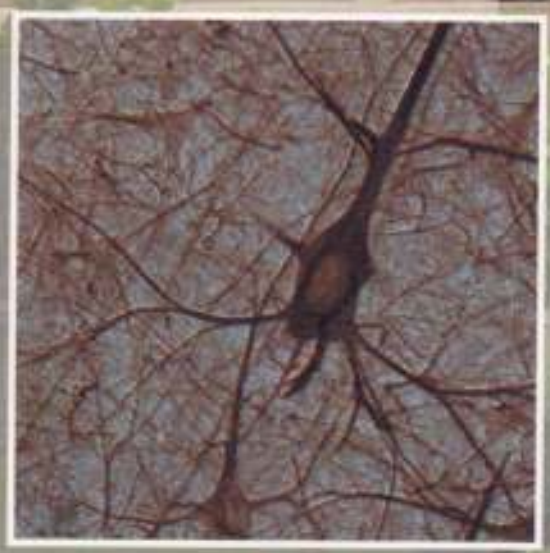
National Brain Research Centre
NBRC



ANNUAL REPORT
2005-2006

NATIONAL BRAIN RESEARCH CENTRE
Manesar, Haryana INDIA

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NATIONAL BRAIN RESEARCH CENTRE
(Deemed University)
An Autonomous Institute of Department of Biotechnology.
Ministry of Science & Technology, Govt. of India
NH-8, Manesar (Haryana), INDIA

CONTENTS

MANDATE

- Pursue basic research to understand brain function in health and disease.
- Generate trained human resources with the capability to carry out inter-disciplinary research in neuroscience.
- Promote neuroscience in India through networking among institutions across the country.

OBJECTIVES

- To undertake, aid, promote, guide and coordinate research of a high caliber in basic and clinical neuroscience related to diseases and disorders of the nervous system.
- To develop NBRC as the national apex centre for neuroscience research and promote neuroscience research at different centres 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 achievement of the objectives of the center.
- 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 deem fit.
- To provide facilities for the advancement research and development for advancement of learning and for dissemination of knowledge.
- To undertake extramural studies, extension programmes and field out reach 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 neurosciences activities comprising biological, psychological, sociological and clinical aspects.
- 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 mediates the perception of the world around us, generates thoughts, memories, and emotions that shape our individual personalities. The effort to understand the structure, function, and development of the human brain represents one of the great scientific challenges. Apart from the interest to understand how human brain performs complex functions such as learning and memory and the linking of the mind and behaviour with brain, there are serious health related issues, such as childhood-related disorders including developmental disorders, mental illnesses and neurodegenerative disorders, which afflict a large number of people. Brain disorders contribute up to one-third of the total disease burden in developing countries. Better understanding of brain in health and disease can improve the development of our children, enrich adult life and promote graceful aging. It is with this understanding that the National Brain Research Centre was established as a centre of excellence with a mandate "to carry out research on brain function in health and disease, generate highly trained human resource and evolve the centre through a networking approach".

Almost 250 million people in the developing world suffer from neurological and psychiatric disorders. The World health Organization projects in 2020 the greatest contributor to disability adjusted life year (a composite measure of man hours lost due to disability) would be brain-related disorders. The prevalence of mental and behavioural disorders amongst children in developing and developed countries appears to have similar incidence rates. If we take into account the increasing life expectancy of the world population, age-related neurodegenerative disorders would potentially contribute enormously to the years lived in disability. In fact Parkinson's disease incidence is 1% of the growing world population. Stroke is another debilitating neurological disorder with prevalence rates of 0.5-0.8%. Recent studies have shown that incidence of stroke in younger population (below 40 years) is higher in India.

We do not understand the etiology and pathogenic mechanisms underlying most of these brains disorders. Most treatment strategies currently used are palliative and provide symptomatic relief. A cure reverses the effects of the disease while therapy provides partial or total relief while not reversing the disease process. Progress in brain research in recent years has provided leads for rationale therapies for some brain disorders, and a hope that the cures are not too far away. The identification of molecules and pathways that mediate neural function at one end of the spectrum and imaging neural activity underlying perception and action are a few of the breathtaking advances that would potentially enable us to offer cures for brain disorders.

At NBRC, a multi-disciplinary group is actively engaged in understanding the pathogenesis and progression of Neurodegenerative disorders such as Parkinson's, Alzheimer's and polyglutamine diseases. The molecular mechanisms underlying the behavioral learning deficit in neuro-developmental diseases such as Angelman's syndrome is also being investigated. One of the common denominators seen in most neurodegenerative disorders is the abnormal accumulation of proteins in the brain regions involved in the disease processes and therefore prevention of protein aggregation has attracted considerable research interest. One of the research areas at NBRC has been to identify molecular targets that can help disaggregation of the abnormally accumulated proteins. For example Huntington's disease is caused due to the presence of expanded repeats of the nucleotides, 'CAG' in the protein huntingtin (also known as polyglutamine disorder), which accumulate in the brain of diseased patients. Research at NBRC has led to the discovery that a protein named CHIP (C terminus of Hsc-70 interacting protein) associates with the expanded polyglutamine proteins and promotes their degradation by proteasome. Overexpression of CHIP also protects expanded polyglutamine-protein induced cell death. Another protein called BAG-1 (BCL2-associated athanogene) has been shown to be associated with the polyglutamine aggregates. Since, BAG-1 is essential for cell survival, its association with polyglutamine aggregates might disrupt its

normal function and thereby promotes polyglutamine-expanded protein-induced cell death. Identificatic of critical pathways involved in the pathogenesis and progression of disease is critical for the developme of rational therapies and cures for these devastating diseases. At a different level of analysis, resear efforts at NBRC are also directed at understanding the behavioural implications of damage caused l neurodegenerative diseases that disrupt the normal functioning of neural circuits. Such research, done collaboration with All India Institute of Medical Sciences, has provided evidence that Parkinson's disea patients have an impaired capacity to inhibit planned responses, a deficit that might explain their inabili to execute a variety of voluntary behaviour.

The neuro-pharmacological effects of plants that are used in traditional system of medicine improving higher mental function are being examined as potential treatment for senile dementia includi Alzheimer's disease. Elucidation of mechanisms pertaining to learning and memory formation molecular, cellular and behavioral levels, especially understanding what goes wrong during mem impairment, such as Alzheimer's disease is another active area of research.

We realise that the most critical component required for realising the objectives that we have forth for ourselves is trained human resource. Therefore, from its inception, NBRC has linked its resea with human resource development. NBRC was awarded Deemed University status in 2002 by the Hur Resources Development Ministry based on the recommendations of the Accreditation Council of University Grants Commission. NBRC conducts both Ph.D. and M.Sc. programmes in neuroscience. recruit students from diverse back-ground for the Ph.D. programme including M.Sc. in any branch rel to neurosciences, M.B.B.S., B.E., or B.Tech or psychology recognizing that understanding brain func requires assimilation of knowledge from multiple disciplines. The goal is to train Ph.D. students wit understanding of different aspects of neuroscience integrating information across traditional bounda The M.Sc. and Ph.D. programmes at NBRC have two components – course work (including lab rotatic and research work. The courses taught by NBRC faculty members cover the major discipline neuroscience, such as neuroanatomy, neurophysiology, neurochemistry, molecular neurobiol development and regeneration, neurogenetics, systems neuroscience, cognitive neuroscience, sys and clinical neuroscience, and computational neuroscience. The encouraging response to our cours the increasing number of applicants are testimony of the enormous interest in brain research. S preliminary results obtained during the last year in this respect are very promising.

NBRC, through its networking with 47 institutions has helped to promote neuroscience i country and established multi-institutional collaborative projects with other institutions in the co such as, IISc., IIT Kanpur/ Mumbai, NIMHANS and AIIMS, thus, establishing a new trend of n disciplinary research involving several institutions. We have initiated a collaborative project on ster research with the Research and Referral Hospital of the Armed Forces. It has played a very importan in re-vitalizing brain research in the country and initiating modern neuroscience research that is h integrative and multi-disciplinary. As we begin the fourth year in our campus at Manesar, the sta students look forward to a productive future fuelled by innovative research.

(Prof. V. Ravindranat

RESEARCH REPORTS

MOLECULAR MECHANISM OF THE PATHOGENESIS OF THE CAG REPEAT NEURODEGENERATIVE DISEASES

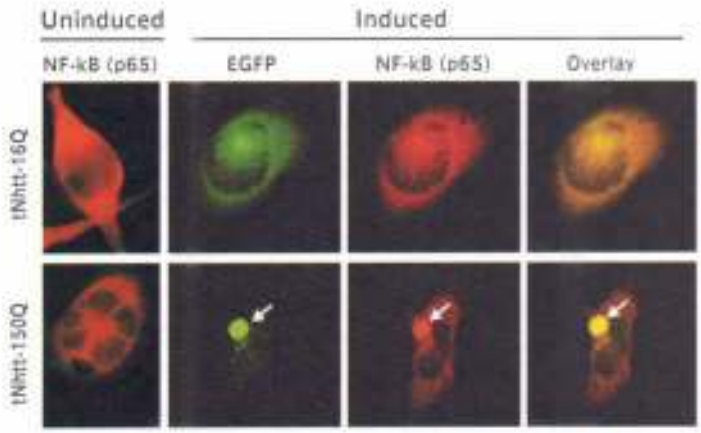
Principal Investigator : *Nihar Ranjan Jana*
Research Fellows : *Anand Goswami, Priyanka Dikshit*
Technical Assistant : *D. Narender*

A common pathological feature of most age related neurodegenerative disorders including polyglutamine diseases is the accumulation of intracellular protein deposits as inclusion bodies. Polyglutamine diseases are a group of familial neurodegenerative disorders that are caused by an abnormal expansion of CAG triplet repeats in the coding region of the target gene. Those include Huntington's disease (HD), dentatorubral pallidoluysian atrophy (DRPLA), X-linked spinal bulbar muscular atrophy (SBMA), and several spinocerebellar ataxias (SCA1, SCA2, SCA3, SCA6, SCA7 and SCA17). All these disorders are dominantly inherited (except SBMA), progressive, usually begin in mid-life, and result in severe neuronal dysfunction and neuronal cell death in the selective region of the brain. A major pathological hallmark of the polyglutamine diseases is the formation of neuronal intranuclear inclusions (NIIs) of the disease proteins that are ubiquitinated and often associated with various transcription factors, chaperones and proteasome components. The appearance of ubiquitinated aggregates implies an underline incapability of the cellular chaperones and proteasome machinery that normally functions to prevent the accumulation of misfolded proteins. But, how the expanded polyglutamine proteins or their aggregates elicit a complex pathogenic responses in the neuronal cells are not fully understood.

Major aims 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) identifying the role of mitochondria in the polyglutamine diseases pathogenesis and (4) screening and identification of small molecules for therapeutic intervention of the polyglutamine diseases.

This year we have observed that the expression of expanded polyglutamine proteins down-regulates the NF-kB-dependent transcriptional activity. Expression of expanded polyglutamine proteins increases the stability and the levels of IkB-a and its phosphorylated form. We have also found that various NF-kB subunits and IkB-a aberrantly interacts with the expanded polyglutamine proteins and associates with their aggregates (Figure 1). Finally, we have shown several NF-kB-dependent genes are down-regulated in the expanded polyglutamine protein expressing cells. Since NF-kB pathway plays a very important role in cell survival, altered regulation of this pathway in expanded polyglutamine expressing cells might be linked with the disease pathogenesis.

It has now been found that oxidative stimuli and curcumin enhance the polyglutamine-expanded truncated N-terminal huntingtin (mutant huntingtin) aggregation and mutant huntingtin-induced cell death. Oxidative stimuli and curcumin also leads to rapid proteasomal dysfunction in the mutant huntingtin expressing cells as compared to normal glutamine repeat expressing cells. Over expression of Cu/Zn superoxide dismutase (SOD1), Hsp40 or Hsp70 reverses the oxidative stress-induced or curcumin-induced proteasomal malfunction, mutant huntingtin aggregation and death of the mutant huntingtin expressing cells. Finally, we show the higher levels of expression of SOD1 and DJ-1 in the mutant huntingtin expressing cells. Our result suggests that oxidative stress or curcumin-induced proteasomal malfunction might be linked with mutant huntingtin-induced cell death.



Association of NF-kB p65 protein with the polyglutamine aggregates. The HD 16Q and HD 150Q cells were plated into 2-well chamber slide. Cell were induced with ponasterone A for 48 hrs and processed for immunofluorescence staining using NF-kB p65 antibody. Rhodamine-conjugated secondary antibody was used to stain the NF-kB p65. Arrow indicates the recruitment of NF-kB p65 to the mutant huntingtin aggregates.

Publications:

Dikshit P, Goswami A, Mishra A, Nukina N, Jana NR (2006) Curcumin enhances the polyglutamine-expanded truncated N-terminal huntingtin-induced cell death by promoting proteasomal malfunction. Biochemical and Biophysical Research Communications. 342: 1323-1328.

Goswami A, Dikshit P, Mishra A, Mulherkar S, Nukina N, Jana, NR (2006) Oxidative stress promotes mutant huntingtin aggregation and mutant huntingtin-dependent cell death by mimicking proteasomal malfunction. Biochemical and Biophysical Research Communications. 342: 184-190.

Jana NR, Nukina N (2005) BAG-1 associates with the polyglutamine-expanded huntingtin aggregates. Neuroscience Letter. 378:171-175.

Presentation:

N. R. Jana. Role of ubiquitin-proteasome system in the pathogenesis of polyglutamine diseases. India-Japan-Korea-China workshop of Neurobiology and neuroinformatics, Xiamen, China, 2005.

Funding:

Molecular mechanism of the pathogenesis of the CAG repeats neurodegenerative diseases. (DBT).

Molecular mechanism of the pathogenesis of polyglutamine diseases. (RIKEN Brain Science Institute, Japan).

Collaborator:

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

UNDERSTANDING THE PATHOGENIC MECHANISM OF ANGELMAN SYNDROME

Principal Investigator : *Nihar Ranjan Jana*

Research Fellows : *Amit Mishra, Sudarsana Purakayastha*

Neurodevelopmental disorders are one of the major problems among children not only in the developed countries but also in the developing countries like India. These disorders are very common among children in India and other SAARC countries and their incidence is on the rise. Approximately, one in every 500 Indian infants have this disorder and there are about 20,000 new cases reported every year. Both genetic and environmental factors possibly plays a very important role in neurodevelopmental disorders. Exposure of pollutants to pregnant mothers or babies and the stressful environment might be important contributory environmental factors. But how genetic and environmental factors are involved in the pathogenic mechanisms of Angelman mental retardation syndrome (AS) and other neurodevelopmental disorders are poorly understood and currently there is no effective therapy for these disorders. Thus, new findings on AS might be applicable to the other neurodevelopmental disorders and it is also possible to find out a common way of prevention and treatment. AS resembles to other neurodevelopmental disorders like Rett syndrome and autism. This syndrome has been widely reported during the past 10 years, mainly due to the newly discovered genetic mechanisms underlying this disorder. There is no clear epidemiological data about the prevalence of these diseases in India. Since the clinical features of AS are very similar with the Rett syndrome and autism, it may not be diagnosed properly.

The major goal of this project is to understand the molecular mechanism underlying the pathogenesis of AS. AS is characterized by severe mental retardation, lack of speech, ataxia, abnormal gait, easily provoked smiling and laughter, seizure and sleep disturbances. The incidence of AS is estimated to be 1 in 15,000 with most cases being sporadic, although the familial occurrence is not rare. The disease is caused by maternal deletion of chromosome 15q11-q13, paternal uniparental disomy of chromosome 15, imprinting defects or loss of function mutation of the UBE3A gene (located within the 15q11-q13). All of these mechanisms lead to absence of functional copy of UBE3A. UBE3A gene shows brain region-specific imprinting in human and mice, but the mechanism behind this brain and region specific imprinting are not known. UBE3A encodes E6-AP ubiquitin protein ligase, an enzyme involved in the intracellular protein degradation through ubiquitin proteasome system (UPS). But how the loss of E6-AP function is linked with the pathogenesis of AS is unknown at present. It is hypothesized that the AS phenotype might be caused by failure of ubiquitination and subsequent degradation of the variety of target substrate proteins of E6-AP and the various environmental and other stress factor might have an influence on the degradation. Therefore, identification of substrates of E6-AP could open a new avenue in understanding the pathogenic mechanism of AS. In the proposed project, we would like to investigate the molecular mechanisms of the AS pathogenesis.

Major objectives of this project are (a) identification and characterization of new protein substrates of E6-AP, (b) analysis of various mutation of E6-AP (reported in AS patients) on the ubiquitination and degradation of its substrate, (c) regulation of the expression of UBE3A gene under different stress conditions both in vitro cell culture and in vivo animal models, (d) to study the role of E6-AP in ubiquitination and degradation of misfolded protein and the protection of cell death under various stress conditions, (e) generation of mouse model of AS using RNAi to study the AS pathogenesis.

This year we have made a remarkable progress in this project. We have identified three interacting proteins of E6-AP. These are Hsp70, p53 and p27kip1. We are now characterising them in detail. The identification of Hsp70 as an interacting partner of E6-AP opened a new avenue in understanding the pathogenesis of AS. We have found that the N-terminus of E6-AP interacts with the substrate-binding domain of Hsp70. The interaction of Hsp70 with the E6-AP most likely helps the E6-AP to degrade the misfolded protein. We have proved this using denatured luciferase or expanded polyglutamine proteins as a misfolded substrate. We have also found that the expression of E6-AP is dramatically up-regulated under different stress conditions that is involved in the accumulation of misfolded proteins. We are also able to reproduce the up-regulation of E6-AP in the Huntington's disease transgenic mice brain as well as in the MPTP-treated mice brain. Since E6-AP is involved in the degradation of misfolded and damaged proteins, we suspects that AS pathogenesis could be due to the accumulation of misfolded and aggregated proteins. We will explore this possibility using the mice model of AS. E6-AP also has a huge implication for other neurodegenerative diseases.

IDENTIFICATION OF THE MODULATORS OF UBIQUITIN PROTEASOME SYSTEM

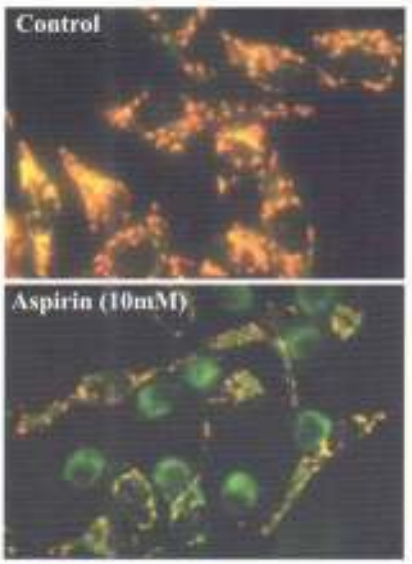
Principal Investigator : *Nihar Ranjan Jana*

Research Fellows : *Anand Goswami, Priyanka Dikshit*

Project Assistant : *Mou Chatterjee*

The UPS is the cell's principal pathway for controlled protein degradation. The pathway has been shown to be involved in the regulation of critical cellular process such as transcription, cell cycle progression, oncogenesis, growth and development, selective elimination of abnormal proteins and antigen processing. Dysfunction of the UPS has been implicated in the pathogenesis of a number of diseases including various neurodegenerative diseases. Therefore, modulators of this pathway would have strong therapeutic potential in various diseases including cancer and neurological disorders. Currently, we are testing the effect of various compounds on UPS based on their structural and functional properties. Major objective of this project is to identify the stimulators and inhibitors of the UPS mediated protein degradation.

This year we have identified several inhibitors of proteasome. Aspirin is one of them and we have characterized the aspirin-induced proteasomal dysfunction in details. Aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) inhibit cell proliferation and induce apoptosis in various cancer cell lines, which is considered to be an important mechanism for their anti-tumour activity and prevention of carcinogenesis. However, the molecular mechanisms through which these compound induces apoptosis are not well understood. We have found that treatment of aspirin to the mouse neuro 2a cells impairs the proteasome function and causes severe mitochondrial abnormalities. Treatment of aspirin leads to dose and time-dependent decrease in the proteasome activity and increase in accumulations of ubiquitinated



Aspirin exposure leads to the changes of mitochondrial membrane potential. Neuro 2a cells were treated with aspirin for 12 hrs and then subjected to JC-1 staining to study the changes in mitochondrial membrane potential. JC-1 is a voltage sensitive fluorescence dye that detects specifically the polarized mitochondria as a red and the depolarized membrane become green.

proteins in the cells, which correlates with cell death. Aspirin exposure also results in the increase of half-life of pd1EGFP, a model substrate of proteasome, as well as various intracellular substrates like IkB-a, p53 and p27kip1. Aspirin induced proteasomal malfunction is responsible for the down-regulation of NF-kB activity and neurite outgrowth. Finally, we have shown that aspirin treatment causes changes in the mitochondrial membrane potential (Figure 1) and release of cytochrome c from mitochondria, which could be the cause or consequence of proteasomal dysfunction. Proteasome inhibitors are considered to be the promising anticancer agents and recently FDA approved the first proteasome inhibitor, Bortezomib (Velcade), for the treatment of multiple myeloma. Therefore, aspirin has enormous potential in the prevention and therapy of cancer apart from its popular use as anti-inflammatory drug.

Publication:

Dikshit P, Goswami A, Mishra A, Chatterjee M, Jana N R (2006). Curcumin induces the stress response and down regulates NF-kB activation by directly inhibiting proteasomal function. Neurotoxicity Research. 9: 29-37.

Presentation:

S. Purkayastha, P. Dikshit and N. R. Jana. Curcumin disrupt the function of ubiquitin proteasome system. Annual conference of Indian Association of Biomedical Scientists, Kolkata, 2005.

REGULATION OF NEUROGENESIS IN THE CEREBELLUM

Principal Investigator : *Shyamala Mani*

Research Fellow : *Rashmi Mishra*

GAP-43 is a major neuronal protein that is required for assembly of a functional cerebral cortex in vertebrates. We now show that failure to express GAP-43 in vivo also disrupts cerebellar patterning. The defect is 100% penetrant in GAP-43 (-/-) mice. These mice also show a 50% reduction in cerebellar size. Developmental analysis demonstrated that absence of GAP-43 had multiple effects: in the cerebellar neuroepithelium Purkinje cells differentiated prematurely, and migrated inappropriately, thereby affecting positioning of the deep cerebellar nuclei. In the germinal trigone and external granule layer granule cell response to sonic hedgehog was inhibited reducing cell proliferation and giving rise to abnormal foliation. Inhibition of granule cell migration leads to ectopia formation. Finally GAP-43 was also expressed by a subset of climbing fibers and its absence resulted in abnormal mediolateral patterning of the Purkinje cells together with defects in the arborization of their dendrites. As a consequence of these disruptions to the functional circuitry of the cerebellum, GAP-43 (-/-) mice are severely ataxic. Moreover, the restriction of the most robust abnormalities to the central zone suggests that GAP-43 mediated signaling may define a functional compartment in the normal cerebellum.

Funding:

This work is supported by a FIRCA-NIH grant as well as intramural support.

Collaborator:

Karina Meiri, Tufts University

INVESTIGATION OF THE MECHANISMS BY WHICH EMBRYONIC STEM CELLS DIFFERENTIATE INTO DISTINCT NEURONAL SUBTYPES

Principal Investigator : *Shyamala Mani*

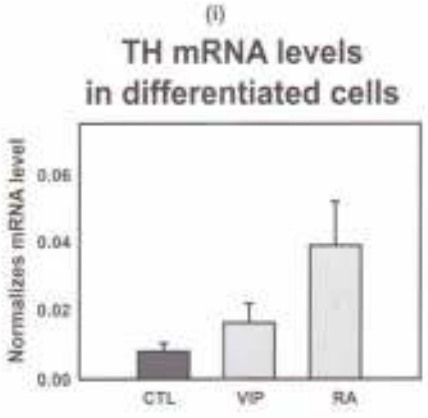
Research Fellows : *Manoj Kumar, Bandita Bagchi*

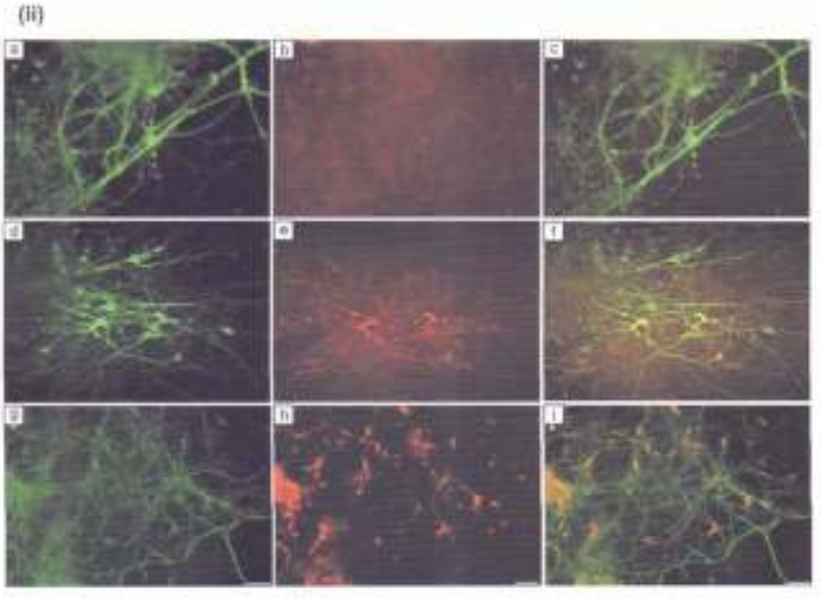
Project Assistant : *Meena A.S.*

In the central nervous system (CNS) generation of phenotypic diversity within the neuronal lineage is precisely regulated in a spatial and temporal fashion. Neural basic helix- loop- helix (bHLH) transcription factors are cell intrinsic factors that control commitment to neuronal lineage and play an important role in neuronal cell type specification. The ability to differentiate human embryonic stem (hES) cells into neurons provides a good model system to address human neuronal specification. Previous studies have shown neurogenin 2 (Ngn2) to be involved in the development of mesencephalic dopaminergic neurons. Towards the goal of correlating neuronal phenotype with early gene expression pattern we have characterized the expression of Ngn2 during hES cell differentiation. Our results show that treatment of embryoid bodies (EB) with retinoic acid (RA) leads to the greatest proportion of tyrosine hydroxylase (TH) positive cells followed by vasoactive intestinal peptide (VIP) treated EB and untreated EB. This increase in the proportion of TH positive neurons was correlated with the unique morphology of RA treated aggregates and the spatial de-localization of the expression of Ngn2 within the EB. Neurospheres (NS) derived from RA treated EB contained many nestin positive cells within regions that expressed Ngn2. Therefore this data seems to suggest that the appearance of TH positive neurons is correlated with the extent of overlap between Ngn2 expression and nestin expression. This is being investigated further.

