

NATIONAL BRAIN RESEARCH CENTRE

NH-8, Manesar (Haryana), India



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CONTENTS

Mandate	-----1
Objectives	-----1
From the Director's Desk	-----3
Research Reports	-----6
Dr. Nihar Ranjan Jana	-----8
Dr. Shyamala Mani	-----16
Dr. Vijayalakshmi Ravindranath	----- 21
Dr. Prabodha Swain	-----28
Dr. Pankaj Seth	-----34
Dr. Ellora Sen	-----39
Dr. Shiv K. Sharma	-----45
Dr. Anirban Basu	-----49
Dr. Shobini L. Rao	-----55
Dr. Aditya Murthy	-----67
Dr. V. Rema	-----74
Dr. Neeraj Jain	-----78
Dr. Soumya Iyengar	-----81
Dr. Narender K. Dhingra	-----87
Dr. Nandini Chatterjee Singh	-----92
Dr. Prasun Roy	-----97
Publications	-----103
Presentations by NBRC Scientists	-----109
Distinctions, Honours & Awards	-----120
Externally Funded Research Projects	-----124
Core Facilities	-----128
Distributed Information Centre (DIC)	-----129
Animal Facility	-----131
Digital Library	-----133
National Facilities	-----135
National Neuroimaging Facility	-----136

Academic Programmes	138
Ph.D. Neuroscience	139
Int.Ph.D.	139
Summer Training & Short-Term Programmes	139
General & Academic Administration	141
Collaborations and Networking	143
International Collaborations	144
Networking	145
Invited Speakers	147
Meetings and Workshops	150
People at NBRC	158
Members of NBRC Society	166
Governing Council	168
Finance Committee	169
Scientific Advisory Committee	170
Building Committee	175
Academic Council	176
Board of Studies	179
M.Sc. (Neuroscience) Coordination Committee Members	181
Annual Financial Statements	184

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 may 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 outreach activities to contribute to the development of society.
- To promote, develop, collaborate or otherwise assist in providing services of research, training, consulting or guidance related to neurosciences activities comprising biological, psychological, sociological and clinical aspects; and

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

FROM THE DIRECTOR'S DESK

The human brain is unique and while being a part of the physical world it creates a parallel universe of visual percepts, thoughts, and emotions that underlies our sense of self. The grand challenge of understanding how networks in the brain generate behaviour is immense and has no comparison in the history of science. The questions that fuel brain research are not merely of academic interest. Their origin is in the everyday life: the agony of our fellow human beings suffering from a host of neurological and psychiatric disorders. How best can we alleviate the incapacitating memory loss of Alzheimer's patients without debilitating their mental faculties in some other domain? How do we add hope to the lives of chronically depressed and thereby help them become productive citizens? How do we diminish the disabling sequelae of developmental disorders and infections of the nervous system that afflict children?

Brain disorders contribute maximally to the disease burden both in developing and developed nations. This is a fact that goes unrecognized in most developing countries because the focus is most often on infectious diseases. In fact brain disorders contribute to one-third of the disease burden in the developing countries. Better public health and better primary health care cannot prevent most brain disorders and the pathogenic mechanisms are least understood. It is only through brain research that one can understand the disease process and discover rationale therapies and cures for these 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 viral infections of the nervous system such as Japanese encephalitis and HIV. A common phenomenology underlying these pathogenic states is the innate immune response. Microglia, the primary immune effector cells of the CNS are activated in response to injury, inflammation or the presence of pathogens. When activated microglia undergo proliferation, chemotaxis, and morphological alteration and generate numerous mediators involved in the inflammatory and immunomodulatory response. Although the net effect of the proinflammatory mediators is to kill unhealthy cells as well as to stimulate the production of molecules that amplify the protective response to damage, it is also evident that in non-regenerating organs, such as the brain, a dysregulated innate immune response would be deleterious. Inhibition of chronic neuroinflammation, particularly of microglial activation, has been suggested to be a practical strategy in the treatment of neurodegenerative and infectious diseases of the nervous system.

Japanese encephalitis virus is a major cause of acute encephalopathy commonly known as brain fever. Japanese encephalitis is the most important form of viral encephalitis seen in Asia. It is caused by Japanese

encephalitis virus (JEV), a member of the *flaviviridae* family of animal viruses. The virus is active over a vast geographic area covering India, China, and most of the south-east Asian region. Approximately three billion people live in the endemic regions and 50,000 cases are reported officially each year, of which 10,000 are fatal. The morbidity is high in survivors due to the neurological and psychiatric complications that arise as a sequel to the primary infection. The disease was first recognized in India in 1955 at Vellore. Japanese encephalitis epidemic occurs in several regions in India. Although there is no consolidated official figure for current Japanese encephalitis cases in India, a rough estimate would indicate a few thousands fatalities every year. The most recent outbreak in Uttar Pradesh (concentrated in and around Gorakhpur, August-September, 2005) left behind more than one thousand dead, mostly children below 15 years of age.

At NBRC, the molecular mechanism underlying the neuroinflammation and the subsequent neurodegeneration seen in Japanese encephalitis is being investigated. One of the common denominators seen in most disorders closely associated with neuroinflammation is the activation of microglia, primary immuno-competent cell of the central nervous system. In addition to basic research initiative to understand the pathogenic mechanisms, discovery of rational therapy, which selectively target molecular pathways and help reduce the devastating process of neuroinflammation and subsequent neurodegeneration in Japanese encephalitis is being actively pursued. Research at NBRC has led to the discovery that *Minocycline*, a semi synthetic second-generation tetracycline, confers complete protection in mice following Japanese encephalitis. Minocycline at relatively low doses is a very effective neuroprotective drug in an experimental model of Japanese encephalitis even when administered after the viral inoculation. This indicates that a clinically relevant therapeutic time window for this is available for treating patients with this tetracycline derivative. In addition, research at NBRC also indicates that the beneficial effect of minocycline is associated with reduction of proinflammatory cytokines, active caspase-3 activity, microgliosis, and neuronal death. Since minocycline is well tolerated, it represents a potential new therapeutic drug for preventing and/or controlling the neurological complications of Japanese Encephalitis. Minocycline is a well-known tetracycline antibiotic which has been used extensively since the 1970s and the current research discovery at NBRC represents a new use for an old drug. Discovery of new drugs is extremely time-consuming and an expensive endeavour and thus discovery of new drugs for diseases that affect distinct regions and specific segments of population is often ignored due to lack of significant financial gains. It is therefore important to search and identify new ways of using old drugs. Pharmacologist and Nobel laureate James Black has said, “the most fruitful basis for the discovery of a new drug is to start with an old drug.”

This also has the advantage that since the pre-clinical toxicology and pharmacokinetics are well established the therapy can be rapidly taken to

clinical trials in patients. It is hoped that the discovery at NBRC can be rapidly translated into patients and the mortality and morbidity seen in patients with Japanese encephalitis can be drastically reduced.

Recognizing that the vitality of any scientific discipline depends on the human resource that pursues the discipline, NBRC is making special efforts to attract bright students to 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 is the first Institute of the Department of Biotechnology to achieve this status. NBRC admits students to Ph.D. programme in neuroscience both after undergraduate degree (integrated Ph.D.) and post-graduate degree. Students from diverse backgrounds such as biology, psychology, mathematical and physical sciences, clinicians and engineers are encouraged to apply for admission recognizing that understanding brain function requires amalgamation of knowledge from multiple disciplines. The goal is to train Ph.D. students with an understanding of different aspects of neuroscience integrating information across traditional boundaries. A nation-wide entrance test is conducted at several centres and the candidates are selected after a rigorous interview. In addition, NBRC has a summer training programme for students of other academic institutions. The need for generation of exceptionally trained human resource cannot be over-emphasized and NBRC is committed to this enterprise.

The resolute commitment of the scientists, students, and staff has helped NBRC stride the path towards realization of the goals that it has set out for itself: conducting world-class basic research, developing exceptional human resource, facilitating collaborations between neuroscientists in India and world-wide and providing the needed infrastructure for the smooth pursuit of internationally competitive research in our country. The impetus provided by these initial successes will be channelled to drive the growth of NBRC into international leadership in this frontier area of science, while being sensitive to brain-related problems specific to our country.

(Prof. V. Ravindranath)

RESEARCH REPORTS

- 1: Molecular & Cellular Neuroscience**
- 2: System & Cognitive Neuroscience**
- 3: Computational Neuroscience**



Molecular & Cellular Neuroscience

MOLECULAR MECHANISM OF THE PATHOGENESIS OF THE CAG REPEAT NEURODEGENERATIVE DISEASES

Principal Investigator : Dr. Nihar Ranjan Jana

Research Fellows : Anand Goswami, Priyanka Dikshit

Technical Assistant : D. Narender

The accumulation of intracellular protein deposits as inclusion bodies is the common pathological hallmark of most age related neurodegenerative disorders including polyglutamine diseases. The Polyglutamine diseases are a group of familial neurodegenerative disorders caused by an aberrant expansion of CAG repeats in the coding region of a target gene. Nine disorders are known to be caused due to such expansions including Huntington's disease (HD), spinal and bulbar muscular atrophy (SBMA), dentatorubral pallidoluysian atrophy (DRPLA) and several spinocerebellar ataxias (SCA1, SCA2, SCA3, SCA6, SCA7 and SCA17). All polyglutamine repeat diseases are progressive, autosomal dominantly inherited, except for X-linked recessive SBMA (also known as Kennedy's disease), typically striking at midlife and have an extended period of neuronal dysfunction followed by neuronal loss and eventually death. The number of CAG repeats shares an inverse relationship with the age of onset and severity of the disease and successive generations of affected families experience anticipation. The transgenic animal studies have supported a toxic gain-of-function mechanism that leads to neuronal dysfunction and death, although recent evidence indicates that loss of normal protein function might also have a role in the disease pathogenesis. The formation of neuronal intranuclear inclusions or aggregates of the disease protein is the major cytopathological hallmark of all these disorders. It has been suggested that the polyglutamine tract expansion leads to formation of misfolded conformations of the target protein. When the cells senses the misfolded polyglutamine protein, initially it tries to refold and failure to refold next leads to their degradation by ubiquitin proteasome system (UPS). The appearance of aggregates of the misfolded expanded polyglutamine proteins indicates that the cells are unable to efficiently degrade them, which eventually overwhelm the cells quality control system. The recruitment of molecular chaperones, UPS components to the polyglutamine aggregates could be an adaptive response of the cells to get rid from the abnormal protein deposits. 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 identified one E3 ubiquitin ligase, E6-AP that suppresses the expanded polyglutamine protein aggregation and expanded polyglutamine protein-induced cell death. E6-AP is a founding member of HECT domain ubiquitin ligase. Loss of function of E6-AP is associated with Angelman mental retardation syndrome. We have found that E6-AP helps in the degradation of misfolded protein in collaboration with Hsp70. Since the expanded polyglutamine proteins are also misfolded and degraded by proteasome, we are interested to study the role of E6-AP in the degradation of misfolded expanded polyglutamine proteins. We have found that E6-AP interacts with the misfolded soluble expanded polyglutamine proteins and associates with their aggregates. Over expression of E6-AP increases the ubiquitination and degradation of polyglutamine proteins and decreases the expanded polyglutamine protein aggregation. Over expression of E6-AP suppresses while knockdown promotes the expanded polyglutamine protein-induced cell death. We are now characterizing the association of E6-AP with the nuclear aggregates in the transgenic mice brain.

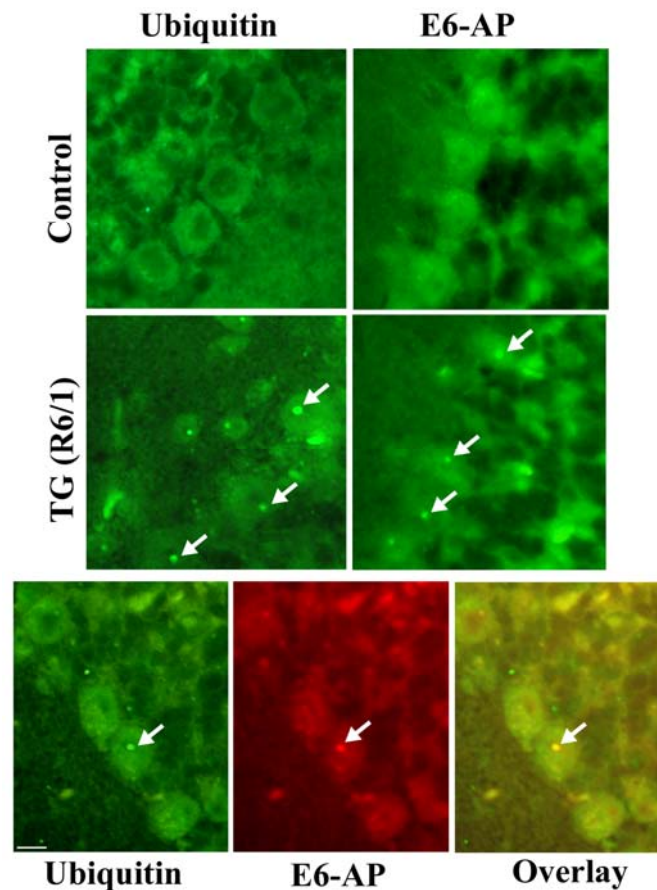


Figure **Co-localization of E6-AP to the NIs in the brain of HD exon1 (R6/1) transgenic mice.** A) Immunofluorescence staining of ubiquitin and E6-AP in the cerebellum of R6/1 transgenic mice. Brain sections from about

36-weeks old mice (both control and transgenic) were used. Arrow indicates the recruitment of E6-AP to the NIs. B) Immunofluorescence double labelling of ubiquitin and E6-AP in the NI. Brain section was incubated with primary antibodies against E6-AP (anti-mouse) and ubiquitin (anti-rabbit). FITC-conjugated secondary antibody was used to label the ubiquitin and Rhodamine-conjugated secondary antibody was used to stain E6-AP. Arrow indicates the NI that are co-localized with both ubiquitin and E6-AP. Scale bar, 20 μ M.

Publications

P. Dikshit and **N. R. Jana** : Role of ubiquitin protein ligases in the pathogenesis of polyglutamine diseases. **Neurochemical Research** (In Press).

P. Dikshit and **N. R. Jana** : The co-chaperone CHIP is induced in various stresses and confers protection to cells. **Biochemical and Biophysical Research Communications**. 357, 761-765, 2007.

A. Goswami, P. Dikshit, A. Mishra, N. Nukina and **N. R. Jana** : Expression of expanded polyglutamine proteins suppresses the activation of transcription factor NF- κ B. **Journal of Biological Chemistry**, 281, 37017-37024, 2006.

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

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

Presentations

Nihar Ranjan Jana. Suppression of polyglutamine neurodegeneration by quality control ubiquitin ligase. Annual meeting of the Indian Society of Neurochemistry, Kolkata, 2006.

Nihar Ranjan Jana. Modulation of polyglutamine neurodegeneration by ubiquitin protein ligase. NBRC International Seminar, 2006.

Anand Goswami and Nihar Ranjan Jana. Inhibition of nuclear factor-kappaB signaling pathway by expanded polyglutamine protein. NBRC International Seminar, 2006.

Anand Goswami, Priyanka Dikshit, Amit Mishra, Shalaka Mulherkar, Nobuyuki Nukina and Nihar Ranjan Jana. Expression of expanded polyglutamine proteins down-regulates the NF- κ B-dependent transcriptional activity. Annual meeting of the Japanese Society of Neuroscience, Kyoto, 2006.

Priyanka Dikshit, Anand Goswami, Nobuyuki Nukina and Nihar Ranjan Jana. Co-chaperone CHIP reduces the polyglutamine protein aggregation and toxicity. Annual meeting of the Japanese Society of Neuroscience, Kyoto, 2006.

Collaborator

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

Funding

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

UNDERSTANDING THE PATHOGENIC MECHANISM OF ANGELMAN MENTAL RETARDATION SYNDROME

Principal Investigator : Dr. Nihar Ranjan Jana

Research Fellows : Amit Mishra

Angelman mental retardation syndrome (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. Major goal of this project is to understand the molecular function of UBE3A gene product. UBE3A gene encodes E6-AP ubiquitin protein ligase, an enzyme involved in the intracellular protein degradation through ubiquitin proteasome system (UPS). E6-AP is the founding member of HECT (homologous to E6-AP C-terminus) domain family of E3 ligase that provides specific recognition of substrate protein. E6-AP was discovered based of its ability to promote the ubiquitin-mediated degradation of tumor suppressor p53 in association with the E6 oncoprotein of the human papilloma virus. 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 also the altered signalling pathways. Therefore identification of substrate protein of E6-AP and the defective signalling cascades could open a new avenue in understanding the pathogenic mechanism of AS.

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 extensively characterized the interaction of E6-AP with tumour suppressor p53 in the neuronal cells. E6-AP is well known to degrade p53 in association with E6 oncoprotein in human papilloma virus (HPV) positive cells. The role of E6-AP in the degradation of p53 in the HPV

negative cells is not clear. Our results suggest that E6-AP is able to degrade p53 in various neuronal cells where it does not require E6 oncoprotein. We have proved this using in vitro and in vivo ubiquitination assays. Over expression of E6-AP in neuronal cells dramatically decreases the turnover of p53. Down-regulation of E6-AP increases the levels of p53 and two p53 dependent genes, bax and p21. Down regulation of E6-AP gene expression also dramatically increases the neuronal cell death. Partial knockdown of E6-AP in mice also increases the p53 levels in different parts of brain. Surprisingly, E6-AP knockdown also increases the mRNA levels of p53 in the mice brain as well as in the neuro2a cells suggesting that E6-AP not only enhances the degradation but also represses the transcription of p53. Now we are investigating the p53-dependent neuronal cell death in E6-AP deficient mice. We are also extensively characterizing the functional significance of the interaction of E6-AP with molecular chaperone Hsp70. We have found that E6-AP degrades the cellular abnormal proteins with the help of Hsp70 and therefore it serves as a cellular quality control ligase.

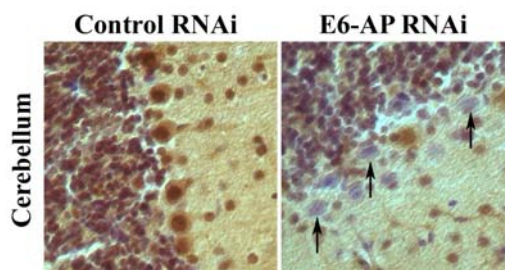


Figure SiRNA mediated knockdown of E6-AP in the mice brain. The control and E6-AP RNAi plasmids were injected into the tail vein of adult male mice. Each mouse received three injections (each injection contains 20 μ g DNA/200 μ l of Ringer's buffer) and sacrificed after 10 days. The brain samples were collected and processed for immunohistochemical staining using E6-AP antibody. Nucleuses were counterstained with hematoxylin. Arrow indicates the E6-AP deficient Purkinje cells.

Presentations

Amit Mishra and Nihar Ranjan Jana. Angelman ubiquitin ligase E6-AP promotes degradation of tumor suppressor p53 by proteasome in the neuronal cells. Annual meeting of Indian Academy of Neuroscience, Lucknow, 2006.

Amit Mishra and Nihar Ranjan Jana. Angelman ubiquitin ligase promotes ubiquitin-mediated degradation of tumor suppressor p53 in the neuronal cells. NBRC International Seminar, 2006.

Funding

Understanding the functional role of E6-AP - a putative ubiquitin protein ligase implicated in Angelman mental retardation syndrome (DBT).

IDENTIFICATION OF THE MODULATORS OF UPS

Principal Investigator : *Dr. Nihar Ranjan Jana*

Research Fellows : *Priyanka Dikshit*

The UPS is the cell's principal pathway for controlled protein degradation. The degradation of a protein through UPS involves two distinct and successive steps: protein ubiquitination and the degradation of the ubiquitylated proteins by 26S proteasome. The ubiquitylation of protein substrates is carried out by a series of cellular enzymes known as E1 (ubiquitin activating enzyme), E2 (ubiquitin conjugating enzyme), and E3 (ubiquitin protein ligase) that result in multibiquitylation of protein. A target protein must be tagged with a multiubiquitin chain composed of at least four ubiquitins before it can be recognized and degraded by the proteasome. The ubiquitin-mediated protein degradation plays a very important role in numerous critical cellular events including regulation of the cell cycle, signal transduction, antigen processing, synaptic plasticity, and transcription. 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 and characterized another proteasome inhibitor named mangiferin. Mangiferin, a natural polyphenol (isolated from *Mangifera Indica*) is known to exhibit anti-inflammatory, antioxidant properties. This compound also induces apoptosis in various cancer cells. However, the molecular mechanism through which this compound induces anti-inflammatory responses or apoptosis is not well understood. We have observed that the exposure of mangiferin to mouse neuroblastoma cells induces proteasomal dysfunction in a dose and time dependent manner, which correlates well with its effects on cell death. Treatment of mangiferin also increases the half-life of d1EGFP (a model substrate of proteasome with half-life of 1 hr) and several known cellular substrates of proteasome. Finally, we have found that treatment of mangiferin led to severe changes in mitochondrial membrane potential and release of cytochrome c from mitochondria. Our result suggests that the mangiferin induces apoptosis in the neuroblastoma cells through the inhibition of proteasomal function.

Publications

P. Dikshit, M. chatterjee, A. Goswami, A. Mishra and **N. R. Jana** : Aspirin induces apoptosis through the inhibition of proteasome function. **Journal of Biological Chemistry**. 281, 29228-29235, 2006.

Presentations

Priyanka Dikshit and Nihar Ranjan Jana. Aspirin inhibits proteasome function in mouse neuroblastoma cells. NBRC International Seminar, 2006.

Regulation of neurogenesis in the cerebellum

Principal Investigator : *Dr. Shyamala Mani*

Research Fellows : *Rashmi Mishra, Shailesh Kumar Gupta*

Control of cell proliferation is essential for normal morphogenesis of the central nervous system. During early cortical development, progenitor cells in the ventricular zone produce daughter cells that are mitotic progenitors. Later, progenitor cells produce a postmitotic neuron and a mitotic progenitor (Chenn and McConnell, 1995). Production of a postmitotic cell versus a mitotic progenitor is controlled by the orientation of the mitotic spindles relative to the ventricular zone (Sanada and Tsai, 2005). Furthermore, migration of the newly born postmitotic neurons out of the ventricular zone, a process that involves polarization and formation of a leading edge, is coupled to the centrosomal position during the last mitotic division (Shu et al., 2004). In the cerebellar cortex, granule neurons are produced from the external granule cell layer (EGL) during the first three postnatal weeks in mice. Analogous to the cerebral cortex, the production of mitotic progenitors is followed by cell cycle exit and migration to form the internal granule cell layer (IGL) (Wechsler-Reya and Scott, 1999).

Orientation of mitotic spindles in the EGL and its impact on progenitor proliferation and cell cycle exit is not known (Zagon and McLaughlin, 1987). Further, although mitotic spindle orientation requires the cooperation of the both the microtubule and actin cytoskeletal elements the mechanism by which positioning of the mitotic spindle and the direction of polarization are regulated by extracellular signals is not understood (Rodriguez et al., 2003; Higginbotham and Gleeson, 2007). GAP-43 is an actin binding phosphoprotein that is involved in the transduction of extracellular signals mediated by FGFs and IgCAMs in the growth cone and is essential for axonal path-finding (Meiri et al., 1998; Maier et al., 1999; Mani et al., 2001). Phosphorylated GAP-43 stabilizes, whereas unphosphorylated GAP-43 inhibits F-actin polymerization. GAP-43 homozygous knockout [GAP-43 (-/-)] mice show decreased cerebellar size and reduced foliation (R.M. unpublished observations). We show that GAP-43 regulates progenitor proliferation and cell cycle exit and is important for normal centrosome duplication and determining spindle orientation in the EGL. In addition we show that GAP-43 is an essential link between centrosome positioning and neuronal polarization in cerebellar granule neurons.

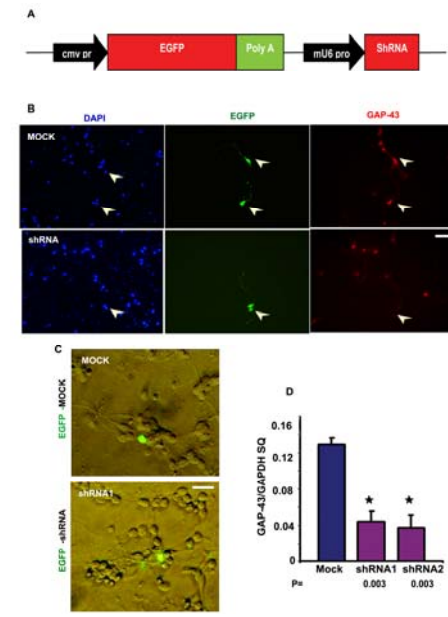


Figure: **GAP-43 ShRNA transfections in primary cerebellar granule cell cultures**

ShRNA construct used to down-regulate expression of GAP-43. b) Nuclei (DAPI), GAP-43 (red) and GFP (green) from mock transfected and GAP-43ShRNA transfected cultures showing that in ShRNA cultures, GFP positive cells do not show high GAP-43 expression (arrowheads) Scale bar = 100 μ m. c) Bright field DIC image with fluorescent GFP overlap of mock transfected and GAP-43 ShRNA transfected cultures showing that the cultures from which analysis was done were healthy following transfection. Scale bar = 25 μ m d) Quantitation by real time PCR of the GAP-43 RNA levels following transfection. Mock (blue bar), ShRNA (purple bars). P value is given below the bar. Error bar = mean $\pm$ s.e.m for 3 independent experimental sets. 2-tailed unpaired Student t-test was used to generate P values.

Publications

Rashmi Mishra, Shailesh Kumar Gupta, Karina Meiri and **Shyamala Mani** : GAP-43 is key to mitotic spindle control and centrosome-based polarization in neurons. (Manuscript submitted, **Neuron**)

Yiping Shen*, Rashmi Mishra*, Shyamala Mani and Karina Meiri : GAP-43 is required for normal patterning of the cerebellum in vivo, and its absence affects cerebellar learning in a sex-specific fashion. (*joint first authors) (Manuscript submitted, **Development**).

Presentations

NBRC 3rd International Conference December 2006 – Regulation of structural modules during morphogenetic events.

Collaborator

Karina Meiri, Tufts University

Funding

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

To investigate the mechanisms by which embryonic stem cells differentiate into distinct neuronal subtypes

Principal Investigator : *Dr. Shyamala Mani*

Research Fellows : *Manoj Kumar, Roopali Srivatsava*

Research Assistant : *Bandita Bagchi*

Serotonergic neurons are found in the ventral rhombencephalon and send diffuse projections to the cortex, hypothalamus and the spinal cord and play an important role in the control of several central nervous system functions. Imbalance of serotonin neurotransmitter has been implicated in several disease states such as depression, schizophrenia, and Parkinson's disease. Serotonin deficiencies have also been associated with disorders such as anorexia, bulimia, obsessive-compulsive disorders, migraines, social phobias and schizophrenia. Therefore understanding factors that are involved in serotonergic neuronal differentiation and being able to produce serotonergic neurons in culture are important in understanding a range of neurodegenerative and psychiatric and in the long term being able to come up with new treatment options.

Human embryonic stem (hES) cells offer a tractable model in which to address the mechanism of serotonergic neuron specification in the context of human neural development. Neuronal phenotype is determined by the interaction of extrinsic signaling molecules and cell intrinsic transcription factors. Recently several transcription factors that are important in specification of serotonergic phenotype have been identified. However it is currently not known whether factors that govern differentiation and development of serotonin neurons is conserved in humans. In addition, there are also extrinsic signaling molecules that are important for specifying serotonergic neurons. How these transcription factors interact with external cues to specify serotonergic phenotype, especially in the context of the differentiation of human embryonic stem cells remains to be seen.

Human fetal neuronal progenitors treated with serotonin, forskolin, BDNF and acidic FGF have been shown to differentiate into serotonergic neurons with an efficiency of about 30%. In addition, in the developing rat striatum, several of these factors such as forskolin, aFGF and serotonin itself were shown to act by inducing tryptophan hydroxylase, the rate-limiting enzyme in the biosynthetic pathway for serotonin production. In addition, studies have shown that BDNF is an important factor for the maturation and survival of several different neuronal phenotypes in human mesencephalic cultures and thus may be a general survival factor rather than an inducing factor for a particular neuronal phenotype. GDNF likewise seems to stimulate serotonin synthesis in neonatal brain of mice.

