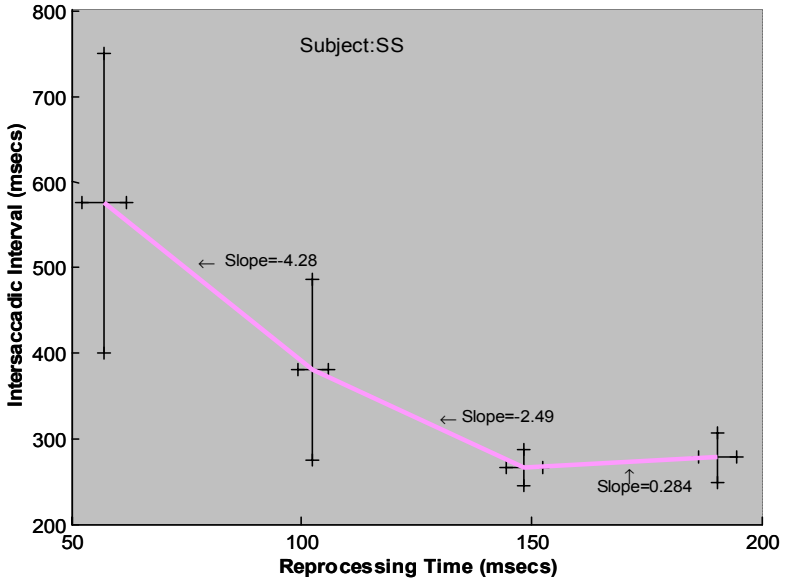


Schematic representation of the programming of the corrective saccade coincides with the erroneous saccade. According to the logic of parallel programming the intersaccadic interval should be inversely proportional to the reprocessing time.

construct we have begun to use the countermanding task to estimate the time it takes for the brain to inhibit a response in normal subjects and patients with focal lesions in different areas of brain. The aim of this line of work is to understand how inhibitory control is implemented in the brain. For this project we will test patients with lesions in the frontal eye fields, parietal eye fields, the basal ganglia, the thalamus and the prefrontal cortex.

Probing Error Correction. In the countermanding task when inhibitory control is successfully implemented, it results in the cancellation of the preprogrammed eye movement. However, as the delay between the appearance of the target and auditory stop signal increases subjects increasingly fail to inhibit their responses leading to errors. Interestingly when subjects made an error we observed they made quick corrective movements. To provide insights into the process that result in error correction we are testing the predictions of a feedforward model of error correction. In this model, the timing of error correction should be related to the stop signal delay since the programming of the corrective response can be initiated as soon as the stop signal occurs. Preliminary data from a subject is consistent with such a pattern indicating that error correction may occur in parallel with the erroneous response. A logical infererence from such preliminary results suggests that error correction may begin prior to the subjects making the errors.

These findings although paradoxical are consistent with computational models of motor control that hypothesize the need for neural mechanisms



The pattern of intersaccadic intervals obtained from human volunteer is consistent with a feedforward model of error correction.

that can predict the consequences of action before they are executed. We will be shortly testing the role of basal ganglia in this form of error control using Parkinson's patients and patients with selective brain lesions

in the prefrontal cortex and anterior cingulate. It is anticipated that such neuropsychological studies will not only contribute to basic research but be of clinical importance as well.

Funding

Department of Science & Technology, Government of India.

Presentations

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Injury induced Changes in Neurophysiological, Molecular and Behavioural Functions following Focal Lesions of the Brain.

Principal Investigator Rema Velayudhan

Post Doctoral Fellow Renuka Ramachandra

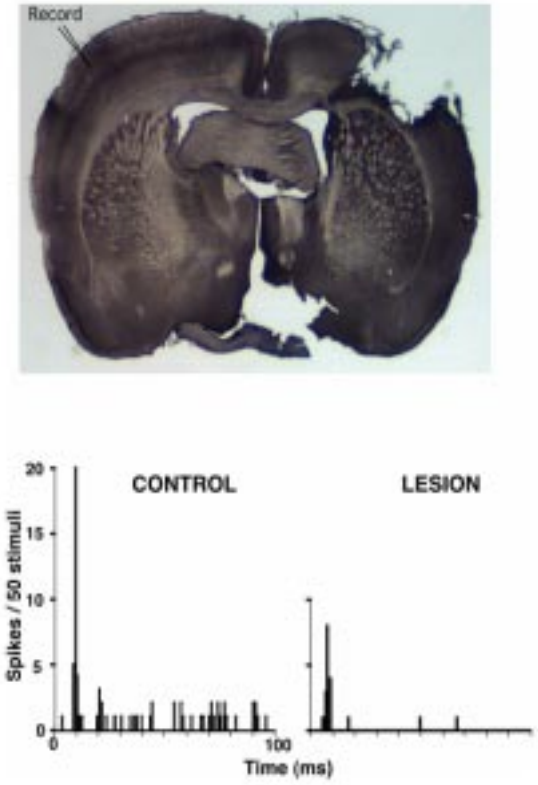
Research Fellow Zia ud Din

Deleterious influences on the brain due to injury, exposure to toxins, nutritional and sensory deprivations etc could cause neurological deficits in people of all ages. These adverse conditions could potentially alter neurotransmission and produce significant, long lasting behavioural and cognitive deficits. The degree of recovery of neurological functions, in most instances would depend on the type, severity and extent of deficits. Interventions using combination of pharmacological and rehabilitative therapy given at the right time could have positive outcomes. Designing optimal interventions require indepth knowledge of response of the brain to the adverse influence: what are the neural mechanisms affected and what are the ongoing changes that occur during recovery.

Our laboratory is interested in examining the spatial and temporal changes following focal injuries to the brain. We use electrophysiological, molecular and behavioural techniques to analyze the changes in both ipsilateral and contralateral cortical functions following surgically induced unilateral lesions of somatic sensory (SI) cortex or motor (MI) cortex in rats. The main questions being addressed in this study are the following:

(1) How do focal injuries affect information processing in the somatosensory cortex and what is the time course of these changes? Following unilateral lesions of somatosensory whisker barrel cortex (SI) or whisker motor cortex (MI) in rats, changes in the fundamental constituents of sensory processing will be determined by measuring (a) spontaneous activity, (b) evoked activity, (c) neuronal excitation and (d) neuronal inhibition. Neuronal responses from ipsilateral and contralateral somatosensory cortices and thalamus will be recorded. The onset and time course of deficits will be determined by recording at various recovery time points. SI lesions will determine the mechanisms underlying the callosally projecting interhemispheric deficits in contralateral SI, whereas MI lesions will determine the nature of intrahemispheric deficits in the ipsilateral SI and whether these deficits in turn affect neuronal processing in contralateral SI.

(2) How do cortical lesions affect the behavioural functions? Effect of SI or MI lesions on the whisker function of rats will be determined by three simple tasks. (a) Pattern of normal whisker movement will be examined using a high-speed camera while rats investigate novel objects. (b) Changes in the ability to use whiskers to judge distances will be determined by a simple whisker dependent task called “gap-crossing”. (c) Determining the ability of rats to learn a conditioned whisker movement task where the rat contacts a computer controlled



Focal lesions in the somatosensory cortex of the rat reduces the response magnitude of neurons to sensory stimuli in the contralateral hemisphere.

piezoelectric wafer with the whiskers to obtain a food reward after a "go" signal.

(3) What are the changes in the molecules involved in excitatory and inhibitory neurotransmission after cortical lesions? At various recovery time points after either SI or MI lesions changes in the levels of molecules involved in: (a) excitatory neurotransmission: NMDA and AMPA receptors; (b) inhibitory neurotransmission: Glutamic acid decarboxylase (GAD) and GABA; (c) neuromodulation: acetylcholine and CaM Kinase II and (d) apoptosis will be determined.

(4) What is the effectiveness of social and pharmacological interventions in enhancing and accelerating functional recovery? Interventions that increase the overall levels of excitation in the brain might be most beneficial. Therefore a combination of increased social interaction in an enriched environment with a larger group of animals with pharmacological intervention using drugs to increase neuronal activity or reduce neuronal inhibition or enhance neuronal survival could be most effective. Currently we are determining the effect of the neuroprotective drug cytidine-5'-diphosphate (CDP)-choline on the neuronal structure. We will examine whether there is increase in the number of spines, and also whether cortical neurons survive longer in the presence of this drug. Initially experiments will be on primary cortical neuronal cultures and later in vivo studies will be carried out. If there is an increase in the spines density and if cell survival is enhanced then it is possible that this drug could accelerate functional recovery following brain injury.

Funding

International Senior Research Fellowship in Biomedical Science. The Wellcome Trust, UK.

Publication

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* Work done elsewhere

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Li. L., Rema V. and Ebner F.F. Inter-hemispheric neural activity is required for normal responsiveness in barrel field cortex. Society for Neurosciece, Nov 2002.

The Algebra of Neural Processing of Contextual Information

Principal Investigator

Posina Venkata Rayudu

It is believed that contextual influences on visual processing are mediated by horizontal synaptic connections within cortical layers while content is carried by vertical connections across layers. Current neural network modelling of both feed-forward and lateral information processing in terms of synaptic weights (numbers) fails to algebraically distinguish the qualitatively distinct functional contributions of vertical and horizontal synapses. Preserving the distinction between content and context in the mathematical models by identifying algebraic objects that are much more structured than mere numbers can help discern hitherto undiscovered principles of contextual computations in the brain.

The Units of Neural Information

The 2-dimensional flow of neural information–vertical & horizontal–mediating contextual influences suggests that the classical information theoretic notion of bit as basic unit of information may not be appropriate for the study of neural information processing. A better model for the basic unit of neural information is a 2-dimensional square with vertical (horizontal) edges of the square representing source/target with respect to horizontal (vertical) structure. The horizontal edges of the square are interpreted as the lateral flow of contextual information and vertical edges as vertical information flow carrying content. Unlike 0-dimensional numbers, which can be put together arbitrarily (e.g. any number can be added to any other number), squares can be put together in two well-defined ways–vertical and horizontal composition–in accord with their geometry. An interchange law relates the vertical and horizontal compositions of squares. We verified the validity of the interchange law in the special case of identity squares (1-dimensional arrows) by interpreting vertical and horizontal composition as serial and parallel processing, respectively, of neural information (Figure-1). The square model of neural information is a foundationally significant contribution of neuroscience to information theory.