Publications:

Kumar M, Bagchi B, Gupta SK, Meena AS, Gressens P, Mani S. Extent of expression of





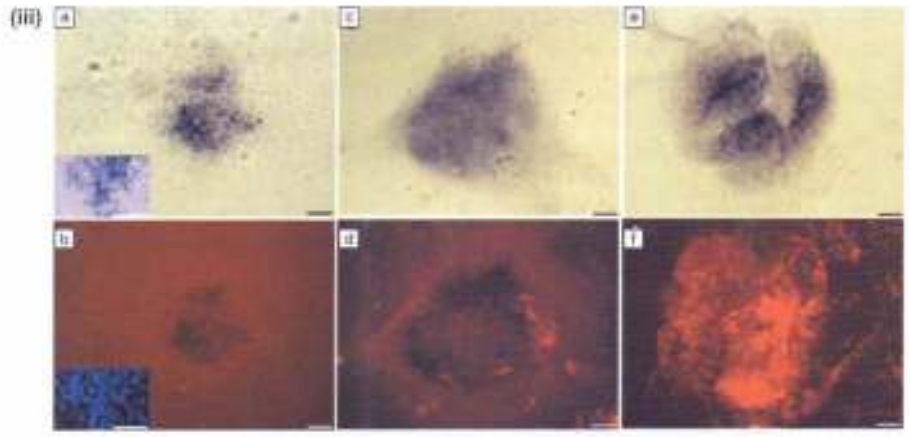


Figure: Appearance of tyrosine hydroxylase positive neurons is dependent on embryoid body treatment. (i) Starting quantity (SQ) value obtained by real time PCR of tyrosine hydroxylase (TH) levels normalized to Neuron Specific Enolase. Mean of three experiments with replicates for each experiment. (ii) Differentiated cultures from NS obtained from control EB(a, b, and c) VIP EB, (d, e, and f) and RA EB (g, h, and i). Panel a, d, and g shows a field with long neurites immunostained with b-III tubulin (green) and with TH (b, e, and h)(red). Panel c, e, and f show the two images merged. Scale bar = 200μm. (iii) Ngn2 in situ (a, c, and e) and nestin immunostain (red) in control NS (a and b), VIP NS (c and d) and RA NS (e and f). Scale = 100μm. Inset in panel a shows DAPI stain of nuclei and the inset in panel b shows Ngn2 in situ reaction product.
Scale bar of inset = 200μm.

neurogenin 2 and nestin in embryoid bodies and neurospheres correlates with the proportion of dopaminergic neurons derived from human ES cells. Stem Cells (Submitted)

Bagchi B, Kumar M, Mani S (2006) CMV promotor activity during ES cell differentiation - potential insight into embryonic stem cell differentiation. Cell Biology International. 30:505-13

Cazillis M, Rasika S, Mani S, Gressens P, Lelièvre V (2006) In vitro induction of neural differentiation of embryonic stem (ES) cells closely mimics embryonic brain development Pediatric Reviews 59: 48-53

Funding:

This work is supported by a grant from DBT as well as intramural support.

CYTOCHROMES P450 DEPENDENT METABOLISM OF DRUGS IN BRAIN

Principal Investigator : *V. Ravindranath*

Research Fellows : *Reddy Peera Kommaddi, Varsha Agarwal*

Technical Assistant : *V.K. Prasanna*

Lab Assistant : *P. Manish*

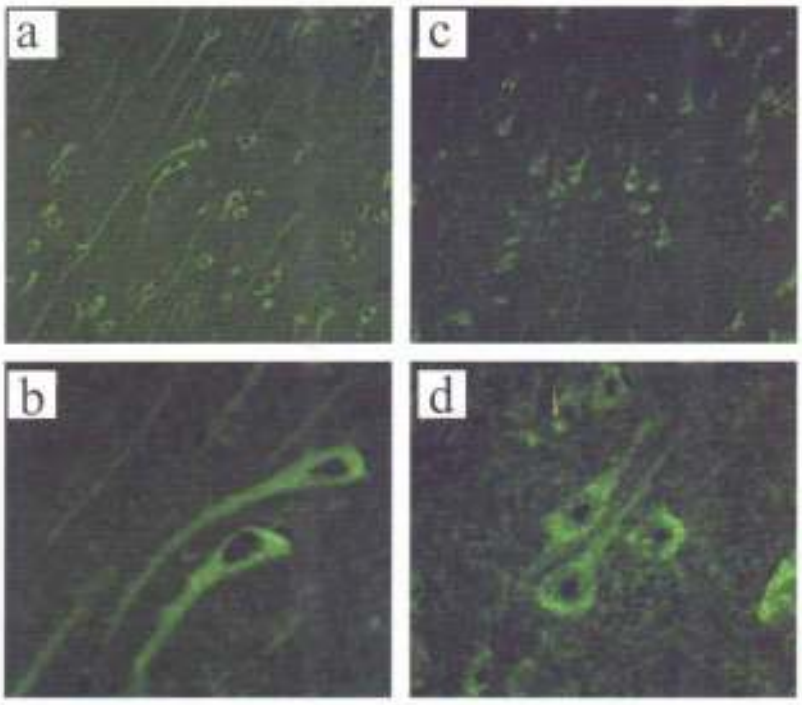
Cytochrome P450 (P450) and associated monooxygenases, a family of heme proteins are the principal class of drug metabolizing enzymes. A supergene family encodes them and the member proteins exist as multiple forms having distinct yet overlapping substrate specificities. Multiple forms of P450, which are selectively induced or inhibited by a variety of drugs, are known to exist in liver, the major organ involved in P450 mediated metabolism. However, the potential to generate active metabolite(s) at the site of action has generated interest in extrahepatic P450. This has prompted extensive investigations into the xenobiotic metabolizing capability of extrahepatic organs, such as lung, kidney, skin and nasal epithelium and the far-reaching consequences of such metabolism, in situ, within specific cells in target organs have been recognized. The preferential localization of drug metabolizing enzymes within specific cell types in these organs renders such cells significant capability to metabolize drugs. Thus, even minor metabolic pathways of xenobiotic metabolism can produce major effects if they take place at the site of action. These observations have prompted investigation into P450 associated monooxygenases in brain with an effort to determine the capability of the brain to metabolize psychoactive drugs. P450 mediated metabolism of psychoactive drugs directly in the brain can lead to local pharmacological modulation at the site of action and result in variable drug response.

We found intrinsic differences in the metabolism of certain drugs in brain and liver. Further investigation revealed the presence of unique P450 enzymes in the brain that are generated through alternate splicing. For example, a frame-shift mutation generated an open reading frame in the pseudogene, CYP2D7 and an alternate spliced functional transcript of CYP2D7 containing partial inclusion of intron 6 was identified in human brain but not in liver or kidney from the same individual. The brain variant CYP2D7 metabolized codeine exclusively to morphine unlike CYP2D6 that metabolizes codeine to nor-codeine (major metabolite) and morphine (minor metabolite). CYP1A1 is a P450 enzyme that bioactivates polycyclic aromatic hydrocarbons to reactive metabolites, which bind to DNA and initiate carcinogenesis. We identified a unique splice variant of CYP1A1 that lacks 87 bp of exon 6. This variant did not metabolize polycyclic aromatic hydrocarbons such as, benzo(a)pyrene and 3-methyl cholanthrene to genotoxic, ultimate carcinogens that form DNA adducts unlike the wild type CYP1A1. Thus, unique P450 enzymes in human brain are generated by alternate splicing and mediate biotransformation reactions that are dissimilar from known pathways in liver.

CYP3A is a very important family of P450 enzymes since it is responsible for the metabolism of a vast majority of drugs currently used. Of the several members of this family, in human liver CYP3A4 is the major P450 enzyme accounting for up to 70% of the total P450 while CYP3A43 is expressed in very small amounts. We had earlier noted distinct differences in the P4503A mediated metabolism of drugs such as, alprazolam in the brain as compared to liver. We, therefore, examined the presence of CYP3A variants in human brain. We identified 3 variants having deletion of exon 7 (149 bps) and exon 8 (12 bps) both of which would result in premature termination. A

third variant having deletion of exon 12 (12 bp) was also identified, which could potentially translate into a functional protein. This is currently being investigated further.

Since there is considerable variation in the metabolism of drugs metabolized by CYP3A family between liver and brain, we quantitated the relative amounts of CYP3A4 and CYP3A43 using real time PCR. In the liver, expression of CYP3A43 was very low and accounted about 10% of the CYP3A4 levels. However, in a majority of the postmortem human brain samples examined, the expression of CYP3A43 was significantly higher than that seen in liver. CYP3A43 is expressed in far higher amounts in brain compared to liver and could potentially play an important role in metabolism of drugs. The metabolism of psychoactive drugs by CYP3A4 and CYP3A43 is being examined.



Immunofluorescence localization of P4503A in human brain hippocampus and midbrain using antiserum to P4503A4. (a) Immunostaining of CA1 pyramidal neurons indicating the presence of P4503A (b) Higher magnification of the immunostained neurons showing the staining of the axons; Bar = 25 µm. (c) Immunostaining of reticular neurons in the midbrain indicating the presence of P4503A was observed; Bar = 100 µm. (d) Higher magnification of the reticular neurons; Bar = 25 µm.

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Ravindranath V, Kommaddi RP, Pai HV. Unique cytochromes P450 in human brain: Implication in disease pathogenesis. J. Neurotransmission (Suppl.) 70:167-172 (2006)

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Cytochrome P4501A1 Variant Generated By Alternate Splicing: Cloning, Expression And Functional Characterization – Oral Presentation at the 14th International Conference on Cytochromes P450: Biochemistry, Biophysics, and Bioinformatics held in Dallas, TX, USA, May 31-June 5, 2005.

R. P. Kommaddi, V. Agarwal, H.V. Pai and V. Ravindranath. Identification and functional characterization of human brain - specific splice variants of cytochrome P450, the major enzyme involved in metabolism of xenobiotics including psychoactive drugs - Presented at the Society for Neuroscience-2005 Annual Meeting held in Washington, DC, USA, November 12-16, 2005.

V. Agarwal, Reddy P. Kommaddi and V. Ravindranath. Cloning, constitutive expression and localization of the major drug-metabolizing enzyme, Cytochrome P4503A43 in human brain - Presented at the XXIII Annual Conference of Indian Academy of Neurosciences held at Bangalore, India, December 2005.

V. Ravindranath. Unique cytochrome P450s in human brain: implication in disease pathogenesis. Invited speaker at the World Congress on Parkinson's disease, Berlin, June 6-9, 2005.

V. Ravindranath. Drug metabolism in human brain by unique cytochrome p450 enzymes generated by alternate splicing. Invited speaker at 14th International Conference on Cytochromes P450: Biochemistry, Biophysics, and Bioinformatics held in Dallas, TX, USA, May 31-June 5, 2005.

Funding:

Cytochrome p450 dependent metabolism of drugs in brain (NIH-RO1 MH70054).

Collaborator:

Prof. H. W. Strobel, Univ. of Texas Medical School, Houston, USA

PROTEIN THIOL HOMEOSTASIS AND MITOCHONDRIAL DYSFUNCTION IN NEURODEGENERATION

Principal Investigator : *V. Ravindranath*

Post Doctoral Fellow : *C. Koumar*

Research Fellows : *Smitha Karunakaran, Uzma Saeed, Latha Diwakar*

Project Assistant : *Sujanitha*

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, Alzheimer's disease and Parkinson's disease. These disorders are progressive and irreversible, and currently no cure is available since the etiopathogenesis of these disorders are poorly understood. Of particular concern, with reference to our country is the fact that with increasing longevity of life, the demographic profile of the country is rapidly changing and a significant proportion of our population would consist of aged individuals.

Parkinson's disease is characterized by loss of dopaminergic neurons in the substantia nigra pars compacta (SNPC). Our overall aim is to understand selective vulnerability of dopaminergic neurons of substantia nigra to oxidative stress, which has been implicated as a major factor in the pathogenesis and progression of Parkinson's disease. In brain, oxidative stress results in loss of glutathione (GSH) and formation of protein glutathione mixed disulfides (PrSSG) at available cysteine residues. Perturbation of protein thiol homoeostasis leads to altered cell signaling. Loss of GSH and increase in PrSSG are early events in 1-Methyl-4phenyl-1,2,3,6-tentrahydropyridine (MPTP) mediated dopaminergic cell loss in SNpc in the mouse model of Parkinson's disease. Pretreatment with a thiol-delivery agent, alpha-lipoic acid prior to MPTP treatment for 8 days protected against complex I depletion and attenuated cell loss in SNpc. We next examined the mechanism underlying alpha-lipoic acid (ALA) -mediated protection against MPTP toxicity by studying the early signal transduction cascade. Perturbation of the protein thiol homeostasis by MPTP was accompanied by activation of key cell death pathways at early time periods after a single dose

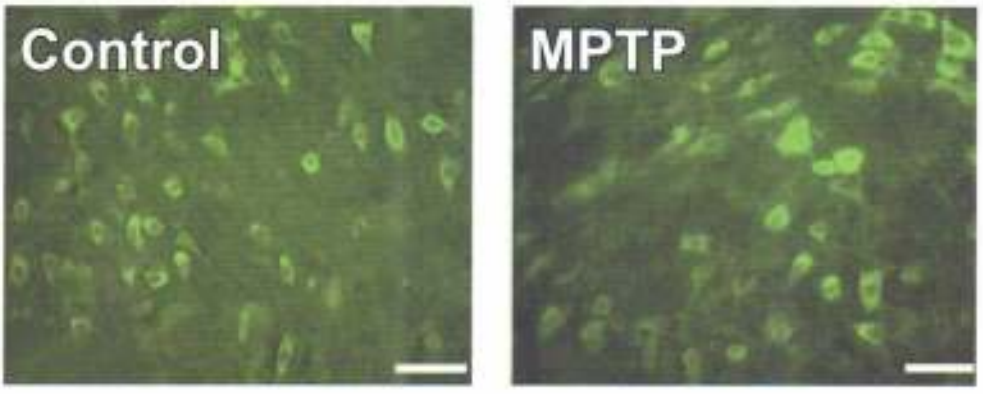

Fig: Activation of apoptosis signal regulating kinase 1 (ASK1) in the substantia nigra pars compacta neurons (SNpc) in an animal model of Parkinson's disease

of MPTP. We observed the translocation of the death associated protein, Daxx from nucleus to cytoplasm. Since Daxx interacts with apoptosis signal regulating kinase 1 (ASK1) in the cytoplasm, we examined ASK1 activation and found increased activation of ASK1, and downstream kinases phosphorylated by ASK1. Thus, we observed increased phosphorylation of MKK4 and c-Jun-N-terminal kinase (SAPK/JNK). Pretreatment with ALA abolished translocation of Daxx and activation of ASK1, MKK4 and JNK. In animals treated with MPTP for 8 days, we observed the translocation of Daxx from the nucleus to the cytoplasm in the SNpc neurons but not in the reticulata. This was abrogated in animals pretreated with ALA. Our studies demonstrate that exposure to MPTP activates redox sensitive death signaling cascade, in vivo, through activation of the Daxx/ASK1/JNK pathway in ventral midbrain, which can be prevented by maintaining the redox homeostasis through pretreatment with thiol delivery agents such as ALA.

Ph.D. Thesis (Awarded) – Latha Diwakar

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General Presentations:

V. Ravindranath: Wired Differences: How Understanding the Brain Can Empower Women on 8th March, 2006 at the workshop entitled "Empowering the Women R&D Professional" on International Women's Day.

V. Ravindranath: Life and the Brain on 3rd March, 2006 at University of Delhi.

V. Ravindranath: Use It or Lose It: How the Human Brain Works on 6th & 7th October, 2005 on Symposium on Excitement of Science at National Academy of Sciences, Allahabad.

V. Ravindranath: Life and the Brain on 1st September, 2005 at Lady Shri Ram College for Women, Delhi.

V. Ravindranath: Brain Research: Recent Advances in Development of Rationale Therapies and Cures for Brain Disorders on 25th June, 2005 at Oration at J.S.S. Medical College, Mysore.

V. Ravindranath: The human brain: From molecules and networks to behaviour at International Conference on Advanced in Network Sciences (ICANS ' 05) held at the National University of Singapore between 29th June, 2005 to 1st July, 2005

V. Ravindranath: "The working of the human brain: From molecules and networks to behaviour" on 6th April, 2005 at Amit Chaudhary Memorial Lecture, IIT, Delhi

UNDERSTANDING THE ROLE OF TRANSCRIPTION FACTORS IN THE DIFFERENTIATION OF PHOTORECEPTORS AND RELATED RETINOPATHIES

Principal Investigator : *Prabodha Swain*

Post Doctoral Fellow : *Madhumita Ghosh*

Research Fellows : *Sandeep Kumar, Dharmesh Patel*

M. Sc Student : *Pranov Oberoi*

Retina is one of the specialized tissues of eye that captures and processes light into chemical signals perceived as vision in the higher centers of brain. Photoreceptors are the sensory neurons that primarily capture light and perform photo transduction reactions in the retina. In mammalian retina, there are two distinct populations of photoreceptor cells known as rod and cones. Each of these photoreceptors has distinct cellular architecture and function in terms of sensitivity to light. Characteristically rods are sensitive to dim-light vision with low special acuity, whereas cone requires bright light for high special acuity and color vision in mammals. Generally, differentiation and functioning of retinal photoreceptors requires thousands of protein that includes several transcription factors. *Few of such transcription* factors including Neural Retina Leucine zipper (NRL) and Photoreceptor specific Nuclear Receptor (PNR) have been implicated in the regulation of differentiation and subsequent maintenance of the photoreceptors in the retina. Several mutations in both NRL and PNR genes have been identified in autosomal retinitis pigmentosa and other retinal diseases that alter the expression of cone photoreceptors *along with the expected* loss of rod photoreceptor function in the affected retina. Such reversal of photoreceptor function indicates an inter-relation between the functions of photoreceptors irrespective of the photoreceptor-specific expression of the transcription factors. In order to understand the molecular role of these transcription factors, we adopted a multi-plunged approach to unravel the molecular interaction of NRL with other proteins that are present in the postnatal retina. Further, phosphorylation of NRL as a target of different cellular signaling pathways exists in the retina.

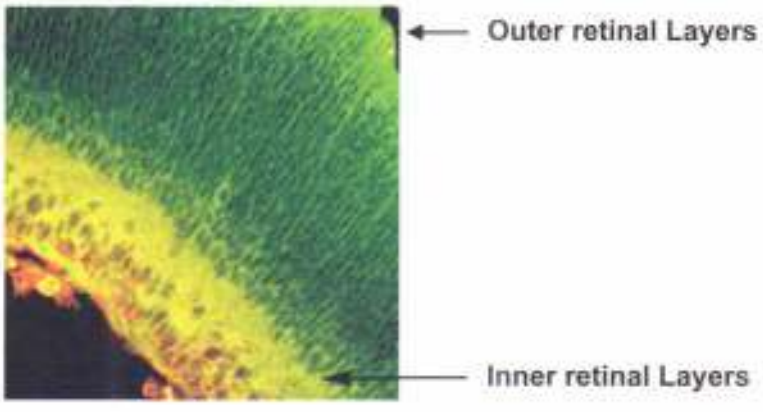
In order to understand the role of different signaling pathways in the expression of NRL, retinal explants or whole mice eyes were treated with different kinase inhibitors and western blot analysis of the total protein was performed to study the expression profile of Nrl in the treated tissues. Retinal explants treated with SB203580, a p38 inhibitor produced significant alteration in the expression of the Nrl-phospho isoforms (mouse homologue of NRL), where as, expression of Nrl in U0126 or DMSO treated explants produced negligible changes in the protein profile. The lack of changes in the protein profile of Nrl can be interpreted as either the result of poor sensitivity of Western blot analysis in detecting subtle changes in the phosphorylation *of Nrl expressed* in the kinase inhibitor treated retinal explants or activation of other signaling pathways by U0126 that compensates the loss of NRL-phosphorylation produced by the inhibition of MEK1/2-dependent signaling pathway. However, the loss of activated-Mapk2 (mouse homologue of MAPK2) expressed in U0126 treated retina suggests that the concentration of inhibitor used is sufficient enough to produce *complete inhibition* of the activated MEK1/2-dependent pathway in the treated retina. Since more than one glutamine synthetase kinase-3 (GSK3) phosphorylation sites is present close to the MAPK-dependent phosphorylation sites of NRL, any change in the domain due to loss of MAPK-dependent phosphorylation can be easily compensated by activated (GSK3)-dependent phosphorylation of Nrl. U0126 is known to activate phosphatidyl inositol-3 (PI3) signaling pathway which activates GSK3-mediated phosphorylation in other tissues. Also, since more

than one sites of phosphorylation present in Nrl, inactivation of a single phosphorylation site or inhibition of a single kinase can produce unpredictable effects depending on the kinases present in the particular developmental window of retina in mice. Different experiments suggest that phosphorylation of Nrl observed in retina is the cumulative effect of different MAPKs expressed in the spatial window of developing retina.

To determine if the expression of Mapks phosphorylating Nrl changes at different postnatal stages of the developing mice retina, immunoblot analyses of the total retinal protein were performed using specific MAPKs antibodies. Westernblot analysis showed an enhanced expression of activated Mapk2/Erk2 in all retinal lysate up to PN 3.5 and the expression was reduced and maintained at a basal level in subsequent days in the retinal development. Since expression analysis of the kinases in total protein is not the true representation of the localization in different layers of retinal cells, we performed fluorescence microscopy to localize the expression of activated Mapk2 and Nrl in age matched retinal sections. The confocal micrographs show strong expression of phospho-Mapk2 in most of the inner retinal layers including ganglion cells immediately after birth (PN 0.5). The expression level is dramatically enhanced in outer retinal layers immediately after PN 3.5 and found co-expressed in neuroblasts expressing Nrl and rhodopsin (at PN 5.5) predominating the outer retinal layers of developing mice. The expression of both Nrl and phospho-Mapk2 in retinal neuroblasts much before the spatio-temporal migration to for mmature photoreceptors implies the important role of Mapk-mediated Nrl-phosphorylation in the development of photoreceptors in mice retina.

The relevance of NRL-phosphorylation mediated by MAPKs is further substantiated by the fact that mutation (S50T/A or P51L) in the transactivation domain of NRL altered activated MAPKs-dependent phosphorylation of the protein, in vitro. Indirectly, NRL-mediated transactivation of rhodopsin minimal promoter was also affected when MAPKs specific signaling

Co-Expression of Yb-1 and Thy1 in Mouse Retina



Co-expression of Yb-1(green) and thy-1 (red) in postnatal day-3 mouse retina. Further studies will focus on the effect of NRL-phosphorylation in the interaction with other retinal proteins. Effect of CaMK II mediated phosphorylation on the recently identified NRL-mutations associated with clumped pigmentary retinal degeneration will also be investigated.

pathways were inhibited in the transfected cells used in the luciferase-based rhodopsin promoter transactivation assay. Retinal explants treated with kinase inhibitors also affected the transcription of NRL in vitro. Analysis of the NRL interaction with other heterodimerizing partners expressed in retina showed that NRL interacts with leucine zipper containing proteins by zipper-zipper dimerization. Interaction with TBP produced a much stronger interaction with the leucine zipper domain of NRL suggesting that multiple domains are involved in NRL-TBP interaction in vitro. Phosphorylation may have a major role in stabilizing such interactions; since the CaMK II mediated phosphorylation sites localized to the carboxyl terminal half of the NRL shown to induce auto-phosphorylation in NRL itself. Also, some of the mutations associated with recently identified clumped pigmentary retinal degeneration altered potential CaMK II phosphorylation sites in NRL.

The interaction between NRL and YB-1 was confirmed by reverse pull-down assay. The interaction domain in NRL is confined to the carboxyl terminal half of NRL, more precisely on the first half of the NRL-zipper domain, where as in YB-1, the region involved in NRL-interaction is confined to 45-203 amino acids of the protein. A specific antibody was raised against GST-YB-1 fusion protein. Mice retinal sections stained with YB-1 antibodies localized the protein in multiple layers of retina including photoreceptors.

Funding:

This work is supported by a grant from DBT.

EFFECT OF NEURAL GENE(S) IN DIFFERENTIATION OF RETINAL CELLS

Principal Investigator : *Prabodha Swain*

Technical Assistant : *Sanjay Kumar*

Project Assistant : *Sushmita Richong*

The major objective of the study is to establish an alternate cell culture model that will help the study of pathways activated by the individual retina specific transcription factor. 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 a major role in the successive steps of differentiation and fate determination of retinal cells. Differentiation of retinal neurons is stage specific. Cell lineage and birth date analysis in rodents suggest ganglion cells are generated early in the embryonic stages; followed by the amacrine, cone and horizontal cells during mid gestation and rod, bipolar and glia are generated at late embryonic stages. Identification of stage specific factor(s) can potentially serve as markers 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 retinoic acid) to produce post-mitotic photoreceptors. These progenitors with limited mitotic activity then can be used as potential replacements for photoreceptors in damaged retinae.

Some recent findings suggest that iris cells can produce retina specific factors when induced with specific retinal genes. Since iris and retina originate from the same inner layer of the optic cup in embryonic retina, it promises to be an interesting model to study the specific pathways that can be triggered by the introduction of retina specific factors.

To understand the role of NRL in the proliferating Iris cells, different constructs of NRL with or without EGFP tags were expressed in the bovine or mice Iris cells and transfected cells were analyzed for the expression of NRL and incorporated BrdU by immuno-histochemistry. After careful analysis, it was observed that expression of NRL reduces the incorporation of BrdU in the transfected Iris cells suggesting role of NRL in the mitotic arrest or proliferation of the expressed cells. Identical properties were also observed in neuronal cell of mice or even in primary brain cells. We are currently analyzing the effect of kinase inhibitors in the nucleo-cytoplasmic shuttling of the NRL in the dissociated Iris cells. Such experiments are performed to substantiate the preliminary results on retinal explants that show nuclear localization of NRL was impaired when treated with specific kinase inhibitors in vivo.