The goal of the present study was to be able to produce homogenous population of neuronal progenitors derived from human ES cells that could be frozen and revived and still retained the potential to differentiate into neuronal phenotypes without loss in efficiency, in this study our focus being in the serotonergic phenotype. Further, our goal was to produce serotonergic neurons from these neuronal progenitors with greater efficiency that had been previously reported in literature. To accomplish these goals, in the present study we have used improved cultured technique to produce homogeneous neural precursor that were then treated with different combination of extrinsic factor to derive neurons expressing serotonin.

Publications

Manoj Kumar, Bandita Bagchi, Shailesh Kumar Gupta, A.S. Meena, Pierre Gressens, and **Shyamala Mani** : Neurospheres derived from human embryoid bodies treated with retinoic acid show an increase in nestin and ngn2 expression that correlates with the proportion of tyrosine hydroxylase-positive cells. **Stem Cells and Development** (in press)

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 : Prof. V. Ravindranath
Research Fellows : Reddy Peera Kommaddi,
Varsha Agarwal
Technical Assistant : Nitin Sharma

Cytochrome P450 (P-450), a superfamily of heme proteins is involved in the metabolism of a vast array of carcinogens, drugs and endogenous compounds. Liver is the major organ involved in P450 mediated xenobiotic metabolism, however preferential localization of xenobiotic metabolizing enzymes within specific cell types in extrahepatic organs renders such cells significant capability to metabolize foreign compounds including carcinogens. Thus, minor metabolic pathways of xenobiotic metabolism can produce major effects if they take place at the site of action. Significant differences are seen in the biotransformation of psychoactive drugs mediated by brain and liver P450 enzymes. For example, drugs, such as, alprazolam are metabolized differently in liver and brain wherein relatively larger amount of the active metabolite is generated in the brain compared to liver. These observations have indicated the existence of unique P450 enzymes in brain that are different from the well-characterized hepatic P450s. Our working hypothesis is that brain cytochromes P-450 play an important role in the pharmacological modulation of drugs acting on the CNS and it is therefore important to understand major P-450-mediated biotransformation and characterize the enzymes mediating such reactions in the human brain. While many isoforms of P450 are expressed in brain, is there anything unique about their presence there? The long-term objective of the proposed project is to understand the role of in situ cerebral drug metabolism in the pharmacological action of psychoactive drugs. The immediate specific aims are to identify human brain specific biotransformation pathways mediated by P450 enzymes and clone, express and characterize brain-specific P450 enzymes and examine the functional relevance of these enzymes.

Major forms of P-450 that have been demonstrated to play a predominant role in the metabolism of psychoactive drugs in both rat and human liver belong to 3A, 2D, 2C and 1A families. P4503A4 is the predominant form of P-450 in human liver and accounts for nearly 60% of the total P-450 present. CYP3A family is a very important family of P450 enzymes and consists of 4 functional genes CYP3A4, CYP3A5, CYP3A7 and CYP3A43 and 2 pseudogenes CYP3AP1 and CYP3AP2. CYP3A genes are arranged adjacent to each other on chromosome 7q21 and there is >75% amino acid homology among the members of CYP3A family.

We focused on identifying the key P450 enzyme that mediates the metabolism of the anxiolytic drug alprazolam to its active metabolite. Alprazolam (ALP) is metabolized in human liver by P4503A4 to 4-hydroxy alprazolam (4-OHALP, pharmacologically inactive) and hydroxy alprazolam (α -OHALP, pharmacologically more active). P4503A mediated metabolism of ALP by human brain microsomes leads to the formation of relatively higher amounts of α -OHALP as compared to liver. We examined the relative expression of the four CYP3A genes in 40 human brain samples and studied the metabolism of ALP in human brain microsomes and recombinant CYP3A enzymes with a view to identify the specific CYP3A enzyme(s) involved in the metabolism of ALP to its active and inactive metabolites.

Quantitation of the expression levels of CYP3A genes showed that CYP3A4 is expressed in higher levels in adult human liver as compared to CYP3A43. In human brain CYP3A43 was expressed in relatively higher levels while CYP3A5 mRNA was expressed in low levels and CYP3A7, a predominantly fetal enzyme, was absent in adult human brain. Recombinant CYP3A43 metabolizes ALP to both its active (α -OHALP) and inactive metabolites while 3A4 metabolizes ALP predominantly to its inactive metabolite (4-OHALP). The expression of CYP3A43 in human brain correlated with the formation of relatively higher levels of α -OH ALP indicating that individuals who expressed higher levels of CYP3A43 in the brain would generate larger amounts of α -OH ALP, the active metabolite of ALP. The production of the active metabolite can prolong drug action due to its delayed clearance from the brain.

CYP4F, a novel member of P450 family mediates leukotriene B₄-hydroxylation and inhibits the pro-inflammatory pathway. It metabolizes arachidonic acid and its derivatives, such as leukotrienes, prostaglandins, lipoxins, and hydroxyeicosatetraenoic acids. Seven CYP4F genes have been cloned from rat and human.

CYP4F11 is present in the human brain. We amplified a region of CYP4F11 to generate a highly specific riboprobe to localize CYP4F11 in the brain by fluorescent in situ hybridization. CYP4F11 mRNA was expressed constitutively in neurons of cerebral cortex, reticular neurons of midbrain and pyramidal neurons of hippocampus. We then examined the relative expression levels of CYP4F11 mRNA by qT-PCR in 30 human brain samples obtained at autopsy. CYP4F11 is maximally expressed in cortex, striatum, cerebellum and pons. Our results demonstrate the constitutive expression of CYP4F11 in the neuronal cells of the human brain we are currently examining its potential role in modulating inflammatory response.

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PhD Thesis Awarded

Reddy Kommaddi

Collaborator

Henry Strobel, University of Texas

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Protein thiol homeostasis and mitochondrial dysfunction in neurodegeneration

Principal Investigator : Prof. Vijayalakshmi Ravindranath

Research Fellows : Smitha Karunakaran, Uzma Saeed,
Lalitha Durgadoss

Idiopathic Parkinson's disease (PD) as opposed to heritable forms of Parkinson's disease (PD) accounts for greater than 90% of the Parkinson's disease incidence world over. Among many of the pathological hallmarks, mitochondrial complex-I (NADH ubiquinone 1 oxidoreductase) dysfunction observed in the skeletal muscles, platelets, and lymphocytes of these patients has been shown to be a primary event in PD. Identification of factors involved in maintenance and restoration of complex I function could potentially help develop prophylactic and therapeutic strategies for treatment of this class of disorders. We had earlier shown that perturbations in redox-status of thiols underlies the mitochondrial complex I dysfunction seen in animal models of neurodegenerative disorders and maintenance of redox-status of protein thiols by protein disulphide oxido-reductases, such as glutaredoxin is important for maintaining/restoring mitochondrial function.

One of the compelling questions in understanding the pathogenesis of neurodegenerative disorders is the selective vulnerability of specific cell types to neurodegeneration. It is our hypothesis that protein thiol modification occurring as a result of oxidative stress results in mitochondrial dysfunction and altered redox signaling leading to activation of cell death pathways. Our overall aim is to understand differential vulnerability of selective cell populations, such as the dopaminergic neurons of substantia nigra. Enzymes such as glutaredoxin and thioredoxin play a critical role in the restoration of protein thiol homeostasis and are important mediators of the redox signaling. Their differential expression and regulation may also help explain some of the gender differences typically seen in both animal models of neurodegenerative disorders and in patient population.

We investigated the early events in ventral midbrain (including substantia nigra) in terms of the activation of the ASK1/p38/JNK and the PI3K/AKT pathway. Within 1-12 hr after a single exposure to MPTP, sustained increase in the expression of apoptosis signal-regulating kinase (ASK1) was seen in midbrain, which was associated with translocation of DAXX (death associated protein) to the cytosol and activation of p38 kinase. Pretreatment with alpha lipoic acid, a thiol delivery agent was able to reverse the above indicating that the pathway was activated through redox signaling. Activation of p38 kinase and the downstream p53 was prominent in midbrain indicating their major contribution to cell death. Further, the anti-apoptotic agents, such as Bcl2 and pAKT were activated to a lesser degree in

midbrain as compared to striatum. Analysis of the early events helps identification of key pathways involved in the cell death seen following MPTP and further point to the role of altered redox signaling in the degeneration of SN neurons.

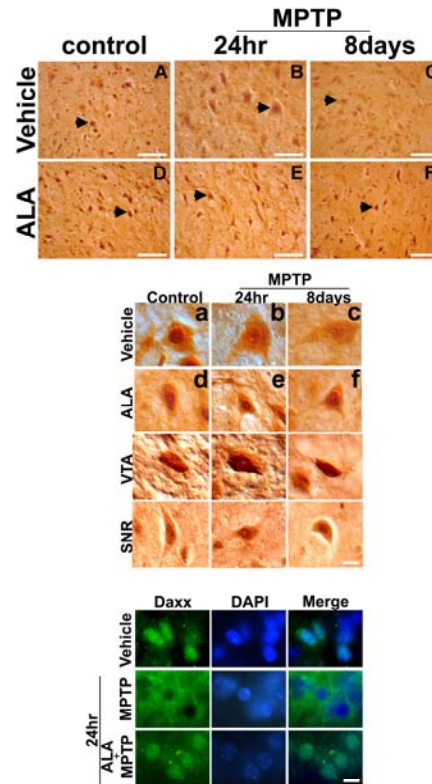


Figure: Translocation of Daxx to the cytosol in dopaminergic neurons of SNpc following administration of MPTP to mice

Animals were treated with a single dose of MPTP and sacrificed 24 hr later. Animals were also treated with a daily dose of MPTP for 8 days and sacrificed on the 9th day. Two subsets of animals were co-administered α -lipoic acid twice daily. Immunohistochemical localization of Daxx revealed the translocation of Daxx to the cytosol in SNpc neurons after MPTP exposure. Daxx is present in the nucleus in control animals (A), while it is present in the cytoplasm following a single dose of MPTP (B), and in the surviving neurons after sub-chronic exposure to MPTP for 8days (C). D, E and F depict the subcellular localization of Daxx in corresponding group of animals co-administered ALA, wherein, Daxx is localized essentially in the nucleus. Scale bar = 25 μ m. a,b,c,d,e,f of the lower panel shows corresponding magnified images of the neurons indicated by arrowheads in the upper panel. The panels indicated by VTA and SNR depict the presence of Daxx in the nucleus in the ventral tegmental area (VTA) and substantia nigra pars reticulata (SNR) neurons following acute and sub-chronic MPTP exposure. Scale Bar = 10 μ m. Immunofluorescent images for Daxx (green) also show the similar pattern of translocation of Daxx to the cytosol following a single dose of MPTP, which is prevented by ALA. Cells were counterstained with DAPI prior to mounting. Scale Bar = 10 μ m.

In order to further delineate the redox signaling pathway and its dysregulation by MPTP, we examined the redox status of key molecules involved in this signaling pathway. SDS PAGE was carried out after derivatization of brain homogenate with a thiol alkylating agent in order to clearly differentiate reduced versus oxidized states of protein thiols. Following a single exposure to MPTP, thioredoxin (a key antioxidant protein thiol) was rapidly oxidized, in fact reduced thioredoxin was barely discernible. Although total thioredoxin levels increased, it was rapidly oxidized in concordance with the activation of ASK1 as observed earlier. Interestingly, we also observed that the phosphorylation of Akt1 was significantly decreased in the ventral midbrain following MPTP exposure. This decrease could be related to oxidation state of Akt1, which is known to hinder its phosphorylation. Thus, the activation of cell death pathway (through the activation of ASK1 and p38) and down regulation of the cell survival pathway (through downregulation of Akt phosphorylation) probably contributes to the degeneration of substantia nigra neurons.

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Understanding the role of transcription factors in the differentiation of photoreceptors and related retinopathies

Principal Investigator : Dr. Prabodha Swain

Research Fellows : Sandeep Kumar, Dharmesh Patel,
Pranav Oberoi

Post Doctoral Fellow : Madhumita Ghosh

Project Assistant : Sushmita Richong

Photoreceptors are specialized neurons that perform phototransduction cascade of reaction in retina. There are two distinct classes of photoreceptors known as rod and cones that possess distinct cellular architecture and function to detect intensity of light in retina. Characteristically rods are sensitive to dim-light vision with low spatial acuity, where-as cones are necessary for colour or bright light vision with high spatial acuity. Neural Retina Leucine zipper (NRL) is a DNA binding protein preferentially expressed in rod progenitors and critical for rod photoreceptor development in retina. Mutations in NRL are associated with autosomal dominant retinitis pigmentosa and clumped pigmentary retinal degeneration that alter photoreceptor function leading to retinal degeneration and loss of vision in affected individuals. Studies on NRL-mediated gene regulation have identified several retinal proteins that interact with NRL and regulate transcription of photoreceptor genes in retina. In knockout mouse, lack of Nrl expression produces drastic changes in the differentiation of photoreceptors and transforms the rod rich retina to a cone rich mouse retina, in vivo. Identical phenotype has also been reported in clumped pigmentary retinal degeneration retina carrying null mutations of NRL.

NRL regulates transcription of several photoreceptor genes in retina. Molecular analyses of NRL-interacting proteins have identified both general and specific transcription factors that interact and are involved with the NRL-mediated transcription of photoreceptor genes in retina. However, the molecular mechanism underlying such NRL-mediated regulation of transcription is not delineated properly. Here, we applied different biochemical techniques to identify novel interacting proteins that actively bind with NRL and are involved in NRL-mediated gene transcription, in vitro. We propose that identifying gene interaction network of NRL will help us to understand its differential role in global photoreceptor gene regulation in retina. Also, the knowledge can be exploited to understand disease process associated with mutated NRL in different retinopathies.

In the earlier year, we have identified that Y-Box binding protein, YB-1 interacts with NRL in vitro. To study the biological relevance of NRL-YB-1

interaction, we performed promoter activation studies to determine whether YB-1 affects NRL-mediated activation of rhodopsin promoter, in vitro. HEK293 cells were co-transfected with plasmids expressing NRL, YB-1 and luciferase based reporter constructs of rhodopsin minimal promoter to perform transactivation assays, in vitro. Analysis of the level of luciferase expression indicated that increased expression of YB-1 represses NRL-mediated transactivation of rhodopsin promoter in a dose dependent fashion. Rhodopsin minimal promoter contains different regulatory elements specific to the interaction of NRL and CRX. In the current study, further analyses of the promoter sequence helped to identify a partial invert CAAT-box sequence that serves as recognition sequence of YB-1 within the consensus NRL-response element in the rhodopsin minimal promoter. To determine if decreased activation of rhodopsin expression is the result of reduced binding of NRL to the cognate regulatory element in presence of YB-1, we performed electrophoretic mobility shift assay to study DNA-protein interactions in vitro. In the study, radiolabeled NRL-response element (NRE) with or without mutation was incubated with NRL, YB-1 or mixture of NRL-YB-1 at different proportion to produce DNA-protein complexes analyzed using denatured polyacrylamide gels. Analyses of the radiolabeled NRE indicated that increased (ten folds excess) concentration of YB-1 decreased more than 90% binding of the NRL-YB-1 complex to the NRE compared to the control. Incubation of both NRL and YB-1 together to form complex prior to bind with radiolabeled NRE produced inefficient interaction and electrophoretic mobility shift than that observed without prior binding in the EMSA. Interestingly, identical studies on NRL-promoter specific YB-1-response element (YRE) produced cumulative binding and shift with both NRL and YB-1 in the EMSA. However, the interaction of YB-1-NRL complex with YRE did not change significantly in different binding conditions in the EMSA. The results indicate that YB-1 can interact with NRL and regulate NRL-mediated gene transcription in a promoter specific manner.

YB-1 is a ubiquitously expressed transcription factor mostly localized in the cytoplasm of the cell. To determine if interaction with NRL alters localization of YB-1 in the cell, we performed co-expression of both NRL and YB-1 in transfected COS-1 cells and co-localized the expressed proteins by fluorescence confocal microscopy. Immunohistochemical analyses demonstrated that YB-1 with or without EGFP-tag localizes predominantly in the cytoplasm of the transfected cells. Co-expression of NRL along with EGFP-YB-1 induced localization of EGFP-YB-1 predominantly in the nucleus of the transfected cells. However, NRL a nuclear protein localizes in the nucleus of the expressing cells with or without addition of additional DSRRed-tag in the protein.

To determine the expression of Yb-1 (mouse) in retinal tissues, we probed postnatal mouse retina with specific anti-YB-1 antibodies and level of expression was examined by both immunoblot and immunocytochemistry analysis. Analyses of the immunoblots indicated that expression of Yb-1

remain unchanged during the entire first postnatal week of development in the mice retina. However, examination of the spatial distribution of Yb-1 by confocal microscopy demonstrated significant changes in the localization of Yb-1 in different retinal layers during the postnatal development of mouse. The intensity of Yb-1 expression remains more or less similar in inner retinal layers throughout the first postnatal week of development. But, the level of Yb-1 expression increased gradually in outer retinal layers in each succeeding day of development in postnatal mouse retina, *in vivo*.

YB-1 has been reported to interact with TBP and p53 and regulate downstream target genes in a context and cell specific manner. We performed GST pulldown assays to demonstrate that both YB-1 and TBP can interact with carboxyl terminal domain of NRL *in vitro*. To determine if both the proteins compete with each other to share the common interaction domain of NRL, we performed a competitive binding of GST-NRL with radiolabeled YB-1 and TBP together in the pulldown assay. Analyses of the binding results indicated that increased concentration of TBP could compete with YB-1 in a concentration dependent manner to interact with GST-NRL, *in vitro*. Since p53 has been reported to interact with Yb-1 directly, we wished to determine the distribution of p53 in developing mouse retina *in vivo*. Immunohistochemical studies using different postnatal mouse retina showed that expression of YB-1 is predominantly nuclear, opposite to the expression of p53, which was detected mostly in the cytoplasm of the retinal neuroblasts *in vivo*. Identical results were also observed in case of the retinal sections co-stained with anti-NRL and anti-p53 antibodies.

Taken together, the results suggest that YB1 actively binds with NRL and regulates NRL-mediated rhodopsin expression *in vitro*. The differential binding of NRL-YB-1 complex to specific regulatory elements and localization of YB-1 in the developing neuroblasts of retina suggest that YB-1 can be a potential repressor of NRL-mediated transcription of photoreceptor genes in retina. The abundance of YB-1 Vs p53 in neuroblasts much before the terminal differentiation of rod photoreceptors may contribute to the differential interaction of NRL with specific regulatory elements promoting NRL-mediated differential expression of photoreceptor genes *in vivo*.

Publication

Prabodha Swain, Sandeep Kumar, Dharmesh Patel, Sushmita Richong, Pranav Oberoi, Madhumita Ghosh, and Anand Swaroop. Mutations associated with Retinopathies alter Mitogen-Activated Protein Kinase-induced Phosphorylation of NRL. **Molecular vision**. (In Press)

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Sandeep Kumar, Dharmesh Patel and Prabodha Swain (2006) Y-Box binding protein-1 represses Neural Retina Leucine zipper-mediated transactivation of rhodopsin promoter. NBRC International Conference, New Delhi

Pranav Oberoi, Susmita Richong and Prabodha Swain (2006) CaMK II α dependent signaling pathway regulates rod-specific gene expression in postnatal mouse retina. NBRC International Conference. New Delhi.

Thesis

Pranav Oberoi: Understanding the role of CaMK II α in NRL-mediated gene transcription in retina.

Effect of neural gene(s) in differentiation of retinal cells

Principal Investigator : *Dr. Prabodha Swain*

Research Fellows : *Pranav Oberoi*

Technical Assistant : *Sanjay Kumar*

The major objective of the study is to establish an alternate cell culture model that will help to study the pathways activated by 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 of the 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.

Earlier experiments using DSRed-NRL produced inconsistent transfection efficiency in cultured iris cells. To overcome some of those problems, NRL was subcloned in pEGFP-C1 and used for transient expression studies in transfected iris cells. The transfected cells were treated with BrdU and incorporation of BrdU was detected by using specific immunohistochemical staining. Analysis of the immunostained cells indicated that expression of EGFP-NRL decreases incorporation of BrdU in most of the transfected cells. EGFP alone expressed as negative control does not affect incorporation of BrdU in the transfected cells. Similar studies with or without treatment of specific kinase inhibitors indicated that U0126 and KN62 enhance EGFP-NRL induced incorporation of BrdU in the transfected cells compared to the control. The results suggest that phosphorylation of NRL may influence NRL-mediated cell cycle regulation in non-retinal cells. Hence, the iris culture

used in the study can be a good in vitro model to examine effect of NRL in regulating expression of retinal photoreceptor protein for potential cell replacement experiments.

Cellular and Molecular Mechanisms in Neurobiology of HIV-1

Principal Investigator : Dr. Pankaj Seth
Research Fellows : Mamata Mishra, Nitin Koul
Project Assistant : S. Vitrevel
Technical Assistant : Durga Lal Meena

Human nervous system infection with HIV-1 can produce a range of clinical disorders that are debilitating and are caused mainly due to irreversible damage to neuronal cells. These disorders develop in advanced stages of HIV infection and are referred to as HIV associated dementia (HAD) or AIDS dementia complex (ADC) and are characterized by neurodegeneration resulting in progressive cognitive and motor impairments that may lead to a vegetative/mute state. HIV-1 virus enters the CNS at very early stages of infection and resides in brain cells as latent infections that serve as viral reservoirs. The pandemic infection of HIV is attributed to its different clades (A-K) that are unequally distributed around the world. In India, HIV-1 clade C accounts for over 95% of HIV-1 infection. Current epidemiological studies reveal that HIV-1 clade C implicated in more than 50% of the cases of HIV infection worldwide. HIV-1 associated dementia is quite common in HIV infected adults having prevalence up to 40% in western countries where clade B prevails. However, the incidence of HAD in India is believed to be quite low compared to western countries which may be due to a different clade HIV-1 C, though there are no experimental studies to prove that. It is surprising that although HIV-1 clade C affects more than half the total HIV-1 infected individuals worldwide, there have been limited studies to understand the biology of HIV-1 clade C. Lack of the animal models for HIV-1 infection has significantly limited the progress in the NeuroAIDS field. At the NeuroAIDS laboratory we are establishing a novel cell culture system of human CNS progenitor cells for use as a tool to investigate viral-cell interactions as well as other cellular and molecular events that may be involved during the course of neuropathogenesis.

We have two main aims under this project-

1. Delineate the cellular and molecular mechanisms underlying HIV-1 induced neurodegeneration and study the differences in HIV-1 B and C strain induced neuropathogenesis.

Damage to CNS cells occurs by HIV-1 virion itself as well as by HIV-1 proteins such as gp120 and Tat. Monocyte Chemoattractant Protein-1 (MCP-1)/CCL2 is an important factor and has been implicated in recruiting activated and potentially neuropathogenic immune cells (monocytes) into

brain. Level of MCP-1/CCL2 has been correlated with degree of neurological deficits observed in AIDS patients.

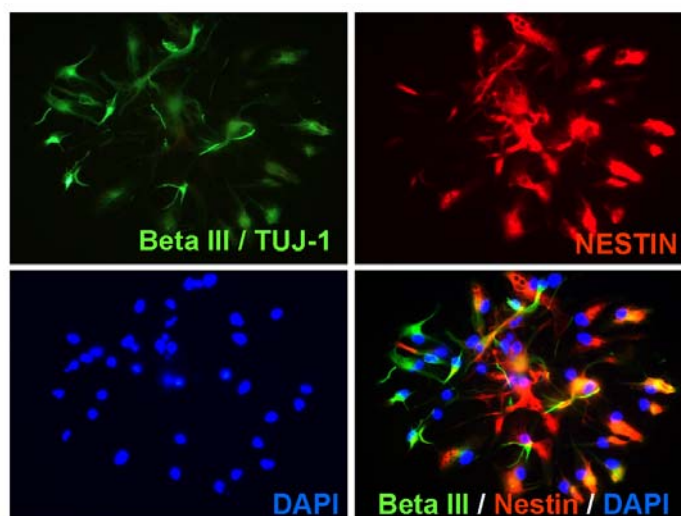


Figure1 Human fetal brain derived CNS progenitor cells growing as neurosphere and undergoing differentiation into neuronal lineage. Human fetal brain cells were immunostained for neuronal marker Beta III tubulin/Tuj-1 (seen in GREEN) and CNS progenitor cell marker Nestin (seen in RED). Composite depicts that at early stages of differentiation process, cells co-express nestin and beta III tubulin/Tuj-1 (seen in YELLOW colour). Cell nuclei are stained with nuclear stain DAPI (seen in BLUE).

The low incidence of HAD in India calls for detailed studies into the HIV-1 Tat induced damage to brain cells and to investigate if there are any clade specific differences in neuropathogenesis. We studied clade specific differences in neurotoxicity following exposure to HIV-1 Tat protein in human fetal CNS progenitor derived astrocytes and neurons, and observed that HIV-1 Tat C is less neurotoxic than Tat B. Damage to neurons by HIV virus is by direct and indirect pathway, hence primary cultures of human astrocytes were transfected with expression vectors for Tat B and Tat C and supernatants collected from these cultures were added to primary cultures of human neurons in various formats to assess neuronal damage by MTT assay, TUNEL assay, Caspase-3 activation and disturbances in mitochondrial membrane potential. We observed that supernatants collected from astrocytes transfected with Tat B expression vectors were more neurotoxic as compared to those from Tat C transfected astrocytes, similar to our observations with Tat B protein treatments in human neuronal cultures. Using site directed mutants of Tat B and C protein, we have determined important motifs in the 101 amino acid protein that are responsible for the HIV-1 clade specific differences in the neurotoxicity of human neurons. We believe that these findings would provide some important details of the neurodegenerative mechanisms by two HIV-1 clades (B and C) that affect the majority of AIDS population around the world.

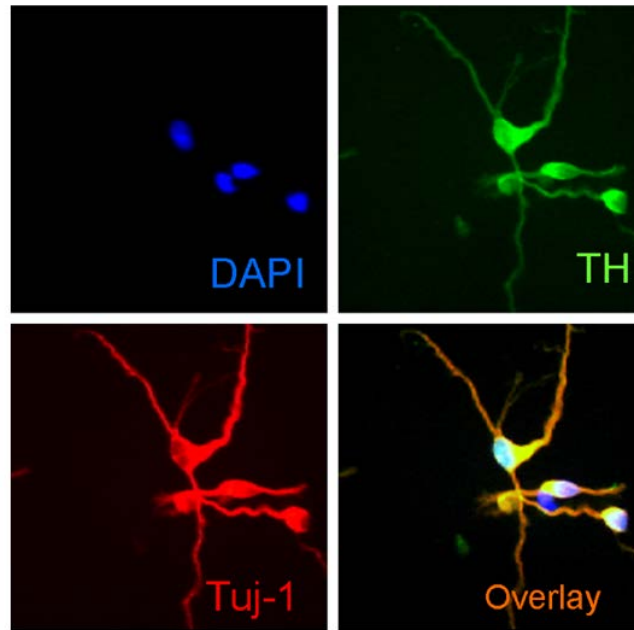


Figure2 Human fetal brain derived CNS progenitor cells differentiated into dopaminergic neurons. Fully differentiated neurons were immunostained with neuronal marker beta III tubulin/Tuj-1 (seen in RED) as well as tyrosine hydroxylase (TH; seen in GREEN). Almost all neurons show co-localization of the two markers (seen in ORANGE). Cell nuclei are stained with nuclear stain DAPI (seen in BLUE).

2. To establish multi-potential human CNS progenitor cell culture system to be used to investigate neurodegenerative diseases.

Understanding HIV neuropathogenesis remains a challenging task mainly due to lack of good animal models for HIV-1 and limited access to brain tissue at different stages of HIV infection or AIDS. An in vitro human fetal brain cell culture system offers a great deal of benefit for studying the modulations at cellular and molecular levels following exposure to viral protein, particularly when animal models for studying HIV-1 neuropathogenesis are not available.

As a long-term goal to establish a novel cell culture model of human fetal CNS progenitor cells, we have successfully isolated and cultured several lines of human fetal CNS progenitor cells in our laboratory. This cell culture system provides an excellent model for our studies with HIV-1 tat protein as well as transfection studies. Characterization studies on the CNS progenitor derived astrocytes reveal that human astrocytes derived from the CNS precursor cells in our laboratory express Glutamine synthetase, GLT-1, GLAST and antioxidant enzyme ceruloplasmin. These astrocytes were also found to be capable of producing inflammatory cytokines and chemokines like IL-6, IL-8, IP-10, MCP-1/CCL2 and RANTES following induction with IL-1beta and eliciting calcium waves like normal human astrocytes. We are also investigating into properties of neurons differentiated from these CNS progenitor cells and we have found that these cells can be differentiated into

tyrosine hydroxylase (TH) positive neurons and these neurons are immunopositive for synaptophysin as well. Detailed characterization of this cell culture system, particularly of the neurons so developed is in progress.