Construction and Composition of Duals

The success of neural network models in accounting for a number of contextual effects suggests that the algebra for modelling contextual influences should not only be more structured but also more general to include neural network models as a special case. Towards the goal of generalizing 0-dimensional neural network models of contextual interactions into 2-dimensional squares, we first generalized content-addressable neural network model of memory to relatively simpler 1-

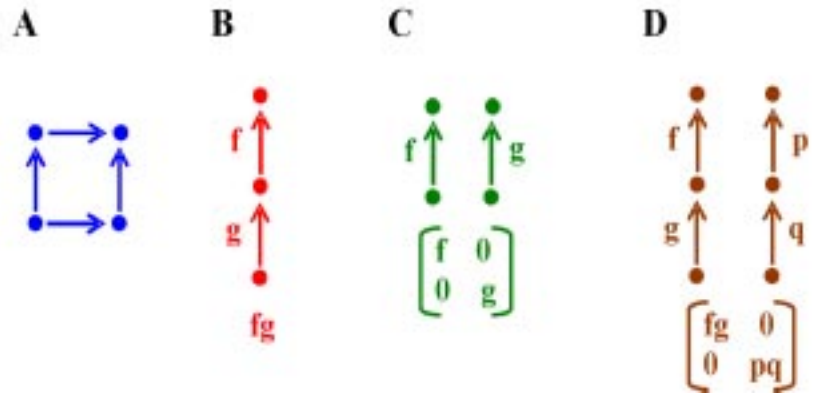

Figure - 1. *Computing with 2-dimensional neural information.* A: *The basic functional unit of neural information is a 2-dimensional square with 4 objects (dots denoting neurons), 2 horizontal arrows (representing horizontal connections within layers), and 2 vertical arrows (denoting synapses connecting neurons across layers).* B: *Vertical composition of identity squares (arrows) can be interpreted as serial processing and formalized as the product of synaptic weights.* C: *Horizontal composition of arrows is interpreted as parallel processing and modelled as a matrix with synaptic weights as diagonal elements.* D: *With these definitions of vertical and horizontal composition, the two ways of composing the given 4 arrows yield the same result thereby satisfying the interchange law of composition of squares.*

dimensional arrows. Replacing the feature vectors and bit-wise computations (dot product) of content-addressable memories with arrows and composition of arrows, respectively, gave a true pattern-recognition algorithm called Form-Addressed Memory. The generalized form-addressed memory model provides a radically different alternative to the correlation-based learning paradigms. In form-addressed memory, neural information processing underlying memorization of perceptual

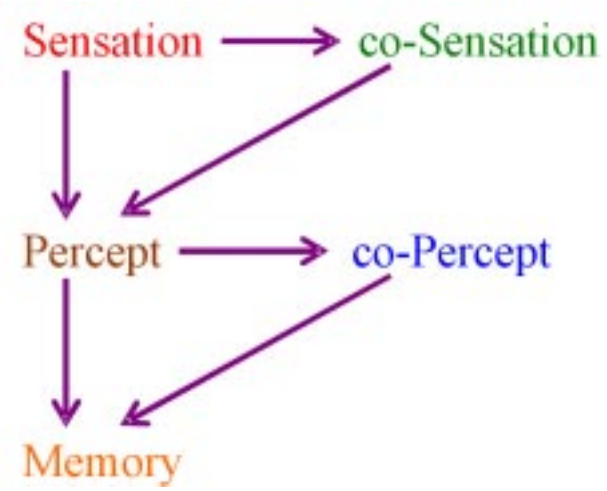

Figure 2. *Construction and composition of duals. Neural information processing underlying the transformation of sensation into percept appears to be formally similar to that implementing the transformation of percept into memory. Given a percept, brain forms a memory of the percept by constructing a dual of the percept and composing it (co-percept) with the percept. Adopting a similar computational strategy, given a sensation, brain constructs the dual i.e., co-sensation, and composes it with sensation to give rise to percept.*

information comprises of composing the given information (an arrow) with its dual, an arrow in the opposite direction. Form-addressed memories brought into sharp focus a key principle of the workings of the brain: 'construction and composition of duals'. The neural transformation of sensation into perception appears to be implemented by the same principle. More specifically, given a sensation, brain constructs the dual of sensation and composes it with sensation to generate the percept (Figure 2). Ongoing work in which we are generalizing the "feature contour system – boundary contour system" model of form perception into squares is indicative of the indispensability of the notion of 2-dimensional square in mathematically modelling the duality in the brain. Our results point to the need to go beyond the symbolic computation paradigm exemplified by the 'weighted summation and threshold' calculations crystallized in model neurons in order to formally capture the more global computational structures unravelled by context and embodied by the brain.

Collaborators

Prof. Ronald Brown and Timothy Porter, Mathematics Division, University of Wales, Bangor, UK.

Prof. Thomas Albright and Terrence Sejnowski, The Salk Institute, La Jolla, USA.

Publication

Rayudu PV, Brown R and Porter T. Higher-Dimensional Algebraic Study of Brain Functions. (*under revision* 2003*).*

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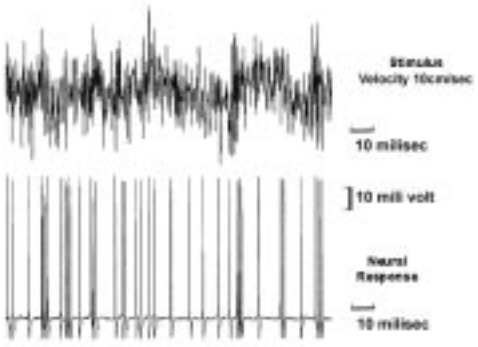
Non-equilibrium Information Theory and spatiotemporal processing in neurons: A Neurocomputational Approach

Principal Investigator Prasun Kumar Roy

Research Fellow Balaraju Battu

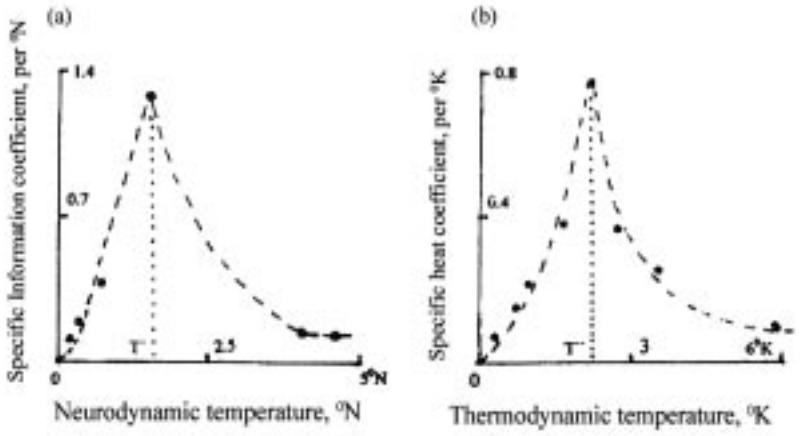
Summer Student Prateek Gupta,
IIT, Kanpur



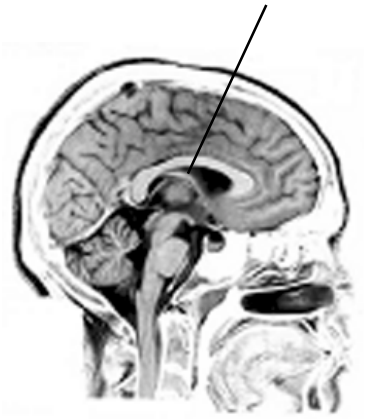
Stimulus-Response recording from neuron.

A grand challenge in neuroscience, information theory and computer vision is to understand the basis of normal and abnormal types of information processing in nervous systems, given the non-linear and nonstationary nature of the neuronal channels and synaptic interconnections, subject to incessant fluctuation or noise. A critical area of investigation is what features of the neuron's performance and characteristics emerge from architectural and/or energetic constraints acting at a 'global systems level', and/or from evolutionary legacy ? Considerable progress toward these goals has been made in recent years through the application of information theory developed during 1920s-1940s by Nyquist and Shannon, who used the logarithmic form for estimating the information transmitted. However, application of Shannon-Weaver's classical model has proven to be more problematic in situations where the neuronal circuit or network is in a non-stationary, non-equilibrium situation (for example, when the system is dynamic or changing with time, such as undergoing adaptation or plasticity or intensive firing as in epilepsy) . This disadvantage of the classical approach is understandable, since Shannon's formulation, inspired by the need to analyze telegraphic communication at its era, used mathematical concepts, as entropy, inspired from Boltzmann's older equilibrium thermodynamic analysis. Our objective is to develop a new generalized theory of information transmission and processing beyond the Shannon paradigm and use the theory to understand and modulate information processing in high throughput conditions of neuronal systems, as in intensive adaptation, plasticity, and epileptic seizures.

Electrophysiological recordings from neurons are amplified and analysed to decipher the basic mathematical and computational transformations through which spatio-temporal information is processed and mapped



Order-Disorder transition (lambda point) in neurodynamics and thermodynamics



Exploring Neuroengineering application: Optimizing efficient frequency-detection by electrodes for neurosurgical electrostimulation.

in the neuronal system. Different types of programmed stimulus are administered such as, sinusoidal, random excitation, pulsed stimulation etc. We have developed a new concept of "Bit-Bel" plot of the neuronal system that plots the information transmitted (in bits) vis-à-vis the energy expenditure in deci-bel. The "Bit-Bel" plot furnishes the regime of most efficient information transmission in the neuron. The process of order-disorder transition in the neuron under variation of input stimulus has been determined and a second order phase transition is observed when the informational capacity is plotted against the electrical Nyquist noise temperature of the neuron. We have also formulated a metric tensor mapping which transforms the input spatio-temporal coordinates of stimulation into its neuronal representation. The research is being done in collaboration with Prof. John Miller, Center of Computational Biology, Montana State University. The practical applications are determining the the determination of the most optimum form of administering electrical impulses to cochlear nerve in auditory deficits, the characterization of resonant frequency from the electrophysiological signatures received by neurosurgical probes for deep brain stimulation treatment, and understanding the abnormal information transmission and processing during epilepsy.

Publications

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Presentations

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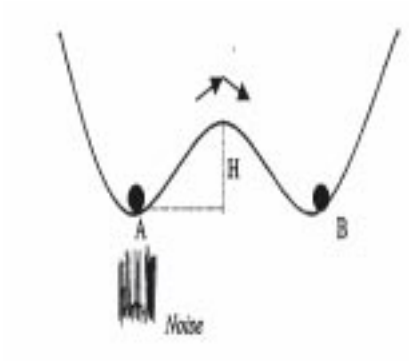
Non-equilibrium Information Theory: Application to Neuronal transmission, *International Conference on Theoretical Neurobiology, New Delhi,* February, 2003.

Application of Stochastic Resonance and Stability analysis for Brain Imaging and Therapy: Using Noise to defeat Noise

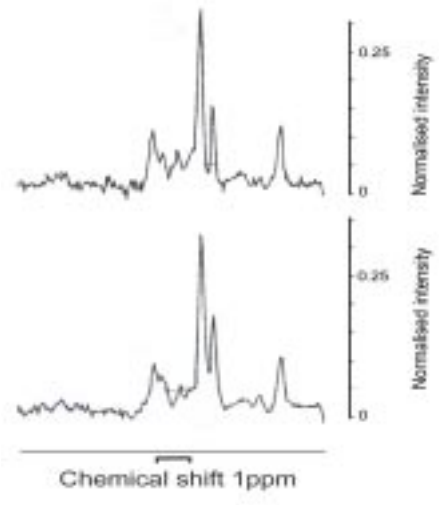
Principal Investigator Prasun Kumar Roy

Summer Student Amit Upadhyay, IIT Kanpur

Computer Programmer Joydev Saha



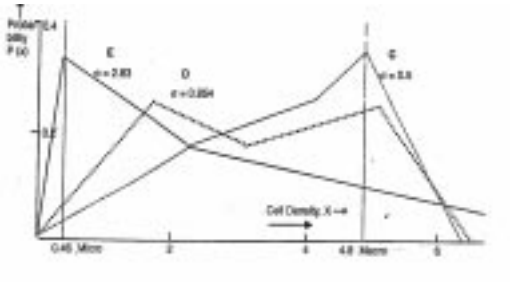
Perturbations induce Stochastic Resonance and surmounting of potential barrier.



Stochastic Resonance in Neuroimaging: Small signal differential in Magnetic Resonance Spectroscopy (MRS) of astrocytoma (upper panel) and oligodendroglioma (lowe panel) needing stochastic resonance for enhancement for differential diagnosis.