CELLULAR AND MOLECULAR MECHANISMS IN NEUROBIOLOGY OF HIV-1

Principal Investigator : *Pankaj Seth*

Research Fellow : *Mamata Mishra*

Project Assistant : *S. Vitrevel*

Technical Assistant : *Durga Lal Meena*

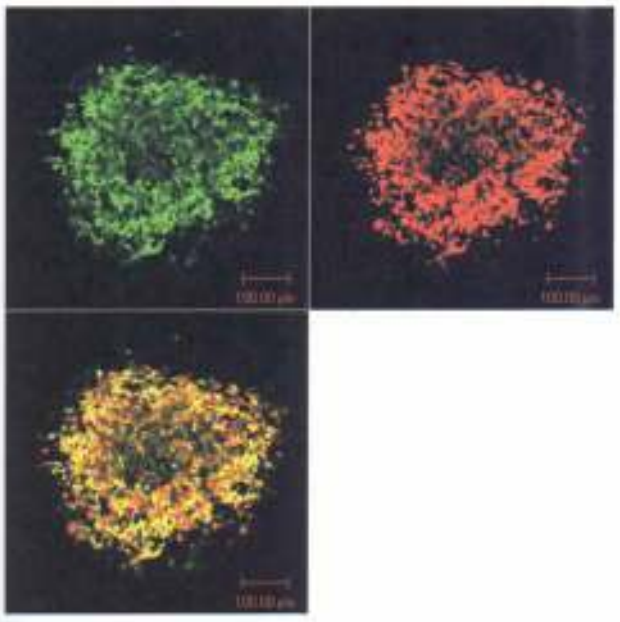
A precise understanding of the cellular and molecular events of virus-cell interactions during the course of infection is important for defining a disease and developing potential therapies. Cell culture systems derived from human fetal brain cells are being developed to investigate viral-cell interactions. Our laboratory is working towards the goal for establishing a novel cell culture system of human CNS progenitor cells that may be used as a tool to investigate virus induced neuropathogenesis. The culture system will have the ability to be maintained in an undifferentiated state or can be differentiated into highly purified populations of neurons or astrocytes for their use to investigate the pathogenesis of human neurotropic viruses, like HIV-1.

AIDS has evolved into a global epidemic that affects more than 40 million people worldwide and around 5.2 million individuals in India. In later stages of the disease, HIV-1 infection often results in neurological complications of central as well as peripheral nervous system and is referred to as human immunodeficiency virus (HIV-) associated dementia (HAD) or AIDS dementia complex (ADC). HIV-associated dementia is an important complication of the central nervous system in HIV-1 infected patients and clinically it involves varying degree of neurological and psychiatric symptoms. The world wide incidence of HIV-associated dementia has been reported to be more than 30% of AIDS population. In India, it is often debated if there is a low incidence of HAD / ADC, however there is only limited data to suggest if that is really the case. HIV-1 causes CNS pathology by the virion itself and its viral proteins. HIV-1 transactivating protein Tat has been found to be neurotoxic. The genetic variation of HIV-1 has led to the classification of viral strains into phylogenetically distinct groups and subtypes that complicate our current understanding of HIV-1 infections and their management. Recently, different clades (A-J) of HIV have been reported, of which clade-C is being implicated for around 50% of AIDS cases worldwide, and more than 90% in India. Most of our current knowledge on HIV-1 induced CNS complications is based on studies with HIV-1B and limited information is available as to how HIV-1C affects brain functioning in HIV infected individuals. Considering the large number of HIV-1 carriers in India, it calls for research studies in this emerging area of neurodegenerative disorders.

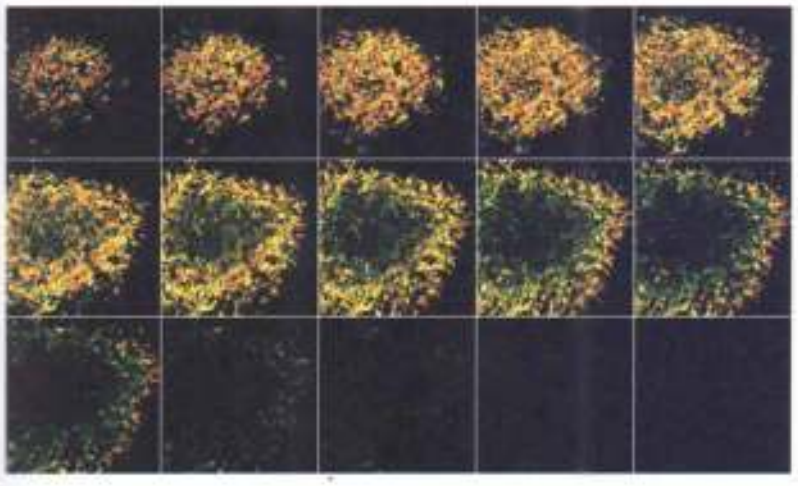
At the NeuroAIDS laboratory at NBRC, we are using human fetal CNS progenitor cells to investigate the effect of viral protein Tat B and C on various parameters to predict its role in HIV-1 neuropathogenesis. We treated human fetal CNS progenitors cells, differentiating CNS progenitors cells into astrocytes, fully differentiated astrocytes and fully differentiated neurons with HIV-1 Tat B and C and carried out cytokine/chemokines assays in supernatants using ELISA and cytokine bead array, as well as immunostained these cells for TUNEL assay/caspase-3 to study the effect of the viral protein on apoptosis. Our findings suggest that there is an increase in the production of monocyte chemoattractive protein-1 (MCP-1) from most of the human astrocyte culture systems following Tat treatments and the increase in MCP-1 production from Tat C is less robust as compared to Tat B. Our experiments with Tat B and C on human neurons differentiated from human CNS progenitor cells reveal that neurons exposed to Tat C show attenuated neuronal apoptosis as

compared to the neurons that were exposed to Tat B. We are looking into possibility of using these primary cultures for infection with HIV-1 B and C strain in collaboration at laboratories with BL-2 plus/BL-3 facility for studying how the viron effect these cells, particularly the human neurons. These studies are expected to provide an insight into different neuropathogenesis mechanisms by two different clades (HIV-1 clade B and C) that affect the majority of AIDS population around the world.

In addition to this, we have established multi-potential human CNS progenitor cell culture system to be used to investigate viral pathogenesis of neurotropic viruses. We culture these human fetal CNS progenitor cells as suspended cultures as neurospheres (Figure 1A), or as adhered cultures as monolayers. We have investigated the temporal expression of these cell specific markers to gain insight into the differentiation timelines so that we can use these cells for our studies with HIV transactivating protein Tat during differentiation. Detailed characterization of this cell culture system, particularly of the neurons so developed is in progress.



A) Confocal images of a human neurosphere differentiating into neuronal lineage that was fixed with 4% paraformaldehyde and immunostained for CNS progenitor cell marker Nestin (RED) and neuronal marker Beta III tubulin/Tuj-1 (GREEN). Figure shows that at early stages of differentiation process, cells (in YELLOW colour) co-express nestin and Tuj-1



B) Composite of Z-stacked images from a human neurosphere. Note that human CNS progenitor cells that are differentiating into neurons co-express (YELLOW) the nestin and Tuj-1 markers mainly at the periphery.

Figure: Human fetal neurospheres.

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* Work done elsewhere

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Funding:

Cellular And Molecular Basis of Neurobiology of HIV-1C in Human CNS cells. (DBT)

Collaborators:

Dr. Neelam Thapar, Civil Hospital, Gurgaon, India.

Dr. Uday K. Ranga, JNCSAR, Bangalore, India.

Dr. Eugene O. Major, NINDS/NIH, Bethesda, USA

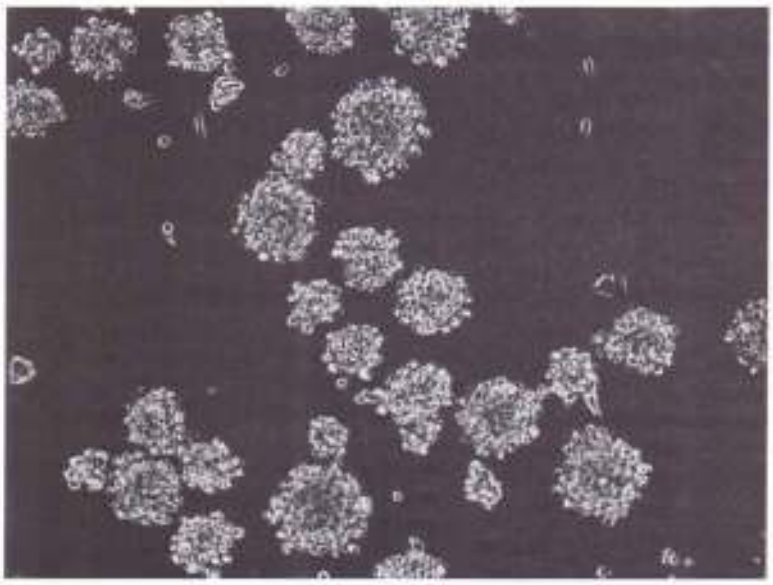
Prof. Avindra Nath, Johns Hopkins University, Baltimore, USA.

STUDY OF THE SIGNALING CASCADES INVOLVED IN THE PROLIFERATION AND DIFFERENTIATION OF CANCER STEM CELLS IN GLIOBLASTOMA

Principal Investigator : *Ellora Sen*

Gliomas of astrocytic, oligodendroglial and ependymal origin are the most common type of primary CNS neoplasm accounting for more than 70% of all brain tumors. Glioblastoma multiformes (GBM) represents one of the most malignant brain tumors characterized by intense proliferation, widespread invasion of poorly differentiated cells and poor prognosis. Primarily because of its diffuse nature, there is no effective treatment for GBM, and relatively little is known about its pathogenesis and malignant progression. Tumor initiating cancer stem cells (CSC), endowed with all the cardinal features of neural stem cells such as self-renewal and multipotency have been found within GBM. Modeling of gliomas by genetic manipulation of mice suggests that deregulation of signaling pathways that control gliogenesis during normal brain development, such as the differentiation of neural stem cells (NSCs) into astrocytes, might contribute to GBM. GBM represents a collection of glial progenitors that are trapped in an undifferentiated and proliferative state. Thus, differentiation and glioma formation appear to be integrally related. Accumulating evidence suggests that GBM may arise from the inability of these CSCs to differentiate. Besides, undifferentiated CSC within GBM may have increased oncogenic potential due to signaling abnormalities leading to their inability to differentiate.

All forms of cancer arise from disturbances of critical cellular functions such as proliferation and apoptosis. Both stem cells and cancer cells are capable of unlimited proliferation. Neural stem cells and lineage restricted



Cancer stem cells isolated from a Glioblastoma cell line

progenitor cells possess features of cancer cells of the CNS such as proliferative potential and diversity of progeny. Importantly, the same cellular pathways that are active in gliomas regulate NSC fate. These pathways include growth factor-induced signal transduction routes and processes that control cell cycle progression and recent data indicate that combinations of mutations in these pathways may contribute to GBM formation. Hypoxia appears to maintain stem cells in a state where a limited proliferation is allowed but not its differentiation towards committed progenitors. Whenever hypoxia is a key feature of stem cell niches in vivo, the balance between differentiation and self-renewal is in favor of the latter. Not only are undifferentiated neural progenitors more sensitive to oncogenic transformation than differentiated cells, but also differentiated astrocytes are relatively less sensitive to the effect of specific signaling abnormalities than undifferentiated neural progenitors. In the light of the growing conviction that GBM contains stem cells, identifying the intrinsic circuitries that regulate gene program(s) involved in determining CSC fate decision (maintenance vs. differentiation), will be instrumental towards understanding the pathogenesis of this disease.

The presence of hypoxic regions within GBM is associated with increased malignancy and poor prognosis. Hypoxia has also been implicated in maintaining NSC in a proliferative stage by preventing its differentiation towards committed progenitors. As hypoxia is known to regulate the balance between differentiation and proliferation of stem cells and since differentiation of CSCs and glioma formation is integrally related, the focus of the laboratory is to investigate whether hypoxia modulates signaling pathways and chromatin modifiers that regulate the fate of CSCs between proliferation and differentiation. This study will enhance our fundamental understanding of (i) the signaling pathways that maintain CSC in an undifferentiated state (ii) whether hypoxia orchestrates the increased proliferation of CSC at the expense of differentiation (iii) signals that are aberrantly expressed during hypoxia that contributes to the oncogenic conversion of CSCs. The ultimate goal of this proposal is to identify the molecular signals that coordinate the differentiation of the CSCs so that these signals can be pharmacologically manipulated or mimicked to enhance the differentiation potential of CSCs within GBM.

Funding:

Study of the signaling cascades involved in the proliferation and differentiation of cancer stem cells in Glioblastoma (DBT).

OLIGODENDROCYTE DIFFERENTIATION FROM NEURAL STEM CELLS: IMPLICATION IN CNS REPAIR

Principal Investigator : *Ellora Sen*

Neural stem cell (NSCs) in the mammalian central nervous system (CNS) are defined as those cells having the ability to self-renew as well as to maintain the potential of generating all three major cell types of the CNS: neurons, astrocytes and oligodendrocytes. Neural Stem Cell research has recently garnered significant momentum due to the extraordinary potential subscribed to NSCs in the repair of the damaged nervous system. Perinatal Hypoxic/Ischemic (H/I) brain injury is a major cause of morbidity resulting from premature birth. One of the histopathological hallmarks of perinatal hypoxic injury is permanent deficit in white matter oligodendrocyte. The resulting dysgenesis that occurs subsequent to perinatal H/I contributes to cognitive and motor deficit that characterize cerebral palsy. At the present time, there are limited therapies available to protect the infant brain from perinatal insults and none to stimulate regeneration. As there is great interest in exploiting stem cells for CNS regeneration, it is our long-term goal that the studies initiated in this proposal will lead to strategies that will stimulate the differentiation of NSCs towards oligodendrocyte lineage, to effect CNS regeneration after perinatal brain damage.

Differentiation of neural precursors into neurons, astrocytes and oligodendrocytes takes place sequentially and extrinsic factors play pivotal role in specifying cell lineages in the developing brain. Perinatal hypoxic injury occurs during the oligodendroglial phase. Certain inducers of astrocyte differentiation are elevated following perinatal H/I and these factors working through their respective downstream transcription factor combinatorially causes the preferential differentiation of bipotential glial progenitors in the subventricular zone (SVZ), - a region of the brain that harbors the multipotential neural stem cells/progenitors, towards astrocytes and away from the oligodendrocyte lineage. Transdifferentiation of a glial progenitor into an astrocyte rather than an oligodendrocyte could underlie the permanent deficit in white matter oligodendrocytes. Recent advances in understanding oligodendrocyte development have revealed the importance of growth factors and relevant downstream transcription factors in regulating oligodendrocyte differentiation. Since transcription factors that regulate NSC fates, act either positively or negatively, and some transcription factors induce the differentiation of one cell lineage while suppressing another, we are interested in investigating (i) whether specific factors known to promote oligodendroglial lineage could antagonize these aberrant extrinsic differentiation signals and (ii) whether hypoxia directly regulates the transcriptome of glial precursors thereby altering their differentiation potential. As the perinatal brain is conducive for oligodendrocyte generation, our long-term goal is to identify strategies to antagonize those factors that induce astrocyte differentiation to promote oligodendrocyte development. Insights gained from these studies could eventually lead to therapeutics that could be administered to infants to enable the damaged infant brain to develop normally from its endogenous stem cells.

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MOLECULAR MECHANISMS OF MEMORY FORMATION BY MASSED AND SPACED TRAINING

Principal Investigator : *Shiv K. Sharma*

Research Fellows : *Chinmoyee Maharana*

Lab Assistant : *Narayan Kumar*

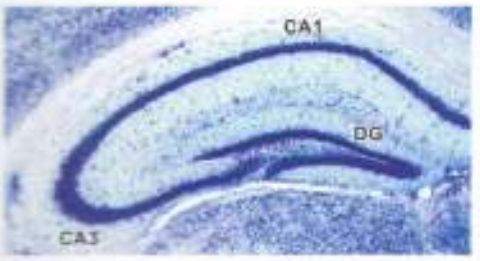
One of the fundamental questions in neuroscience has to do with how we learn and remember. Our memories link us with our past and help in planning our future. Having a good memory is wonderful, but the consequences of memory loss are devastating. At one end of the spectrum is simple, age related senile forgetting (senior moments), at the other end is the severe memory loss due to memory impairment conditions, such as the Alzheimer's disease that can affect even day-day proper functioning. Thus, a lot of effort is directed towards examining the mechanisms that govern memory formation and retrieval.

A closer look at memory research involving several model systems and preparations has revealed that memory formation follows a few key principles across different systems and memory tasks: (1) long-term memory (LTM) typically requires multiple training trials, (2) LTM formation requires new RNA and protein synthesis, and (3) massed training is less effective in inducing LTM than spaced training.

The third basic property of memory is currently the focus of my lab. Memory is more robust and longer lasting when the trials during training are distributed over time (spaced training) than when they are presented with little or no inter-trial interval (massed training). This effect is commonly referred to as the "spacing effect". The interesting feature of this effect is that the superiority of spaced training over massed does not appear to be a general phenomenon for all temporal domains of memory, but the effect is pronounced with respect to memories in the longer time domain. This phenomenon has been extensively studied at behavioral levels. However, the molecular and cellular mechanisms of the spacing effect are not well understood. It is thought that different training patterns induce a differential change in the molecular and synaptic substrates of memory. Collectively, these changes determine the duration and strength of memory induced by massed and spaced training.

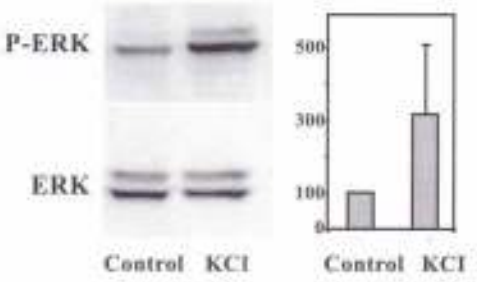
My lab is involved in examining the molecular mechanisms that may contribute to the differential induction of memory by massed and spaced training protocols. We are particularly interested in extracellular signal-regulated kinase (ERK) pathway that is critically involved in plasticity and memory. We focus our studies on the changes in the CA1 region in the rat hippocampal slice (Fig. 1). We have examined the activation of ERK in the CA1 region by KCl depolarization event, an activity-mimicking stimulus (Fig. 2). After establishing the treatment conditions, we are now examining the temporal activation profile of ERK activation in the CA1 region of hippocampal slices by NMDA applied in massed and spaced patterns. NMDA receptor signaling is critical for several different forms of plasticity and memory. The massed and spaced patterns of NMDA stimulation serve as the *in vitro* analog of these two training paradigms. We will further examine the critical factors important for regulation of ERK activation, and its downstream effects.

Fig.1



Hippocampus

Fig.2



ERK activation by KCl

Fig 1. A hippocampal slice showing different regions of hippocampus: CA1, CA3 and dentate gyrus (DG).
Fig 2. KCl activates ERK in the hippocampus. A representative Western blot (left) and summary data (right) show that a 3 min treatment of hippocampal slice with 90 mM KCl induces ERK activation in CA1 region of the hippocampus.

Presentations:

*SK Sharma, CM Sherff, S Stough and TJ Carew: Brain-derived neurotrophic factor signaling is critical for long-tem memory, long-term synaptic facilitation and ERK activation in *Aplysia*. Society for Neuroscience Abstracts, program no. 504.18, (2005).

*JL Shobe, SK Sharma and TJ Carew: Long-term memory for sensitization in *Aplysia* requires sustained ERK activity. Society for Neuroscience Abstracts, program no. 540.10, (2005).

*JL Ye, SK Sharma, JL Shobe and TJ Carew: Identification, cDNA cloning and functional analysis of the small GTP-binding proteins RAS and RAP in the CNS of *Aplysia*. Society for Neuroscience Abstracts, program no. 504.17, (2005).

* Work done elsewhere.

Funding:

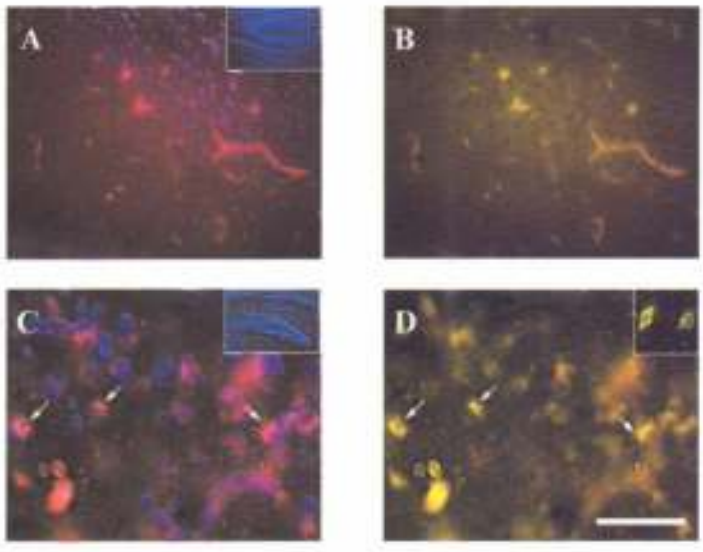
Molecular and cellular mechanisms of memory formation by massed and spaced training regimens (DBT).

MOLECULAR APPROACHES TO UNDERSTAND THE PATHOPHYSIOLOGY AND PHARMACOLOGY OF INFLAMMATION IN CNS DISORDERS

Principal Investigator	:	Anirban Basu
Post Doctoral Fellow	:	Soumya Ghosh
Research Fellow	:	Manoj Kumar Mishra
M. Sc Students	:	Ayan Ghoshal, Sourojit Bhowmick
Project Assistants	:	Preeti Koli, Amit Saxena

The focus of our laboratory is to understand the pathophysiology and pharmacology of inflammation in CNS disorders.

So far one project has been initiated to understand the molecular mechanism of inflammation in Japanese Encephalitis. We have characterized the functional significance of astroglial and microglial activation following JE. We have observed that growth factors like NGF and CNTF are also increased following viral infection, which further supports the role of astrocytes in neuronal survival. We are presently working with a membrane based cytokine array to find out more proinflammatory mediators which are regulated during viral infection. We have found Cyclooxigenase-2 (Cox-2) is upregulated during JE infection. Microglia are the predominant source of Cox-2 in brain following infection. In microglial activation and in infection there is more region specificity. Microglia of hippocampus are more vulnerable to JE infection. Occasionally, we have observed colocalization between a neuronal antibody and JE specific antibody. JE infects hippocampus microglia more than cortical or thalamic microglia. Emerging evidence indicate that the inflammation inhibits neurogenesis. There is gradual decrease in NeuN (a transcription factor for mature neuron) following JE. We have also observed that there is a temporary blockade in neurogenesis following JE. There are experiments going on to find out a direct correlation between inflammation and neurogenesis in this model.



Microglia produce Cox-2 following JEV infection. Cryostat sections from control and JEV-infected BALB/c mice brain were double-stained for CD11b and Cox-2 and mounted using Vectashield containing DAPI. A & B: The control brain showed negligible presence of activated microglia (A) as well as lack of expression of Cox-2 (B) as observed by the absence of staining for both CD11b (Alexa Fluor, red) and Cox-2 (FITC, green). The inset picture depicts the representative hippocampal field. C: A robust activation of microglia however was seen in the infected brain sections (co-localization of CD11b with DAPI). D: Co-localization of CD11b and Cox-2 as shown by the arrows in the same hippocampal field indicates the release of Cox-2 by the activated microglia. Inset shows higher resolution picture of the same. Scale bar: 20 µm.

Publications:

* Krady J K, Basu A, Allen CM, Xu Y, LaNoue KF, Gardner TW Levison SW (2005) Minocycline Reduces Pro-Inflammatory Cytokine Expression, Microglial Activation And Caspase-3 Activation In A Rodent Model Of Diabetic Retinopathy. Diabetes 54:1559-65

Lazovic J, #Basu A, Krady JK, Rothstein RP, Smith MB, Levison SW (2005) Neuro-protection following hypoxia-ischemia in IL-1 type 1receptor deficient mice: suppression of inflammation and inducible nitric oxide synthase (iNOS) production Stroke. 36: 2226-2231 (#co first author).

Lin HW, #Basu A, Drukman C, Cicchese M, Krady JK, Levison SW (2006) Astrogliosis is not solely depend upon activating the type 1 Interleukin-1 receptor. J.Neuroinflammation. 3(1): 15 (#co first author).

*Work done elsewhere

Presentations:

A. Basu, "Human brain: what is revealed is exciting, what is hidden is critical", Government Girls' School, Faridabad, September 5th (Popular lecture) (2005).

A. Basu, "Clinical Proteomics: Translating Today's Benchside Promise Into Tomorrows Bedside Reality", PGI Chandigarh, November 6th (A meeting organised jointly by DBT and PGI to chalk out the roadmap of Clinical Proteomics research in India) [Invited speaker] (2005).

J Lazovic, A. Basu, R P Rothstein, M B Smith and S W Levison, Direct evidence that activating the Interleukin-1 type 1 receptor enhances ischemic brain damage. Annual meeting of Society for Neuroscience, Nov 12th-16th, Washington DC. (Oral Presentation) (2005).

H W Lin, A. Basu, J K Krady and S W Levison., IL-6 family cytokines differentially activate mouse versus rat microglial. Annual meeting of Society for Neuroscience, Nov 12th-16th, Washington DC. (Poster) (2005)

A. Basu, Molecular mechanism of CNS infection and inflammation, Dept of Neurology, SGPGI, Lucknow, 18thNovember (Invited Lecture) (2005).

S Bhowmick, P Koli, M K Mishra, M B Appaiahgiri, S Vrati and A. Basu, Differential expression of IP-10 (CXCL-10) in brain following Japanese Encephalitis

Annual conference of Indian Academy of Neurosciences, 11-14thDecember, NIMHANS, Bangalore. (Poster) (2005)

A Ghoshal, P Koli, M B Appaiahgiri, S Vrati and A. Basu, Microglial Microglial activation and induction of multiple proinflammatory mediators in Japanese Encephalitis. Annual conference of Indian Academy of Neurosciences, 11-14thDecember, 2005, NIMHANS, Bangalore (Oral presentation) (2005)

A Ghoshal, K Saheb, P Koli, M B Appaiahgiri, S Vrati and A. Basu, Microglial activation and neurodegeneration in Japanese Encephalitis, Annual conference of society of Neurochemistry India, 16-17 December, Dept of Biochemistry and Toxicology, University of Madras, Chennai. (Invited speaker) (2005).

A. Basu, Infection and inflammation: Are they missing links that determine neuronal fate following Japanese Encephalitis? "Molecular Immunology Forum"-Bhubneswar. (Invited Speaker) (2006)

Funding:

Study of the molecular mechanisms of microglia/macrophages mediated neuro inflammation in Japanese encephalitis, (DBT).