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V. Sharma, M. Mishra, S. Ghosh, R. Tewari, A. Basu, **P. Seth** and E. Sen (2007) : Modulation of Interleukin-1 β mediated inflammatory response in human astrocytes by flavonoids: Implications in neuroprotection. **Brain Research Bulletin** 73(1-3):55-63.

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P. Seth. Neuronal Apoptosis and Chemokine Production By HIV-1 Tat Protein Derived From Clade B And C In Human Fetal Neural Precursor Cells. Invited Speaker, in International Society of Neurochemistry, Symposia on Neuropathogenesis of HIV-1 Dementia, Silver Jubilee meeting of Indian Acad. of Neuroscience, Lucknow, Dec 2006.

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Collaborators

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

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

Funding

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Characterization of Human Fetal Brain Derived Neural Stem Cells as a Model for studying neurodegenerative disease. PI- Pankaj Seth. Dept. of Biotechnology, Ministry of Science and Technology, Govt. of India.

For three years – No. BT/PR6615/Med/14/857/2005.

Study of the signaling cascades involved in the proliferation and differentiation of Cancer Stem Cells in Glioblastoma

Principal Investigator : Dr. Ellora Sen

Research Fellow : Vivek Sharma

Technical assistant : Uttam Kumar Saini

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. 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 signalling abnormalities leading to their inability to differentiate.

Both stem cells and cancer cells are capable of unlimited proliferation. Neural stem cells and lineage restricted progenitor cells possess features of cancer cells of the CNS such as proliferative potential and diversity of progeny. 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. Importantly, NSCs are regulated by the same cellular pathways that are active in gliomas. 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 contain 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.

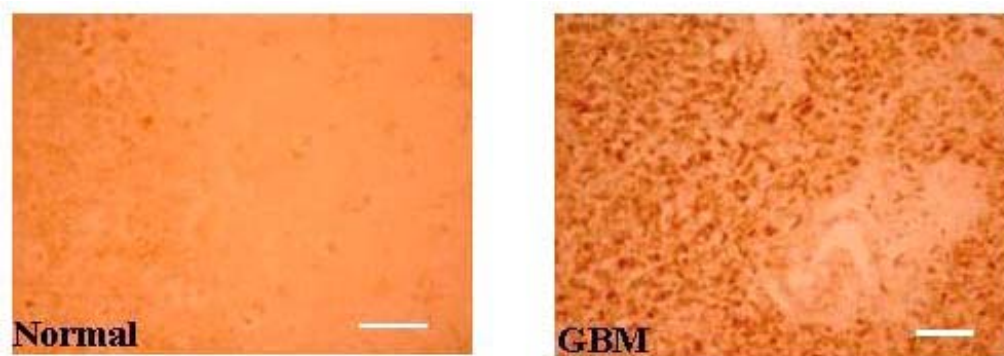


Figure: Increased expression of Hypoxia Inducible Factor (HIF) in Glioblastoma biopsy as compared to normal sample

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 signalling 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.

We have been able to isolate stem like cancer cells as free floating neurospheres both from glioblastoma cells line and GBM patient biopsy samples. These spheres were positive for the expression of neural stem cell markers-Nestin and Mushashi and IQGAP-1-a marker of brain cancer stem cell. These cells were able to differentiate into both neuronal and glial lineages-as demonstrated by expression on neuronal marker Tuj1 and glial marker GFAP. An increased expression of IL-1 β was observed in GBM patient sample as compared to the normal tissue adjacent to the tumor. We have also demonstrated that hypoxia induces IL-1 β expression in glioblastoma cell lines

Presentations

“Hypoxia and cell fate: Implication in Neuropathologies” at IICB, Kolkata, 2006.

“Inside story of glioblastoma: Proliferation and differentiation of Cancer stem cells” (Invited speaker National Symposium on 21st Century Research in Biochemistry and Biophysics, Kalyani University, 2007).

Understanding the molecular mechanisms involved in inflammation mediated glioblastoma progression. Presented at All India Cell Biology Conference, 2006.

Collaborators

Dr. VS Mehta, Paras Hospital

Funding

Department of Biotechnology

Role of Lipid rafts and Membrane Fluidity in GBM progression

Principal Investigator : Dr. Ellora Sen

Research Fellow : Richa Tewari

Progression of GBM is associated with alterations in growth promoting and cell cycle control pathways. The signal to divide is typically provided by growth factors and interaction of such ligands to its respective receptors modulates signal transduction cascades whose activity is linked with cellular processes such as mitosis and invasion. Most receptors are known to be associated with lipid rafts (subdomains of the plasma membrane rich in cholesterol and glycosphingolipids). By assembling a spectrum of signaling molecules, lipid raft facilitates cross talk between different signaling pathways. Lipid rafts also participate in signal transduction pathways activated by oxidative stress and inflammation- both of which have been implicated in the prognosis of glioblastoma. We therefore chose to investigate whether altered localization of receptors in the rafts versus non-raft portion in glioblastoma, could possibly contribute to the aberrant signaling associated with the pathogenesis of this disease under oxidative stress and inflammation. As modulation and functionality of lipid rafts can be achieved with cholesterol modulating agents, the feasibility of suppressing aberrant signaling through lipid rafts in GBM by agents that affect cellular cholesterol level will also be investigated.

We have been successful at isolating Lipid Raft fractions from different glioblastoma cell lines using optiprep gradient. That the fractions are lipid raft have been confirmed by Western Blot analysis using raft specific markers Caveolin and Flotillin and non-raft marker Transferrin. We are currently investigating whether inflammation affects the localization of receptors and signaling molecules in the rafts, and its consequences on the progression of GBM.

Presentations

Lipid Rafts: An organizing platform for signal transduction events in Glioblastoma multiforme. Presented at Indian Academy of Neuroscience, 2006

Involvement of lipid rafts in modulating signal transduction events associated with Glioblastoma survival, Presented at All India Cell Biology Conference, 2006

Oligodendrocyte Differentiation from Neural Stem Cells: Implication in CNS repair

Principal Investigator : Dr. Ellora Sen

Project Assistant : Christy Joseph

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.

We have been successful at isolating Neurospheres from the subventricular zone of rat pups. Since transdifferentiation of a glial progenitor into an astrocyte rather than an oligodendrocyte could underlie the permanent deficit in oligodendrocytes, the ability of hypoxia to affect the differentiation of glial progenitor cells into one lineage at the expense of the other is currently being investigated.

Publications

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Funding

Department of Biotechnology

Molecular and Cellular Mechanisms of Memory Formation

Principal Investigator : Dr. Shiv Kumar Sharma
Research Fellow : Chinmoyee Maharana
Project Assistant : Vivek Mahadevan, Seethalakshmi
Lab Attendant : Narayanan

The number of trials and temporal spacing between trials during training play a deterministic role in memory formation: memory is more robust when the trials are temporally spaced (spaced training) than when they are presented together (massed training). Also, multiple trials applied in a spaced pattern are more effective than a single trial. Activity-dependent molecular and synaptic changes are thought to contribute to synaptic plasticity and memory.

We are examining the changes in signaling molecules that may contribute to differential memory formation by a single trial and multiple trials applied in a massed or spaced pattern. We focus our study on the adult hippocampus, a preparation that has been commonly used for the studies of long-term potentiation in mammals and is particularly important for memory. Two different protocols of in vitro stimulation of adult hippocampal slices are used: KCl depolarization and NMDA application. These protocols rely on different mechanisms of Ca^{++} influx, a primary event in the induction of synaptic plasticity. We are examining the activation profile of extracellular signal regulated kinase (ERK) because this kinase appears to serve as a molecular node during the induction of synaptic plasticity and memory.

- (i) ERK activation by KCl depolarization. We induce activity-mimicking depolarization by application of KCl pulses to the in vitro prepared adult rat hippocampal slices and examine ERK activation in the CA1 region. We find that a single pulse, multiple spaced pulses or a massed pulse of KCl, all activate ERK immediately after stimulation. However, there is a difference in the activation profile by these patterns of stimulation. Preliminary results suggest that there is a difference in the activation profile of ERK by massed and spaced KCl applications. Given the observation that long-term synaptic plasticity and long-term memory require new protein synthesis, we are examining whether sustained activation of ERK requires new protein synthesis.
- (ii) ERK activation by NMDA. Given the importance of NMDA receptor signaling in synaptic plasticity and memory, we are examining ERK activation by NMDA also. We find that a single pulse, multiple spaced pulses or a massed pulse of NMDA activate ERK immediately after

stimulation. The interesting question that we are now asking is whether ERK is differentially activated by different patterns of stimulation.

Mechanisms of Neurodegeneration and Synaptic Plasticity Impairment by Oligomeric Form of Amyloid Beta

Principal Investigator : Dr. Shiv Kumar Sharma

Research Fellows : Shilpa Mishra

Alzheimer's disease is the most common form of dementia in the elderly. The disease is characterized by the presence of amyloid plaques and neurofibrillary tangles. The presence of amyloid fibrils in the plaques led to the suggestion that this form of amyloid beta may primarily be responsible for the development of the disease. However, there is little or no correlation between the plaque burden and the extent of memory impairment. The presence of oligomeric form of amyloid beta in the brains of AD patients and the transgenic animals models, led to the suggestion that this form of amyloid beta may have a role in this disease. Recent studies suggest that the oligomeric form of amyloid beta may be more relevant than the fibrillar form for synaptic loss, synaptic plasticity impairment and neuronal cell death at least in the initial stages of the disease.

Our primary aim is to examine the mechanisms of neurodegeneration and synaptic plasticity impairment by amyloid beta oligomers. Currently our efforts are directed towards examining the mechanisms of neurodegeneration. For these studies, we are using a hippocampal cell line that can be differentiated using tetracycline. We are examining the toxicity of amyloid beta from two angles: (1) direct toxicity to neurons, and (2) toxicity caused by the effect of amyloid beta on microglial cells (inflammation-mediated toxicity). For direct neuronal toxicity experiments, we used freshly prepared, oligomeric (prepared by two different protocols) as well as aggregated forms of amyloid beta (1-42). All three forms of amyloid beta caused cell death of the differentiated hippocampal neurons in a concentration dependent manner. Moreover, the undifferentiated cells seem to be more susceptible to oligomeric amyloid beta toxicity than the differentiated cells. For indirect neuronal toxicity experiments, we used a microbial cell line. Treatment of the microglial cell line with amyloid beta oligomers increased the secretion of several chemokines and cytokine. We are now examining the molecular mechanisms of both direct and indirect cell death caused by amyloid beta oligomers.

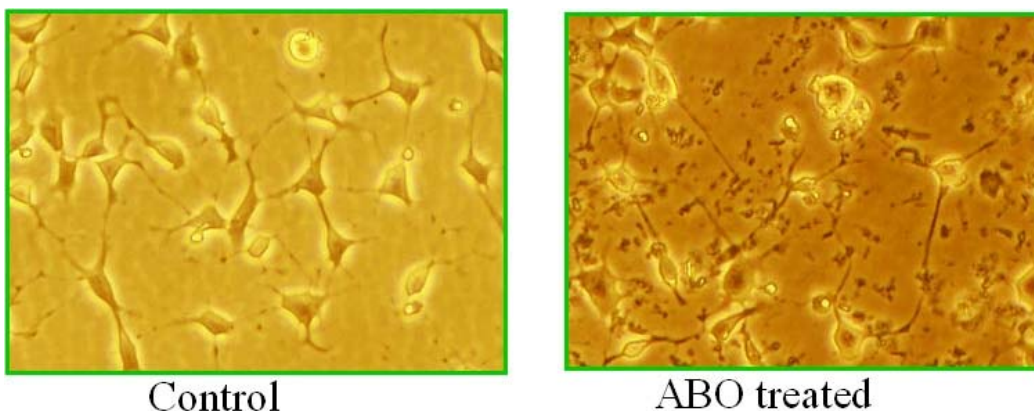


Figure: ABO cause neuritic degeneration. Differentiated HC2S2 cells were treated with in vitro prepared amyloid beta oligomers (ABO). The amyloid beta treated cells show extensive degeneration of neurites.

Publications

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Presentations

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Funding

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Molecular approaches to understand the pathophysiology and pharmacology of infection and inflammatory disorders of Central Nervous System

Principal Investigator : Dr. Anirban Basu
Research Fellow : Manoj Kumar Mishra, Rachna Duseja, Sulagna Das
MSc student : Vivek Swarup
Project Assistant : Joydeep Ghosh
Technical Assistant : Kanahaiya Lal Kumawat

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

Our initial focus is to understand the pathophysiology of infection in Japanese Encephalitis. We have found that the induction of proinflammatory cytokines following JEV infection exhibited region selective expression in the brains of animals, with the highest expression observed in the hippocampus. We have further observed that the expression of neuron specific nuclear protein NeuN was markedly downregulated during progressive infection indicating neuronal loss. In vitro studies further confirmed that microglial activation and subsequent release of various proinflammatory mediators induces neuronal death following JEV infection. We have also continued our work with astrogliosis following JE. Using a cell culture model system we are now trying to dissect the molecular mechanism how JE virus infection modulates the various physiological events related to astrocytes's function or dysfunction. Last year we had just initiated our work on how inflammation following JEV infection modulates neurogenesis and gliogenesis. At this point of time we found that JEV infection causes a profound loss in number of neuronal stem cells as well as number of immature neurons. Neurospheres isolated from the SVZ of JEV infected animals have 1) less potential to form multipotential neurospheres and, 2) their average diameter is smaller when compared to a neurosphere isolated from the SVZ of uninfected animals.

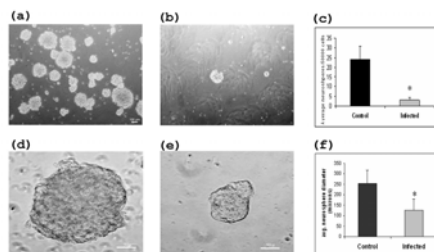


Figure1: Neurospheres as cultured from control and JEV-infected BALB/c mice pups (P7) under 10X magnification. Numerous spheres were formed from control animals (a) as compared to only a few from the JE infected animals (b). The graph represents the average number of spheres formed per 50,000 cells in control and infected animals (c). Moreover, significant difference in the size of the spheres grown from control (d) and infected (e) animals is noted (as seen under 40X magnification). The graph represents the larger diameter of the control neurospheres as compared to the JE infected ones.

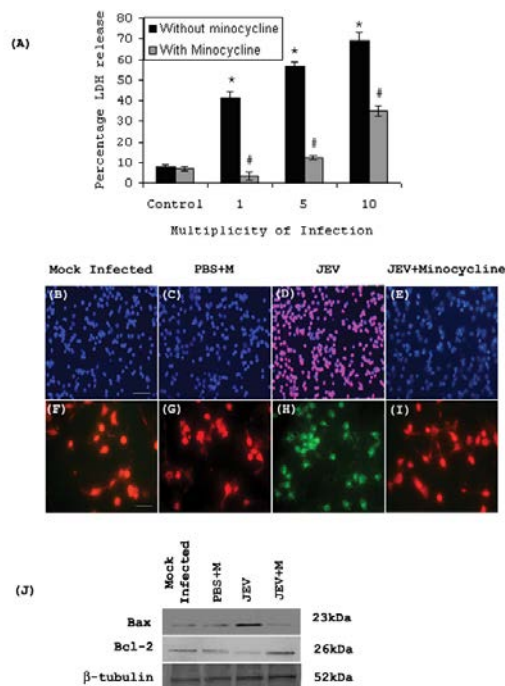


Figure 2 : Neuro2a cells were pre-treated for 1 hr with minocycline at concentration of 20nM in serum-free media. Cells were then incubated with JE virus at different multiplicity of infection (MOI) for 1 hr. The virus was removed and the plates were then washed with 1X PBS to remove the unbound virus. The plates were further incubated in minocycline (20nM) containing serum-free media at 37° C for next 24 hrs. JEV infected Neuro2a cells show significant increase in release of LDH, compared with mock infected cells and after pre- and post-treatment with minocycline (20 nM) show significant reduction in LDH release, compared with only JEV infected N2A cells (Fig.6A). TUNEL assay of mouse neuronal cells (N2a), showing TUNEL positive cells (red) co-localized with DAPI. Negligible cell death was observed in control whereas profound increase in the number of TUNEL positive cells seen when N2a was co-cultured with JE virus. Moreover, almost negligible TUNEL positive cells were seen in minocycline treated cells. A dramatic decrease in TUNEL positive cells was noted, indicating anti-apoptotic role of minocycline (Fig.6B-E). Neuro 2a cells were exposed to minocycline for 24 hrs. and then subjected to JC-1 staining to study the changes in the mitochondrial membrane potential. JC-1 specifically detects the polarized mitochondria as red,

and the depolarized membrane becomes green (Fig.6F-I). The JEV infection profoundly decreased the mitochondrial membrane potential as evident from the loss of red mitochondrial staining. Western blot showing Bax and Bcl-2 expressions in N2A cells after JEV co-culture for 24 hrs (Fig.6J). Minocycline robustly reverses these effects. SEM from 3 independent experiments performed in duplicate. $P < 0.01$. Scale Bar = 50 μ m.

Increasing experimental, clinical, and epidemiological studies point to the pivotal role of inflammation in the pathogenesis of acute and chronic neurodegenerative diseases and to the protective effects of anti-inflammatory drug therapies. Given the potential therapeutic role of these compounds in neuro-inflammation, we have initiated a project to evaluate the role of understanding the molecular mechanisms of action of both known and newly synthesized chemical entity in conferring protection from CNS inflammation and infection. Work in our laboratory for last one year identified the neuroprotective role of minocycline in JE. Our findings clearly indicates that minocycline 1) reduce enhanced microgliosis 2) decrease the elevated level of proinflammatory cytokine and 3) enhance neuronal survival by reducing the severity of apoptotic cascades following JE. Recently we have identified Rosmarinic acid, a phenolic compound found in various Labiatae herbs, as a potent anti viral agent against Japanese Encephalitis.

Publications

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Presentations

A Basu, Molecular mechanisms of microglial activation and neurodegeneration in Japanese Encephalitis (2006), 6th NBNI meeting, 23-24th July, Kyoto, Japan. (Invited speaker)

M K Mishra, P Koli, and A Basu, Neuroprotection conferred by astrocytes is insufficient to protect animals from succumbing to Japanese Encephalitis (2006), 75th Annual Meeting of the Society of Biological Chemists, 8-11 December, JNU, New Delhi.

V Swarup, S Das and A Basu, Molecular Mechanism of Japanese Encephalitis Virus (JEV) Induced Neuronal Apoptosis (2006), 3rd NBRC International Conference, 13-15 December, IARI campus, New Delhi.

V Swarup, S Das and A Basu, Japanese Encephalitis Virus (JEV) Infection Induces Tumor Necrosis Factor Receptor-1 Mediated Neuronal Apoptosis (2006), 24th Annual Meeting of the Indian Academy of Neurosciences, 17-20 December, Lucknow.

M K Mishra and A Basu, Astrocyte activation by Japanese Encephalitis Virus triggers enhanced expression of Glutamate Transporters, Acute Phase Protein and Neurotrophic Factors (2006), 24th Annual Meeting of the Indian Academy of Neurosciences 17-20, December, Lucknow.

A Basu, Pathogenesis of Japanese Encephalitis: Do we need to look differently? (2006), 26th December, National Institute for Cholera and Enteric Diseases (NICED), Kolkata. (Invited speaker).

V Swarup, S Das, S Ghosh and A Basu, TRADD: A double Edged Sword- Implications in Viral Encephalitis (2007), 30th All India Cell Biology Conference, 2-4 February, Department of Zoology, University of Delhi, Delhi.

R Duseja, V Sharma, R Tewari, M K Mishra and A Basu, Modulation of Membrane Dynamics of Neuron and Glia following Japanese Encephalitis: Implication in the progression of Disease (2007), 30th All India Cell Biology Conference, 2-4 February, Department of Zoology, University of Delhi, Delhi.

A Basu. Human Brain: The Final Frontier of Science (2007). National Science Day (28th February), Kendriya Vidyalaya, NSG Campus, Manesar. (Popular Lecture)

Patent Applied

Minocycline as a therapy in Japanese Encephalitis. A Basu and M K Mishra [Application No: 211/DEL/2007]

MSc Thesis

Ayan Ghoshal : Microglial activation and induction of multiple pro-inflammatory mediators in an experimental model of Japanese Encephalitis.

Sourojit Bhowmick : Differential Expression of IP-10 (CXCL-10) following Japanese Encephalitis.

Collaborators

Dr. Sudhanshu Vrat, National Institute of Immunology, New Delhi

Dr. U.K. Misra, Department of Neurology, SGPGIMS, Lucknow

Funding

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



System & Cognitive Neuroscience

Capacity limitations in visual perception and the effect of modulation of attention on the capacity in perception

Principal Investigator : Dr. Shobini L. Rao

M.Sc. Student : Sucharit Katyal

Attention is capacity limited and places a limitation on information processing in perception. Capacity is limited according to early selection theories, while it is unlimited according to late selection theories. The load theory attempts to resolve the conflict by proposing that late selection occurs at low perceptual load and early selection takes place at high perceptual load. No resolution has yet been reached though, as to what is the capacity of perception or indeed what effect does attentional modulation has on the perceptual capacity. In the present study 3 experiments were conducted to investigate the capacity of visual perception and the effect of modulation of attention on the capacity in perception.

A novel paradigm was designed to investigate the perceptual capacity, in which a probe alphabet was presented in the centre surrounded by multiple alphabets as distractors. The probe may or may not have matched with one of the surrounding alphabets. The accuracy of the participants to detect the presence or absence of a match was used to estimate the capacity in perception. The sample for each experiment was 30 normal adult volunteers. In Experiment 1 the surrounding distractors were presented in four set-sizes, of 2, 4, 6 and 8. Attention of the participants was modulated by presenting the stimulus in four levels of stimulus to background contrast. In Experiment 2 the number of distractors was increased and the arrangement of the stimuli modified to prevent a word reading effect that might have been present in Experiment 1. Set-sizes of 4, 6, 8 and 12 were used for Experiment 2. Finally, Experiment 3 was conducted to investigate the effect of uncertainty in responding matched or non-matched using the same four display sizes as in Experiment 2. The uncertainty was tested by giving an additional response choice to the participants to respond with a 'don't know' along with responding 'Yes' and 'No' for the matched or non-matched conditions respectively. The stimulus display and response recording was computer controlled with the 'Psytask' software developed by Mr. Sucharit Katyal at NBRC.

Results from Experiment 1 and 2 indicated that in the matched condition, the accuracy decreased significantly between set-sizes 2 to 4 and set-sizes 4 to 6. However, there was no significant decrease in accuracy between set-sizes 6 to 8 as well as set-sizes 8 to 12. This counter-intuitive effect was referred to as the plateau effect which is shown in figure 1.

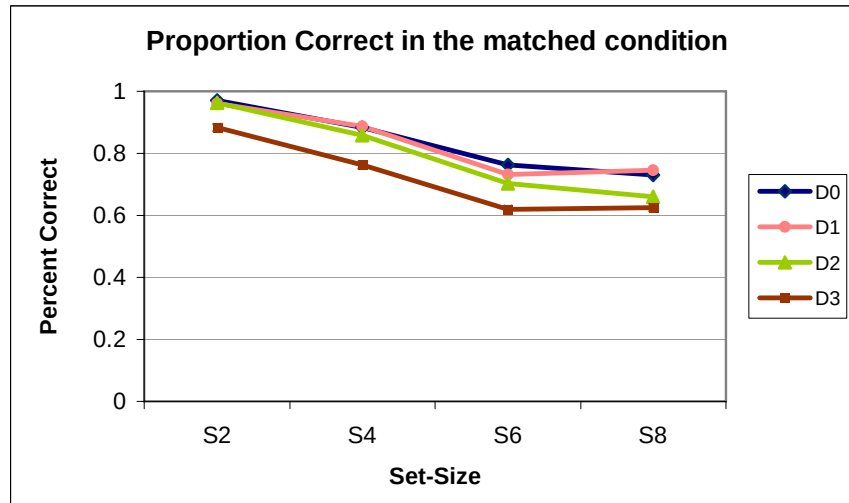


Figure1: Experiment I - Proportion Correct in the matched condition for each degradation level (D0-D3), at each set-size (S2-S8)

The plateau effect was consistent with the load theory in perception. According to the load theory when the perceptual capacity limit is exceeded, the information to be processed has to be selected. In accordance with this proposition both in Experiment 1 and 2, late selection occurred up to set-size 6, beyond which early selection took over. Further, the plateau effect was present for all the four degradation levels. It is significant that even when the stimulus display became circular, the plateau effect persisted in the matched condition of experiment II as indicated in figure 2.

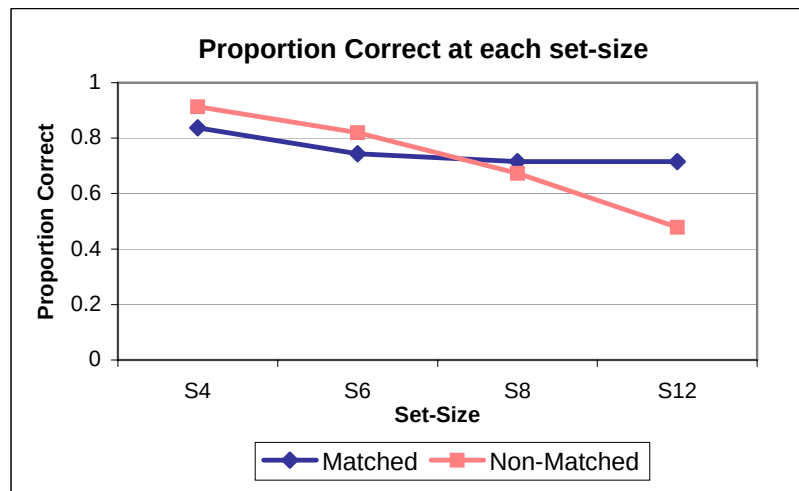


Figure2: Experiment II - Proportion correct for Matched and Non-Matched condition at each set-size

Experiment 3 showed that uncertainty was higher in the non-matched condition than the matched condition, with well below chance level accuracy for the non-matched condition at set-size 12 and above chance level accuracy for the matched condition even at set-size 12.

It was concluded from the study that the capacity of visual perception is limited to about 6 channels and the capacity in perception was not affected by modulation of attention.

Functional Neuroanatomy of Perceptual Load and Effect of Emotion on Capacity for Visual Perception of Words

Principal Investigator : Dr. Shobini L. Rao

M.Sc. Student : Anasuya Das

Emotional stimuli capture our attention by preferentially accessing the focus of attention. As attention limits the capacity for perception, the project examined whether the perception of emotional stimuli would be capacity limited. Emotional words were used to study the effect of emotion on the capacity limits for visual perception.

Two behavioral experiments were conducted with 30 normal adult volunteers in each experiment. A match to sample paradigm was used, wherein a central probe word was matched with one of the surrounding words. There were three types of stimulus displays, neutral, positive valence and negative valence. In the Task I a block design with all the stimulus displays belonging to the same valence was followed. Increase in the number of words, i.e. 2, 4, 6 & 8 increased the perceptual load. Results showed that as the level of perceptual load increased there was a decrease in performance. Performance was maximal at set size 2 and at chance for set size 8 with a plateauing in performance between set size 4 and 6. Effect of emotional valence was non significant and attributed to habituation. Figure 1 shows the results of Task I.

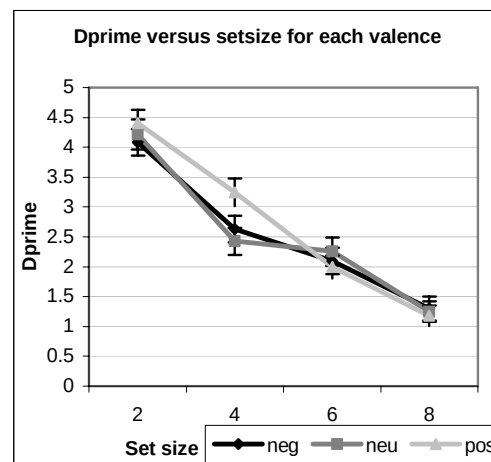


Figure1: Task I

Task II randomised emotional valence and showed a significant main effect of emotional valence. Performance was at chance level in set size 6. Negative valence maintained speed of response at the cost of accuracy as would be expected of a system that is geared for a fight or flight response. Positive valence maximized accuracy at the cost of speed implying that accuracy is more important than speed in the context of reward. Neutral words had a

performance that was intermediate to negative and positive valence with no trade-off on speed or accuracy.