A major recently-discovered advancement is the remarkable phenomenon of the Stochastic Resonance Effect (SRE), whereby optimized perturbation or statistical fluctuation is used to dramatically enhance the behaviour or sensitivity of a system to an input parameter or signal. SRE occurs because the positive peak of the weak signal, under specific conditions, adds up with positive peaks of the perturbation, resulting in a considerable stronger signal. The diagram along side schematically captures the basic mechanism of how perturbations enable a system to jiggle around an potential barrier or hump, and go to a new state associated with increased system activation. SRE has been used to enhance optical, EPR, microscopic and raman images or spectra. Here we aim to apply the SRE paradigm for increasing the efficiency of of diagnostic and therapeutic radiology, especially in neuroimaging, MRI, MRS, tomography and tomotherapy. Though CT and MRI have revolutionized the study of brain in health and disease, a major problem is increasing the signal:noise ratio (SNR). We have designed the pathways through which perturbation can be administered during the process of MRI, tomography and tomotherapy. We have devised a preliminary algorithm to induce stochastic resonance in the system. To induce SRE, the power of the perturbation is varied until one obtains a peak enhancement, as observed on monitoring the output at each circuit or stage where SRE is used.

Recent studies indicate that India faces a bursting load of brain tumour cases that are devastating conditions, often rapidly fatal (mean survival of anaplastic glioma is 58 weeks), and drugs may have difficulty in crossing the blood-brain barrier. Though radiotherapy is the long-term mainstay of brain tumour treatment, the major problem is that the high dose often is intolerable as it produces severe toxicity. Experiments show that stochastic fluctuation of radiation flow rate markedly enhances its ionizing efficiency, and it is this behaviour that we exploit. This approach of using perturbations for treatment, called 'functional' stochastic resonance, is an interdisciplinary field of seminal promise, where theoreticians, experimentalists and clinicians with diverse background, collaborate. Using computational models of the brain and tumours therein (digital radiological phantoms), we are investigating the amplified effect of perturbation of radiotherapetic inflow (flux rate) on brain tumours. Indeed, system perturbations can produce striking changes on population dynamics of target cells. Rather than the usual practice of administering a steady radiotherapetic beam exposure to tumour, we computationally fluctuate the flux rate of the photon radiation so that one can induce a resonant enhancement of the antitumour efficiency in



Cell population

Stochastic perturbation of radiotherapeutic flux reduce tumour cell population. As perturbation (σ value) increases, the cell population reduces from C to D to E.

radiotherapy. This project work is being done with cooperation from Institute of Nuclear Medicine and Allied Science, Delhi.

Technical Report

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Presentations

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Stochastic Transition and Stochastic Resonance as an Enhancement Technique in Biomedicine: Using Noise to Defeat Noise, *Mathematical Biosciences Seminar, Ohio State University, Columbus, Ohio,* February, 2003.

Computational Analysis of language Impairments in Children and Development of Subsequent Therapy

Principal Investigator

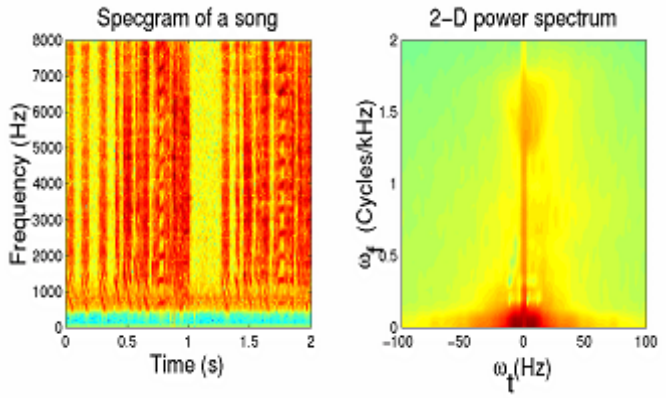
Nandini Chatterjee Singh

Language is a code that we learn to use in order to communicate ideas and express our wants and needs. Reading, writing, speaking, and some gesture systems are all forms of language. Speech is the spoken form of language. We know that the most basic unit of any language is the phoneme, the smallest unit of sound that differentiates meaning. As phonemes are physically complex acoustic stimuli, the role that complex auditory processing plays in the development of phonological systems has been a topic of increased research concentration.

Most children develop language relatively effortlessly, but some others have unusual difficulty in mastering this skill. Often there is no obvious explanation for a child's language difficulties: hearing is normal, nonverbal ability is sufficient, the child does not have any apparent physical or psychiatric disability and comes from a normal home background. This is known as specific language impairment, or SLI. The source of this problem has been poorly understood and standard speech therapy techniques used to treat the disorder have proved unsatisfactory. One popular theory maintains that, although children with SLI have normal hearing, they may have difficulty in distinguishing sounds that are brief or rapid. Researchers have also found that children with SLI are affected much more profoundly than unimpaired children by a phenomenon known as "masking". Masking refers to a natural limitation in the human ability to detect any particular sound that is presented simultaneously or within a small fraction of a second of other "masking" sounds. Speech fits into the category of masking because it consists of a stream of auditory stimuli occurring sequentially in time. In normal individuals, the masking of individual speech sounds by preceding or following sounds is not sufficient to impair speech processing. Research has also found that compared to normal children those with disorder in some masking situations required that tones be about 45 dB more intense before they could be heard over masking noise. This is comparable to the difference between the sound level in a quiet room and at the side of a highway.

From a signal processing approach, human speech signals have a time-varying frequency structure and thus require joint representations of time and frequency. Towards building such a picture, scientists have begun to "visualize" sound in terms of temporal and modulations of the amplitude envelope. In this framework sounds are characterized by broadband spectra with energy at many different frequencies and elaborate spectral and temporal structure. We have developed a modulation spectrum which presents a representation where any sound

can be broken into a series of temporal and spectral modulations. Thus we have a joint representation of both temporal and spectral components. The figure below shows the spectrogram of a zebra finch song and its corresponding modulation spectrum.



A sound spectrogram, like a musical score, is a visual representation of sound. As in musical notation, the horizontal dimension corresponds to time (reading from left to right), and the vertical dimension corresponds to frequency (or pitch), with higher sounds shown higher on the display. Frequency is measured in Hertz (Hz), or cycles per second; and in kilohertz (kHz) or thousands of cycles per second. The relative intensity of the sound at any particular time and frequency is indicated by the darkness of the spectrogram at that point. The most obvious feature of a speech spectrogram is the energy modulations, both in time in any given frequency channel, and along the spectral axis at any instant, due to formant peaks and their transitions, spectral edges and rapid amplitude modulations at onsets and offsets. We have recently developed a new method to analyze sound called the modulation spectrum. The modulation spectrum presents a representation where any sound can be broken into a series of temporal and spectral modulations. Thus we have a joint representation of both temporal and spectral components of sound. The modulation spectrum is obtained by taking the 2-D Fourier transform of the auto-correlation matrix of sound in its spectrographic representation.

The Wt which are plotted on the x-axis are the temporal modulations and Wx are the spectral modulations present in the song of the zebra finch. The colour in the figure is a measure of the power and the dark colour indicates that in the song of the zebra finch, most of the energy is found for low spectral and temporal modulations and shows that most of the high frequency spectral modulation power is found at the very lowest temporal modulation and vice versa. In other words there is a scarcity of sounds with both high spectral and high temporal modulations.

Since the modulation spectrum is a representation of sound in terms of

temporal and spectral modulations, one would expect that a modulation spectrum of the speech sounds of children with SLI would reflect the modulations missing in their speech versus the speech of normal children. Such an approach could also test the hypothesis that children with LLI (Language Learning Impairment) often require longer time periods between acoustic events to discriminate them as compared to normal children. Our study and analysis will address some of these issues and make an attempt to obtain easier and earlier clues of this impairment. Based on our results, attempts will also be made to made to design some therapy.

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* Work done elsewhere

Presentation

Nandini C Singh**.** Modulation spectra of natural sounds, *Int. Workshop on Neural Coding*, Mathematical Biosciences Institute, Ohio State University, Columbus, USA.

Development of a DSP based Helium Speech Unscrambler

Principal Investigator
Nandini Chatterjee Singh

Research Fellow Latika Singh

Deep-sea diving to depths exceeding about 140 feet of seawater requires the use of heliox (a mixture of helium and oxygen) as a breathing gas, rather than compressed air. Heliox eliminates the danger of nitrogen narcosis and reduces the risk of decompression sickness that would otherwise be present. However, heliox presents another risk. The diver's speech is rendered unintelligible because the higher velocity of sound in the diver's vocal tract shifts the frequency components of the diver's speech to much higher frequencies - an effect that has been likened to the "Donald Duck" voice. Thus, communications with the surface tender and with other divers are severely compromised. Normal speech and helium speech will be analysed using the modulation spectrum analysis and the descrambler will be developed using nonlinear analysis of digital signals.

What helium does to speech

The first diagram shows a schematic picture of the spectrum for a particular configuration of the vocal tract *filled with air*. The solid line is the spectral envelope; the vertical lines are the harmonics of the vibration of the vocal folds. The second diagram shows the effect of replacing air with helium, but keeping the tract configuration the same (i.e. trying to pronounce the same sound as before, but with a throat full of helium). The speed of sound is greater, so the resonances occur at higher frequencies: the second resonance has been shifted right off scale in this diagram. The flesh in the vocal folds still vibrates at the same frequency, so the harmonics occur at the same frequency. The speech does however sound 'like Donald Duck'. There is less power at low frequencies so the sound is thin and squeaky. This alteration to the timbre changes vowels in a spectacular way. Although we can understand whole sentences (using contextual clues) we find that individual vowels are very difficult to identify.

Since the modulation spectrum is a plot of the power at different temporal and spectral modulations a comparison of the modulation spectra of

helium speech will be different from that of normal speech. Samples of helium speech and normal speech are obtained from the same person and their corresponding modulation spectra are set up to characterize the differences between them and also quantify the differences between these spectra.

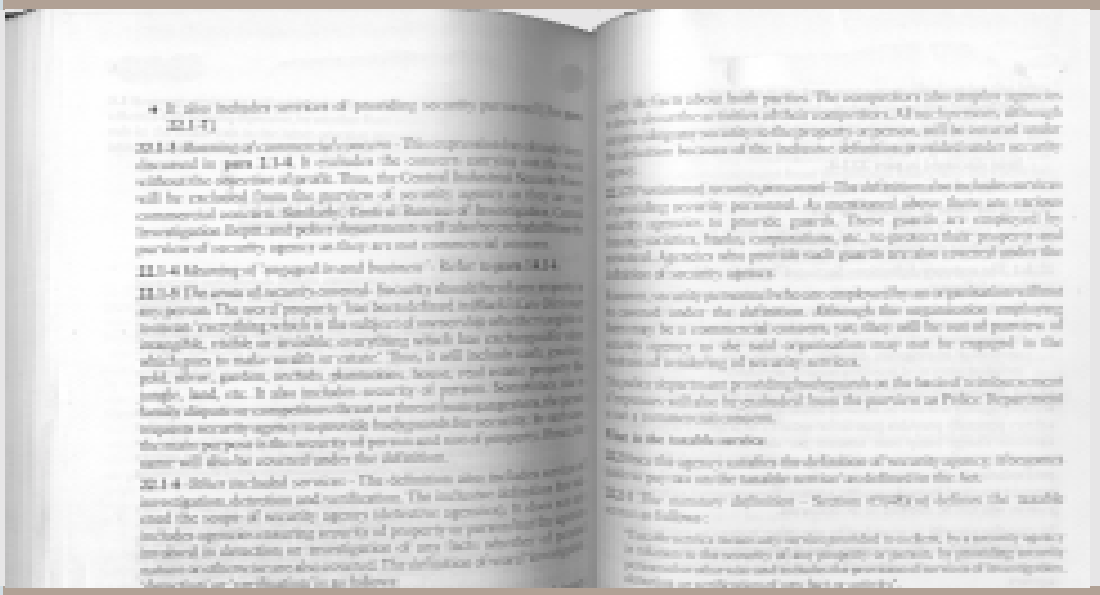
Further speech intelligibility is critically dependent on the clarity of these spectro-temporal modulations. It has been shown that speech reconstructed from smoothed spectrograms along either dimension (temporal or spectral) suffers from progressive loss of intelligibility. Our approach is focused on extracting the auto-correlations of the underlying amplitude envelope in the spectrographic representation. We will define various quantifiers to characterize the modulation spectra and use these to set up measures to determine the speech intelligibility index. Based on the analysis of the helium speech and normal speech and the speech intelligibility index we will use digital signal processing techniques to design a descrambler that will transform the diver's speech. Further phonetic information can be **"filled in"** from higher-level structures as well as from the acoustic signal and could also be used in designing the descrambler.