PROBING THE CONTROL OF ACTION USING SACCADIC EYE MOVEMENTS

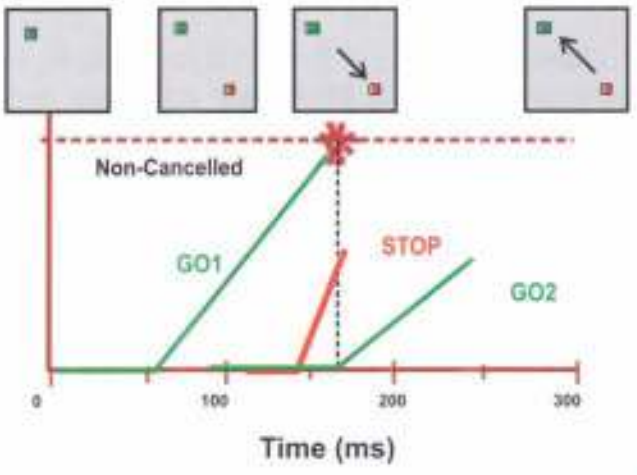
Principal Investigator : *Aditya Murthy*

Research Fellow : *Supriya Ray*

M. Sc. Students : *Sharika K.M., Vishal Kapoor*

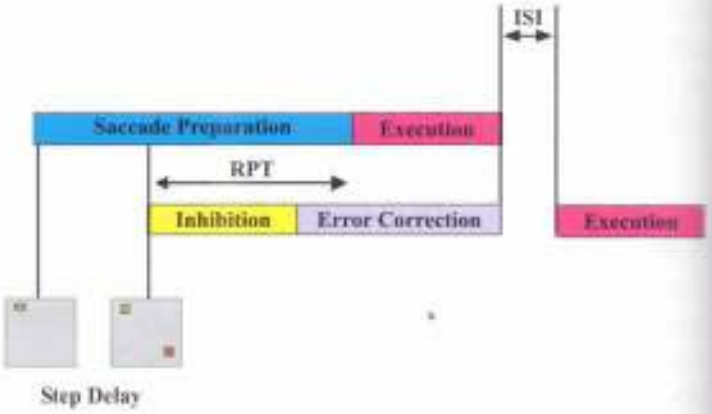
Human visual sensitivity is not uniform but rapidly declines centrifugally from the centre of gaze as a result of which objects in the periphery cannot be identified clearly. To counter this problem our brain has evolved a mechanism whereby the visual scene is explored in discrete steps, each of them corresponding to an eye movement called a saccade, followed by a fixation. By carefully observing the pattern of fixations a number of behavioral studies have shown that saccades are not random but direct gaze to objects of interest. Therefore, before each gaze shift, perceptual processing must identify potential targets for the eye movement and motor processing must prepare and execute the motor command. The role of cognition also provides an added level of complexity since behavior is not strictly dictated by perceptual processes: internal goals are important.

The challenge therefore is to understand the representations of the image that guides orienting responses and the computations that subserve and link visual and cognitive processing, and eye movement programming. The long term goals of the proposed project are to understand how vision and cognition guide action. These questions will be approached through investigations of visually guided saccades in novel paradigms designed to probe the oculomotor control in normal human subjects.



Our study posits a sequential participation of inhibitory and error correcting processes during the preparation of a corrective saccade.

Hypothesized model of processing stages involved in parallel preparation of corrective saccade. Failure of STOP process, leads to the activation of GO2 process responsible for generation of the corrective saccade.



The nature of self-control during errors. The capacity to detect and correct errors is due to self-monitoring capacity of the brain. To probe the nature of such control in relation to eye movements we have been using a version of the classic double-step task called REDIRECT task in which the appearance of second target on some trials serves as a signal to cancel the initial saccade and REDIRECT gaze to the final target location. Errors of action are induced when subjects fail to cancel the partially prepared responses. In such instances subjects are able to automatically correct the initial error with a second corrective saccade to the second target.

Previous work has provided behavioral evidence to suggest that some degree of parallel processing between erroneous first and corrective second saccade occurs during processing of action errors. However, it remains unspecified whether only visual processing occurs in parallel or whether post perceptual processing also may occur concurrently. To test whether motor preparation of the two saccades occurred concurrently during error correction we made subjects perform a modified triple-step REDIRECT task in which the final target location was perturbed on a random fraction of trials during the production of the errors.

Consistent with the idea of predictive error correction we found corrective saccades were often directed at the location originally occupied by the target prior to the third step. For this we assume that some motor preparation leading to corrective saccades must have occurred prior to the occurrence of the error. An implication of these results is subjects making the errors. We also tested the hypothesis that the brain uses an estimate of the time it takes to cancel a response to make predictions of outcomes.

Publication:

Ray S, Murthy A. Chronometric analysis of saccadic suppression. J. Neurophysiology (In Review).

Presentations:

A. Murthy. Computational Issues in visuomotor control. Lecture for Computational Neuroscience workshop, given at IIT, Mumbai (2005).

A. Murthy., Sharika K.M., Supriya Ray, Hierarchical control of action during error correction Indian Academy of Neuroscience. Bangalore, India. (2005).

Funding:

Control of visually guided movements in humans. (Dept. of Science & Technology)

MECHANISMS OF ACTION CONTROL IN HUMANS

Principal Investigator : *Aditya Murthy*

Research Fellow : *Arjun Ramakrishnan*

Project Assistant : *Shrikant Kulashekhar*

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. Two subcortical areas that have been implicated in motor control are the basal ganglia and the cerebellum that are reciprocally connected to motor cortical areas. However, the specific nature of control exerted by these two areas remain unclear. 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 is being carried out in collaboration with Dr. Sarat Chandra and Dr. Madhuri Behari of A.I.I.M.S. where a facility to measure eye movements in real time under computer control has been set up by NBRC.

Inhibitory control of action. A hallmark of the voluntary control of action is the ability to inhibit a planned movement when confronted with situations that render current goals inappropriate. This ability to inhibit inappropriate actions is of considerable interest because it involves an internal act of control, which redirects overt movement. Inhibitory control can be probed in the REDIRECT task that entails inhibiting a preprogrammed eye movement for successful performance. Using a simple theoretical construct we have used the REDIRECT double-step task to estimate the duration it takes to inhibit a partially prepared movement in normal subjects. More recently we have begun investigating how inhibitory control is implemented to regulate gaze shifts characterized by multiple saccades. Here inhibition can occur at multiple levels; inhibition can occur either before the gaze shift begins; or inhibition can occur during the intersaccadic interval separating intervening saccades. Using a version of the saccade countermanding task we tested whether a unitary mechanism suffices to account for inhibitory control during multi-step gaze shifts by having subjects make a sequence of saccades to single targets as a result of induced saccadic dysmetria.

On random catch trials a second target appeared which instructed subjects to cancel the partially prepared response to the initial target. Using a race model framework we obtained two important results. First, a unitary inhibitory mechanism can account for subjects' performance in this task. Second, although a race model predicted the reaction times of the erroneous primary saccades that escaped inhibition, the model underestimated the reaction times of the secondary saccade. This finding indicates that the intersaccadic interval between two saccades in a multi-gaze shift is not subject to voluntary inhibitory control and provide evidence of a ballistic stage in decision making during multi-gaze shifts.

Using the multi-step gaze saccade task we are now investigating the relative contributions of two important subcortical circuits in the control of saccades: the basal ganglia and the cerebellum. We are addressing this issue by recording the behavior of patients with lesions in the cerebellum and Parkinson's disease patients having compromised basal ganglia function. The aim of this line of work is to understand how inhibitory control is implemented in the basal ganglia and cerebellum during the programming of relatively complex actions.

Publication:

Joti P, Kulashekhar S, Behari M, Murthy A.

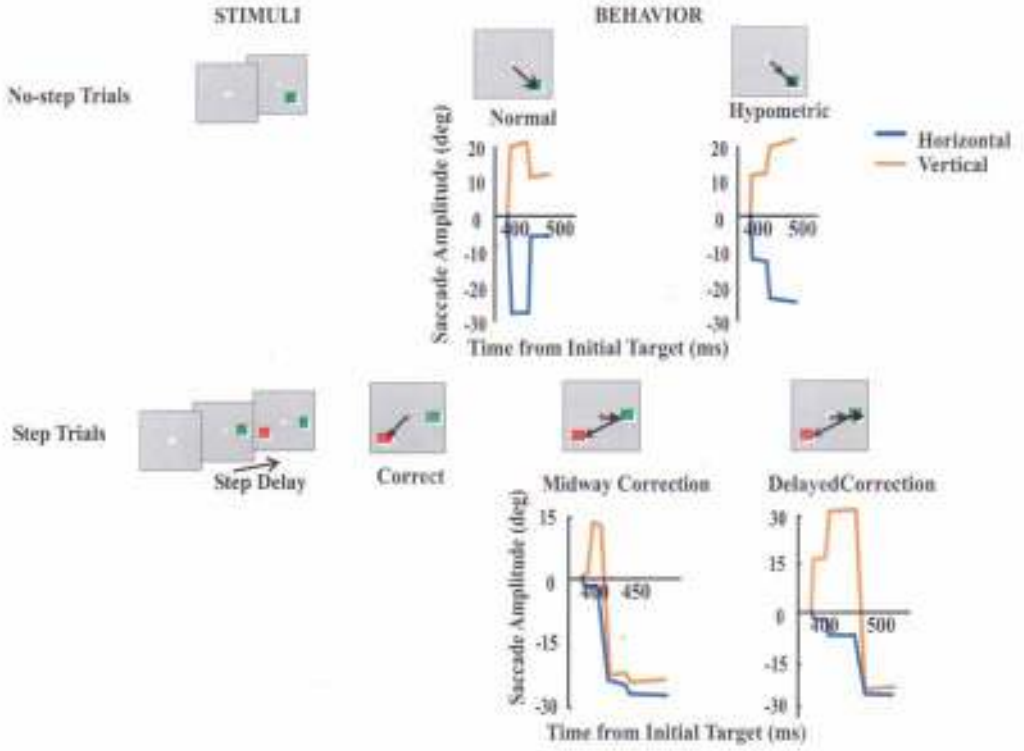


Illustration of the temporal sequence of stimuli and the behaviour in the Redirect Task. The task comprises of no-step trials where a target appears and the subjects respond by foveating the target. Randomly interleaved with the no-step trials are step trials where the appearance of the second peripheral target serves as a " redirect signal" instructing subjects to inhibit the pre-planned saccade and direct gaze to the location of the second target. Targets are located at eccentricities of ~ 30 degrees; so subjects typically directed their gaze in nostep trials with two saccades: an initial primary hypometric saccade followed by a second saccade that foveates the target. In steps trials such saccades may therefore be controlled at different stages: before the initial saccade is made (correct); or after the execution of the primary saccade (mid-way correction); or after the second saccade (delayed correction)

Impaired inhibitory control in patients with Parkinson's disease. Experimental Brain Research (In Press).

Presentation:

Arjun Ramakrishnan, Chokandre S. Ahmad F.U., Sarat Chandra P., Madhuri Behari and A. Murthy, Hierarchical control of action during error correction Indian Academy of Neuroscience. Bangalore, India (2005).

Funding:

Control of visually guided movements in humans. (Dept. of Science & Technology).

Collaborators:

Dr. Faiz-Udin Ahmed, Resident, Dept. of Neurosurgery, AIIMS.

Dr. Sarat Chandra, Assoc. Prof., Dept. of Neurosurgery, AIIMS.

Prof. M. Behari, Dept of Neurology, AIIMS

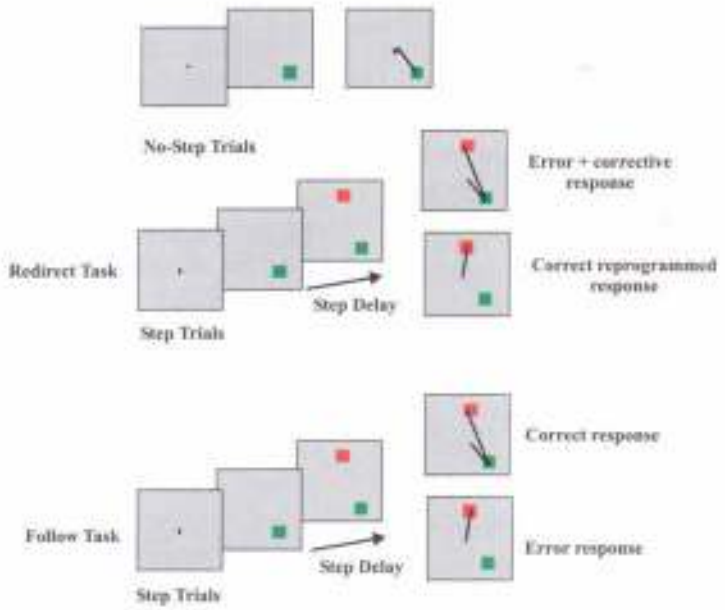
NEURAL CONTROL OF ACTION BY FRONTAL-BASAL GANGLIA NETWORKS

Principal Investigator : *Aditya Murthy*

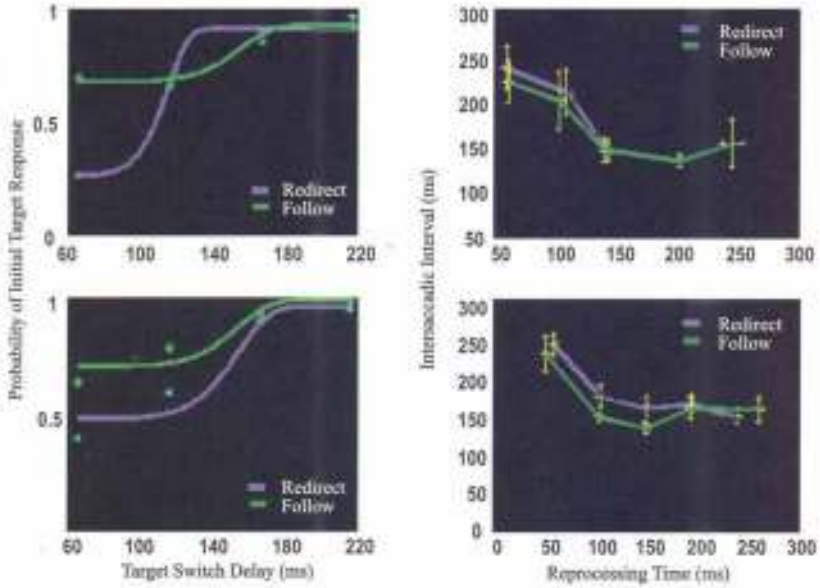
Research Fellows : *Supriya Ray, Arjun Ramakrishnan*

While much progress has been made in understanding the function of sensory and motor networks, the nature of neural networks mediating their interactions remain obscure. As a consequence we have a poor understanding of how sensory information is transformed into a movement. One of the key structures that is thought to play an important role in the transformation of sensory signals into motor commands is the basal ganglia network, which receive no direct sensory input and send little direct output to the spinal cord. Rather, their primary input is from the cerebral cortex and their output is sent back to the cortex via the thalamus.

Within this general scheme the basal ganglia-thalamocortical circuit implements a number of functionally distinct loops involving different modalities in which information from somatomotor, oculomotor, cognitive and limbic systems are processed in parallel. Although the anatomical significance of such loops between cortex and basal ganglia have been appreciated their functional significance remains largely unspecified. Here we use the non-human primate model to study the function of one such loop, namely the oculomotor loop in which information from the frontal eye fields (FEF), is relayed to the basal ganglia, processed and sent to the mediodorsal nucleus of the thalamus and sent back to the FEF. Here we propose to study the sensorimotor transformations in this loop in the context of how basal ganglia thalamocortical circuitry initiates actions, how actions maybe cancelled and reprogrammed by this circuit and



Monkeys performed a double-step task under different instructions: to FOLLOW the appearance of successive targets; or to cancel the initial saccade and REDIRECT gaze to the final target location. Saccade sequences occurred in the FOLLOW and REDIRECT conditions where they represented correct and corrective behavior, respectively.



Left Panels: Representative performance of a non-human primate in two sessions of the REDIRECT and FOLLOW task.

how this circuit may help in the correction of erroneous actions.

To address these issues we are training non-human primates in a modified double step task in which they need to cancel a preprogrammed saccade following the appearance of a new target. As a control, subjects will also perform double step tasks in which they followed the sequence of target steps with successive saccades. The two tasks will be designed such that the identical pattern of saccades yielding correct performance in the follow task is incorrect in the cancel task. This comparison enables us to examine how the FEF/basal ganglia neurons help inhibit actions and corrects errors induced by sudden changes in instructions that render current goals inappropriate.

Publication:

Murthy A, Ray S, Thompson KG, Jacobi SS, Schall JD. Predictive error correction in frontal eye field, J. Neurophysiology (In Review).

Funding:

Neural control of action by basal ganglia networks. (DBT).

NEURONAL PROCESSING IN NORMAL AND IMPAIRED BRAINS

Principle Investigator	:	*V. Rema*
Research Fellows	:	*Zia Ud Din, Manisha Chugh, Anshul Srivastava*
Project Assistant	:	*Kiran Kumar Bali*
M Sc. Student	:	*Rahul Chaudhary*

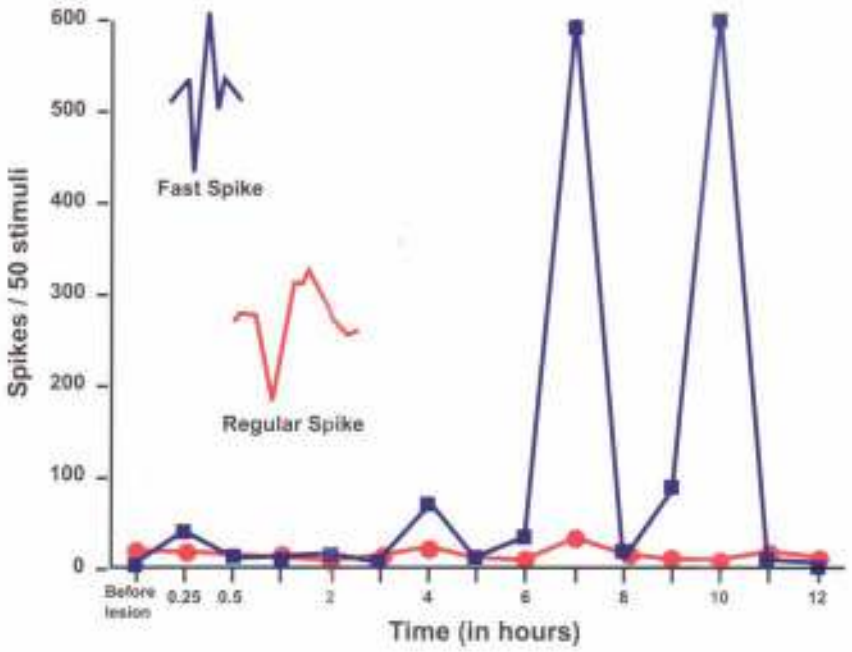
In the normal adult nervous system certain features of neuronal information processing and encoding exhibit plasticity throughout life whereas others retain some rigidity to change. Research interest of our laboratory is directed towards understanding these features and to determine to what extent detrimental influences such as stroke, injury, nutritional deficiencies or ageing influence the modulation of information processing in the sensory system.

The current research focuses on determining the synaptic changes that occur following brain injury. One of the apparent consequences of cortical injury is degeneration of neurons at the site of injury, which in turn could lead to disruption and reorganization of synaptic contacts formed by these neurons. As a result there would be loss of both functional synaptic connectivity and integration of synaptic responses. The ensuing disruption in flow of excitation in the cortical network can be postulated to be the primary reason for disabilities of both neuronal and behavioural functions. Earlier studies showed that lesions in the somatosensory cortex of one hemisphere result in reduction of neuronal responses in the interconnected contralateral somatosensory cortex even after long survival periods. Recovery of these deficits was very limited. To understand these deficits better and to determine the onset we are currently assaying the immediate ongoing changes in neuronal activity patterns that occur following lesions. Spontaneous activity, evoked activity and receptive field are measured by single channel electrophysiological recording using carbon fibre microelectrodes following unilateral focal lesions of somatosensory cortex.

In the rat somatosensory cortex despite the callosal input between both hemispheres being comparatively small we found that several features of neuronal activity were affected in the intact hemisphere contralateral to injury in the initial 12 hours. The spontaneous and evoked activities were affected spatiotemporally. Area exactly opposite the lesion showed very little change in activity pattern for 4-6 hours after lesion. Beyond this time there was rapid modulation in neuronal activity with increase in response magnitude for about an hour followed by rapid reduction in response levels. This increase and decrease seem to be occurring in waves. Interestingly the change in activity levels in the cortical region that surrounds this area (i.e. the region homotopic the edge of the lesion) is different. The modulation in activity pattern starts within one hour with waves of increase and decrease in response magnitudes.

Each layer of somatosensory cortex receives and processes information differently. Neurons in layer IV receive somatosensory information from the thalamus. This information is then relayed to layers II/III and V. It has been shown that use dependent plastic changes occur initially in layers II/III. Hence we recorded neuronal activity from layers II/III and from layer IV before and after focal lesion in the somatosensory cortex. We found that the magnitude of change in layers II/III was about 10 times more than that seen in layer IV.

The effect of cortical injury on the rate at which the neurons can process information was tested by recording responses of the neurons to different frequency of stimuli ranging from 0.3 Hz to 12 Hz. A normal rat at rest moves its



Fast spiking inhibitory neurons seem to be modulated more strongly than slow spiking excitatory neurons as seen by increase in response magnitude.

whiskers at a frequency of 7-10 Hz. The lesioned animal exhibited changes in activity levels only when the frequency of stimulation was 0.3 Hz. This indicated that one of the consequences of injury to the brain is that the neurons require longer time to process the sensory information and the brain is functioning at less than optimum level.

The effect of brain injury on excitatory and inhibitory neurons was examined. Response of fast spiking inhibitory neurons were analyzed separately and compared with that of regular spiking excitatory neurons. We find that the inhibitory neurons are much more affected than the excitatory neurons as shown in the figure above.

The reason for this increase in response magnitude could be due to release of active inhibition being exerted by contralateral hemisphere on neuronal responses. We are investigating this hypothesis. Another possibility for the modulation of activity in the hemisphere contralateral to the injury could be ongoing changes in the molecules that regulate excitation and inhibition. We therefore assayed for changes in levels of NMDAR1, GAD and BDNF after unilateral lesions to somatosensory cortex at 2, 4, 6 and 12 hours post lesion using immunohistochemistry. NMDAR1 expression is high around the lesion edge at all time points whereas there was marked reduction in staining in the penumbra. GAD on the other hand shows increased expression around the lesion both at the edge and in the penumbra of lesion. BDNF is reduced at edge of the lesion and in the penumbra. The changes of these molecules in the lesion site could also be influencing the neuronal activity of the contralateral hemisphere.

Publications:

Rema V, Armstrong-James M, Jenkinson N, Ebner FF (2006) Short exposure to an enriched environment accelerates plasticity in the barrel field (whisker) cortex of adult rats. Neuroscience. 140(2):659-72.

Li, Rema V, Ebner FF (2005) Chronic suppression of activity in barrel field cortex downregulates sensory responses in contralateral barrel field cortex. J. Neurophysiology, 94(5): 3342-56.

Presentations:

"Effects of cortical injury on patterns of cortical activity." The 7th China-India-Japan-Korea Joint Workshop on Neurobiology and Neuroinformatics – 2005 ; November 2-5, 2005 in Xiamen, China.

"Brain reorganization following injuries." Third symposium on "Frontiers in Molecular Medicine". 19-20th January 2006; Organized by Special Centre for Molecular Medicine, Jawaharlal Nehru University New Delhi.

"Injuries and neuronal response." U.G.C. working conference on recent concepts in cell & animal physiology. 10th –11th March 2006 Department of Zoology, Panjab University, Chandigarh.

"Sensory behaviour and sensory information processing in rodents." 6th IBRO School of Neuroscience, Asia Pacific Region held during 8th to 20th August 2005 at NCBS Bangalore.

"The Brain: A Methodological View." Lecture given for Brain Awareness Programme held in Department of Life Sciences, Jawaharlal Nehru University on April 5, 2006

Funding:

Effect of cortical injuries on the neurophysiological, molecular and behavioural functions. (International Senior Research Fellowship from the Wellcome Trust, UK).

Collaborators:

Prof. Ford F Ebner

Vanderbilt University, Nashiville, TN, USA

BRAIN REORGANIZATION FOLLOWING SPINAL CORD INJURIES

Principal Investigator : *Neeraj Jain*

Research Fellows : *Shashank Tandon, Niranjan Kambi, Leslee Lazar*

Project Assistant : *Gunjan Joshi*

Tactile inputs are processed in multiple somatosensory areas in the lower brain stem, thalamus and cortex. These areas are interconnected by both serial and parallel pathways. Motor areas, which initiate and control movements, continuously modify their outputs based on feedback from the somatosensory system. This enables fine control of movements such as during palpation and grasp. My research program aims to understand how the sensorimotor system processes sensory information to enable tactile perception and motor control, and how spinal cord injuries affect functional organization of the system.

We perform unilateral lesions of the dorsal columns of the spinal cord, leaving spinothalamic and other ascending and descending pathways intact. Using multiunit mapping and intracortical microstimulation techniques we determine the effects of these injuries on the somatosensory and motor areas of the brain. These plastic changes in the brain organization are then related to the behavioural effects of the injuries in order to understand the mechanisms of recovery of behaviour and to develop interventions for better recoveries. We use both rat and primate model systems for these studies.

In order to determine the time course of behavioural recovery following unilateral lesions of the dorsal columns of the spinal cord, we use 'tactile stimulation' test and 'grid walking' test. Tactile stimulation test measures the time it takes for the rats to initiate removal of small stickers placed on the forepaws. Normal rats proceed to remove the stickers immediately while the rats

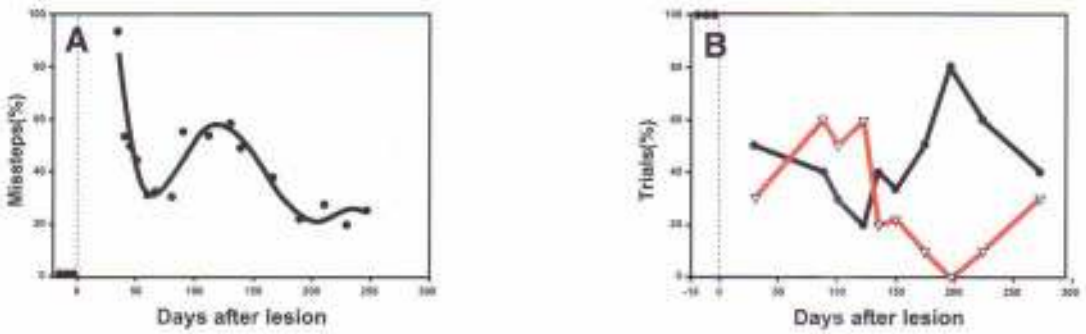


Figure: Performance of rats on grid walking and tactile stimulation tests. (A) Number of missteps as a percentage of total number of steps taken by the forepaw ipsilateral to the unilateral dorsal column lesion. The x-axis shows the number of days post-lesion, zero being the day of the lesion. Prior to the lesion (data shown on the left of the vertical dashed line) there are no missteps. Post-lesion the performance shows a rapid improvement followed by deterioration and a second improvement phase. (B) The tactile stimulation test. The black curve shows the percentage of trials in which the rat makes an attempt to remove a sticker placed on the forepaw ipsilateral to the lesion within 30 seconds. The red curve shows the percentage of trials in which the rat does not make any attempt to remove the sticker for the first 90 seconds. The trials were aborted after 90 seconds. Other conventions, as for 'A'.

with spinal cord lesions take much longer to remove the sticker from the paw ipsilateral to the lesion. In the grid-walking test the rats are allowed to walk on a wire grid. Normal rats place their paws on the wires without any missteps. However, rats with unilateral dorsal column injuries show missteps while placing the ipsilateral deafferented forepaw. The forepaw tends to slip through the openings in the grid. Our tests show that in both of these tests the initial recovery proceeds in phases (see Figure). The first recovery phase is followed by deterioration in the behavioural abilities as assessed by these tests. However, the maximal extent of emerging deficits is much less than seen immediately after the lesion. Subsequently there is a second recovery phase. The data from behavioural tests and the time course of recovery will be used to evaluate the extent of recovery and effectiveness of interventions such as stem cell transplantation and stimulation using implanted epidural electrodes.

