

NATIONAL BRAIN RESEARCH CENTRE



ANNUAL REPORT

2008 – 2009

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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 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

What is the most unique characteristic of the brain that sets it apart from any other entity known in the universe? The brain is the sole entity which actively seeks to fashion the world in its own image. It is this piece of biological tissue which produced the turning points of human capability from the *Hamlet* to Hiroshima. Indeed, it has been well documented that it was the intensive study of neuroscience that enabled the birth of the present era of the information technology revolution. A century ago, the father of integrative neuroscience, Raman y Cajal, discovered the brain's neuronal circuitry, whose operations were translated in terms of symbolic logic by McCulloch and Pitts, and this enabled the mathematician Turing to devise an abstract machine code, thereby initiating the first digital computer over sixty years. However, the brain that can discover can also debilitate.

To understand the brain and its operation, one needs to comprehend its grammar in terms of the full spectrum of cognate sciences ranging from molecular biology and genetics, through physiology and psychology, to mathematics and engineering. From an applied point of view, research in neurosciences has limitless opportunities for studying the structure and function of the normal and the diseased brain, and it is here that the appeal of the translational sciences of medicine and engineering beckons. As India ages, an alarmingly increasing proportion of its populace will suffer from brain related illnesses, involving neurological and psychiatric diseases. Indeed, by thirty years there would be about 57 million people suffering from neurodegenerative diseases in developing countries, and this will conceivably have greater economic and social impact than cardiac diseases and cancer put together. At NBRC a multidisciplinary group of scientists, encompassing from molecular and system scientists to cognitive and imaging scientists with clinicians, are working on major classes of brain disorders, such as neurodegenerative, neuro-oncological, infective, developmental and neuropsychiatric ones.

Infections and inflammations of the brain is a major neurological problem in the tropical countries as India. The infective agents that NBRC scientists have been investigating, has now reached the eventual microscale level, like infective protein molecules. NBRC has set up this year, a Prion Lab, to study cellular pathology of this disease cluster which encompass scrapie and bovine spongiform encephalopathy (known as mad cow disease), and human variants. The uniqueness of these molecular agents is well emphasized by Stanley Prusiner in his Nobel Lecture as "all prion diseases involve the aberrant metabolism and resulting accumulation of the prion protein, an entirely new genre of disease-causing agents". Needless to say, the theoretical prediction of prion disease almost half a century ago, was one of the great triumphs of applied mathematics when the behaviour of such

infective diseases were forecasted by biocomputationists as J S Griffith. NBRC has also initiated the setting up of a Neural Information Processing Lab to study the Hippocampal Formation as a cognitive map, which has considerable implication to study how the brain makes a representation of the external space and enables how the organism can navigate in the environment, thereby offering significant insights to clinical neurophysiology, robotics and neural engineering. The institute has also established the Neurospectroscopy Lab with ^1H and ^{31}P MRS facility to investigate the molecular milieu of neurodegenerative diseases in the patient, thus furnishing an important probe to peer into the chemical dynamics and kinetics of the brain.

In this year we have met some seminal progress in NBRC. True to its founding spirit, NBRC has played a proactive role this year to work collaboratively, under its extramural program, with neuroscientists across its nearly fifty network centres. A collaborative effort has been nucleated by NBRC under the proposal of Indian Study for Ageing and Cognition (ISAC) whose aim is to track the ageing brain from 50 years of age onwards. This endeavor will involve centres in the 8 states of India, with the view of evolving, in the national scenario, the biomarkers and imaging markers of Alzheimer's dementia and vascular dementia, as well as decipher the markers that may predict which ageing individuals might convert to dementia, later. Another notable attainment of the year is the DELCON centre which NBRC has initiated. This is functioning as the digital documentation resource centre for all the research institutions of the Dept. of Biotechnology, Ministry of Science & Technology, Govt. of India. Virtually the full gamut of biological sciences is accessible now, with almost a thousand journals, e-resources and bibliometric engines, along with resource sharing among the premier life science institutions in the country. Early this winter, in cooperation with coordinators from Salk Institute and our institute, an incisive International Workshop on Cognitive Neuroscience was organized at NBRC, with the sponsorship of International Brain Research Organization (IBRO), where 35 promising young students from across the country, were exposed to a distinguished spectrum of 30 international experts in the field.

NBRC's endeavor from "the bench to the bedside" has completed its first full year, and the Translational Neuroscience Centre with its clinic has well progressed at its location in the leading public hospital in the region, the Gurgaon Government Hospital. It is heartening to note that patients from different neighbouring states also take help of the unit. At the National Neuroimaging Facility, the Transcranial Magnetic Stimulation set-up has been installed, which has the singular ability to temporarily inhibit any desired region of the brain, and this can open up a new arena for investigation into cognitive processes as well as therapeutic intervention in neurological and psychiatric disorders. Furthermore, this year marks the

beginning of NBRC being a self contained campus. The second hostel has become functional enabling the transfer of all the students and project assistants staying in the earlier Gurgaon hostel to our centre in Manesar. Two other buildings, conceived for the residential requirements essential service staff, are on the verge of completion. This year marks the beginning of a new community life in the campus, the students have started organizing the annual NBRC festival, *Tantrika*, where games, sports, music and social events orchestrate for a week, culminating in a weekend get-together where students, staff and faculty have an enthralling participation.

On the academic front, the labs of NBRC have welcomed a significant number of undergraduate students from India's finest colleges and universities, for a very rewarding but intensive exposure, under the visiting student fellowship program of the three Science Academies of the nation. Our teaching programs, the integrated MSc-PhD program and the direct PhD program, have blossomed further attesting to the interdisciplinary vision that neuroscience is. We are delighted to note that an increasing number of students with background in biological sciences are pursuing their thesis work in the computational neuroscience areas, while an appreciable fraction of the studentship coming from the physical or engineering sciences, are working on their research problem in neurobiological fields. What more could a neuroscience faculty ask for!

In all these attainments of the past year, there is a deep plaintive note. The founder Director of NBRC, Prof. Vijaylakshmi Ravindranath, is relocating to take up the position of founder Chairperson of the Centre of Neuroscience, Indian Institute of Science – Bangalore that has been a long-standing partner institution of the NBRC network. Over almost a decade ago, she took the herculean task of turning the wilderness of Manesar into the thriving research centre that NBRC is today. It is indeed a solemn moment for all at NBRC, her colleagues, staff and students, to bid her goodbye, and wish her best in her new endeavor. Indeed, a country as India, with a population of over a billion, does undeniably deserve a number of dedicated centres to study brain function and disease for its myriad populace. As enshrined in its vision, NBRC would ceaselessly strive forward in the nation's goal to usher in the critical mass of neuroscientists across the country. This will thereby enable Indian neuroscience to have significant international impact, both in research and human resource development.

Prof. Prasun K. Roy
Director (in-charge)



RESEARCH REPORTS

- (i) Molecular and Cellular Neuroscience
- (ii) Systems and Cognitive Neuroscience
- (iii) Computational Neuroscience and Neuroimaging



Molecular & Cellular Neuroscience

Dr. Nihar Ranjan Jana

Dr. Shyamala Mani

Prof. V. Ravindranath

Dr. Pankaj Seth

Dr. Ellora Sen

Dr. Shiv Kumar Sharma

Dr. Anirban Basu

Dr. Ranjit Kumar Giri

Molecular Mechanism of the Pathogenesis of the CAG Repeat Neurodegenerative Diseases

Principal Investigator : *Dr. Nihar Ranjan Jana*

Research Fellows : *Amit Mishra, Swetha K. Godavarthi, Megha Maheswari*

Technical Assistant : *D. Narender*

Accumulation of intracellular protein deposits as inclusion bodies is the common pathological hallmark of many age-related neurodegenerative disorders including polyglutamine diseases. Polyglutamine diseases consist of a group of familial neurodegenerative disorders caused by expression of proteins containing expanded polyglutamine stretch. The group includes Huntington's disease (HD), Dentatorubro pallidoluysian atrophy (DRPLA), Spinobulbar muscular atrophy (SBMA) and several spinocerebellar ataxias (SCA1, SCA2, SCA3, SCA6, SCA7 and SCA17). These disorders are progressive, inherited dominantly, usually begin in mid-life, and result in severe neuronal dysfunction and neuronal cell death. Increasing length of glutamine repeats in the affected individual strongly correlates with earlier age of onset and disease severity. The repeats show both somatic and germline instability and the successive generations of the affected families experience earlier age of disease onset and rapid disease progression. Interestingly, only a particular group of neurons is affected in each of these diseases, despite the ubiquitous expression of the relevant disease proteins throughout the brain and other tissues. The normal function of most of these proteins remains unknown.

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 feature of all these disorders. The soluble expanded polyglutamine proteins or their aggregates can aberrantly interact and associate with several proteins and disrupt the cellular function in many ways including transcriptional dysregulation and impairment of proteasome function.

When the cells sense 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 is not fully understood.

Major goal of this project is to identify the mechanisms through which cell can enhance the clearance of the misfolded and aggregated proteins. We are particularly working on the interplay between cellular chaperones and ubiquitin proteasome system (UPS) to deal with the misfolded and aggregated proteins. We are also exploring the role of UPS dysfunction on inflammation and neurodegeneration.

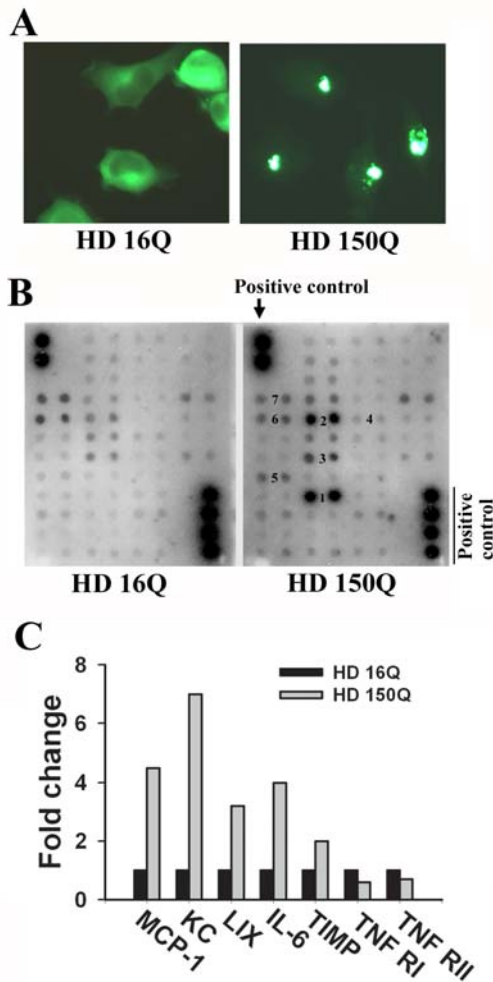


Figure: Up-regulation of several inflammatory genes in the mutant huntingtin expressing neuro 2a cells. Spots 1-7 are as follows: 1, KC; 2, MCP-1; 3, LIX; 4, IL-6; 5, TIMP; 6, TNF-RI; 7, TNF-RII.

Last year we have demonstrated extensive characterization of the role of UBE3A/E6-AP ubiquitin ligase in the degradation of expanded polyglutamine proteins and its neuroprotective role in the cellular model of HD. This year we have found that the expression of mutant huntingtin in the mouse neuroblastoma cell results in massive transcriptional induction of several chemokines including MCP-1 and KC (see Fig.1). The mutant

huntingtin expressing cells also exhibit proteasomal dysfunction and down-regulation of NF- κ B activity in a time dependent manner and both these phenomena regulate the expression of MCP-1 and KC. The expression of MCP-1 and KC are increased in the mutant huntingtin expressing cells in response to mild proteasome inhibition. However, the expression of MCP-1 and KC and proteasome activity are not altered and inflammation is rarely observed in the brain of 12 weeks old HD transgenic mice in comparison with their age-matched controls. Our result suggests that the mutant huntingtin-induced proteasomal dysfunction can up-regulate the expression of MCP-1 and KC in the neuronal cells and therefore might trigger the inflammatory process. Presently, it is not clear why the symptomatic HD mice brain do not show much inflammation. Possibly the interplay between proteasome dysfunction and NF- κ B activity regulates the magnitude of inflammation. This aspect is now under investigation. We are also continuing our study on the role of E6-AP in HD pathogenesis using transgenic mice model (R6/2 line).

Publications:

1. S. K. Godavarthi, D. Narender, A. Mishra, A. Goswami, S. Rao, N. Nukina and **N. R. Jana** (2009). Induction of chemokines MCP-1 and KC in the mutant huntingtin expressing neuronal cells because of proteasomal dysfunction. **Journal of Neurochemistry**, 108, 787-795.
2. Mishra, P. Dikshit, S. Purkayastha, J. Sharma, N. Nukina and **N. R. Jana** (2008). E6-AP promotes misfolded polyglutamine proteins for proteasomal degradation and suppresses polyglutamine protein aggregation and toxicity **Journal of Biological Chemistry**, 283, 7648-7656.

Presentations:

1. Nihar Ranjan Jana: Suppression of polyglutamine neurodegeneration by ubiquitin protein ligases. Society of Neurochemistry, India, Amritsar, 2008.
2. Nihar Ranjan Jana: Protein aggregation in neurodegenerative diseases. Invited talk in the 3rd National Medical Students Research Conference, Gwalior, 2008.

Funding:

This work is supported by NBRC Core fund.

Collaborator:

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

Understanding the Function of the Angelman Mental Retardation Syndrome Ubiquitin Ligase, UBE3A/E6-AP

Principal Investigator : Dr. Nihar Ranjan Jana

Research Fellows : Shalaka Mulherkar, Amit Mishra, Swetha K. Godavarthi

Technical Assistant : D. Narender

E6-AP encoded by UBE3A gene was first identified as a cellular protein to be involved in the ubiquitin-mediated degradation of tumor suppressor p53 in collaboration with E6 oncoprotein of the human papilloma virus. Later, it has been characterized as a HECT (homologous to E6-AP C terminus) domain family of ubiquitin ligase, an E3 enzyme of the ubiquitination cascade of ubiquitin proteasome system (UPS). The UPS is the cells major non-lysosomal intracellular protein degradation pathway responsible for the degradation of many critical proteins involved in the regulation of cell growth and differentiation, response to stress and pathogenesis of various diseases. A protein to be degraded through this pathway is first covalently attached with multiple ubiquitin molecules and then the multi-ubiquitinated protein is targeted for degradation by proteasome. The ubiquitination is carried out by a series cellular enzymes known as E1 (ubiquitin activating enzyme), E2 (ubiquitin conjugating enzyme), and E3 (ubiquitin protein ligase) that result in multi-ubiquitination of protein. A target protein must be tagged with a multi-ubiquitin chain composed of at least four ubiquitins, before it can be recognized and degraded by the proteasome. E3s play a key role in the ubiquitin-mediated proteolytic cascade, as they bind the target substrates and serve as the specific recognition elements of the system.

In addition to its ubiquitination activity, E6-AP also function as a transcriptional coactivator for steroid hormone receptors. It has been shown to interact with various steroid hormone receptors in a ligand-specific manner and serve to enhance their transcriptional activity. E6-AP-null mice also show tissue-specific steroid hormone resistance and defect in reproduction.

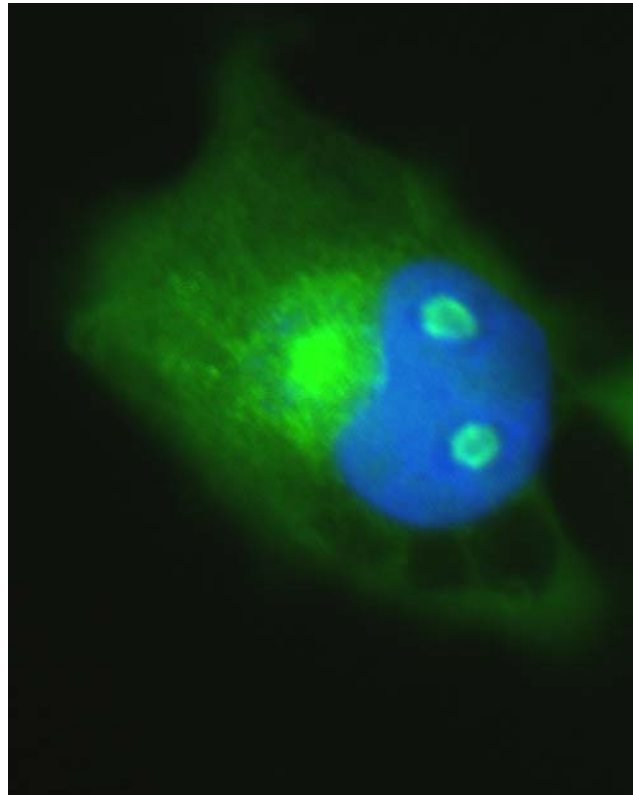
UBE3A gene is imprinted in the brain with preferential maternal-specific expression particularly in neurons but not in glia. Loss of function of the maternally inherited allele for the *UBE3A* gene causes Angelman mental retardation syndrome (AS), a neurodevelopmental disorder. AS is characterized by severe mental retardation, lack of speech, ataxia, abnormal gait, seizures, easily provoked smiling and laughter. The incidence of AS is estimated to occur in 1 of every 15,000-20,000 births. E6-AP-maternal deficient mice displays deficit in both context-dependent learning and

hippocampal long-term potentiation, in addition to motor and other behavioral abnormalities. These mice also show altered function of hippocampal calcium/calmodulin-dependent protein kinase II and abnormal dendritic spine morphology. However, the molecular mechanisms underlying these abnormalities are not known.

Since E6-AP is an ubiquitin ligase, 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. Loss of coactivator function might also be linked with the disease pathogenesis. Therefore identification of substrate protein of E6-AP and the defective signaling cascades could open a new avenue in understanding the pathogenic mechanism of AS.

Major objectives of this project are (1) identification and functional characterization of new protein substrates of E6-AP, (2) study the altered gene expression profile and signaling cascades in the E6-AP deficient mice, (3) study the role of E6-AP in ubiquitination and degradation of misfolded protein and the protection of cell death under various stress conditions.

Figure: Recruitment of ubiquitin ligase E6-AP (green) into the microtubule organizing center as well as possibly nuclear stress bodies in response to inhibition of proteasome function in Cos-7 cells. Nucleus is stained blue with DAPI (4', 6-diamidino-2-phenylindole).



Last year we have shown that E6-AP might be involved in the degradation of misfolded protein with the help of Hsp70 and hence probably functioning as a cellular quality control ligase. We have further characterized the role of E6-AP in the degradation of misfolded proteins. Earlier we have also shown that

E6-AP interacts with the substrate-binding domain of Hsp70/Hsc70 chaperones and promotes the degradation of chaperone bound substrates. The expression of E6-AP was also dramatically induced under a variety of stresses and overexpression of E6-AP was found to protect against endoplasmic reticulum stress-induced cell death. This year we have observed that the inhibition of proteasome function not only increases the expression of E6-AP but also causes its redistribution around microtubule-organizing centre, a subcellular structure for the degradation of the cytoplasmic misfolded proteins (see Fig.). E6-AP is also recruited to aggresomes containing CFTR or expanded polyglutamine proteins. All these findings suggest that E6-AP functions as a cellular quality control ubiquitin ligase and therefore, can be implicated not only in the pathogenesis of Angelman syndrome but also in the biology of neurodegenerative disorders involving protein aggregation. In fact, we have found the association of E6-AP with the Lewy bodies in the post mortem brain of Parkinson's disease patient. In the cell culture model, we have also observed the co-localization of endogenous E6-AP with the juxtannuclear α -synuclein aggregates. Over expression of E6-AP promotes the degradation of wild-type as well as the mutant forms of α -synuclein and decreases their toxic oligomeric forms. Our finding suggests that E6-AP is involved in the clearance of α -synuclein and therefore can be implicated in the Parkinson's disease. Interestingly, many AS patients also show classical parkinsonian features like resting tremor, cogwheel rigidity and bradykinesia and are respond well with levodopa. We are also characterizing the E6-AP maternal deficient mice (model mice for Angelman syndrome) using various behavioural tests (rota rod test, gait analysis and radial arm maze test).

Publication:

1. Mishra, S. K. Godavarthi, M. Maheshwari, A. Goswami and **N. R. Jana** (2009). The ubiquitin ligase E6-AP is induced and recruited to aggresomes in response to proteasome inhibition and may be involved in the ubiquitination of Hsp70 bound misfolded proteins. **Journal of Biological Chemistry**, 284, 10537-10545.

Funding:

This work is supported by a grant from DBT, India.

Degree Awarded (Ph.D.):

Mr. Amit Mishra

Regulation of neurogenesis in the cerebellum

Principal Investigator : *Dr. Shyamala Mani*

Research Fellows : *Shailesh Kumar Gupta, Parthiv Haldipur*

Project Assistants : *Upasna Bharati, Vinod Babu*

The cerebellum is important for motor coordination and this function depends on the precise synaptic wiring of the different types of cell in the cerebellum. The most abundant type of cell in the cerebellum is the glutamatergic granule cells. They control the output of the Purkinje cells and thus regulate cerebellar output. 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. Production of a postmitotic cell versus a mitotic progenitor is controlled by the orientation of the mitotic spindles relative to the ventricular zone. 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. 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). Orientation of mitotic spindles in the EGL and its impact on progenitor proliferation and cell cycle exit is not known. Further, although mitotic spindle orientation requires the cooperation of the both the microtubule and actin cytoskeletal elements the extent and the mechanism by which positioning of the mitotic spindle and the direction of polarization are regulated by extracellular signals is not understood. GAP-43 is an actin binding phosphoprotein that is involved in the transduction of extracellular signals mediated by fibroblast growth factors (FGFs) and neural adhesion molecules of the immunoglobulin superfamily class (IgCAMs) in the growth cone and is essential for axonal path-finding. 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. We are interested in elucidating two aspects of EGL proliferation - 1) The role of spindle orientation in controlling cell cycle exit in the EGL and 2) the role of extracellular cues in determining the position of the future axon in cerebellar granule neurons. The GAP-43 knockout mouse has given us insights into both these processes.

We worked on our hypothesis that GAP-43 is important in transducing extracellular signals that serve to link the position of the centrosome to that

of the leading process during migration and to position the centrosome at the base of the axonal process. To this end we first showed that GAP-43 is required in polarizing granule cell precursors to be able to respond to extracellular cues. We focused on the molecule sonic hedgehog and the matrix molecules vitronectin and laminin. We present data that the position of the centrosome was sensitive to laminin and vitronectin but that Shh had no effect on the position of the centrosome. We also showed that in the absence of GAP-43 the cell was no longer responsive to either laminin or vitronectin. We further went on to check whether the integrin receptors are involved in the orienting of the centrosome on extracellular matrix molecules. To show this we plated P0 and P8 granule cell neurons on extracellular cues printed on glass coverslips as was done previously. We then studied the orientation of the centrosome in the presence and absence of specific integrin receptor blocking antibodies. To confirm that the Shh pathway was not involved in this response we blocked this pathway in two ways. First, we blocked Shh with an antibody to prevent it binding to its receptor. Next we blocked the downstream signaling with cyclopamine. We then plated granule cells on either laminin, vitronectin or on poly-d-lysine and prepared cell lysates. Western blots of the cell lysates showed that there was an increase in PI3K in the presence of laminin and vitronectin. Blocking the integrin receptor could block this increase in PI3K. In addition we showed through immunocytochemistry that there was an increase in the localization of GAP-43 at the site of polarization. Finally we showed that we could block centrosomal orientation if we blocked the increase in PI3K by using a PI3K inhibitor. In summary we made the following important observations –

- a) Laminin and vitronectin orient the centrosome very specifically via their respective integrin receptors.
- b) The Shh pathway plays no role in this orienting response. This is in contrast to cell proliferation and differentiation where it has been shown that these molecules bind to Shh and function by inhibiting the Shh pathway.
- c) The integrin receptors work through the PI3K pathway and blocking the increase in PI3K inhibits the orienting of the centrosome.
- d) GAP-43 is phosphorylated and accumulates in the direction of the external cue.

Publications:

1. Jennifer L. Moran, Emily T. Shifley, John M. LeVorse, **Shyamala Mani**, Kristin Ostmann, Ariadna Perez, Dawn M. Walker, Thomas F. Vogt, and Susan E. Cole (2009). Expression and deletion analyses of

Manic fringe indicates that it is not required for embryonic development, and that FRINGE proteins are not functionally redundant. **Developmental Dynamics**, 238(7):1803-1812. [Epub ahead of print]

2. Kim-Da Destot-Wong, Kun Liang, Shailesh Kumar Gupta, Géraldine Favrais, Leslie Schwendimann, Michael Spedding, Vincent Lelièvre, **Shyamala Mani** and Pierre Gressens (2009). The AMPA receptor positive allosteric modulator, S18986, is neuroprotective against neonatal excitotoxic and inflammatory brain damage through BDNF synthesis. **Neuropharmacology**, Jun 3. [Epub ahead of print].
3. Shailesh Kumar Gupta*, Rashmi Mishra*, Soumya Kusum, Michael Spedding, Karina F. Meiri, Pierre Gressens, and **Shyamala Mani** (2009). GAP-43 is essential for the neurotrophic effects of bdnf and positive ampa receptor modulator S18986. **Cell Death and Differentiation**, 16(4):624-37 (* Joint first authors).

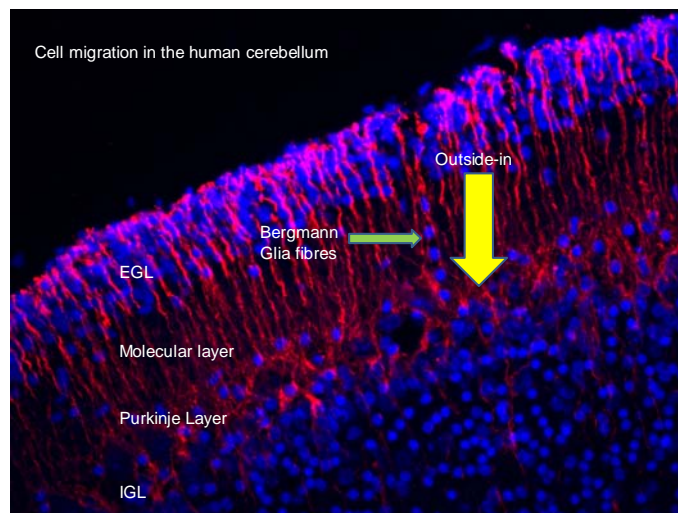
Funding

This work is supported by NBRC Core fund.

Collaborator:

Karina F. Meiri, Tufts University School of Medicine.

Figure: Section through the cerebellum of a 32 week old fetus shows a chain of nuclei originating in the external granule layer (EGL) migrating along glial fibers to form the inner granule layer (IGL) of the cerebellum.



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

Principal Investigator : Dr. Shyamala Mani

Research Fellows : Rupali Srivatsava, Pavan Kumar Rambatla

Intrinsic factors that control the commitment to neuronal lineage and that play a role in neuronal differentiation and cell type specification are largely controlled by transcription factors that contain the basic helix- loop- helix (bHLH) motif. Proneural bHLH factors are involved in the commitment of a multipotent neuroepithelial progenitor cell to the neuronal lineage. These include the neurogenins and Mash. Terminal neuronal differentiation further involves a second class of bHLH factors known as neuronal differentiation factors. This includes NeuroD, NDRF and Nex. Expression of neuronal differentiation factors results in cell cycle arrest and differentiation of neurons in culture. The pattern of expression of neural differentiation genes in vivo is overlapping but not identical. In fact some of these genes are expressed in specific subsets of neurons and suggests an additional important function of these factors, that they may be involved in specifying neuronal cell type. Knock out mice have been generated in order to study whether these differentiation factors are involved in the specification of neuronal subtype. However single knockouts of NeuroD, Nex or the double knockout do not show an obvious defect in a subpopulation of neurons missing. Our goal is to elucidate the function of proneural and neural differentiation bHLH genes using ES cells as a model system for studying neuronal differentiation.

The commonest strategy to produce a given cell type from ES cells is to add to the medium the extrinsic factors known to induce the desired fate in vivo with the hope that the developmental program will be recapitulated in vitro. A relevant alternative would be to induce with an on/off system, a controlled over-expression of an intrinsic master gene at a selected stage of ES cells differentiation program. This year we worked on lentiviral construct to transfect ES cells to overexpress bHLH transcription factor that is important for the specification of cerebellar granule neurons. In the case of granule cells, Math1 controlled over-expression may trigger the differentiation program of cerebellar granule precursors (CGPs). In case such a strategy would turn out efficient, we could further expect to generate highly homogeneous CGPs cultures, an issue which is critical when an ES cell-based therapy is further considered. To this end, we are deriving a (TET)-ON D3 cell line engineered to monitor expression of Math1 under the control of a doxycycline-inducible promoter. The functionality of tetracycline (TET)-ON based approaches has been recently demonstrated in murine and human ES

cells with no alteration of pluripotentiality, marker expression, karyotype, or ability to generate multiple tissues of different germ layer origin. By adding doxycycline and/or different previously determined extrinsic factors to the culture medium, we will assess the ability of the neurospheres to give rise to a homogeneous population of CGPs.

Funding:

This work is supported by a grant from DBT, India and NBRC Core fund.

Collaborator:

Pierre Gressens, INSERM, France.

Prof. V. Ravindranath

The unifying goal of the laboratory is to understand pathogenic mechanisms underlying neurodegenerative disorders that would potentially lead to identification of drug targets that can be used to develop rational disease modifying therapies. To this effect, we adopt a combinatorial approach involving biochemical and histochemical techniques to elucidate pathogenically important cellular pathways in animal models of Parkinson's and Alzheimer's disease. From the therapeutic angle, we are also defining the mode of action of traditional medicinal preparations used in the treatment of neurodegenerative disorders, particularly senile dementia, which help us to screen natural products that can be developed as potential drugs. Drug targets alone do not ensure successful therapeutic strategies, as *in situ* drug metabolism in the brain is critical for drug action. In this regard, we are identifying and characterizing brain CYP450 enzymes with particular emphasis on brain-specific biotransformation pathways of both drugs and endogenous compounds that play a role in pathogenic phenomena, such as inflammation in the brain.