The functional neuroanatomy of perceptual load was studied with fMRI. A modified version of task I with only neutral words (neutral word task) was used. 10 normal adult volunteers were scanned at 3 Tesla. Successful localization in the visuo-motor and verb-generation task validated the activations obtained in the neutral word task. The activations in the visuo motor task and the verb generation task are shown in figures 2, 3 and 4.

Figure 2 Motor activation associated with finger tapping by the left hand

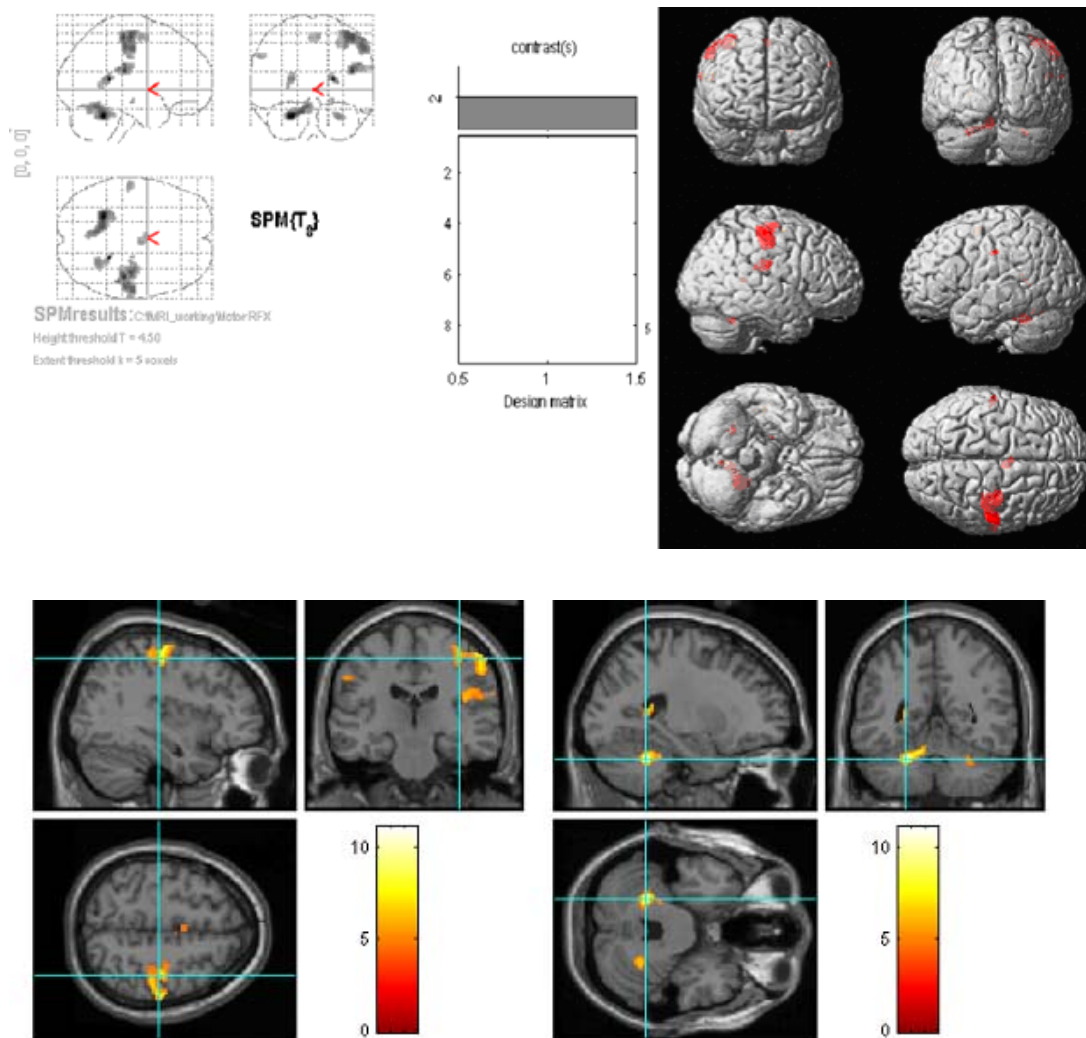


Figure 2: Activation obtained for the motor- visual contrast. a) Maximum intensity projection on a glass brain showing all significant voxels. b) Section-wise overlays showing activation in the right post-central (contralateral to left hand finger tapping) and pre-central gyrus i.e somato-motor cortex. c) Section overlays showing predominantly left cerebellar activation. (Global maxima was in the left cerebral cortex). Intensity scales for b and c are based on increasing t-values. The activations have been overlaid on a single subject T1 image. d) Surface rendering on a single subject T1 brain.

Figure3 Visual activation associated with visual stimulation by the checkerboard
&
Visual Activation - Brain regions showing activation for Visual-Motor condition

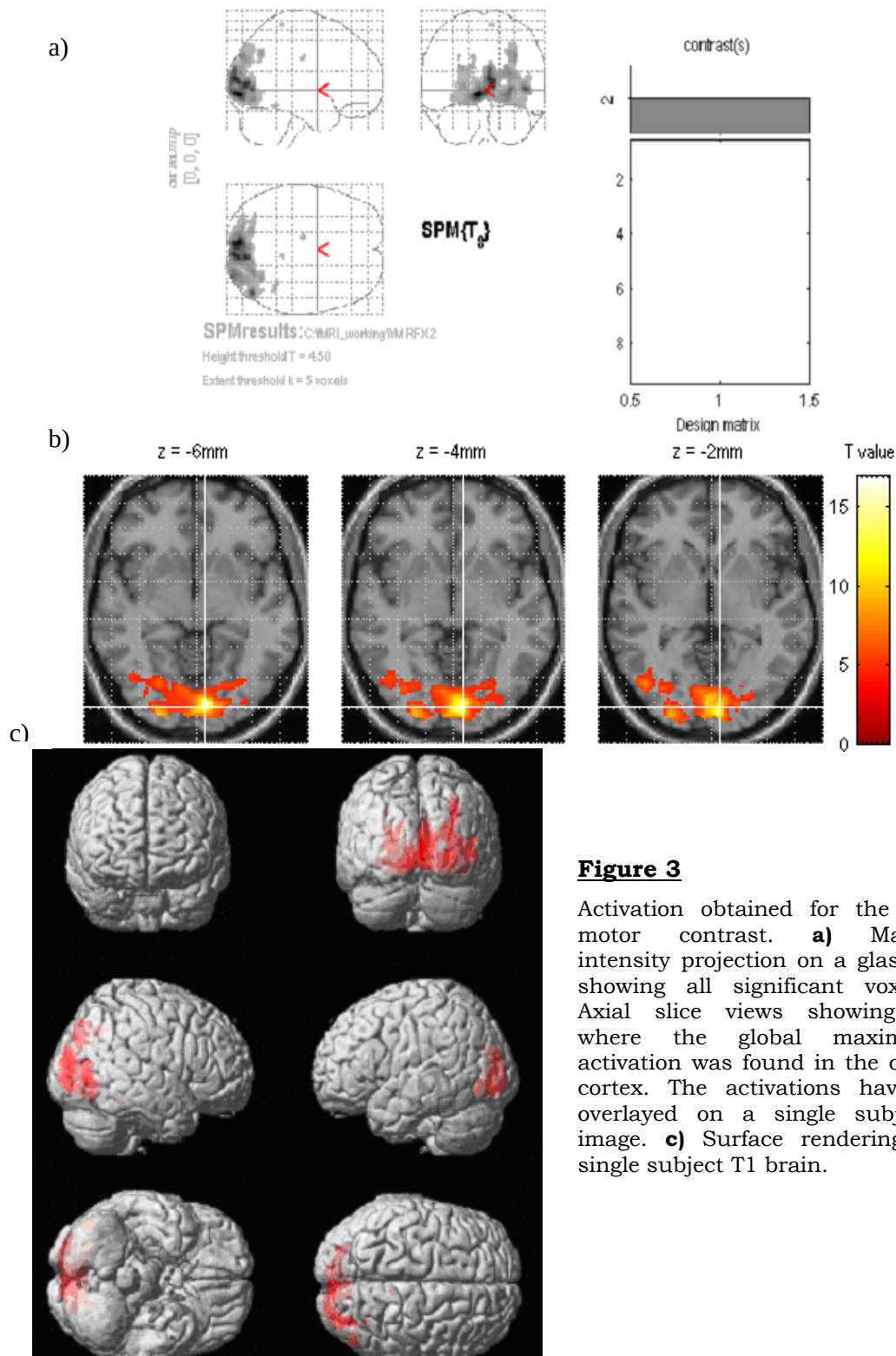
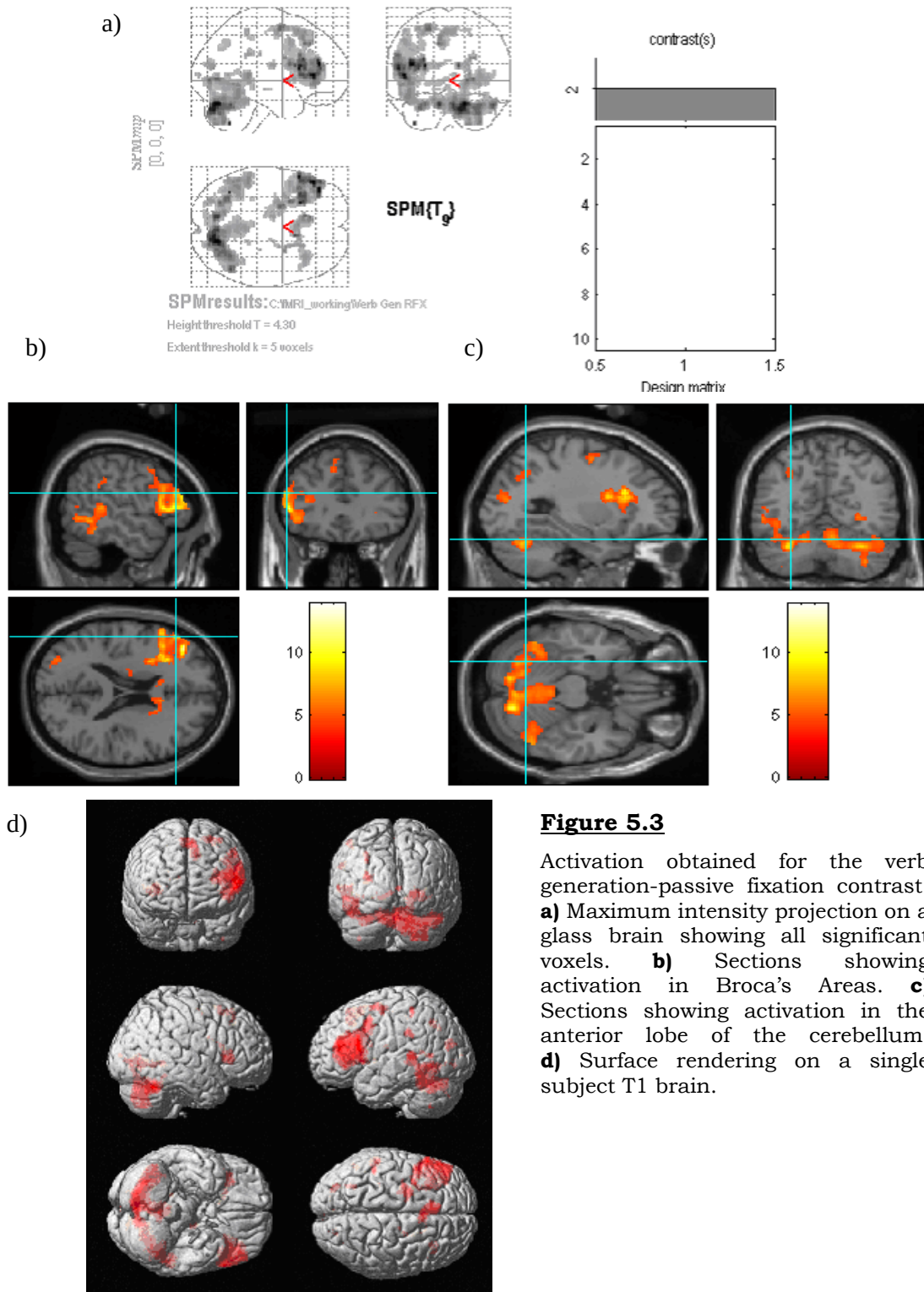


Figure 3

Activation obtained for the visual-motor contrast. **a)** Maximum intensity projection on a glass brain showing all significant voxels. **b)** Axial slice views showing slices where the global maxima for activation was found in the occipital cortex. The activations have been overlaid on a single subject T1 image. **c)** Surface rendering on a single subject T1 brain.

Figure 4: Verb Generation -Brain regions for the verb generation -passive fixation condition



In the neutral words task designed to examine the brain areas mediating perceptual load, predominantly motor activity was seen in set size 2. Increased left lateralized activity was observed as perceptual load increased.

Increased activation in the visual word form area was found as the number of words presented increased. Different nodes in the fronto-parietal attention network were activated for set size 4 and set size 6. Posterior parietal activations were greater in set size 4 indicating a recruitment of spatial attention. Dorsolateral prefrontal activations were greater in set size 6 indicating the recruitment of executive attention. A double dissociation was seen between low vs. high perceptual load and spatial vs. executive attention.

A Study of Working Memory in Infants

Principal Investigator : *Dr. Shobini L. Rao*

M.Sc. Student : *Rubeena Shamsudheen*

Project Assistant : *Anuradha Sharma*

Developmental cognitive neuroscience studies the development of cognition in infancy and childhood and relates it to brain development. The field has led to discoveries of cognitive capacities of infants which far exceeds the expectations of the infant as a 'tabula rasa'. Working memory, the online storage and manipulation of information, is an important component of cognitive capacities such as memory, learning, thinking and reasoning. Infants possess working memory for locations and objects known as spatial and object working memory respectively. The project aimed to examine the developmental trajectory of spatial and object working memory in infancy.

The sample consisted of normal infants in the age range of 3-11 months, divided into three different age levels of 3-5 months, 6-8 months and 9-11 months. A cross sectional design was used with the above 3 age groups and three delay intervals of 3, 6 and 9 seconds. The delayed response paradigm was used. The experiments were video recorded and offline analysis was performed.

Spatial Working Memory

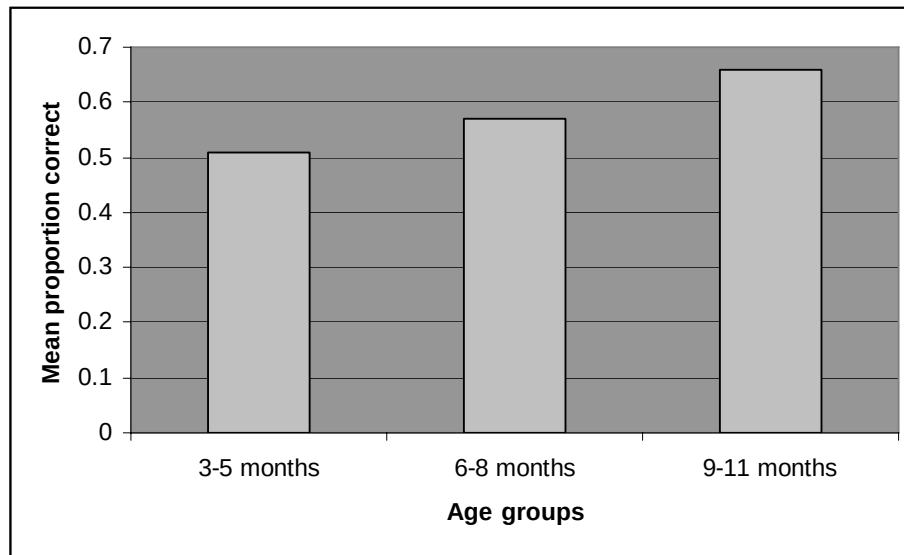
In the spatial working memory task, conducted on 55 infants, the infant seated on the mother's lap faced a table with two boxes. The experimental set up is shown in figure 1.

Figure 1 **Experimental set up for Spatial working memory**



A toy was shown from one box and after a variable delay the toy was shown again from the same box. Infant's gaze direction to the box from which the toy had appeared indexed spatial working memory. The results found that spatial working memory developed from 3 to 11 months and did not reach maximum levels even at 11 months. Across the ages spatial WM was better at the shorter delay duration of 3 seconds compared to the longer delay duration of 9 seconds. Figure 2 shows the proportion correct of gaze direction in the three age groups across the delay intervals.

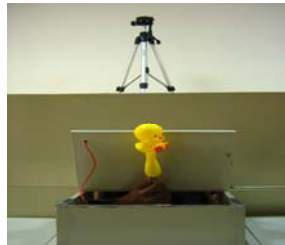
Figure 2 Mean proportion correct of gaze direction across delay intervals



Object Working Memory

Object working memory was also tested with the delayed response paradigm on 33 infants belonging to the age groups of 3-5 months , 6-8 months and 9-11 months. In this task, the infant seated on the mother's lap faced a table with one box. A toy appeared from the box and after a delay of either 3 or 9 seconds, the same toy or a different toy appeared from the same box. The experimental set up is shown in figure 2

Figure 2 Experimental set up for Object working memory



Infants have a strong novelty preference because of which they gaze longer at novel objects. Infants of gazed at the novel toy longer indicating working memory for the previously seen object. Object working memory was present even in the 3-5 months age group and even at the delay of 9 seconds.

The developmental trajectory of object and spatial working memory are different. Object working memory appears to develop early and is robust even at a long delay. Spatial working is continuing to develop even at 11 months and is disrupted by long delays. The developmental differences between the ventral and dorsal visual pathways is hypothesized to mediate these differences. The ventral pathway develops earlier, while the dorsal pathway develops later. Hence, object working memory mediated by the ventral pathway develops earlier than spatial working memory, mediated by the dorsal pathway which develops later.

Presentations

Rao S.L., Translational Research in Cognitive Neuroscience, Second International Conference on Cognitive Science, CBCS, University of Allahabad, December 2006.

Rao S.L., Translational Insights from Cognitive Neuroscience into the Clinical Management of Head Injury, Indo-US workshop on Developmental Neuroscience and Imaging, Indo-US Technology Forum, NBRC, February, 2007

Rao S.L., Environmental effects on brain, Brainstorming Meeting, NBRC, Mussorie, May 2006

Rao S.L., Brain Mediation of Behavior, Second National Conference in Mental Health – Mental Health Challenges 2020-A Vision for the Future, Amity Institute of Behavioral (Health) & Allied Sciences, Amity University, NOIDA, U.P., August 2006.

Rao S.L., Understanding and Assessment of Mental Load, Key note Address, National conference on Emerging Paradigms in Psychology, Defence Institute of Psychological Research, (DRDO), New Delhi, September 2006.

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Rao S.L., Cognitive deficits in Brain Damage, Dept. of Biological Sciences, Annual Talks, Tata Institute of Fundamental Research, Mumbai, August 2006.

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Rao S.L. Neuropsychological Assessment, CEN-2007, Continuing Education in Neuropsychology, NIMHANS, February, 2007.

Rao S.L., HIV and Counseling, Composite Hospital, National Security Gaurds, Manesar, (Haryana), May 2007.

Rao S.L., How to enhance student's memory?, In service course of TGT Social Science teachers, Kendriya Vidyalaya, NSG, Manesar, (Haryana), May 2007.

Rao S.L., Brain and Consciousness, India International Center, New Delhi, June 2006

Das, A. & Rao S.L. (2006) Effect of emotion on constraints in perceptual capacity, Third NBRC International conference, NBRC, Manesar, December 2006

Katyal, S. & Rao S.L. (2006) The capacity of perception and the role of attention, Third NBRC International conference, NBRC, Manesar, December 2006

Shamsudheen, R. & Rao S.L. (2007) A Study of Spatial Working Memory in Infants, Indo-US Workshop on Developmental Neuroscience and Imaging, NBRC, Manesar, February, 2007

Probing the control of action using saccadic eye movements

Principal Investigator : *Dr. Aditya Murthy*

Research Fellows : *Supriya Ray, Arjun Ramakrishnan, Sarika K.M., Vishal Kapoor*

Our visual sensitivity is not uniform but rapidly declines centrifugally from the centre of gaze as a result of which objects in the periphery cannot be identified clearly. To counter this problem our brain has evolved a mechanism whereby the visual scene is explored in discrete steps, each of them corresponding to an eye movement called a saccade, followed by a fixation. 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.

Long Term Goals: 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.

Self-control of internally guided/delayed responses

A planned action awaiting execution requires withholding a prepared response. We asked whether such a form of inhibition would interact with online decision processes that require changes in planned responses when new goals are unexpectedly specified. To investigate this issue with respect to oculomotor control, subjects performed, in separate sessions, standard visually (SV) guided saccades, or memory guided (MG) and delayed visually (DV) guided saccades, both of which required withholding of a planned saccade. To probe control, a second target (target-step) was presented in some trials after a variable delay, which instructed subjects to redirect their gaze to the newly specified target. The time taken to cancel or inhibit the saccade directed at the initial target, the target step reaction time, was calculated using a race model that hypothesizes a covert inhibitory process, and was found to be significantly smaller for MGR (94.8 ms; N=13) and the DVR (95.5 ms; N=11) compared to SVR (116.3 ms; N=12), suggesting facilitation of online inhibition in MGR and DVR. These results indicate that a tonic level of inhibition interacts with online decision processes to

potentiate inhibitory control during double-step tasks. Based on our results we propose a model to account for our findings.

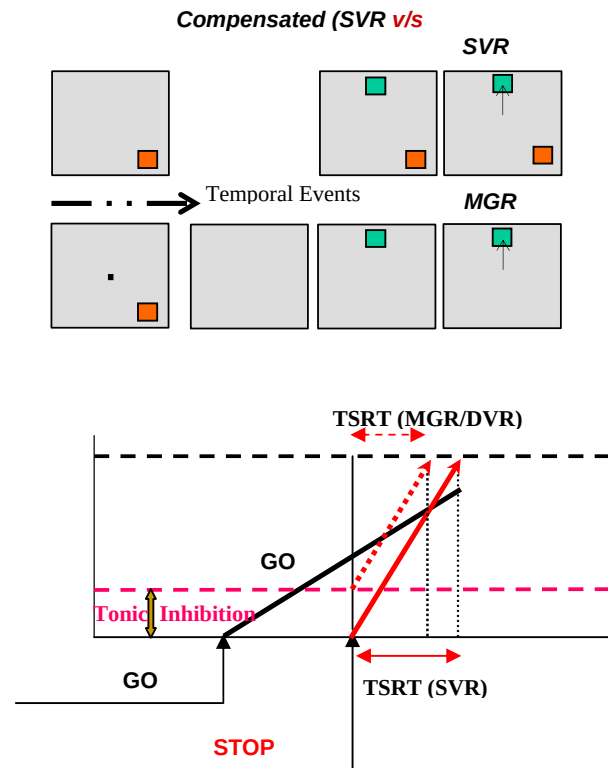


Figure: Proposed race model to understand the how covert inhibition interacts with online control in the redirect task

Publications

Kapoor V., and **A. Murthy** : Covert inhibition potentiates online control in a double-step task (submitted to **Journal of Vision**).

Presentations

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Aditya Murthy. The control of voluntary action during errors 6th Indo-Japan-Korea-China-Australia workshop in Neurobiology & Neuroinformatics, Kyoto, Japan. (2006)

Aditya Murthy, Supriya Ray & Sharika K.M. The control of saccadic eye movements during errors. Asian Conference on Vision, Matsue, Japan. (2006)

Vishal Kapoor & Aditya Murthy. Does covert inhibition potentiate online inhibitory control? Indian Academy of Neuroscience, Lucknow, India. (2006)

Aditya Murthy. To go or not to go: In search of the point of no-return in decision-making. 3rd International Conference in Neuroscience, NBRC, Manesar, India. (2006)

M.Sc. Thesis

K.M. Sharika : Cognitive control in the programming of sequential saccades.

Vishal Kapoor : Control of internally and externally guided actions.

Funding

A grant from DST, India

Brain Mechanisms of Action Control in Humans

Principal Investigator : Dr. Aditya Murthy

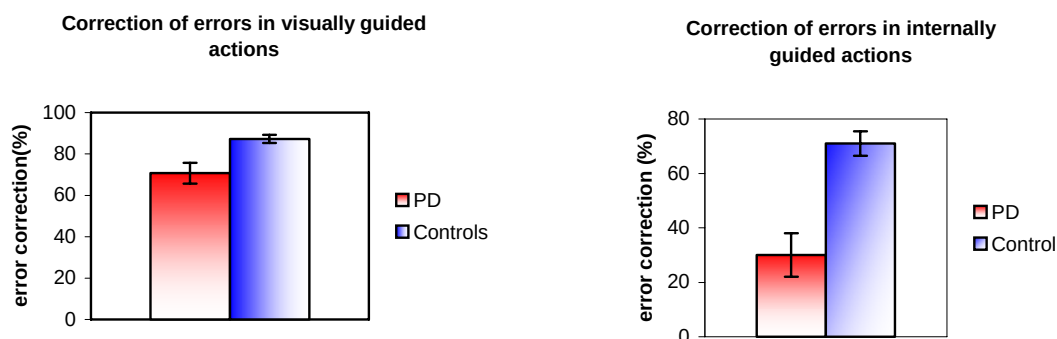
Research Fellows : Dr. Ausaf Farouqui, Shrikant
Kulashekhar, Anoop Raj K.

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. Madhuri Behari of CNS, A.I.I.M.S. where a facility to measure eye movements in real time under computer control has been set up.

Long Term Goals: The long term goal of these experiments is to understand the nature of control mediated by cerebellum and basal ganglia.

Brain mechanisms of error correction in basal ganglia.

Basal ganglia are strongly interconnected with areas of the medial frontal cortex, a critical node in the brain's performance monitoring system. On this basis we hypothesized an impairment in performance monitoring in Parkinson's disease (PD) patients. To test this hypothesis PD patients and age matched control subjects were tested on two "Redirect" tasks, which entailed canceling a partially prepared saccade on a fraction of trials, and redirecting the eyes to the new target. One version of the task required canceling a reflexive saccade (an external guided movement), while the other version of the redirect task required canceling a memory-guided saccade (internally generated movement). Errors (failure to cancel the initial saccade) occurred on some trials. The percentage of error correction i.e., corrective saccades was found to be significantly low in PD patients in both paradigms.



The error correction impairment in PD relative to controls was more pronounced for memory-guided saccades. These results suggest a role of basal ganglia circuitry in performance monitoring.

Publications

Joti, P., Kulashekhar, S., Behari, M. and **A. Murthy** : Impaired inhibitory control in patients with Parkinson's disease. **Experimental Brain Research** 177:447-57 (2007).

Presentations

Ausaf Farooqui, Srikanth Kulashekhar, Madhuri Behari* and Aditya Murthy : Performance monitoring in Parkinson's disease patients. 3rd International Conference in Neuroscience, NBRC, Manesar, India. (2006)

Collaborators

Prof. Madhuri Behari, Dr. Vinay Goyal and Dr. Aditya Gupta, All India Institute of Medical Sciences, New Delhi

Funding:

A grant from DBT provides support for the project.

Neural control of action by frontal-basal ganglia networks

Principal Investigator : *Dr. Aditya Murthy*

Research Fellows : *Arjun Ramakrishnan, Sarika K.M. Supriya Ray*

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

Long Term Goals : The long term goal of this project is to understand the neural representations that control our actions in basal ganglia/frontal cortex.

The role of FEF/basal ganglia to inhibitory control and error correction

We have trained two monkeys to perform a modified double-step task in which they need to cancel a preprogrammed saccade following the appearance of a new target. In some trials errors are produced that are quickly corrected resulting in the programming of sequential saccades. To understand how cognitive context modulates the programming and control of sequential saccades monkeys were also trained on double-step tasks in which they followed the sequence of target steps with successive saccades.

Based on the behavioral data of humans and macaques we have developed a computational model of sequential saccades that attempts to bridge the

conceptual gap between psychological theories of dual task performance and neurophysiologically inspired models of reaction time. We show that our model is not only able to account for the behavioral reaction times but is also able to explain how cognitive context maybe instantiated in neural networks that control sequential eye movements. We are currently in the process of testing our model by neurophysiological recordings and electrical stimulation of the Frontal Eye Fields in awake behaving monkeys.