We are also continuing our experiments on monkeys. We have transected dorsal columns in four additional adult monkeys. In order to determine behavioural correlates of the brain reorganization following the lesion, we determined the time taken by the monkeys to pick small food items from different wells of the Klüver Board before the lesions were made. The behavioural testing will continue during recovery from the lesion till the monkeys are mapped to determine reorganization of the areas S2/PV, 1, 2 and 4.

Publication:

*Iyengar S, Qi HX, Jain N, and Kaas JH. Cortical and thalamic connections of the representations of the teeth and tongue in somatosensory cortex of New World Monkeys, Journal of Comparative Neurology (Communicated).

* Work done elsewhere

Presentations:

'Reorganization in mammalian brains following spinal cord injuries'. Molecular Reproduction, Development and Genetics, Indian Institute of Science, Bangalore. March 21, 2006.

'Plasticity of sensory and motor systems in mammalian brains'. At 'Recent concepts in cell and animal physiology', UGC working conference at Department of Zoology, Panjab University, Chandigarh. March 10 – 11, 2006

Funding:

Information Processing in the Somatosensory system and the Effects of Spinal and Cortical Injuries (International Senior Research Fellowship from the Wellcome Trust, UK).

Spinal Cord Plasticity and Rehabilitation after Spinal Cord Injuries (Department of Science and Technology, India under Indo-Russian ILTP programme).

EMERGENCE OF PRIMARY AND NON-PRIMARY AUDITORY CORTICAL AREAS DURING LATE FOETAL AND EARLY POSTNATAL AGES IN HUMANS

Principle Investigator : *Soumya Iyengar*

Technical Assistants : *OP Sharma, Arvind Singh Pundir*

Project Assistant : *Subashini Sudarshan*

This study focuses on the development of primary and surrounding non-primary (association) auditory cortical areas in humans. Whereas the primary auditory cortex (area TC) is mainly important for perceiving pure tones, the non-primary auditory areas (areas TA, TB and TD) appear to perceive speech related sounds in adulthood. However the exact developmental time-line of how and when these areas develop is not known. Our immediate goal is to identify these areas using histochemical and immunohistochemical markers in post mortem brain tissue at different stages of development.

We had earlier found that the cytoarchitecture and expression patterns of different calcium binding proteins (CBPs) of an adolescent (14 years of age) is similar to that seen in adults, suggesting that the organization of the auditory cortex is adult-like by this age. In the past year, we have completed studying the pattern of expression of the CBPs calretinin (CR) and calbindin (CB) in the auditory cortex at term (37 and 39 gestation weeks and 1 day old) and at a paediatric age (7 years). We found that there was greater expression of calbindin (CB) in neurons at term than at 7 years or at adulthood in TC. Similarly, CB expression in TA was higher during development (between birth and 7 years), then decreased until adulthood. We also found that CB expression increased in fibres by adulthood in auditory areas TC and TA compared to the younger ages (Figure 1 A, B).

The number of neurons expressing CR also increased between term and 7 years and then decreases in Layers 5-6 by adulthood in TC and TA. We also observed a reticulum of fibres which was positive for CR in layers 5 and 6 of TA and TB at term which were not present at older ages (Fig. 1B).

Our results demonstrate that a greater number of neurons express CB or CR, especially in layers 5 and 6 of the auditory cortex at term than at later ages. Although the functional significance of these changes is not known, it is possible that they reflect changes in the auditory cortex related to learning languages. We have also found that the patterns of expression of both CB and CR can be used to differentiate between the primary and non-primary auditory areas at term. Interestingly, parvalbumin (PV), the third CBP that was present at postnatal ages was not expressed in the auditory cortex in any of the brains at term. Since PV is expressed strongly in foci within the association areas which are important for perceiving speech and other aspects of processing complex sounds, our results suggest that these areas may not be fully formed at birth and may develop later during the postnatal period.

Cortical columns

Cortical columns are a basic anatomical and functional unit of the brain and consist of approximately 80-100 neurons which are arranged as vertical columns, spanning layers 2-6 of the neocortex and are clearly visible in Nissl-stained sections. Earlier studies (Seldon et al., 1981; Galuske et al., 2000) have demonstrated that the intercolumnar spaces are larger in Wernicke's area in the left than in the right hemisphere, which is dominant for language, suggesting that these differences reflect the functions of these areas. Since the smallest auditory cortical areas are specialized for processing different aspects of sound such as speech, environmental sounds and music, we hypothesized that the cortical columns in these areas may be different from the surrounding auditory cortex in which they are embedded. We decided to measure the width of the cortical columns in areas AA and STA which are part of the larger auditory association area TA. In addition, we also decided to compare the size of

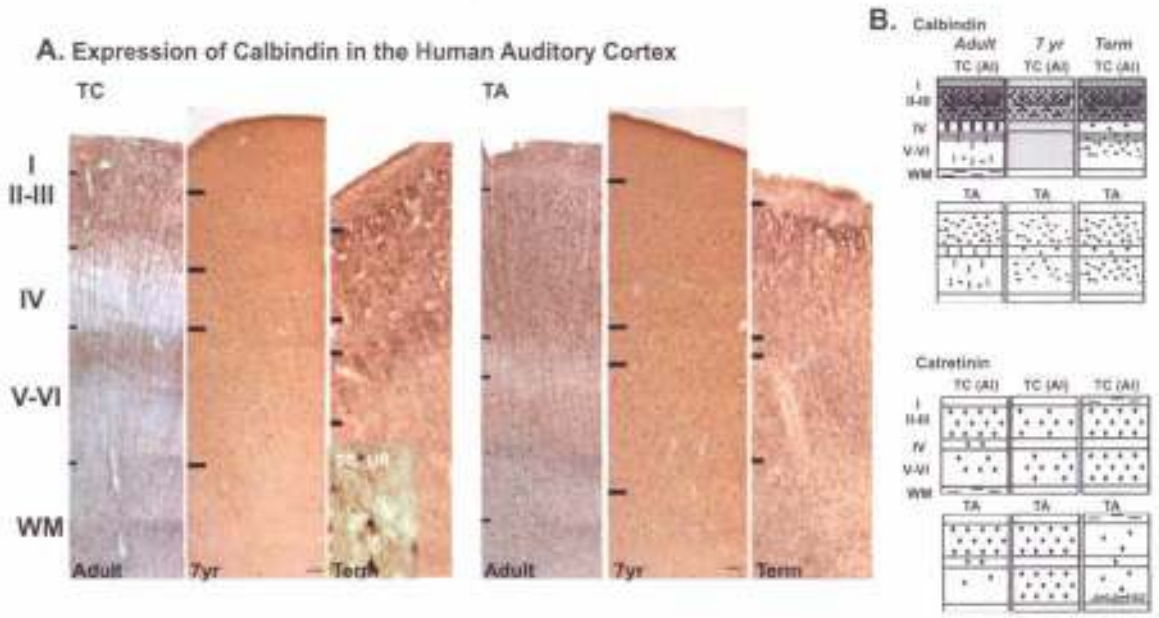


Fig. 1 A. Expression of the calcium binding protein calbindin in coronal sections of areas TC and TA of the auditory cortex in adulthood, at 7 years of age and at birth (term) in humans. B. Schematic of layers I-VI of TC and TA demonstrating the expression patterns of calretinin and calbindin from birth to adulthood in humans. Shading demonstrates positive neuropil labeling and vertical lines demonstrate fibres positive for the calcium binding proteins.

these columns at different ages in different parts of the auditory cortex.

We found that the width of cortical columns ('minicolumns') and the intercolumnar space were greater in the human auditory cortex in adulthood than at term or in an adolescent. Area AA (which is important for perceiving environmental sounds and music) had wider intercolumns and smaller pyramidal neurons in Layer III and V compared to the surrounding auditory association area TA in an adult and an adolescent. In contrast, area STA (which is important for perceiving words and speech) had wider columns and intercolumns than those in area TA in the adult and adolescent and also had large pyramidal neurons in LIII and V compared to TA. However, there were no differences between the width of cortical columns throughout TA at term, suggesting that the smallest auditory areas may not have developed at this age. Although we need a large sample size to validate our results, we have found that measurements of cortical columns can be used for differentiating between the various subdivisions of the auditory cortex including its smallest functional areas.

We will now measure cortical columns at different pediatric age groups for comparison with data obtained from adults. The results from this study will indicate when the smallest auditory areas emerge during development.

Funding:

Emergence of primary and non-primary auditory cortical areas during late fetal and early postnatal ages in humans (DBT).

Collaborators:

Dr. T. Asha, Guntur Medical College, Guntur
Dr. S Shankar, NIMHANS, New Delhi
Dr. S. Bishnoi, Gurgaon Civil Hospital, Gurgaon
Dr. N. Thapar, Gurgaon Civil Hospital, Gurgaon
Dr. S. Sharma, Gurgaon Civil Hospital, Gurgaon
Col. P. Kumar, Army Base Hospital, New Delhi
Dr. PC Dikshit, MAMC, New Delhi
Dr. K. Joshi, PGIMER, Chandigarh

NEUROGENESIS IN THE SONG CONTROL SYSTEM OF ZEBRA FINCHES

Principle Investigator : *Soumya Iyengar*

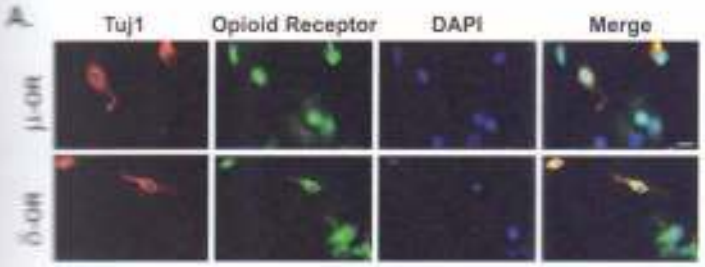
Research Fellow: : *Nazia Khurshid*

Technical Assistant: : *Arvind Singh Pundir*

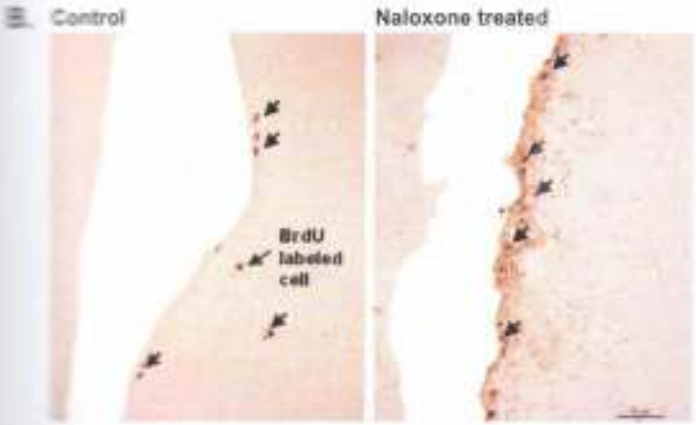
M. Sc. Student: : *Geetika Phukan*

Zebra finches are a species of Passerine birds which are excellent for studying brain-behaviour relationships. In male birds, new neurons are continuously added to the brain throughout their adult life and are incorporated into functional circuits which are important for learning and producing songs. Since zebra finches produce a highly stable or 'stereotyped' song which does not change during adulthood, it can be easily quantified. In addition, the effects of different manipulations in the neural circuitry of zebra finches which is important for the control of singing can be linked to changes in their songs. Since the songs of male zebra finches remain stereotyped throughout their adult life, it is still not known why neurons have to be replaced in the song control regions.

The goal of this project is to study whether changing levels of neurogenesis in song bird brains would change the pattern of their songs. An additional outcome of this project would be to find whether the levels of neurogenesis in adulthood are regulated and maintained at a particular level. The specific aim of this project is to use the opioid system as a tool to change the levels of neurogenesis in the zebra finch brain



A. Colocalization of μ - and δ -opioid receptors with Tuj1 in primary cultures of ventricular zone cells of an adult male zebra finch



B. Blocking opioid receptors with naloxone in vivo causes an increase in cell proliferation in the ventricular zone of an adult male zebra finch compared to a saline-treated control bird.

since it has been shown that blocking opioid receptors increases the level of neurogenesis in mammalian systems.

We found that μ and δ opioid receptors are localized in the VZ and in different brain regions including the song control nuclei in zebra finches of both sexes and at different ages throughout development. Since these receptors are expressed by cells in the VZ and SVZ, it is possible that they may play a role in modulating cell proliferation and/or differentiation either directly or indirectly through their action on other factors. The localization of opioid receptors at different sites throughout the brain has also been confirmed by performing western blots on the brain and VZ obtained from adult and juvenile male zebra finches.

Experiments have also been initiated wherein cells of the VZ and subventricular zone (SVZ) of zebra finches are maintained as primary cultures. Some of these cells expressed Tuj1 which marks neuronal precursors and also expressed the μ- and δ- opioid receptors. Preliminary data obtained by blocking the opioid receptors with the antagonist naloxone in cultured VZ cells also increased neuronal proliferation. We have also injected different doses of naloxone into adult male zebra finches for a period of four days and have found the number of dividing cells increased in the VZ of these birds (Figure 2).

We have already started studying the patterns of expression of the μ- and δ- opioid receptors in adult and juvenile female zebra finches and will compare them with those in male birds. We are also planning long-term experiments on adult male birds to see whether cells generated as a result of the naloxone treatment differentiate into new neurons and if the incorporation of these neurons in song control areas would lead to changes in singing in these birds.

Publications:

*Iyengar S, Qi HX, Jain N, and Kaas JH. Cortical and thalamic connections of the representations of the teeth and tongue in somatosensory cortex of New World Monkeys, Journal of Comparative Neurology (Communicated).

*Kaas JH, Qi HX, Iyengar S (2006) Cortical network for representing the teeth and tongue in primates. Anat Rec A Discov Mol Cell Evol Biol. 288(2): 182-190

*Work done elsewhere

Funding:

Effects of altering the levels of neuronal proliferation on the learning and production of song behavior in male zebra finches (DBT)

REPLACEMENT OF DEGENERATING RETINAL NEURONS BY RETINAL PROSTHESES OR STEM CELLS - A STUDY ON CONNECTIVITY AND INFORMATION PROCESSING IN RETINA

Principal Investigator : *Narender K. Dhingra*

Project Assistants: : *K. Vidhyasankar, Sonia Baloni, K. J. Stanley*

Mammalian retina comprises several well-characterized type of neurons and synapses organized in discrete layers. The primary flow of visual information is from photoreceptors to bipolar cells to retinal ganglion cells (RGCs), and eventually to the brain. This transmission is disrupted in retinal degenerative diseases such as Retinitis Pigmentosa (RP) and Age-Related Macular Degeneration (AMD) where typically photoreceptors are degenerated, but other cells including RGCs that carry information to the brain are relatively preserved. One treatment protocol that holds promise involves replacing the degenerated photoreceptors with a prosthetic device. Retinal prosthesis is a complex electronic gadget surgically implanted in eye to stimulate the surviving retinal cells through an array of miniature electrodes. The underlying assumption is that the device would correctly encode the visual signals, transmit them to the surviving ganglion cells, and thus produce artificial vision in blind patients. Tremendous progress has been made in the field in terms of bioengineering, microelectronics and surgical implantation. However, the functional outcome has been primitive at best: a retinal prosthesis can produce only a subjective visual sensation of spots of light, called phosphenes, which unfortunately is not sufficient to improve the quality of a patient's life. One fundamental problem is that our understanding of how exactly different types of RGCs receive information from their presynaptic partners and how they encode it for transmission to the brain remains inadequate.

Our lab is interested in investigating how different type of RGCs receive, encode and transmit visual information. We characterize physiologically a given cell by recording its electrophysiological responses to a spatio-temporally optimized light stimulus (derived by using a white-noise stimulus and reverse-correlation analysis; Fig. 1), and by measuring its contrast sensitivity using an "ideal observer" analysis. We also characterize the cell in terms of its morphology, distribution across retina, and dendritic stratification using various staining

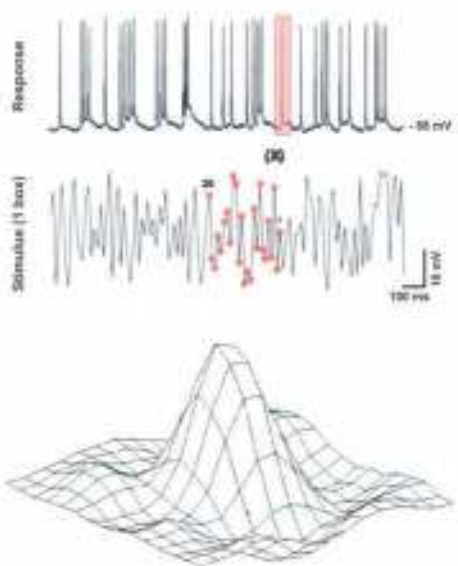


Fig.1. Measuring receptive field profile of a ganglion cell. Electrophysiological response of a RGC (top panel) to a white-noise visual stimulus (middle panel) is recorded, using an intracellular sharp glass electrode A reverse correlation of spike response with the stimulus that just preceded (highlighted in red) at several locations in the visual field gives spatio-temporally optimal receptive field profile for that particular cell, which includes a positive, prominent center and a negative, shallow surround (bottom panel). The optimized stimulus is then presented back to the same cell to characterize it physiologically.

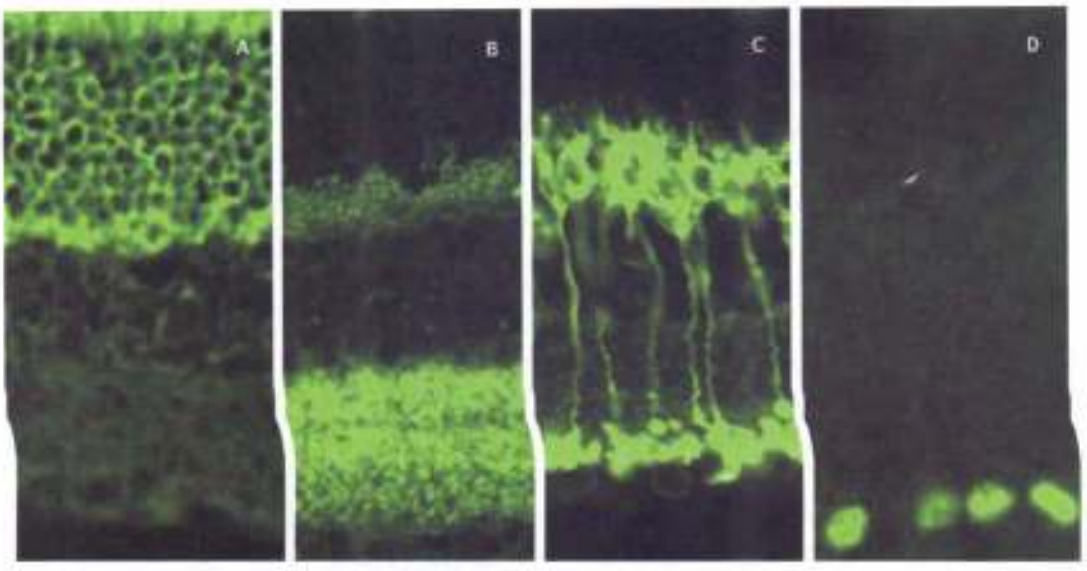


Fig.2. Morphological characterization of specific cells and synapses in retina. A) Photoreceptors are localized with antibody to Recoverin. B) Ribbon synapses in retina are identified in outer and inner plexiform layers with antibody to Bassoon. C) Rod bipolar cells are detected by their expression of PKC. D) A subset of RGCs are identified by antibody to a specific transcription factor. The identified cells are intracellularly injected with a dye to visualize their distribution, dendritic pattern and stratification.

techniques. With this approach we have started to focus on specific retinal cells and synapses (Fig. 2). After we characterize a specific type of RGC we will pharmacologically isolate its bipolar and amacrine cell inputs, and mimic them with injections of electrical current by dynamically adjusting its various parameters.

To be able to apply this knowledge in producing normal-like RGC responses in diseased retina we will inject the optimized electrical current into specific RGCs of a genetically engineered *rd1* mouse, or a drug-induced mouse model that expresses degenerating photoreceptors (Fig. 3). These animal models are also tested behaviorally to assess their visual function. Results from these experiments will have implications for developing retinal prostheses capable of transmitting physiologically relevant visual signals in patients with retinal degenerations.

Recently there has been tremendous interest in treating retinal degenerative diseases, including RP and AMD by stem cell transplantation. Transplantation of stem cells of

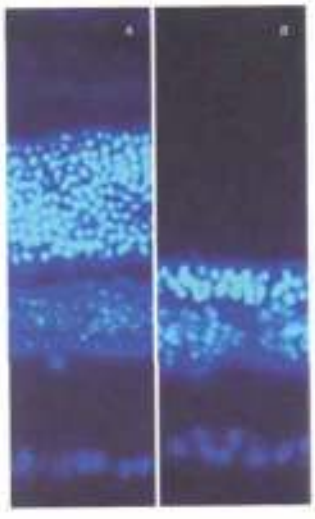


Fig.3. Chemically induced Photoreceptor Degeneration:. N-Methyl-Nitrosourea causes specific degeneration of photoreceptors, resulting in their progressive loss, with no apparent affect on other cell types. A) normal retina, B) 6 days after treatment showing loss of majority of photoreceptors.

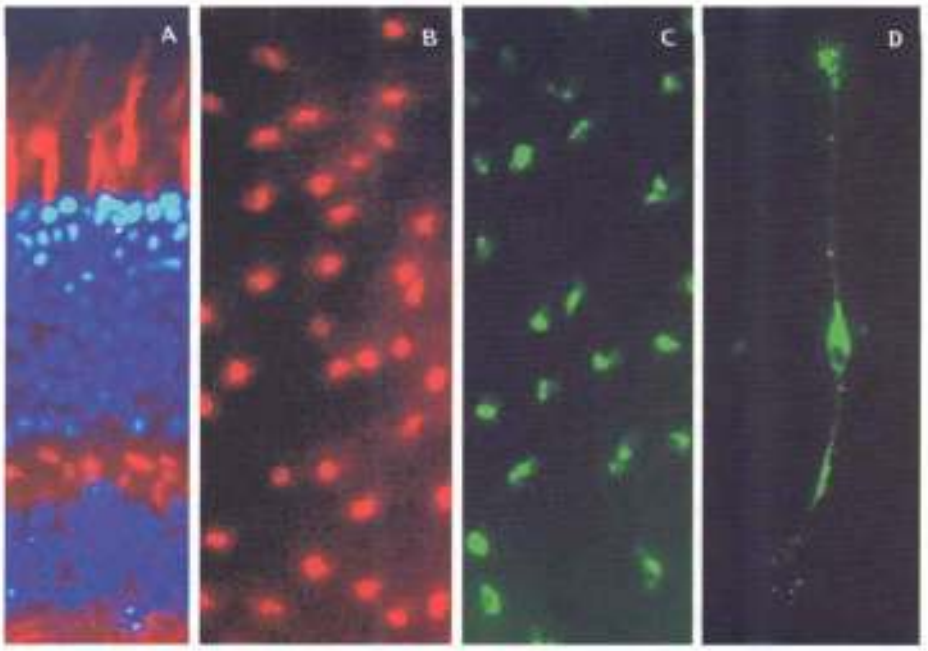


Fig.4 Identification of cone photoreceptors with PNA, in vivo and in vitro. A) Outer segments of cones are identified by staining with PNA (red) in a 10 µm cryosection. The photoreceptor and bipolar soma are stained by DAPI (blue). B & C) Cross sections of cone outer segments stained with PNA in wholemount retina in vivo (B, Texas Red) and in vitro (C, FITC). We are also able to identify cone photoreceptors in dissociated retinal neurons grown in culture (D).

various origins has been attempted in humans and experimental animals and the results are promising. The transplanted stem cells have been shown to differentiate into retinal cells, especially photoreceptors, which integrate with the host retinal neurons. However, evidence that the putative photoreceptors respond to light and make specific synaptic connections has been lacking. A project in our lab envisages to transplant embryonic stem cells from D3 mouse cell line into mouse models of the disease, both in vivo and in vitro. After transplantation we will look for

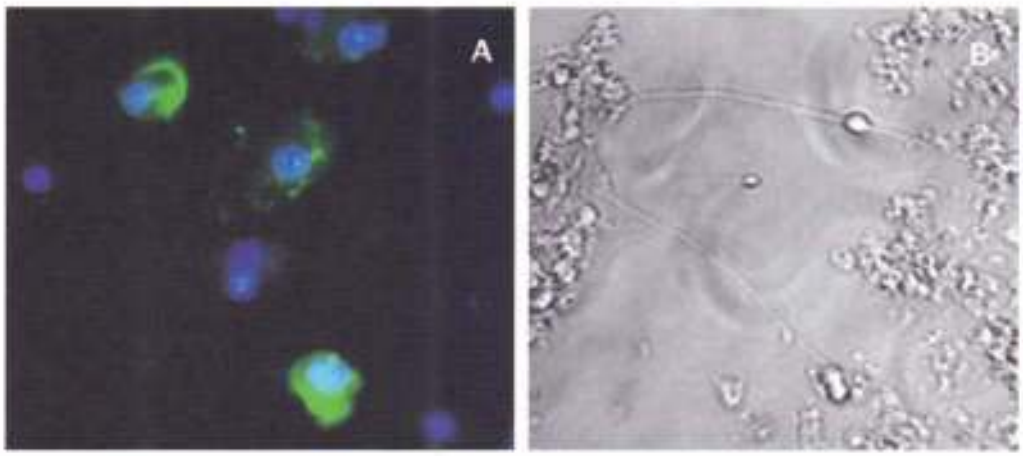


Fig. 5: Retinal neurons in culture. A) Retinal ganglion cells were detected in retinal cultures by expression of *thy1* protein (green; blue–DAPI.) B) Two cell populations were grown in a customized culture chamber with a gap of about 150 µm between the populations. This approach is useful to study specific synapses made by stem cells onto host retinal neurons.

evidence that the transplanted cells migrate to the preferred location, differentiate into photoreceptors, and make identifiable and specific synapses with the host neurons. Since cone photoreceptors in humans mediate the most important components of vision, including daylight and color vision, we are primarily interested in studying if stem cells differentiate into cones, both in vivo and in vitro (Fig. 4).