Cytochromes P450 Dependent Metabolism of Drugs in Brain

Principal Investigator : Prof. V. Ravindranath

Research Fellows : Varsha Agarwal, Neha Sehgal

Technical Assistant : Khader Valli

Cytochrome P450 (P450), a superfamily of heme proteins is involved in the metabolism of xenobiotics and endogenous compounds. While liver is the major organ involved in P450-mediated biotransformation, functional P450 enzymes are also present in the brain wherein they metabolize a variety of compounds. The P4504F subfamily comprises of 7 functional enzymes in humans, 4 in rat and 5 in mice. All of the enzymes of the P450 4F family (Cyp4f) catalyze at varying rates the hydroxylation of the inflammatory cascade product leukotriene B₄ (LTB₄) to its inactive 20-hydroxylated product. LTB₄ is a product of action of 5-lipoxygenase on arachidonic acid, while another class of inflammatory products, the prostaglandins are formed from arachidonic acid by cyclo-oxygenases to epoxy products. The Cyp4f subfamily can also metabolize hydroxyeicosa-tetraenoic acid (HETE) and hydroperoxyeicostetraenoic acid (HPETE), which are also metabolic signals for vasoconstriction/dilation or other functions. Cyp4fs thus play a significant role in modulating the inflammatory cascade by hydroxylating and inactivating both leukotrienes and prostaglandins. While Cyp4f enzymes have previously been shown to be present in human and rat brain, what is less clear is whether the Cyp4fs play a neuroprotective role in brain during an inflammatory insult.

Inflammatory processes are seen as acute response following conditions such as traumatic brain injury or infections of the central nervous system. It is also observed in chronic neurodegenerative disorders such as, Alzheimer's and Parkinson's disease. Such inflammation can occur either through the entry of monocytes into the brain during inflammation in the periphery or can be mediated through the generation of inflammatory response *in situ* in the brain through the microglia, which are generally recognized as the primary mediators of the inflammatory response in the brain.

Our working hypothesis is that brain cytochromes P-450 4Fs play an important role in the metabolism of endogenous compounds and therefore can influence the inflammatory response. The long-term objective of the proposed project is to understand the role of *in situ* metabolism in the brain in determining the pharmacological response to psychoactive drugs as well as endogenous compounds that regulate important cellular responses, such as inflammation.

There are 5 functional genes of Cyp4f in mouse, Cyp4f13, Cyp4f14, Cyp4f15, Cyp4f16 and Cyp4f18. We amplified, cloned and expressed all the Cyp4f enzymes from mouse brain and studied their role in LTB₄ metabolism. Recombinant Cyp4f14, CYP4f15 and Cyp4f18 efficiently metabolized LTB₄ to 20-OH LTB₄. We then studied the constitutive expression of these genes in mouse cortex and found that Cyp4f15 has the highest expression, while Cyp4f18, the least. Thus, it is likely that given the quantum of expression and the LTB₄ hydroxylase activity Cyp4f15 may be the major contributor to LTB₄ metabolism. We developed an acute model of inflammatory response using LPS, in vivo in mice and in vitro in BV2, a mouse microglial cell line. During acute inflammation caused by LPS treatment the expression of Cyp4f15, 16 and 18 was significantly up-regulated in the mouse brain (but not in liver), while Cyp4f13 and 14 remained unaffected indicating a compensatory response to the inflammatory stimuli. Pretreatment with a general inhibitor of Cyp4f, in vivo resulted in exacerbation of inflammatory response, while fenofibrate, a PPAR α agonist enhanced the expression of Cyp4f15 and substantially attenuated the cytokine and chemokine levels in the brain.

To pursue the mechanism involved, we turned to a cell culture approach. Pre-treatment with 17-ODYA, the inhibitor of Cyp4f mediated ω -hydroxylation resulted in increased inflammatory response of LPS in BV2 cells in a manner similar to that seen in mice. We next developed a single shRNA that accomplished down-regulation of all Cyp4fs by developing an shRNA sequence against a homologous element within the Cyp4f family. Further, we also developed an shRNA with a sequence unique to Cyp4f15. A scrambled shRNA sequence was also cloned to serve as negative control. Both active shRNAs markedly reduced the expression of Cyp4f15 in BV-2 cells whereas the scrambled sequence did not significantly change Cyp4f15 expression. Both the shRNA sequences significantly enhanced the release of inflammatory cytokines such as TNF- α (3 fold) and IL-6 (50%) into the culture medium indicating the extent to which cytokine release is dependent on the levels of Cyp4f expression and thus the effect of Cyp4fs on inflammation. Treatment of cells with fenofibrate resulted in substantial induction of Cyp4fs and attenuated LPS-mediated release of cytokines such as TNF- α and IL-6. In order to ascertain whether fenofibrate acts through the inhibition of Cyp4f and not through other mechanism(s), we transfected BV-2 cells with the shRNAs to Cyp4fs and Cyp4f15 prior to treatment with LPS or LPS and fenofibrate. Transfection of shRNA abolished the fenofibrate-mediated induction of the mRNA expression of Cyp4f and failed to protect LPS treated cells that were transfected with shRNA-4f indicating that when Cyp4f is down-regulated, fenofibrate was unable to afford neuroprotection to the cells. The study demonstrates that Cyp4fs are indeed involved in detoxifying the mediator(s) of inflammation and therefore may

serve as potential new drug targets for developing novel class of anti-inflammatory agents for use in brain disorders.

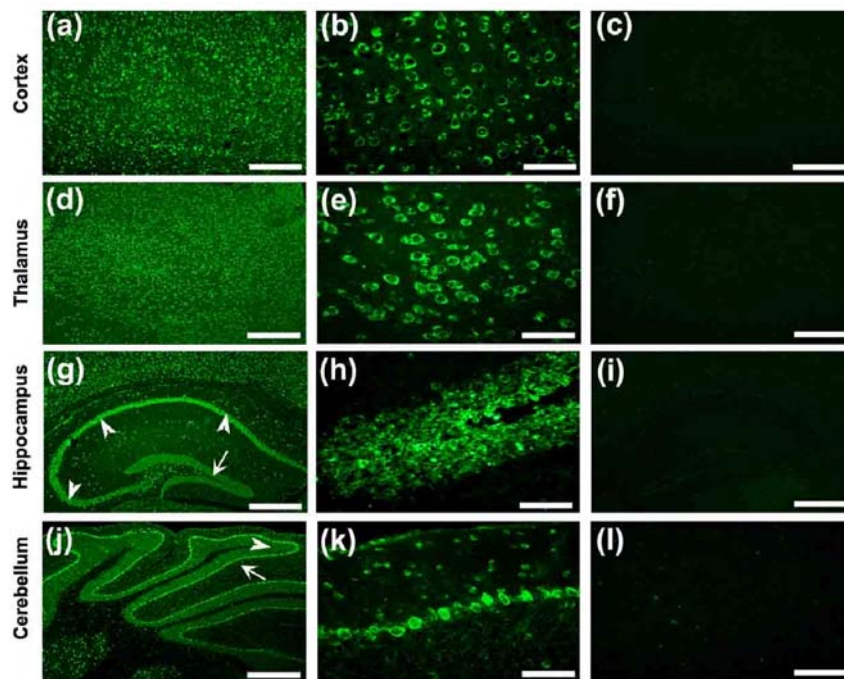


Figure: Localization of Cyp4f15 in different regions of mouse brain.

Fluorescence in situ hybridization of coronal sections showing the presence Cyp4f15 in different regions of mouse brain is depicted. Increased expression of Cyp4f15 mRNA was observed in the neurons of cerebral cortex (A,B; Bar = 25 μ m and 100 μ m, respectively) and thalamus (D,E; Bar = 25 μ m and 100 μ m, respectively), as seen in low and high magnification. Intense fluorescence was seen in the pyramidal cells of the CA1, CA2 and CA3 regions (arrowhead) and granule cells of the dentate gyrus (arrow) in the hippocampus (G,H; Bar = 25 μ m and 100 μ m, respectively). Intense fluorescent labeling was seen in the Purkinje cells in the cerebellum which express Cyp4f15 mRNA (J,K). The granular layer (arrowhead) was more intensely stained than the molecular layer (arrow) of the cerebellum (K,L; Bar = 25 μ m and 100 μ m, respectively). Corresponding control sections hybridized with sense probe are also shown (C, I, F, L; Bar=100 μ m).

Funding:

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Collaborator:

Henry Strobel, University of Texas Medical School, Houston.

Cell Specific Redox Driven Apoptotic Signaling in Parkinson's Disease

Principal Investigator : *Prof. V. Ravindranath*

Research Fellows : *Smitha Karunakaran, Lalitha Doss, Uzma Saeed, Ajit Ray*

Project Assistant : *Durgapraveen Meka*

Technical Assistant : *Shanker Datt Joshi*

Parkinson's disease (PD), a neurodegenerative disorder is characterized by loss of dopaminergic neurons in the substantia nigra pars compacta. 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. One of the compelling questions in understanding the pathogenesis of neurodegenerative disorders is the selective vulnerability of specific cell types to neurodegeneration.

The redox status of proteins regulate signaling pathways that govern both cell survival and death. 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 and suppression of survival pathways. Our overall aim is to understand differential vulnerability of selective cell populations, such as the dopaminergic neurons of substantia nigra to neurodegeneration.

Dopaminergic neurons have been shown to undergo apoptosis in animal models of PD, which has led to considerable interest in targeting the c-Jun NH₂-terminal kinase (JNK) pathway for slowing down the progression of the disease. However clinical trial with the JNK inhibitor CEP 1347 was discontinued recently as significant neuroprotection was not observed in patients with early PD.

Our focus was to discern if distinct pathways were activated in cell-specific manner within the substantia nigra. We demonstrated the selective phosphorylation of p38 MAP kinase within the dopaminergic neurons while JNK activation occurred predominantly in the microglia. p38 activation results in downstream phosphorylation of p53 and increased p53 mediated transcription of Bax and Puma in the ventral midbrain. Treatment with p38 inhibitor, SB239063 protected primary dopaminergic neurons derived from human progenitor cells from MPP⁺ mediated cell death and prevented the downstream phosphorylation of p53 and its translocation to the nucleus *in vivo*, in the ventral midbrain. The increased staining of phosphorylated p38 in the surviving neurons of SNpc in human brain sections from patients with

PD and in MPTP treated mice but not in the ventral tegmental area provides further evidence suggesting a role for p38 in the degeneration of dopaminergic neurons of SNpc. Selective inhibitors of p38 may help preserve the surviving neurons in PD and slow down the disease progression.

We observed that p38 activation results in downstream phosphorylation of NF- κ B and accumulation of NF- κ B p65 selectively in ventral midbrain but not in striatum. Treatment with p38 inhibitor, SB239063 prevented downstream phosphorylation of I κ B α and NF- κ Bp65 subunit translocation to the nucleus, in vivo, in the ventral midbrain. Phosphorylation of antiapoptotic Bcl2, an NF- κ B target gene by p38 to inactive pBcl2ser87 was also attenuated by SB239063. In agreement with the above, sustained caspase activation is seen in the ventral midbrain but not in striatum. We demonstrate the region specific p38 mediated activation of NF- κ B following MPTP treatment demonstrating the role of p38/NF- κ B signaling in the pathogenesis and progression of the disease.

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1. Karunakaran, S., Saeed, U., Mishra, M., Valli, R.K., Joshi, S.D., Meka, D.P., Seth, P. and **Ravindranath V** (2008). Selective activation of p38 mitogen-activated protein kinase in dopaminergic neurons of substantia nigra leads to nuclear translocation of p53 in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-treated mice. **J. Neurosci.** 28: 12500-12509.
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* (Reported as submitted last year).

Presentations:

1. V Ravindranath: “Therapeutics for Alzheimer’s Disease: Current Trends and Future Prospects” at NEUROLINKS 2009 at New Delhi on February 15-16, 2009.
2. V Ravindranath: Plenary Lecture “Neurodegeneration and Brain Aging: Basic Science to Therapy” at NEUROCON 2009 Conference at IPGME&R, Kolkata held on 8th February, 2009.
3. V Ravindranath: “Disease Modifying Therapies for Neurodegenerative Disorders” at NIPER, Hyderabad seminar on organic Chemistry – Its importance in industries and health held on 3rd February, 2009.
4. V Ravindranath: “The future of MRI imaging Neuroscience” at “The Brain Storming Session on Future Directions of Biomedical Magnetic Resonance” at Centre of Biomedical Magnetic, Lucknow held on 23 and 24 December, 2008.
5. V Ravindranath: “Current research progress in understanding Alzheimer's disease and new hopes for treatment” at NSI CME program held on 17th December 2008 at Pune.
6. V Ravindranath: "P38 but not JNK is activated in substantia nigra neurons in Parkinson's disease" presented in XXVI Annual Conference of Indian Academy of Neurosciences at Cochin from December 12-14, 2008.
7. V Ravindranath: Plenary Lecture “Brain Research: Recent Advances in Development of Rationale Therapies and Cures for Brain Disorders” at An international symposium on “Recent Advances in Organic Chemistry at Andhra University, Visakhapatnam held on 12th December, 2008.
8. V Ravindranath: Plenary lecture “The working of the human brain - molecules and networks to behaviour” at The Army Science Conference held on December 02, 2008 in Florida.
9. V Ravindranath: “Knockdown of cytosolic glutaredoxin 1 leads to loss of mitochondrial membrane potential: implication in neurodegenerative diseases” presented at Society for Neuroscience held from November 14-19, 2008.

10. V Ravindranath: “Unraveling molecular pathways of pathogenesis of complex neurodegenerative disease by identifying cell-specific signaling in animal model in Parkinson’s disease” at NCBS, Bangalore held from Oct 2 and 3, 2008.
11. V Ravindranath: “Redox driven activation of cell specific signaling pathways in neurodegeneration » at fourth Amyotrophic Lateral Sclerosis Symposium held in Montreal on 25 and 26 September 2008.
12. V Ravindranath: “Cell-specific activation of redox driven death signaling pathways in neurodegeneration” at Brain and Mind research in the Asia/Pacific (BMAP) symposium at Singapore held during 01-03 September, 2008.
13. V Ravindranath: Valedictory Speech of the National Workshop on “Trauma and Pain Management” at University of Hyderabad, Hyderabad held on August 04, 2008.
14. V Ravindranath: “Redox signalling in Parkinson's disease: Emerging role of sulfur metabolism”Invited speaker, Gordon Research Conference, Italy held on 25th to 30th May, 2008.

Cellular and Molecular Mechanisms of HIV-1 Neuropathogenesis

Principal Investigator : *Dr. Pankaj Seth*

Research Fellows : *Mamata Mishra, Shaily Malik*

Project Assistants : *Hena Khalique, Manisha Taneja*

Technical Assistant : *Durgalal Meena*

Central nervous system (CNS) infection with human immunodeficiency virus-1 (HIV-1) and subsequent development of acquired immunodeficiency syndrome (AIDS) are often accompanied with severe and debilitating neurological disorders. Such neurological complications are characterized by neurodegeneration in the cortical region of human brain, resulting in progressive cognitive and motor impairments typically involving behavioral abnormalities, deficits in executive functions and dementia. These disorders usually develop in advanced stages of HIV-1 infection due to irreversible damage to neurons by HIV or its viral proteins gp120 and Tat. They are collectively referred to as HIV-1 associated dementia (HAD) or AIDS dementia complex (ADC).

Neural precursor cells have the ability to replenish ageing or damaged brain cells till late in life, although that ability progressively diminishes with age. Neurogenesis occurs throughout adulthood in the dentate gyrus of hippocampus, the center for learning and memory. However, adult neurogenesis is reported to be impaired in several psychiatric disorders and neurodegenerative diseases including HAD. Until recently, HIV-1 was believed to be affecting only the astrocytes and microglial cells in the brain as neurons are rarely infected. However, recently HIV-1 virus is found to be present in areas of neurogenesis in autopsy brain sections from pediatric AIDS patients, suggesting that human neural stem/precursor cells may harbor HIV-1. The presence of HIV-1 in neural precursor cells raises concern about the consequence of harboring of HIV-1 in hNPCs.

Human neural precursor cells grow as undifferentiated, highly proliferative, adhered monolayers cultures. These cells can also form neurospheres that grow in culture with time as attached or floating spheres, which is related to the self-renewing property of neural stem cells. We adopted a stepwise approach to answer our research question as to whether HIV transactivating protein Tat affects human neural precursor cells, and if yes, how?

First, to investigate the effect of HIV Tat protein on proliferation rate of human fetal neural precursor cells we exploited the ability of high proliferation rate of these cells. Alterations in viability and proliferation rate

in growing neurospheres were assessed and compared with neurospheres cultured in presence of various concentration of HIV-1 Tat. The growth of neurospheres cultured in the presence of HIV Tat protein was significantly impaired as compared to untreated neurospheres. To confirm if this was due to decrease in the cell proliferation of human neural precursor cells, we looked into proliferation markers like BrdU incorporation in growing neurospheres and stained the fixed neurospheres with Ki67, a well accepted marker of cell proliferation.

Human neurospheres cultured in presence of HIV Tat showed a remarkable decrease in number of BrdU stained cells as compared to neurospheres of vehicle control group. Similar observation was made with Ki-67 staining where a clear reduction in number of Ki-67 positive cells was noticed in Tat treated group. This confirmed that the decrease in growth and size of neurospheres was due to decrease in cell proliferation ability of the neurospheres. Interestingly, the attenuation in proliferation rate by HIV Tat treatment did not affect the viability of hNPCs, which suggested that the cells may be “stalling” in their cell cycle phases. We observe that HIV Tat induced alterations in hNPCs functions involves cyclin D1, which is one of the important components that drive cell cycle via interaction with cyclin dependent kinases 4 and 6 (CDK4 and CDK6). Our assessment of cyclin D1 levels by immunocytochemistry as well as western blotting revealed that HIV-1 Tat substantially down-regulated cyclin D1 in hNPCs cultured in presence of HIV-1 Tat protein.

In quest to understand how HIV Tat effects the proliferation and differentiation of human neural precursor cell properties, we studied several genes important for human neural stem cell and neurogenesis, and proteome array for phosphorylated forms of mitogen activated kinases (pMAPKs).

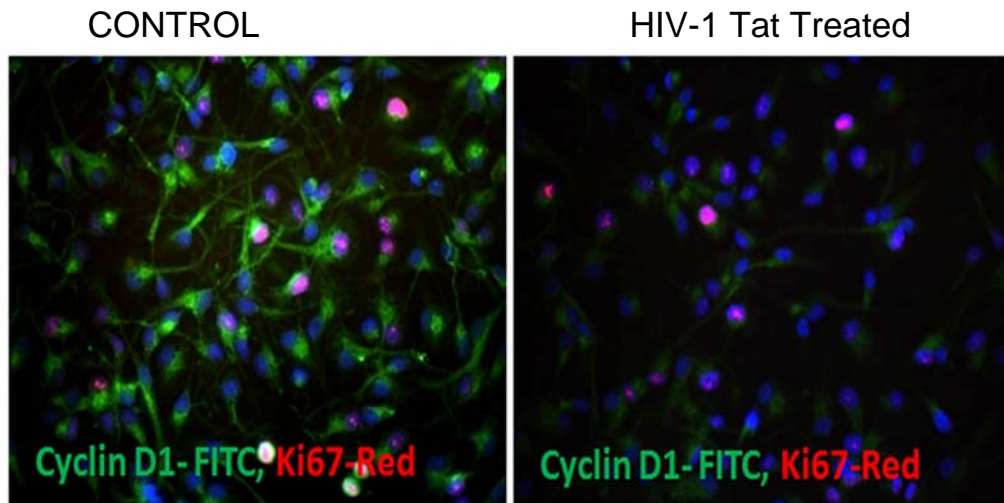


Figure1: Cyclin-D1 Expression is Down-regulated by HIV-1 Tat Exposure in Human Neural precursor Cells. Human neural precursor cells exposed to HIV-1 Tat protein for 24 hour. Cells from control and Tat treated groups were fixed and immunostained for cyclin-D1 (FITC; Green) as well as proliferation marker, Ki67 (Texas red; Red). Nucleus of cells were stained with DAPI (Blue).

We observed that HIV Tat attenuates the growth, proliferation as well as differentiation capabilities of human fetal brain derived neural stem/precursor cells. HIV-1 Tat may have serious implication in neurogenesis that may occur following HIV-1 induced damage to brain cells, particularly neural precursors.

We have unraveled a previously unrecognized role of HIV-1 Tat on human neural stem cell property, including neurogenesis. We believe our findings would help in better understanding the role of HIV transactivating protein Tat in neurological complications seen in neuroAIDS and warrant therapeutic approach directed against it.

Publications:

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2. S. Karunakaran, U Saeed, M. Mishra, R. K Valli, S. Datt Joshi, D. Meka, **P. Seth**, and V. Ravindranath (2008). Selective activation of p38 mitogenic-activated protein kinase in dopaminergic neurons of substantia nigra leads to nuclear translocation of p53 in 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine-treated treated mice. **J Neuroscience** 28: 12500-12509.

* Reported in press last year.

Presentations:

1. P. Seth: INDO-US Forum Meeting, Organized by US National Academy of Science, Agra, India, March 2009.
2. P. Seth: National Frontiers of Science Meeting, Indian National Science Academy, New Delhi, India, Jan 2009.
3. P. Seth: Annual Meeting of Indian Academy of Neurosciences at Cochin University, Cochin. December 2008.
4. P. Seth: Neuro Update 2008 Kolkata, Calcutta National Medical College Hospital and Indian Institute of Chemical Biology, Kolkata, India, September 2008.
5. P. Seth: Science Popularization Series Lecture, Organized by Haryana State Council for Science and Technology, Gurgaon, India, August 2008.

6. P. Seth: "Stem cells: Good, Bad and Ugly." At Haryana Government Girls College, Gurgaon for refresher's course for degree college teachers, May 2008.

Funding:

This work is supported by two grants from DBT, India.

Collaborators:

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Understanding aberrant transcriptional circuitries and signaling cascades in Glioblastoma multiforme

Principal Investigator : *Dr. Ellora Sen*

Research Fellows : *Vivek Sharma, Richa Tewari, Nitin Koul*

Technical Assistant : *Uttam Kumar Saini*

Glioblastoma multiformes (GBM) represents one of the most malignant brain tumors characterized by intense proliferation, widespread invasion of poorly differentiated cells and poor prognosis. The tumor microenvironment plays a major factor in inducing malignancy and elevated expression of pro-inflammatory cytokines has been implicated in the progression of GBM. The focus of our laboratory is to understand the importance of inflammatory mediators and growth factors on the transcriptional regulation of genes associated with GBM progression and survival. The signal provided by growth factors and its interaction with 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. The aim is to understand how aberrant transcriptional circuitries and signal transduction pathways contribute to the progression GBM. The highly resistant nature of GBM to chemotherapy has also prompted us to identify new treatment strategies.

Objectives:

- a. Dissecting the role of cytokine and growth factors in the transcriptional regulation of genes involved in resistance to apoptosis, proliferation, survival and evasion of immune response in glioma cells is an active area of research in the lab.
- b. Investigating whether lipid rafts functions as an organizing platform crucial for cell signaling events.
- c. Understand mechanisms that confer resistance of GBM to apoptosis and identify new treatment strategies that can manipulate the aberrant signaling pathways to induce apoptosis.

We observed elevated levels of the pro-inflammatory cytokine IL-1 β in GBM tumor samples. Since Hypoxia-inducible factor-1 α (HIF-1 α) plays a crucial role in linking inflammatory and oncogenic pathways, we investigated the effect of IL-1 β on HIF-1 α expression in glioma cells under normoxia. IL-1 β mediated elevation of HIF-1 α transcriptional activity was dependent on Ras induced NF- κ B activation. Elevated HIF-1 α activation by IL-1 β was accompanied by enhanced interaction of HIF-1 α with HIF responsive

element (HRE) on the IL-1 β promoter under normoxia, suggesting the existence of an HIF-1 α -IL-1 β autocrine loop in GBM that may act independent of hypoxia to promote tumorigenesis. We have observed that altered distribution of death receptors between the raft and non-raft domains effect cascade of downstream signaling events that sensitizes glioma cells to tumor necrosis factor α (TNF α) induced apoptosis. We have also identified novel mechanism of induction of apoptosis in GBM cells by Scriptaid- an HDAC inhibitor. Scriptaid reduced glioma cell viability by increasing JNK activation and decreasing telomerase activity.

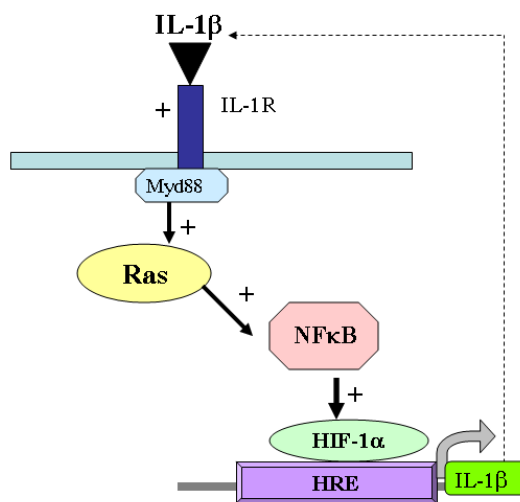


Figure: Proposed model for HIF-1 α regulation in glioma cells exposed to pro-inflammatory cytokine IL-1 β . Ras is the major signaling molecule that regulate IL-1 β induced NF κ B dependent HIF-1 α activation in glioma cells. In addition to Ras mediated induction in HIF-1 α activation in IL-1 β treated cells, the existence of an IL-1 β -HIF-1 α autocrine loop ensures that increased IL-1 β production is sustained to enhance HIF-1 α activity.

Publications:

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3. Tewari R., Sharma V., Koul N., Ghosh A., Joseph C., Hossain U. Sk and **Sen E.** (2008). Ebselen abrogates TNF α induced pro-inflammatory response in glioblastoma. **Molecular Oncology** 3 (1):77-84.
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2. Vivek Sharma, Nitin Koul, Christy Joseph, Deobrat Dixit, Sadashib Ghosh and Ellora Sen: HDAC inhibitor Scriptaid induces glioma cell apoptosis through JNK activation and inhibition of telomerase activity. International Symposium on Complex Diseases: Approaches to Gene Identification and Therapeutic Management Satellite Symposium, Kolkata, August 2008.
3. Vivek Sharma, Richa Tewari, Nitin Koul, Deobrat Dixit, Sadashib Ghosh and Ellora Sen: Re-evaluating the role of Ras in glioma therapeutics. International symposium on Molecular aspects of brain aging and neurological disorders and Annual meeting of Society for Neurochemistry, Amritsar, November 2008.
4. Vivek Sharma, Richa Tewari, Nitin Koul, Deobrat Dixit, Sadashib Ghosh and Ellora Sen: Ras and Glioblastoma therapy: Where does the truth lie? INDO-US symposium on emerging concepts in Cancer, Trivandrum December 2008.
5. Deobrat Dixit, Vivek Sharma, Sadashib Ghosh, Nitin Koul, Prakash Kumar Mishra and Ellora Sen: Manumycin inhibits STAT3, telomerase activity and growth of glioma cells by elevating intracellular reactive oxygen species generation. Indian academy of Neurosciences Cochin, December 2008.
6. Richa Tewari, Vivek Sharma, Nitin Koul and Ellora Sen: Inducing GBM Cell Death through Lipid Raft Intervention. Indian academy of Neurosciences Cochin, December 2008.
7. Ellora Sen: Interleukin-1 β induced HIF-1 α activity in glioma cells is modulated by RAS via NF κ B. Indian Academy of Cancer Research, Bangalore February 2009.
8. Ellora Sen: Inflammation and Oncogenesis: Partners in crime. Sphaera Pharma Pvt.Ltd, 5th March 2009.

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Collaborator:

Dr. VS Mehta, Paras Hospital, Gurgaon, Haryana, India.

Signaling cascades regulating the differentiation of glial progenitors along specific lineages

Principal Investigator : *Dr. Ellora Sen*

Research Fellows : *Deobrat Dixit, Sadashib Ghosh*

Project Assistant : *Christy Joseph*

Neural stem cell (NSCs) in the mammalian central nervous system (CNS) possesses 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. 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. The decisive instructive and permissive signals, that govern these developmental choices, are provided by cell external cues and cell intrinsic programs. Recent advances in understanding NSC differentiation into glial lineages have revealed the importance of growth factors and relevant downstream transcription factors. These factors working through their respective downstream transcription factor combinatorially induces the preferential differentiation of one cell lineage while suppressing another. Recent studies suggest that hypoxia promotes the survival and proliferation of NSCs. Our focus is to understand the differentiation ability of NSCs expanded under hypoxia. We are investigating whether hypoxia regulates the transcriptome of bipotential glial progenitors in the subventricular zone (SVZ), - a region of the brain that harbors the multipotential neural stem cells/progenitors, to induce preferential differentiation towards one lineage at the expense of another.

Objectives

To understand how extrinsic cues in a hypoxic environment regulate downstream transcription factors that effect NSC differentiation towards astrocytic lineage.

We observed an increase in the expression pro-inflammatory cytokine IL-1 β when neurospheres were subjected to a hypoxic environment. Astrocyte differentiation is known to involve a complex formation composed of STAT3 with transcriptional co-activator p300. Treatment of NSCs with IL-1 β increased phosphorylation of STAT3 - which is known to promote astrogliogenesis. This elevation in pSTAT3 was accompanied by its increased interaction with p300.