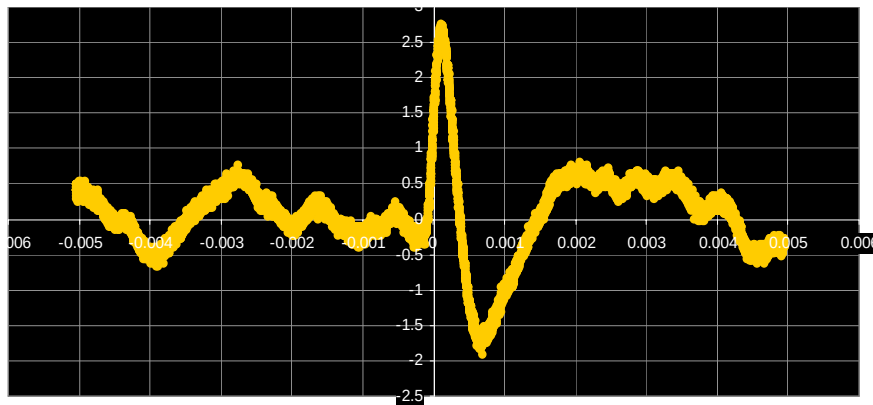


Figure: Neurophysiological recording of a single neuron in macaque frontal cortex during an oculomotor behavior.

Publications

A. Murthy, Ray, S., Shorter-Jacobi, S.M., Schall, J.D. and K.G. Thompson : Frontal eye field contributions to rapid corrective saccades. **J. Neurophysiology** 97: 1457-1469 (2007).

*C.R.Camalier, A. Gotler, **A. Murthy**, K.G. Thompson, G.D. Logan, T.J. Palmeri, J.D. Schall : Race model analysis of double-step and search-step saccade production in human and macaque. (**Vision Research**; In Press).

*Work done elsewhere

Funding

A grant from DBT

Processing and integration of tactile information in the somatosensory cortex

Principle Investigator : Dr. V. Rema

Research Fellows : Zia Ud Din, Manisha Chugh, Anshul Srivastava, Rahul Chaudhary

Project Assistant : Kiran Kumar Bali

Each of our sensory system is highly specialized to process the stimulus it receives. Despite this specialization the key mechanisms by which different modalities process sensory information would follow common principles. Our laboratory is interested in understanding the mechanisms by which somatic sensory system transduces and process patterns of tactile stimuli and how this information is encoded and integrated with motor performance. We are using electrophysiological and behavioural methodology to study somatosensory functioning of the adult rats and how it is affected by cortical injuries.

In the rat tactile stimuli is detected by the 25 large whiskers on each side of snout. Whiskers are moved across an object at different frequencies and this information is relayed to the somatosensory cortex via the brainstem and thalamic nuclei. In the cortex sensory information from each whisker is processed by neurons within a specific region called barrel column. In addition, the neurons within the barrel column integrate sensory information from adjacent barrel columns and from contralateral sensory cortex.

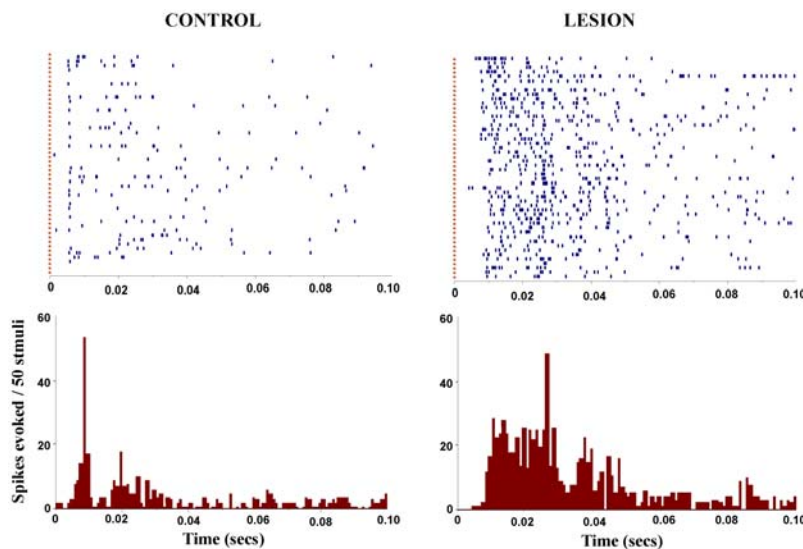


Figure: The figure shows the influence of motor cortex lesions on stimulus driven activity of neurons in the somatosensory cortex in rats. Top two panels show rasters plots from control (left) and lesioned animals (right). Each orange dot represents time at which stimulus was given.

Each blue dot represents an action potential generated by the neuron in response to the stimulus. Following each stimulus the response of the neurons was examined for 0.01sec. The raster plot shows the response profile for 50 stimuli.

The data is represented as post stimulus time histograms (PSTH) below the raster plot. The PSTH display shows the total activity of the neurons for each time bin. Significant increase in response magnitude of the somatosensory cortical neurons following injury to the motor cortex is seen. This suggests that motor cortex lesions cause disinhibition of neurons in the somatosensory cortex.

We have shown that a unilateral injury to a small area of the somatosensory cortex affects neurotransmission within somatosensory cortex of the intact opposite hemisphere.

Although the main sensory pathway to the unlesioned hemisphere is intact several alterations in sensory processing could be discerned to occur during initial 12 hour post-lesion time interval. The type and extent of changes in neuronal responsiveness depend on the location of the neurons with respect to the site of injury. The neurons exactly opposite the injury show reduction in response to sensory stimuli whereas neurons opposite to the edge of injury show increase in response magnitude. Responses of barrel column neurons to sensory information from the main whisker pathway are impaired. We also observe that these neurons do not integrate information arriving from adjacent whiskers. These changes seen in neuronal activity can be correlated to changes we see in the levels of molecules involved in excitatory (NMDA receptors) and inhibitory (GAD) neurotransmission. These early abnormal modulations in neuronal activity could be the cause of long-term deficiencies including experience-dependent plasticity seen after unilateral injury.

Behavioural consequence of injury to somatosensory cortex was tested using GAP-cross task. In this task a normal rat jumps across a gap from one platform to another if it can touch the edge of the platform with its whiskers. Animals with unilateral lesions cannot cross the GAP even if the whiskers from both sides of snout can contact the platform. Based on these results we conclude that bilateral integration of sensory information is crucial for information processing within the somatosensory cortex.

We also investigated whether somatosensory information processing is influenced by interconnected motor cortex. Though it is known that sensory input influences motor behaviour but the extent of reciprocal influence is not clear. To address this we removed the motor cortex and measured neuronal activity in the ipsilateral somatosensory cortex. Our results show that motor cortex regulates inhibition within somatosensory cortex

Presentations

Spatiotemporal changes in neuronal excitation and inhibition following unilateral somatosensory cortex injury. Zia Ud Din Darokhan, Manisha Chugh, Anshul Srivastava, Rahul Chaudhary & V. Rema. Poster

presentation. Wellcome Trust Senior Fellows' Meeting, 25-26 October 2006, London, UK

Modulation of neuronal activity in barrels of adult rats at early post-lesion times following injury to contralateral somatosensory cortex. Zia Ud Din Darokhan, Manisha Chugh & V. Rema. Poster presentation. Third NBRC International Conference, December 13-15 2006.

Stroke-like injury of motor cortex damage increases neuronal activity in ipsilateral somatosensory cortex. Manisha Chugh, Zia Ud Din Darokhan & V. Rema. Poster presentation. Third NBRC International Conference, December 13-15 2006.

Anomalous flow of sensory information in vibrissal system of protein malnourished rats. Anshul Srivastava, Zia Ud Din Darokhan, Manisha Chugh & V. Rema, Poster presentation. Third NBRC International Conference, December 13-15 2006.

Chronic protein malnourishment reduces sensory behaviour and NMDAR1 expression in rat cortex. Kiran Kumar Bali, Rahul Chaudhary, Anshul Srivastava, & V. Rema. Poster presentation. Third NBRC International Conference, December 13-15 2006.

Somatosensory processing is altered by photothrombotic stroke-like lesions in motor cortex. Manisha Chugh, Zia Ud Din Darokhan & V. Rema. Poster presentation. International Update on Basic and Clinical Neuroscience Advances and Annual Conference of Indian Academy of Neurosciences, December 17-20 2006, Lucknow, India

Effects of unilateral injuries to somatosensory cortex on receptive field properties in contralateral hemisphere. Zia Ud Din Darokhan, Manisha Chugh & V. Rema. Poster presentation. International Update on Basic and Clinical Neuroscience Advances and Annual Conference of Indian Academy of Neurosciences, December 17-20 2006, Lucknow, India

Somatosensory Processing is Deficient in Rats with Protein Malnutrition. Anshul Srivastava, Zia Ud Din Darokhan, Manisha Chugh & V. Rema. Poster presentation. International Update on Basic and Clinical Neuroscience Advances and Annual Conference of Indian Academy of Neurosciences, December 17-20 2006, Lucknow, India.

Protein Deficiency Alters Sensory Behaviour. Rahul Chaudhary, Anshul Srivastava, Kiran Kumar Bali & V. Rema. Poster presentation. International Update on Basic and Clinical Neuroscience Advances and Annual Conference of Indian Academy of Neurosciences, December 17-20 2006, Lucknow, India.

Enhanced neuronal branching in rats following CDP-choline treatment Kiran Kumar Bali, Renuka Ramachandra, Shailesh Gupta and V. Rema. Poster presentation. Indo-US workshop on Developmental Neuroscience and Imaging 2007, Feb 19-21, 2007 New Delhi, India

Funding

International Senior Research Fellowship from Wellcome Trust, UK
Department of Biotechnology.

Brain Reorganization following Spinal Cord Injuries

Principal Investigator : Dr. Neeraj Jain
Ph.D. students : Shashank Tandon, Niranjana Kambi,
Leslee Lazar, Radhika Rajan,
Mohammed Hisham
M.Sc. student : Shruti Muralidhar
Project Assistant : Hema Nawani

Information from tactile receptors is processed in a network of neurons located in the lower brain stem, thalamus and cortex. Motor areas, which initiate and control movements, receive inputs from the somatosensory system, which enables fine control of movements such as during palpation and grasp. Research in my laboratory is focused on understanding how the sensorimotor system processes sensory information to enable tactile perception and motor control, and how spinal cord injuries affect the functional organization of the system. The goal is to develop effective interventions for better recoveries in patients with spinal cord injuries by using the ability of the brain to undergo plastic changes.

In our experimental model the injury is induced by unilaterally lesioning the tracts in the dorsal funiculus of the spinal cord. This leaves the spinothalamic and other ascending pathways intact. Using multiunit mapping and intracortical microstimulation techniques we are determining effects of such injuries on the organization of the somatosensory and motor areas of the brain. The 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. We use both the rodent and the primate system for our study. Work done during the year is described below.

Considerable uncertainty exists regarding the normal organization of the primary motor cortex in rats and its variability across animals. Our experiments on normal rats reveal that organization of the motor cortex as determined by intracortical microstimulation is affected by the anaesthetic level at the time of the experiment. At low anesthetic levels when spontaneous whisking is present the medial most eye movement region in M1 is bordered laterally by whisker movement zone. Lateral to the whisker representation there is a region with representation of the arm movements and a small area with representation of the movements of the neck muscles. However, in rats mapped under deeper anesthesia no whisker region was seen in the primary motor cortex. The neck movement region expanded medially into the whisker region. Thus careful control of the anesthetic levels reveals overlapping representations of the neck and the whisker regions in the motor cortex (M1) of rats.

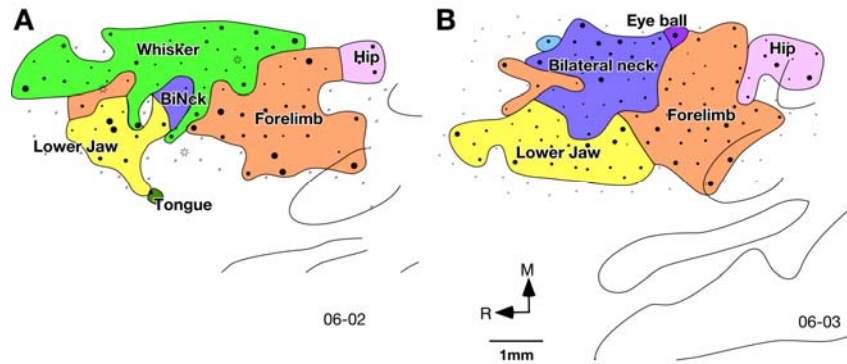


Figure: Organization of the movement map in the primary motor cortex of rats determined by intracortical microstimulation under (A) low and (B) high depth of anesthesia. Note that in the rat mapped under deeper anesthetic level the whisker movement could not be evoked. Instead movement of the neck was evoked from the same region

We mapped rats with unilateral lesions of the dorsal funiculus of the spinal cord at upper cervical levels. The rats were mapped 4– 14 months after the injury. Stimulation of neurons in the arm region of the motor cortex in these rats evokes movement of the ipsilateral arm, which is rarely seen in normal animals. Movement of the contralateral arm could not be elicited. Whisker movement was seen depending upon the level of anesthesia as described above. The results show emergence of new movement fields in the primary motor cortex of adult rats as a result of dorsal spinal injury.

We have also determined how organization of somatosensory areas S2/PV is affected by unilateral lesion of the dorsal columns at upper cervical levels adult monkeys. Our preliminary results show that in monkeys neurons in the hand region in area S2 becomes unresponsive to the stimulation of the hand as a result of the deafferentation. This indicates that area S2 shows reorganization similar to that for area 3b.

Multiple mechanisms have been proposed that might mediate brain plasticity. It is likely that reorganization at the subcortical levels contributes towards the plastic changes that are seen at the cortical levels. We are currently determining how organization of the somatosensory cortex is affected lesions of the cuneate nucleus of the brain stem.

Publications

Soumya Iyengar, Hui-Xin Qi, **Neeraj Jain** and Jon H Kaas (2007) : Cortical and thalamic connections of the representations of the teeth and tongue in somatosensory cortex of New World monkeys. **J. Comparative Neurology**. 501:95-120.

Presentations

Shashank Tandon, Niranjana Kambi and Neeraj Jain (2006) Reorganization of the motor cortex and effects on sensorimotor abilities following dorsal spinal

cord injuries. 24th Annual Meeting, Indian Academy of Neurosciences, Dec 17-20, 2006, Lucknow, India.

Shashank Tandon, Niranjana Kambi and Neeraj Jain (2006) Emergence of abnormal movement representations in the motor cortex of adult rats following lesion of the dorsal spinal cord. Third NBRC international Conference, Dec 13 - 15, 2006, New Delhi, India.

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'Changes in the organization of the brain following spinal cord injury.' 4th South Asian Neurosurgical Congress, India Habitat Centre, New Delhi, India. February 15-18, 2007.

'Simultaneous multisite multielectrode neuronal recordings from mammalian brain – new insights into neuronal coding', International Workshop on Complex Dynamics of Physiological Systems: From Heart to Brain. organized by Department of Physics, Presidency College, Kolkata in collaboration with Centre for Applied Mathematics and Computational Science, Saha Institute of Nuclear Physics, India and West Bengal University of Technology, Kolkata, India. Feb 12 – 14, 2007.

'Simultaneous recordings from many neurons in mammalian brain for brain-machine interface devices', one day Workshop on Intelligent Assistive Systems for Health Care Applications, Indian Institute of Technology Kanpur, Kanpur. January 30, 2007.

'Brain plasticity following spinal cord injuries: search for the mechanisms', National Symposium on 'Neural Plasticity and Repair' organized by Department of Anatomy and Physiology, AIIMS, New Delhi and Indian Society of Pain Research and Therapy. October 18-19, 2006.

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Funding

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Department of Science and Technology, India under Indo-Russian ILTP program.

Defense Research and Development Organization.

Department of Biotechnology.

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

Principle Investigator : Dr. Soumya Iyengar

Technical Assistants : OP Sharma, Arvind Singh Pundir

Project Assistants : Subashini Sudarsan, Souvik Kar

We have been studying the development of the development of primary and surrounding non-primary (association) auditory cortical areas in humans. Recent fMRI studies on adults have shown that smaller auditory areas embedded within TA, TB and TD process complex sounds including environmental sounds and speech. Further, the anatomical counterparts of these areas can be delineated by staining for the enzyme acetylcholinesterase and calcium binding proteins (Chiry et al., 2003). The present study used a combination of histology and immunohistochemistry to delineate the auditory association areas and their subdivisions at different stages of development using post mortem human brain tissue.

Cortical columns (also called minicolumns or microcolumns) are vertically organized columns which traverse Layers II-VI and can be considered the basic anatomical and functional units of the neocortex. We found that cortical columns and intercolumns were narrow and uniform in width in the primary and association auditory cortical areas between the third trimester (one each at 24 GW, 37 GW and 39 GW) and term (n = 2) and increased significantly by adulthood (p<0.001, data shown for the primary auditory cortex TC and the auditory association area TA in Fig. 1). These findings suggest that the volume and length of dendritic arbors of neurons in the auditory cortex increase over the course of development.

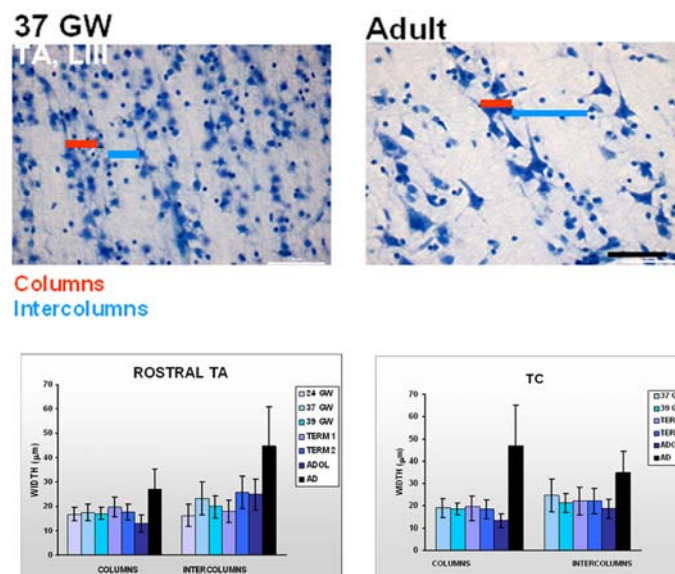


Figure : Nissl-stained coronal sections from the human auditory association cortex at the third trimester of gestation and in an adult. Columns are marked with a red bar and intercolumnar spaces are marked with a blue bar in these figures. Bar graphs (lower panels) show differences in width of cortical columns and intercolumns in the auditory association area TA and the primary auditory cortex TC between the third trimester of gestation and adulthood. The increase in width of columns and intercolumns between the third trimester of gestation and adulthood likely results from an increase in dendritic arbors of the neurons of the columns and increase in myelination of the axons within the intercolumns.

We also found that two of the smaller auditory areas which were important for perceiving speech (STA, superior temporal area) and environmental sounds (AA, anterior area) could be delineated from the surrounding auditory association cortex (TA) based on the width of intercolumns and pyramidal cell size in adults ($n = 2$) and an adolescent. That is, STA can be delineated from the surrounding caudal TA since it has wider intercolumns than those in area TA. Area AA can also be delineated from TA since there are smaller pyramidal neurons in Layer III and V in this area compared to those in TA. Our results suggest that there are changes in connectivity within parts of the auditory association areas, which can be related to functional differences in the way the auditory cortex processes complex sounds. However, these areas appear not to be completely developed before or at birth, based on our measurements of cortical columns and intercolumns. This finding is supported by our immunohistochemistry and immunoblot results wherein we have demonstrated that whereas the calcium binding proteins calbindin and calretinin are present in the auditory cortex before and at birth, parvalbumin appears later. Since parvalbumin labels the specialized auditory association areas more intensely than the surrounding cortex, our results suggest that these areas may not be present until some time after birth. These findings will be confirmed by carrying out western blots on more samples of the fetal, pre- and antenatal postmortem brains to study when parvalbumin appears in the auditory cortex. Taken in conjunction with the measurements of cortical columns and staining for calcium binding proteins, these findings will help us in understanding the time-line for development of association auditory cortical areas in humans.

Collaborators

Dr. P. C. Dikshit, MAMC, New Delhi

Dr. K Joshi, PGIMER, Chandigarh

Dr. S Shankar, NIMHANS, New Delhi

Dr. S. Bishnoi, Dr. N. Thapar and Dr. S. Sharma, Gurgaon Civil Hospital, Gurgaon, Haryana

Cl. P. Kumar, Army Base Hospital, New Delhi

Funding

“Emergence of primary and non-primary auditory cortical areas during late fetal and early postnatal ages in humans” in 2005 (DBT).

NEUROGENESIS IN THE SONG CONTROL SYSTEM OF ZEBRA FINCHES

Principle Investigator : Dr. Soumya Iyengar
Research Fellow : Nazia Khurshid
Technical Assistant : Arvind Singh Pundir, Shalini Sharma
M.Sc Student : Anushree Tripathi
Project Assistant : J. Navin

Zebra finches are amongst the best models to study interactions between the brain and behaviour. Singing is a highly sexually dimorphic behaviour in these birds since only adult males sing and their songs are biologically important since they are used to attract mates. Earlier research has shown that new neurons are continuously being added to neural circuitry important for singing in males. We are interested in studying how neurogenesis is regulated in adult birds and whether changing the levels of neurogenesis in adult male zebra finches would change their songs. Our immediate aim is to increase the levels of neurogenesis in these birds by blocking opioid receptors expressed by the ventricular zone which is known to increase cell proliferation in other species. Since the opioid receptors are present in different components of the song control system of adult male zebra finches, we also thought it would be important to study the short-term effects of blocking these receptors on singing.

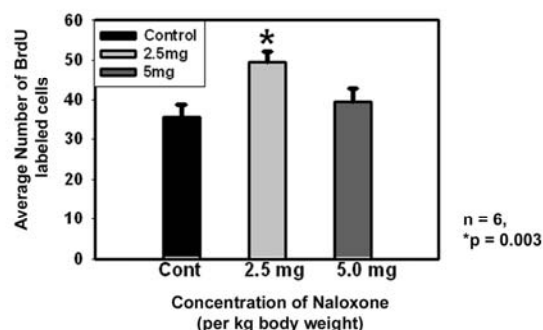
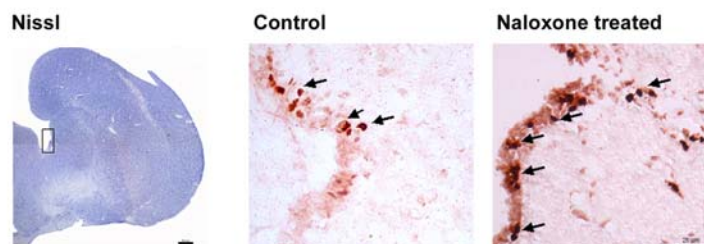


Figure: Blocking opioid receptors with the opioid antagonist naloxone increases cell proliferation in the ventricular and subventricular zone of an adult male zebra finch compared to a saline- treated control. A Nissl-stained coronal section is shown to demonstrate that these images have been taken from a proliferative 'hot spot' close to the anterior commissure. There was a significant increase in cell proliferation in the VZ and SVZ after naloxone administration at a dose of 2.5mg/kg body weight for four days compared to control birds.

We found that systemic injections of the opioid receptor antagonist naloxone for four days led to a significant increase in cell proliferation in a dose-dependent manner (highest levels of cell proliferation were observed with 2.5 mg/kg body weight and slightly lower levels with 5mg/kg body weight of naloxone, Fig. 2) compared to saline treated controls. These results suggest that the opioid system can be used as a tool to change levels of cell proliferation in the brains of adult zebra finches. We would further like to study how many of the newly formed cells (after naloxone treatment) differentiate into neurons and glial cells by staining brain sections of experimental birds with markers for cell proliferation and neuronal and glial markers.

We also found that blocking the opioid receptors with naloxone lead to a decrease in the total number of songs sung by birds compared to saline-treated controls in a dose-dependent manner, despite the increase in cell proliferation. These results can be explained by the fact that the motivation to sing may be affected by the direct action of naloxone on opioid receptors expressed by song control areas and the limbic system. Our future goal is to test whether newly differentiated neurons formed after the increased cell proliferation (caused by blocking opioid receptors) will contribute to changes in singing after they have reached their final destinations in different song control nuclei.

Publications

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Karunakaran S, Diwakar L, Saeed U, Agarwal V, Ramakrishnan S, **Iyengar S**, and Ravindranath V (2007) : Activation of apoptosis signal regulating kinase 1 (ASK1) and translocation of death-associated protein, Daxx, in substantia nigra pars compacta in a mouse model of Parkinson's disease: protection by alpha-lipoic acid. **The FASEB Journal** (in press).

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Presentations

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Tripathi, A. and Iyengar, S. (2006) Expression patterns of opioid receptors in the ventricular and subventricular zone in the human fetal brain. Presented at the Third NBRC International Conference, New Delhi.

Smitha Karunakaran, Latha Diwakar, Uzma Saeed, Sujanitha Ramakrishnan, Soumya Iyengar and Vijayalakshmi Ravindranath (2006) Activation of apoptosis signal regulating kinase 1 (ASK1) and translocation of death-associated protein, Daxx, in substantia nigra pars compacta in a mouse model of Parkinson's disease: protection by alpha-lipoic acid. Presented at the Third NBRC International Conference, New Delhi.

Guest lectured for the 5th NMR School entitled "A New Dimension to NMR: From molecules to Human Behaviour" held at MAHE, Manipal, (May 22 - June 2, 2006).

Thesis

Geetika Phukan : Role of opioid receptors in behaviour and neurogenesis in adult male zebra finches (*Taenopygia guttata*).

Funding

"Effects of altering the levels of neuronal proliferation on the learning and production of song behavior in male zebra finches" in 2007 (DBT).

Replacement of Degenerating Retinal Neurons by Retinal Prostheses or Stem Cells - A Study on Connectivity and Information Processing in Retina

Principal Investigator : Dr. Narender K. Dhingra

Project Assistants : K Vidhyasankar, Sonia Baloni, KJ Stanley, Shilpashree B, Kailash Tiwari

M.Sc. Student : Cherukuri Pitchaiah

Retinal degenerative diseases such as Retinitis Pigmentosa and Age-Related Macular Degeneration have high incidence rates (RP: 1 in ~3700; AMD: ~4% at 43-54 years of age, ~46% above 75 years), and are among the leading causes of blindness. These diseases have varied etiology but are characterized by degeneration and loss of outer retinal neurons, mainly photoreceptors. However, the inner retinal neurons, especially retinal ganglion cells (RGCs) that transmit the retinal signal to the brain, are preserved. This has interested vision scientists in replacing the degenerated retinal neurons with a prosthetic device or stem cells. Retinal prosthesis is an electronic device surgically implanted in eye to stimulate the retina through an array of miniature electrodes. The hope is that the retinal prosthesis would correctly encode the visual signals, transmit them to the surviving RGCs, and thus produce artificial vision in blind patients. Similarly, the transplanted stem cells are expected to differentiate into preferred retinal neurons and functionally integrate with the host neurons. Both of these approaches have shown promise in recent years, but have not produced the desired clinical outcome so far. The clinical success of these treatments is critically linked to our understanding of the retinal circuitry, synaptic development, and how electrical signals are transmitted across various retinal layers. Our lab is interested in addressing these fundamental questions. In addition, we are interested in testing these treatment approaches in animal models of the retinal degenerative diseases.

To understand how different types of RGCs receive, encode and transmit visual information to the brain we characterize them by recording their electrical response to a spatio-temporally optimized light stimulus, and by measuring their contrast sensitivity. The loose-patch and intracellular recordings are made under visual control from a single RGC in a wholemount guinea pig or mouse retina maintained at 37°C. Visual stimuli are generated in Matlab and presented via the microscope optics to the cell under recording using a miniature CRT. The recorded data is filtered, amplified and stored as binary files for online and offline analysis. In addition, we also study an RGC in terms of its soma diameter, dendritic arbor, IPL stratification, density profile and retinal distribution. One cell we are currently interested in, is a Brn3-positive ganglion cell. About 70% of all

RGCs are known to express the transcription factor, Brn3, but it is not known if these cells represent specific morphological and physiological classes. We are characterizing these cells using electrophysiology, immunocytochemistry and morphometric analysis (Fig. 1).