Collaborator

DEBEL , the Defence Engineering and Biomedical Engineering Laboratory, Bangalore.

Publication

Nandini C. Singh. The healing sounds of Music in Music and the Human Brain. *Society for Gerontological Research*: In press



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PUBLICATIONS

E.A. Zemshov, N.R. Jana, M. Kurosawa, H. Miyazaki, N. Sakamoto and N. Nukina. Pro-apoptotic protein kinase Cδ in associated with intranuclear inclusions in a transgenic model of Huntington's disease. *J. Neurochem*: 87, 395-406.2003*

N. R. Jana and N. Nukina Recent advances in understanding the pathogenesis of polyglutamine diseases: involvement of molecular chaperones and ubiquitin-proteasome pathway. *J. Chem. Neuroanat 26: 95-101, 2003.*

N. R. Jana and N. Nukina. Assessment of impaired proteasomal function in a cellular model of polyglutamine diseases. In "*Triplet repeats protocol*" ed by G. Bates: Humana Press. 2003.

N. R. Jana. Neurodegenerative diseases involving expanded CAG repeats. In "*Neurobiology in post genomic era*": In press.

A. Goswami and N. R. Jana. Mutation in Cu/Zn superoxide dismutase1 and familial amyotrophic lateral sclerosis. In "*Neurobiology in post genomic era*": In press.

N. R. Jana. Recent advances in understanding and developing therapies for Alzheimer's disease. In "*Alzheimer's disease in India*" Published by Society for Gerontological Research.

Chinta S.J, Pai H. V, Upadhya S.C, Boyd M.R. and Ravindranath V. Constitutive expression and localization of the major drug metabolizing enzyme, cytochrome P4502D in human brain. *Mol. Brain Research* 103: 49-61, 2002.

Upadhya S.C. and Ravindranath V. Detection and localization of protein -acetaldehyde adduct(s) in rat brain following chronic ethanol treatment. *Alcoholism Clinical and Experimental Research* 26 (6): 856-863, 2002.

Pai H.V, Upadhya S.C, Chinta S.J, Hegde S.N. and Ravindranath V. Differential metabolism of alprazolam by liver and brain cytochrome P4503A to pharmacologically active metabolite: constitutive expression and localization of CYP3A in rat and human brain. *The Pharmacogenomics Journal, Nature Press Journal* 2: 243-258, 2002.

Kenchappa R.S, Diwakar L, Boyd M.R. and Ravindranath V. Thiol transferase (glutaredoxin) mediates recovery of motor neurons from excitotoxic mitochondrial injury. *Journal of Neuroscience* 22: 8402-8410, 2002.

Kenchappa R.S, and Ravindranath V. Glutaredoxin maintains functional activity of mitochondrial complex-I: Studies with MPTP. *FASEB J* 17: 717-719, 2003.

Kenchappa R.S and Ravindranath V. -Glutamyl cystine synthetase is up-regulated during recovery of brain mitochondrial complex I following neurotoxic insult in mice. *Neurosci.lett.* 350 (1): 51-55, 2003..

Mitton KP, Swain PK, Dowd M, Apel IJ and Swaroop A. Interaction of retinal bZIP transcription factor NRL with Flt3-interacting Zinc-finger protein Fiz1: possible role of Fiz1 as a transcription repressor. *Hum. Mol. Genetics* 12(4): 365-73, (2003). *

Wang X, Xu S, Rivolta C, Li LY, Peng GH, Swain PK, Sung CH, Swaroop A, Berson EL, Dryja TP, Chen S Barrier to autointegration factor interacts with the cone-rod homeobox and represses its transactivation function. *J Biol Chem* 277 (45): 43288-300, (2002). *

Neeraj Jain, Pamela S Diener, J.-O Coq and Jon H Kaas. Patterned activity via dorsal quadrant inputs is necessary for the formation of organized somatosensory maps. *Journal of Neuroscience*: *In Press.* *

David C. Lyon, Neeraj Jain and Jon H. Kaas. The Visual Pulvinar in Tree Shrews I. Multiple Subdivisions Revealed Through Acetylcholinesterase and Cat-301 Chemoarchitecture. *J. Comparative Neurology*: *In Press.**

David C. Lyon, Neeraj Jain and Jon H. Kaas. The Visual Pulvinar in Tree Shrews II. Projections of Four Nuclei to Areas of Visual Cortex. *J. Comparative Neurology*: *In Press.* *

Pei-Chun Fang, Neeraj Jain and Jon H Kaas. Few intrinsic connections cross the hand-face border in area 3b of New World monkeys. *J. Comparative Neurology* 454: 310-319, 2002. *

Neeraj Jain. Adult brain plasticity: What is revealed is exciting, what is hidden is critical. *J. Biosciences*. 27: 439-442, 2002

Schall J., K.G. Thompson, N. P. Bichot, A. Murthy and T. Sato Visual. Processing in the macaque frontal eye field. The Primate Visual System. Edited by J. Kaas and C. Collins, *CRC Press Boca Raton*, FL: 2003. *

A. Murthy. Neural control of eye movements. *IETE Journal of Research:* 2003. Institution of Electronics and Telecommunication Engineers 49 (2): 135-143, 2003.

Ray S. J.D. Schall and A. Murthy (2003). Parallel programming of double step saccade sequences: modulation by cognitive context. (*submitted to Vision Research*).

V. Rema, M. Armstrong-James and F. F Ebner. Experience-dependent plasticity is impaired in adult rat barrel cortex after whiskers are unused in early postnatal life. *The Journal of Neuroscience* 23: 358-366, 2003.*

Rayudu PV, Brown R and Porter T. Higher. Dimensional Algebraic Study of Brain Functions. (*under revision* 2003*).*

P K Roy and J Miller. A Control Analysis of Neuronal Information Processing. *Springer Lecture Notes on Artificial Intelligence* 2275: 98-110, 2002.

P K Roy and R Kozma. Neurocomputation model and algorithm for phase transition and instability. *IEEE Transactions on Evolutionary Computing* 5(3): 292-305, 2002.

Nandini C. Singh and F. E. Theunissen. Modulation spectra of natural sounds and ethological theories of auditory processing. *Journal of Accoustical Society of America*: In Press 2003.*

Julie A. Grace, Noopur Amin, Nandini C. Singh and F. E. Theunissen. Modulation spectra of natural sounds and theories of Ethological Theories for Auditory Processing, Selectivity of conspecific song in the avian auditory forebrain. *J. Neurophysiology* 89: 472-487, 2003.*

Nandini C. Singh. The healing sounds of Music in Music and the Human Brain. *Society for Gerontological Research*: In press

* Work done elsewhere


INTERNATIONAL CONFERENCE ON
THEORETICAL NEUROBIOLOGY
February 24- 26, 2003, New Delhi

[redacted]

DISTINCTIONS, HONOURS AND AWARDS

N.R. Jana. Awarded visiting scientist fellowship by RIKEN Brain Science Institute, Japan, November/December, 2002.

S.Mani. Member of the Stem Cell Task Force, Department of Biotechnology.

P.K. Roy. Travel fellowship award from Mathematical Biosciences Institute, Ohio State University, Columbus, to participate as a visiting scientist in the institute and to take part in the Neural Coding Workshop, February 2003.

P.K. Roy. Member of Curriculum Development Committee, Indian Institute of Information Technology, Allahabad, June 2002.

Nandini C Singh. Travel fellowship award from Mathematical Biosciences Institute, Ohio State University, Columbus, to participate as a visiting scientist in the institute and to take part in the Neural Coding Workshop, February 2003.

Ravindranath V. Member, Research Advisory Council, CSIR (EMR).

Ravindranath V. Member, Advisory Committee of Animal Sciences and Biotechnology, CSIR.

Ravindranath V. Chairman, Building Committee, Institute of Life Sciences, Bhuvaneshvar.

Ravindranath V. Member, Editorial Board, Neurotoxicity Research, USA.

Ravindranath V. Member, Editorial Board, Indian Institute of Biochemistry & Biophysics.

Ravindranath V. Awarded "The Woman Scientist of the Year", December 2002.

Ravindranath V. Elected Fellow, "International College of Neuropsychopharmacology".

Ravindranath V. Secretary of the "Federation of Asian-Oceanian Neurosciences Societies (FAONS)".

Ravindranath V. President, Biological Sciences of the Meeting of National Academy of Sciences, 2002.

Ravindranath V. Meera Memorial Oration, December 2002

Ravindranath V. Dhanuja Oration, Delhi Neurological Society, 2003.

Rajappa S. Kenchappa.Awarded a visiting scientist fellowship by RIKEN Brain Science Institute, Japan, November/December, 2002.

Harish V. Pai. Travel fellowship award to attend the 3rd IBRO workshop on functional Genomics held at Hongkong in December 2002. Recieved award for the best work carried by the student participating in the workshop.

PRESENTATIONS BY NBRC SCIENTISTS

N. R. Jana, Svetlana E. Kotliarova, Munenori Nekooki and N. Nukina Direct visualization of the expression, selective nuclear accumulation, aggregate formation and possible proteolytic processing of the transgene in a HD exon 1-EGFP transgenic mice model. *4th Japan-Korea-China-India joint workshop on neurobiology and neuroinformatics*. RIKEN Brain Science Institute, Japan, 2002.

N. R. Jana, Svetlana E. Kotliarova, Munenori Nekooki and N. Nukina. Direct visualization of the transgene expression and fate of the transgene product in the brain of HD exon1-EG FP transgenicmice. *Indian academy of Neuroscience*, Udaipur.

S. Mani. Regulation of Neurogenesis in the Cerebellum. *The 4th Japan-Korea-China-India conference on Neuroinformatics and Neurobiology:* RIKEN, Japan. 2002.

S. Mani. Regulation of Neuronal Differentiation by GAP-43. *Neuroprotection and early life, ICMR-INSERM workshop*: Bangalore. 2003.

S.Mani. Neural Stem Cells. Lecture, given at *A.I.I.M.S. New Delhi,* 2002.

V. Ravindranath. "Functional genomic in the understanding and treatment of brain disorders" – Invited lecture at the " *Symposium on Brain Genomics*" at University of Hyderabad, Hyderabad, 9th – 10th December, 2002.

V. Ravindranath. "Distinctive features of drug metabolizing enzyme in human brain: Existence of splice variant forms" *Annual Meeting of the Society for Neuroscience*, Orlando, USA held in November, 2002.

V. Ravindranath. "Drug metabolism in brain: implication in the treatment of mental illnesses" *Prof. K.P. Bhargava Memorial Lecture at 20th Annual conference of Indian Academy of Neurosciences*,Udaipur, 21st February, 2003.