Funding:

This work is supported by a grant from DBT, India.

Molecular Mechanisms of Synaptic Plasticity and Memory: Activity-Dependent Protein Acetylation.

Principal Investigator : *Dr. Shiv Kumar Sharma*

Research Fellows : *Chinmoyee Maharana, Kaushik Pramod
Sharma, Kiran Pandey*

Project Assistants : *Sarah Dalpa, Preeti Yadav*

Intense efforts have been focused on finding out the molecular and synaptic mechanisms of memory formation. Activity-dependent molecular and synaptic changes play important roles in memory formation. Long-term potentiation (LTP) is a rather persistent increase in the synaptic strength, and is considered a cellular mechanism for memory formation. Despite extensive investigation, the molecular changes involved in LTP and memory are far from understood. The role of several signaling cascades that are regulated in an activity-dependent fashion is well established in LTP and memory. It is also known that, in addition to regulation of signaling molecules, LTP and memory involve changes at the translational and transcriptional levels.

In this project, we are examining how activity brings about changes in chromatin modifications that may be involved in gene regulation during LTP and memory. For our studies, we use in vitro prepared rat hippocampal slices and stimulate them with KCl. KCl brings about depolarization in the cells and leads to Ca⁺⁺ influx, which is a primary requisite for LTP and memory formation. Moreover, KCl can induce LTP in the hippocampus that requires NMDA receptor activity. The requirement of NMDA receptor activity is a hall mark of many forms of LTP as well as memory. These studies should help us understand the mechanisms that contribute to the regulation of gene expression during LTP and memory.

During this year we have focused our efforts to characterize activity-dependent histone acetylation. Previous studies have examined the regulation of histone H3 acetylation during LTP and memory, and also by pharmacological treatments that bring about relevant changes in the signaling cascades. Since the nucleosome consists of other histones in addition to H3, we asked whether the acetylation of other histones is also regulated in an activity-dependent manner.

Our results show that KCl depolarization enhances acetylation of histone H2B. Since KCl treatment activates extracellular signal-regulated kinase (ERK), we next examined whether ERK activity is required for H2B acetylation. We found that inhibition of ERK by the MEK inhibitor completely blocks depolarization-induced H2B acetylation. DNA methylation

is an epigenetic mark that is known to regulate gene expression. During LTP and memory formation, DNA methylation acts in concert with histone acetylation in the regulation of gene expression. Hence, we examined whether DNA methylation status has any effects on H2B acetylation. The results show that inhibition of DNA methyltransferase inhibits H2B acetylation. These results indicate that KCl depolarization of cells increases H2B acetylation in an ERK-dependent manner. Furthermore, DNA methylation status plays a critical role in this process.

While we were examining the acetylation of histones, we noticed that treatment with histone deacetylase inhibitor, trichostatin A (TSA) lead to an increase in acetylation of a protein of about 55 kDa in the hippocampal slices. TSA treatment is known to enhance acetylation of a p55 in the insular cortex, and p55 acetylation is regulated in taste memory formation. Hence, using different molecular techniques, we have characterized this protein in the hippocampus. Currently, we are examining how p55 acetylation may contribute to LTP and memory.

Publication:

1. *Ye, X, Shobe, JL, **Sharma, SK**, Marina, A and Carew, TJ (2008). Small G proteins exhibit pattern sensitivity in MAPK activation during the induction of memory and synaptic facilitation in Aplysia. **Proc. Natl. Acad. Sci. USA**, 105:20511-20516.

* work done elsewhere.

Funding:

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Neurodegeneration and Impairment in Synaptic Plasticity and Memory by Amyloid Beta

Principal Investigator : *Dr. Shiv Kumar Sharma*

Research Fellow : *Shilpa Mishra*

Project Assistant : *Soumee Bhattacharya*

Lab Attendant : *Narayanan*

Alzheimer's disease (AD) is the most common form of dementia in the elderly. AD is characterized by the presence of amyloid plaques and neurofibrillary tangles in the brain. Amyloid beta (A-beta), the principal component of the plaques, exists in monomeric, oligomeric and the fibrillar forms. Recent studies suggest that the A-beta oligomers cause neuronal cell death. In addition, these toxic species of A-beta cause deficits in long-term potentiation (LTP) and memory. However, the mechanisms of neurodegeneration and the impairment in synaptic plasticity and memory are not clearly understood. In this project, we aim to (1) Identify neuroprotective agents and study their mechanisms of action, and (2) examine the effects of A-beta on growth factor signaling important for LTP and memory.

Curcumin is one of the neuroprotective agents that has received attention due to its antioxidant activity. We are examining the neuroprotective effects of a curcumin metabolite. For these studies, we are using primary hippocampal cultures prepared from rat embryos. We found that the curcumin metabolite reduces A-beta oligomer-induced toxicity in the hippocampal neurons. We further examined the mechanisms that are involved in the protective effects of this metabolite. We find that the curcumin metabolite affects the increase in mitochondrial potential caused by A-beta oligomers. Furthermore, A-beta oligomer-induced levels of reactive oxygen species and caspase activity are reduced upon curcumin metabolite treatment. These results suggest that the curcumin metabolite protects neurons by affecting the apoptotic machinery. Not only in rat neuronal cultures, the curcumin metabolite shows protective effects in human neurons also. We are currently examining whether curcumin metabolite affects the generation of cytokines in the microglial cells, and thus could offer indirect neuroprotection also.

We have started examining the effects of oligomeric A-beta on the growth factor-induced signaling in the hippocampal neurons. Initial results suggest that growth factor signaling is impaired by A-beta.

Presentation:

- I. Amyloid beta-induced neuronal toxicity: protective effects of a flavonoid. Poster presentation in the Indian Academy of Neurosciences Conference, 2008.

Funding:

This work is supported by NBRC Core fund.

Collaborator:

Dr. Pankaj Seth, NBRC, India.

Molecular Approaches to Understand the Pathophysiology and Pharmacology of Infection and Inflammatory Disorders of Central Nervous System

Principal Investigator : *Dr. Anirban Basu*

Research Fellows : *Manoj Kumar Mishra, Sulagna Das, Deepak Kumar Kaushik*

Post Doctoral Fellow : *Dr. Kallol Datta*

Project Assistants : *Debapriya Ghosh, Swarupa Chakrabarty*

Technical Assistant : *Kanhaiya Lal Kumawat*

Lab Attendant : *Manish Dogra*

The focus of our laboratory is to understand the pathophysiology and pharmacology of infection and inflammation in CNS. Our research question evolves around the understanding the molecular basis of host-pathogen interaction in Viral infection of the brain and the signaling events associated with neuro-inflammation. In last few years our research have been primarily focused on neuropathology of host pathogen interaction in Japanese encephalitis Virus, causative agent of most common viral encephalitis in Asia-pacific region. Increasing experimental, clinical, and epidemiological studies point to the pivotal role of inflammation in the pathogenesis of acute and chronic neuro-degenerative diseases. Recently we have initiated one more project to understand the consequences of tobacco carcinogen induced neuro inflammation and neuronal damage.

Japanese encephalitis virus (JEV), a member of the flaviviruses, is the most common cause of arthropod borne human encephalitis in Asia. The primary sites for JEV multiplication are likely to be in either myeloid and lymphoid cells or vascular endothelial cells. JEV is able to infect neurons, although their role in JEV infection has not been clearly defined. Viral persistence in the human nervous system has been reported in approximately 5% of patients with JEV associated encephalitis. This suggests that, following the acute infection phase persistent JEV infection might also be responsible, in part, for the neural sequelae occurring in approximately 70% of survivors. The host response to infection is central to the effective control and ultimate clearance of invading pathogens. A detailed understanding of the disease pathogenesis is therefore crucial for the prevention of the neurological sequel mediated by JEV in human beings.

We have showed that JE Virus can infect neural stem cells/progenitors (NSPs) and harbor in them. Interestingly, the virus does not induce robust

NPC death, but with progressive infection arrests their proliferative ability. This eventually culminates in depletion of NPC pool upon JEV infection, which could lead to long-term neurological sequel in JE survivors. Further validation of proliferation arrest in NPCs with progressive infection was obtained from cell cycle analysis, which clearly depicted that JEV indeed blocks S-phase entry with a very low percentage of cells residing in S-phase of the cycle. This observation emphasized cell cycle arrest as a possible mechanism of diminishing the NPC pool following infection. We have also found that by enhancing the expression of checkpoint inhibitors (p27 and p21) JEV leads to G1 phase arrest in the NPCs eventually resulting in suppression of their proliferation.

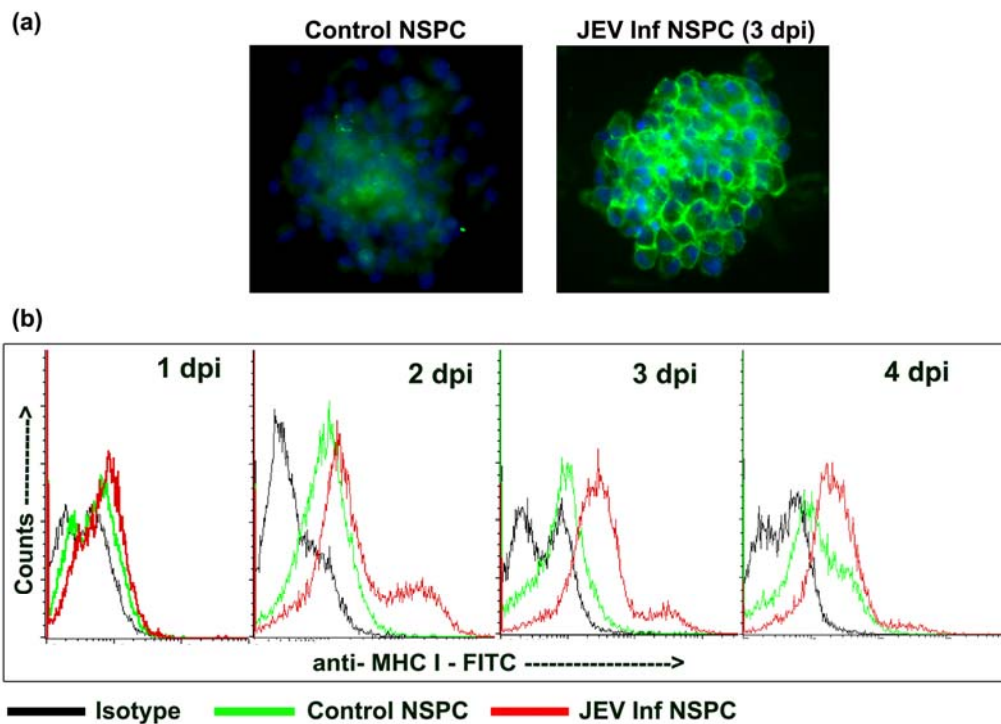


Figure1 Induction of MHC class I in Neuronal Stem/Progenitor cells (NSPCs) following JEV infection. (a) MHC class I expression was detected by immunocytochemistry in control (uninfected) and JEV infected neurospheres following 3 days post JEV infection. A robust increase in the surface expression of MHC-I (H2k^d) was observed following 3 days post infection compared to uninfected neurospheres. (b) The surface expression of MHC-I was confirmed by examining MHC-I (H2k^d) stained NSPCs on Flow cytometry at different days post infection (1 day, 2 days, 3 days, and 4 days). A gradual and significant upregulation of MHC-I was found in the JEV infected NSPCs with days post infection, and maximum expression observed at 3 dpi of JEV infection.

Recently we have initiated work to investigate whether JE virus infection induce immunogenicity in NSPs. We initially investigated the expression of MHC-I antigen expression upon JEV infection. As in the case of all viral

infections, the expression of MHC-I antigen was upregulated greatly following JEV infection. We performed a time course study till 4 day post infection (dpi), and maximal expression was noted at 3 dpi (which is the time needed for viral replication in the cells). We also observed significant increase in the expression of the various co-stimulatory molecules like CD40, CD80 and CD86 at 3 and 4 dpi in infected NSPs. We performed double immunohistochemistry for Nestin and the various co-stimulatory molecules and MHC-I protein with Nestin positive cells in the SVZ of 4 day JEV infected pups. Interestingly, an increased expression of these molecules was observed, which also colocalised with the Nestin positive NSPs in the SVZ. We have also evaluated whether NSPs behaved as immunogenic cells and produced various cytokines and chemokines. Interestingly, cytokine bead array showed that the JEV infected NSPs produced significant amount of the pro-inflammatory molecules like IL-6, TNF- α , MCP-1 and IL-12p40.

Regarding our work with virus entry into neural stem/progenitor cells (NSPs) we have found that a progressive increase in intracellular JEV antigen was observed starting from 24 hours post infection till 72 hours post infection. We have also determined whether the envelope protein of JEV, associates with the membrane of NSPs at early time points post infection. As early as 10 mins post infection, the envelope protein (glycoprotein E) associates with the membrane of NSPs, and with increasing time, more viral protein is bound. We next investigated whether receptor mediated endocytosis plays a role in viral entry in NSPs. Indeed, we found prominent colocalisation of JEV glycoprotein E with Transferrin Receptor (which usually undergoes clathrin-mediated endocytosis) in cells.

In continuation of our earlier work with minocycline, recently we have showed that minocycline and a number of antioxidant compounds inhibit the JEV induced free radical generation in mouse neuronal cells. In addition, we have showed that the beneficial effect of minocycline is associated with reduction of (i) membrane fluidity, (ii) apoptosis/necrosis, (iii) stress related proteins, (iv) neuronal death. Very recently we have found minocycline restore blood brain barrier (BBB) integrity following JE virus infection. We have also observed that minocycline plays a pivotal role in regulating peripheral immune response following JE virus infection.

Last year we have initiated a work to study the role of different tobacco carcinogen in neuroinflammation and subsequent neuro-degeneration. Almost one billion men and 250 million women in the world smoke – about 35 percent of men in developed countries, 50 percent of men in developing countries and even 22 percent of women in developed countries smoke daily. It is quite well known that cigarette smoke is the major cause of the lung cancer of the world. Several compounds of the cigarette smoke have been identified to be having carcinogenic potency. 4-N-Methyl-N-nitrosamino)-1-

(3-pyridyl)-1-butanone (NNK), a major nitrosamine formed in tobacco smoke, is a very potent carcinogen. It can systemically induce a high incidence of lung, liver and nasal cavity tumors in rats. Concentrations of NNK in tobacco substances may vary from 1-20 $\mu\text{g}/\text{gm}$ in snuff, to 20-310 ng/cigarette in cigarette mainstream smoke and while tobacco exposed areas such as indoor air have ≤ 26 ng/ m^3 of NNK. Hence, both direct and second-hand tobacco-smoke exposures lead to substantial measures of NNK intake.

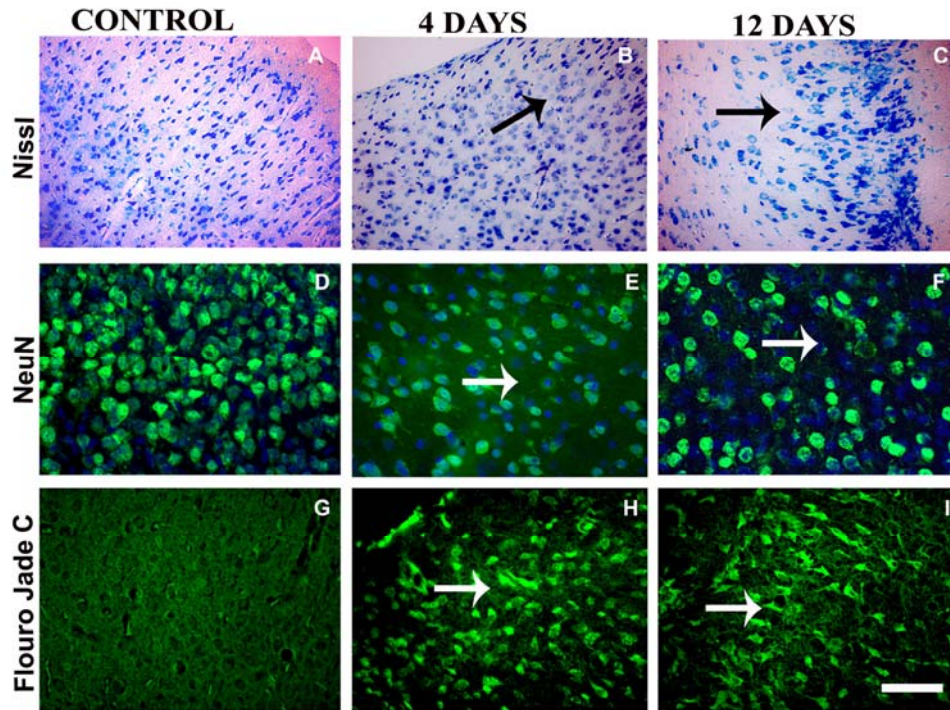


Figure 2 NNK treatment causes acute neuronal damage *in vivo*: Mice were treated with 15mg/kg body wt of NNK for 4 and 12 days. Then cryostat sections of brain from control and treated mice of both the treatment groups were stained with the thionin (A - C), NeuN (D - F) and Fluoro Jade C (G - I). Thionin staining shows distinct neuronal loss along with morphological alteration in the 4th day and 12th treatment groups respectively. Substantial neuronal loss in both the treatment groups is evident by NeuN staining, while Fluoro Jade C staining shows foci of neurodegeneration. The images are of cerebral cortex around the hippocampal region. Figures represent cryosections of mouse brain from each group as a representative of six animals from the group. (Fig A - C are of 20X magnification, scale bar is 50 μm and D-I are of 40 X magnifications and scale bar is 25 μm)

One of the most important aspects of the diseases that have been studied in the recent years is inflammation. Infact, inflammation plays a role in extremely wide array of disease conditions ranging from viral diseases of CNS to neurodegenerative disorders. Few studies provide some insights of the effect of tobacco smoke and inflammation. Although NNK has been reported to induce oxidative stress in the microsomal fraction of brain, little

work has been done to elucidate whether NNK can trigger neuroinflammation in brain and whether the inflamed milieu can cause any neuronal damage. Considering the statistics of the number of direct and indirect smokers in the world, we can easily predict the enormous number of people who are exposed to NNK everyday. It is extremely important from medical, social and economic point of view, to elucidate whether NNK could cause neuroinflammation. Thus this study besides being a scientific responsibility bears immense social and moral importance.

We have investigated whether NNK causes inflammatory upheaval in the brain by activation of resident microglia and astrocyte and result in bystander neuronal damage. We have carried out the work in both in vitro and in vivo models. We have found that treatment with NNK causes significant activation of mouse microglial (BV2) cell line as evident by increase in ROS and NO level. Western blot analysis has showed increase in proinflammatory signaling proteins, proinflammatory effector proteins and other stress related proteins. Interestingly, increased levels of proinflammatory cytokines like IL-6, TNF- α , , MCP-1 and IL-12p70 were also detected. Work from our in vivo studies has demonstrated similar increase in proinflammatory signaling and effector molecules along with the proinflammatory cytokine levels, following NNK treatment. Immunohistochemical staining of the brain sections of NNK treated mice revealed massive microglial and astroglial activation along with distinct foci of neuronal damage. Both in vitro and in vivo results provide strong indication that NNK causes significant upheaval of the inflammatory condition of brain and inflicts subsequent neuronal damage.

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1. D Ghosh and **A Basu** (2009). Japanese Encephalitis - A Pathological and Clinical Perspective **PloS Neglected Tropical Diseases** (In press).
2. M K Mishra, K Datta, S K Saheb and **A Basu** (2009). Understanding the molecular mechanism of blood brain barrier damage in an experimental model of Japanese Encephalitis: Correlation with minocycline administration as a therapeutic agent. **Neurochemistry International** (In Press).
3. D Ghosh, M K Mishra, S Das, D K Kaushik and **A Basu** (2009). Tobacco carcinogen induces microglial activation and subsequent neuronal damage. **J Neurochem** 110:1070-1081.
4. K Datta, D Ghosh, and **A Basu** (2009). Curcumin protects neuronal cells from Japanese Encephalitis virus mediated cell death and also inhibits infective viral particle formation by dysregulation of Ubiquitin proteasome system. **J Neuroimmuno Pharmacology** (In press)

5. M K Mishra, D Ghosh, R Duseja, and **A Basu** (2009). Antioxidant potential of Minocycline in Japanese Encephalitis Virus infection in murine neuroblastoma cells: Correlation with membrane fluidity and cell death **Neurochemistry International** 54 : 464-470.
6. R Mukhopadhyay, M K Mishra, **A Basu**, and B Bishayi (2009). Modulation of steroidogenic enzymes in murine lymphoid organs after immunization with soluble antigen. **Immunological Investigations** 38(1):14-30.
7. M K Mishra, K L Kumawat and **A Basu** (2008). Japanese Encephalitis Virus differentially modulate the induction of multiple pro inflammatory mediators in human astrocytoma and astrogloma cell lines. **Cell Biology International** 32: 1506-1513.
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9. *S Das and **A Basu** (2008). Japanese Encephalitis virus infects neural progenitor cells and decreases their proliferation. **J Neurochem** 106(4):1624-36. (News and views reported and published by **Nature India** and as a part of several national and international press release)

*In press last year

Patent Applied:

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

Presentations:

1. A Basu: Host pathogen interaction in Japanese Encephalitis Virus infection: from bench to bedside. Department of Physiology, University of Calcutta, 6th April, 2009
2. A Basu: Japanese Encephalitis: from basic research to therapeutic intervention. IISC Centenary Conference and 10th Sir Dorabji Tata Symposium, Mechanisms of Microbial Pathogenesis, National Science Seminar Complex, IISC, Bangalore; 10-12th March, 2009
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4. M K Mishra and A Basu: Unraveling the signaling cascades associated with astroglial response in Japanese Encephalitis. Indian Academy of Neuroscience, Cochin, December 2008.
5. M K Mishra and A Basu: Microglial activation and innate immune response: Implication in the pathogenesis of Japanese Encephalitis. Indian Academy of Neuroscience, Cochin, December 2008.
6. M K Mishra and A Basu: Neuroprotective Effect of Minocycline in Japanese Encephalitis. Annual meeting of Indian Academy of Neuroscience, Cochin, 11-14th December 2008
7. D Ghosh, M K Mishra, S Das, D K Kaushik and A Basu: Tobacco carcinogen induces microglial activation and subsequent neuronal damage. Annual meeting of Indian Academy of Neuroscience, Cochin, 11-14th December 2008
8. S Das and A Basu: Japanese encephalitis virus infects neural progenitor cells and modulates their proliferative ability. Society for Neuroscience Meeting, Washington DC, 15-19th November, 2008
9. M K Mishra and A Basu: Neuroprotective effect of minocycline in Japanese Encephalitis. Society for Neuroscience Meeting, Washington DC, 15-19th November, 2008
10. A Basu: Japanese encephalitis virus infects neural progenitor cells and modulates their proliferative ability. Annual Meeting of Society for Neurochemistry, Guru Nanak Dev University, Amritsar, 28-29th November, 2008.
11. A Basu: Neuron- Glia Communication in Health and diseases. IIT-Delhi, 6th September, 2008.
12. A Basu: Japanese Encephalitis: from basic research to therapeutic intervention. Premas Biotech, IMT Manesar, 1st July, 2008
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Funding:

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Development of A Novel in vitro Model of Alzheimer's Disease Employing Neurosphere Culture from TgAPPswePS1 Δ E9 mouse

Principal Investigator : Dr. Ranjit Kumar Giri

Research Fellow : Pankaj Ghate

Project Assistant : Priyanka Patel

Technical Assistant : Sanjay Kumar

Lab Attendant : Pankaj Chopra

Alzheimer's disease (AD) is a progressive and irreversible neurodegenerative disease and it is the most common form of dementia affecting more than 5% of the population over the age 65 years. Genetic studies on early onset familial AD has identified three causative genes: amyloid precursor gene (APP), presenilin 1(PSEN1) and presenilin 2 (PSEN2). Mutation/s in these genes ultimately increases the production of beta amyloid peptides, A β ₁₋₄₀ and A β ₁₋₄₂. In Alzheimer's disease, the multimerization of the A β peptide is an early and central process in the pathogenic cascade. However, very little is known about the exact role of beta amyloid peptides towards neurotoxicity. This specific question remains mystery even after a century of research on AD. To understand this human disease, transgenic lines expressing human FAD genes were developed and these mice showed beta amyloid deposits, astrogliosis, impaired learning process and mild neurodegeneration in few transgenic mice lines. However, the exact role of beta amyloid towards neurotoxicity remains puzzled. This could be due to the complexity in network and cell types of an adult brain. A typical adult brain parenchyma contains various types of neuronal cells, astrocytes, oligodendrocytes and microglia. Which cells are primary target of beta amyloid-mediated neurotoxicity is not known. Therefore, an alternative model, which has the power to segregate all the cell types of brain yet producing beta amyloid endogenously as produced in AD brain, is warranted. No such model is available.

In addition, extensive researches have pointed out the presence of CNS stem cell in adult brain both in animals and in humans. These CNS stem cells possess the potential to differentiate towards major cell types of brain except microglia in vitro and in vivo. Therefore, it is not clear why these cells fail to replenish the neuronal cell loss seen in AD, specially, in hippocampus where CNS stem cells are enriched. Thus, I hypothesize that beta amyloid peptides might be affecting the normal function of CNS stem cells. To address these issues the main objectives are

1. Development of an in vitro model of AD employing CNS stem cells from

mice expressing human FAD genes

2. The effect of beta amyloid peptides on CNS stem cell behavior.

To begin with, my lab is currently working on developing an in vitro model of Alzheimer's disease. Since multimerization of the A β peptide is an early and central process in the pathogenic cascade, endogenous production of human A β peptide and its oligomerization is our main target. However, identification of other pathological features of AD in our proposed model will be our ultimate test.

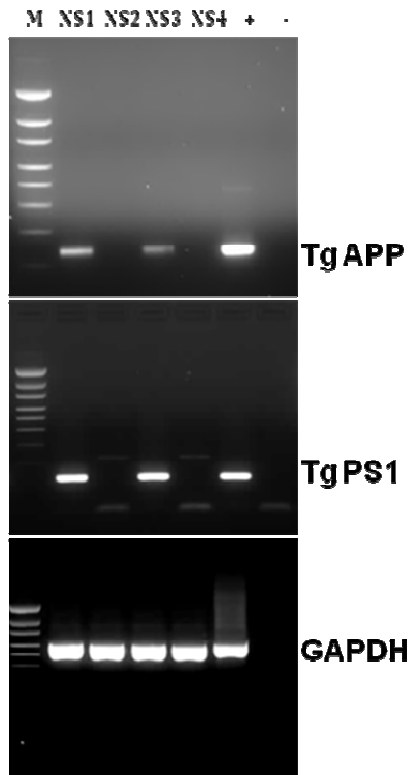
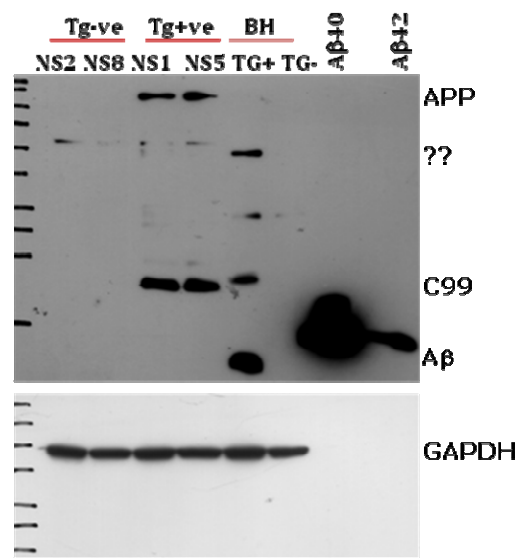


Figure1: Expression of HuAPPswe and HuPS1 Δ E9 transcripts in neurosphere cultures by RT-PCR. Upper panel indicates the presence of human APPswe transcripts in NS1 and NS3 but not in NS2 and NS4 neurospheres. Same neurosphere cultures are also positive huPS1 Δ E9 transcript (middle panel). Primers were designed in such a way that no PCR products will be formed from endogenous gene expression. Expression of GAPDH demonstrates any loading artifacts, which is not present in this case (lower panel).

We have isolated and developed 4 separate neurosphere lines positive for Hu APPswe and Hu PS1 Δ E9 gene as shown in my previous annual report. Four other non transgenic neurosphere lines were also developed as corresponding controls. Both these transgenes are under the control of prion gene promoter. Mouse prion gene is functionally active during embryonic day 13. Since our neurosphere cultures were isolated during E13-15, we expected the transcription product of both these genes. As to our expectation, both transgenic transcripts were detected using RT-PCR (Figure 1) from Tg positive neurospheres but not in corresponding controls.

Figure 2: Detection of APP protein and its products by Western blot analysis. A, Equal amount of total proteins from two Tg negative and two Tg positive neurospheres were analyzed. Tg -ve brain homogenate was loaded as negative control and Tg+ve brain homogenate, A β ₁₋₄₀ and A β ₁₋₄₂ were loaded as positive controls. After electrophoresis, the proteins were transferred onto nitrocellulose membranes and probed with 6E10 antibody specific for human APP and its products (upper panel). After autoradiography, the membrane was stripped and re-probed with anti GAPDH antibody to normalize any unequal loading.