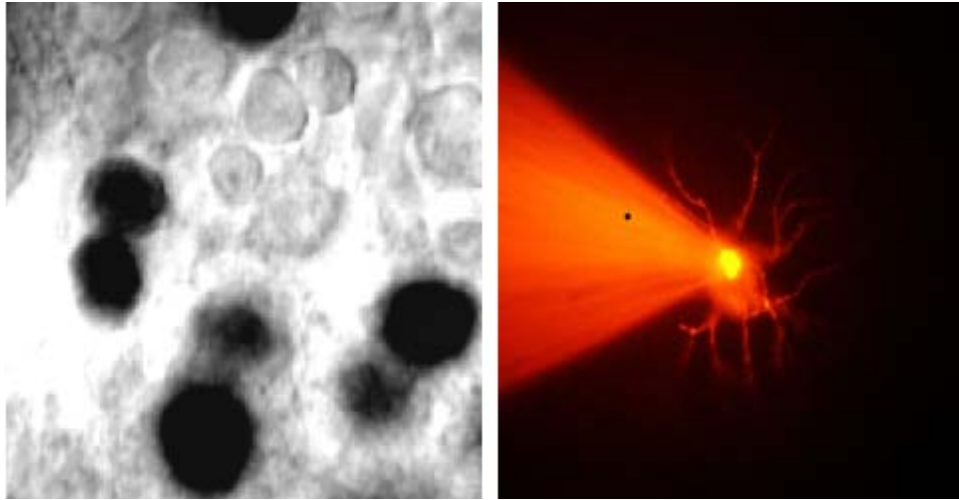


Figure1: Brn3-positive cells can be specifically stained immunocytochemically (A) and filled with DiI (B) to see its complete dendritic arbor. These cells are then analyzed for their density, radial location, IPL stratification and dendritic diameter etc.

We have produced in our lab a mouse model of photoreceptor degeneration where a single i/p injection of MNU (60 mg/kg bw) induces a progressive and selective degeneration of photoreceptors. To examine the effect of MNU on gross visual function we have also developed 2 behavioral tests: Object Avoidance and Cliff Tests. We have also characterized the effects of MNU-induced photoreceptor loss on the surviving retinal cells using western blot analysis and immunocytochemistry (Fig. 2).

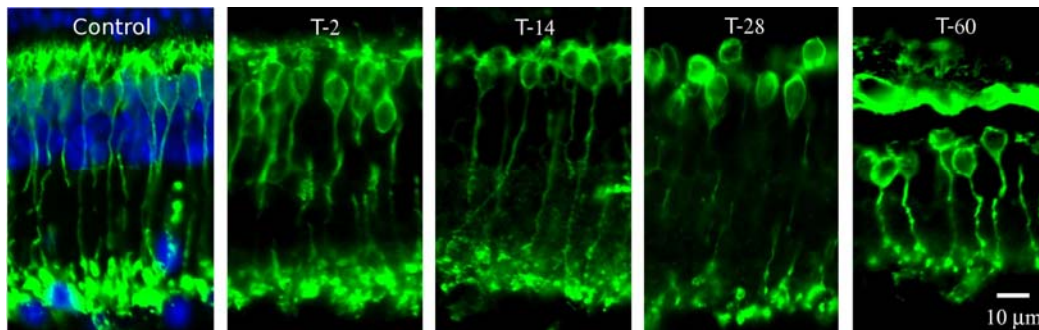


Figure2 : MNU-induced photoreceptor loss affects other retinal neurons. Here, rod-bipolar cells (identified with PKC immunoreactivity; green) are shown to have their dendrites retract and disappear progressively at 2, 14, 28 and 60 days after MNU treatment. Retinal nuclei in Control are stained with DAPI (blue) for reference.

Retinal degenerative diseases are currently diagnosed based on personal and family history, and a group of non-specific signs and symptoms. There is no

clinical test that would allow direct viewing of photoreceptors in a living human or an animal, which makes it difficult to assess accurately the progression of the disease. We have developed a novel method of specifically staining cones in a living animal. We hope this method would allow early diagnosis of degenerative diseases involving photoreceptors, and thus enable ophthalmologists to initiate suitable therapies before considerable retinal remodeling sets in. We have submitted this to the Department of Biotechnology (Ministry of Science and Technology) for a review on its suitability for obtaining a patent.

Previous data suggests that as much as 75% of information is lost during transmission from photoreceptor outer segments to behavioral level in a stimulus detection task. We have shown an information loss of ~50% during spike generation in a brisk-transient ganglion cell. We have now made a realistic cone model to determine overall information loss in retina for a small stimulus that covers the dendritic field of a single RGC. For this we have measured outer segment length, inner segment diameter, and density of cones in the visual streak of guinea pig. Based on these measurements and published data we have measured contrast sensitivity of the modeled photoreceptors and compared it to that of the RGC measured from actual recordings. These data will be useful not only in advancing our understanding of retinal functioning but also in designing functionally more useful retinal prostheses.

Publications

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Presentations

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Baloni S, Dhingra NK (2006) Characterization of Brn3b -positive Retinal Ganglion Cells in Mouse. Poster presented at 3rd NBRC International Neuroscience Conference (Dec. 13-15, 2006) at Delhi.

Pitchaiah C, Vidhyasankar K, Stanley KJ, Baloni S, Dhingra NK (2006) Morphological and Behavioral Characterization of MNU-induced Mouse Model of Retinal Degeneration. Poster presented at 3rd NBRC International Neuroscience Conference (Dec. 13-15, 2006) at Delhi.

Dhingra NK (2006) Information Processing in Retina: Molecules to Behavior In: Symposium on Advances in Neurophysiology at 52nd National

Conference of Association of Physiologists and Pharmacologists of India (Dec. 19-23, 2006) at Surat. Ind. J. Physiol. Pharmacol. 52 (5): pg 54.

Patents

In Vivo Staining of Cone Photoreceptors by a Fluorescently Labeled Compound (submitted to DBT).

Collaborators

Dr. Shyamala Mani (NBRC, Manesar)

Dr. Robert G. Smith (University of Pennsylvania, Philadelphia)

Drs. Jayesh Ballare and Uday Sheorey (IIT, Mumbai)

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).

Transplantation of Stem Cell in Degenerating Retina: A Study on Formation of Functional Synapses Between Stem cells and Host Retinal Neurons In Vivo and In Vitro (DBT).



Computational Neuroscience

Phonological maps for spoken language.

Principal Investigator : Dr. Nandini Chatterjee Singh

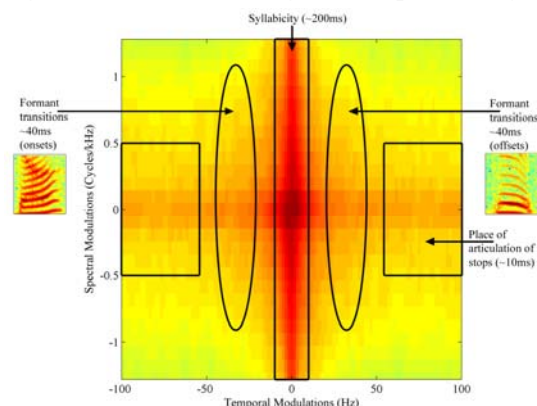
Research Fellows : Latika Singh, Tanusree Das

Project Assistant : T. Padma Subhadra

“Clinically, spoken language or speech is one of the earliest markers for development or acquired pediatric neurological disorders. The primary focus of our laboratory is to develop quantitative measures to study spoken language with the idea that such an approach could provide algorithms to the research and clinical community to study normal and abnormal language”

Spoken language, when analysed from a signal processing perspective, can be described as a signal with information at multiple time scales. This information is embedded in the form of amplitude fluctuations, which are at different time scales and encode various features of language. For example, fluctuations at 200-400 milliseconds encode speech/language rhythm, whereas fluctuations at 10-20 milliseconds encode place of articulation. Extensive research in speech has shown that spoken language can be characterized by four articulatory features namely language rhythm, formant transitions, place of articulation and voiced pitch, wherein each feature is associated with a different time scale. In the current scenario each of these features is estimated using a different measurement technique, and all these techniques are rather laborious. Using advanced techniques of spectral analysis, we have developed a novel computational tool called the speech modulation spectrum, provides information on all four articulatory features at the same time quite easily. It allows us to plot a “language phonological map” which is a map of how energy is distributed in different articulatory features in any given language. Figure 1 shows the phonological map for English.

Figure1: Phonological map for English



Such language maps can have numerous applications. They could be used to study the phonological structure of different languages. They also enable comparisons between different languages and could provide information on how various languages could be similar or dissimilar.

From a clinical perspective such language maps could provide objectives measures to study phonological changes after during speech therapy.

The development of articulatory features in children.

Principal Investigator : Dr. Nandini Chatterjee Singh

Research Fellows : Latika Singh

Project Assistant : T. Padma Subhadra, Chetan Nagraja

We use the language phonological map to study when children in a population acquire different articulatory features of language. Using the modulation spectrum analysis, we are able to capture all the four articulatory signatures in adult speech. We use the modulation spectrum analysis to study the development of these features in children. Since each feature is associated with a different time scale, this analysis also allows us to study the development of speech motor skills in children. We make comparisons with adult speech and find age dependence in the appearance of these features. Our results shown in figure 2 indicate that as children get older they exhibit increasingly more power in features associated with shorter time scales, thereby indicating the maturation of fine motor control in speech.

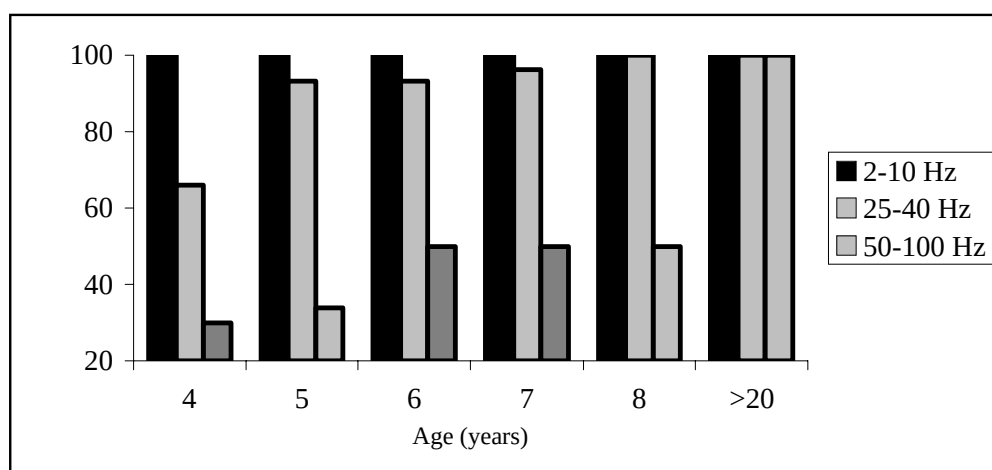


Figure : Bar chart showing the percentage of children exhibiting various time scales as a function of age.

Characteristics of spectral and temporal features of speech in children with autism

Principal Investigator : Dr. Nandini Chatterjee Singh
Research Fellows : Latika Singh, Tanusree Das
Project Assistant : Vishnudev Ramachandra, Chetan Nagraja

A second area of interest in the laboratory has been the study of speech produced by children with autism. We examine speech samples from autistic children with speech and compare them with age matched control data.

A modulation spectrum analysis has been carried out with speech samples obtain from high functioning children with autism. The pilot study carried in 2004-05 showed differences in various spectral and temporal parameters between typically developing children and those with autism. Besides data from children we have recently also obtained speech samples from autistic adults. A comparison of the modulation spectrum shows distinct differences between children with autism and age-matched controls.

We have also carried a comparison of task performance on different speech production tasks with children with autism. We make comparisons with age matched controls and find significant differences on all tasks between the two groups.

Earlier studies have indicated speech perception deficits in children with autism. We now suggest deficits in speech motor development in children with autism.

Publications

Latika Singh, P. Shantisudha, **Nandini C Singh** : Developmental patterns of speech in children, **J. of Applied Acoustics**, 68, 260-268, 2007.

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Latika Singh and **Nandini C Singh** : The development of articulatory signatures in children, **Developmental Science** (in press).

Mohini Verma and **Nandini C Singh** : Cross-cultural language rhythms – effects of emotion recognition in speech, **J. of Cross-cultural psychology** (under revision).

T.Padma Subhadra, Tanusree Das, and **Nandini C Singh** : Speech rhythms in children learning two languages, Proceedings of the Workshop on Complex Dynamics of physiological systems: **From Heart to Brain**, Life Sciences Series, published by Springer.

Presentations

‘Spectro-temporal analysis of speech’, Dept. of Linguistics, Jawaharlal Nehru University, New Delhi, 30th September 2006.

Time scales in speech productions from children, Abstract, Society for Neuroscience, Atlanta, USA, October 2006.

Temporal processing in children - new insights from a computational approach, International workshop on computational models for mind and brain, organised by Saha Institute of Nuclear Physics, Kolkata, November 20-23rd 2006.

Temporal processing in children learning two languages, Dynamics Days, organized by Dept. of Physics, Delhi University, November, 2006.

Speech motor skills in children, Indian Association of Neuroscience, Lucknow, December 17-20, 2006.

‘Complex dynamics in physiological systems : from heart to brain, Feb. 12-14, 2007, Presidency College, Kolkata.

‘The development of speech motor skills in children’, Indo-US Workshop on developmental neuroscience and Imaging, organised by NBRC, Feb. 19-21, 2007, New Delhi.

Collaborators

- 1) The project on children with autism is being carried out in collaboration with Dr. Shobha Srinath and Dr. Shivshankar from NIMHANS, Bangalore and is supported by NBRC. We have applied for financial support to the Ministry of Information Technology.
- 2) We also obtained data from children with autism from Dr. Amit Sen at the Sitaram Bhartia Institute for Science and Research, New Delhi.
- 3) We have also obtained autistic data from the Action for Autism in New Delhi.

Funding

This project is supported by a grant from the Ministry of Communications and Information Technology and intramural support.

Application of Stochastic Activation and Stability analysis for Brain Imaging and Therapy

Principal Investigator : Dr. Prasun Kumar Roy

Research Fellow : Subhadip Paul

Postdoctoral Fellow : Vani Kashyap

R&D engineer : V. P. S. Rallabandi

A major recent advancement in biophysics is the incisive phenomenon of the Stochastic Activation Effect whereby optimized perturbation or random-wave fluctuation is used to enhance the behaviour or sensitivity of a system to an input parameter or signal. A promising prospect to enhance the efficiency of neuroradiological processes, whether diagnostic or therapeutic, is offered by stochastic activation, an emerging research field in computational neuroscience and bioengineering. Stochastic activation, noise-aided resonance or fluctuation-induced transition, is a general principle of nonlinear dynamics 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 x-ray/ γ -ray/Raman spectra or electron paramagnetic resonance signals of organic chemicals. However the practical application of stochastic activation effect as a novel technique in diagnostic or therapeutic radiology has not been systematically pursued, and the applicability is the aim of our project.

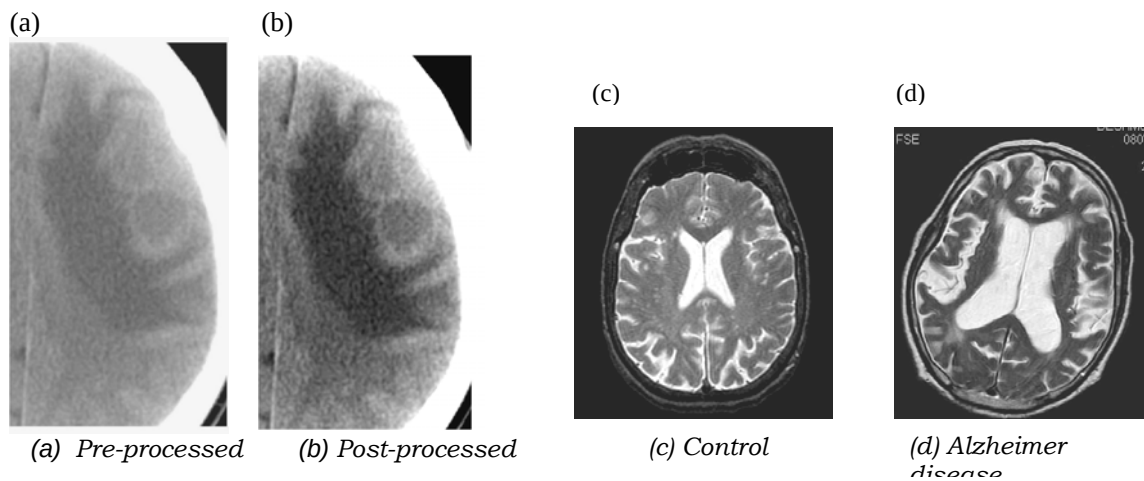
Image delineation and lesion discrimination

We developed a new approach of using stochastic activation using Radon Transform for image enhancement and processing. We applied it to MRI and CT images. This uses a stochastic resonance Radon transform (SRRT) for the enhancement of images of brain lesions. When the images are embedded in very strong noise, or in indistinct hazy background, there is a need for a clear image for neuro-radiological diagnosis. We elucidate an approach for the image enhancement using SRRT. After enhancing the image we can discriminate various zones of a gliomatous tumour, such as necrotic and proliferative zones of the tumor. Delineation of these zones are much needed for optimal therapy planning. Our approach has been tested for various brain lesions such as meningioma, glioma, neurocysticercosis, tuberculoma and infarction. The results for various test cases shows the method to be satisfactory [fig. 1(a)-(b)].

Fractal dynamics of ventricular and cellular flow gradient

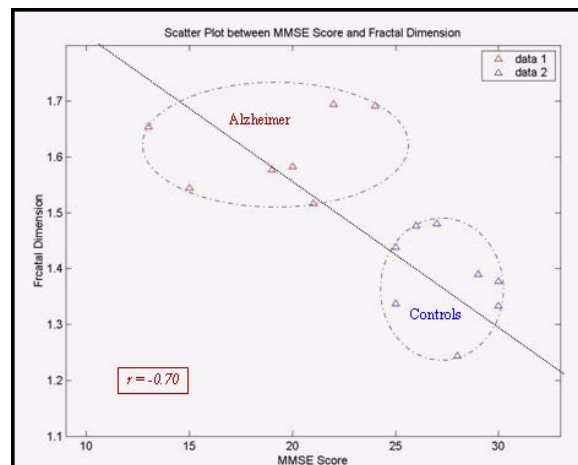
Using MR image analysis, we show that CSF flow and the ventricular/subventricular fluid dynamics is a fractal system, a select

orchestration of turbulent and lamellar flow of CSF that seek to optimize resource dissemination and energetics of the cerebroventricular system. We have elucidated the physiological basis of the fractal alteration from an embryological perspective, namely that the subventricular zone (SVZ) needs a particular optimally-contoured ependyma to optimize gradient of chemorepulsive agents for neuronal migration and neuroblast transport, which is affected in the above-mentioned pathologies (AD/NPH/OH) that hinders reparative neurogenesis. Thus changes in ventricular lining are occurring due to pathological changes and biomechanical deformation. We also show the fractal index correlates well with cognitive deterioration (measured by MMSE scoring) and fractal index may be explored as a suitable indicator of the disease pathology and behavioral dysfunction [fig. 1(c)-(e)]. The fractal observations are accounted by a model of heterogeneity of ciliary dynamics and MR signal attenuation/accentuation due to differential directional CSF flows (orthogonal CSF flows due to ciliary and choroidal flow components).



Stochastic resonance enhancement in CT
Neurodegenerative diseases

Fractal analysis of MR images in



(e)

Figure1 (a)-(b):

Stochastic Resonator based enhancement of computed tomographic image of glioma. Note the enhancement in the

primary and secondary oedema regions and proliferative zone of the tumour. (c-d): MRI image of trans-callosal slice of patient of Alzheimer's disease and of normal control (spin-spin relaxation weighted image), which are subjected to fractal analysis. (e): Plot of fractal dimensionality of MR image vis-à-vis cognitive scores (mini-mental state examination) of Alzheimer's patients and normal control subjects, age/sex/education-matched. Note the clear distinction between Alzheimer cluster and normal cluster.

Publications

V.P. Rallabandi and **Prasun Roy**. Stochastic Resonance-Based Tomographic Transform for Image Enhancement of Brain Lesions, **J. Computer Assisted Tomography** [In Press].

Presentations

Vani Kashyap, Tanuj Gulati, Subhadip Paul, Prasun Roy, Stochastic Approach to MRI Diagnosis using Fractal Morphometry, Neurobiology & Neuroinformatics Workshop, Kyoto, June 2006.

Tanuj Gulati, Stochastic Fractal Morphometry of Brain using MRI, Neuroimaging Centre, Max Planck Institute of Biological Cybernetics, Tübingen, June 2007.

V.P. Rallabandi and Prasun Roy, Tomographic Enhancement in Neuroimaging using Stochastic Resonance, Indo-US Workshop on Neuroimaging, New Delhi, Feb 2007.

Prasun Roy, Imaging of Neurodegenerative Disorders using Fractal Morphometry of Ventricular Zone, Silver Jubilee Conference of Indian Academy of Neurosciences, Lucknow, Dec 2006.

Subhadip Paul, Kanad Basu and Prasun Roy, Image Guided Radiotherapy: Using Stochastic Analysis for Treatment Optimization in Brain Tumours, Int. Conf. on Neuroscience, New Delhi, Dec 2006.

M.Sc. Thesis

Tanuj Gulati : Stochastic Approach to Neuroimaging Diagnosis using Fractal Morphometry.

Collaborators

Dr. K. L. Chakrabarty, Institute of Nuclear Medicine & Allied Sciences, Delhi

Dr. James Becker, University of Pittsburg

Funding

Intramural funds of NBRC.

Defense Ministry (DRDO).

Spatiotemporal neural processing and Non-equilibrium information theory

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A basic problem in neuroscience is comprehending how information transmission and connectivity occurs across different regions of the brain. Customary scalar theoretic models of information transmission have difficulty in accounting for neural operations during varying intensity variations as adaptation or plasticity during hyperexcitatory conditions as epilepsy or migraine. One needs a quantitative mathematical computation approach that can account for information transmission and its neuromodulation across the brain. The recent advance of tensor neuroimaging, beyond simply scalar imaging, 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.

Tensor Image Reconstruction

We have developed the proof-of-principle of a generalized tensor image reconstruction approach using simulations, reducing the tensor field to products of scalar projections. We can thus reconstruct transport tensor fields in the biological tissues using different imaging modalities. The feasibility of transport tensor imaging of flowing CSF or blood in the brain has been thus delineated. We have rigorously developed new projection theorems and convolution backprojection reconstruction algorithms for tensor tomography. We are able to obtain the reconstruction of the irrotational and solenoidal components of the tensor fields.

Clinical Implications

We validate the projection theorems and backprojection formulas by synthetically scanning and reconstructing a tensor field and its components. This tensorial approach furnishes much more detailed rheological information on viscosity of blood and CSF flow, than conventional methods. Using techniques of computational fluid dynamics (CFD), the transport tensor across different voxels can provide a new window to studying pathophysiology and therapeutic monitoring of fluid flow, such as cerebrospinal fluid flow in cerebral ventricles, or blood flow in cerebral vessels or aneurysms (fig. 2). Our results indicate the practical possibility of

transport tensor imaging as a promising window for studying brain dysfunction. We also showed the feasibility of realizing the transport tensor imaging by using a Magnetic Resonance scanner.

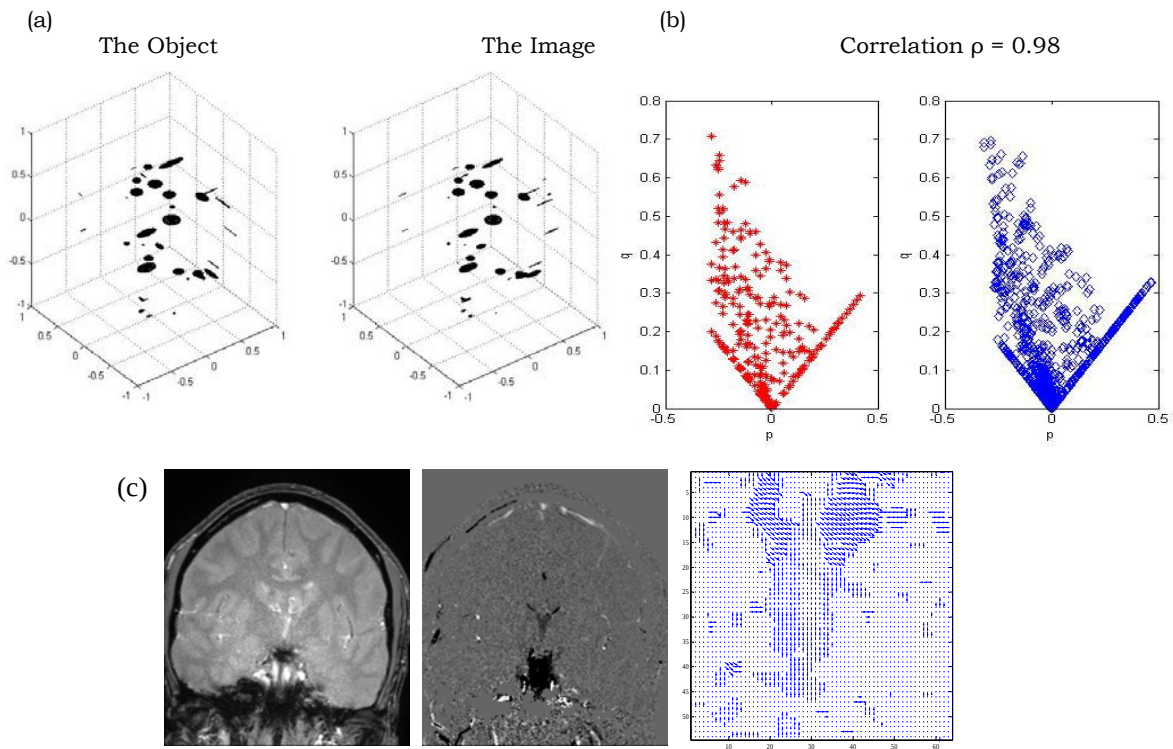


Figure : (a) Computed scanning of digital brain phantom template with voxel-wise transport tensorial flows; left panel: the original brain phantom ('the object'); right panel: the reconstructed representation of the brain phantom using backprojection scanning ('the image'). (b): Plots of $p : q$ ratio of the voxel-wise transport tensors, namely the ratio of anisotropic : isotropic component of tensor. The very high correlation between the object phantom (left panel) and the image produced (right panel) may be observed. (c): Transport imaging of CSF flow in lateral and third ventricles of brain. Structural MR image of brain (spin-spin relaxation weighted image, first panel); motion-sensitized flow image of CSF in ventricles (second panel); CSF mobility vector mapping in ventricle, enlarged (third panel).

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K. Budhachandra and **Prasun Roy**. Thermal Conductivity Tensor Imaging of Brain using DTI: Therapeutic Implications, **J. Mathematical Biology** (under review).

Presentation

Prasun Roy and Kh. Budhachandra, Computed Hyperthermic Therapy of Malignant Glioma using Tensor Imaging, XVIth International Cancer Congress, Washington DC, July 2006.

Kh. Budhachandra and Prasun Roy. Information Tracking in the Epileptic Brain, International Conference on Epilepsy, All-India Institute of Medical Sciences, New Delhi, Nov 2006.

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Sponsored Projects

Stochastic Resonance Effect as a new technique for enhancement in Computed Tomography and Tomotherapy (Ministry of Defence, Govt. of India).

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

Collaborators

Prof. T. R. Sheshadri, University of Delhi

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

Funding

Intramural funds of NBRC

Ministry of Education & Research, Italian Govt. has approved a collaborative project



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A Basu, Molecular mechanisms of microglial activation and neurodegeneration in Japanese Encephalitis (2006), 6th NBNI meeting, 23-24th July, Kyoto, Japan.

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Kiran Kumar Bali, Renuka Ramachandra, Shailesh Gupta and **V. Rema** : Enhanced neuronal branching in rats following CDP-choline treatment Poster presentation. Indo-US workshop on Developmental Neuroscience and Imaging 2007, Feb 19-21, 2007 New Delhi, India

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Vani Kashyap, Tanuj Gulati, Subhadip Paul, **Prasun Roy** : Stochastic Approach to MRI Diagnosis using Fractal Morphometry, Neurobiology & Neuroinformatics Workshop, Kyoto, June 2006.

Tanuj Gulati : Stochastic Fractal Morphometry of Brain using MRI, Neuroimaging Centre, Max Planck Institute of Biological Cybernetics, Tübingen, June 2007.

V.P. Rallabandi and **Prasun Roy** : Tomographic Enhancement in Neuroimaging using Stochastic Resonance, Indo-US Workshop on Neuroimaging, New Delhi, Feb 2007.

Subhadip Paul, Kanad Basu and **Prasun Roy** : Image Guided Radiotherapy: Using Stochastic Analysis for Treatment Optimization in Brain Tumours, Int. Conf. on Neuroscience, New Delhi, Dec 2006.