Pai, H. V, Chinta, S. J, Kommaddi, R. P and V. Ravindranath. Existence of new cytochrome P4502D isoform in human brain that mediates a novel cerebral drug metabolism pathway. *20th Annual Conference of Indian Academy of Neurosciences*, Udaipur, February 21-23, 2003.

Kommaddi, R. P, Chinta, S. J, Pai, H. V and V. Ravindranath. Constitutive expression and localization of cytochrome P4501A1 in brain: Identification of a unique splice variant. *20th Annual Conference of Indian Academy of Neurosciences*, Udaipur, February 21-23, 2003.

Ravindranath V. “Towards understanding the pathogenesis of neurodegenerative disorders”. *Invited talk at the fourth Japan-Korea-China-India workshop on Neurobiology and Neuroinformatics*, RIKEN Brain Science Institute, Japan, 25th –26th November 2002.

Ravindranath V. “Rational therapies and cures for brain disorders: Hopes and challenges”. *Invited lecture at the Golden Jubilee of the DNA Double Helix discovery*, New Delhi,12-14th February 2003 .

Ravindranath V. “Gender differences in Brain Injury”. *Invited lecture at the Silver Jubilee of the A Lakshmipathi Neurological Centre*, Chennai, 21–22nd, February 2003.

Ravindranath V. “Protein Thiols, Mitochondrial Dysfunction and Neurodegeneration”.*Invited talk at the satellite symposium of the Annual Meeting of society for Toxicology*, USA held in March, 2003.

Kenchappa R S, Diwakar L, Smitha K and Ravindranath V. Female mice are resistant to L-BOAA toxicity; Implications in Neurolathyrism. *20th Annual Conference of Indian Academy of Neurosciences*, Udaipur, 21-23rd February 2003.

Diwakar L, Smitha K and Ravindranath V. Ovarecaomy makes female mice vulnerable to excitotoxicity caused by L-BOAA: Implications in Neurolathyrism. *20th Annual Conference of Indian Academy of Neurosciences*, Udaipur, 21-23rd February 2003.

Ravindranath V. “Recent advances in Brain Research and Hope for Treatment of Brain Disorders”. *Invited talk presented for the Meera Memorial Lecture*, Bangalore, 3rd December 2002.

Ravindranath V. **“**Recent advances in Understanding Brain related Disorders: Hope and Tribulations”. *Invited talk presented for 90th Indian Science Congress Meeting,* Bangalore, 3 - 7th January, 2003.

Ravindranath V. “Brain research: Recent advances and Hope for Brain Disorders”. I*nvited talk at National Academy of Sciences*, North Eastern Hill University, Shilong, 25 - 27 October 2002.

Ravindranath V. “The Human Brain: From Birth to Old Age”. *Invited lecture at the Children Science Congress*, Bangalore, 3 - 7th January, 2003.

Ravindranath V. “Neuroinformatics: Indian Perspective”. *Invited talk at the ICONIP*, Singapore, 18 - 22nd September 2002.

Ravindranath V. " Fifth Annual Conference of the DNA Neurocon 2003". *Invited talk at the Dr. (Mrs.) Dhamija Oration of the Delhi Neurological Society,* New Delhi, 2nd February 2003.

Prabodh Swain. Participated as a delegate member in the *Indo-US symposium on neuroscience/neurobiology sponsored by the Indo-US forum*, Orlando, Florida, USA. 1st –7th November, 2002.

S. Iyengar, N. Jain, H.-X. Qi and J.H. Kaas. Cortical and thalamocortical connections of the oral cavity representations in area 3b of New World monkeys. 32nd Annual Meeting, Society for Neuroscience, Nov. 2-4, Orlando, FL, USA. 2002.

M.S. Remple, N. Jain, P.S. Diener and J.H. Kaas. Bilateral effects of spinal overhemisections on the development of the somatosensory system in rats. 32nd Annual Meeting, Society for Neuroscience, Nov. 2-4, Orlando, FL, USA. 2002.

Neeraj Jain. Normal and altered organization of the somatosensory system of primates'. International Conference on Theoretical Neurobiology, New Delhi, February 24 – 26, 2003.

Neeraj Jain. Changes in the brain after nerve and spinal injuries'. Sri Venkateswara College, University of Delhi. November 15, 2002.

Neeraj Jain. A short-term course on computational neuroscience. Indian Institute of Technology, Kanpur, July 7-18, 2003. (1) 'Some general principles of the brain organization', and (2) Reorganization of the brain following spinal injuries – a multidimensional view.

Neeraj Jain. "Healthy Upbringing of the Brain – Leads from Traditional Medicine and Modern Science"- *a mini-symposium* Organized by Unilever Research India and Hindustan Lever Research Centre, Bangalore, India. October 23 - 24, 2002.

Shorter-Jacobi S.M., A. Murthy, K.G. Thompson and J.D. Schall. Neural Correlates of divided orienting in frontal eye field in a search-step task. *Soc. Neurosci. Abstracts* , 2002 .

A. Murthy. Computational Vision. *Computational Neuroscience Workshop*, given at IIT Delhi, 2002.

A. Murthy. The saccadic eye movement system as a marker of brain dysfunction. Lecture, given at *A.I.I.M.S. New Delhi,* 2002.

A. Murthy. The role of frontal cortex in overt and covert orienting. *The 4th Japan-Korea-China-India conference on Neuroinformatics and Neurobiology*. RIKEN, Japan, 2002.

Ray S., A. Murthy. A fast online error correction facilitates parallel

programming of saccades. *Indian Academy of Neuroscience*. Udaipur, India , 2003.

Rema V. Armstrong - James and Ebner F.F. Neonatal sensory - deprivation impairs transmission between layers of barrel field cortex. *Society for Neuroscience.* Orlando, Florida. Nov 2002.

Li. L., Rema V. and Ebner F.F. Inter-hemispheric neural activity is required for normal responsiveness in barrel field cortex. *Society for Neurosciece*, Orlando, Florida. Nov 2002.

Rayudu PV. Higher Dimensional Algebraic Study of Brain Functions. *International Conference on Theoretical Neurobiology*, New Delhi, 2003.

Rayudu PV. Brain as Mathematics. *4th Japan-Korea-China-India Joint Workshop on Neurobiology and Neuroinformatics*, Tokyo, 2002.

Ravindranath V and Rayudu PV. Neuroinformatics: Indian Perspective. Ninth International Conference on Neural Information Processing, Singapore, 2002.

P.K. Roy. A Nonlinear thermodynamic approach to computational neuroscience, *Summer course on Computational Neuroscience*, IIT Delhi, May 2002.

P.K. Roy. Stochastic activation as a new therapeutic approach to Medicine, *Bioinformatics Seminar Series*. JNU, New Delhi, December, 2002.

P.K. Roy. Non-equilibrium Neuro-dynamics in Neuronal Information Processing, *Neural Coding Workshop*, Ohio State University, Columbus, Ohio, February, 2003.

P.K. Roy. Stochastic Transition and Stochastic Resonance as an Enhancement Technique in Biomedicine: Using Noise to Defeat Noise, Mathematical Biosciences Seminar, Ohio State University, Columbus, Ohio, February, 2003.

P.K. Roy. Non-equilibrium Information Theory: Application to Neuronal transmission, *International Conference on Theoretical Neurobiology*, New Delhi, February, 2003.

P.K. Roy. Participated in the meeting of conference on *Neuroscience for Clinicians*, All India Institute of Medical Sciences, New Delhi, August, 2003.

P.K. Roy. Participated in the meeting on *Advances in Deep Brain Stimulation and Neuronavigation*, India International Centre, New Delhi, May, 2003.

Nandini C Singh**.** Modulation spectra of natural sounds, *Int. Workshop on Neural Coding*, Mathematical Biosciences Institute, Ohio State University, Columbus, USA.

PRESENTATIONS BY SCIENTISTS VISITING NBRC

Dr. Y. Singh. Centre for Biochemical Technology, New Delhi. "*Tackling Anthrax*". 23rd April 2003.

Dr. Awadesh Prasad. Arizona State University,USA. "*Hysterisis in Compled Chaotic Oscillators: An application to Epileptic Seizure*". 22nd May 2002.

Dr. B. Bandyapodhyay. University of Maryland, USA. "*Molecular Cloning of TRP ion channel in Limulus Ventral eye photoreceptor*". 2nd July 2002.

Dr. Jamuna R. Subramaniam. IIT, Kanpur. "*Value of transgenic/gene-targeted model in neurodegenerative disease*". 15th July 2002.

Dr.Nimesh G.Desai. Institute of Human Behaviour and Allied Sciences (IHBAS), Dilshad Garden, New Delhi. **"***Emerging trends inbasic Neurosciences for clinicians*" 27th August 2002.

Prof. Rajani R. Joshi. BJM School of Biosciences & Bioengineering and Department of Mathematics, Indian Institute of Technology, Bombay. "*Epitope – Paratope Recognition by knowledge based correlation mapping on Hopfield network*". 18th November 2002

Dr. Bapi Raju. "*Visuo-Motor Sequence Learning & Representation: Results from Behavioural and functional Magnetic Resonance Imaging (fMRI) Experiments*". 29th November 2002.

Dr. Surojit Paul. Yale University School of Medicine, USA. "*Regulation of STEP: a Striatal Enriched Tyrosine Phosphatase*". 3rd December 2002.

Prof. Yu. P. Gerasimenko. I.P. Pavlov Institute of Physiology St.Petersburg, Russia. "*Adaptive abilities of isolated spinal cord in motor control and new methods for rehabilitation of spinal patients*". 3rd December 2002.

Dr. Sourav Mukhopadhyay. School of Computing National University of Singapore. "*Edge detection using wavelets based compression*". 24th December 2002

Dr. Eugene O. Major. National Institute of Neurological Disorders and Stroke (NINDS), USA.. "*The Molecular Pathway of a Common Virus From the Site of Infection to the Brain".* 9th January 2003.

Dr. Shravan Vasishth, Department of Computational Linguistics, Saarland University, Germany. "*Argument-head distance as an index of sentence comprehension difficulty*". 14th January 2003

Dr. Harish C. Pant. Laboratory of Neurochemistry, National Institutes of Health, Maryland. "Neuronal Cyclin dependent Kinase 5 (CDK5); Regulation and role in nervous system". 28th January 2003.

Prof.Shen. Institute of Biophysics, Chinese Academy of Sciences, Beijing, China. "*Azimuth tuning characteristics of the auditory cortical neurons in the bat*". 18th February 2003.

Prof. Thomas Albright. Salk Institure, La Jolla, USA. "*More than Meets the Eye: Contextual Influences on Visual Processing".* 27th February 2003.

LIST OF RESEARCH PROJECTS FUNDED BY EXTERNAL AGENCIES

Nihar Ranjan Jana

Molecular Mechanism of the Pathogenesis of the CAG Repeats in Neurodegenerative Diseases (DBT, RIKEN Brain Research Centre, Japan).

Shyamala Mani

Developmental Neurobiology & Regulation of Neurogenesis in the Cerebellum (DBT).

To Investigate the Mechanisms by which Neural Stem Cells Differentiate into Distinct Neuronal Subtypes (FIRCA)

Ravindranath V.

Psychoactive Drug Metabolism By Brain Cytochrome P-450 (National Institute of Health - RO1).

Mitochondrial Dysfunction and Protein Thiol Homeostasis In Neurodegenerative Diseases (US-India fund for Cultural, Educational and Scientific Co-operation).