Furthermore, since dissociated cells grown in culture provide a good model to study synaptic connectivity we have started to grow both the stem cells and normal retinal neurons in culture, and have standardized methods to identify specific cells in culture, especially cones (Fig. 4D) and RGCs (Fig. 5A). In addition, we have developed in-house a culture chamber that allows us to grow and maintain two different populations of cells in adjacent lanes separated by 100-200 µm cell-free areas (Fig. 5B). These chambers are useful to study specific synapse formation between stem cells and host retinal neurons.

Publications:

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* Ying Xu, Dhingra NK, Smith RG (2005) Sterling P.Sluggish and brisk ganglion cells detect contrast with similar sensitivity. J. Neurophysiology. 93: 1-8

* Work done elsewhere

Presentations:

Dhingra NK. Invited lecture on "Retinal Structure and Function - How Neurons Process Information" at 6th IBRO (Asia Pacific) School of Neuroscience held at NCBS, Bangalore, Aug. 2005

Dhingra NK. Popular Science Lecture on "Brain Electricity" in collaboration with Haryana State Council for Science and Technology (HSCST) at Sr. Sec. School Rewari, Aug. 2005.

Dhingra NK. Invited lectures on "Retina: How We Start to See" and "Psychophysics to Biophysics: How Retinal Ganglion Cells Process Visual Information" at 31st Mahabaleshwar Seminar in Modern Biology on "From Molecules to Networks and Behavior" at Mahabaleshwar, Jan. 2006.

Borghuis BG, Dhingra NK, Smith RG, Sterling P. Neighboring Retinal Ganglion Cells Provide Independent Channels for Contrast Detection. Poster # 2278 at ARVO, USA, May 2005.

Funding:

Replacement of Degenerating Retinal Neurons by Electronic Prosthesis: A Study on Parameter Optimization of Electrical Stimulus, and on Signal Processing in Different Types of Retinal Ganglion Cells (DBT).

COMPUTATIONAL ANALYSIS OF SPEECH SAMPLES FROM NORMALLY DEVELOPING CHILDREN

Principal Investigator : *Nandini Chatterjee Singh*

Research Fellow : *Latika Singh*

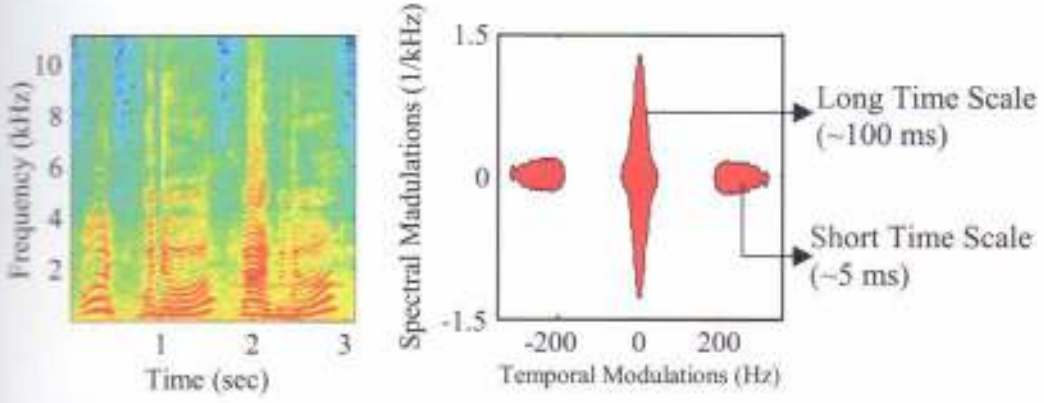
Project Assistants : *Chetan, T. Padma Subhadra*

Speech development milestones provide essential cues to caregivers or doctors, about the underlying cognitive development of children. However, there is hardly any studies of acoustic development in children, which have implications in such approaches. It is thus necessary to obtain speech data from normally developing children acquiring language skills, to enable pediatricians, psychiatrists to develop better diagnostic criteria.

The primary focus of our laboratory is to investigate speech production in normally developing children and children with communication disorders and develop quantitative measures of speech skills. This provides insights into development of speech and language skills in children and could also aid clinicians in developing newer diagnostic criteria. We use various tools of signal analysis.

Speech productions can be characterised by fluctuations in frequency and time. The temporal fluctuations in the speech signal not only encode information regarding rhythm and prosody but also fine linguistic detail. A visual display of this information is provided in a spectrogram (see figure). We notice fluctuations in energy across time and frequency. Spectral modulations (ω_x) are energy fluctuations across a frequency spectrum at particular times and temporal modulations are energy fluctuations at a particular frequency over time. Vocal utteranaces can thus be characterised by spectro-temporal modulations. We capture the spectro-temporal modulations contained in speech utterances and the corresponding power associated with them and display them in a modulation spectrum (MS).

The figure shows such a MS for vocal utterances by an adult directed to an adult. The contour lines enclose the spectro-temporal modulations contained in these utterances and show the presence of two distinct regions. A large region comprising of low frequency temporal modulations (2-50 Hz) and (0- 1.5cycles/Khz) spectral modulation and a second region at high temporal modulation around 200 Hz. The spectral modulations encode information regarding



The figure on the left shows a spectrogram for a spoken utterance by an adult. The figure on the right shows the modulation spectrum of such an utterance wherein temporal modulations are seen at both long and short time scales.

harmonic and formant structure of speech. We currently focus on the temporal modulations. The low frequency temporal modulations (2-50 Hz) encode rhythm and syllabicity, whereas the high frequency temporal modulations (50-500 Hz) encode fine linguistic content like cues to voicing which aid in manner identification as well as marking stress locations.

There is currently no information available regarding the emergence of these modulations in development. We collected speech samples of children in the age-group 4-8 years from different schools to build a database. This is a sensory motor integration phase where rhythms and emotions in speech are established. We obtained data from 220 children in response to three tasks namely picture naming, reading and repetition. We set up modulation spectra for children from different age groups.

Our results indicate age dependence for temporal modulations. The low frequency temporal modulations, which encode information regarding rhythm and prosody is observed at 4 years of age while the high frequency temporal modulations are absent. The presence of the high frequency temporal modulations is seen in the population only at 7 years of age. This encodes fine linguistic aspects of the language and contains cues regarding voicing and place of articulation. This suggests that children achieve adult-like speech productions around 7-8 years of age.

A database of speech samples from normally developing children between the ages of 4-8 years has also been set up.

CHARACTERISTICS OF SPEECH PRODUCTIONS FROM CHILDREN W COMMUNICATION DISORDERS

Principal Investigator : *Nandini Chatterjee Singh*

Post Doctoral Fellow : *Dr. Ramesh Mishra*

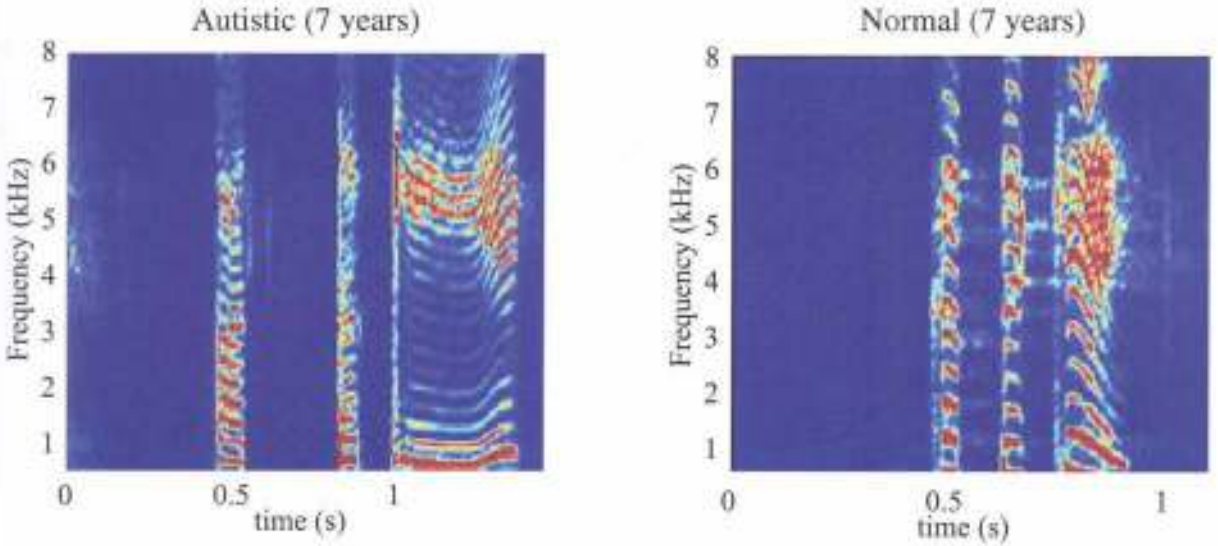
Project Assistant : *Vishnudev Ramachandra*

We have currently obtained speech samples from children with autism. It has been reported that speech and language skills are delayed in children with autism. Though there have been studies showing differences in perception there is hardly any data on speech productions from children with autism.

We obtained vocal utterances and calculated various spectral and temporal parameters like durations and formant frequencies. We compare these with age matched controls and find differences.

Figure shows a comparison of the same speech utterance from a child with autism and an age-matched normal child. We see differences in the total duration of the utterance between the two cases. Differences are also seen for the time taken for each word utterance and for the pauses between words. We are currently analyzing all the samples we have obtained to study this effect in other children with autism too.

We have also set up modulation spectra and are currently comparing these with the control population.



Spectrographic display of the phrase 'cut the cake' as uttered by a child with autism (left) and a typically developing age matched child on the right.

Publications:

Singh L, Shantisudha P, Singh NC. Developmental patterns of speech in children. J. of Applied Accoustics (In press)

Ramachandra V, Kumar BN, Singh NC. Complexity in sound. Physical Review Letters (submitted)

Singh L, Singh NC. Phonological development in typically developing children. Development Science (submitted)

Presentations:

Invited seminar entitled 'Developmental patterns of speech in children', seminar on 'The Cochlear and Beyond' organised at NIMHANS, 28-29th January 2006.

Invited seminar entitled 'A new computational approach to study speech impairments in children', at "Dynamics Days", School of Physical Sciences, Jawaharlal Nehru University, New Delhi, November 2005.

Computational tools to study neural data, IIT, Mumbai, workshop on Computational Neuroscience. October 2005.

Funding:

A Computational Analysis of Speech Impairments and Development of Subsequent Therapies (Ministry of Communications and Information Technology and Intramural support).

Collaborator:

The project on children with autism is being carried out in collaboration with Dr. Shobha Srinath and Dr. Shivshankar from NIMHANS, Bangalore and Dr. Amit Sen from Sitaram Bhartia Institute for Science and Research, New Delhi.

NON-EQUILIBRIUM INFORMATION THEORY AND SPATIOTEMPORAL NEURAL PROCESSING

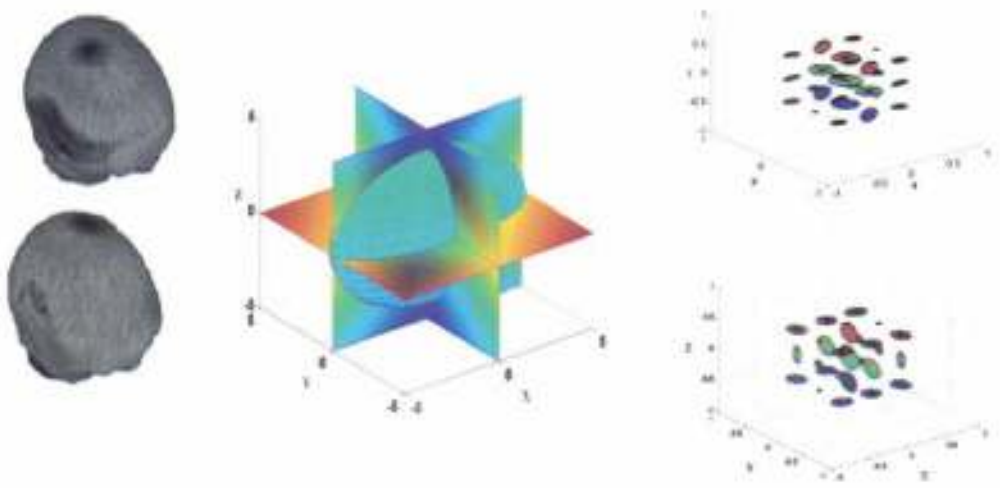
Principal Investigator : *Prasun Roy*

Research Fellow : *Kh. Budhachandra Singh*

Comprehending how information transmission and connectivity occurs across the brain is a fascinating problem of neuroscience, that bears directly on the problem of how the brain thinks. There are multiple modes (multiplexing) of information transmission through a channel under more intensive or demanding conditions requiring high throughput of information or activation. Customary theoretic models cannot satisfactorily account for information transmission during such conditions as neural plasticity or high intensity adaptation, or in clinical hyperexcitatory conditions as epilepsy, migraine, neuralgia or tinnitus. One needs a quantitative computational approach that can account for information transmission and its neuromodulation across the brain.

The recent advance of tensor neuroimaging implies a broad general methodology; here one can study various transport processes or flow parameters in the layered anisotropic brain, as diffusion, permeability, electrical conduction and information flow. We have delineated the approach of functional tensor neuroimaging and elucidated tensor maps to describe permeability flux and information flux or connectivity in brain: indeed information flux is the most fundamental currency in neural systems.

We aim to construct an information flow image of the brain, representing it graphically by information flux tensor, a concept adapted from telecommunication engineering. We treat the tensor imaging methodology of the brain from



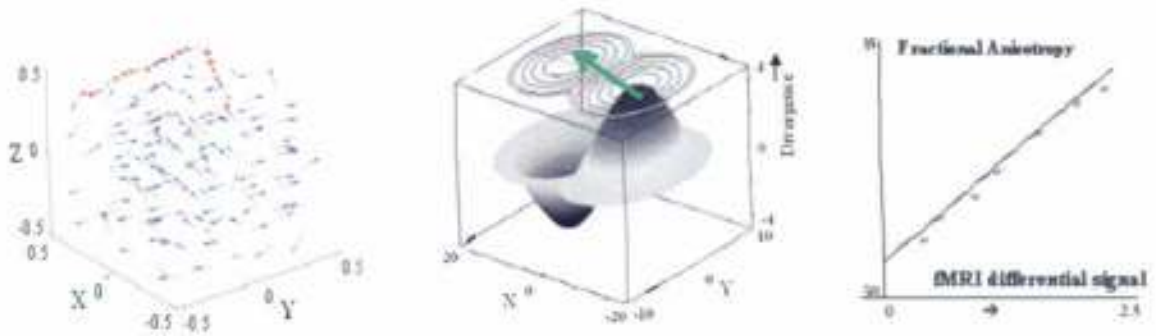
(a) (b) (c)

Fig. 1. (a) The necessity of tensorial analysis: Distribution of electric field map of brain obtained from isotropic brain model (scalar conductivity, upper panel) and anisotropic layered brain model (tensorial conductivity, lower panel). The latter is biophysically correct and difference is to be noted. (b) Nine-component ellipsoid tensor, the generalized transport parameter (as conductivity or permeability), in a voxel. (c) Algorithm testing: Original tensor field voxel-wise (upper), and reconstructed tensor field at low sampling number (lower). As sampling number increases, the reconstructed field increasingly resembles the original field.

two converging approaches, the intrinsic approach (using thermodynamics of flow tensor) and the explicit approach (using scalar projections of flow tensor). In the explicit approach, we use a tensor tomographic methodology using backprojection algorithms and obtain the tensor field voxelwise across the volume of interest. We simulate the tensor reconstruction using a 33 sampling, then a 55 sampling, whereby the accuracy increases as sampled points increase. It is found that the reconstructed tensor field closely matches the original tensor field in the object. One can also find the conductivity tensor field of brain, and using surface potential recordings (EEG field map) we can find the precise location and intensity of electrical focus in brain, an approach that can be useful in accurate epileptic source localization (fig. 1).

In the intrinsic approach, we consider diffusion transport tensor analysis, from which we formulate an axiomatic model of generalized transport tensor using irreversible thermodynamic relationship. Using permeation tissue model for the brain, we obtain a normalized relationship between eigenvalue of diffusivity tensor, conductivity tensor and information flux tensor. By tensorline voxel tracking algorithm, we construct the schema of flux mapping across brain tissue (Fig.2a). Divergence analysis indicates the deterministic direction of neural causality, i.e. which area M causes excitation in which area N (Fig.2b). Our approach predicts linearity between tensorial directionality (fractional anisotropy of diffusivity) and synaptic information transmission (fMRI differential signal) and we elucidate corroborating experimental evidence from occipital cortex (Fig. 2c).

The advantage of the divergence approach is that it is a deterministic approach to neural causality, in contrast to a probabilistic approach that is followed in usual models to outline functional connectivity based on statistical coherences or correlations. The convergence of the intrinsic and explicit approaches corroborates the ready applicability of our methodology to signal transmission. The transmission tensor image of brain can enable a precise functional understanding and location of compromise in neurological or psychiatric disorders, and this can help to delineate dynamic connectivity and to monitor the efficacy of therapy.



(a) (b) (c)

Fig. 2: (a) Tensorline algorithm to track transport tensor voxel-wise across 3-D brain tissue (b) Direction of causality from divergence analysis: arrow (c) Linear relationship between tensorial directionality (fractional anisotropy of diffusivity) and information transmission (fMRI differential signal).

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Funding:

Information theoretic analysis of brain connectivity: Tools for clinical applicability (Ministry of Research, Govt. of Italy).

Collaborators:

Prof T R Seshadri, University of Delhi.

Prof Patrizia Baraldi, University of Modena & Reggio Emilia, Italy

APPLICATION OF STOCHASTIC ACTIVATION AND STABILITY ANALYSIS FOR BRAIN IMAGING AND THERAPY

Principal Investigator : *Prasun Roy*

Post Doctorate Fellow : *Vani Kashyap*

Computer Operator : *Ashish Upadhyay*

M. Sc Student : *Tanuj Gulati*

To upgrade the target expediency of neuroradiological processes, whether diagnostic or therapeutic, an innovative approach is offered by stochastic activation, based on the principles of nonlinear dynamics and computational biology. Stochastic activation, noise-aided resonance or fluctuation-induced transition, is a general principle of complex systems applicable to various systems, whether physical or biological, and occurs basically due to the statistical kinetic nature of the components that exhibits probabilistic fluctuations of parameters.

Stochastic activation has been used to enhance various processes relevant to neurobiologists, such as information processing or 1-D signals. Nevertheless the clinical application of stochastic activation effect as a novel technique in neuroimaging or therapy has not been systematically pursued, and the applicability is the aim of our project. An important aim is to use stochastic activation to enhance diagnosis and classification of MR images. We have concentrated on two important areas of clinical imaging, namely neuroproliferative diseases (as glioma) and neurodegenerative diseases (as dementia). For the former, we used a stochastic parameter based on Boltzman entropy, while for the latter we used a stochastic parameter based on topological fluctuations.

Grading of brain tumours as glioma is essential for therapy planning. We first explored the possibility of using the approach of stochastic approach to characterize and classify images of brain tumours, with special attention to glioma. The advantage of the stochastic classification (SC) is that (i) SC does not need expensive spectroscopic coils or software, (ii) SC is immediate and automatic (iii) SC takes into consideration the whole tumour volume without giving scope of sampling errors that arises when discrete small tissue samples are tested. Errors would be minimized if one can devise an approach that takes the whole lesion is taken into

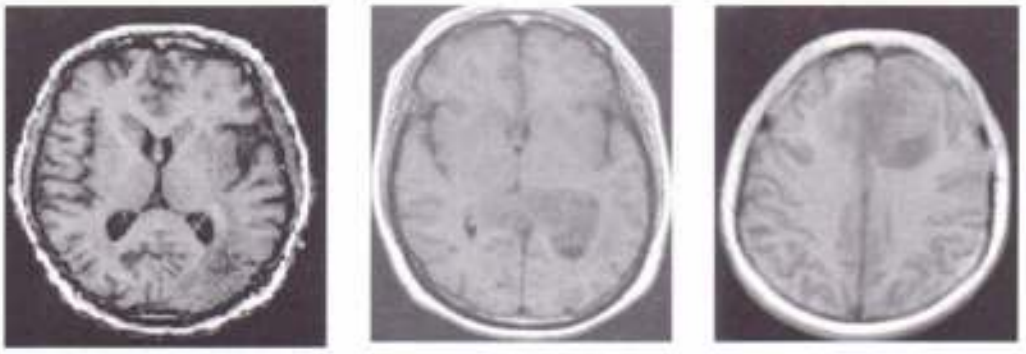

Fig.1. Images of glioma: grade II, III, IV as confirmed spectroscopically. The stochastic classifier categorizes the images as that of medium, upper and highest entropic types, thus effectively grading them.

account, and this is exactly satisfied by stochastic activation as it acts on the entire region of interest. We administer an optimal intensity of stochastic fluctuation to the T1 image and obtain a measure of Boltzmann entropy of image. An entropic-landscape classifier system is constructed to classify the image as Grade I, II, III or IV glioma. The classification logic is accounted for using an entropic heterogeneity model of tissue. A trial of entropic classifier module is then done against a test set of tumour images, and we find that the grade evaluated by minimax entropic classifier corresponds with pathological reports where available (biopsy or spectroscopy) (fig. 1).

Diagnosis of neurodegenerative diseases pose a great challenge in contemporary neurology, a ready automated imaging approach, without expensive software, would be of topical utility.. We have probed the feasibility of pathophysiological classification by utilizing the approach of stochastic perturbation in the geometry of the region of interest. Here we concentrated on an important area of neurology, dementia; we particularly attended to two imaging questions, namely the design of a MRI-based classifier to (i) characterize Alzheimer's Disease, AD, and Huntington's disease, HD, and to (ii) differentiate between Normal Pressure Hydrocephalus, NPH, from Obstructive Hydrocephalus, OH. The stochastic perturbation in scale geometry is characterized by a stochastic topological index L. As alteration in periventricular, ventricular and fascicular region is a significant characteristic of AD and NPH, we decided to see whether the differentiation could be done by the L index. It is found that the L coefficient can satisfactorily distinguish moderate versus advanced Alzheimer's disease. Further, the topological L index can also differentiate between NPH and OH (fig. 2). The observations are theoretically accounted for using a model of parenchymal interstitial pressure heterogeneity. Thus the stochastic topological index can be taken to be a quantitative signature of pathophysiology to help the diagnosis of neurodegenerative processes as Alzheimer's disease and hydrocephalic dementia.

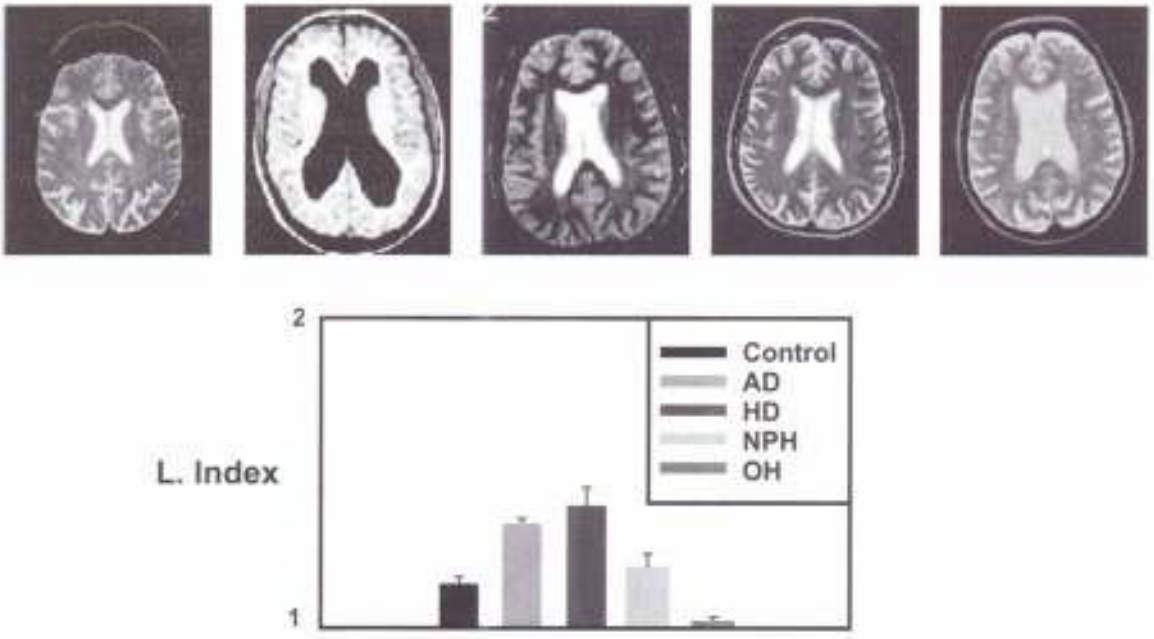

Fig. 2. Upper row: Axial images of normal brain (control), obstructive hydrocephalus (OH), normal pressure hydrocephalus (NPH), Alzheimer disease (AD) and Huntington's disease (HD). Lower row: The corresponding L index of the disorders.

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MENTAL LOAD DEFICITS IN BRAIN DAMAGE

Principal Investigator : *Shobini L. Rao*

The field of Cognitive Neuroscience answers macro level questions of brain functioning. Research in this area addresses how the brain mediates cognition. The brain is able to process information that it gathers from perception and memory using the tools of executive functions. Examples of executive functions are planning, inhibitory control of irrelevant responses, shifting of cognitive sets, fluency of processing stimuli and generating responses.

Executive functions are those processes which manipulate information to enable the organism to set goals and to achieve the same. Attention modulates both perception and executive functions. Behavior is goal directed when the various cognitive processes mentioned above are functioning adequately. Cognitive functions are interrelated. Perception influences memory and both of them are influenced by attention. Executive functions can access or inhibit memory.

The efficiency of executive functions influences perception and memory formation. Thus cognitive processing is an interlinked system with feed forward and feedback influences. Functional modularity is preserved with linkages across functions. The brain mediates cognition by commitment of structures to functions. Sensory cortices mediate the perceptual functions, memory is widely distributed in the cortex and the prefrontal cortex mediates executive functions with contributions from the basal ganglia and the cerebellum. The prefrontal cortices and the sensory association cortices mediate attention regulation. A functional network of anatomically connected brain structures mediates functional modularity.