The result was verified few more times. Presence of transgenic mRNA encouraged us to check the expression of these transgenes at protein level. Western blot analysis of neurosphere lysates indicates the presence of human APP protein and its fragments in all the transgenic positive neurosphere lines but not in transgenic negative neurosphere lines (Figure 2). However, beta amyloid peptides are not detected in any transgenic positive neurosphere lines unlike Tg+ve mouse brain homogenate. It could be possible that intracellular beta amyloid pool may not be in detectable range by Western blotting. Therefore, other approaches need to be examined. Neurosphere cultures are three dimensional cultures. We expect some A β peptide might have been trapped within the neurospheres. However, beta amyloid peptides in physiological condition will have a tendency to form beta structure and its interaction with 6E10 antibody requires denatured conformation by heat. We wanted to explore this property of A β peptides using conformation dependent immunocytochemistry. Neurosphere sections were obtained and were either treated with heat or left untreated, followed by immunocytochemistry. Figure 3 demonstrates increase intensity of 6E10 interaction in Tg+ve neurosphere (NS1) than Tg-ve neurospheres (NS2) in non-denatured and denatured condition. Thus, Expression of APP and APP products are more in tg+ve neurosphere than Tg-ve neurospheres. Interestingly, upon denaturation, the intensity of NS1 neurosphere sections are more than the non-denatured NS1 neurosphere sections, indicating human A β peptides might be present in Tg+ve neurosphere cultures. Therefore, alternative approaches such as immunoprecipitation and extracellular detection of beta amyloid peptide is our next approach. In addition, other pathological features of AD will also be explored to strengthen the proposed in vitro model.

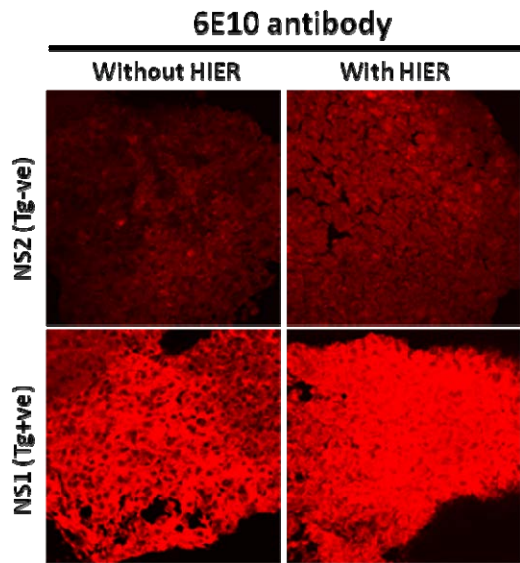


Figure3: Analysis of huAPP^{swe} protein expression by Immunofluorocytochemistry. Optical section of NS1 neurosphere (Tg+ve) indicates much higher expression of huAPP protein than NS2 neurosphere (which is Tg-ve). 6E10 signal was further enhanced by heat induced epitope retrieval in NS1 sections indicating a possible presence of A β peptides.

Funding:

This work is supported by Ramalingaswami Fellowship (DBT) and NBRC Core fund.

Understanding the Cellular and Molecular Pathology of Prion Disease using CNS Stem Cell Cultures Replicating Mouse Prions

Principal Investigator : *Dr. Ranjit Kumar Giri*

Research Fellow : *Himakshi*

Project Assistant : *Chetan Chandola*

Technical Assistant : *Sanjay Kumar*

Lab Attendant : *Pankaj Chopra*

Although rare, prion disease itself includes varieties of irreversible neurodegenerative disorders such as Kuru, Creutzfeldt-Jakob disease (CJD), variant CJD (vCJD), Gerstmann-Sträussler-Scheinker syndrome (GSS) and fatal familial insomnia (FFI) in humans; scrapie in sheep and goats; and bovine spongiform encephalopathy (BSE) in cattle. Unlike other neurodegenerative diseases, all prion diseases generate a defective protein which itself is infectious. Infectious nature of prion disease poses a serious health risk to cattle, deer, goat, sheep, as well as to human. Human food cycle is directly linked with these listed animals. Therefore, prion disease in any of these animals can effect human population including India. In prion disease, the normal cellular prion protein (PrPC) is converted post-translationally to pathological, infectious and alternatively folded isoforms (PrPSc). Similar to Alzheimer's disease, replication of PrPSc and subsequent multimerization and accumulation in brain parenchyma is the hallmark pathology of prion disease. How PrPSc accumulation causes neurotoxicity is not known. Both human diseases and animal models of these diseases have not been able to differentiate the effect of prion protein on various brain cell types including CNS stem cells. Cell culture models those have been used to study prion biology fail to address various mature brain cell types and replicate defective protein. CNS stem cells containing neurosphere cultures can be isolated both from embryonic and adult brains, can be grown over long period of time and differentiate towards major adult brain cell types such as, neurons, astrocytes and oligodendrocytes. There is no in vitro model which can address other pathological features of PD other than prion replication. Since CNS stem cells can differentiate towards mature brain cell types, we propose the feasibility of testing other cytopathological changes to prion replication using neurosphere cultures. In addition, nothing is known about the effect of prion replication on CNS stem cells.

To address these questions the immediate Goals are

- To study cellular pathology of prion disease using neurosphere cultures that support prion replication.
- To study the effect of prion replication on CNS stem cell survival and

differentiation.

Currently, we are working towards establishing CNS stem cell lines from CD1 mouse embryos. We have isolated three independent CNS stem cell lines from CD1 embryos (Figure 1, A). These cultures express PrP^C protein (Figure 1, B) the substrate for PrP^{Sc} replication. Upon infection to RML scrapie inoculum, CD1 neurospheres readily replicated PrP^{Sc} as observed by cell blot analysis (Figure 1, C). It is necessary to mention here that, CD1 mouse requires more than 120 days to manifest prion disease, where as in the current model we can replicate the disease pathology by 60 days reducing the time by half.

Long Term Goals: The idea behind developing such in vitro model is to study the molecular and cellular mechanisms behind prion-mediated pathogenesis such as

- Alteration in the neurogenesis and its associated genetic and epigenetic events in prion replicating CNS stem cells.
- Effect of microglia on neuronal loss to prion aggregation. Whether defective protein is sufficient to direct neuronal cell death or directed by prion stimulated microglia can be studied utilizing CNS stem cells cultures.

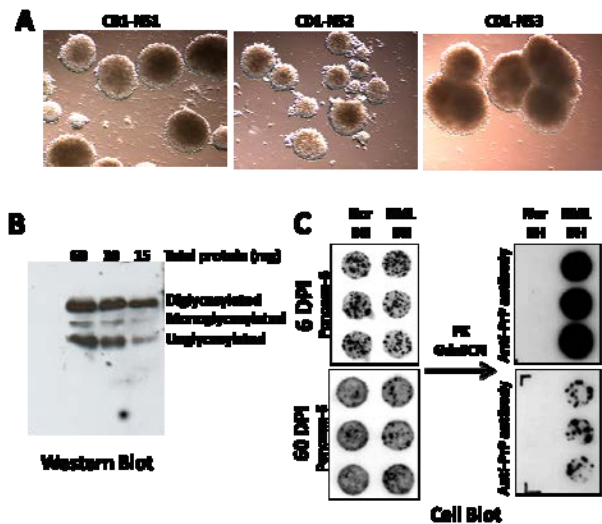
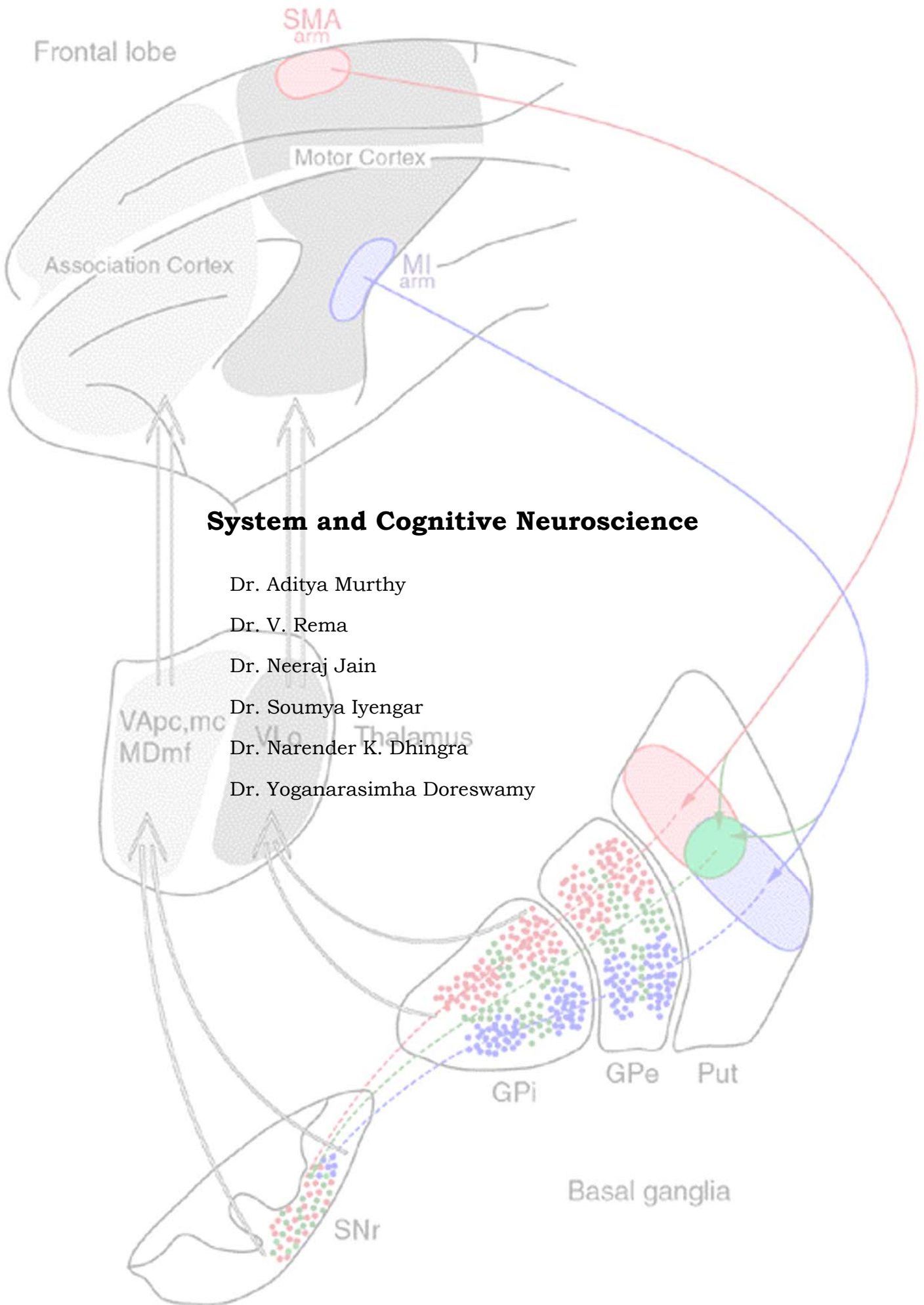


Figure. Development of prion disease in CNS stem cultures. A) Three independent neurosphere cultures were established from E13 CD1 mouse embryos. B) Western blot analysis indicates the expression of PrP^C (the substrate for prion replication) in these cultures. C) Cell blot analysis indicates the presence of PK-resistant PrP^{Sc} protein in RML scrapie infected CD1 neurosphere but not in uninfected neurosphere cultures indicating, CD1 neurospheres have machineries to replicate prion.



Probing the Control of Action using Saccadic Eye Movements

Principal Investigator : *Dr. Aditya Murthy*

Research Fellow : *Sharika K.M.*

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 with eye movement programming.

Objectives:

Behavioral evidence of chunking of saccades

In the past years our laboratory has been focusing on aspects of control such as response inhibition and error correction. In the last two years we have begun to address these issues in relation to more complex behaviors that may involve grouping of individual saccades into preprogrammed sequences. The strategy of categorizing events and objects and then retrieving them in groups lies at the heart of intelligent behavior. By grouping different items into a common unit, we ascribe generalized properties to all members of a class and are able to manipulate that knowledge more efficiently. Chunking is such a strategy to code multiple items in a relational structure and is known to be widely used for remembering verbal and spatial sequences. Likewise, improved performance of a complex action (consisting of several individual movements) is known to involve restructuring of the entire long sequence into 'chunks' of short sequences. The movements within a chunk are assumed to be then carried out automatically which considerably reduces the cognitive demand needed to perform the entire action. However, how the individual components of a chunk are organized and executed keeping the final goal into account is not well understood. Using saccades as a model, we hope to provide insights into nature of control during the programming and execution of chunks.

Mechanisms for serial programming

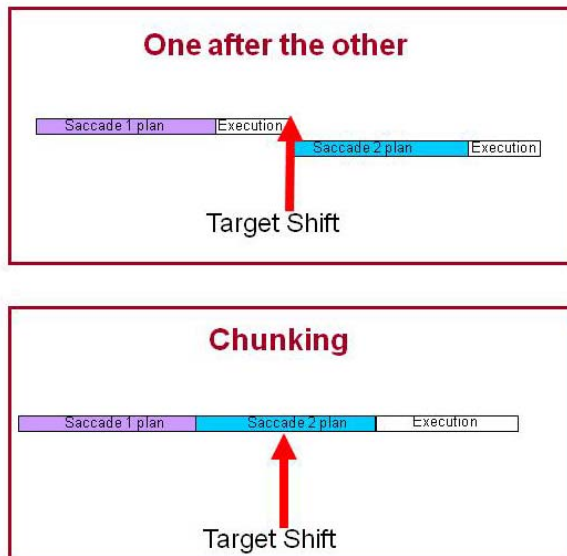
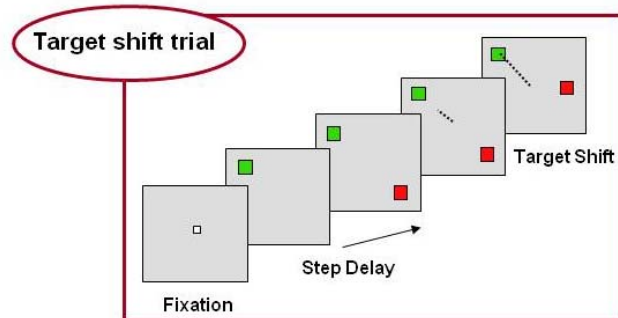


Figure 1: Conceptual framework to understand how sequential saccades may be programmed. In the top panel saccades are programmed one after another. In the bottom panel saccade programming is chunked together as a single packet with the execution of each saccade occurring sequentially.

To investigate the control of preprogrammed saccade sequences we have begun using a memory guided 100% follow double-step saccade. We tested whether the saccades were planned and executed one after another or planned together and then executed as a chunk. This was done by introducing a probe – a shift in the position of the final target - during the execution of the first saccade to the initial target. The hypothesis was that if the two saccades were planned completely one after another, then one would expect all second saccades to be directed towards the new, shifted position of the final target. On the other hand, if the second saccade was programmed with the first one as a chunk during the reprocessing time, then we would observe instances of the second saccade ending at the old position of the final target, despite the subsequent shift in the latter's position. We also added a positive control by having two sets of target shift trials. In one set, as before, the final target would shift during the first saccade; in the second set of target-shift trials also shifted the initial target in addition to the final target. We reasoned that if subjects had programmed the two saccades as a chunk then changing the first saccade should also affect the programming of the second saccade. Behaviorally, this should manifest as producing a lesser proportion of second saccades towards the old position of the final target during these target shift trials compared to when the initial target did not shift. The results from 4 subjects tested so far appear to bear out this prediction and further lends support to the notion that the oculomotor system is able to chunk multiple saccades together to generate a single goal-directed actions. Currently in collaboration with Drs. Sebastian Neggens and Chris Dijkerman at the University of Utrecht, we are examining whether

inactivation of medial frontal areas such as supplementary motor area and the supplementary eye fields, using transcranial magnetic stimulation, can temporally decouple the chunking of saccades.

Figure2: Target shift are expected to produce more saccades directed at the old target positions during chunking of responses.



Publication:

1. Sharika, K.M., Ramakrishnan, A. and **Murthy A.** (2008). Control of predictive error correction during a saccadic double-step task. **Journal of Neurophysiology** 100:2757-70.

Presentation:

1. Murthy, Sharika, K.M., and S. Ray: Attention for action during error correction. Centre for Behavioral and Cognitive Science, University of Allahabad, 2008.

Funding:

This work is supported by NBRC Core fund.

Brain Mechanisms of Action Control in Humans

Principal Investigator : Dr. Aditya Murthy

Research Fellow : Neha Bhutani

Because eye movements can provide a behavioral measure of sensorimotor processing and cognitive functions of the brain, their study can provide an elegant and simple system to understanding the neural basis of voluntary control. From animal, human lesion and neuroimaging studies, the major brain areas underlying saccadic eye movements have been identified. These include the parietal cortex, the dorsolateral prefrontal cortex, the frontal eye fields, the supplementary eye fields, the anterior cingulate cortex, the basal ganglia, the superior colliculus and the brainstem. Since goal directed eye movements involve participation of a number of different brain areas a conceptually challenging question is to understand how computations done locally in one area integrate or affect the computations performed elsewhere and how these computations contribute to goal directed behaviors. One approach that we are using to address these questions is to study the pathology of saccadic eye movements, which can provide information on the functional status of the underlying neural circuitry in brain disorders such as schizophrenia, obsessive compulsive disorders, attention deficit disorders, and Parkinson's disease, in which components of this distributed network are thought to be compromised. In the last few years we have been focusing on Parkinson's disease patients. These series of experiments is being carried out in collaboration with Dr. Madhuri Behari and Dr. Vinay Goyal Dept. of Neurology, A.I.I.M.S. In the future we hope to recruit patients from the NBRC clinical research center at Gurgaon as well.

Objecives:

The role of basal ganglia in temporal control of information processing.

In double-step tasks such as the FOLLOW task that involve subjects making sequences of two saccades in rapid succession, the potential for the temporal overlap of decisions corresponding to the individual movements in a sequence is high. We further assumed that such collision of decisions lead to instances when the saccade lands in the middle of the two targets producing what we define as midway saccades. To test his hypothesis we analyzed data from 14 normal subjects performing the FOLLOW task and measured the number of midway saccades as a function of target step delay. Using the LATER model that describes saccadic reaction time distributions we predicted the number of midway collisions that should have occurred. Comparison of the predicted and observed number of midway collisions revealed two important differences. First, the number of observed midways was much less than predicted. Second, the number of midways was

invariant across target step delays unlike the predicted midways that decreased with increasing target step delays. These two points of departure suggests that the brain implements a form of inhibitory control that prevents the overlap of simultaneously evolving decisions, thereby maintaining distinct representations of individual decision processes.

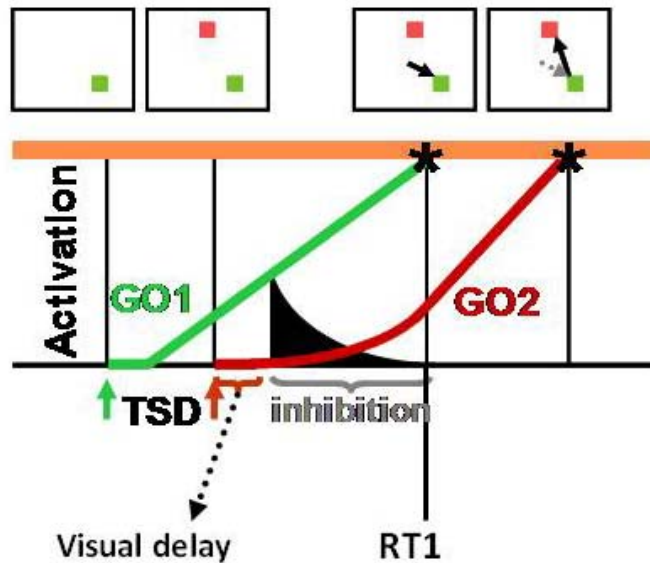


Figure1: The LATER model of saccade decision making modified to incorporate inhibition (black filled) that reduces the temporal overlap of two saccade programmes by delaying the GO2 process.

Since such representations must also implicitly include temporal order in order to successfully perform the FOLLOW task, we also hypothesized that the basal ganglia play an important role in this aspect of temporal control. To address this question we recording from 10 PD patients and a similar number of aged matched controls performing the FOLLOW task. Comparison between the two groups revealed two interesting findings. First, the numbers of midways were greater in PD. Second, the number of midways varied inversely with target step delay unlike controls. These two findings suggest that impaired inhibitory control in PD is the cause of increased midways. To test these ideas further we implemented Monte Carlo computer simulations of the LATER model along with an exponential decaying inhibitory signal to fit the control data. This model revealed that in order to fit the PD data the strength of inhibition had to be reduced. Taken together these data reveal how inhibition may maintain temporal distinct neural representations of evolving decisions to realize goal directed sequential behavior. While indirect, we believe these data provide a basis to initiate neurophysiological investigations in the basal ganglia of behaving primates.

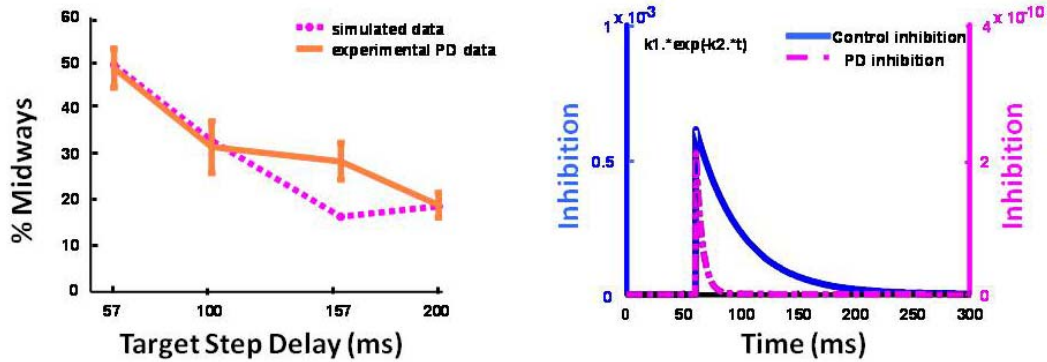


Figure 2: Simulations of the %midways in Parkinsons disease patients and aged matched controls (left panel) reveal that the strength of inhibition is markedly reduced in PD subjects (right panel).

Presentation:

1. A. Murthy, N. Bhutani, S. Ray, A. Farooqui: Control of saccadic averaging during sequential eye movements. Soc. for Neuroscience Abstract (2008).

Funding:

This work is supported by a grant from DBT, India.

Collaborators:

Prof. Madhuri Behari, Dept. of Neurology, A.I.I.M.S., India.

Dr. Vinay Goyal, Dept. of Neurology, A.I.I.M.S., India.

Neural Control of Action by Frontal /Basal Ganglia Networks

Principal Investigator : *Dr. Aditya Murthy*

Research Fellow : *Arjun Ramakrishnan*

Project Assistant : *Ramakrishnan*

While much progress has been made in understanding the function of sensory and motor networks, the nature of neural networks mediating their interactions remain obscure. As a consequence we have a poor understanding of how sensory information is transformed into a movement. One of the key structures that is thought to play an important role in the transformation of sensory signals into motor commands is the basal ganglia network, which receive no direct sensory input and send little direct output to the spinal cord. Rather, their primary input is from the cerebral cortex and their output is sent back to the cortex via the thalamus. Within this general scheme the basal ganglia-thalamocortical circuit implements a number of functionally distinct loops involving different modalities in which information from somatomotor, oculomotor, cognitive and limbic systems are processed in parallel. Although the anatomical significance of such loops between cortex and basal ganglia have been appreciated, their functional significance remains largely unspecified. Here we use the non-human primate model to study the function of one such loop, namely the oculomotor loop in which information from the frontal eye fields (FEF), is relayed to the basal ganglia, processed and sent to the mediodorsal nucleus of the thalamus and sent back to the FEF. Here we propose to study the sensorimotor transformations in this loop in the context of how basal ganglia thalamocortical circuitry initiates actions, how actions maybe cancelled and reprogrammed by this circuit and how this circuit may help in the correction of erroneous actions. The long term goal of this project is to understand the neural representations that control our actions in basal ganglia/frontal cortex.

Objectives:

II. Control of decision-making by frontal cortex

Having trained monkeys on the contextual double-step task we have begun a series of experiments in which electrodes inserted into the frontal eye fields are used to deliver small currents during saccade decision-making tasks. Based on previous work by others we hypothesize an interaction between the electrically evoked saccade and the evolving saccade decision. By observing the deviation of the fixed vector saccade as a function of time of target onset we attempted to study the temporal evolution of decision-making in a

double-step task. During the last year we have continued the micro stimulation experiments to increase the sample size and have started microstimulation experiments on a second monkey. Our current analysis so far indicates that we are able to not only access the changing decision during a REDIRECT task in real time but also measure the duration it takes to inhibit an ongoing decision process. In addition we have also extended the time course of the micro-stimulation pulse to enable us to study the evolution of error correction in addition to inhibitory control.

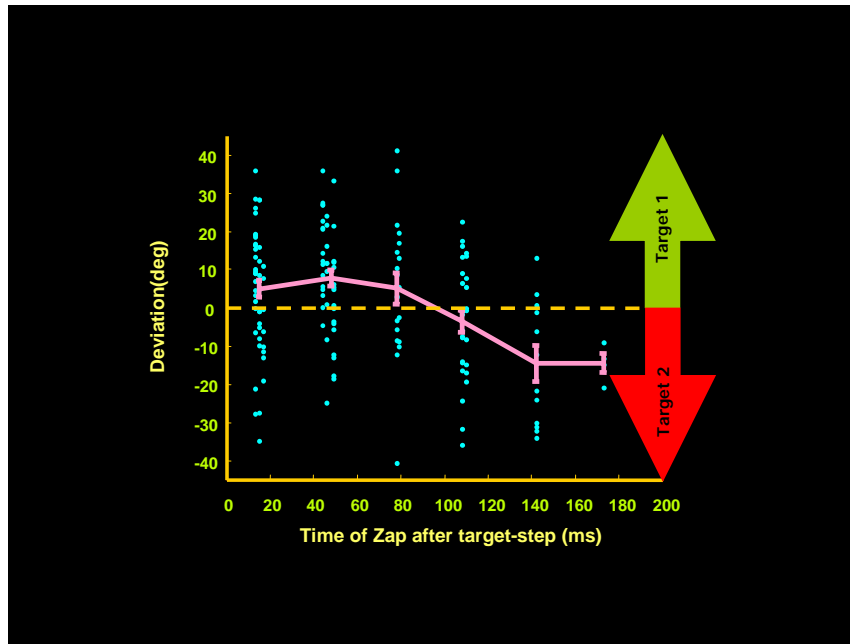


Figure: Data from a single microstimulation session showing how the deviation of the microstimulated saccade reflects the monkeys decision to cancel the planned saccade to target 1 and redirect its gaze to target 2.

Publication:

1. **Murthy A**, Ray S, Shorter SM, Schall JD, Thompson KG (2009). Neural Control of Visual Search by Frontal Eye Field: Effects of Unexpected Target Displacement on Visual Selection and Saccade Preparation. **J. Neurophysiology** 101: 2485-2507.

Funding:

This work is supported by a grant from DBT, India.

Processing and Integration of Somatosensory Information in Normal and Impaired Brains

Principle Investigator : Dr. V. Rema

Research Fellows : Zia ud Din, Manisha Chugh, Rahul Chaudhary

Project Assistant : Praseeda Venugopalan, R. Ethiraj, M. Shakti Kumar

The somatosensory system processes tactile sensations that are essential requisite for our survival. In addition the somatosensory system provides continuous feedback to the motor system to regulate our movement. The various features, such as texture, size, shape or temperature of objects evokes activity in the neurons of the somatosensory cortex. Sensory experiences are known to modify the responsiveness of the neurons to sensory stimuli. In normal somatosensory cortex, the neurons can adapt to novel experiences rapidly using Hebbian form of synaptic plasticity. This type of learning is called experience-dependent plasticity or use-dependent plasticity. The focus of my research is to understand the mechanisms that are involved in experience-dependent plasticity and how do impairments such as cortical injury or nutritional deficiency affect experience-dependent plasticity. We are using the rat somatosensory system for our studies. We use electrophysiological recording techniques to determine changes in the neuronal activity in somatosensory cortex and also examine the somatosensory behavior of the rats to correlate the deficits in neuronal activity with behavior.

Results of our experiments done during last year are described below.

- i. *Effect of focal injuries (acute, invasive insult) to the cerebral cortex on neuronal and behavioral functions of the reciprocally connected intact somatosensory cortex.*

There is a large amount of information on brain injuries. Yet we still lack effective therapy to prevent or reduce the neurophysiological as well as behavioral deficits associated with brain injury. The ineffectiveness of most interventions could be attributed to the multifaceted reactions that result from cortical injuries. The resultant complex plastic changes in response to injury can be partly ascribed to anatomical connectivity between various regions in the brain. Given the complex anatomical connectivity the effect of a focal injury on brain cannot be limited to the site of impact alone. We have seen that surgical lesions in somatosensory cortex in one hemisphere in adult rats reduced the activity of neurons in the interconnected intact contralateral somatosensory cortex. The decrease in spontaneous as well as

stimulus driven activities persist for long post-lesion times. Focal injuries within the same hemisphere, such as surgical lesions of the motor cortex on the other hand had increased activity of specific population of neurons in the interconnected somatosensory cortex. The effect of such neurophysiological changes on behavior is not very well understood.

During this year our experiments were directed towards understanding the behavioral consequences of focal injuries to the cerebral cortex. We addressed the following questions:

1. To what extent does a focal injury affect behavioral functioning of axonally connected intact regions of the brain?
2. What is the possible mechanism for injury-induced behavioral deficits?