Genomic micro-array R&D programmes on infectious diseases and neurological disorders (DBT).

Evaluation of the Molecular basis of the Pharmacological action of Traditional Medicinal Preparations used in the Treatment of Mental Illnesses including Dementia (DBT).

Neeraj Jain

Brain Reorganization following Spinal Cord Injuries (Wellcome Trust, UK.).

Aditya Murthy

Control of Saccade Target Selection (TWAS)

Voluntary Control of Action (DST).

Rema Velayudhan

Injury induced Changes in Neurophysiological, Molecular and Behavioural Functions following Focal Lesions to the Brain (Wellcome Trust, UK.).

Abbreviation

DBT : Department of Biotechnology, Government of India.

DST : Department of Science and Technology, Govenment of India.

FIRCA : Fogarty International Research Collaboration Award, NIH, USA.

TWAS : Third World Academy of Science, Italy.

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ACADEMIC COURSES

Ph. D. Programme.

Last year NBRC was accorded the status of Deemed University by the Ministry of Human Resource Development based on the recommendations of the University Grants Commission (UGC). NBRC recruits students from diverse backgrounds for the Ph.D. programme including M.Sc. from any branch related to neurosciences, M.B.B.S., B.E., or B.Tech recognising that understanding brain function requires fusion of knowledge from multiple disciplines. The goal is to train Ph.D. students with an understanding of different aspects of neuroscience integrating information across traditional boundaries. Ph.D. Programme at NBRC has two components – course work including lab rotation, and research work. The courses are taught by NBRC faculty in addition faculty members from different institutition with expertise in specific areas are invited to give lectures as part of the course work. The course work spread over two semesters covers major disciplines of neuroscience, such as neuroanatomy, neurophysiology, neurochemistry, molecular neurobiology, development and regeneration, neurogenetics, systems neuroscience, cognitive neuroscience, systems and clinical neuroscience, and computational neuroscience. Assignments and seminars constitute an integral part of the course work. Students are also required to participate in the Journal Club where recent important new findings pertaining to neuroscience research are presented and

discussed. The lab rotation consists of at least two rotations of three months each. Currently 18 students are enrolled for Ph.D. programme.

Students accepted for the Ph.D course during 2002-2003.

1. Harish V. Pai
2. Rajappa S. Kenchappa
3. Supriyo Ray
4. K.Reddy Peera
5. Rashmi Mishra
6. Smitha K
7. Anand Goswami
8. Latika Singh
9. Sandeep Kumar
10. Priyanka Dikshit
11. S.Srirangan
12. Vinod Kumar U
13. Manoj Kumar
14. Balaraju Battu
15. Zia ud Din
16. Suboohi Rizvi
17. Latha Diwakar
18. Prashant S.Patole


NATIONAL BRAIN RESEARCH CENTRE

DISTRIBUTED INFORMATION CENTRE

Since its inception in December 1999, the Distributed Information Centre (DIC) has played an active role in providing computing support to NBRC.

The Infrastructure

DIC has set up a state of art high speed computing facilities in the form of a SUN Enterprise 420R server with four processors, connected to fast T300 storage arrays that run the web server on a Solaris 8 operating system. The T300 storage array is used as a repository for neural data and high-resolution graphics. The IBM server, which provides file service, runs the Windows 2000 Server operating system and acts as the Primary Domain controller. All the users are connected to this server through the local area network. DIC has got balanced manpower to deliver greater throughput. There are four programmers focusing on in-house development, seven computer operators assisting in solving technical problems in addition to helping the scientists and three system managers handling the servers. All the technical associates and non-technical members of NBRC have been provided with powerful PCs running Windows 2000 Professional/XP. All the servers and PCs are hooked on to the network to access and share resources.

DIC Activities

Virtual Private Network – BioGrid, India

As a long term goal towards integrating scientific research among Indian research institutes, DIC of NBRC manages the private network called Virtual Private Network (VPN) on behalf of Department of Bio-Technology (DBT), which connects 11 DBT locations with NBRC through which scientific information and data is shared. The VPN uses 4Mbps-shared bandwidth, which can be utilized by various professionals viz, scientists and students belonging to the 11 locations connected across India. The objective of the VPN is to enhance research facility in India among these 11 locations. In due course the VPN facility will be extended to several other research institutes.

NBRC has recently shifted to its permanent campus at Manesar in March 2003. The whole network infrastructure has been shifted from Gurgaon to Manesar and DIC has re-established the local area network at the permanent building.

The official web site of NBRC is www.nbrc.ac.in and hosted on a SUN server which is managed by DIC. Even though NBRC is a new institute there has been a seamless integration of the administration tasks to become paperless and digital. This has been primarily possible because of the efforts of DIC. Towards achieving this DIC has developed intranet

applications which provides services like email facility, office forms, information about seminars, journal club meetings, links to all subscribed journals, circulars, and chemicals status list from anyone's desk. In addition to our primary web site, another web site www.nbrcindia.org is also being managed by DIC. A FTP server has been set up which has sharable information about neuroscience and neuroinformatics. Any user connected to the internet apart from VPN users can access the server.

New Initiatives

Efforts are now being directed to develop specialized manpower at DIC. We will soon be in a position to impart training for the analysis of data obtained from the Microarray, and analysis of software related to gene sequencing, both national facilities made available by NBRC. We are also making efforts to develop new computational techniques for faster and efficient data analysis obtained from various experiments. These efforts in neural coding would be beneficial to the neuro-science community at large.

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LIBRARY AND INFORMATION SERVICES

Keeping in view the vision and mission of the Institute, the library and information services play a vital role in supporting, teaching and learning activities and provide the main source for individual research at NBRC. NBRC Library is an advanced modern digital library specializing in Neuroscience.The library also subscribes to major scientific journals in various other fields such as Biochemistry, Genetics, Molecular Biology, Pharmacology & Toxicology, Psychology and Information Technology. Its fast growing collection includes a collection of over approximately 620 books, 52 print format periodicals and 451 online periodicals with access to full text articles. The library has an excellent collection of audio and video cassettes on educational and research topics. These cassettes deal with the various subjects like Neuroscience, Biochemistry, Pharmacology, Computer science, etc. The library also has a collection of about 148 CDs related to research and computer fields.

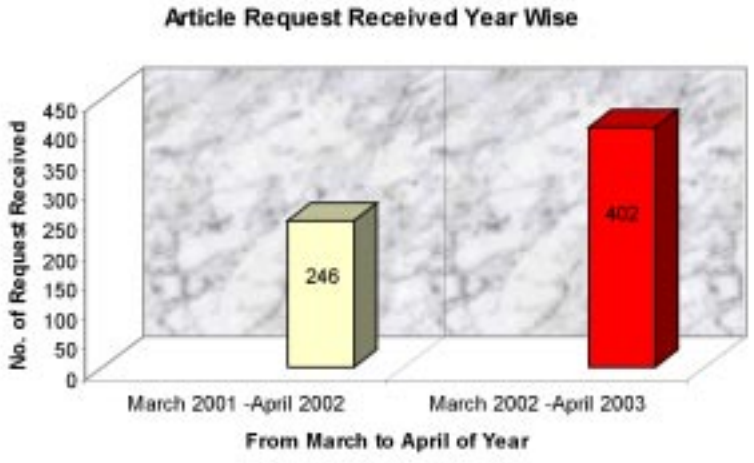
The library is an automated open access library system, which is kept

open all year round. The library staff aims to provide excellent services to the scientists, researchers, research associates, students and visitors. A library committee supervises it.

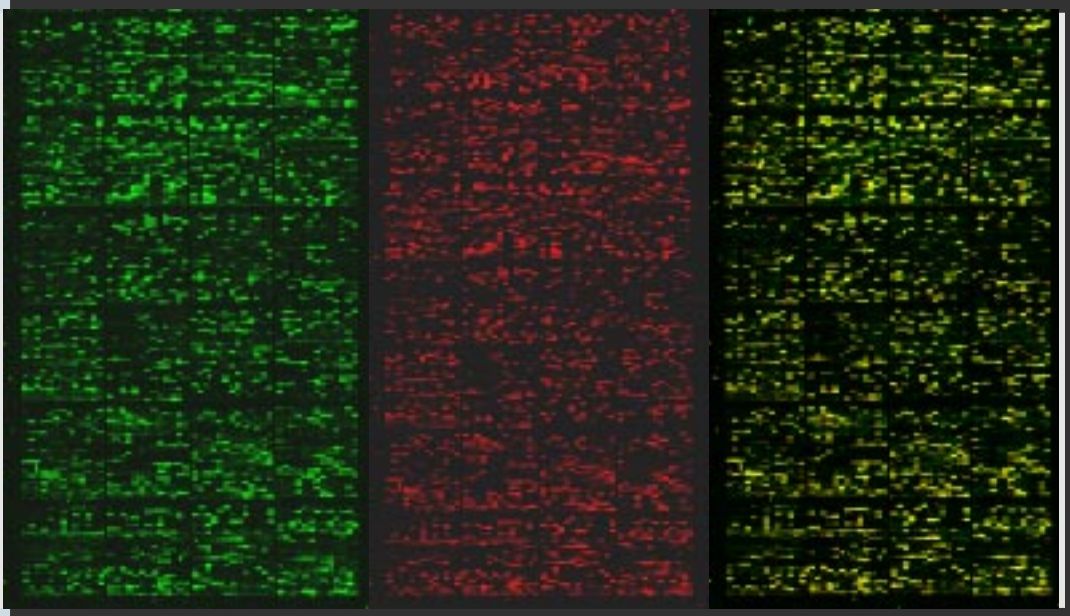
The Digital Library and Free Document Delivery

The most important feature of the library facility is the digital library. In the electronic mode it provides free of cost, references, papers, full text articles, copies of reprints of relevant literature to users all over India. For in house use the Library has 10 IBM PC-Pentium-IV Computers with ISDN Internet facility to provide best services for researchers at NBRC. NBRC is providing selected articles as required by scientists, researchers, doctors and research students working in institutions that are networked with NBRC. The scientists and students send their requirement of articles through e-mail to library@nbrc.ac.in. NBRC library

staff download the articles as a PDF file and sends the same to the requestor. NBRC Library receives on an average of 324 requests per year for articles / papers from its networked centres. The requests received per year have been shown in the following diagram.



It has proved to be a role model for other libraries and was prominently displayed and discussed on the website of the International Brain Research Organisation.



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DNA MICROARRAY FACILITY

Genomic micro-array R&D programmes on infectious diseases and neurological disorders

Progress Report

The National Brain Research Center has initiated the setting up of a core microarray programme specially to cater the needs of the neuroscience research community in India. This facility is available to scientists who are interested in using this technique to ask neuroscience related questions through the institute and collaborating research centers.

The microarray facility was commissioned in September 2002 at the NBRC interim facility at Gurgaon. The procurement of equipments and recruitment of staffs are completed within the specified time frame to run the facility. The major equipments purchased in the facility includes a Typhoon 9210, which is a versatile microarray scanner, and an Automated hybridisation station, both purchased from Amersham Biosciences, India. The Icycler procured from BioRad Laboratories India Pvt. Ltd is for the real time quantitative PCR applications. To expedite the standardization of labelling procedures and scanning operations we purchased pre-

printed microarray slides from Microarray Centre, Toronto, Canada through the microarray transfer agreement (MTA). Four NBRC scientists have been enrolled in the agreement to obtain slides in regular intervals depending on the experimental demands. Initial standardization was performed with the low-density human slides containing 1.7K ESTs. Subsequent experimental conditions were also optimised to use both human 19 K (19000 human ESTs) and mouse 15K ESTs (15000 mouse ESTs) pre-arrayed glass slides of Microarray Center. We have been using

post-labelling strategies to incorporate Cy-fluorescent dyes into the cDNA. Total RNA isolated from different research samples (human or mouse tissue, cell lines) have been used as the starting material. We optimised the labelling steps using ~20 ug of total RNA. The hybridisation condition and image acquisition is reproducible and upto the standard.