Patients with neurological and neurosurgical conditions such as head injury, brain tumors, epilepsy and stroke suffer from damage to the brain structures or brain networks which mediate cognition. Consequently these patients complain of inability to attend, poor memory and difficulties in thinking efficiently. My clinical experience of diagnosing and treating brain damaged patients over 2 decades at the National Institute of Mental Health and Neurosciences has shown that a range of cognitive dysfunctions are present in these patients. Associated with the cognitive deficits are disruptions of behavior such as irritability, anxiety and depression. The quality of life of the brain-damaged patients is compromised because of cognitive deficits. Cognitive retraining, which improves cognitive functioning, is an effective treatment of brain damaged patients. Development of clinically effective cognitive retraining programs, which are based on scientific research in cognitive neuroscience, is necessary to reduce the morbidity following brain damage.

A frequent complaint of the brain-damaged patient is an inability to follow rapid speech, work under distraction, and remember even moderately complex instructions. If the patient is forced to process information rapidly symptoms of irritability, anxiety, depression and sleep disturbances follow. The symptoms point to an inability to bear high mental load. Mental load is a sense of effort, which arises when one performs complex tasks or tasks under high levels of speed. Performance of concurrent tasks also leads to mental load. If the conditions leading to mental load persist for a long time, the person develops symptoms of stress as described above.

The brain-damaged patient complains of mental load even when they perform tasks, which are simple for non-brain damaged individuals. Ordinary tasks such as remembering shopping lists, doing routine work, which one is accustomed to in the office or attending lectures in the college require a lot of effort for the brain, damaged patient. This inability to bear mental load is evident in head injury patients. The cause of reduced ability to bear mental load could be a reduced capacity to process information.

Capacity limitation is a basic constraint in information processing. The brain has

tremendous capability to process information in parallel because of its estimated trillion neuronal connections. However, the capacity to process information is restricted to 3-4 bits of information. The bottleneck of capacity limitation needs to be investigated to find its locale in the modular cognitive domain. The project aims to identify the cognitive domain, which is giving rise to the capacity limitation. The results would lead to measuring abnormalities of capacity limitations in brain-damaged patients and their treatment though cognitive retraining.

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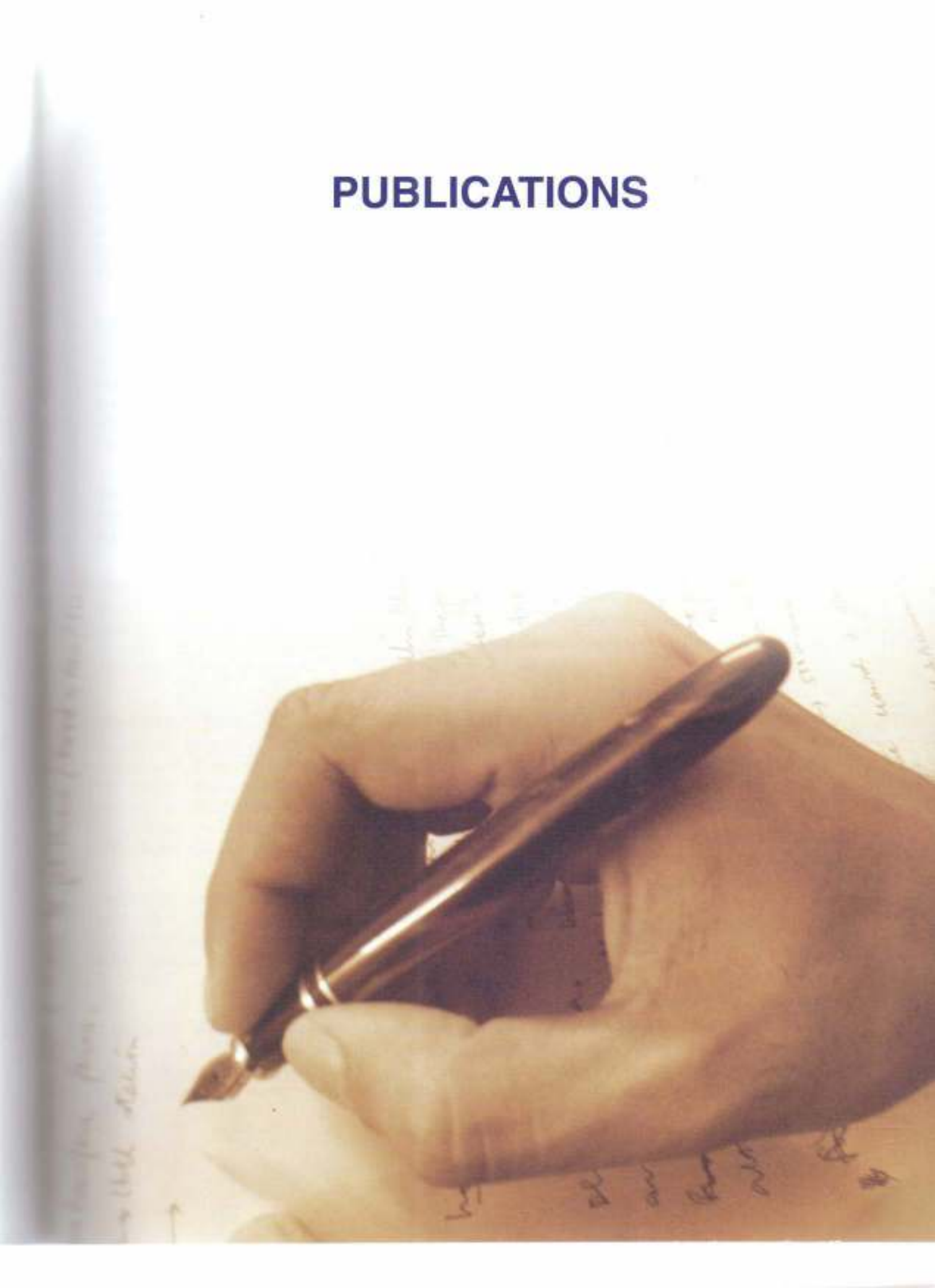

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N. R. Jana. Role of ubiquitin-proteasome system in the pathogenesis of polyglutamine diseases. India-Japan-Korea-China workshop of Neurobiology and neuroinformatics, Xiamen, China, 2005.

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R. P. Kommaddi, V. Agarwal, H.V. Pai and V. Ravindranath. Identification and functional characterization of human brain - specific splice variants of cytochrome P450, the major enzyme involved in metabolism of xenobiotics including psychoactive drugs - Presented at the Society for Neuroscience-2005 Annual Meeting held in Washington, DC, USA, November 12-16, 2005.

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V. Ravindranath. Unique cytochrome P450s in human brain: implication in disease pathogenesis. Invited speaker at the World Congress on Parkinson's disease, Berlin, June 6-9, 2005.

V. Ravindranath. Drug metabolism in human brain by unique cytochrome p450 enzymes generated by alternate splicing. Invited speaker at 14th International Conference on Cytochromes P450: Biochemistry, Biophysics, and Bioinformatics held in Dallas, TX, USA, May 31-June 5, 2005.

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V. Ravindranath. Wired Differences: How Understanding the Brain Can Empower Women on 8th March, 2006 at the workshop entitled "Empowering the Women R&D Professional" on International Women's Day.

V. Ravindranath: Life and the Brain on 3rd March, 2006 at University of Delhi.

V. Ravindranath. Use It or Lose It: How the Human Brain Works on 6th & 7th October, 2005 on Symposium on Excitement of Science at National Academy of Sciences, Allahabad.

V. Ravindranath: Life and the Brain on 1st September, 2005 at Lady Shri Ram College for Women, Delhi.

V. Ravindranath. Brain Research: Recent Advances in Development of Rationale Therapies and Cures for Brain Disorders on 25th June, 2005 at Oration at J.S.S. Medical College, Mysore.

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Pankaj Seth

M. Mishra, S. M. Reddy and P. Seth. HIV-1 Tat Induced Apoptosis in Human Fetal Brain Derived Neural Stem Cells, Symposia on Neurobiology of Diseases, Indian Academy of Neuroscience, Bangalore, India, Dec 2005 (Invited Speaker).

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A. Basu, Infection and inflammation: Are they missing links that determine neuronal fate following Japanese Encephalitis? "Molecular Immunology Forum"-Bhubneswar. (Invited Speaker) (2006)

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"Injuries and neuronal response." U.G.C. working conference on recent concepts in cell & animal physiology. 10th –11th March 2006 Department of Zoology, Panjab University, Chandigarh.

"Sensory behaviour and sensory information processing in rodents." 6th IBRO School of Neuroscience, Asia Pacific Region held during 8th to 20th August 2005 at NCBS Bangalore.

"The Brain: A Methodological View." Lecture given for Brain Awareness Programme held in Department of Life Sciences, Jawaharlal Nehru University on April 5, 2006

Neeraj Jain

'Reorganization in mammalian brains following spinal cord injuries'. Molecular Reproduction, Development and Genetics, Indian Institute of Science, Bangalore. March 21, 2006.

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Dhingra NK. Invited lecture on "Retinal Structure and Function - How Neurons Process Information"at 6th IBRO (Asia Pacific) School of Neuroscience held at NCBS, Bangalore, Aug. 2005

Dhingra NK. Popular Science Lecture on "Brain Electricity" in collaboration with Haryana State Council for Science and Technology (HSCST) at Sr. Sec. School Rewari, Aug. 2005.

Dhingra NK. Invited lectures on "Retina: How We Start to See" and "Psychophysics to Biophysics: How Retinal Ganglion Cells Process Visual Information" at 31st Mahabaleshwar Seminar in Modern Biology on "From Molecules to Networks and Behavior" at Mahabaleshwar, Jan. 2006.

Borghuis BG, Dhingra NK, Smith RG, Sterling P. Neighboring Retinal Ganglion Cells Provide Independent Channels for Contrast Detection. Poster#2278 at ARVO, USA, May 2005.

Nandini Chatterjee Singh

Invited seminar entitled 'Developmental patterns of speech in children', seminar on 'The Cochlear and Beyond' organised at NIMHANS, 28-29th January 2006.

Invited seminar entitled 'A new computational approach to study speech impairments in children', at "Dynamics Days", School of Physical Sciences, Jawaharlal Nehru University, New Delhi, November 2005.

Computational tools to study neural data, IIT, Mumbai, workshop on Computational Neuroscience. October 2005.

Prasun Roy

P. Roy, Multimodal tensor imaging across brain, Defence Scientists Training Course, Institute of Nuclear Medicine & Allied Sciences, Delhi, Jan. 2006.

P. Roy, Neurobiological Networking in the Brain, Systems Biology Conference, Delhi University-South Campus, New Delhi, March 2006.

P. Roy, Information Connectivity in Neuroimaging using a Tensorial Analysis, Symposium on Neuroinformatics & Neuroimaging, Singapore, Nov. 2005.

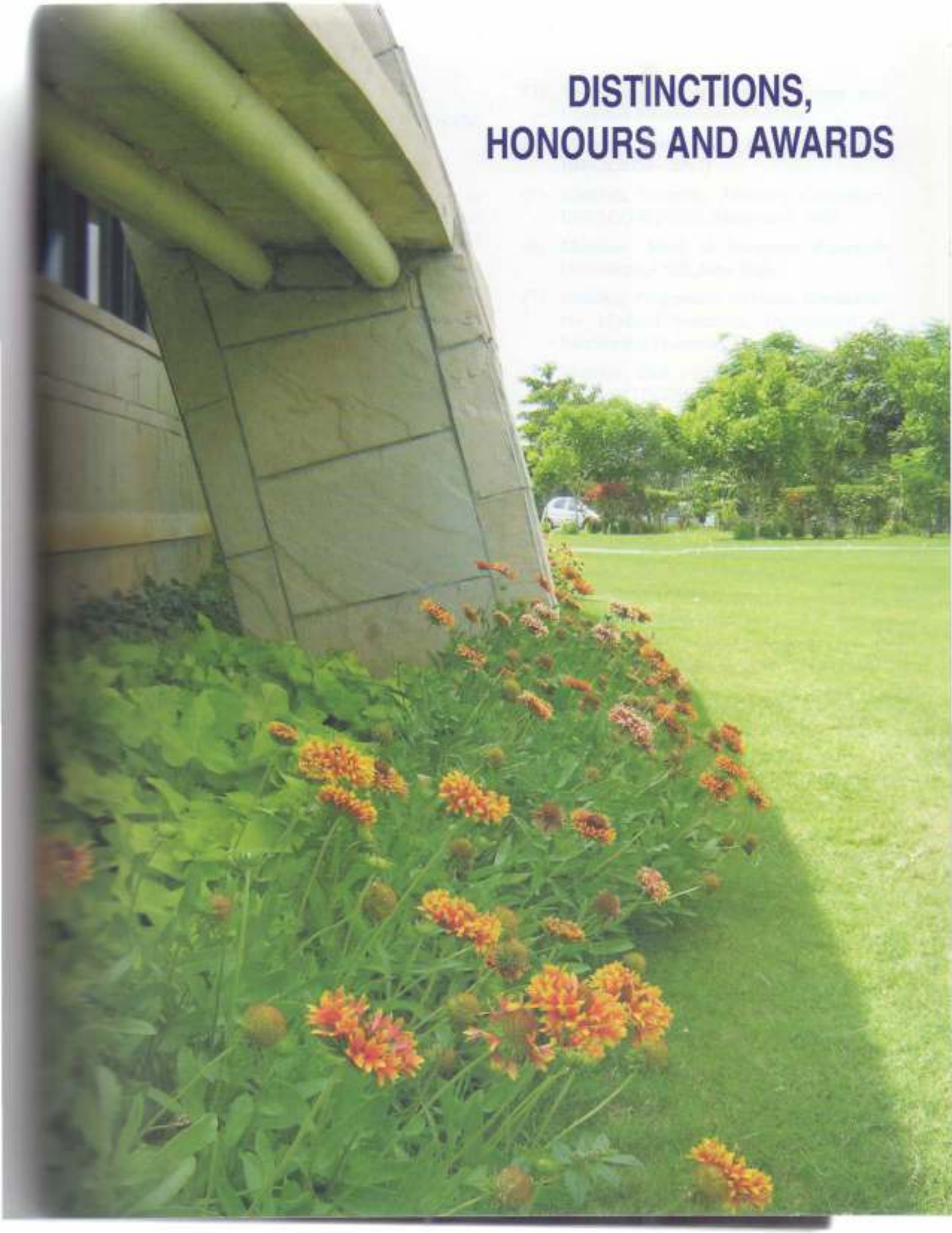
P. Roy, Kh Budhachandra, Deterministic Information Connectivity: Neurodegenerative Disorders, Sree Chitra Institute of Medical Science, Trivandrum, Nov. 2005.

P. Roy, K Vani, T Ray, A Banerjee, Stochastic Resonance Enhancement in diagnostic and therapeutic neuroscience, Indian Academy of Neuroscience, National Institute of Mental Health & Neurosciences, Bangalore, Dec. 2005.

P. Roy, Use Stochastic Activation technique for studying Brain disorders, Jawaharlal Nehru University, New Delhi, Nov. 2005

Shobini L. Rao

S.L. Rao. The nature of cognitive deficits and their measurement. 11th National Conference of Alzheimer's & Related Disorders Society of India, DEMCON 2005, Depts. Of Neurology & radiology, Sree Chitra Tirunal Institute for Medical Sciences & Technology, Trivandrum, November 2005.



DISTINCTIONS, HONOURS AND AWARDS

Dr. Anirban Basu

Nominated and selected as a member 'Molecular Immunology Forum' (2006).

Selected as an advisory committee member to coordinate the functioning of the Proteomic Facility at National Center for Plant Genomics Research (NCPGR).

Ayan Ghoshal was awarded Dr D M Kar prize for his oral presentation at the Annual conference of Indian Academy of Neurosciences, 11-14th December, 2005, NIMHANS, Bangalore.

Dr. Narender K. Dhingra

K. Vidhyasankar was selected for a short-term course on Human Embryonic Stem Cell Techniques and International Symposium on Stem Cells and Regenerative Medicine at Reliance Life Sciences, Mumbai, Feb. 2006.

Dr. P.K. Roy

Travel award from Howard Florey Institute to participate in Symposium on Neuroinformatics & Neuroimaging, at International Conference on Biomedical Engineering, Singapore, Nov. 2005.

Ashish Upadhyay awarded the Best Participant Award, National Workshop on NMR: From Molecules to Mind, North Eastern Hill University, Shillong, May 2005.

Prof. Vijayalakshmi Ravindranath

(1) Foreign Secretary, National Academy of Sciences, India

(2) Member, Governing Council of International Brain Research Organisation

(3) Secretary, Federation of Asian and Oceanian Neuroscience Societies

(4) Member, Asia Pacific Regional Council, IBRO (2004 – 2007)

(5) Member, Scientific Advisory Committee, IBRO CONGRESS, Melbourne, 2007.

(6) Member, Medical Sciences Research Committee, CSIR, New Delhi

(7) Member, Programme Advisory Committee for Medical Sciences, Department of Science and Technology.

(8) Member, Task Force on Chronic Disease Biology (TFCDB), Dept. of Biotechnology.

(9) Member, Life Sciences Research Development Board (LSRDB), Department of Biotechnology.

(10) Member Research Advisory Council (RAC) of the Human Resource Development Group, CSIR.

(11) Member, Standing Committee for Emeritus Scientists and One Time Grant Research Committee, CSIR.

(12) Chairman, Building Committee, Institute of Life Sciences, Bhubaneswar.

(13) Member, Advisory Committee of Special Centre for Molecular Medicine, Jawaharlal Nehru University.

(14) Member of the Senate, Indian Institute of Technology, Delhi.

Membership of Editorial Board of Journals:

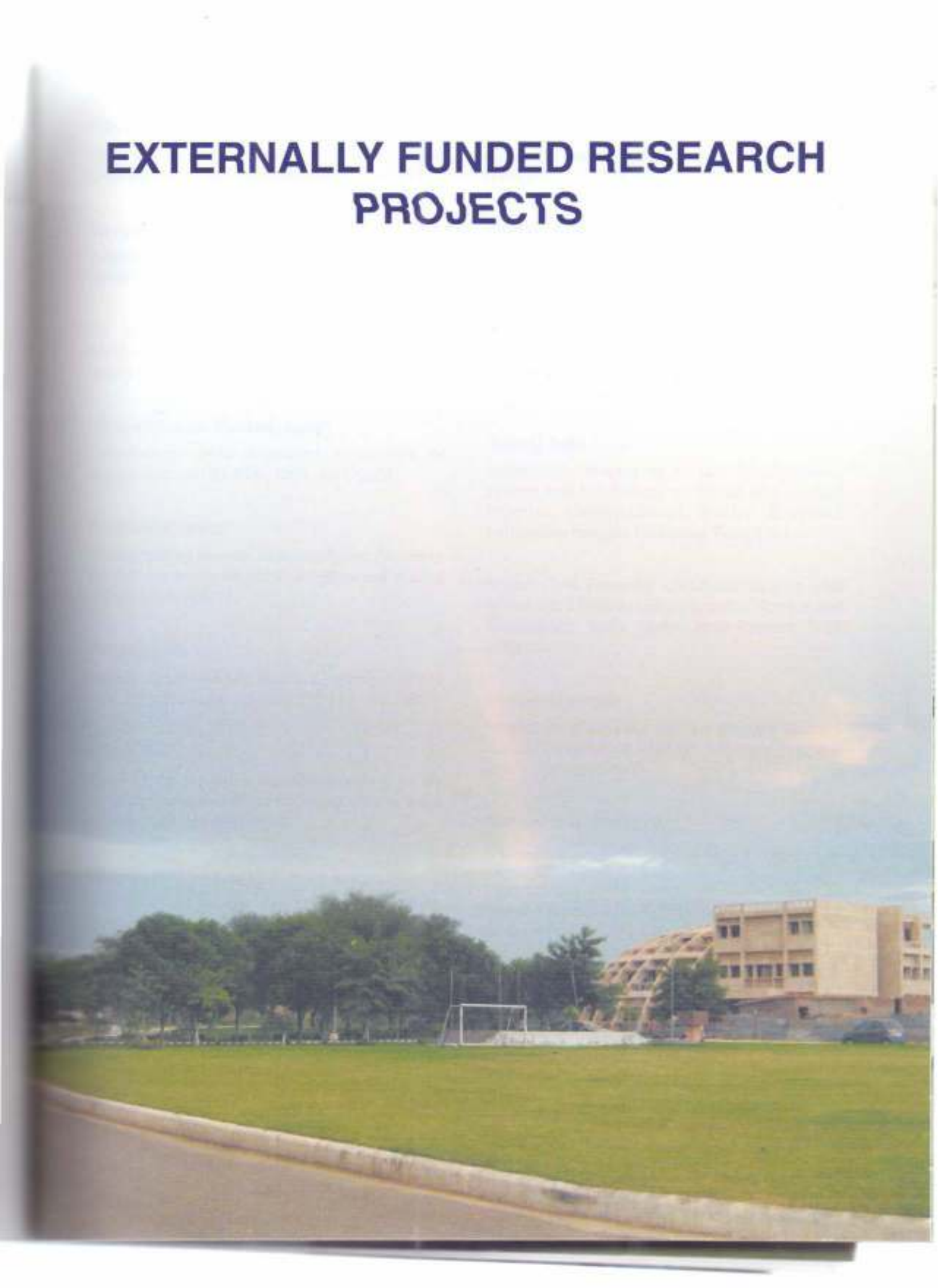
(1) Member, Editorial Board of the International Journal, "Neurotoxicity Research", USA.

(2) Member, Editorial Board, Neuroscience Research, Japan

(3) Member, Editorial Board, Indian Journal of Biochemistry and Biophysics

(4) Member, Editorial Board, Current Science

EXTERNALLY FUNDED RESEARCH PROJECTS



Nihar Ranjan Jana

Molecular mechanism of the pathogenesis of the CAG repeats neurodegenerative diseases (DBT).

Shyamala Mani

Regulation of neurogenesis in the cerebellum (FIRCA-NIH, USA).

To investigate the mechanisms by which embryonic stem cells differentiate into distinct neuronal subtypes (DBT).

Vijayalakshmi Ravindranath

Cytochromes p450 dependent metabolism of drugs in brain (NIH-RO1, USA, MH70054).

Prabodha Swain

Understanding the role of transcription factors in the differentiation of photoreceptors and related retinopathies (DBT).

Pankaj Seth

Cellular And Molecular Basis of Neurobiology of HIV-1C in Human CNS cells (DBT).

Ellora Sen

Study of the signaling cascades involved in the proliferation and differentiation of cancer stem cells in Glioblastoma (DBT).

Shiv Kumar Sharma

Molecular and cellular mechanisms of memory formation by massed and spaced training regimens (DBT).

Anirban Basu

Study of the molecular mechanisms of microglia/macrophages mediated neuro inflammation in Japanese encephalitis (DBT).

Aditya Murthy

Control of visually guided movements in humans (DST).

Neural control of action by basal ganglia networks (DBT).

Rema Velayudhan

Effect of cortical injuries on the neurophysiological, molecular and behavioural functions. (International Senior Research Fellowship from the Wellcome Trust, UK).

Neeraj Jain

Information Processing in the Somatosensory system and the Effects of Spinal and Cortical Injuries (International Senior Research Fellowship from the Wellcome Trust, UK).

Spinal Cord Plasticity and Rehabilitation after Spinal Cord Injuries (Department of Science and Technology, India under Indo-Russian ILTP programme).

Soumya Iyengar

Emergence of primary and non-primary auditory cortical areas during late fetal and early postnatal ages in humans (DBT).

Narender K. Dhingra

Replacement of Degenerating Retinal Neurons by Electronic Prosthesis: A Study on Parameter Optimization of Electrical Stimulus, and on Signal Processing in Different Types of Retinal Ganglion Cells (DBT).

Nandini Chatterjee Singh

A Computational Analysis of Speech Impairments and Development of Subsequent Therapies (Ministry of Communications and Information Technology).

Prasun Roy

Information theoretic analysis of brain connectivity: Tools for clinical applicability (Ministry of Research, Govt. of Italy).

Stochastic Resonance Effect as a new technique for enhancement in Computed Tomography and Tomotherapy (MOD).

Abbreviations:

DBT: Department of Biotechnology, Govt. of India.

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

MOD: Ministry of Defence, Govt. of India.

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

NIH : National Institutes of Health, USA

CORE FACILITIES

DISTRIBUTED INFORMATION CENTRE (DIC)

The Distributed Information Centre (DIC) of the National Brain Research Centre manages computing infrastructure and provides research support in terms of analysis to research at NBRC

Infrastructure :

High speed computing is available in the form of a SUN Enterprise 420R server with four processors, which is connected to T300 storage arrays . The T300 storage array is also used as a repository for neural data and high-resolution graphics. DIC has upgraded internet bandwidth & network tools ensuring high speed network for NBRC. As part of network expansion, campus wide high speed network has been established with multicore fibre optics. Cyberoam box has been implemented at gateway level to provide a secure network. A centralised distributed network has been setup in the form of thin clients, windows servers & Network attached storage.

All the users are connected to this server through the local area network. DIC has balanced manpower with are four programmers focusing on in-house development, seven computer operators assisting in 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.

Research Support

Over the past year, efforts have been made to develop specialized manpower in DIC. Training is being imparted to DIC personnel for the analysis of MRI images. DIC staff is also playing an active role in assisting the speech and language laboratory for acoustic analysis. The DIC staff continues to provide assistance to students and faculty in the analysis of microarray data and DNA sequencing. DIC has also set up a neuroscience portal to enhance information and associations amongst neuroscientists in India and across the world.

New Initiatives

In lieu of the upcoming Imaging facility at NBRC, DIC is involved in integrating the fMRI facility to the existing network and to procure increased storage to handle new image data. We are also making efforts to develop new computational techniques for faster and efficient analysis of neural data which would benefit the neuroscience community .

ANIMAL FACILITY

NBRC has an excellent animal facility, which meets all national and international standards. In order to meet the diverse requirements of scientists at NBRC the animal facility is maintaining and breeding many species of laboratory animals which includes seven strains of mice including transgenic mice, knock-out mice and mutant mice, three strains of rats, rabbits, guinea pigs, zebra finches and non-human primates.

The animals are maintained under controlled environmental conditions as specified in CPCSEA guidelines with temperature between 22 ± 2°C, humidity between 45-55 %, 12:12 hr light- dark cycle and 12-15 air changes per hour with 100% fresh air.

All animal species are housed in cages that meet or exceed CPCSEA guidelines. The outdoor play area for non-human primates has six large interconnected enclosures that provide a flexible layout for optimising enrichment and social interactions. The transgenic, knock out and mutant mice are housed in individually ventilated cage system (IVC) and filter top cages. Feed and water analysis is carried out periodically to ensure nutritional quality and microbial contamination.

The animal facility has a state of art surgical operation theatre equipped with gas anaesthesia machine, heart rate monitor, pulse oximeter, surgical microscope, intensity controlled surgical lights, bead sterilizer and ethylene oxide sterilizer for sterilization of surgical instruments, and an ultrasonic instrument cleaner. The facility is equipped with a necropsy room, perfusion room with a custom made perfusion hood for use with paraformaldehyde, deep freezer and incinerator.