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Rao S.L. : Translational Insights from Cognitive Neuroscience into the Clinical Management of Head Injury, Indo-US workshop on Developmental Neuroscience and Imaging, Indo-US Technology Forum, NBRC, February, 2007

Rao S.L. : Translational Research in Cognitive Neuroscience, Second International Conference on Cognitive Science, CBCS, University of Allahabad, December 2006.

National Presentations

Nihar Ranjan Jana : Suppression of polyglutamine neurodegeneration by quality control ubiquitin ligase. Annual meeting of the Indian Society of Neurochemistry, Kolkata, 2006.

Amit Mishra and **Nihar Ranjan Jana** : Angelman ubiquitin ligase E6-AP promotes degradation of tumor suppressor p53 by proteasome in the neuronal cells. Annual meeting of Indian Academy of Neuroscience, Lucknow, 2006.

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P. Seth : Neuronal Apoptosis and Chemokine Production By HIV-1 Tat Protein Derived From Clade B And C In Human Fetal Neural Precursor Cells. Invited Speaker, in International Society of Neurochemistry, Symposia on Neuropathogenesis of HIV-1 Dementia, Silver Jubilee meeting of Indian Acad. of Neuroscience, Lucknow, Dec 2006.

P. Seth : AIDS and Brain. Invited Lecture for Science Popularization Activities at Haryana State Council of Science and Technology, Kurukshetra, August 2006.

M. Mishra and **P. Seth** : HIV-1 Tat From Clade B And C Differentially Modulate Neurotoxicity and Inflammation in Human Fetal CNS Precursor Cells. Presented at Silver Jubilee meeting of Indian Academy of Neuroscience, Lucknow, India, December 2006.

E. Sen : Hypoxia and cell fate: Implication in Neuropathologies at IICB, Kolkata, 2006.

E. Sen : Inside story of glioblastoma: Proliferation and differentiation of Cancer stem cells at National Symposium on 21st Century Research in Biochemistry and Biophysics, Kalyani University, 2007.

E. Sen : Understanding the molecular mechanisms involved in inflammation mediated glioblastoma progression. Presented at All India Cell Biology Conference, 2006.

E. Sen : Lipid Rafts: An organizing platform for signal transduction events in Glioblastoma multiforme. Presented at Indian Academy of Neuroscience, 2006

E. Sen : Involvement of lipid rafts in modulating signal transduction events associated with Glioblastoma survival, Presented at All India Cell Biology Conference, 2006

M K Mishra, P Koli, and **A Basu** : Neuroprotection conferred by astrocytes is insufficient to protect animals from succumbing to Japanese Encephalitis

(2006), 75th Annual Meeting of the Society of Biological Chemists, 8-11 December, JNU, New Delhi.

V Swarup, S Das and **A Basu** : Japanese Encephalitis Virus (JEV) Infection Induces Tumor Necrosis Factor Receptor-1 Mediated Neuronal Apoptosis (2006), 24th Annual Meeting of the Indian Academy of Neurosciences, 17-20 December, Lucknow.

M K Mishra and **A Basu** : Astrocyte activation by Japanese Encephalitis Virus triggers enhanced expression of Glutamate Transporters, Acute Phase Protein and Neurotrophic Factors (2006), 24th Annual Meeting of the Indian Academy of Neurosciences 17-20, December, Lucknow.

A Basu : Pathogenesis of Japanese Encephalitis: Do we need to look differently? (2006), 26th December, National Institute for Cholera and Enteric Diseases (NICED), Kolkata. (Invited speaker).

V Swarup, S Das, S Ghosh and **A Basu**, TRADD: A double Edged Sword- Implications in Viral Encephalitis (2007), 30th All India Cell Biology Conference, 2-4 February, Department of Zoology, University of Delhi, Delhi.

R Duseja, V Sharma, R Tewari, M K Mishra and **A Basu** : Modulation of Membrane Dynamics of Neuron and Glia following Japanese Encephalitis: Implication in the progression of Disease (2007), 30th All India Cell Biology Conference, 2-4 February, Department of Zoology, University of Delhi, Delhi.

A Basu : Human Brain: The Final Frontier of Science (2007). National Science Day (28th February), Kendriya Vidyalaya, NSG Campus, Manesar.

A. Murthy : Introduction to Cognitive Neuroscience. Lecture for Computational Neuroscience workshop, given at Indian Institute of Technology (IIT), Madras (2006).

Vishal Kapoor & **A. Murthy** : Does covert inhibition potentiate online inhibitory control? Indian Academy of Neuroscience, Lucknow, India. (2006)

Manisha Chugh, Zia Ud Din Darokhan & **V. Rema** : Somatosensory processing is altered by photothrombotic stroke-like lesions in motor cortex. Poster presentation. International Update on Basic and Clinical Neuroscience Advances and Annual Conference of Indian Academy of Neurosciences, December 17-20 2006, Lucknow, India

Zia Ud Din Darokhan, Manisha Chugh & **V. Rema** : Effects of unilateral injuries to somatosensory cortex on receptive field properties in contralateral hemisphere. Poster presentation. International Update on Basic and Clinical Neuroscience Advances and Annual Conference of Indian Academy of Neurosciences, December 17-20 2006, Lucknow, India

Anshul Srivastava, Zia Ud Din Darokhan, Manisha Chugh & **V. Rema** : Somatosensory Processing is Deficient in Rats with Protein Malnutrition. Poster presentation. International Update on Basic and Clinical Neuroscience Advances and Annual Conference of Indian Academy of Neurosciences, December 17-20 2006, Lucknow, India.

Rahul Chaudhary, Anshul Srivastava, Kiran Kumar Bali & **V. Rema** : Protein Deficiency Alters Sensory Behaviour. Poster presentation. International Update on Basic and Clinical Neuroscience Advances and Annual Conference of Indian Academy of Neurosciences, December 17-20 2006, Lucknow, India.

Shashank Tandon, Niranjana Kambi and **Neeraj Jain** (2006) : Reorganization of the motor cortex and effects on sensorimotor abilities following dorsal spinal cord injuries. 24th Annual Meeting, Indian Academy of Neurosciences, Dec 17-20, 2006, Lucknow, India.

Neeraj Jain : 'Brain Plasticity: Tale of Two Spinal Cords', 'Biosparks' organized by School of Life Sciences, Jawaharlal Nehru University, New Delhi, February 23, 2007.

Neeraj Jain : 'Simultaneous multisite multielectrode neuronal recordings from mammalian brain – new insights into neuronal coding', International Workshop on Complex Dynamics of Physiological Systems: From Heart to Brain. organized by Department of Physics, Presidency College, Kolkata in collaboration with Centre for Applied Mathematics and Computational Science, Saha Institute of Nuclear Physics, India and West Bengal University of Technology, Kolkata, India. Feb 12 – 14, 2007.

Neeraj Jain : 'Simultaneous recordings from many neurons in mammalian brain for brain-machine interface devices', one day Workshop on Intelligent Assistive Systems for Health Care Applications, Indian Institute of Technology Kanpur, Kanpur. January 30, 2007.

Neeraj Jain : 'Brain plasticity following spinal cord injuries: search for the mechanisms', National Symposium on 'Neural Plasticity and Repair' organized by Department of Anatomy and Physiology, AIIMS, New Delhi and Indian Society of Pain Research and Therapy. October 18-19, 2006.

Neeraj Jain : 'Revising and reworking the brain after injuries' Symposium "Biology Today" organized by Indian Academy of Sciences, Bangalore, July 13, 2006.

Khurshid, N. and **Iyengar S** (2006) : Localization of opioid receptors in male zebra finches. Presented at the XXIV Annual Meeting of the Indian Academy of Neurosciences Meeting, Lucknow.

Iyengar S (2006) : Studies on developmental and adult neural plasticity using songbirds as a model system. Presented at the National Symposium on Neural Plasticity and Repair, New Delhi, organized by AIIMS, New Delhi and Indian Society of Pain Research and Therapy.

Iyengar S : Guest lectured for the 5th NMR School entitled "A New Dimension to NMR: From molecules to Human Behaviour" held at MAHE, Manipal (May 22 -June 2, 2006).

Dhingra NK : Popular Science Lecture on Brain Electricity at Sarthak Model School, Panchkula (23/8/2006).

Dhingra NK (2006) Information Processing in Retina: Molecules to Behavior In: Symposium on Advances in Neurophysiology at 52nd National Conference of Association of Physiologists and Pharmacologists of India (Dec. 19-23, 2006) at Surat. Ind. J. Physiol. Pharmacol. 52 (5): pg 54.

Nandini C. Singh : lysis of speech', Dept. of Linguistics, Jawaharlal Nehru University, New Delhi, 30th September 2006.

Nandini C. Singh : Temporal processing in children - new insights from a computational approach, International workshop on computational models for mind and brain, organised by Saha Institute of Nuclear Physics, Kolkata, November 20-23rd 2006.

Nandini C. Singh : Temporal processing in children learning two languages, Dynamics Days, organized by Dept. of Physics, Delhi University, November, 2006.

Nandini C. Singh : Speech motor skills in children, Indian Association of Neuroscience, Lucknow, December 17-20, 2006.

Nandini C. Singh : Complex dynamics in physiological systems : from heart to brain, Feb. 12-14, 2007, Presidency College, Kolkata.

Prasun Roy and Budhachandra Kh : Information Connectivity in Neuroimaging using a Tensorial Analysis, Annual Conference on Applied Mathematics-2006, Delhi University, South Campus, Oct 2006.

Kh. Budhachandra and **Prasun Roy** : Information Tracking in the Epileptic Brain, International Conference on Epilepsy, All-India Institute of Medical Sciences, New Delhi, Nov 2006.

Prasun Roy : Imaging of Neurodegenerative Disorders using Fractal Morphometry of Ventricular Zone, Silver Jubilee Conference of Indian Academy of Neurosciences, Lucknow, Dec 2006.

Rao S.L. : Environmental effects on brain, Brainstorming Meeting, NBRC, Mussorie, May 2006

Rao S.L. : Brain Mediation of Behavior, Second National Conference in Mental Health – Mental Health Challenges 2020-A Vision for the Future, Amity Institute of Behavioral (Health) & Allied Sciences, Amity University, NOIDA, U.P., August 2006.

Rao S.L. : Understanding and Assessment of Mental Load, Key note Address, National conference on Emerging Paradigms in Psychology, Defence Institute of Psychological Research, (DRDO), New Delhi, September 2006.

Rao S.L. : The Relation of Cognitive Neuroscience with Neuropsychology and Mental Health, DST Sponsored National Meeting on Cognitive Science, National Institute of Advanced Studies, Bangalore, September 2006.

Rao S.L. : Cognitive deficits in Brain Damage, Dept. of Biological Sciences, Annual Talks, Tata Institute of Fundamental Research, Mumbai, August 2006.

Rao S.L. : Cognitive Behavioral Therapy, 12th Annual conference of Alzheimer's & Related Disorders Society of India, AIIMS, New Delhi, November, 2006.

Invited Presentations in Training Programs

Rao S.L. delivered lectures on Cognitive Neuroscience at the National School on A New Dimension to NMR, MAHE, Manipal, May 2006:

Rao S.L. : Neuropsychological Assessment, CEN-2007, Continuing Education in Neuropsychology, NIMHANS, February, 2007.

Rao S.L. : Brain and Consciousness, India International Center, New Delhi, June 2006

Katyal, S. & **Rao S.L.** (2006) : The capacity of perception and the role of attention, Third NBRC International conference, NBRC, Manesar, December 2006



DISTINCTIONS, HONOURS AND AWARDS



Prof. V. Ravindranath

Scientific and Academic Recognitions

1. J.C. Bose Fellowship (2006 – 11)
2. Member, Governing Council of International Brain Research Organisation
3. Council Member, Federation of Asian and Oceanian Neuroscience Societies
4. Member, Asia Pacific Regional Council, IBRO
5. Member, Medical Sciences Research Committee, CSIR
6. Chairman, SRF & RA Selection in medical sciences, CSIR
7. Committee for selection of Emeritus Scientists, CSIR
8. Member, Task Force on Chronic Disease, DBT
9. Member, Life Sciences Board, DBT
10. Member, Governing Body, Centre of Biomedical Magnetic Resonance, Lucknow
11. Member, Senate, Indian Institute of Technology, Delhi
12. Council Member, National Academy of Sciences, Allahabad
13. Member, Special Education Panel of Academies (NASI/ IASc./ INSA)
14. Chairperson, Institute of Life Sciences, Building Committee
15. Member, Programme Advisory Committee in Health Sciences, Department of Science and Technology, India

Membership of Editorial Board of Journals:

1. Member, Editorial Board, Progress in Neurobiology, USA
2. Member, Editorial Board of the International Journal, "Neurotoxicity Research", USA.
3. Member, Editorial Board, Neuroscience Research, Japan
4. Member, Editorial Board, Current Science

Dr. Nihar Ranjan Jana

Nominated as a member of the National Academy of Sciences, India.

Editorial Board member of International Journal of Cancer Research, Academic Journals Inc.

Dr. Anirban Basu

Awarded International travel support fund from DBT to attend 6th NBNI meeting held at Kyoto, Japan.

Dr. Prasun K. Roy

Prasun Roy, Zavoisky Award, International Society for Magnetic Resonance in Medicine, Berkeley, 2007.

Prasun Roy, Visiting Scholarship Award, American Cancer Society, Atlanta, 2006.

Prasun Roy, Invited Organizer, Session on Computational Neuroscience and Neuro-Imaging, Silver Jubilee Conference of Indian Academy of Neuroscience, Lucknow, 2006.

Dr. Shobini L. Rao

Nominated by UGC the advisory committee of the ASIHSS programme of the Dept. of Psychology, Osmania University, Hyderabad

Invited as member of the National Oncology Interface Committee of the Centre of Psycho-oncology for Education & Research, Bangalore

Invited as Member of Board of Studies in Psychology (PG), University of Calicut, Kerala

Invited as Member of the Textbook Development team of Class XII for Psychology, National Council of Education Research and Training, New Delhi

Students Awards

Priyanka Dikshit was selected for JNS travel award to attend the 29th Annual Meeting of the Japan Neuroscience Society to be held on July 19-21, 2006 at Kyoto.

Anand Goswami was selected for JNS travel award to attend the 29th Annual Meeting of the Japan Neuroscience Society to be held on July 19-21, 2006 at Kyoto.

Amit Mishra was awarded for best poster presentation at Indian Academy of Neuroscience meeting held at Lucknow, 2006.

Sulagna Das was selected for 8th IBRO School of Neuroscience, 2-9 September, 2006, TIFR, Mumbai.

Vivek Swarup was awarded for best platform presentation (S. V. R Kar prize) for his talk at the 30th All India Cell Biology Conference, 2-4 February, Department of Zoology, University of Delhi, Delhi.

Kh. Budhachandra Singh, Best Presentation Award, Organized by Nature Neuroscience at International Symposium on Neuroscience, New Delhi, 2006.

V. P. Subramaniam Rallabandi, Best Participant Award, Workshop on Magnetic Resonance: From Molecules to Mind, NMR Society of India, 2007.

Smitha Karunakaran, Best Presentation Award, Organized by Nature Neuroscience at International Symposium on Neuroscience, New Delhi, 2006.

Shailesh Kumar Gupta, Best Presentation Award, Organized by Nature Neuroscience at International Symposium on Neuroscience, New Delhi, 2006.



EXTERNALLY FUNDED RESEARCH PROJECTS

Prof. V. Ravindranath

Cytochromes P450 dependent metabolism of drugs in brain. (NIH-RO1).

Identification of multifactorial risk factors (genetic and nutritional) in the pathogenesis of stroke in the young (DBT)

Dr. Nihar Ranjan Jana

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

Understanding the functional role of E6-AP - a putative ubiquitin protein ligase implicated in Angelman mental retardation syndrome (DBT).

Dr. Shyamala Mani

BASIC BIOLOGY OF NEURAL STEM CELLS - Program Support from DBT.

Neural differentiation of embryonic stem cells - Indo-French Centre for the Promotion of Advanced Research.

Maternal malnutrition and periods of vulnerability and reversibility in the developing brain: A focus on cognitive functioning, molecular correlates and neuroprotection. FRENCH-INDIAN MEDICAL RESEARCH COOPERATION INSERM-ICMR PROGRAM.

Dr. Pankaj Seth

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

Characterization of Human Fetal Brain Derived Neural Stem Cells as a Model for studying neurodegenerative disease. (DBT)

Dr. Ellora Sen

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 (DBT).

Dr. Shiv Kumar Sharma

Molecular and Cellular Mechanisms of Memory Formation. (DBT)

Dr. Anirban Basu

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

Dr. Aditya Murthy

Probing the control of action using saccadic eye movements (DST).

Brain Mechanisms of Action Control in Humans(DBT).

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

Dr. Rema Velayudhan

Processing and integration of tactile information in the somatosensory cortex
(International Senior Research Fellowship from Wellcome Trust, UK)

Embryonic stem cell therapy for brain injury (DBT).

Dr. Neeraj Jain

"Information processing in the primate somatosensory system and the effects of spinal and cortical injuries, The Wellcome Trust., London, UK

"Spinal cord plasticity and rehabilitation after spinal cord injuries", Department of Science and Technology, India under Indo-Russian ILTP Program.

"Autonomous Navigation using Brain-Machine Interface (BMI)" Defence Research and Development Organization, India.

"Transplantation of Stem Cells for Recoveries from Spinal Cord Injuries".
Department of Biotechnology, India.

Dr. Soumya Iyenger

Emergence of primary and non-primary auditory cortical areas during late fetal and early postnatal ages in humans in 2005 (DBT).

Effects of altering the levels of neuronal proliferation on the learning and production of song behavior in male zebra finches in 2007 (DBT).

Dr. 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).

Transplantation of Stem Cell in Degenerating Retina: A Study on Formation of Functional Synapses Between Stem cells and Host Retinal Neurons In Vivo and In Vitro (DBT).

Dr. Nandini Chatterjee Singh

Characteristics of spectral and temporal features of speech in children with autism (Ministry of Communications and Information Technology).

Dr. P. K. Roy

Application of Stochastic Activation and Stability analysis for Brain Imaging and Therapy (DRDO).

Spatiotemporal neural processing and Non-equilibrium information theory (Ministry of Education & Research, Italian Government, Italy).

Abbreviations

DBT	:	Department of Biotechnology.
DST	:	Department of Science & Technology.
DRDO	:	Defence Research & Development Organization.
FIRCA	:	Fogarty International Research Collaboration Award, NIH-USA.
NIH	:	National Institute of Health, USA



CORE FACILITIES



Distributed Information Centre(DIC)

DIC at NBRC has grown from a small computational section to a department managing IT infrastructure across the campus. Overall aim of Distributed Information Centre (DIC) is to serve the scientific community from the best computational methods by providing modern IT infrastructure. During the year DIC focused on strengthening the activities in the following areas:

- (a) IT Infrastructure
- (b) Research Support

IT Infrastructure Development

DIC is responsible for the administration and maintenance of Internet and Local Area Network (LAN). The LAN in NBRC is running over a gigabit fiber backbone with switches for remote management and intranet facility. Nokia IP390 Checkpoint High availability firewall has been configured at the gateway level to ensure infrastructure security. A 2 Mbps dedicated Internet bandwidth line is provided to scientists, students and staff. Wireless access in side the campus for roaming laptop users has also been provided. The centralized heterogeneous network attached storage server for data warehousing has grown to 10 Terabyte and is accessible across the network with LDAP authentication for aiding data security and integrity. High performance SUN and IBM multiprocessor servers have been added to work as authentication server (Primary Domain controller), Print server, DNS and application server, 50 diskless thin client used in common facilities and for computation intensive tasks

There are 5 computer operators in the DIC team supporting and solving technical problems in addition to helping the faculties and students and two system managers managing all the servers. Various specialized software for fMRI analysis, Microarray, Sequencing has been in use by DIC staff such as Brain Voyager, E-Prime, SPSS, Matlab etc., for aiding in research activities. DIC staff is involved in design, development and implementation of computerized software for administration department and scientist. Central facilities such as e-mail facility, Internet, printing facility, scanning, troubleshooting for software and hardware are also managed by DIC. All the scientific associates and administration members of NBRC have been provided with powerful PCs running Windows 2000 Professional/XP and are connected under the domain controller to access and share resources.

Research Support

DIC has specialized trained manpower that assist in fMRI analysis, MRI image analysis and DNA sequencing. They also provide support in development and coding of specialized use using Matlab, SPSS etc,. Training is being imparted to DIC staff for assisting speech and language laboratory for research in acoustic analysis. DIC developed in-house database for antibody/Enzyme and cell line for assisting students and faculty. DIC

provide support to NBRC scientific community in analysis, customized program development and computational support.

New Initiatives

DIC is working towards developing specialized manpower; particularly for fMRI image analysis and computational neuroscience to further enhance our capabilities. NBRC is making efforts to set up a Video conferencing facility at the institute to provide lectures to various university students across the country in the field of Neuroscience & Neuroinformatics. We are also making effort to host NBRC neuroscience portal website and develop web based intranet facility.



ANIMAL FACILITY

The animal facility of NBRC procures and breeds a wide variety of species of laboratory animals to meet the requirement of all the investigators in the institute. It adheres to the highest standards of laboratory animal care and complies with all the regulations regarding the care and use of animals in research at NBRC. The animal facility staff ensures humane and appropriate animal care. A high degree of hygienic conditions are maintained by practising regular cleaning and sterilization of cages, water bottles, bedding and feed, and regular disinfection of rooms. Heavy-duty steam autoclaves are used for sterilization of cages, water bottles, bedding and feed. High pressure hot vapour jet machine is used for cleaning and sanitizing rabbit and monkey cages. Animal house staff is required to take shower and change clothing, and wear facemasks and gloves before entering the animal rooms. Two veterinarians oversee all animal health concerns, provide all necessary veterinary care to ensure that healthy animals are available for research. They also assist in surgical procedures and train the users.

All different animals species are housed in cages which are designed as per the CPCSEA guidelines. The animals are maintained in controlled environmental conditions as per CPCSEA guidelines with temperature maintained between $22\pm 2^{\circ}\text{C}$, relative humidity between 45-55 %, 12:12 hr light dark cycle and 12-15 air changes per hour with 100% fresh air. The transgenic, knock-out and mutant mice are housed under strict sterile conditions in filter top cages with individually ventilated cage system (IVC). All regular procedures such as changes of cages are done in laminar hoods under Hepa filtered air. 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 animal facility has a state of art surgical suite equipped with gas anaesthesia machine, monitoring equipment such as heart rate monitor, pulse oximeter, digital thermometer, intensity controlled surgical lights and surgical microscope. For cleaning and sterilization of surgical instruments there is an ultrasonic instrument cleaner, bead steriliser and ethylene oxide gas steriliser.

Animal facility also has designated necropsy room, perfusion room with a perfusion hood specially designed for heavy paraformaldehyde fumes, deep freezer for carcass storage and incinerator for disposal of animal carcass.

The animal facility is equipped with a controlled access card reader security system. All personnel with access to the animal facility are required to a current tetanus vaccination. Those who handle non-human primates are required to be screened for tuberculosis and trained in first aid required in case of an animal bite or scratch. Close circuit cameras have been installed at various locations in the facility to help in effective monitoring of the animal facility.

The animal facility is currently maintaining and breeding the following species and strains of laboratory animals.

1. Mice: Swiss, BALB/c, C57BL/6J, CD1
2. Transgenic Mice: B6C3-Tg mice (Alzheimer disease model)
3. Knock Out Mice: GAP-43 knock out mice
4. Mutant Mice: CBA/J mice (Retinal degeneration model), Nude mice.
5. Rat Strains: Long Evans and Sprague Dawley.
6. Rabbits: New Zealand white
7. Guinea pigs: Duncan Hartley
8. Non-human primates: *Macaca mulatta* and *Macaca radiata*..
9. Zebra finches

All the mice strains are maintained by inbreeding and both the rat strains by outbreeding. The transgenic and knockout mice are maintained by specialised breeding program after the investigators provide the molecular genotyping of these strains based on presence or absence of the gene of interest. Guinea pig and zebra finch colonies are maintained by outbreeding.



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 521 journals among of them 444 are online (including some free journals) 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 off the centre.

A total of 245 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 48 Networked Centres at all over India. The 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 450 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.

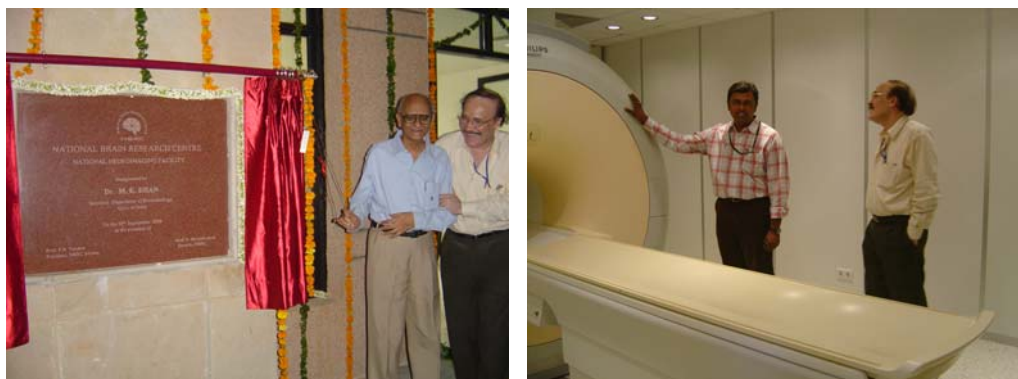




NATIONAL FACILITIES

National Neuroimaging Facility

The National Neuroimaging Facility has been set up at NBRC to map the human brain activity in both high temporal and spatial resolutions simultaneously with a vision to be an apex center of Neuroscience in the country. For this wide gamut of goals, the facility has capability for performing structural and functional MRI, MR spectroscopic imaging, diffusion tensor tractography, arterial spin labeling and multinuclear chemical shift imaging. There is also a high-resolution 64-channel EEG system that can be used to monitor electrical activity in the brain while the subject is being scanned for MRI and is performing demanding cognitive tasks therein. This enables simultaneous measurements of recording brain reactivity, such as evoked potentials and contingent variation. The facility was dedicated to the nation by Dr M.K. Bhan, Secretary, Department of Biotechnology, Govt. of India on 29th September, 2006. This MRI/fMRI facility, the first of its kind in India, and one of the few in the world, is housed in a new building on the NBRC campus and consists of a 3 Tesla Phillips whole body MRI system capable of obtaining very high resolution images of the brain while subjects perform cognitively demanding tasks. In addition to understanding brain function, the center also is closely interacting closely with researchers worldwide to develop new and better methods to image brain function.



In addition to the basic machine we have also procured state-of-art software and hardware for the delivery of auditory and visual stimulation, (NEUROSCAN, 'Eloquence' and E-prime systems) to programme proper sophisticated sequencing and timing of such cognitive tasks. It is anticipated that such a non-invasive approach utilizing human subjects will provide deep insights into how the brain areas interact to enable complex functions such as decision-making, object perception and language and thought. In order to enhance its capabilities the NEUROSCAN system can be run in conjunction with the fMRI, enabling the simultaneous measurement of electrical activity and blood flow changes non-invasively from human brains performing cognitive tasks. We hope that the use of such state-of-art technology will help us develop novel diagnosis, therapeutic monitoring and

evidence-based treatment planning in brain dysfunction, characteristic of a host of neurological and psychiatric disorders.

In the field of functional imaging, research is being pursued in neural control of action using eye movements, language acquisition during child development, Semantic-syntactic response in linguistic processing, and somatosensory processing and object recognition. Another active area of research is neuroimaging of central executive function of working memory in normal and schizophrenics, especially with respect to information manipulation and processing. Further, in the field of structural imaging, the investigations focus on localization of primate cortical processing areas, an MRI/EEG study of decision making and control (to provide spatial and temporal resolution), as well as harnessing newer image processing techniques for proper diagnoses of brain tumours and neurodegenerative diseases as dementia. Since the center has been created as a national facility we expect and actively encourage researchers from across the nation to make use the imaging center to fully utilize its potential.

NBRC is a premier institute whose objective is to pursue research in frontier areas of neuroscience and to understand brain function in health and disease. Research areas include

- 1- Developmental Neuroscience
- 2- Molecular and Cellular Neuroscience
- 3- Systems and Cognitive Neuroscience
- 4- Computational and Theoretical Neuroscience

Details about research activities are available at www.nbrc.ac.in. Admission to the following are open.