The real time PCR is one of the essential components to validate the results obtained by microarray. Preliminary calibrations of the Icycler were completed and will be used extensively after first set of analysed data available from the Microarray experiments.

In collaboration with Amersham Biosciences India NBRC organized a workshop to train students in the effective use of the microarray facility. This workshop also included modules on subsequent data analysis which is an integral part of the microarray technology. Coincidentally, this workshop is also important in fulfilling the other major objectives of NBRC i.e. to produce trained personnel who are well versed in the latest techniques in molecular biology. We are encouraged with the feedback to organize more hands on training programs on microarray technology and applications.

DNA SEQUENCING FACILITY

The National Brain Research Centre has established a centralized DNA sequencing facility to meet the demand of cellular and molecular neurobiologists. Currently, NBRC has MegaBACE™ 1000 DNA Analysis System (from Amersham Bioscience), a high-throughput, fluorescence-based DNA sequencing system utilizing capillary electrophoresis with up to 96 capillaries operating in parallel. The system automatically performs sample injection, gel matrix replacement, DNA separation, detection, and data analysis. This system has the ability to sequence 96 samples in just 2 hours and perform up to 9 runs per day. Average read length with dye primer chemistry is 550 bp. This system can also be used for genotyping and SNP analysis.

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NETWORKING ACTIVITIES

One of the major goal of NBRC is to network the existing neuroscience group / institutions in the country and promote multidisciplinary research in neuroscience. The networking of the existing neuroscience centers with NBRC is aimed to prevent unnecessary duplication of the work and facilities already existing. At the same time it enables sharing of expertise and available infrastructure for mutual benefit. It helps to bring together researchers from varying backgrounds to pursue common objectives that may be beyond the capacity of an individual investigator, group or institution. This is important since the major achievements in neuroscience are being made through a multidisciplinary approach bringing together scientists working in different disciplines into the main stream of neuroscience and brain research activity. The following institution and universities are member of our network activities so as to facilitate neuroscience research across the country.

List of Network Centres

1. All India Institute of Medical Sciences (AIIMS), New Delhi
2. A. Lakshmipathy Neurosurgical Centre, Chennai
3. Banaras Hindu University (BHU), Varanasi
4. Centre for Biotechnology, New Delhi
5. Centre for Cellular & Molecular Biology (CCMB), Hyderabad
6. Central Drug Research Institute (CDRI), Lucknow
7. Centre for DNA Fingerprinting and Diagnostics, Hyderabad
8. Central Food and Technological Research Institute (CFTRI), Mysore
9. Cochin University of Science and Technology, Cochin
10. Delhi University, South Campus, Delhi
11. Indo American Hospital Brain and Spine Center, Kerala
12. Institute of Cybernetics, Systems and Information Technology, Kolkata
13. International Centre for Genetic Engineering and Biotechnology (ICGEB), New Delhi
14. Institute of Genomics and Integrative Biology (IGIB), Delhi
15. Institute of Human Behaviours & Allied Sciences (IHBAS), Delhi
16. Indian Institute of Information Technology (IIIT), Allahabad
17. Indian Institute of Technology (IIT), Mumbai
18. Indian Institute of Technology (IIT), Delhi
19. Indian Institute of Technology (IIT), Kanpur
20. Indian Institute of Science (IISc), Bangalore
21. Indian Institute of Chemical Biology (IICB), Kolkata
22. Institute of Nuclear Medicine and Allied Sciences (INMAS), New Delhi.
23. Industrial Toxicology Research Centre (ITRC), Lucknow
24. Indian Statistical Institute, Kolkata
25. International School of Photomics, Cochin
26. Jawaharlal Nehru University (JNU), New Delhi
27. Jawaharlal Nehru Centre for Advance Scientific Research (JNCASR), Bangalore
28. Jiwaji University, Gwalior

29. M.S. University of Baroda (Dept. of Microbiology and Biotechnology Centre), Baroda
30. National Centre for Biological Sciences (NCBS), Bangalore
31. National Informatics Centre (Medical Informatics and Telemedicine Division), (NIC) New Delhi
32. National Institute of Mental Health & Neuroscience (NIMHANS), Bangalore
33. Nizams Institute for Medical Sciences (NIMS), Hyderabad
34. National Neuroscience Centre (NNC), Kolkata
35. Shree Chitra Tirunal Institute for Medical Sciences and Technology, Thiruvanthapuram
36. Sanjay Gandhi Post-Graduate Institute of Medical Sciences (SGPGIMS), Lucknow
37. Sri Venkadeswara Institute of Medical Sciences, Tirupati
38. Tata Institute of Fundamental Research (TIFR), Mumbai
39. University College of Medical Sciences (UCMS), Delhi
40. University of Hyderabad, Hyderabad
41. University of Calcutta, Kolkata
42. Vidyasagar Institute of Mental Health and Neuroscience (VIMHANS), New Delhi
43. Bangur Institute of Neurology, Kolkatta

TRAINING

Summer Training and Short-Term Programmes.

NBRC hosts students from various academic institutions for project work as part of their post-graduation training and for summer training programme. Students apply for the training programme through their parent institutions. The applications are screened and the candidates are selected based on the availability of space in the various laboratories. The students are assigned to a NBRC scientist for guidance and can avail of the NBRC facilities during their stay.

Students accepted for the training programmes during 2002-2003.

Student	Institution	Supervisor
Ashitosh Chaudhary	Chaudhary Charan Singh University, Meerut	Shyamala Mani
Prateek Gupta	IIT, Kanpur	Prasun K Roy
Kapil Kumar	IIT, Kanpur	Nandini C Singh
Prashant Kumar	Chaudhary Charan Singh University, Meerut	Shyamala Mani
Sunita	Kurushetra University, Haryana	Nihar R. Jana
Santhanu Sur	IIT, Kharagpur	Aditya Murthy
Amit Upadhyay	IIT, Kanpur	Prasun K Roy
Timsy Arora	IIT, Mumbai	Aditya Murthy
Rubeena Memom	IIT, Mumbai	Shyamala Mani
Joydeep Saha	IIT, Mumbai	Prasun K. Roy

Computer Training

As part of the mandate to create awareness and interest in neuroscience among students NBRC jointly holds workshops on Computational Neuroscience at various Institutions. The objective of this series of workshops is to make students with technical backgrounds aware of the current state of knowledge and outstanding problems in Neuroscience, for example, the need to develop tools and algorithms to analyse the large amounts of complex data obtained from neural experiments by emphasizing the nature of computations carried out by the brain.

Last year the workshop was held at Indian Institute of Technology, Delhi,

between 14th to 24th May 2002. The workshop was coordinated by Prof. Basabi Bhaumik, Department of Electrical Engineering, Indian Institute of Technology, Delhi. Participants were undergraduate and postgraduate students of science, engineering, and medicine. The course consisted of 30 hours of lecture and 20 hours of laboratory. On the last day of the course the participants visited National Brain Research Centre to interact with the scientists and researchers.

The faculty included experts in a variety of areas from leading research centres in the country. Some of the topics included were : Single Neuron Models, Neural Network modelling, Modelling visual pathway, Computation in sensory systems, Optical Spectroscopy and Imaging to study functions of brain, Biologically Motivated Computer Vision, Neuronal Information theory and Neuro-thermodynamics.

NBRC has an active programme to train extramural fellows, in various neuroscience centres. The candidates and their supervisors are appended below.

Dr. Kavita Seth, ITRC. "*In-Vitro studies on the mechanism of neurotoxicity of pesticides and metals using neural cell lines". Project* under the supervision of Dr. A.K.Agarwal.

Dr. Vaishali Subhedar, CCMB, Hyderabad. *"Effect of membrane environment on ligand binding and G-protein-coupling of the Hippocampal Serotonin$_{1A}$ (5-HT$_{1A}$) receptor and exploring the oligomerization of the receptor"* under supervision of Dr. Amitabha Chattopadhyay.

Dr. L. M. Patnaik, IISc, Bangalore. *"Signal Processing Algorithms for Brain Images"* .

Dr. Vaishali Kulkarni, TIFR, Mumbai. *"Role of Catecholamines and plant adaptogens in the control of ongoing neurogenesis in the adult mammalian brain"* under supervision of Dr. V. Rodrigues.

Dr. K. Ramakrishna Rao, University of Hyderabad, Hyderabad. *"Role of DNA-Polymerases and glutam dynamics in aging of rat brain"* under supervision of Prof. K. Subba Rao.

Dr. Sabita Mishra & Dr. Suman Jain, AIIMS, New Delhi. *"Morphological and Neurochemical study of Human cochlea and cochlear nuclein prenatal and Development of Auditory Perception following Prenatal Enrichment with Species"* under supervison of Prof. Shashi Wadhwa.

Dr. Sunil Dutt Shukla, NCBS, Bangalore, under supervision of Dr. K. Vijayaraghavan.

[illegible] [illegible]

INDO-US ROUNDTABLE ON NEUROSCIENCES, ORLANDO, FLORIDA, USA, 1ST NOVEMBER, 2002.

The third Indo-US roundtable on Neurosciences met on the 1st of November at Orlando, Florida, USA at the Rosen Centre Hotel. The goal of this series of meetings was to bring together neuroscientists from India and USA to help explore possible future collaborations through formal presentations and informal discussions. In addition, senior officials from different granting agencies were invited to discuss with the scientists the possible funding avenues that promote such collaborations.

This year there were a total of 47 participants, 8 from India and 39 from the USA. Opening remarks and the purpose of the roundtable were set out in the talks by Prof. Richard Nakamura, Acting Director, National Institute of Metal Health, USA and by Prof. Vijayalakshmi Ravindranath Director, NBRC, India. Prof Nakamura said that NIMH valued collaborations in neuroscience with India and he looked forward to an increase in such collaborations. He mentioned that the incoming NIMH Director also welcomed the collaboration between the two countries. Prof Vijayalakshmi Ravindranath outlined advantages of collaborative research. She highlighted the positive outcome of these collaborations for India in terms of access to latest technologies, training of manpower, and building partnerships in the global arena. The leaders of the two delegations emphasized the importance of workshops for fostering collaborative research.

Scientists from both countries presented their work and invited collaborations in specific areas. Seven members of the Indian delegation and 12 scientists from the USA presented their work. Their areas of interests ranged from Neuroinformatics, Functional Neuroimaging, Cognitive Neuroscience, Psychiatric disorders, Specific Learning Disabilities, Pharmacology, Neurochemistry, Genetics and Neurophysiology. In addition, Dr. Kathleen Michels, from the Fogarty International Center outlined the aims of the Fogarty foundation and procedures for obtaining funds for collaborative research.

The programme in the USA was coordinated by Dr. Tim Hays.

NEUROBIOLOGY AND NEUROINFORMATICS WORKSHOP

The brain stands as a major challenge to science and technology in the 21st century, and brain science covers, and is supported by, biological sciences, information sciences, mathematics, and engineering sciences, to understand the functions and mechanisms of information processing in the brain. This is useful not only for understanding, healing, nurturing the brain, but also for creation of new information technology inspired by the brain. We need integration of many different disciplines for this purpose. Towards this end it was decided to hold as an annual event a Neurobiology and Neuroinformatics (NBNI) workshop.