The experiments were done using the Long-Evans rats. Rats acquire tactile information by sweeping their large whiskers (25 whiskers on each side of snout) across an object at different frequencies. This information is conveyed to the somatosensory cortex (known as whisker barrel cortex in rodents). The neurons in the whisker barrel cortex process sensory information from periphery. In addition, these neurons also receive sensory input from the contralateral sensory cortex. We made lesions of the whisker barrel cortex in one hemisphere in adult rats. The behavioral functions of intact somatosensory cortex in the contralateral hemisphere were then examined to determine whether there are any deficits. For this we measured the performance of the whisker-specific somatosensory behavior- the “gap-crossing” task (Figure 1A). In this task the rat contacts a goal platform with its whiskers and uses the sensory information obtained by the whiskers to cross a gap between two raised platforms for a food reward. At smaller gap-widths the animal can touch the goal platform with its nose in addition to its whiskers to sense and cross the gap. However at larger gap-widths the rat can touch the goal platform only with its whiskers i.e. “*whisker contact gap-width*” (see Figure 1B). Successful crossing of whisker contact gap-width requires intact barrel cortex suggesting that processing of sensory input from whiskers by barrel cortex is essential for this behavior. At the start of the experiment each animal was trained to perform the gap-crossing task with all whiskers until stable performance was achieved at maximum whisker contact gap-width. Following unilateral injury to somatosensory cortex we quantified specific deficits in sensory behavior of intact somatosensory cortex.

We found that the rats had deficits in somatic sensory behavior regulated by the intact somatic sensory cortex following a focal lesion in the contralateral barrel cortex. These impairments were present in all animals that were tested and were long-lasting (see Figure 1C). The characteristic feature of the deficit was in the inability of rats to perform the gap-crossing task at the maximal whisker-contact distance that they crossed prior to lesion. Even

though the whiskers could contact the goal platform the failure of the lesioned rats to cross the gap suggests that the sensory information conveyed by the whiskers to the intact cortex is not being processed normally. It is well known that reciprocal interactions of callosal inputs are involved in processing of sensory information. Therefore based on this fact we proposed that the behavioral dysfunction related to the intact hemisphere is likely to be caused by disruption of synaptic activity from the lesioned region in the contralateral hemisphere. If so, then we should see similar deficit if sensory activity to one hemisphere is reduced. We therefore examined whether there was any deficit in whisker sensory gap-crossing behavior when sensory input from one side is removed even in the absence of any cortical lesion. To achieve this we trained and recorded gap-crossing behavior of normal rats. We then removed all whiskers on one side of face for all the animals. Following whisker trimming we tested the gap-crossing ability of the animals. Trimming of whiskers on one side of face produced significant reduction in the maximum gap-width the animals could cross. Similar to the animals with unilateral focal lesions the main deficit of using the whiskers only on one side of face was the inability of rats to cross the maximum gap-width which they had crossed previously when all whiskers were intact. These results support our hypothesis that focal lesions disrupt sensory integration in intact interconnected regions of the brain leading to behavioral dysfunctions.

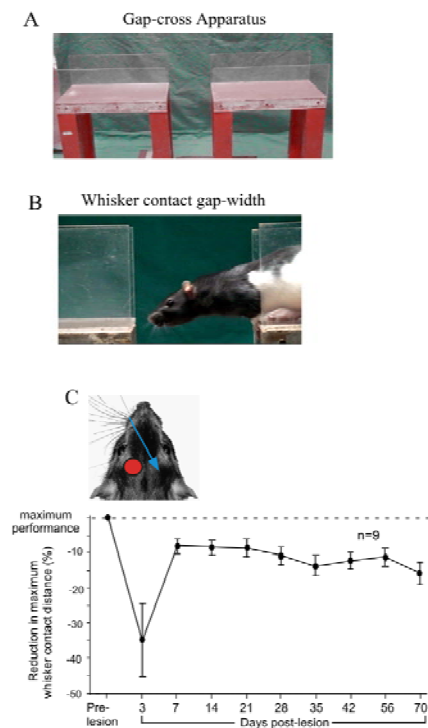


Figure:

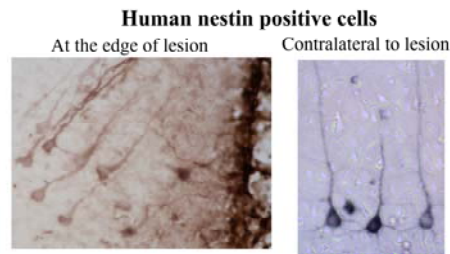
Figure 1A is a photograph of the gap-crossing apparatus.

Figure 1B is a video frame showing the rat contacting the goal platform with whiskers. The gap crossing experiments were recorded at this magnification.

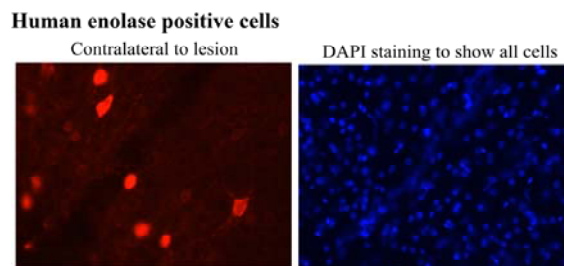
Figure 1C illustrates line graph showing long-lasting reduction in the performance of gap-crossing task by animals with a lesion. The animals used the whiskers projecting to the intact cortex (blue arrow) to do the task.

We have also performed experiments to determine whether the long-lasting deficits can be reduced/prevented by transplanting stem cells in the lesioned brains. Mouse embryonic stem cells and human fetal neural progenitor cells were used for transplantation. Transplanted cells were observed in the area around the lesion upto 35 days postlesion (the longest time we analyzed). Some transplanted cells were also seen in other parts of the brain. Immunohistochemical staining showed that the some of the transplanted cells expressed neuronal markers whereas others expressed astrocytic markers (see figure 2).

Figure 2. Photomicrographs of sections from brains of rats with lesions to show the presence of transplanted human fetal neural progenitor cells on post-lesion day 21. Upper panel shows human nestin immunoreactive cells with neuron-like morphology at the edge of the lesion (left) as well as in the contralateral hemisphere (right).



Bottom pane, left picture, shows few transplanted cells that are positive for human enolase in the contralateral hemisphere by immunofluorescence). DAPI staining of the same section is shown in the right picture.



ii. *Effect of non-invasive global insult e.g. exposure to nutritional deficiency through gestation up to adulthood on neurophysiological and behavioral functions of somatosensory cortex.*

A diet balanced in all nutrients is essential for normal functions of all systems in our body. Deficiencies in nutrition have been shown to have profound effects on the developing central nervous system. However there is very little information on the effect of deficiencies of specific nutrients on sensory transmission. We investigated the effects of chronic protein malnutrition and chronic iron malnutrition on sensory neurotransmission in adult Long Evans rats. The rats were exposed to either protein-deficient or iron-deficient diet from gestation through adulthood. Extra-cellular spike recordings were made from somatosensory cortex in the adult protein deficient and iron deficient rats. Results show significant reduction in the response of neurons to sensory stimulation in the cortical layer that receives sensory inputs in both protein-deficient as well as iron deficient animals. However, neurons within other layers of the cortex are highly active. Analysis of somatosensory behavior shows that both protein-deficient as well as iron-deficient animals are significantly impaired. These results suggest

that deficiencies in nutrients such as protein and iron can potentially alter synaptic activity in the brain and thereby modify behavior.

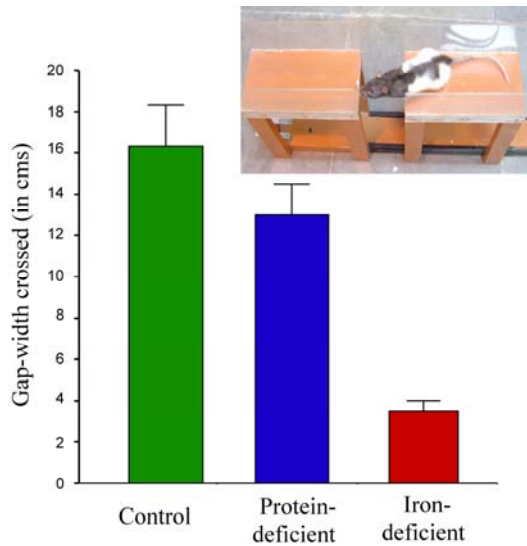


Figure 3 Bar graphs depicting comparison of somatosensory functions of control rats to those fed either protein-deficient diet or iron-deficient diet. The whisker sensitive gap-crossing task was used to measure the somatosensory functions in these animals. Rats chronically deprived of protein or iron show deficiency in their tactile sensation.

Publication:

1. **Rema. V**, Bali KK, Ramachandra R, Chugh M, Darokhan Z, Chaudhary R (2008). Cytidine-5-diphosphocholine supplement in early life induces stable increase in dendritic complexity of neurons in the somatosensory cortex of adult rats. **Neuroscience** Aug 13 155(2):556-64. Epub 2008 Apr 16

Presentations:

Invited talks

1. V. Rema: “*Structure and function of somatosensory system*”. Cognitive Neuroscience IBRO workshop, NBRC, India; January 2009.
2. V. Rema: “*Influence of focal injuries in the cerebral cortex on somatosensory functions.*” Indian Academy of Neuroscience, Cochin, India; December 2008.
3. V. Rema: “*Injury-induced plasticity in the barrel cortex of adult rats.*” Barrels XXI, Washington D.C. USA; November 2008.
4. V. Rema: “*Information processing in the sensory cortex*”. Imaging Neurodegeneration- from molecules to systems, IIT Delhi, India; September 2008.
5. V. Rema: “*Stem cell therapy following cortical injury*”. International Conference on Recent Developments in Stem Cell Research; Kannur, India; August 2008.
6. V. Rema: “*Stroke-like injuries of motor cortex modifies somatosensory functions*”. Current Perspectives and future trends in psychology.

Refresher course for college teacher of Haryana, Dept. of Psychology, Govt. College for Women, Rohtak, India; May 2008.

Poster presentation

1. Manisha Chugh, Ziauddin Darokhan, Rahul Chaudhary and V. Rema: Ischemic injury of motor cortex affects spatial and temporal processing of somatosensory information. Wellcome Trust Senior Research Fellows meeting. October 2008.
2. Rahul Chaudhary, Praveen. K, Ziauddin Darokhan, V. Rema: Bilateral effect on forelimb behaviour following unilateral lesions of forelimb cortex. Society for Neuroscience Annual meeting Nov. 2008.
3. Manisha Chugh, Ziauddin Darokhan & V. Rema: "Motor cortex lesions effects sensory behaviour of Gap cross task in rats." Society for Neuroscience Annual meeting November 2008.
4. Praseeda Venugopalan, Rahul Chaudhary and V. Rema: Investigating the potential of embryonic stem cells in enhancing recovery of neuronal function following cortical injury. "Annual meeting of the Indian Academy of Neuroscience, Cochin, India, December 2008".
5. Ziauddin Darokhan, Manisha Chugh and V. Rema: Cortical injuries reduce activity of output layer neurons adjacent to the lesion, however increase neuronal activity in the intact hemisphere opposite the lesion. "Annual meeting of the Indian Academy of Neuroscience, Cochin, India, December 2008".
6. Rahul Chaudhary, K Praveen, Ziauddin Darokhan and V. Rema: Extent and nature of recovery of forelimb behaviour after unilateral lesion cortical forelimb area. "Annual meeting of the Indian Academy of Neuroscience, Cochin, India, December 2008"

Funding:

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

Brain Reorganization Following Spinal Cord Injuries

Principal Investigator : *Dr. Neeraj Jain*

Research Fellows : *Shashank Tandon, Niranjan Kambi, Leslee Lazar, Radhika Rajan, Mohammed Hisham*

Project Assistant : *Rajiv Kumar Mishra*

Multiple somatosensory areas of the brain are involved in processing tactile inputs. The information processing network involves both serial and parallel pathways. Motor areas, which initiate and control movements, depend on feedback from the somatosensory system for fine control of the movements. My research program aims to understand how the sensorimotor system processes sensory information to enable tactile perception and motor control, and how spinal cord injuries affect functional organization of the system. We are also interested in developing technology for recoveries from spinal cord injuries.

We perform unilateral lesions of the dorsal columns of the spinal cord leaving spinothalamic and other ascending and descending pathways intact. Using multiunit mapping and intracortical microstimulation techniques we are determining the effects of these injuries on the somatosensory and motor areas of the brain. We use both primate as well as rodent models for our studies due to specific advantages of each system. Work done during the year is described below.

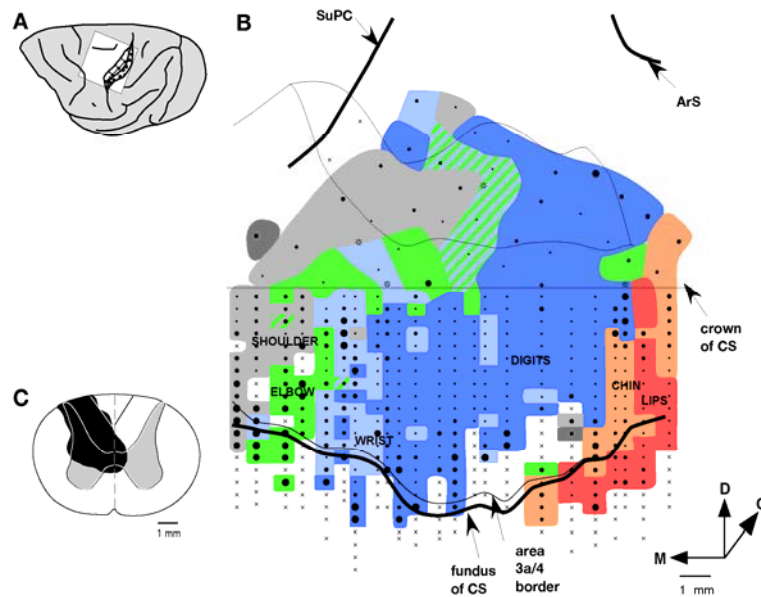
Brain reorganization following dorsal spinal cord injuries in primates. We determined how organization of the motor cortex of monkeys is affected by chronic lesions of the dorsal columns of the spinal cord at cervical levels. We have previously shown that the primary somatosensory area 3b and the somatosensory areas of the lateral sulcus (areas S2 or secondary somatosensory area, and area PV or parietal ventral area) undergo large-scale reorganization after such injuries. In the brains of these monkeys, the intact face inputs expand into the deafferented parts of the somatosensory cortex. Since the motor system depends on the somatosensory feedback for control of movements, we determined if long-term abnormal inputs from the somatosensory cortex affect functional organization of the motor cortex. We mapped motor cortex of the monkeys using intracortical microstimulation, many months after unilateral lesions of the dorsal columns. The data show that the overall organization of the motor cortex remains normal with face to hindlimb representations in a lateral to medial sequence (Fig. 1). There were no large differences in the threshold currents required to evoke movements as compared to normal animals. Thus despite abnormal sensory feedback and abnormal behavioural use of the hand, the organization of the motor cortex remains unaltered following lesions of the dorsal columns.

Use of stem cells for recovery from spinal cord injuries. We have used mouse embryonic stem cells and human neural progenitor cells for transplant in injured spinal cord of rats.

Our experiments, in collaboration with Dr Shyamala Mani, on the transplant of mouse embryonic stem cells show that the transplanted cells are able to differentiate into neuron-like and oligodendrocytic morphology. However, embryonic stem cells result in tumor formation in all the transplanted rats. Similar results are seen if the transplanted cells are pre-differentiated into embryoid bodies or neurospheres.

In collaboration with Dr Pankaj Seth we have transplanted human neuronal progenitor cells in rats with spinal cord injuries. These cells do not result in any tumor formation. The transplanted cells remain nestin positive for the initial 3-4 weeks after transplantation (Fig. 2). Around these times the cells become beta III tubulin (Tuj1) positive and begin to lose nestin staining as determined by immunohistochemistry. We could track Tuj1 positive cells until 73 days post-transplantation. The cells also migrated over a distance of many millimeters towards to rostral end of spinal cord. A detailed analysis of the behavioural performance of the rats with transplant of neural progenitor cells is currently in progress.

Figure 1: (A) A dorsolateral view of the macaque monkey brain. The white box marks the region illustrated in 'B'. (B) Topographic organization of the motor cortex in a macaque monkey many months after unilateral lesion of the dorsal columns at cervical levels. The part of the figure below the horizontal straight line shows the face of the anterior bank of the central sulcus, and the part above the line shows the adjacent pre-central gyrus. Note that the topography of the movement representation in the motor cortex appears as in normal monkeys. (C) Reconstruction of the spinal cord in a coronal plane showing extent of the lesion (black). SuPC, superior pre-central dimple; ArC, arcuate sulcus; CS, central sulcus; M, medial; D, dorsal; C, caudal.



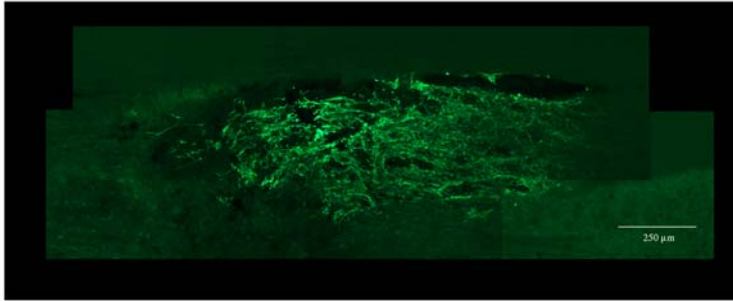


Figure2: Nestin positive human neural progenitor cells 8 days following transplant into the spinal cord of a rat that had earlier received lesion of the dorsal funiculus. Rostral is towards left.

Publication:

1. Aatira G Nedungadi, G Rangarajan, **Neeraj Jain** and Mingzhou Ding (2009). Analyzing multiple spike trains with nonparametric Granger causality. **Journal of Computational Neuroscience**. (In press)

Presentations:

1. Niranjan Kambi, Shashank Tandon and Neeraj Jain: Extensive motor cortex plasticity following dorsal spinal cord injuries in adult rats. Neuroscience 2008, Annual Meeting of the Society for Neuroscience, Washington, DC, USA, November 15-19, 2008
2. Mohammed Hisham and Neeraj Jain: Corticocortical connections of representation of the whiskers and adjacent regions of the rat motor cortex. 26th Annual Meeting, Indian Academy of Neurosciences, Cochin, India, December 12-14, 2008.
3. Neeraj Jain: Spinal Cord Injury and Brain Plasticity. Trends in translational medicine, PGIMS, Rohtak, Haryana. January 9, 2009.
4. Neeraj Jain: IBRO workshop Cognitive Neuroscience, NBRC, Manesar, January 5-16, 2009.

Funding:

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1. International Senior Research Fellowship, The Wellcome Trust, UK.
2. Defense Research and Development Organization, India
3. Department of Biotechnology, India

Collaborators:

Prof. G. Rangarajan, IISc Bangalore, India
Prof. Ashitava Ghoshal, IISc Bangalore, India
Dr. M Srinivasan, MIT Boston
CAIR Bangalore, India.
Dr. Shyamal Mani, NBRC, India
Dr. Pankaj Seth, NBRC, India

Emergence of Primary and Non-Primary Auditory Cortical Areas During Late Foetal and Early Postnatal Ages in Humans

Principle Investigator : Dr. Soumya Iyengar

Project Assistant : Senthil Krishnasamy

Technical Assistants : OP Sharma, Arvind Singh Pundir

Small foci within primary and non-primary (association) auditory cortical areas are activated when adult humans hear complex sounds, such as speech, environmental sounds and music. Studies on post-mortem brains have shown that these areas express higher levels of calcium binding proteins (CBPs, calretinin, CR, calbindin, CB, and parvalbumin, PV), compared to the surrounding cortex. Whereas it has long been known that human foetuses begin to respond to sound during the 5th month in utero and can discern complex sounds such as segmented speech, gender of the speaker, prosody and pitch during the third trimester of gestation, little is known about the structure of the human auditory cortex before birth. Our objectives were therefore to delineate areas within the association auditory cortex which are important for perceiving complex sounds during development by using post-mortem samples of the human brain. We also wanted to study the relative maturity of auditory cortical areas at different time points across development.

We had earlier shown that different cell types in the auditory cortex (pyramidal, stellate and bipolar) were immuno-positive for CR and CB before and at term. Histological observations also suggested that the density of CR+ and CB+ neurons was greater in the infragranular layers (Layers 5 and 6) and the white matter underlying the auditory cortex at term compared to adults. We have now been able to confirm that CB+ neuronal density was greater in the infragranular layers and white matter underlying the auditory association cortex at term by using stereology to perform a layer-wise measurement of cell density in two areas of the auditory cortex (TA and AA) at term and in adulthood. We also found that the density of CR+ neurons was greater in Layer 6 and the underlying white matter in one of the auditory foci (anterior area, AA) at term compared to that in adults. However, there were no significant differences in CR+ neuron density in any of the layers in TA of foetuses versus adults. These results suggest that there may be subtle differences in the auditory foci specialized for perceiving complex sounds which can be detected by stereological methods. Our results also suggest that there may be an inside-out maturation of the GABAergic CBP+ neurons in the auditory cortex, as has been reported earlier for other cortical areas (Hendrickson et al., 1991; Honig et al., 1996).

The decrease in density of CBP+ neurons between term and adulthood appears to result from the increase in volume of the cortex as well as an increase in dendritic arborisation of neurons in auditory regions.

In addition to localizing CBPs, we have also begun to localize SMI-31 and SMI 312 (markers for phosphorylated neurofilaments) in the auditory cortex during development. Both markers are important for identifying thick and thin axons and dendrites of neurons in the auditory cortex at term and at birth. Our preliminary results suggest that a small number of fibres positive for neurofilaments are present in supragranular layers of the auditory cortex before birth, which need to be confirmed.

Funding:

This work is supported by a grant from DBT, India.

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Neurogenesis in the Song Control System of Zebra Finches

Principle Investigator : *Dr. Soumya Iyengar*

Research Fellow : *Nazia Khurshid*

Project Assistants : *Naveen Jayaprakash, L. Shahul Hameed,
Sivaraj Mohanasundaram*

Technical Assistant : *Arvind Singh Pundir*

Zebra finches, a species of songbirds, are excellent models to study adult neurogenesis, since there is constant turnover of neurons in the brains of these birds. Neurons born during adulthood are incorporated into functional circuits in the brain (the song control nuclei), which give rise to a highly stereotyped and easily quantifiable song. Earlier studies have shown that the decrease in incorporation of new neurons in specific song control regions in adulthood can be correlated with an increase in stereotypy of syllables and a decrease in variability of the acoustic parameters of song. Thus, zebra finches provide a good model system to study the effects of altering cell proliferation and neurogenesis on behavior. Our objectives were to localize the opioid receptors (ORs) in different regions of the adult zebra finch brain. Further, we wanted to study whether the levels of endogenous cell proliferation in the ventricular and subventricular zones (VZ and SVZ) of adult zebra finches could be increased by blocking the opioid system, a manipulation which is known to increase cell proliferation in the brains of mammals. We would also like to study whether increasing the number of new neurons in the song control circuitry underlying vocalization would change their songs, which under normal conditions are highly stereotyped.

We had earlier shown that both μ - and δ -OR subtypes were present throughout the brain of zebra finches including song control areas and the VZ and SVZ. We have recently found that in addition, ORs are also expressed by the substantia nigra compacta – ventral tegmental area (SNc-VTA) complex (Fig. 1A) and other areas in zebra finches, which play a role in reward and the motivation to sing. Studies on mammals have shown that when μ -OR agonists bind to their receptors present on GABAergic neurons in the VTA-SNc complex, dopaminergic VTA-SNc neurons are disinhibited and release dopamine into the striatum to mediate feelings of reward. Results from our experiments on the effects of blocking ORs on song behavior in the short term suggest that the opioid system modulates the mesolimbic dopaminergic pathway in zebra finches, since administering naloxone to male birds affects their motivation to sing to females. Adult male zebra finches sing in different social contexts – either to court females (directed songs) or in isolation (undirected song), which is thought to be

important for practice. Recent studies suggest that in addition to differential activation of the VTA-SNc complex, different subsets of the song control circuits underlie the production of song in directed and undirected contexts. We found that male zebra finches sang significantly fewer songs (directed and undirected) when they were administered low doses of naloxone (2.5mg/kg body weight), compared to saline-treated controls. Surprisingly, high doses of naloxone (≥ 5 mg/kg body weight) significantly decreased undirected song but had no effect on songs directed towards females. Whereas the mesolimbic dopaminergic pathway and/or the song control system may be the site for the action of naloxone on directed song, the site for the action of naloxone on undirected song is, at present, unknown.

Besides altering the motivation to sing, we found that administration of naloxone altered the spectral features (decrease in goodness of pitch, frequency and amplitude modulation) and temporal features of song (increase in the duration of intersyllable intervals). Our immunohistochemistry data demonstrated that μ -ORs were present throughout nXIIIts (the tracheosyringeal part of the twelfth nerve nucleus, (Fig. 1B), which innervates the syrinx, and vocal control nuclei (HVC and RA; Khurshid et al., 2009), suggesting that endogenous opioids can modulate the acoustic features of song. Further, since the analyses of different behaviors have been standardized for naloxone treatment, we can now begin to analyze the effects of increasing cell proliferation and neurogenesis on these behaviors.

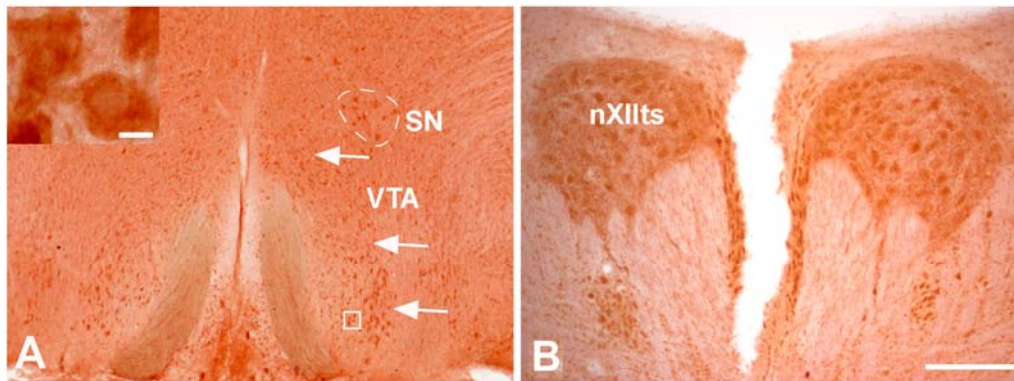


Figure: Neurons and neuropil in the substantia-nigra-ventral tegmental compacta (A) and (B) the nXIIIts (tracheosyringeal branch of the hypoglossal nerve) are intensely immunoreactive for μ -ORs in adult male zebra finches. Inset in (A) shows μ -OR label in the neuropil and dendrites of VTA neurons. Scale bars for A=400 μ m, for inset in A=20 μ m, for B=200 μ m.

We had earlier demonstrated that administering low doses of naloxone for four days led to an increase in cell proliferation in adult male zebra finches. We have completed some of our long-term experiments which entailed waiting for 3 weeks after treating birds with naloxone and injecting them

with BrdU on the fourth day of treatment. We found that some of the BrdU-labeled cells were incorporated into song control nuclei such as HVC and Area X. These results suggested that some of the cells which had been induced to proliferate as a result of naloxone treatment may have been incorporated into song control regions. Further, cells in primary cultures of the VZ and SVZ which were treated with naloxone were double-labeled with both BrdU and β -tubulin III (a marker for neuronal differentiation), also suggesting that some of the cells which were induced to divide by naloxone treatment may have differentiated into neurons.

Publication:

1. Khurshid N, Aggarwal V and **Iyengar S.** (2009). Localization of μ - and δ - opioid receptors in song control regions of adult male zebra finches (*Taenopygia guttata*). **J. Chem. Neuroanat.** 37(3); 158–169.

Presentations:

1. Iyengar S: Methods in Neuronal and Axonal Tracing. Presented at the workshop entitled “Imaging Neurodegeneration: Molecules to mind”, organized by IIT-Delhi, Sept 5-6, 2008.
2. Iyengar S: Auditory System. Presented at the Cognitive Neuroscience Workshop (organized by IBRO and NBRC) entitled “The Making of Mind”, NBRC, Manesar, Jan 5-16, 2009
3. Iyengar S: The role of the opioid system in singing and other behaviours in adult male zebra finches. Presented at a workshop entitled “Functional Biology: Comparative Aspects” which was a part of the Second Meeting of the Indian Subcontinent Branch of the International Peptide Society, organized by the Dept. of Zoology, University of Lucknow, March 19-21, 2009.

Funding:

This work is supported by a grant from DBT, India.

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

Principal Investigator : Dr. Narender K. Dhingra

Research Fellows : Varsha Jain, Saumya Nagar, Deepak Poria,
Manvi Goel

Project Assistants : Santhosh Sethuramanujam, Sabyasachi
Maiti, Orthis Saha, V. Krishnamoorthy

Lab Attendant : Tikaram

Retinal degenerative diseases such as Retinitis Pigmentosa and Age-Related Macular Degeneration are characterized by photoreceptor degeneration, and are among the leading causes of blindness. Although photoreceptors degenerate progressively, the inner retinal neurons, especially retinal ganglion cells (RGCs) are relatively preserved. This observation forms the basis of some of the novel therapeutic strategies, e.g., stem cell transplantation or retinal prosthesis to treat the retinal degenerative diseases. A retinal prosthesis is an electronic device designed to transform visual information into a spatiotemporal set of electrical stimuli that would be applied to the surviving retinal neurons via an array of microelectrodes. The underlying assumption is that the information about the visual world would be correctly encoded in the electrical stimuli. Similarly, the transplanted stem cells are expected to differentiate into photoreceptors and synaptically connect to the second-order retinal neurons. These promising strategies are being tried in animal models and in humans, but have produced only limited clinical outcome thus far. We believe that the success of these strategies is critically linked to our understanding of the retinal circuitry and projections, the factors that regulate retinal synaptogenesis, and how information is transmitted through retinal neurons and to the brain. Our lab is interested in addressing these fundamental questions, and in testing some of these treatment approaches in animal models of retinal degeneration.