Ph.D. in NEUROSCIENCE

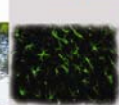
Eligibility : Masters degree in any branch of science or in any subject related to the general area of Neurosciences (e.g. psychology) M.B.B.S. / B.E. / B.Tech. / M.E. / M.Tech. Degree. Candidates who have already qualified CSIR /UGC /GATE /ICMR examinations are particularly encouraged to apply.

Int. Ph.D. in NEUROSCIENCE

Eligibility : A Ph.D. degree in any branch of science or in any subject related to the general area of Neurosciences (e.g. Psychology). M.B.B.S. / B.E. / B.Tech. / M.E. / M.Tech. Degree.

POST DOCTORAL FELLOWSHIPS

Eligibility : A Ph.D. degree in any branch of science or in any subject related to the general area of Neurosciences (e.g. Psychology).



ACADEMIC PROGRAMMES

Ph.D. in Neuroscience

NBRC was awarded Deemed University status in 2002 under Sector 3 of UGC Act, 1956(3 of 1956) vide notification No.F.9-52/2001-U.3 dated 20th May, 2002 issued by Ministry of Human Resources Development, Government of India. NBRC is the first Institute among the Institutes of the Department of Biotechnology to attain this status.

NBRC inducts students for its Ph.D. programme 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.

Stipend for Junior Research Fellows is Rs.8, 000/- per month and for Senior Research Fellows is Rs.9, 000/ as per Government of India norms.

Integrated-Ph.D in Neuroscience

NBRC has started an Integrated Ph.D Programme in Neuroscience to develop trained manpower having a broad overview of different aspects of neuroscience.

NBRC inducts students for its Integrated Ph.D. programme from diverse backgrounds including Bachelor's 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.

Integrated Ph.D Students are provided a stipend of Rs. 3000/- per month for the first two years. From third year onwards they will be paid fellowship on par with Ph.D students. After completion of the Integrated Ph.D programme, the students will be given dual degree (M.Sc and Ph.D). NBRC is one of the first Institutes in the country to develop an integrated multi-disciplinary teaching programme in life sciences.

NBRC offers certain benefits to its students in the form of Fellowships, Stipend, Hostel accommodation, Transportation facility, Medical reimbursement to its students.

Summer Training and Short-Term Programmes

NBRC conducted Summer Training Programme for the Students who were in their penultimate year of their undergraduate / postgraduate course. Students from different academic backgrounds from varied academic Institutions applied against our advertisement published in various National Dailies and in our website during the month of December, 2006. The applications were screened by a Committee constituted for this purpose, based on a certain criteria, depending upon availability of vacancies in

different laboratories at NBRC. The summer training was for a period of 8 weeks (2 months). The Trainees were provided a stipend of Rs.1000/- per month along with free accommodation in the Hostel of NBRC during their training period. Summer trainees were 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 understanding about problems in Neuroscience, amongst students with technical background. This year it was conducted at Chennai in joint collaboration of NBRC and IIT Madras on Computational Neuroscience course (CNS-2006).

A Science awareness camp for students from 4 schools selected by Haryana State Council for Science and Technology was organized at NBRC in December, 2006. Participation certificates were issued to the students who attended the programme. Science Popularisation lectures were conducted in Rohtak, Kurukshetra, Gurgaon, Panchkula and Narnaul located in Haryana and 5 Scientists visited the respective places to deliver the lectures.

National Science day Celebration was also conducted at Kendriya Vidyalaya, NSG Campus, Manesar on 28th February, 2007 and 1st March, 2007 and 11 students and 1 faculty of NBRC had participated in the celebration.



General & Academic Administration – A Profile

The General Administration of the Institute consists of the following major wings:

1. General Administration, headed by the Chief Administrative Officer, is responsible for Establishment, Personnel & Administration Wing, Stores & Purchase Wing, Import & Project Cell, Finance & Accounts Wing, Estate Management & Engineering Maintenance Wing – Civil, Electrical & Mechanical.
2. Academic Administration is headed by the Registrar, responsible for the students administration, project co-ordination, Entrance test administration, course co-ordination etc.

During the year under review, the Administration Wing strived hard in providing the excellent support services and in achieving the following milestones to go into the annals of NBRC.

- Inauguration and dedication of the National Neuro Imaging Facility i.e. fMRI with successful commissioning of the turnkey project through M/s Philips Medical Systems.
- Helping to Organise an International Neuro Science Conference in New Delhi.
- As a measure of commitment towards staff welfare a Group Mediclaim Insurance scheme is introduced for covering Hospitalisation expenses for all employees and their dependents.
- Conducted a nation-wide Entrance test for admission into the Ph.D and Integrated Ph.D Programmes.
- Making due diligence and compliance to the Right to Information Act, 2005 including compilation and hosting of the required disclosure data on the website.
- Making major imports from different countries in terms of equipments and other consumables with a meticulous planning and precise schedule.
- Office automation requirement was placed on the fast track.

Implementation of Official Language

NBRC though a scientific research organization is making effort the usage of Hindi in all the administrative jobs such as internal official meetings, questioning in the interviews, debate and essay competition, general applications etc. The welcome board shows a Hindi moral line everyday. The official language committee with worthy members is actively looking into the use of Hindi and is being reviewed every quarter. Thus, the organization has manifold use of Hindi by way of nameplates, letterheads, and visiting

cards, Boards etc. A proposal for creation of posts for Hindi Officer/Assistant and other positions has already been sent to the Department of Biotechnology for further consideration. The Brochure of International Brain Research Organization has been translated in Hindi for wide circulation among the Scientific Community in India

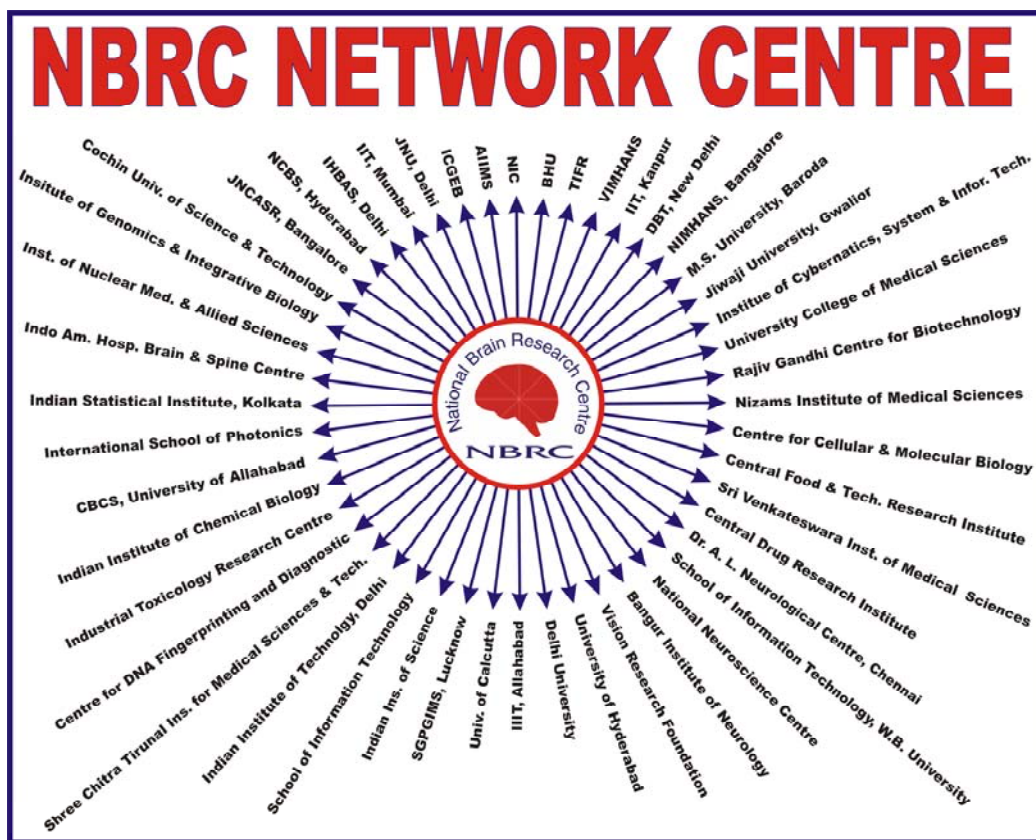
Women Empowerment

NBRC has a distinct feature of giving equal opportunity to women by words and deed. The Committees, constituted to do various work of Administration, Academics and Scientific activities, have women members which ensure fair participation and protection of women. There is a complaints committee for redressal of grievances, if any, from aggrieved girl students/women employees of NBRC, who are subjected to harassment. If any lady / woman of NBRC, among the Students / Employees, is subjected to sexual harassment, can approach the Registrar, the Person-in-charge for redressal of the grievance and the Person-in-charge along with the Director would initiate action with help of the Complaints Committee constituted for this purpose.

Major initiatives in hand include

- Introduction of doorsteps banking services in the premises.
- Notification under section 80G of the Income Tax Act enabling the payees/donor to claim relief from their taxable income.
- Registration under section 12 A of the Income Tax Act enabling the NBRC to claim income tax exemption.
- Bringing out a Booklet entitled: **“Service Terms, pay & allowances and other benefits – At a glance”** for easy and handy ready reference.
- Improvement in the Accounting systems and reporting standards.
- Adoption of user-friendly tools and techniques to reach the information through MIS for concerned users.





INTERNATIONAL COLLABORATIONS

International collaborations aimed at promoting neuroscience enabling the Centre to evolve cross border relationship for Indian Neuroscientists with the international neuroscience community through such exchange programs. Towards this endeavour of excellence 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. Following are a few notable collaborative arrangements:

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 repeat disorder.

Russia

Dr Neeraj Jain has a collaborative research project entitled "Spinal cord plasticity and rehabilitation after spinal cord injuries" with Dr Yuri Gerasimenko & Dr Valerie Avelev at Pavlov Institute, Russia to develop technology to improve recovery 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.

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.

Canada

A Memorandum of Understanding was signed by National Brain Research Centre, Manesar, and Montreal Neurological Institute, McGill University, Canada during November 2006, to express their commitment to cooperate and to develop programmes which will foster the advancement of Neuroscience at both the Institutes.

The cooperation will be carried through the activities that include (i) pursuit of collaborative scientific projects (ii) exchange of scientific personnel (iii) procurement of funds through joint effort for use in collaborative projects and exchanges (iv) a visit to the National Brain Research Centre by a delegation from the Montreal Neurological Institute.

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

Sr. No.	Name of the Speaker	Name of the Institute	Title of the presentation	Date
1.	Dr. Nivedita Chatterjee	Unit of Molecular Cell Biology, Institute for Biology, Johannes Gutenberg universitaet, Mainz	"Glial Cells in health and disease-exploring the depths of the cerebral iceberg."	April 4 th 06
2.	Dr. Sanjay Kumar	University of Birmingham, UK	"Understanding cognitive architecture from working memory perspective."	April 5 th 06
3.	Dr. Atanendu Shekhar Mandal	IC Design Group, CEERI, Pilani	"Modelling the short and long range corticocortical connections in the visual cortex area 1(VI)"	April 7 th 06
4.	Dr. Kumar Sumasundaram	Associate Professor, Microbiology and Cell biology, IISc, Bangalore	"Notch signaling : Role in progressive Astrocytoma development identified Microarray analysis and Cancer Chemoresistance."	April 27 th 06
5.	Prof. Tom Albright	Salk Institute		April 27 th 06
6.	Dr. Bhupinder Vohra	Washington University School of Medicine, Dept. of Pediatrics	"Pathological mechanism in slow channel syndrome and differential gene expression and functional analysis implicates novel mechanisms in enteric nervous system precursor migration and neuritogenesis"	May 24 th 06
7.	Prof. Torsten Wiesel		"Do we learn to see- Role of innate and environmental factors"	May 25 th 06
8.	Dr. Susan Donath	Product manager, Stem Cell products, Miltenyi Biotech, Germany	"Non hematopoietic Stem Cells and their potential for Cell Therapy"	May 26 th 06
9.	Dr. Smita Ghanekar	Senir Scientist, BD, R&D Division, San Jose, CA, USA	"Cytokine analysis by flow cytometry"	June 14 th 06
10.	Prof. Iqbal Ahmad	Dept. of Ophthalmology & Visual Sciences, Postdoctoral Educations, Omaha	"Identification and activation of endogenous neural stem cells: a concept of treating neurodegeneration from within. "	July 26 th 06
11.	Prof. Mandayam A. Srinivasan	Director, The touch Lab Massachusetts Institutes of Technology	"Haptics : Hands, Brain and Virtual environments"	August 11 th 06
12.	Dr. Kripamoy Aguan	Neurogenetics Lab, Brain Science Institute, RIKEN, Japan	"EFHC1 & Astroglial basis of Eplilepsy : shifting paradigm."	Sept 12 th 06
13.	Dr. Paul Vershure	ICREA Research Professor	"Real world perception and cognition: the synergies between behaviour, neuronal system, circuits and Cells"	Sept 12 th 06
14.	Dr. Bettina Hadrich	Global Product Manager Gene silencing Qlagen		Oct 30 th 06

15.	Mr. C.M. Gaind	Sr. Manager(IPR), national Research Development corporation, New Delhi	"Patenting in India"	Nov 9 th 06
16.	Prof. Ralph Freeman	Professor of vision science and optometry, university of California, Berkeley	"Neurometabolic coupling in the cerebral cortex"	Nov 10 th 06
17.	Dr. David Juncker	Assistant Professor, Micro and Nanobioengineering Lab, McGill University, Montreal, Canada		Nov 23 rd 06
18.	Dr. Sefano Stifani	Associate Professor, Neurology, Neurosurgery McGill University Montreal, Canada		Nov 23 rd 06
19.	Prof. E. Sylvester Vizi	Head of Dept of Pharmacology, Institute of Experimental Medicine, Hungarian Academy of Sciences, Budapest, Hungary	"Non- synaptic transmission in the brain"	Nov 25 th 06
20.	Dr. Vinodh Narayanan	Barrow Neurological Institute, USA	"Neurobiology of Neurogenetic Disorders: Tuberous Sclerosis Complex"	Dec 8 th 06
21.	Prof. Richard Nakamura	Deputy Director, National Institute of Mental Health, NIH, Bethesda	"New Research for Mental Disorders"	Dec 8 th 06
22.	Dr. Surajit Ganguly	National Institute of Child Health and Human Development, NIH	"Regulation of the Circadian "output" in Brain by a 'Photo- neural' Network"	Dec 20 th 06
23.	Dr. Narinder Kapur	Head, Neuropsychology Dept., Addenbrookes Hospital, Cambridge	"The paradoxical Brain"	Dec 29 th 06
24.	Prof. Mriganka Sur	Sherman Fairchild Professor of Neuroscience and Head, Dept. of Brain and Cognitive Science, MIT	"Cortical Wiring and Plasticity"	Jan 4 th 07
25.	Dr. Mani Mahadevan	Associate Professor, Dept of Pathology, University of Virginia	"RNA toxicity in Disease"	Jan 5 th 07
26.	Dr. D. P. Mohapatra	Department of Pharmacology, University of California	"Homeostatic plasticity in hippocampal neurons during epileptic seizures: Neuroprotective role of the voltage-gated potassium channel Kv2.1"	Jan 9 th 07
27.	Dr. Shubo Chakrabarti	Penn State College of Medicine, Dept. of Neural and Behavioural Sciences	"Barrels and septa: components of separate cortical circuits?"	Jan 15 th 07
28.	Dr Sudeshna Kar	National Cancer Institute, National Institutes of Health, USA	"When friends turn to foes: Conversion of benign, commensal bacteria to invasive pathogens by chromosome modeling"	Jan 18 th 07

29.	Dr. Neena Singh	Associate Professor, Case Western Reserve University, USA	"The ironic role of iron in prion disorders"	Jan 22 nd 07
30.	Dr Siddarth Ramakrishnan	Dept of Physiology, UCLA	"Master Manipulators: Hormones as controllers of overt behavior and shapers during development"	Jan 29 th 07
31.	Dr. Koustav Ganguly	Institute of Inhalations Biology(IHB), Germany	β B2 Crystallin (CRYBB2) in eye and brain: <i>Crybb2</i> may alter sensorimotor gating and schizophrenia-related cognitive domains in mice and humans	Feb 6 th 07
32.	Dr Gautam Karan	Research Fellow, HHMI, Dept. of Human Genetics, University of Utah	A potential Mouse Model for Macular degeneration	Feb 7 th 07
33.	Dr Robert Balderas	Senior R&D Scientist, BD Biosciences, USA	Novel Flow Cytometric Techniques for Analysis of Protein Phosphorylation and Signaling Networks	Feb 9 th 07
34.	Dr. Samit Chakrabarty	Columbia University	"Restoring motor function (using 'least' used pathways and creating new ones)".	Feb 12 th 07
35.	Dr. Shruti Mitkus	post doctoral fellow NIMH	"Gene expression changes in postmortem schizophrenia brains".	Feb 13 th 07
36.	Prof S. Ogawa	Discoverer of Bold Phenomenon which is the basis of functional NMR, Japan		Feb 14 th 07
37.	Prof Abhijit Guha	Prof. Surgery (Neurosurgery), Western Hospital, Univ. of Toronto	"Genetically Engineered Murine (GEM)Models of Gliomas:Study of Genetic Interactions & Discovery of Novel Glioma Genes"	Feb 22 nd 07
38.	Dr. Scott K Holland	Cincinnati Children's Hospital Medical Center, Ohio	"Basics of fMRI"	Feb 23 rd 07
39.	Dr Muralidharan Jayaraman	Department of Cell Biology and Physiology Washington University	"Novel mechanism to accelerate modulatory G protein signaling during synapse maturation"	March 2 nd 07
40.	Dr Ranjit Giri	Associate Research Scientist, McLaughlin Research Institute, Montana	"b-amyloid mediated inflammation in monocytes"	March 12 th 07
41.	Dr R. M. Adibhatla	Dept. of Neurological Surgery University of Wisconsin, Madison, WI. USA	"Lipid metabolism and cytokines in stroke"	March 28 th 07



MEETINGS AND WORKSHOPS

Brainstorming Meeting (May 20 –23, 2006)

NBRC organized a brainstorming meeting at Mussoorie to generate ideas to strengthen the ongoing activities and to identify new initiatives for neuroscience research in India. More than 20 Indian participants from diverse disciplines of neuroscience attended the meeting. Prof. Torsten Weisel was a special invitee for this meeting. Below are some key points that emerged from discussions during the meeting.

1. A comprehensive approach aimed at epidemiological studies, genetic analyses and molecular signaling mechanisms, needs to be developed for tackling various brain disorders, which account for a significant proportion of the global burden of disease.
2. Closer interaction between experimental and theoretical / computational neuroscientists is the need of the hour.
3. Building prosthetic devices is one of the greatest challenges in applied neuroscience. Thus, a detailed study of brain-machine interface (BMI) is warranted.
4. In the light of about 47% children in India being undernourished, a comprehensive understanding of the effects of under-nutrition should be obtained.
5. In India, the research efforts directed towards systems neuroscience are highly inadequate. We should expand research programs in these areas, particularly on non-human primates. Given the resources available and the advantage of low cost, India has a potential to become a leader in this field.



Hindi Day Celebration at NBRC (September 14th 2006)

National Brain Research Centre celebrated “Hindi Day” at NBRC Campus on the day of 14th September 2006. To promote and advertise the use of Hindi in Official work of the Institute, NBRC has announced various prizes &

promotional encouragement programmes. Mr. D.D. Lal has produced a brief data (in detail) for development work of Hindi at NBRC.

On the Hindi Day, NBRC has organized Hindi Vad-Vivad (Hindi debate) and other competitions. On this occasion short lectures (in Hindi) given by some officers Registrar, Administrative Officer & other Scientists to use of Hindi. Senior Scientist Dr. Shobini L. Rao also addressed the people and participants to promote Hindi.

Prizes and Certificates of merit were awarded to the winners as first, second and third in various competitions by the Senior Scientist – Dr. Shobini L. Rao. Hindi Day was made full success by students, staff and participants.

Addressing by Officers



Prize Distribution



Workshop on Computational Neuroscience 2006

A regular feature of the NBRC calendar is the course on Computational Neuroscience conducted every year to provide students from the engineering, physics, computer science and mathematics community a detailed exposure to basics of neuroscience and computational methods. In 2006, the CNS course was conducted at IIT, Madras from December 4th – 12th. 50 students from different colleges in India participated and lectures were exposed 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. Eminent researchers working in various institutions such as NBRC, NCSS, IIT Bombay, IIT Delhi, IIT Madras, University of Hyderabad, and delivered lectures. A highlight of CNS2006

was a demonstration of neuroanatomy in a medical school in Chennai. This institute, A.L.M. Post Graduate Institute for Basic Medical Sciences (ALMPGIBMS),

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.



Third NBRC International Conference (Dec 13-15, 2006)

Understanding how the brain develops and performs various sophisticated functions is one of the greatest scientific challenges of the 21st century.

Keeping with the mandate of NBRC to identify and conduct cutting edge neuroscience research, to coordinate with different research centers, and to help develop trained and competent neuroscience research personnel in India, NBRC organized the Third NBRC International Conference at New Delhi, from Dec 13-15th, 2006.



This international conference brought together experts in different areas of neuroscience from leading international and national laboratories. The participants from USA, Canada, France, Belgium, Japan and India discussed recent advances in various areas of neuroscience including molecular, cellular, systems, computational and cognitive neuroscience. Poster sessions were planned for young investigators, students and postdoctoral fellows. The conference was highly successful in achieving its goals.

Third Foundation Day Celebration

NBRC organized a popular lecture in the INSA auditorium in New Delhi on its 3rd foundation day. Prof. Albert Aguayo, President, International Brain Research organization (IBRO) delivered the lecture on "Progress in Brain Repair- on the centenary of the first Nobel Prize in Neuroscience" to a packed audience. Prof. MK Bhan, Secretary, DBT presided over the meeting. This very well appreciated lecture was followed by questions from the audience and answers by Prof. Aguayo. Prof. Aguayo is a renowned scientist in the field of nerve regeneration after injury. He is the head of a national research group in Canada that studies regeneration of neurons in the brain. He was the first scientist to demonstrate regeneration of nerve cells after damage. Although more research is needed, Prof. Aguayao's seminal discovery has provided hope to a lot of brain injury patients



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 second lecture in this series was delivered by Dr T. Ramasami, Secretary, Department of Science and Technology, Govt. of India on the 31st of January 2007, 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 and nephew Dr Sridhar 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. Dr Manju Sharma, former Secretary, Department of Biotechnology, Govt. of India and President and Executive Director of Indian Institute of Advanced Research also attended the function.

In his scientific oration, Dr Ramaswami discussed the human cognition and consciousness. He have mentioned in a very lucid way that what does implicit cognition tell us about consciousness. The lecture was widely attended by members of the scientific community besides the staff and students of the Institute.

Indo-US Workshop on Developmental Neuroscience and Imaging (Feb 19th - 21st 2007)

An Indo-US workshop on Developmental Science and Imaging was organized by the National Brain Research Centre from 19-21st February 2007. The objective of the workshop which was funded by the Indo-US Science and Technology Forum was to provide a platform for updating, discussing and establishing research collaborations to advance the application of brain imaging technology and to understand the developmental brain processes in humans. The breadth of the workshop covered entire life span starting from the fetus to adulthood. This workshop brought together scientists from various US universities such as University of Pennsylvania, University of Cincinnati, University of South California, University of Oregon, Rutgers University, University of Arkansas for Medical Sciences and faculty from premiere Indian institutes such as National Brain Research Center (NBRC), All India Institute of Medical Sciences (AIIMS), NIMHANS (National Institute of Mental Health and Neurosciences), University of Hyderabad, Sree Chitra Tirunal Institute for Medical Science and Technology (SCTIMST) and many others.

The technical sessions held included the following topics- Imaging technologies, auditory, cognitive and language development. The last session of the workshop was devoted to identifying areas of common interest and possible collaboration. The outcome of this discussion resulted in a multi-modal approach to brain development and human behaviour. This would involve the combination of computational, neuroanatomical and functional imaging techniques like MEG and MRI. The complementary research capabilities of the Indian and US researchers were evident in that the computational and neuroanatomical expertise was available from the Indian side whereas the US researchers had strong imaging capabilities. A number of collaborations have been proposed which will be followed up the principal investigators and will be submitted in a detailed report later.

The program and details of technical sessions has been attached. The response was overwhelming and a large number of students and researchers attended the workshop.





PEOPLE AT NBRC

SCIENTIFIC STAFF

Scientists

1. Prof. V. Ravindranath
2. Dr. Shobini L. Rao
3. Dr. Neeraj Jain
4. Dr. Rema Velayudhan
5. Dr. P.K. Roy
6. Dr. Narender K. Dhingra
7. Dr. Pankaj Seth
8. Dr. Shiv Kumar Sharma
9. Dr. Shyamala Mani
10. Dr. Aditya Murthy
11. Dr. Nihar Ranjan Jana
12. Dr. Anirban Basu
13. Dr. Ellora Sen
14. Dr. Nandini C. Singh
15. Dr. P. K. Swain
16. Dr. Soumya Iyengar

Post Doctorate Fellows

1. Dr. Sudarshana Purkayasta
2. Dr. Ramesh Kumar Mishra
3. Dr. P. R. Kavitha
4. Dr. Soumya Ghosh
5. Dr. K. Vani
6. Dr. Sayali Ranade
7. Dr. Madhumita P. Ghosh

PhD Students

1. Mr. Reddy Peera.K.
2. Mr. Supriya Ray
3. Ms. Rashmi Mishra

4. Mr. Anand Goswami
5. Ms. Latika
6. Mr. Sandeep kumar
7. Ms. Priyanka Dikshit
8. Mr. Manoj Kumar
9. Ms. Smitha Karunakaran
10. Mr. Ziauddin
11. Mr. Shashank Tandon
12. Ms. Uzma Saeed
13. Mr. Amit Kumar Mishra
14. Ms. Varsha Agarwal
15. Ms. Manisha Chugh
16. Mr. Shailesh K.Gupta
17. Ms. Chinmoyee Maharana
18. Mr. Alok Gupta
19. Mr. Leslee Lazar
20. Ms. Nazia Khurshid
21. Ms. Shalaka Mulherkar
22. Mr. Kh.Budhchandra Singh
23. Dr. Raka Maitra
24. Ms. Mamata Mishra
25. Mr. Arjun
26. Mr. Manoj Kumar Mishra
27. Mr. Niranjan A.Kambi
28. Mr. Anshul Shrivastava
29. Mr. Patel Dharmeshkumar
30. Ms. Sulagna Das
31. Ms. Rupali srivastava
32. Ms. Neha Sehgal
33. Mr. Mohammad Hisham P.M
34. Ms. D.Lalitha
35. Mr. Vivek Sharma
36. Ms. Richa Tewari
37. Ms. Tanushree Das
38. Ms. Radhika Rajan

39. Mr. Nitin Koul
40. Ms. Shilpa Mishra
41. Mr. Subhadip Paul
42. Mr. Parthiv Haldipur
43. Mr. Jai Prakash Sharma
44. Ms. Rachna Duseja
45. Mr. Kaushik Pramod Sharma
46. Ms. Neha Bhutani
47. Ms. K.M.Sharika
48. Dr. Sudheendra Rao N.R
49. Mr. Rahul Chaudhary
50. Ms. Shilpa Harshan
51. Ms. Monika Gothwal
52. Mr. Pranav Oberoi
53. Mr. Madhusudhana Rao

Ph.D. (integrated)

1. Ms. Saumya Nagar
2. Ms. Swetha Kameswari
3. Ms. Deepti Chugh
4. Ms. Varsha Jain
5. Mr. Ajit Ray

M. Sc Students

1. Mr. Tanuj Gulati
2. Ms. Bhavana Shrivastava
3. Mr. Vishal Kapoor
4. Ms. Geethika Phukan
5. Ms. K.M.Sharika
6. Mr. Ayan Ghoshal
7. Mr. Pranav Oberoi
8. Mr. Rahul Chaudary
9. Mr. Dhruvjyothi Chowdhury
10. Mr. Sourojit Bhowmick
11. Mr. Sucharit Katyal

12. Ms. Anasuya Das
13. Ms. Anindita Agarwal
14. Mr. Cherukuri Pitchaiah
15. Mr. Vivek Swarup
16. Ms. Anushree Tripathi
17. Mr. Ausaf A.Farooqui
18. Ms. Shruti Muralidhar
19. Ms. P.M.Rubeena
20. Ms. Garima Singhal

Project Assistant

1. Mr. Kiran Kumar Bali
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** W.e.f. 13th Finance Committee Meeting

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