A high degree of hygiene is maintained by practicing regular cleaning and sterilization of cages, water bottles, bedding, feed, and regular disinfection of rooms. Heavy-duty steam autoclave is used for sterilization of the cages, water bottles, bedding and feed. A hot water vapour jet machine is used for cleaning rabbit and primate cages.

DIGITAL LIBRARY

The NBRC Library plays a vital role in the collection, development and dissemination of scientific and technical information to meet the present and future needs of the centre It also provides facilities and support to the Scientists, researchers, students, staff and its networked centers.

The NBRC library has good collection of Journals, books and other relevant research materials on Neuroscience, Biochemistry, Genetics, Molecular Biology, Immunology & Microbiology, Pharmacology and Toxicology, Psychology, Physics, Mathematics, Computer Science and General Subjects. NBRC Library is currently subscribing to 500 journals, of which 393 are online and others are in the printed hard copy formats. Library is also subscribing Newspapers, News Letters. The Collection of NBRC Library is growing rapidly in view of the extensive research and knowledge in the field of Neuroscience and related areas.

The list of collections available at NBRC is now being digitized to provide optimum service and full access to the users. LSEASE software is being used for digitization of collections. It also helps in efficient library operations viz. administration, acquisition, circulation, serial control, cataloguing, information retrieval etc.

The NBRC Library has setup 20 IBM PC-Pentium-IV Computers with ISDN Internet facility in the common room to provide services for use of researchers and students at NBRC. The Library provides access to the most current reference sources available in order to assure the accuracy of information. The Library has been providing electronic access to the subscribed journals within campus portal. It is maintaining digital archives and clippings of the centre.

A total of 240 registered users including Scientists, Researchers, students and other staff use the NBRC library facilities. The NBRC Library also provides the services of "Inter Library Loan" to the 47 Networked Centres at all researchers, scientists and students send their requirement for research material or journal articles through email to NBRC Library (library@nbrc.ac.in) and staff of library download the articles / papers / information and send the same to the requestors free of cost. The library entertains an average of approximately 380 articles every year and such requests are increasing

The NBRC Library regularly evaluates its information services to ensure that the Institution's requirements are met. The Library promotes resource sharing and cooperation activities amongst libraries by providing efficient and reliable means of resource sharing .It does this by providing inter library loan for maximum users of resources, and copies of the documents that are not available in their respective libraries.

The Main Activities of NBRC Library

1. Book Acquisition
2. Periodicals Acquisition
3. Selective Dissemination Information (SDI),
4. Current Awareness Services (CAS)
5. Inter Library Loan
6. Resource Sharing
7. Circulation services
8. Reference Services, Bibliographic services
9. Indexing and Special Services
10. Collects maintains, store and retrieves information and data keeping in the view of evolving needs of its researchers
11. Help to Network Centres.

The main aim to the NBRC Library staff is to provide excellent services to the scientists, researchers, research associates, students of NBRC and all centers associated with the institute.

NATIONAL FACILITIES

DNA MICRO-ARRAY FACILITY

(Genomic microarray R&D program on Infectious diseases and neurological disorders)

The core DNA microarray facility established at National Brain Research Centre has a broad goal of catering the need of high throughput genetic tools required for answering neuroscience related questions posed by the scientist working in the field. The facility provides all basic platforms to execute a microarray experiment using pre-arrayed microarray slides. The facility is available to all scientists across the country inclined to work on neuroscience related fields.

The microarray facility was commissioned in September 2002 at the NBRC interim facility at Gurgaon. Different instruments that form the part of current set-up includes a versatile scanner (Typhoon 9210), both for fluorescence and phosphorescence scanning applications; an automated hybridization station; robotic liquid handling system and Real-Time PCR. The research areas that have been using such microarray experimentation in NBRC includes monitoring changes in the neurodegenerative diseases, changes in nutritional deficient mice brain and understanding role of different signaling molecules in the functioning of retinal photoreceptors. NBRC has also provided hands on training to students and faculty from other institutes. They use both labeling of microarray and subsequent down-stream processing of the data acquired in the microarray experiments. Personnel from DIC at NBRC have been trained to provide basic services required in data acquisition, and statistical normalization of the microarray data.

DNA SEQUENCING FACILITY

NBRC uses the MegaBase TM 1000 DNA Analysis system to perform DNA sequencing. Raw data generated by this system is processed using a sequence analyser to determine the order of base pairs in DNA samples. Base calling algorithms are used to analyse the raw data. The accuracy and length of the sequence generated depends on quality and quantity of the DNA prepared. Once the analyzed sequence is obtained, the sequence is subjected to a BLAST search to verify the cloned gene.

ACADEMIC PROGRAMMES

Ph.D. NEUROSCIENCE

NBRC was awarded Deemed University status in 2002 by the Human Resources Development Ministry based on the recommendations of the Accreditation Council of the University Grants Commission and it is the first Institute of the Department of Biotechnology to achieve this status.

NBRC recruits students for its PhD. program from diverse backgrounds including Masters degree in any branch related to Neurosciences, M.B.B.S., B.E., or B.Tech or Psychology. NBRC recognizes that understanding brain functions requires a fusion of knowledge from multiple disciplines. The admission notification to neurosciences is published through advertisements in widely circulated national newspapers and on the NBRC website and prospective students can also download application forms from the website. Students are chosen after a rigorous screening process and two rounds of interviews with members of the faculty to ensure that only the most deserving are chosen for the Ph.D. programme.

Fifteen students were admitted to NBRC for its PhD programme in 2005. The Ph.D. programme at NBRC has two components – course work (including lab rotations), and research work. The first year of the programme consists of course-work encompassing different aspects of neuroscience. Courses are taught by NBRC faculty members as well as external faculty members from the industry and institutes with expertise in specific areas. These include the major disciplines of neuroscience, such as neuroanatomy, neurophysiology, neurochemistry, molecular neuro-biology, development and regeneration, neurogenetics, systems neuroscience, cognitive neuroscience, systems and clinical neuroscience, and computational neuroscience. Students also do three month long laboratory rotation during this period in three labs, choosing from amongst faculty working in the major areas of molecular, systems and computational neuroscience. In addition students also complete written assignments and present seminars as part of their course-work. Throughout their tenure at NBRC, Ph.D. students are required to attend and present scientific papers related to neuroscience at the weekly Journal Club, which is assessed by NBRC faculty. First year Ph.D. students who successfully complete their coursework and a comprehensive viva-voce examination conducted by a panel of external examiners and NBRC faculty members, can register for obtaining their Ph.D. degrees. Students then join different laboratories at NBRC to complete their dissertation research work. The goal is to train Ph.D. students with an understanding of different aspects of neuroscience integrating information across traditional boundaries.

M.Sc. NEUROSCIENCE

NBRC conducts a two-year course M.Sc. programme in Neuroscience to develop trained manpower having a broad overview of different aspects of neuroscience. This course was first initiated in 2004. Ten students from various backgrounds such as MBBS/BE/B.Sc./B.A. were admitted to NBRC for its M.Sc programme in 2005. The first year comprises of course-work taught mainly by the NBRC faculty. Subjects include theory and practical knowledge of neuroanatomy, neurophysiology, neurochemistry, molecular neurobiology, systems neuroscience, computational and theoretical neuroscience, cognitive and clinical neuroscience.

Experts in different fields from other institutions and universities are also invited to teach students as part of the course work. Students join different laboratories in their second year and work on a research project under guidance of NBRC faculty towards fulfilling one of the requirements for their masters' degree. Students are provided hostel accommodation and a stipend of Rs. 1000/- per month. The students who complete the M.Sc programme become highly skilled candidates for the Ph.D. programme in neurosciences that are currently being conducted in the country. NBRC is one of the first institutes in the country to develop an integrated multi-disciplinary teaching programme in life sciences.

Summer Training and Short-Term Programmes

NBRC has a summer training programme for students of other academic institutions for project work as part of their post-graduate training. Students from different academic institutions and universities in the country were accepted in 2005 for summer training. Their applications were screened and they were selected based on availability of vacancies in different laboratories at NBRC. Each student completed a short project with an NBRC faculty member and learnt research methodologies pertaining to a specialized area of neuroscience. Summer trainees were also encouraged to attend seminars and journal clubs organized at the Institute. The summer training projects give students an exposure to neuroscience and to encourage them to consider it as a future career option. The Institute also conducts joint workshops with various institutions on Computational Neuroscience to raise the level of awareness and problems in Neuroscience amongst students with technical background. NBRC also has a programme to train post-doctoral fellows at various other neuroscience centres. A science awareness camp for students from 5 schools selected by Haryana State Council for Science and Technology was organized at NBRC in December 2005.

COLLABORATIONS AND NETWORKING

INTERNATIONAL COLLABORATIONS

International collaborations help building bridges between Indian neuroscientists and the international neuroscience community through exchange programs and promote excellence in science. In a very short span of time, NBRC has made great strides in establishing such collaborations with various prestigious neuroscience institutions in different countries around the world.

United States

NBRC signed an MOU with the National Institute of Mental Health (NIMH), USA. Significant progress has been made since then and there is communication channel open between scientists from the two countries for exchanging ideas and expertise. An NIH-RO1 grant has also been awarded to Dr. Ravindranath.

Japan

Dr. Nihar R. Jana's laboratory at NBRC is collaborating with Dr. Nobuyuki Nukina of the RIKEN Brain Science Institute, Japan to study the pathogenesis of the CAG.

Russia

Dr Neeraj Jain and other NBRC scientists have a collaborative research project entitled "Spinal cord plasticity and rehabilitation after spinal cord injuries" with Dr Yuri Gerasimenko. Dr Valerie Avelev and other scientists at Pavlov Institute, Russia to develop technology to improve recoveries from spinal cord injuries.

France

Dr. Pierre Gressens and Dr. Shyamala Mani have been awarded an INSERM-ICMR collaborative grant to study the effect of maternal malnutrition on the developing brain of the fetus and also plan to use stem cells for neonatal neuroprotection. In addition, Dr. Hicks and Dr. Prabodha Swain have written a grant proposal for funding under Indo-French programs to facilitate their research collaborations.

Italy

An Indo-Italian agreement on neuroinformatics has been signed under the auspices of which research will be initiated in memory and language impairments in the early stages of Alzheimer's Disease using multimodal imaging techniques (PET, SPET; MRI) and the development of grid computing networks in research areas of common interest. Furthermore, the Italian Ministry of Education and Research has approved for funding a collaborative proposal between Dr Prasun Roy, NBRC, and Dr Patrizia Baraldi, University of Modena and Reggio Emilia, on tensor imaging and brain connectivity.

NETWORKING

A major goal of NBRC is to network the existing neuroscience groups/ institutions in the country and promote multidisciplinary research in neuroscience. This is aimed to prevent unnecessary duplication of the work and facilities already existing. It also facilitates sharing of expertise and available infrastructure for mutual benefit. Networking also 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 because major achievements in neuroscience are being made through a multidisciplinary approach by bringing together scientists working in different disciplines into the main stream of neuroscience and brain research activity. The networking is possible by information sharing through electronic network and identifying "Collaborating" centres for mutual interaction. Currently 47 centres throughout India are networked to NBRC. The following institutions/universities are member of our network activities

LIST OF NETWORK CENTRES:

1. All India Institute of Medical Sciences (AIIMS), New Delhi.
2. Banaras Hindu University (BHU), Varanasi.
3. Bangur Institute of Neurology, Kolkata.
4. Centre for Behavioural and Cognitive Sciences (CBCS), University of Allahabad, Allahabad.
5. Centre for Cellular & Molecular Biology (CCMB), Hyderabad.
6. Central Drug Research Institute (CDRI), Lucknow.
7. Centre for DNA Fingerprinting and Diagnostic, Hyderabad.
8. Central Food and Technological Research Institute (CFTRI), Mysore.
9. Cochin University of Science and Technology, Cochin.
10. Department of Biotechnology. New Delhi.
11. Delhi University, South Campus, Delhi.
12. Dr. A. L. Neurosurgical Centre, Chennai.
13. Indo American Hospital Brain and Spine Center, Kerala.
14. Institute of Cybernetics, Systems and Information Technology, Kolkata.
15. International Centre for Genetic Engineering and Biotechnology (ICGEB), New Delhi.
16. Institute of Genomics and Integrative Biology (IGIB), Delhi.
17. Institute of Human Behaviour & Allied Sciences (IHBAS), Delhi.
18. Indian Institute of Information Technology (IIIT), Allahabad.
19. Indian Institute of Technology (IIT), Mumbai.
20. Indian Institute of Technology (IIT), Delhi.
21. Indian Institute of Technology (IIT), Kanpur.
22. Indian Institute of Science (IIS), Bangalore.
23. Indian Institute of Chemical Biology (IICB), Kolkata.
24. Institute of Nuclear Medicine and Allied Sciences (INMAS), New Delhi.
25. Industrial Toxicology Research Centre (ITRC), Lucknow.
26. Indian Statistical Institute, Kolkata.
27. International School of Photomics, Cochin.
28. Jagadguru Sri Shivarathreeshwara Medical College, Mysore
29. Jawaharlal Nehru University (JNU), New Delhi.
30. Jawaharlal Nehru Centre for Advance Scientific Research (JNCASR), Bangalore.
31. Jiwaji University, Gwalior.
32. M.S. University of Baroda (Dept. of Microbiology and Biotechnology Centre), Baroda.
33. National Centre for Biological Sciences (NCBS), Bangalore.
34. National Informatics Centre (Medical Informatics and Telemedicine Division), (NIC) New Delhi.
35. National Institute of Mental Health & Neuroscience (NIMHANS), Bangalore.
36. Nizams Institute for Medical Sciences (NIMS), Hyderabad.
37. Rajiv Gandhi Centre for Biotechnology, Trivandrum
38. National Neuroscience Centre (NNC), Kolkata.
39. Sanjay Gandhi Post-Graduate Institute of Medical Sciences (SGPGIMS), Lucknow.
40. School of Information Technology, West Bengal University.
41. Shree Chitra Tirunal Institute for Medical Sciences and Technology, Thiruvanthapuram.
42. Sri Venkateswara Institute of Medical Sciences, Tirupati.
43. Tata Institute of Fundamental Research (TIFR), Mumbai.
44. University College of Medical Sciences (UCMS), Delhi.
45. University of Hyderabad, Hyderabad.
46. University of Calcutta, Kolkata.
47. Vidyasagar Institute of Mental Health and Neuroscience (VIMHANS), New Delhi.

INVITED SPEAKERS

S. No.	Name of the Speaker	From	Title of the seminar	Date
1	Prof. Sushanta Dattagupta	Director, SN Bose Centre for Basic Sciences, Kolkata	"The Myth about Einstein"	April 26th 2005
2	Dr. Hari Shankar Sharma	Laboratory of Cerebrovascular Research, Dept. of Surgical Sciences, Div. of Anaesthesiology & Intensive Care Medicine, University Hospital, Uppsala, Sweden	"Pathophysiology of Hyperthermic Brain Injuries and Neuroprotection. Recent Perspectives and Future Strategies"	April 29th 2005
3	Dr. Gary Egan	Principal Research Fellow & Associate Professor, Group Leader, Neuroimaging & Neuroinformatics, Howard Florey Institute, University of Melbourne, Victoria 3010, Australia	"Understanding human mathematical and reasoning ability using fMRI imaging and computational modeling."	April 29th 2005
4	Dr. Ellora Sen	Research Associate at the Dept of Neurology and Neurosciences, New Jersey Medical School, University of Medicine and Dentistry, New Jersey	" Transcriptional Networks and Differentiation: Familiar Terms, New understanding".	May 2nd 2005
5	Dr. Ravinder Singh	Associate Professor, University of Colorado, USA	Bioinformatics, RNA Processing and Sex determination	May 27th 2005
6	Dr. Verrareddy Anantharam	Department of Biomedical Science Iowa State University (ISU), Ames, IA, USA	Role of alpha synuclein in oxidative stress induced dopaminergic cell death: Relevance to the Pathogenesis of Parkinson's disease	July 1st 2005

7	Dr. Parvesh Bubber	Weill Medical College of Cornell University, New York	Abnormalities in TCA cycle in Alzheimer's disease.	Sept 15th 2005
8	Dr. Arun Sripati	Johns Hopkins University	"What does the hand tell the brain? A model for mechanoreceptive afferent responses."	Oct 24th 2005
9	Dr. Olivier Faugeras	Research Director, INRIA France	"The new frontier: observing and modeling the human brain"	Nov 25th 2005
10	Prof. Hari Eswaran	College of Medicine, University of Arkansas, USA	"Development of Visual system in the fetal brain"	Dec 6th 2005
11	Dr Tej Kumar Pareek	Functional Genomics Section, National Institute of Dental and Craniofacial Research, USA	CDk5 activity regulates pain signaling	Dec 14th 2005
12	Dr. Mani Mahadevan	University of Virginia, USA	"RNA toxicity a novel disease paradigm: A reversible mouse model of RNA toxicity and cardiac conduction defects"	Dec 20th 2005
13	Mr. C.S. Shashikant	Associate Professor, Molecular & Developmental Biology, The Pennsylvania State University	"Comparative regulatory analysis of a vertebrate Hox gene"	Dec 22nd 2005
14	Dr. Raj Puri, MD, PhD	Director, Division of Cellular and Gene Therapies, Office of Cellular, Tissue and Gene therapies, FDA/Center for Biologics Evaluation and Research, NIH Building 29B Room 2NN20, 29 Lincoln Drive, HFM 710, Bethesda	"Expression and targeting of Interleukin-13 receptor for Brain Tumor therapy"	Dec 29th 2005

15	Dr. Anand Kumar	Neuropsychiatric Institute, Los Angles, CA, USA	"Late-life clinical depression-clinical and neuroimaging correlates."	Jan 4th 2006
16	Dr. Mriganka Sur	Sherman Fairchild Professor of Neuroscience, Department Head, Department of Brain & Cognitive Science, MIT	How brain wiring creates brain function	Jan 10th 2006
17	Dr. Anuradha Ratnaparki	Division of Biology, California Institute of Technology, California, USA	"Folded Gastrulation: a secreted ligand involved in embryonic axon guidance and glial morphogenesis in Drosophila."	Jan 12th 2006
18	Prof. Matsumoto Nobuyoshi	Kyushu Institute of Technology, Graduate School of Life Science and Systems Engineering, Department of Brian Science and Engineering	"Neural Mechanisms underlying behavioural control by the optic tectum of the frog."	Jan 20th 2006
19	Dr. Amiya Ghosh	University of Connecticut Medical School, Farmington, CT	"Fibroblast Growth Factor(FGF-2) mediated signal transduction in primary oligodendrocytes- its implications in multiple sclerosis"	Jan 25th 2006
20	Dr. Ted Rothstein, MD	Assistant Professor of Neurology, The George Washington University, USA	"New concepts in the pathophysiology and treatment of Parkinsons's disease"	Jan 27th 2006
21	Dr. Rama Jayasundar	Department of NMR, AIIMS, New Delhi	"Magnetic resonance and neuro-spectorscopy"	Jan 31st 2006
22	Dr. Sayan Pathak	University of Washington, Seattle	"Three dimensional digital atlas based neuroimage informatics"	Feb 14th 2006

23	Dr. M.V. Padma Srivastava	Professor, Department of Neurology, AIIMS, New Delhi	"Hyperacute treatment of ischemic stroke: Present strategies and future avenues."	March 2nd 2006
24	Dr. Rajesh Varma	University of California Los Angeles, CA, USA	"Magnetic Resonance Imaging in Patients with Congenital Central Hypoventilation Syndrome and Heart Failure"	March 6th 2006
25	Prof. Juergen Kurths	University of Portsdem, Germany	"Complex Synchronization -a general approach to analyze physiological and neuroscientific data."	March 9th 2006
26	Dr. Harish C Pant	Chief, Cytoskeletal, Regulatory Protein Section, Laboratory of Neurochemistry,NIH, Bethesda	"Cyclin dependent kinase 5 (Cdk5) : Role in nervous system function."	March 30th 2006

MEETINGS AND WORKSHOPS

WORKSHOP ON COMPUTATIONAL NEUROSCIENCE 2005

The course on Computational Neuroscience 2005 conducted at IIT Bombay provided a detailed exposure to basics of neuroscience and computational methods. Computational models and experiments addressing information processing at various levels such as cellular, systems and cognitive were the central theme of this course. Additionally, related topics in Artificial neural networks, Neuroimaging, Machine learning and AI were covered. NEURON, Matlab, Genesis, and SciLab toolkits were used for demonstrations and exercises to gain a deeper understanding of the concepts and methods introduced in the course. Participants were assigned mini-projects involving computer simulations to be completed by the end of the course. Eminent researchers working in various institutions such as NBRC, NCBS, IIT Bombay, IIT Delhi, IIT Madras, University of Hyderabad, and Johns Hopkins University (USA) delivered lectures. The course was planned with 5 theory sessions every day between 9:30am and 4pm, followed by 2 lab sessions between 4:30 and 6:30pm. Thus the course comprised a total of 50 one-hour theory sessions and 20 one-hour lab sessions, adding up to a fairly intensive week for the participants. The speakers and participants represented all regions of our country and this was very significant and gratifying.

SECOND FOUNDATION DAY CELEBRATION

The 2nd Foundation Day of NBRC was celebrated on 16th December, 2005 at NBRC premises. The chief guest Dr. M.K. Bhan delivered an inspiring speech to the students and faculty members. The day was also declared an open day. Around hundred students from five schools in Haryana were invited to NBRC on open day. They took keen interest in gathering knowledge on the brain and its functions. A quiz programme on the brain was conducted and two students represented each school. Prizes were

distributed to the winners and runners up teams and participation certificates were given to all participants. A Poster exhibition was also organized for the public and students depicted on posters the various aspects of research that was being undertaken at NBRC. As part of Foundation day rank certificates were handed over to the 1st and 2nd rank holders for the M.Sc-2004 and Ph.D-2004 batch.

THE LATE DR. B. RAMAMURTHY MEMORIAL LECTURE

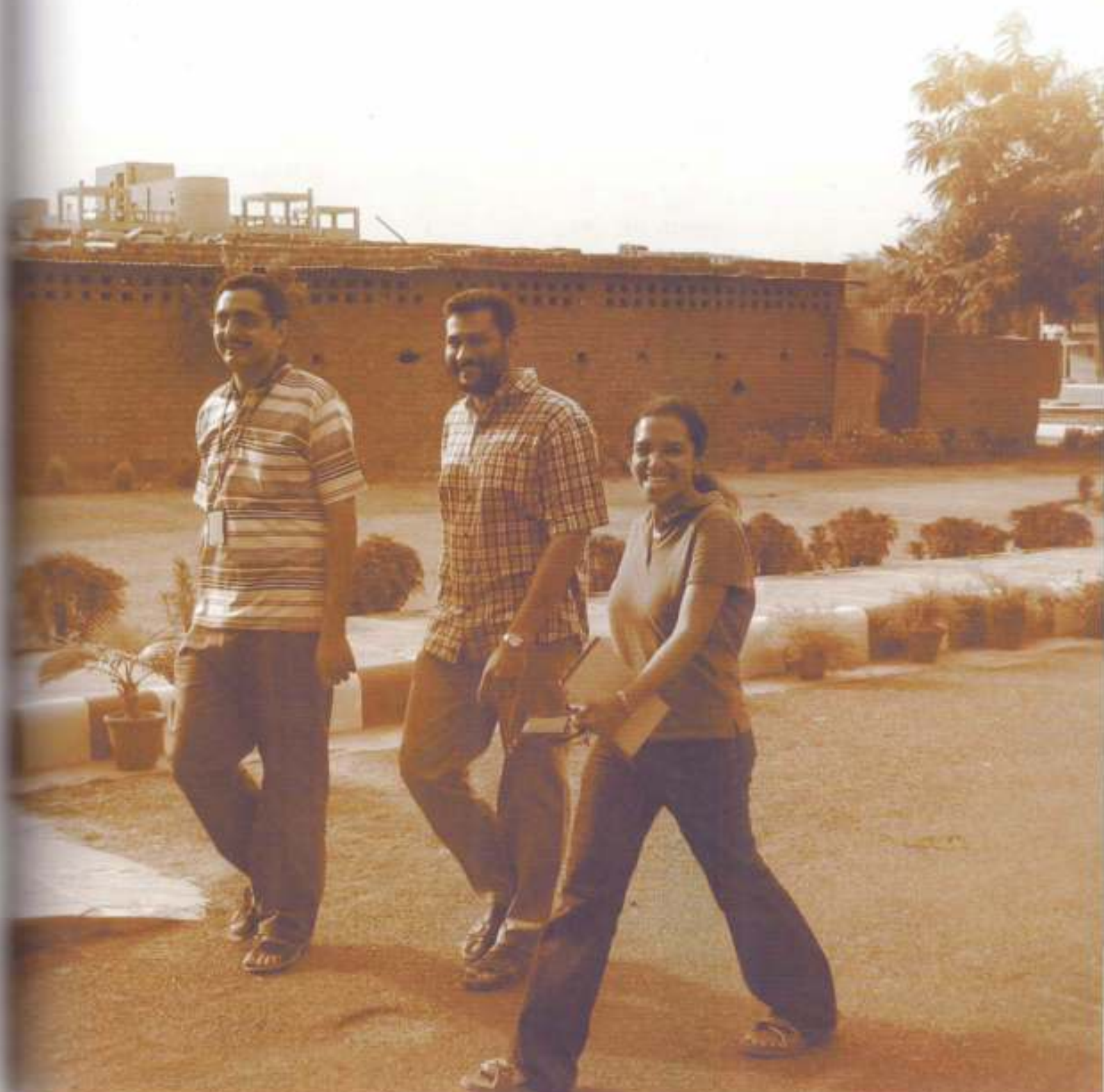
The National Brain Research Centre initiated a lecture series in memory of the late Dr. B. Ramamurthy who played a pivotal and important role in setting up this center. The first lecture in this series was delivered by Prof. P. Balaram, Director, Indian Institute of Science, Bangalore on the 30th of January 2006, which was also the birth anniversary of the late Dr. B. Ramamurthy at the Institute campus in Manesar.

Prof. P.N. Tandon, the Chairman of the NBRC Society presided over the function. Dr. B. Ramamurthy's son Dr. Ravi Ramamurthy also attended the function and spoke on the occasion. Prof. Tandon and Prof. Ravindranath, the director of the institute both reminded the gathering about the important role played by the late Prof. B. Ramamurthy in the setting up of a centre devoted to research in Neuroscience.

In his scientific oration, Prof. Balaram discussed the isolation and characterization of novel peptides from venom extracts of marine cone snails. He showed how these peptides were able to specifically target subtypes of ion channels that are very closely related.

The lecture was widely attended by members of the scientific community besides the staff and students of the Institute.

PEOPLE AT NBRC



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