We have been studying in animal models of photoreceptor degeneration the nature of changes in retina that follow the degeneration and the underlying mechanism. We recently showed that photoreceptor degeneration induced by N-methyl-N-nitrosourea (MNU) leads to several morphological changes in the second-order neurons (Nagar et al., 2009). To address the question whether MNU produces a rod/cone sparing model, we have studied the temporal profile of their degeneration using rod- and cone-specific markers, and showed that both type of photoreceptors are similarly affected by MNU

(Figure). In addition, we have found early and sustained biochemical and physiological changes in the third-order retinal neurons, suggesting that a third-order neuron is able to respond to the loss of photoreceptors early on. For example, we have found aberrant spiking pattern in the retinal ganglion cells, some of which show rhythmic bursts. Presently we are carrying out experiments to understand the mechanism underlying these changes in third-order retinal neurons.

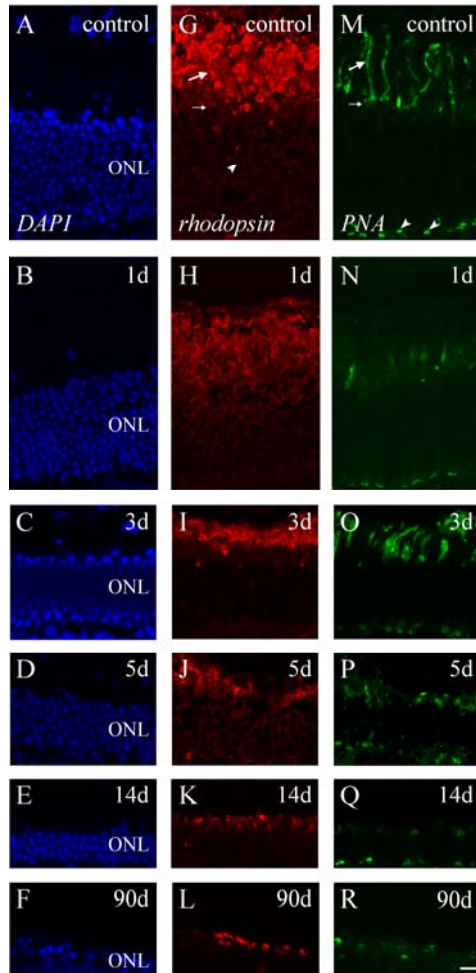


Figure: MNU affected both rods and cones (A-F) DAPI- Stained retinal sections showing progressive decline in the number of photoreceptors. (G-L) Same sections, immunostained for rhodopsin showing progressively degenerating rods. Rhodopsin was localized mainly in the outer segments (arrow), inner segment (thin arrow) and cell body (arrowhead). (M-R) Same sections, stained with PNA-fluorescein showing progressively degenerating cones. PNA labeled the cone outer segment (arrow), inner segment (thin arrow) and synaptic terminals (arrowhead). Scale bar: 10 micrometer.

In another project we are interested in a specific type of retinal ganglion cell that expresses POU-IV domain transcription factor, Brn3. We have been characterizing these cells in terms of their morphological and physiological properties. In addition, we are studying their projections to various parts of brain via labeling these cells retrogradely by injecting fluorescent markers in these brain areas. We have found interesting differences in the projections of Brn3a- and Brn3b-expressing RGCs.

We have continued our efforts on intravitreally transplanting cells of various origins in rd1 mouse, both in vivo and in vitro. In our pilot experiments we have found some of the injected cell types to survive, migrate, and integrate with the host retina.

Publications:

1. Smith RG, **Dhingra NK** (2009). Ideal observer analysis of signal quality in retinal circuits. **Prog Retin Eye Res**, doi:10.1016/j.preteyeres.2009.05.001.
2. Nagar S, Krishnamoorthy V, Cherukuri P, Jain V, **Dhingra NK** (2009). Early remodeling in an inducible animal model of retinal degeneration. **Neuroscience**, 160: 517-529.
3. Krishnamoorthy V, Jain V, Cherukuri P, Baloni S, **Dhingra NK** (2008). Intravitreal injection of fluorochrome-conjugated peanut agglutinin results in specific and reversible labeling of retinal cones In vivo. **Invest Ophthalmol Vis Sci**, 49 (June): 2643-2650.

Patents:

Dhingra NK, Krishnamoorthy V (2008) In Vivo Labeling of Mammalian Cone Photoreceptors by Intravitreal Injection of Fluorescently Tagged Peanut Agglutinin (PCT filed on May 21, 2008; Application No. PCT/IN08/000321; Priority No. 2136/DEL/2007 dated October 11, 2007).

Presentations:

1. NK Dhingra, V Krishnamoorthy, V Jain, P Cherukuri, S Baloni: In vivo labeling of mammalian cones with fluorophore-conjugated peanut agglutinin –A potential clinical tool to assess retinal degenerative diseases. International Conference on Nanomedicine & Recent Advances in Ophthalmic Research, Sankara Nethralaya, Chennai, September 3-5, 2008
2. D Poria, S Maiti, NK Dhingra: Novel therapeutic strategies to restore vision. 5th Foundation day of NBRC (Poster presented by DP and SM for high school students), December 16 2008.
3. NK Dhingra: Retina: What it does, and what we can do. Cognitive Neuroscience workshop, NBRC, Manesar, January 5-16 2009.
4. Saha, S Baloni, V Jain, S Balakrishnan, NK Dhingra: Morphological characterization of Brn3-expressing retinal ganglion cells. Asia-ARVO meeting, Hyderabad, Jan. 15-18, 2009.
5. S Nagar, V Krishnamoorthy, P Cherukuri, V Jain, NK Dhingra: Remodeling in retinal degeneration – More than meets the eye. Asia-ARVO meeting Hyderabad, Jan. 15-18, 2009.

Funding:

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Neural Network Mechanisms Underlying Spatial Learning and Navigation

Principal Investigator : Dr. Yoganarasimha Doreswamy

Hippocampus is a major brain structure involved in learning and memory. The discovery of “place cells” which shows selective firing at specific location in an environment, suggests that the hippocampus may form the locus of a “cognitive map” of the surrounding environment. Research in this field focused on the description of different sensory inputs in generation and control of place fields. However, role of hippocampus in episodic-memory, context-dependent learning, learning of spatiotemporal sequences, indicates that the place cell firing may also reflect encoding of behaviorally salient nonspatial information onto the spatial framework provided by place cells. Some of recent studies have tried to address this issue, however further advancement is limited by the relative paucity of knowledge of the properties of the neurons that interact with the hippocampus. To understand the specific role of the hippocampus in learning and memory, it is critical to understand the nature of neural representations already formed in related brain areas, which sheds lights on how these representations are processed within the hippocampus and in its afferent and efferent structures.

Entorhinal cortex, which provides major cortical inputs to the hippocampus, is suggested to receive most of its spatial inputs through postrhinal cortex and nonspatial information through perirhinal cortex, which is then transferred to different sub-regions of the hippocampus for conjunctive representation of the external environment. While, the role of perirhinal cortex in nonspatial information processing has been documented, the postrhinal cortical neurons are weakly spatially modulated, indicating that other brain areas may be involved in transfer of spatial information to the entorhinal cortex. Postsubiculum, an area of the subicular complex, has anatomical connections with different cortical areas and connected to the hippocampus and entorhinal cortex, two major brain areas involved in processing of spatial information. Postsubiculum is also connected to anterodorsal thalamic nuclei, which contains “head direction cells”, providing directional information. Thus, the postsubiculum may act as an interface between these brain areas in the integration of spatial and directional information.

Postsubiculum contains head direction cells and show location correlates, although the spatial tuning has been reported to be less specific than that of the hippocampal place cells. Further, theta modulated place by direction cells have been reported in postsubiculum, which may act as internal units allowing updating of position from one location to another based on the current directional heading. The postsubiculum cells also encode head

angular velocity and running speed, two properties that are necessary to allow self-motion information to update representation of head direction and location. Considering the anatomical connections with other brain regions involved in spatial and directional information processing, it is essential to understand the functional properties of postsubiculum neuronal firing in order to identify the amount of processing performed by different brain areas. In vivo single unit activity of postsubicular neurons will be recorded in normal behaving rats, using multitetrode electrophysiological recording technique. The outcome of this study will help understand the relative contribution of these different brain regions in spatial learning and navigation.



Computational Neuroscience & Neuroimaging

Dr. Nandini Chatterjee Singh

Prof. Prasun Kumar Roy

Dr. Pravat Kumar Mandal

Nandini Chatterjee Singh

Background – Multilingualism is a distinguishing feature of the Indian sub-continent, which also promotes the development of reading skills in different orthographies (English-Hindi, Urdu-Hindi, for example). Whilst reading pathways in single scripts are well studied, there is little understanding of how reading pathways are shaped for second language reading. We capitalize on the unique population of bilinguals in India and study the organization of speech and reading pathways in multilinguals using a combination of behavior and neuroimaging paradigms.

Additionally, the laboratory is also interested in developing computational techniques to study the articulatory features of spoken language, which could be potentially useful in providing early screening for different communication disorders.

The laboratory is currently involved in two specific projects, which are described below.

Neural Pathways for Reading Different Orthographies

Principal Investigator : *Dr. Nandini Chatterjee Singh*

Research Fellow : *Tanusree Das*

Post Doctoral Fellow : *Uttam Kumar*

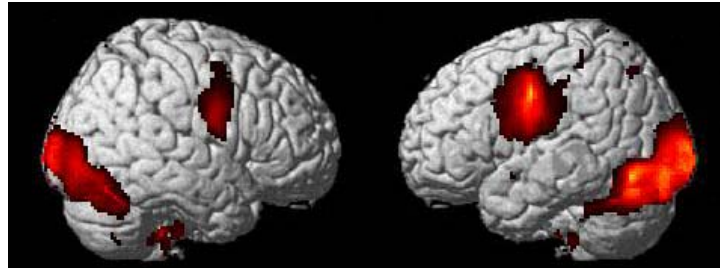
Project Assistant : *T. Sumathi*

The process of reading can be achieved through two distinct routes, the grapho-phonological or indirect route and the lexico-semantic or direct route. For shallow orthographies, like Hindi or Italian, wherein the letter-sound mapping is unique, the indirect route is engaged and visual words are transformed into their auditory counterparts using the letter to sound correspondence. For deep orthographies like English, where the letter to sound rule is not unique, (the difference between cough and bough, for example) in addition to the indirect route, a direct route is also believed to be recruited, wherein the visual form of words are directly mapped to meaning. Since brain organization for reading different orthographies is influenced by factors such as, the age at which the language is acquired, competence in the language, and properties specific to different languages, our laboratory has been interested in studying reading in biscriptals, which are bilinguals with abilities to read different scripts.

The first project in the laboratory was focused on studying the neural representation of Devnagari. Unlike English which is alphabetic and linear, in that vowels and consonants are arranged sequentially, Devanagari, is an alphasyllabary which is visually non-linear in that vowels are placed around consonants making it a visually complex script. Additionally, the grapheme to phoneme mapping in English is opaque (the difference between /mint/ and /pint/ for example) while Devanagari is transparent. We used functional brain imaging to study brain activation patterns when 16 native speakers read phrases in Devanagari, a writing system with alphabetic and syllabic properties. Our results show that true to its nature, Devanagari exhibits activation patterns that correspond to brain regions related to both syllabic and alphabetic writing systems, namely temporo-parietal, inferior parietal lobule seen for alphabetic systems and the superior parietal lobule seen in syllabic writing systems. Therefore Devanagari presents a novel example of a complex script, which places increased demands on visuo-spatial processing. In order to study the non-linearity of Devnagari, a word reading task associated with different orthographic structures would be useful and has already been undertaken.

The second project in the laboratory focused on reading in late biculturals, who acquired reading skills in the second script (English) sequentially, in this case, after 9 years of age. The cortical activations observed while reading Devnagari and English, two markedly different orthographies were studied in 12 late adult biculturals. Since English is an opaque orthography, neuroimaging studies have shown that monolinguals reading in English follow both the direct and the indirect route. As shown in Figure 1, despite the differences in the two orthographies, we find a common reading network along the indirect route for reading in English and Devnagari comprising of bilateral cerebellum, occipital areas, middle temporal gyrus and thalamus. This suggests that in late biculturals, reading networks in the second language (English) are shaped by the native language (Hindi) and are not orthography-specific. However direct comparison of Hindi-English show orthography effects, wherein activation was seen in visual-processing areas in right hemisphere. Thus late biculturals read later learnt orthographies in terms of the native orthography.

Reading in English



Reading in Hindi

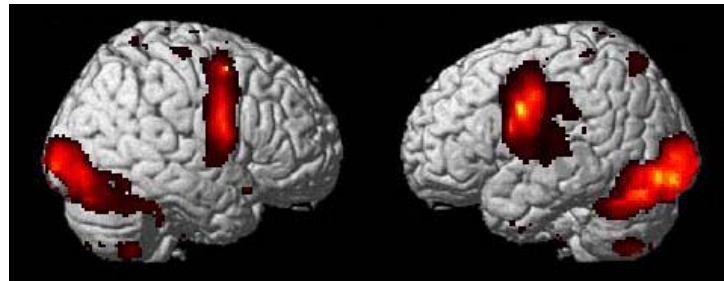


Figure Shows the different brain activated when late bilinguals read phrases in English and Hindi .

A Computational Analysis of Speech Motor Skills in Typically Developing Children and those with Autism Spectrum Disorder (ASD)

Principal Investigator : Dr. Nandini Chatterjee Singh

Research Fellow : Tanusree Das, Megha Sharda

Post Doctoral Fellow : Uttam Kumar

Project Assistant : T. Padma Subhadra

Background

Whilst the first project has been focused on adults, a major interest in the laboratory has also been the acquisition of multiple languages in children. Additionally, speech is one of the earliest markers for development or acquired pediatric neurological disorders and though there is detailed information regarding milestones in language development in infants, there is very little information regarding the development of language skills in young children. In particular, there is hardly any quantitative information regarding the development of second language skills. In India, most school going children learn their mother tongue in infancy and then a second language like English or Hindi at school. In the light of disorders like SLI, dyslexia and PDD, which are now widely reported even in India, it is important that we obtain quantitative data in typically developing children learning a second language. In India it is also crucial that such data be easily obtained and analysed at low cost so that it becomes easily accessible to speech-language pathologists.

Earlier work in the laboratory has demonstrated the use of the speech modulation spectrum as a techniques to study different articulatory features and their development in children aged 4-13 years. More recently the laboratory has focused on characterising the articulatory features of children with autism spectrum disorder (ASD). ASD is also marked by impairments in language. Since there has been some evidence to show that early speech and language abilities might be significant predictors of the communication impairment in autism, the laboratory has also been trying to identify speech parameters, which might be predictors of later language abilities in such populations. We have been studying speech samples from children with autism and comparing them with age-matched control data. Based on the speech modulation spectrum analysis our most notable finding has been the presence of a larger articulatory space for children with autism spectrum disorder (ASD) when compared with typically developing children (Figure2). The deviation in features of autistic speech versus control increases as we proceed from longer time scales (syllabic rhythm) to shorter

time scales encoding formant transitions and place of articulation. We attribute the larger space to the presence of non-speech sounds in ASD speech and are currently collecting data.

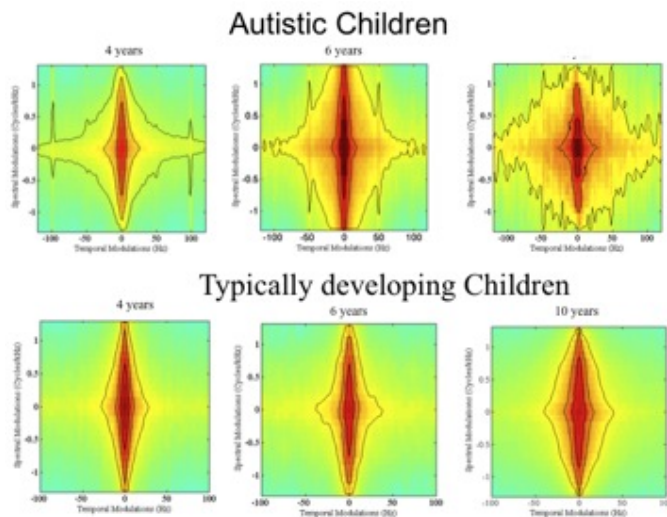


Figure Speech Modulation Spectra plots of children with ASD when compared with typically developing children show increased space which we attribute to the presence of non-speech sounds.

Long Term:

With our advent into fMRI analysis we would now like to use an approach wherein we can correlate our spectral analysis results with functional MR and will shortly be initiating experiments in children using functional MRI.

Publications:

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2. R. Reddy, V. Ramachandra, N. Kumar and **N.C. Singh** (2009). Categorisation of environmental sounds. **Biological Cybernetics**. DOI: 10.1007/s00422-009-0299-4.
3. P. Padakannaya, N.B. Ramachandra and **N.C. Singh** (2008). Dyslexia, orthography, and brain. **Current Science**, 1381

Presentations:

1. Nandini C. Singh: Development of articulatory features in children, Department of Speech and Hearing, University of Maryland, USA.
2. Nandini C. Singh: Influence of native language reading networks on the second language – an fMRI study, Abstract, Society for Neuroscience, Washington, USA, November 2008.
3. Nandini C. Singh: Signatures for reading proficiency, Abstract, Society for Neuroscience, Washington, USA, November 2008.

Funding:

Research grant from the Ministry of Communications and Information Technology.

Research grant from Department of Science and Technology.

Collaborators:

1. Dr. Prakash Padakannaya, Professor & Coordinator for UGC Innovative Program on learning disability and dyslexia, Department of Psychology, University of Mysore.
2. Dr. R. S. Bapi, Dept. of Computer and Information Sciences, University of Hyderabad.
3. Dr. Amit Sen, Sitaram Bhartia Institute for Science and Research, New Delhi.

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

Principal Investigator : Prof. Prasun Kumar Roy

Research Fellows : VPS Rallabandi, Suhela Kapoor

Project Assistant : Anupam Ghosh

It is well-known that a notable contemporary attainment in computational neuroscience is the incisive phenomenon of the Stochastic Activation Effect whereby optimized random-wave fluctuation is used to enhance the behaviour or sensitivity of a system to an input parameter or signal. A promising prospect to upgrade the efficiency of neuroradiological processes, whether diagnostic or therapeutic, is offered by stochastic activation. Stochastic activation, noise-aided resonance or fluctuation-induced transition, is a general behaviour exhibited by various systems, whether physical or biological. Stochastic activation has been used to enhance various processes relevant to neurobiologists, such as x-ray/ γ -ray/Raman spectra. Nevertheless, the practical application of stochastic activation as a novel technique in diagnostic or therapeutic radiology has not been systematically pursued. Such application is the objective of our project.

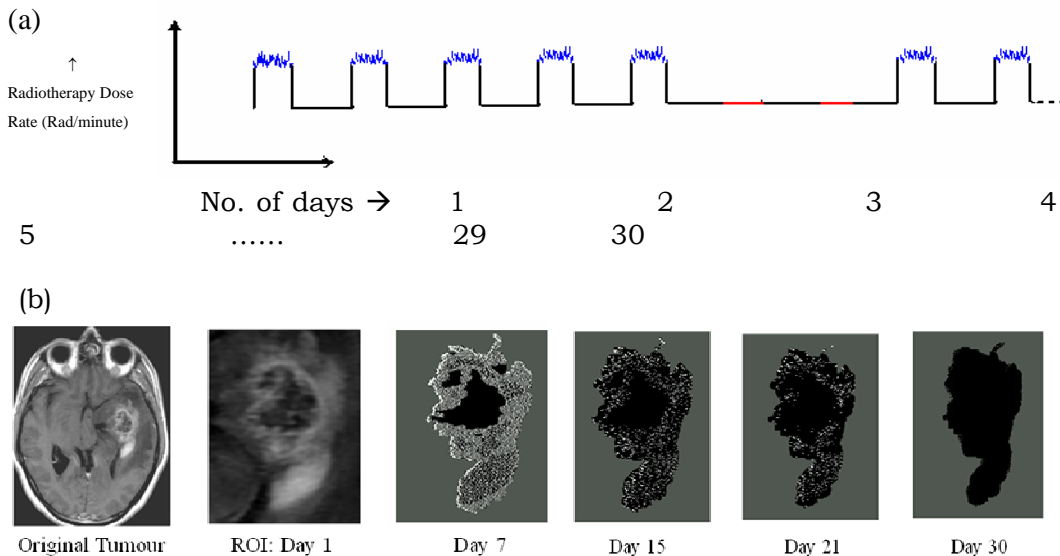


Figure 1: Image-guided Enhancement of Radiotherapy using perturbation of beam flux; (a) Dose protocol: Perturbation function administered to dose rate (b) Therapy planning platform for Perturbative Radiotherapy of Glioma tumour (ROI = region of interest); successive panels show temporal progression of treatment; the density of the white points denote density of tumour cells, observe the exclusion of tumour cells in last panel.

Diagnostic and Therapeutic Radiology

We have performed a clinically-oriented trial of using stochastic resonance (SR) for automated enhancement and diagnosis of brain tumours using histologically-confirmed MRI images of patients from teaching hospitals in New Delhi and Gurgaon. The accuracy of our SR-MRI diagnostic methodology was 95% in distinguishing the grade of the tumour as confirmed by histopathology. Double-blind diagnosis of over 50 patients have been tested in this way, so as to increase the sample size for obtaining sufficient statistical power. Additionally, we have also tested, as case-study, the power of stochastic radon enhancement algorithm on CT images of cerebral malaria patients and shown its efficiency on enhancing images for differentiating cytotoxic and vasogenic oedema, an important information helpful to the treating physician. Further, we have optimized the radiobiological algorithms stochastic resonance has been used to increase efficiency of radiotherapy of malignant lesions (fig. 1). The stochastic enhancement methodology, both for diagnostic and therapeutic radiology, has been filed for patenting and publication done.

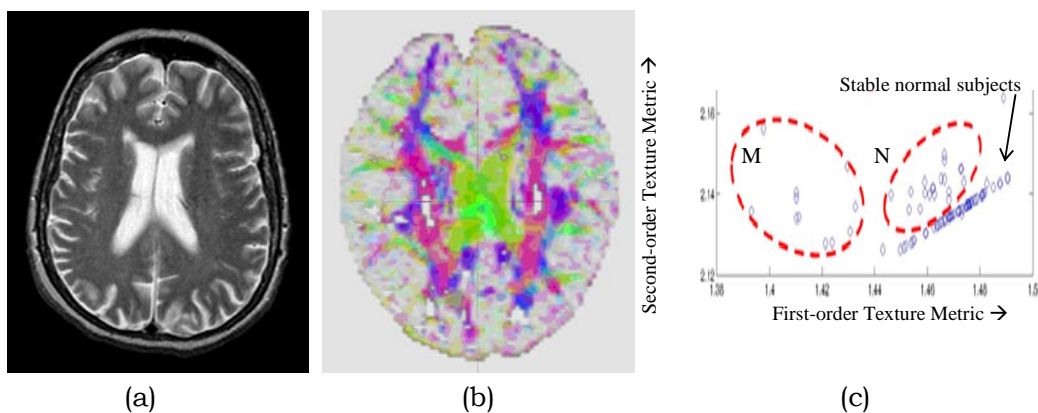


Figure 2: MRI-based differentiation of stable normal subjects from unstable normal subjects who would convert to mild cognitive impairment [‘converters’ to MCI]: (a) Structural MR image (b) Transport tensor image consonant with the elastoporous structure of brain parenchyma (c) Elastoporosity-based plot of first- and second-order texture indices, showing differentiation of stable normal subjects (linear locus), unstable converters (cluster M), and metastable normal subjects who move away from the linear locus but do not convert to MCI (‘non-converters’, cluster N).

Neurodegenerative disease

Based originally on MRI images of dementia patients obtained from Delhi, Bombay, Trivandrum and Calcutta, we have developed a textural analysis of scans to diagnose the grade of dementia, and we heuristically evolved the algorithm and ensured that it was applicable to scanners at different cities and of different manufacturers. Thereafter, we constructed a support vector

machine based algorithm to automatically classify MRI images into normals, pre-MCI, MCI, and mild or moderate Alzheimer's disease (AD). Tested on 200 subjects, using blind allocation, the overall accuracy was titrated to 98.5%, when optimized for processing time. We then developed an elasto-plastic temporal deformation analysis of the brain under intracranial pressure, and obtained the quantitative formulation of brain ageing based on the two-phase nature of brain parenchyma (fig. 2). As there is increasing amyloidogenesis across time, the two-phase medium structurally alters, and the images undergo distortion, departing away from the normal ageing curve. A patent has been filed on the diagnostic classifier technique.

Funding:

1. Intramural funds of NBRC.
2. Defense Ministry (DRDO).

Collaborators:

1. Dr Peter Luijten, Dutch National Centre for Translational Medicine & Utrecht University.
2. Dr Jamie Seaman, University of California, San Francisco, USA.
3. Dr K L Chakrabarty, Institute of Nuclear Medicine & Allied Sciences, Delhi, India.

Spatiotemporal Neural Processing and Transmission

Principal Investigator : Prof. Prasun Kumar Roy

Research Fellow : Kh. Budhachandra

Project Assistant : Vinay Shukla, Arnab Mukherjee

Comprehending how information transmission, volume conduction and connectivity occurs across the brain is a grand challenge in neuroscience. Simplistic scalar/vector models cannot satisfactorily account for information transmission during such conditions as in neural plasticity, high intensity adaptation, or clinical hyperexcitatory conditions as epilepsy or migraine. Hence the urgent need of quantitative tensor models that can account for information transmission and its neuromodulation across the brain, heeding the anisotropy or layeriness of the neural fibre architecture. The contemporary advancement of tensor neuroimaging implies a broad general methodology; here one investigates various transport processes or flow parameters in the layered anisotropic brain, as diffusion, permeability, electrical conduction and information flow. We have studied the approach of dynamic functional tensor neuroimaging, thereby constructing tensor maps to describe the permeability flux, information flux or connectivity in brain: indeed information flux is the most fundamental currency in neural systems. Needless to say, there is considerable potentiality for clinical applications, diagnosis as well as therapy.

Stress Imaging

The MRI pulse sequences and algorithm has been generalized for accessing flow processes of different body fluids. The necessary MRI pulse sequence and protocol has been improved to minimize “partial volume effects” which produces signal smear. The procedure has been adapted to delineate stress image of blood flow in the cerebrovascular system as carotid arteries (fig. 1). Based on the image, formulations have been worked out to calculate (i) shear force on blood vessel wall that diagnoses the risk of aneurysm during blood flow, or (ii) strain effect on the ventricular wall that estimates turbulence during CSF flow obstruction. This process has been done in cooperation with Delhi University, and the IPR procedure is being jointly pursued with that university.

Cortical Deformation & Conductivity Imaging

We are investigated more improved acquisition and processing of different transport or mobility tensors of the brain, including deformation tensor and the electrical or thermal conductivity tensors, using MRI and EEG data. We have performed MRI-based electrical conductivity tractography for exploring

epileptogenesis pathway, as well as thermal conductivity tractography for estimating heat generation from DBS electrodes. We are also studying the deformation tensor mapping of the brain, using MRI of Mild Cognitive Impairment and Alzheimer's disease of Indian patients from Chennai and Delhi, and this gives a very accurate representation of quantitative distortion and atrophy of patient brains in Indian scenario. Sample of the images are from Indian patients being treated with indigenous preparations used in treating dementia. Using MRI and fMRI image processing, the sample size of connectivity analysis has been increased. The deformation imaging methodology affords a precise early visualization and measurement of connectivity deficits.

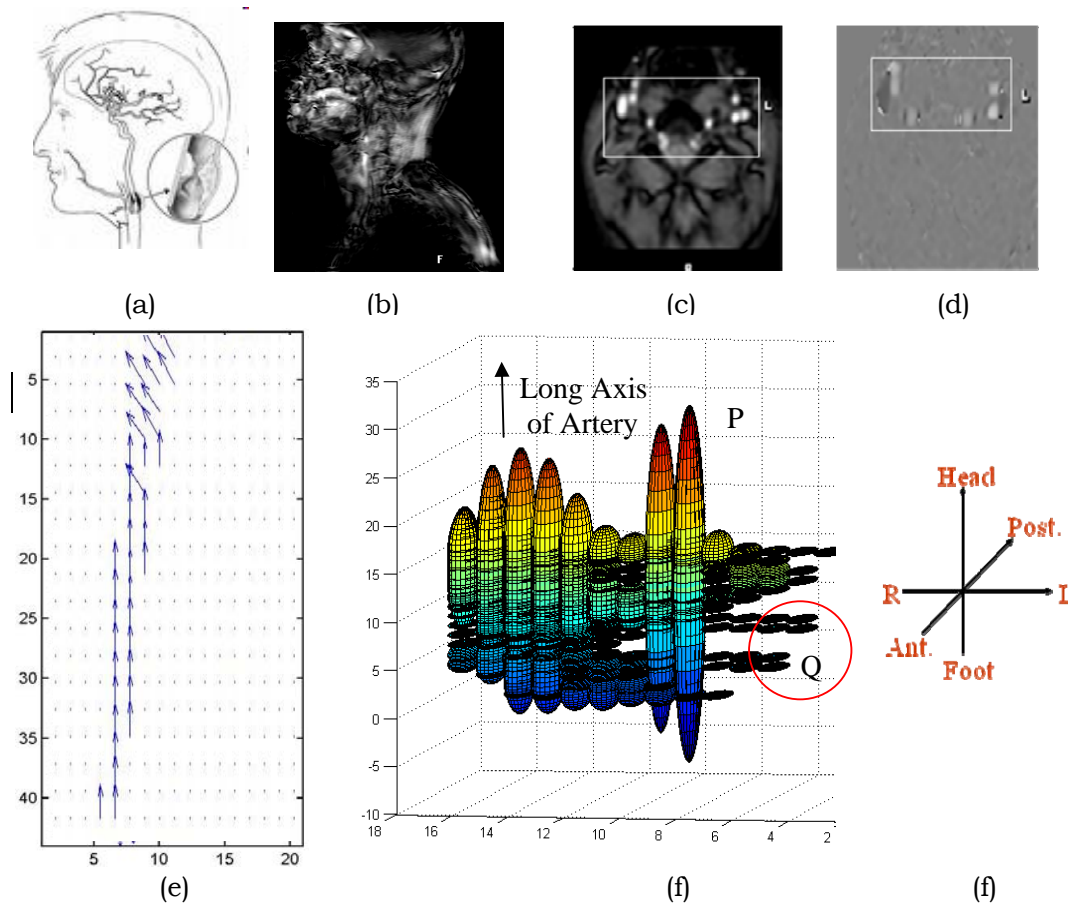


Figure 1: Magnetic Resonance Imaging of the Stress of blood flow in Carotid Artery of Brain to predict or detect shear strain, atheroma formation and flow irregularity: (a) Anatomical schema (b) Structural MRI: Saggittal scan of head (c) Transverse scan (b) Phase contrast image, sensitive to fluid mobility (d) Directional flow map of blood in carotid artery (e) Stress ellipsoids, point-by-point, of the flowing blood at the level of the arrow shown in the first panel. The majority of the flow ellipsoids, as around P, have spindle-like geometry, with the major axis of the ellipsoids along the flow direction, i.e. parallel to the artery wall, while some ellipsoids, as around Q, have disc-like geometry, with the major axis in perpendicular to arterial wall , i.e. these flow ellipsoids impacts the wall radially, thus later predisposing to wall damage, atheroma deposition and flow irregularity.