Recognizing the emerging vitality of Indian neuroscience the fourth NBNI was further enlarged to include India as a participant among the original members - Japan, Korea, China. The Indian delegation was led by Prof. Ravindranath, Director of NBRC, and included NBRC scientists as well as scientists from our networked centers. The NBNI workshop was held at RIKEN Brain Science Institute, Japan. 25-26 November, 2002.

The workshop focused on neurobiology and neuroinformatics, which covered broad areas in brain research. The attendees included biologists, medical doctors, cognitive scientists, physicists, mathematicians, information scientists and various fields of engineering scientists. The workshop was intended for interactions and collaborations among researchers belonging to various disciplines and countries.


INTERNATIONAL CONFERENCE ON
THEORETICAL NEUROBIOLOGY
Februa 24-26, 2003, New Delhi
Organized by

INTERNATIONAL CONFERENCE ON THEORETICAL NEUROBIOLOGY

The National Brain Research Centre organized an International Conference on Theoretical Neurobiology from 24th-26th February 2003 at the Habitat Centre in New Delhi. The Wellcome Trust, The Dept. of Bio-technology and the Council for Scientific & Industrial Research sponsored the conference. The objectives of the conference were to bring together experimental, computational neuroscientists and mathematicians working in the field of category theory and higher dimensional algebra and to develop newer mathematical methods collectively to better meet the demands of neurobiological data. The conference was inaugurated by Dr. (Mrs) Manju Sharma, Secretary of the Department of Biotechnology on 24th February 2003 at the India Habitat Centre.

Scientists from different parts of the world participated in the conference, which was spread over three days and comprised of various lecture sessions and two poster sessions. Each session comprised of three lectures delivered by an experimentalist, a computational scientist and a mathematician and this was followed by a joint discussion. The first technical session was on contextual processing. The theme of the first lecture by Tom Albright from the Salk Institute demonstrated how context influences perception. This was followed by a talk by Ennio Mingolla from Boston University on the Visual Units of Perception. Posina Rayudu from NBRC discussed the mathematical approach in his talk entitled – Higher dimensional algebraic study of brain functions.

The post lunch session on the first day was on modularity and integration. Lisa Stefanacci, also from the Salk Institute presented clues to emotion via studies of the amygdala. Kevin O' Regan from CNRS, France presented a novel sensorimotor approach to consciousness. Finally, Ronnie Brown

from the University of Wales, presented a new set of mathematical tools from higher dimensional to study local and global problems, which could have applications in neurobiology.

The first session on 25th March was on neuronal information processing. The first talk was by an experimentalist – Edward Callaway, from the Salk Institute. The important question he addressed was how do visual circuits generate receptive fields in V1. This was followed by a talk on neuroinformatics in vision science by Shiro Usui from Riken, Japan on the Visiome platform. He emphasised the importance of pooling information and outlined the need for neuroinformatics databases. Guiseppe Longo then presented a new conceptual framework for complexity, information and causality from a mathematician's perspective. The post lunch session focused on different numerical techniques, which are used to analyze brain data. Narayanan Srinivasan from NTU, Singapore demonstrated the use of independent component analysis (ICA). Prof. Lalit Patnaik from Indian Institute of Science, Bangalore, then went on to calculate computing costs while trying to implement various neural network models. Neeraj Jain from NBRC, presented a talk on the normal and altered processing in the somato-sensory system of primates. He showed that the somato-sensory cortex of a monkey can reorganize if the input is altered but the mechanism underlying this phenomena is still not clearly understood. Basabi Bhaumik from IIT, Delhi presented neural network models for orientation selectivity in layer 4 cells in V1.

Dr. Shobhini Rao from NIMHANS, Bangalore discussed some interesting results regarding the effects of age and education on neuropsychological functions and its effects on brain plasticity. This was followed by a talk by Prof. Prem Kalra from IIT, Kanpur on a new mathematical model of neural networks particularly in the light of the history of the neuron mathematical modeling. Dr. Prasun Roy from NBRC, discussed a new non-equilibrium thermodynamic approach to neural information processing.

In the afternoon, Prof. Stephen Koslow from NIMH, in his talk on Neuroinformatics, discussed the human brain project and its objectives

This was followed by a panel discussion, which was presided over by Prof. M G K Menon. Members of the panel summarized the conference and also highlighted the fact that a new language needs to be developed whereby scientists from experimental, computational and mathematical backgrounds would be able to talk to each other and develop new ideas collectively. Students from various institutes and universities also participated in the conference and presented posters.

The final panel discussion, which was presided over by Prof. M G K

Menon summarized the conference and also highlighted the fact that a new language needs to be developed whereby scientists from experimental, computational and mathematical backgrounds would be able to talk to each other and develop new ideas collectively. The meeting also highlighted the need for enhanced interactions among experts from different specialties, a greater need to share data amongst the scientific communities and creation of databases and platforms for this purpose as highlighted in the talks by Shiro Usui on Visiosome Platform and Stephen Koslow, NIMH, on neuroinformatics and the human brain project.

WORKSHOP ON COMPUTATIONAL NEUROSCIENCE

As part of the mandate to create awareness and interest in neuroscience among students NBRC jointly holds workshops on Computational Neuroscience at various Institutions. The objective of this series of workshops is to make students with technical backgrounds aware of the current state of knowledge and outstanding problems in Neuroscience, for example, the need to develop tools and algorithms to analyse the large amounts of complex data obtained from neural experiments by emphasizing the nature of computations carried out by the brain.

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The faculty included experts in a variety of areas from leading research centres in the country. Some of the topics included were : Single Neuron Models, Neural Network modelling, Modelling visual pathway, Computation in sensory systems, Optical Spectroscopy and Imaging to study functions of brain, Biologically Motivated Computer Vision, Neuronal Information theory and Neuro-thermodynamics.

NATIONAL TECHNOLOGY DAY

As always May 28th is celebrated nationally as Technology Day. Recognising the need to promote and educate the public about neuroscience and the impact of such research in alleviating health problems in our country, NBRC took this opportunity to deliver public lectures in Delhi and Gurgaon. NBRC scientist, Dr. Shyamala Mani spent

a day with students at Vasant Valley School in Delhi, interacting with them and explaining to them the mysteries of how a complex structure such as the brain, with billions of neurons and trillions of connections, develop from a single cell. Dr. P.K. Roy and Dr. Aditya Murthy delivered powerpoint presentations in Salwan Public School, Gurgaon explaining how our brains process information and the diseases caused as a result of malfunctioning of the brain. Students and teachers greatly appreciated these talks and recommended that NBRC organize similar such events.

NATIONAL SCIENCE DAY

NBRC organized two different activities for the National Science Day on Feb 28th, 2003.

Senior students from American Montessari School, DLF Phase II, Gurgaon, visited NBRC accompanied by three teachers-in-charge. Dr Neeraj Jain welcomed the students and told them about NBRC, our goals and current research activities. Thereafter, Dr Prasun K Roy and Dr Aditya Murthy introduced the students to the wonders of the human brain, its major subdivisions and their functions in a very simple fashion. A preserved specimen of human brain and multimedia presentations were used to make the presentation attractive. Students were also told by all the three scientists about their own research and how they use specialized techniques in their work to decipher the functioning of the brain. The whole session was interactive and the students were encouraged to ask questions, which they did with great enthusiasm.

Afterwards, the students were divided into two groups and taken around the laboratory by two of our Ph.D. students, Mr Harish Pai and Mr Supriya Ray to show them neuroscience research *'in action'* and describe various instruments that are used in the laboratory.

S.Mani, talked to the 12th standard students at Vasant Valley School, New Delhi. Ton the development of the brain and the changes that take place during adolescence. She also talked about learning disorders, teenage depression, mental illnesses, and stressed upon the deleterious effects of smoking and alcohol abuse.

LECTURES

Neeraj Jain delivered a talk titled 'Brain' at the local Book Club in the Gallerie Alternatives, DLF Phase 1, Gurgaon on December 28, 2002.

P.K. Roy and Aditya Murthy jointly delivered a seminar on "The wonder of Neuroscience" at Salwan Public School, Gurgaon, May, 2003.

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ANIMAL FACILITY

NBRC has a modern animal facility approved by Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) for small animals as well as large animals. The salient features of the facility include central air conditioning with laminar airflow and 12-15 times per hour 100% fresh air changes, remote monitoring of the temperature and humidity, facility to regulate day/light cycle in individual rooms, necropsy room with a laminar flow hood, deep freezer and a fire alarm system. There is a state of the art sterile surgery suite equipped with gas anesthesia machine, hear rate monitor, pulse oximeter, Zeiss surgical microscopes, surgical lights with intensity control, ultrasonic instrument cleaner, and provision for sterilization of

equipment using steam autoclaving or ethylene oxide. There is an outdoor play area for non-human primates which has eight interconnectable large enclosures that provide flexible layout for optimizing enrichment and social interactions. The facility currently houses inbred and outbred stocks of mice and rats, and rabbits. The facility will soon house non-human primates.

DIGITAL LIBRARY

The NBRC library is an automated open access library system which is kept open all the year round. It is supervised by a library committee. The books include collections of scientific subjects supported by research works & other works. The NBRC library subscribes to important scientific journals in the field of various subjects (mainly Neuroscience, Biochemistry, Genetics, Molecular Biology, Pharmacology & Toxicology, Psychology etc.) which are mostly online and some as hardcopy. NBRC Library is an advanced modern digital library in the country specializing in Neuroscience in India. In the electronic mode it provides free of cost references, papers, full text articles, copies of reprints of relevant literature

to users all over India. NBRC Library has 10 IBM PC-Pentium-IV Computer with ISDN Internet facility to provide best services for researchers of NBRC. The library staff aims to provide excellent services to the scientists, researchers, research associates, students and visitors.

Aims & Objectives of Library Network

The basic purpose for creating a network is to provide information services to members through sharing of resources. The main aim and objective of NBRC library networking is as follows :

- To promote resource sharing and co-operation activities among libraries by providing efficient and reliable means of resource sharing i.e. inter library loan for maximum user of resources, document delivery services – providing the copies of the documents that is not available in their respective libraries.
- To improve resource utilization and service levels
- To coordinate efforts for suitable collection development and reduce necessary duplication wherever possible.

Work Areas and Activities of NBRC Library

It is organized in the following areas :

- Book Acquisition : for books, reports, reprints, monographs, video/audio cassettes, CD-Roms
- Periodicals Acquisition : For journals (online & hardcopy), magazines, newspapers
- Selective dissemination of information services (SDI)
- Current awareness services (CAS)
- Electronic document delivery
- Resource sharing
- Inter library loan facility
- Reference services, bibliographic services (reader's services).
- Circulation services (Transaction overnight, reserve sequence etc.)
- Indexing and special services : Current contents of periodicals, database access etc.
- Collects, maintains, stores, and retrieves information and data keeping in view of evolving needs of its researchers
- Analysis, synthesizes and evaluates information and data
- Literatures / articles Search.
- Help to our network centers.
- Replies of queries

The Future Plan of NBRC Library

NBRC library provides an electronic document delivery systems on request basis to its network centers. It has proposed to implement the following procedures :

- To develop software tools for better library management
- To develop a database of books, series, journals and non-book materials
- To develop a Web based form for Electronic Document Delivery System (EDDS), so that people can send their request through our website.
- To develop databases of research projects.
- To promote sharing of resources among the network libraries
- To flash arrival of new books, journals, announcement of events like seminars, workshops, training programmes etc.
- To create awareness in the field of latest information technology, research and development areas.

□□□□□□

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