Publications:

1. *V.P.S. Rallabandi and **Prasun Roy** (2008). Stochastic-Resonance-based Tomographic Transform for Image Enhancement of Brain Lesions, **J. Computer Assisted Tomography**, 32(6), 966-974.
2. *Kh. Budhachandra and **Prasun Roy** (2009). Informational Tracking of Epileptic Focus in the Brain, **Advances in Developmental Neuroscience and Neuroimaging** (edited volume), p. 105-109.

[*Reported as 'in press', last year].

Patents:

1. **Prasun Roy** and Subhadip Paul, A Technique to Enhance the Clinical Efficiency of Radiotherapy and Radiosurgery using Perturbative Beaming and Tissue-specific Radiobiology (filed).
2. **Prasun Roy**, Kh. Budhachandra and T R Seshadri, A non-invasive technique to produce the stress image of fluid flow within nonuniform objects, with applications to map inaccessible fluid flows and obstructions in medicine (communicated).

Presentation:

1. Vinay Shukla, Prasun Roy: Multimodal tractographic approach to brain dynamics, Workshop on Integration of Physics and Mathematics to study Biological Systems, Bose Institute, Calcutta, Dec 2008.
2. Suhela Kapoor, VPS Rallabandi, Prasun Roy: Quantitative Analysis of the Role of Turbulence of Cerebrospinal Fluid: Therapeutic Modulation of Neurogenesis for Cerebrovascular Disorders, International Conference on Nonlinear Dynamics, Indian Institute of Science, Bangalore. July 2008.
3. Ashish Upadhyay, Prasun Roy: Nonlinear Dynamics-based Activation of MRI signal for Estimating Microvascular Turbulence of Blood Flow, International Conference on Nonlinear Dynamics, Indian Institute of Science, Bangalore. July 2008.
4. Prasun Roy: Imaging of Transport Processes in the brain, Indian Institute of Technology, Delhi, Sept. 2009.
5. Prasun Roy: Chairman of Imaging Session, International Workshop on Epilepsy, All-India Institute of Medical sciences, New Delhi, Oct 2008.
6. Prasun Roy: A Glimpse of Multimodal Tensor Neuroimaging in understanding the human brain in normality and disease. IBRO Workshop on Cognitive Neuroscience, Jan. 2009.

7. Prasun Roy: Planning of MRI, SPECT and PET Imaging Protocols for Dementia screening, Workshop on Ageing and Cognition, Institute of Neurological Sciences, Chennai, Feb. 2009.

Funding:

1. Intramural funds of NBRC.
2. Ministry of Education & Research, Italian Govt. under program of European Commission.
3. Utrecht University Foundation & Philips Research (research projects of students).

Collaborators:

1. Dr Patrizia Baraldi, University of Modena/CNRS-Rome.
2. Dr T R Seshadri, Delhi University.
3. Dr. Alan Evans, Montreal Neurological Institute, McGill University.
4. Dr Manjari Tripathi, All-India Institute of Medical Sciences, New Delhi, India.

Brain Neurochemical Analysis of Alzheimer Patients using in vivo Magnetic Resonance Spectroscopy

Principal Investigator : Dr. Pravat Kumar Mandal

Research Student : Ms. Ruchi Bansal

Project Assistant : Sushil Kumar

Alzheimer's disease (AD) is a major neurodegenerative disorder affecting millions of people worldwide. There is a dedicated global search for early clinical, molecular and neuroimaging marker of this disease. It is indicated that oxidative stress, energetic stress, and irregular membrane phospholipid metabolism play an important role in AD pathology. In vivo Magnetic Resonance Spectroscopic (MRS) technique can play important role to identify the causal molecular process in AD.

Before applying the MRS imaging modality to AD patients, one needs to apply the MRS protocol on phantom first and then on normal human volunteer. Therefore, we focused our attention on standardization of MRS experimental protocol that includes better shimming procedure of magnetic fields, pulse calibration and operationalization/optimization of different MRS pulse sequences and test retest reliability of these pulse sequences on phantoms using the Philips 3T scanner at NBRC. We then applied MRS protocol on normal human volunteers. Parallel to the work on standardization of the MRS protocol, we have installed different MRS data processing software (LCModel, 3DiCSI, JMRUI and FitMan). We also have established image processing protocol for seamless data transfer, storage and MRS data processing.

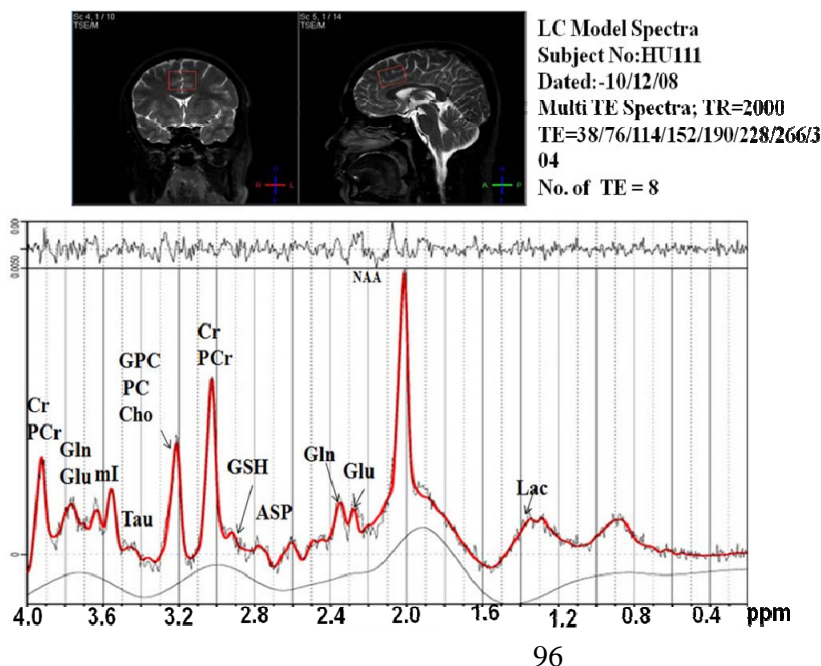


Figure : Single voxel (multi TE) PRESS data was collected using 3T Philips scanner in the cortex region of a normal volunteer. Data was processed using LCModel software.

The MRS data generated by the 3T Philips scanner on normal volunteer and processed using our image processing protocol is shown in Figure Experimental and image processing protocols are now being extended to Alzheimer patients and patients with other neurodegenerative disorders.

Publication:

1. **Pravat K. Mandal** and Vincenzo Fodale (2009). "Smaller molecular-sized anaesthetics oligomerize Abeta peptide simulating Alzheimer's disease: a relevant issue. **European Journal of Anesthesiology**, Editorial. (In Press).
2. **Pravat K. Mandal**, Daniela Schifilliti, Federica Mafra, and Vincenzo Fodale (2009). "Inhaled Anesthetics and Cognitive Performance. **Drugs of Today** (45: 47-54, 2009).
3. **Pravat K Mandal**, Vincenzo Fodale (2009). Isoflurane and desflurane at clinically relevant concentrations induce amyloid beta-peptide oligomerization: An NMR study. **Biochemical and Biophysical Research Communications**. (379: 716-720, 2009)

Presentation:

1. Pravat K. Mandal: Application of in Vivo Magnetic Resonance Spectroscopy for Alzheimer patients to understand early causal molecular process. International Conference on 'Functional Materials: Controlled Synthesis, Discrete Molecular Processes and Engineering' IIT, Madras, Invited speaker, Nov. 27-29, 2008.

Funding

This work is supported by NBRC Core fund.

Collaboration:

Dr. Subbulakshmy Natarajan, NBRC, India.

Dr. Partha Raghunathan, NBRC, India.

Dr. Manjari Tripathi, Department of Neurology, AIIMS, India.

Dr. Sada Nand Dwivedi, Dept. of Biostatistics, AIIMS, India.

The Journal of Neuroscience

PUBLICATIONS & PATENTS

SOCIETY FOR NEUROSCIENCE

Publications and Patents:

1. S. K. Godavarthi, D. Narender, A. Mishra, A. Goswami, S. Rao, N. Nukina and **N. R. Jana** (2009). Induction of chemokines MCP-1 and KC in the mutant huntingtin expressing neuronal cells because of proteasomal dysfunction. **Journal of Neurochemistry**, 108, 787-795.
2. Mishra, P. Dikshit, S. Purkayastha, J. Sharma, N. Nukina and **N. R. Jana** (2008). E6-AP promotes misfolded polyglutamine proteins for proteasomal degradation and suppresses polyglutamine protein aggregation and toxicity **Journal of Biological Chemistry**, 283, 7648-7656.
3. Mishra, S. K. Godavarthi, M. Maheshwari, A. Goswami and **N. R. Jana** (2009). The ubiquitin ligase E6-AP is induced and recruited to aggresomes in response to proteasome inhibition and may be involved in the ubiquitination of Hsp70 bound misfolded proteins. **Journal of Biological Chemistry**, 284, 10537-10545.
4. Jennifer L. Moran, Emily T. Shifley, John M. Levors, **Shyamala Mani**, Kristin Ostmann, Ariadna Perez, Dawn M. Walker, Thomas F. Vogt, and Susan E. Cole (2009). Expression and deletion analyses of Manic fringe indicates that it is not required for embryonic development, and that FRINGE proteins are not functionally redundant. **Developmental Dynamics**, 238(7):1803-1812. [Epub ahead of print]
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7. Karunakaran, S., Saeed, U., Mishra, M., Valli, R.K., Joshi, S.D., Meka, D.P., Seth, P. and **Ravindranath V** (2008). Selective activation of p38 mitogen-activated protein kinase in dopaminergic neurons of substantia nigra leads to nuclear translocation of p53 in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-treated mice. **J. Neurosci.** 28: 12500-12509.
8. Diwakar L, Rudresh Kumar KJ, Bachnalkar A, **Ravindranath V.**, Christopher R, Nagaraja D. (2008). The influence of MTR A2756G

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9. *Agarwal, V., Kommaddi, R.P., Valli, R.K., Ryder, D., Hyde, T.M., Kleinman, J.E., Strobel, H.W. and **Ravindranath V.** (2008). Drug Metabolism in Human Brain: High Levels of Cytochrome P4503A43 in Brain and Metabolism of Anti-anxiety Drug Alprazolam to its Active Metabolite. **PLoS ONE** 3:e2337.
 10. *Saeed U, Durgadoss L, Valli, RK, Joshi, D.C., Joshi, P.G. and **Ravindranath V.** (2008). Knockdown of Cytosolic Glutaredoxin Leads to Loss of Mitochondrial Membrane Potential: Implication in Neurodegenerative Diseases. **PLoS ONE** Jun 18;3(6):e2459.
 11. Karunakaran, S. and **Ravindranath V.** (2009). Activation of p38 MAP kinase in substantia nigra leads to nuclear translocation of NF-kB in MPTP treated mice: Implication in Parkinson's disease. **J. Neurochem.** May 11. [Epub ahead of print].
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 13. **P. Seth** and N. Koul (2008). Astrocytes, the star avatar: Redefined. **J Biosciences** 33:405-421.
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- the induction of memory and synaptic facilitation in Aplysia. **Proc. Natl. Acad. Sci. USA**, 105:20511-20516.
19. D Ghosh and **A Basu** (2009). Japanese Encephalitis - A Pathological and Clinical Perspective **PloS Neglected Tropical Diseases** (In press)
 20. D Ghosh, M K Mishra, S Das, D K Kaushik and **A Basu** (2009). Tobacco carcinogen induces microglial activation and subsequent neuronal damage. **J Neurochem** (In press)
 21. K Datta, D Ghosh, and **A Basu** (2009). Curcumin protects neuronal cells from Japanese Encephalitis virus mediated cell death and also inhibits infective viral particle formation by dysregulation of Ubiquitin proteasome system. **J Neuroimmuno Pharmacology** (In press)
 22. M K Mishra, D Ghosh, R Duseja, and **A Basu** (2009). Antioxidant potential of Minocycline in Japanese Encephalitis Virus infection in murine neuroblastoma cells: Correlation with membrane fluidity and cell death **Neurochemistry International** 54 : 464-470.
 23. R Mukhopadhyay, M K Mishra, **A Basu**, and B Bishayi (2009). Modulation of steroidogenic enzymes in murine lymphoid organs after immunization with soluble antigen. **Immunological Investigations** 38(1):14-30.
 24. M K Mishra, K L Kumawat and **A Basu** (2008). Japanese Encephalitis Virus differentially modulate the induction of multiple pro inflammatory mediators in human astrocytoma and astrogloma cell lines. **Cell Biology International** 32: 1506-1513.
 25. **J Ghosh, V Swarup, A Saxena, S Das, A Hazra, P Paira, S Banerjee, N B Mondal and **A Basu** (2008). Therapeutic Effect of a Novel Anilidoquinoline derivative- 2-(2-methyl-quinoline-4ylamino)-N-(2-chlorophenyl)-acetamide In Japanese Encephalitis: Correlation with in vitro neuroprotection. **Int J Antimicrob Agents** 32 (2008) 349-354.
 26. **S Das and **A Basu** (2008). Japanese Encephalitis virus infects neural progenitor cells and decreases their proliferation. **J Neurochem** 106(4):1624-36. (News and views reported and published by Nature India and as a part of several national and international press release)
 27. **A Basu** and M K Mishra. Minocycline as a therapy in Japanese Encephalitis. [Patent Application No: 211/DEL/2007]
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 29. **Murthy A.**, Ray S, Shorter SM, Schall JD, Thompson KG (2009) Neural Control of Visual Search by Frontal Eye Field: Effects of Unexpected

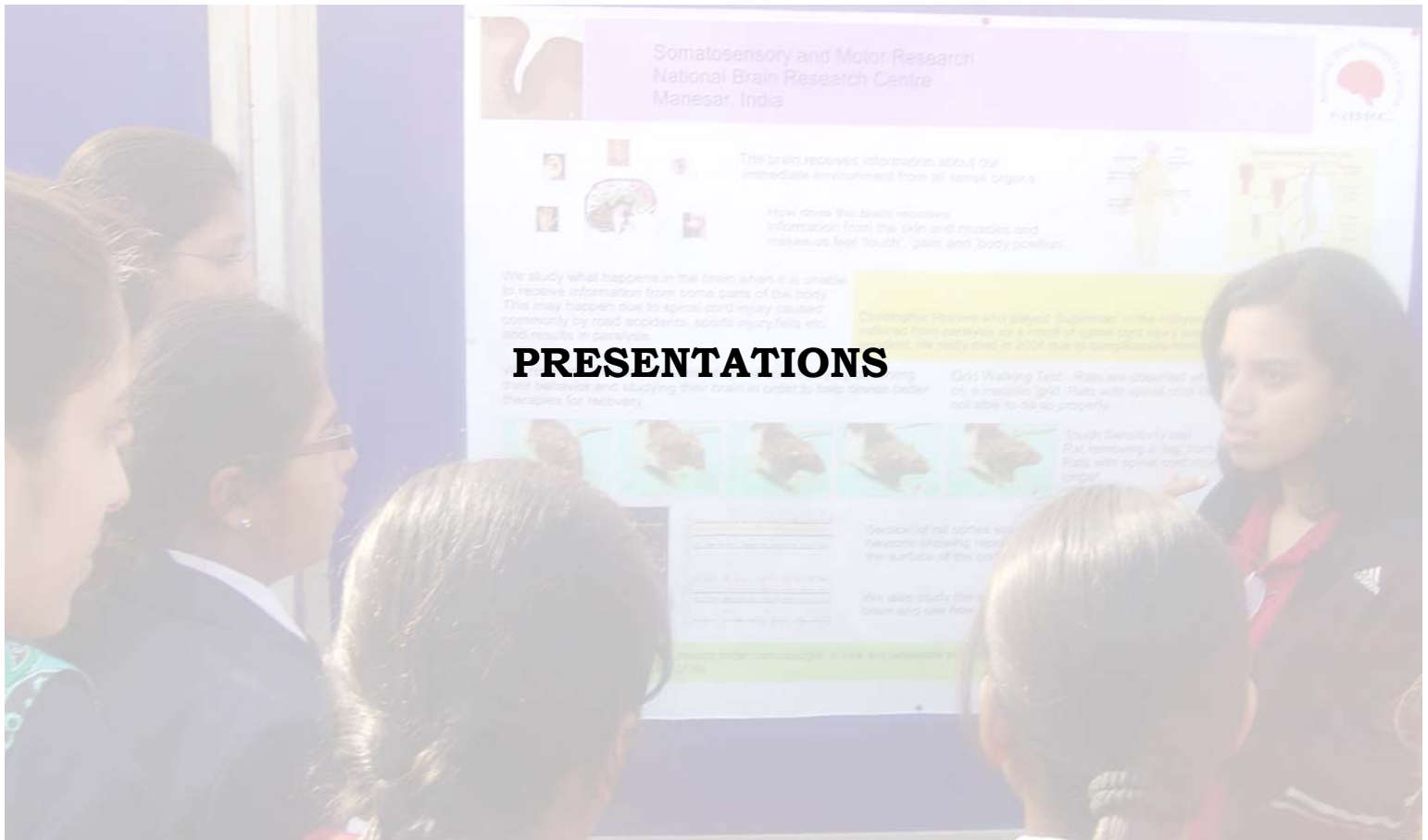
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 38. P. Padakannaya, N.B. Ramachandra and **N.C. Singh** (2008). Dyslexia, orthography, and brain. **Current Science**, 1381
 39. **V.P.S. Rallabandi and **Prasun Roy** (2008). Stochastic-Resonance-based Tomographic Transform for Image Enhancement of Brain Lesions, **J. Computer Assisted Tomography**, 32(6), 966-974.
 40. **Kh. Budhachandra and **Prasun Roy** (2009). Informational Tracking of Epileptic Focus in the Brain, *Advances in Developmental Neuroscience and Neuroimaging* (edited volume), p. 105-109.

41. ***Prasun Roy** and Subhadip Paul, A Technique to Enhance the Clinical Efficiency of Radiotherapy and Radiosurgery using Perturbative Beaming and Tissue-specific Radiobiology (No. 2494/DEL/2008).
42. **Pravat K. Mandal** and Vincenzo Fodale (2009). "Smaller molecular-sized anaesthetics oligomerize Abeta peptide simulating Alzheimer's disease: a relevant issue. **European Journal of Anesthesiology**, Editorial. (In Press).
43. **Pravat K. Mandal**, Daniela Schifilliti, Federica Mafrica, and Vincenzo Fodale (2009). "Inhaled Anesthetics and Cognitive Performance. **Drugs of Today**. 45: 47-54.
44. **Pravat K Mandal**, Vincenzo Fodale (2009). Isoflurane and desflurane at clinically relevant concentrations induce amyloid beta-peptide oligomerization: An NMR study. **Biochemical and Biophysical Research Communications**. 379: 716-720.

Work done elsewhere

*Reported as submitted last year

**Reported as Press in last year



PRESENTATIONS

International Presentations:

2. V Ravindranath: Plenary lecture “The working of the human brain - molecules and networks to behaviour” at The Army Science Conference held on December 02, 2008 in Florida.
3. V Ravindranath: “Knockdown of cytosolic glutaredoxin 1 leads to loss of mitochondrial membrane potential: implication in neurodegenerative diseases” presented at Society for Neuroscience held from November 14-19, 2008.
4. V Ravindranath: “Redox driven activation of cell specific signaling pathways in neurodegeneration’ at fourth Amyotrophic Lateral Sclerosis Symposium held in Montreal on 25 and 26 September 2008.
5. V Ravindranath: “Cell-specific activation of redox driven death signaling pathways in neurodegeneration” at Brain and Mind research in the Asia/Pacific (BMAP) symposium at Singapore held during 01-03 September, 2008.
6. V Ravindranath: “Redox signalling in Parkinson's disease: Emerging role of sulfur metabolism” Invited speaker, Gordon Research Conference, Italy held on 25th to 30th May, 2008.
7. P. Seth: INDO-US Forum Meeting, Organized by US National Academy of Science, Agra, India, March 2009.
8. Vivek Sharma and Ellora Sen: “Interleukin-1 β induces HIF-1 α accumulation in glioma cells.” AACR Centennial meeting Translational Cancer Medicine: Bridging the lab and the clinic in Cancer Medicine Jerusalem, November 2008.
9. Vivek Sharma, Nitin Koul, Christy Joseph, Deobrat Dixit, Sadashib Ghosh and Ellora Sen: “HDAC inhibitor Scriptaid induces glioma cell apoptosis through JNK activation and inhibition of telomerase activity.” International Symposium on Complex Diseases: Approaches to Gene Identification and Therapeutic Management Satellite Symposium, Kolkata, August 2008.
10. Vivek Sharma, Richa Tewari, Nitin Koul, Deobrat Dixit, Sadashib Ghosh and Ellora Sen: “Ras and Glioblastoma therapy: Where does the truth lie?” INDO-US symposium on emerging concepts in Cancer, Trivandrum December 2008.
11. S Das and A Basu: “Japanese encephalitis virus infects neural progenitor cells and modulates their proliferative ability.” Society for Neuroscience Meeting, Washington DC, 15-19th November, 2008
12. M K Mishra and A Basu: “Neuroprotective effect of minocycline in Japanese Encephalitis.” Society for Neuroscience Meeting, Washington DC, 15-19th November, 2008

13. V. Rema: "Structure and function of somatosensory system." Cognitive Neuroscience IBRO workshop, NBRC, India, January 2009.
14. V. Rema: "Injury-induced plasticity in the barrel cortex of adult rats." Barrels XXI, Washington D.C. USA, November 2008.
15. Manisha Chugh, Ziauddin Darokhan, Rahul Chaudhary and V, Rema: "Ischemic injury of motor cortex affects spatial and temporal processing of somatosensory information." Wellcome Trust Senior Research Fellows meeting. October 2008.
16. Rahul Chaudhary, Praveen. K, Ziauddin Darokhan,V. Rema: "Bilateral effect on forelimb behaviour following unilateral lesions of forelimb cortex." Society for Neuroscience Annual meeting, November 2008.
17. Manisha Chugh, Ziauddin Darokhan, V. Rema: "Motor cortex lesions effects sensory behaviour of Gap cross task in rats." Society for Neuroscience Annual meeting November 2008.
18. Niranjana Kambi, Shashank Tandon and Neeraj Jain: "Extensive motor cortex plasticity following dorsal spinal cord injuries in adult rats." Neuroscience 2008, Annual Meeting of the Society for Neuroscience, Washington, DC, USA, November 15-19,2008.
19. Neeraj Jain: IBRO workshop Cognitive Neuroscience, NBRC, Manesar, January 5-16, 2009.
20. Iyengar S: "Auditory System" Presented at the Cognitive Neuroscience Workshop (organized by IBRO and NBRC) entitled The Making of Mind. NBRC, Manesar, January 5-16 2009.
21. NK Dhingra: "Retina: What it does, and what we can do." Cognitive Neuroscience workshop, NBRC, Manesar, January 5-16, 2009
22. Saha, S Baloni, V Jain, S Balakrishnan, NK Dhingra: "Morphological characterization of Brn3-expressing retinal ganglion cells." Asia-ARVO meeting, Hyderabad, January 15-18, 2009.
23. S Nagar, V Krishnamoorthy, P Cherukuri, V Jain, NK Dhingra: "Remodeling in retinal degeneration – More than meets the eye." Asia-ARVO meeting, Hyderabad, January 15-18, 2009.
24. Nandini C. Singh: "Development of articulatory features in children." Department of Speech and Hearing, University of Maryland, USA.
25. Nandini C. Singh: "Influence of native language reading networks on the second language – an fMRI study." Abstract, Society for Neuroscience, Washington, USA, November 2008.
26. Nandini C. Singh: "Signatures for reading proficiency," Abstract, Society for Neuroscience, Washington, USA, November 2008.

27. Prasun Roy: Chairman of Imaging Session, International Workshop on Epilepsy, All-India Institute of Medical sciences, New Delhi, Oct 2008.
28. Pravat K. Mandal: “Application of in Vivo Magnetic Resonance Spectroscopy for Alzheimer patients to understand early causal molecular process.” International Conference on 'Functional Materials: Controlled Synthesis, Discrete Molecular Processes and Engineering' IIT, Madras, Invited speaker, Nov. 27-29, 2008.

National Presentations:

1. Nihar Ranjan Jana: "Suppression of polyglutamine neurodegeneration by ubiquitin protein ligases." Society of Neurochemistry, India, Amritsar, 2008.
2. Nihar Ranjan Jana: "Protein aggregation in neurodegenerative diseases." Invited talk in the 3rd National Medical Students Research Conference, Gwalior, 2008.
3. V Ravindranath: "Therapeutics for Alzheimer's Disease: Current Trends and Future Prospects" at NEUROLINKS 2009 at New Delhi on February 15-16, 2009.
4. V Ravindranath: Plenary Lecture "Neurodegeneration and Brain Aging: Basic Science to Therapy" at NEUROCON 2009 Conference at IPGME&R, Kolkata held on 8th February, 2009.
5. V Ravindranath: "Disease Modifying Therapies for Neurodegenerative Disorders" at NIPER, Hyderabad seminar on organic Chemistry – Its importance in industries and health held on 3rd February, 2009.
6. V Ravindranath: "The future of MRI imaging Neuroscience" at "The Brain Storming Session on Future Directions of Biomedical Magnetic Resonance" at Centre of Biomedical Magnetic, Lucknow held on 23 and 24 December, 2008.
7. V Ravindranath: "Current research progress in understanding Alzheimer's disease and new hopes for treatment" at NSI CME program held on 17th December 2008 at Pune.
8. V Ravindranath: "P38 but not JNK is activated in substantia nigra neurons in Parkinson's disease" presented in XXVI Annual Conference of Indian Academy of Neurosciences at Cochin from December 12-14, 2008.
9. V Ravindranath: Plenary Lecture "Brain Research: Recent Advances in Development of Rationale Therapies and Cures for Brain Disorders" at An international symposium on "Recent Advances in Organic Chemistry at Andhra University, Visakhapatnam held on 12th December, 2008.
10. V Ravindranath: "Unraveling molecular pathways of pathogenesis of complex neurodegenerative disease by identifying cell-specific signaling in animal model in Parkinson's disease" at NCBS, Bangalore held from Oct 2 and 3, 2008.
11. V Ravindranath: Valedictory Speech of the National Workshop on "Trauma and Pain Management" at University of Hyderabad, Hyderabad held on August 04, 2008.
12. P. Seth: National Frontiers of Science Meeting, Indian National Science Academy, New Delhi, India, Jan 2009.

13. P. Seth: Annual Meeting of Indian Academy of Neurosciences at Cochin University, Cochin. December 2008.
14. P. Seth: Neuro Update 2008 Kolkata, Calcutta National Medical College Hospital and Indian Institute of Chemical Biology, Kolkata, India, September 2008.
15. P. Seth: Science Popularization Series Lecture, Organized by Haryana State Council for Science and Technology, Gurgaon, India, August 2008.
16. P. Seth: "Stem cells: Good, Bad and Ugly" at Haryana Government Girls College, Gurgaon for refresher's course for degree college teachers, May 2008.
17. Vivek Sharma, Richa Tewari. Nitin Koul, Deobrat Dixit, Sadashib Ghosh and Ellora Sen: "Re-evaluating the role of Ras in glioma therapeutics." International symposium on Molecular aspects of brain aging and neurological disorders and Annual meeting of Society for Neurochemistry, Amritsar, November 2008.
18. Deobrat Dixit, Vivek Sharma, Sadashib Ghosh, Nitin Koul, Prakash Kumar Mishra and Ellora Sen: "Manumycin inhibits STAT3, telomerase activity and growth of glioma cells by elevating intracellular reactive oxygen species generation." Indian academy of Neurosciences Cochin, December 2008.
19. Richa Tewari, Vivek Sharma, Nitin Koul and Ellora Sen: "Inducing GBM Cell Death through Lipid Raft Intervention." Indian academy of Neurosciences Cochin, December 2008.
20. Ellora Sen: "Interleukin-1 β induced HIF-1 α activity in glioma cells is modulated by RAS via NF κ B." Indian Academy of Cancer Research, Bangalore February 2009.
21. Ellora Sen: "Inflammation and Oncogenesis: Partners in crime." Sphaera Pharma Pvt.Ltd, 5th March 2009.
22. Shiv Kumar Sharma. "Amyloid beta-induced neuronal toxicity: protective effects of a flavonoid." Poster presentation in the Indian Academy of Neurosciences Conference, 2008.
23. A Basu: "Host pathogen interaction in Japanese Encephalitis Virus infection: from bench to bedside." Department of Physiology, University of Calcutta, 6th April, 2009
24. A Basu: "Japanese Encephalitis: from basic research to therapeutic intervention." IISC Centenary Conference and 10th Sir Dorabji Tata Symposium, Mechanisms of Microbial Pathogenesis, National Science Seminar Complex, IISC, Bangalore; 10-12th March, 2009
25. A Basu: "Neuropsychological sequelae in Japanese Encephalitis: Do Neural Stem cells play a role?" National FOS meeting, INSA, 21-22nd January, 2009.

26. M K Mishra and A Basu: "Unraveling the signaling cascades associated with astroglial response in Japanese Encephalitis." Indian Academy of Neuroscience, Cochin, December 2008.
27. M K Mishra and A Basu: "Microglial activation and innate immune response: Implication in the pathogenesis of Japanese Encephalitis." Indian Academy of Neuroscience, Cochin, December 2008.
28. M K Mishra and A Basu: "Neuroprotective Effect of Minocycline in Japanese Encephalitis." Annual meeting of Indian Academy of Neuroscience, Cochin, 11-14th December 2008
29. D Ghosh, M K Mishra, S Das, D K Kaushik and A Basu: "Tobacco carcinogen induces microglial activation and subsequent neuronal damage." Annual meeting of Indian Academy of Neuroscience, Cochin, 11-14th December 2008
30. A Basu: "Japanese encephalitis virus infects neural progenitor cells and modulates their proliferative ability." Annual Meeting of Society for Neurochemistry, Guru Nanak Dev University, Amritsar, 28-29th November, 2008.
31. A Basu: "Neuron- Glia Communication in Health and diseases." IIT-Delhi, 6th September, 2008.
32. A Basu: "Japanese Encephalitis: from basic research to therapeutic intervention." Premas Biotech, IMT Manesar, 1st July, 2008
33. A Basu: "Japanese Encephalitis: from Neuropathology to therapeutic intervention." School of life science, JNU. 5th June, 2008.
34. Murthy, Sharika, K.M., and S. Ray: "Attention for action during error correction." Centre for Behavioral and Cognitive Science, University of Allahabad, 2008.
35. Murthy, N. Bhutani, S. Ray, A. Farooqui: "Control of saccadic averaging during sequential eye movements." Society for Neuroscience Abstract (2008).
36. V. Rema: "Influence of focal injuries in the cerebral cortex on somatosensory functions." Indian Academy of Neuroscience, Cochin, India, December 2008.
37. V. Rema: "Information processing in the sensory cortex." Imaging Neurodegeneration- from molecules to systems, IIT Delhi, India, September 2008.
38. V. Rema: "Stem cell therapy following cortical injury." International Conference on Recent Developments in Stem Cell Research; Kannur, India, August 2008.
39. V. Rema: "Stroke-like injuries of motor cortex modifies somatosensory functions." Current Perspectives and future trends in psychology. Refresher course for college teacher of Haryana, Dept. of Psychology, Govt. College for Women, Rohtak, India, May 2008.

40. Praseeda Venugopalan, Rahul Chaudhary, V. Rema: "Investigating the potential of embryonic stem cells in enhancing recovery of neuronal function following cortical injury." Annual meeting of the Indian Academy of Neuroscience, Cochin, India, December 2008.
41. Ziauddin Darokhan, Manisha Chugh V Rema: "Cortical injuries reduce activity of output layer neurons adjacent to the lesion, however increase neuronal activity in the intact hemisphere opposite the lesion." Annual meeting of the Indian Academy of Neuroscience, Cochin, India, December 2008.
42. Rahul Chaudhary, K Praveen, Ziauddin Darokhan, V. Rema: "Extent and nature of recovery of forelimb behaviour after unilateral lesion cortical forelimb area." Annual meeting of the Indian Academy of Neuroscience, Cochin, India, December 2008.
43. Mohammed Hisham and Neeraj Jain: "Corticocortical connections of representation of the whiskers and adjacent regions of the rat motor cortex." 26th Annual Meeting, Indian Academy of Neurosciences, Cochin, India, December 12-14, 2008.
44. Neeraj Jain: "Spinal Cord Injury and Brain Plasticity." Trends in translational medicine, PGIMS, Rohtak, Haryana. January 9, 2009.
45. Iyengar S: "The role of the opioid system in singing and other behaviours in adult male zebra finches." Presented at a workshop entitled Functional Biology: Comparative Aspects which was a part of the Second Meeting of the Indian Subcontinent Branch of the International Peptide Society, organized by the Dept. of Zoology, University of Lucknow, March 19-21 2009.
46. Iyengar S: "Methods in Neuronal and Axonal Tracing" Presented at the workshop entitled Imaging Neurodegeneration: Molecules to mind. organized by IIT-Delhi, September 5-6 2008.
47. NK Dhingra, V Krishnamoorthy, V Jain, P Cherukuri, S Baloni: "In vivo labeling of mammalian cones with fluorophore-conjugated peanut agglutinin –A potential clinical tool to assess retinal degenerative diseases." International Conference on Nanomedicine & Recent Advances in Ophthalmic Research (Sankara Nethralaya, Chennai, Sep. 3-5, 2008). Abstract book, pp. 73.
48. D Poria, S Maiti, NK Dhingra: "Novel therapeutic strategies to restore vision." 5th Foundation day of NBRC. (Poster presented by DP and SM for high school students), December 16 2008.
49. Vinay Shukla, Prasun Roy: Multimodal tractographic approach to brain dynamics, Workshop on Integration of Physics and Mathematics to study Biological Systems, Bose Institute, Calcutta, Dec 2008.
50. Suhela Kapoor, VPS Rallabandi, Prasun Roy: Quantitative Analysis of the Role of Turbulence of Cerebrospinal Fluid: Therapeutic Modulation

of Neurogenesis for Cerebrovascular Disorders, International Conference on Nonlinear Dynamics, Indian Institute of Science, Bangalore. July 2008.

51. Ashish Upadhyay, Prasun Roy: Nonlinear Dynamics-based Activation of MRI signal for Estimating Microvascular Turbulence of Blood Flow, International Conference on Nonlinear Dynamics, Indian Institute of Science, Bangalore. July 2008.
52. Prasun Roy: Planning of MRI, SPECT and PET Imaging Protocols for Dementia screening, Workshop on Ageing and Cognition, Institute of Neurological Sciences, Chennai, Feb. 2009.



DISTINCTIONS, HONOURS AND AWARDS

Dr. Shyamala Mani

Knight of the Order of the Academic Palms (Chevalier des Palmes Académiques)

Dr. Ellora Sen

1. Nominated as EC member of “NeuroOncology Society of India” (2008).
2. Nominated as a member ‘American Association of Cancer Research’ (2008).

Dr. V. Rema

Review Editor for Journal “Frontiers in Neuroscience.”

Dr. Prasun Kumar Roy

1. Editorial Board, International Journal of Artificial Intelligence and Soft Computing.
2. Board of Reviewers, Annals of Bio-Medical Engineering.
3. Member, Expert Committee on Neuroimaging Procurement, All-India Institute of Speech and Hearing, Mysore.
4. Expert Member, Review Panel, Indo-US Science & Technology Forum, New Delhi.

Students Awards

1. **Subhadip Paul:** International scholarship award, Utrecht University Research Foundation, The Netherlands, Jan 2009.
2. **VP Subramanyam Rallabandi:** International scholarship award, Royal Philips Electronics/Utrecht University Research Foundation, The Netherlands, Oct 2008.
3. **Suhela Kapoor:** Student Fellowship Award, School on Computational Statistical Physics, Indian Institute of Technology, Guwahati, Dec. 2008.
4. **Vinay Shukla:** Selected workshop participant, School on Computational Neuroscience, University of Delhi, Delhi, Dec 2008.
5. **Ashish Upadhyay:** Trainee Fellowship Award, Nonlinear Dynamics Workshop, Indian Institute of Science, Bangalore, July 2008.
6. **Suhela Kapoor:** Trainee Fellowship Award, Nonlinear Dynamics Workshop, Indian Institute of Science, Bangalore, July 2008.



**EXTERNALLY FUNDED RESEARCH
PROJECTS**

Dr. Nihar Ranjan Jana

Understanding the Function of the Angelman Mental Retardation Syndrome Ubiquitin Ligase, UBE3A/E6-AP. (DBT, India)

Dr. Shyamala Mani

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

Dr. Vijayalakshmi Ravindranath

Cytochromes P450 Dependent Metabolism of Drugs in Brain. (NIH-RO1, USA)

Dr. Pankaj Seth

Cellular and Molecular Mechanisms of HIV-1 Neuropathogenesis. (DBT, India)

Dr. Ellora Sen

Understanding aberrant transcriptional circuitries and signaling cascades in Glioblastoma multiforme. (DBT and DRDO, India)

Signaling cascades regulating the differentiation of glial progenitors along specific lineages. (DBT, India)

Dr. Shiv Kumar Sharma

Molecular Mechanisms of Synaptic Plasticity and Memory: Activity-Dependent Protein Acetylation. (DBT, India)

Dr. Anirban Basu

Molecular approaches to understand the pathophysiology and pharmacology of infection and inflammatory disorders of Central Nervous System. (DBT and CSIR, India)

Dr. Ranjit Kumar Giri

Development of A Novel in vitro Model of Alzheimer's Disease Employing Neurosphere Culture from TgAPPswePS1 Δ E9 mouse. (Ramalingaswami Fellowship, DBT, India)

Dr. Aditya Murhty

Brain Mechanisms of Action Control in Humans. (DBT, India)

Neural Control of Action by Frontal /Basal Ganglia Networks. (DBT, India)

Dr. V. Rema

Processing and Integration of Somatosensory Information in Normal and Impaired Brains. (Welcome Trust, UK and DBT, India)

Dr. Neeraj Jain

Brain Reorganization Following Spinal Cord Injuries. (Welcome trust, UK, DRDO and DBT, India)

Dr. Soumya Iyengar

Emergence of Primary and Non-Primary Auditory Cortical Areas during Late Foetal and Early Postnatal Ages in Humans. (DBT, India)

Neurogenesis in the Song Control System of Zebra Finches. (DBT, India)

Dr. Narender Kumar Dhingra

Replacement of Degenerating Retinal Neurons by Retinal Prostheses or Stem Cells - A Study on Retinal Circuitry and Information Processing. (DBT, India)

Dr. Nandini Chatterjee Singh

A Computational Cnalysis of Speech Motor Skills in Typically Developing Children and those with Autism Spectrum Disorder (ASD). (Ministry of Communication and Information Technology and DBT, India).

Dr. Pravat K. Mandal

Characterization of Molecular Interactions of Anesthetics with beta amyloid. (Italian Ministry for University and Research Program)

Dr. Prasun Kumar Roy

Application of Stochastic Activation and Stability Analysis for Brain Imaging and Therapy. (DRDO, India)

Spatiotemporal Neural Processing and Transmission (Ministry of Education & Research, Italian Govt. under a program of the European Commission.

High-field experimental neuroimaging methodology development (Utrecht University Foundation and Philips Research, for support for research projects of students).



CORE FACILITIES

Distributed Information Centre (DIC)

The Distributed Information Centre (DIC) of the National Brain Research Centre manages computing infrastructure and provides campus-wide IT services to the research community. It provides an integrated digital environment for researchers and facilitates e-service.

Infrastructure:

Central IT infrastructure and services provided by DIC are listed as under :

- Campus wide LAN over gigabit fiber backbone with wi-fi hotspots for students and faculty.
- Dedicated lease line connectivity (4 Mbps 1:1 with additional 1 Mbps RF backup for redundancy operations) secured by Nokia-checkpoint firewall cluster.
- Centralized data storage (NAS) to the tune of 11 TB with inbuilt antivirus scanning and online tape archiving facility.
- State-of-the-art video-conferencing facility for collaborating research and teaching.
- Core servers host NBRC (<http://webmail.nbrc.ac.in>), dns/dhcp, and application services in linux, solaris and windows platforms. In addition, third party websites (<http://www.nbrc.ac.in>,<http://neuroscienceacademy.org.in>, <http://snci.nbrc.res.in>) are also hosted on NBRC servers.
- DIC also provides support and undertakes in-house development of softwares, web-tools and web servers for aiding in the research and teaching activities of the centre.

Research Support:

DIC personnel have started to help in paradigm design and data analysis for functional neuroimaging experiments. The computing facilities at the fMRI centre have been integrated into the existing network and new software and machines have been procured to handle increased data processing and storage. DIC personnel continue to aid the development of newer and faster computational techniques for faster and efficient analysis of neural data

New Initiatives:

High performance-computing (HPC) cluster for efficient data analysis in functional MRI experiments are being initiated. Implementing Disaster recovery to protect important aspect of computing hardware and critical research data is already underway. DIC is also working on server virtualization and consolidation of critical server using vmware infrastructure products (like ESX server, vmware server and workstations)

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 by providing for the animals daily care needs. A high degree of hygienic conditions are maintained in the animal house by practicing regular cleaning and sterilization of cages, water bottles, bedding and feed and regular disinfection of rooms. Heavy-duty steam autoclaves have been provided for sterilization of cages, water bottles, bedding and feed and hot vapour jet machine for cleaning rabbit and monkey cages. Animal house staff also takes shower and changes clothing before entering the animal rooms and wear facemasks and gloves before handling animals.

All animal species are housed in cages, which are designed as per the CPCSEA guidelines. The outdoor play area for non-human primates has six large interconnected enclosures that provide a flexible layout for optimising enrichment and social interactions. The transgenic, knock out and mutant mice are housed under strict sterile conditions in filter top cages and individually ventilated cage system (IVC) and all animal manipulations too are done in laminar hoods and cages are changed in cage changing station under hepa filtered air.

The animals are maintained under controlled environmental conditions as specified in 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 veterinarians oversee all animal health concerns and provide all necessary veterinary care to ensure that healthy animals are available for research.

The animal facility has a state of art surgical suite equipped with gas anaesthesia machine, variety of monitoring equipment like heart rate monitor, pulse oximeter and rectal 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.

Besides this there is a necropsy room, perfusion room with a perfusion hood, deep freezer for carcass storage and incinerator for disposal of animal carcass.

The animal facility has been equipped with a card reader security system and access cards are issued only to animal house staff, maintenance staff and to investigators who are listed in IAEC approved protocols. Also before

the access card is issued it is ensured that all personnel who handle animals have a current tetanus vaccination and those who handle non human primates get themselves screened for tuberculosis and are aware of the initial first aid to be provided in case of animal bite or scratch. Cameras have also been installed at various locations in the facility, which help in effective monitoring of routine cleaning in the animal facility.

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

Mice Strains

SWISS, BALB/c, C57BL/6J, CD1

Transgenic Mice

B6C3-Tg(APP695)85DboTg(PSEN1)85Dbo (Alzheimer disease model)

UBC-GFP (Green fluorescent protein)

B6CBA-Tg(Hdaxon1)62Gpb/3J (Huntington disease model)

B6.Cg-Mapttm1(EGFP)KltTg(MAPT)8cPdav/J (Alzheimer disease model)

B6.129P2-Gsk3btm1Dgen/J (Alzheimer disease model)

Knock Out Mice

GAP-43 knock out mice,

UBE3A null mice (Angelman syndrome model)

Mutant Mice

CBA/J mice (Retinal degeneration model)

Rat Strains

Long Evans

Sprague Dawley

Rabbits

New Zealand white

Guinea Pigs

Duncan Hartley

Non-human primates

Macaca mulata

Macaca radiata

Birds

Zebra finches

All the mice strains are maintained by inbreeding and both rat strains by outbreeding. Guinea pig and zebra finch colonies are maintained 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.

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 and is also providing the facilities and support to the Scientists, researchers, students, staffs 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 530 journals (including free journals and complimentary journals) among of them 448 are online and others are in the printed hard copy formats. Library is also subscribing newspapers, news letters. The collection of NBRC library is growing day-by-day in the view of research and knowledge in the field of neuroscience and related areas. These resources were kept to fully meet the present day requirements of the users such as faculty, research scholars, students and staffs.

To provide optimum service to all users we are digitizing the list of collections available at NBRC and giving full access to the users. We are using the LSEASE software for the digitization of collections. The NBRC library has installed a barcode technology through LSEASE software for accurate and speedy circulation (check-in and check-out) and household management of the library documents. It also helps in efficient library operations viz. administration, acquisition, circulation, serial control, cataloguing, information retrieval etc.

The NBRC library has setup 22 IBM PC-Pentium-IV Computers with ISDN Internet facility to provide services for use of researchers and students at NBRC in the NBRC Common room. 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 258 registered users including Scientist, Researchers, students and other staff used the NBRC library facilities. The NBRC library also provides the services of “Inter Library Loan” to the 48 networked centres all over India. The researchers, scientists and students send their requirement for research material or journal articles through email to NBRC library (library@nbc.ac.in) and staff of library download the articles / papers / information and send the same to the requestors free of cost. The library is entertaining an average of approximately 420 articles every year and the requests are increasing day-by-day.

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

The Main Activities of NBRC Library

1. Book Acquisition
2. Periodicals Acquisition
3. Selective Dissemination of 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.

A Separate two storied library building is already under construction, which will have the provision for reading room, reference room, video conferencing, online journal access facility, book section, Internet access facility, reprographic facilities etc. The main aim of 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. The NBRC library is presently, well equipped with every type of resources required by the faculty, researchers and students.

DBT Electronic Library Consortium (DeLCON)

Introduction about DeLCON

The Department of Biotechnology (DBT), Ministry of Science and Technology, Government of India has launched its DBT e-Library Consortium called as "DeLCON" since January 2009 to promote the use of electronic databases and full text access to large number of high impact journals by the research and academic community in the country. Currently, the Consortium comprises of 8 DBT Institutions, DBT (HQ) and ICGEB.

DeLCON comprises the following ten research centres:

- National Brain Research Centre (NBRC), Manesar
- Department of Biotechnology (DBT), New Delhi
- National Institute of Plant Genome Research (NIPGR), New Delhi
- National Institute of Immunology (NII)-New Delhi
- National Centre for Cell Science (NCCS) - Pune
- Institute of Life Sciences (ILS) - Bhubaneswar
- Institute of Bioresources and Sustainable Development (ISBD) - Imphal
- Centre for DNA Fingerprinting and Diagnostics (CDFD) - Hyderabad
- Rajiv Gandhi Centre for Biotechnology (RGCB) - Thiruvananthapuram
- International Centre for Genetic Engineering Biotechnology (ICGEB), New Delhi

Objectives of DeLCON

- To promote better, faster and more cost-effective ways of providing information resources to the officials at the consortia member institutions.
- To avoid duplication of subscription of journals and e-resources and promote the rational use of funds by the consortia members.
- To ensure continuous subscription of e-resources and availability of these to the scientists working at the consortia member institutions.
- Better rates and terms for purchase of electronic journals
- Availability of a larger spectrum of journals to the DBT Institutions with lesser costs.

Scope and Goal of DeLCON

- To strengthen library resources and services and co-operation and communication amongst the member libraries.
- To strengthen the pooling, sharing and electronically accessing the library resources.

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- To provide access to worldwide literature to users.
- To nucleate the culture of electronic access resulting into evolution of digital libraries.
- Efficient interlibrary loan system between the member institutions.

Subject coverage of 'DeLCON'

The DeLCON covers all the disciplines and subjects coming under Life Sciences i.e. Biotechnology, Bioinformatics, Biology, Sciences, Immunology, Neuroscience, Plant Genome, Microbiology, Physiology, Physiotherapy, Psychology, Genome, Gene, DNA, etc.

How does DeLCON operate?

The DBT Institutions and other participating institutions will be connected through DeLCON network connectivity. Individual Institutions will then have unique IP address through which access is given by the publishers for which subscriptions made. However entire programme will be administered, monitored and maintained by DeLCON Nodal Centre (NBRC).

Journals Coverage under DeLCON

At present the DeLCON subscribes to 899 full-text e-resources of 16 publishers listed below. The member institutions are provided full access to these resources.

Electronic Resources Subscribed by the DeLCON

These e-resources are accessible to the DeLCON member institutions only. The complete list alongwith their URL is given below:

1	Am. Assoc. for Adv. of Science	http://www.sciencemag.org	(1 Jn.)
2	Am.Association for Cancer Res.	http://www.aacr.org	(8 Jns.)
3	American Chemical Society (ACS)	http://pubs.acs.org	(37 Jns.)
4	Annual Reviews	http://www.annualreviews.org	(23 Jns.)
5	Am. Soc. for Biochem. Mol. Biol.	http://www.jbc.org	(1 Jn.)
6	Cold Spring Harbor Lab. Press	http://www.cshl.edu	(4 Jns.)
7	Informa Healthcare	http://www.informaworld.com	(7 Jns.)
8	Lippincott William & Wilkins	http://ovidsp.ovid.com	(11 Jns.)
9	Marry ANN Liebert	http://www.liebertonline.com	(7 Jns.)
10	Nature Publications	http://www.nature.com	(40 Jns.)
11	Oxford University Press (OUP)	http://www.oxfordjournals.org	(18 Jns.)

12	Springer India	http://www.springerlink.com	(237 Jns.)
13	Society for General Microbiology	http://mic.sgmjournals.org	(3 Jns.)
14	Society for Hematology	http://bloodjournals.hematologylibrary.org	(1 Jn.)
15	Wiley-Blackwell	http://www3.interscience.wiley.com/cgi-bin/home	(86 Jns.)
16	Elsevier Science (ScienceDirect)	http://www.sciencedirect.com	(415 Jns.)

Who gets benefit of DeLCON?

The faculties, scientist, research scholars, students and project assistants of Institutions covered under DBT are the primary beneficiaries.

E-subscription under DeLCON

DBT sponsored the entire expenses for DBT organizations for providing e-Journals access through 'DeLCON'. The list of journals covered in the scheme is updated from time-to-time and is available on the DeLCON website currently at <http://www.nbrc.ac.in/delcon>.

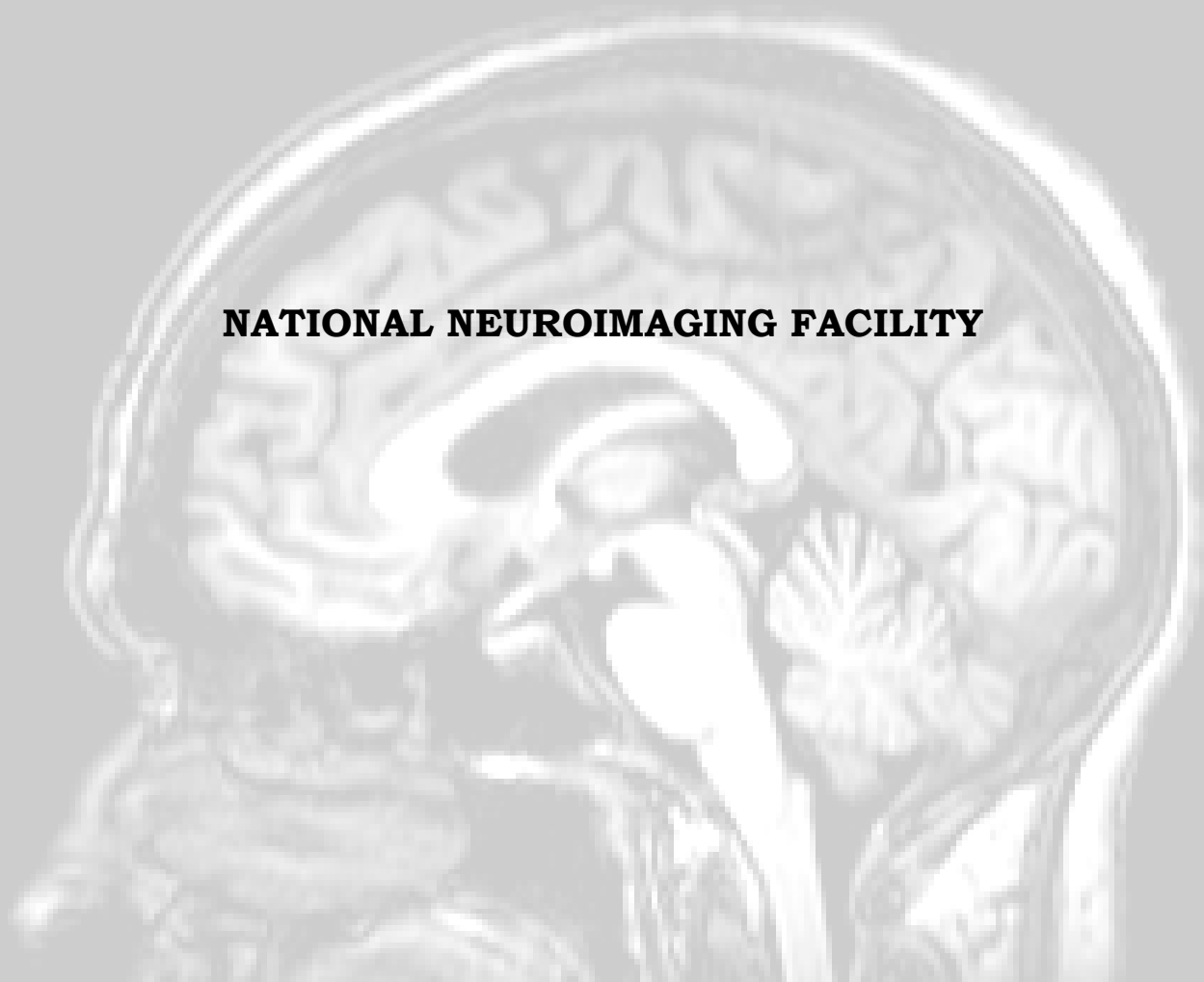
How long DeLCON subscription would last?

Initially the resources subscribed under the DeLCON subscription would be available for three years (i.e. upto 2011) and will be reviewed after three years for its effectiveness and after that it could be extended further.

How to get the full text access of subscribed journals under DeLCON?

Full text access to journals can be had either directly visiting the publisher site or through the bibliographic databases. Many of the bibliographic databases will have facility to browse the publications or search as per your query. Journals can be accessed by publishers wise and as well as alphabetic orders also.

For more information you may contact 'DeLCON Administrator' by writing an email or letter.



NATIONAL NEUROIMAGING FACILITY

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National Neuroimaging Facility

National neuroimaging facility was established by Department of Biotechnology, Govt. of India in the year 2006. The facility is equipped with four state-of-the-art equipments such as,

- 1) Electroencephalography (EEG)
- 2) Evoked Response Potential Recording (ERP)
- 3) Transcranial Magnetic Stimulation (TMS)
- 4) Magnetic Resonance Imaging (MRI)

Electroencephalography (EEG) is a test that measures and records the electrical activity of the brain. Special sensors are attached to the head and hooked by wires to a computer. The computer records brain's electrical activity on the screen or on paper as wavy lines. Certain conditions, such as epilepsy, dementia, and sleep disorders can be studied by EEG.

Evoked Response Potential Recording (ERP) is an electrical potential recorded from the nervous system of a human or other animal following presentation of a stimulus. Evoked potential amplitudes tend to be low, ranging from less than a microvolt to several microvolts.

Transcranial magnetic stimulation (TMS) is a non-invasive method to excite neurons in the brain: weak electric currents are induced in the tissue by rapidly changing magnetic fields (electromagnetic induction). This way, brain activity can be triggered with minimal discomfort, and the functionality of the circuitry and connectivity of the brain can be studied. Its earliest application was in the demonstration of conduction of nerve impulses from the motor cortex to the spinal cord. By stimulating different points of the cerebral cortex and recording responses, e.g., from muscles, one may obtain maps of functional brain areas. By measuring functional imaging (e.g. MRI) or EEG, information may be obtained about the cortex (its reaction to TMS) and about area-to-area connections.

Magnetic Resonance Imaging (MRI) is yet another major and distinct milestone in the history of neuroimaging. MRI provides much greater contrast between the different soft tissues of the body than computed tomography (CT), making it especially useful in neurological (brain), musculoskeletal, cardiovascular, and oncological (cancer) imaging. Scope of MRI extends beyond structural imaging to various imaging modalities as:

- (1) Functional MRI (fMRI) which, as the name suggests correlates functional (haemodynamics) activity with images of brain activation
- (2) MR Spectroscopy (MRS), which provides non-invasive neurochemical level estimations and enables clinical correlation.
- (3) Diffusion weighted tensor imaging (DTI) is yet another specialized imaging modality.

The 3 Tesla Philips whole body MRI machine, is housed in the MRI unit of NBRC as a national Facility. This 3T Philips scanner is equipped with state-of-the-art data processing software, as well as hardware required for each imaging modality. The facility is being used for performing structural, metabolic (multinuclear, e.g. proton and phosphorous) and functional MRI. In addition to understanding brain function and clinical research, the center also is closely interacting with leading imaging centers across the globe to advance the technology development and clinical application.

The Neuroimaging and Neurospectroscopy laboratory at NBRC is working on metabolic analysis of different neurodegenerative disorders (e.g. Alzheimer, Parkinson etc) using MRS technique. The clinical research is focused to identify biomarkers of disease, and this is accomplished by the understanding of specific and selective neurochemical changes for the different neurodegenerative disorders. Figure 1 shows ^{31}P MRS spectra of the cortex region of a normal control subject for different neurochemical containing phosphorous atom.

^{31}P MRS spectra of hippocampus region of normal volunteer (Male, 32 years old)

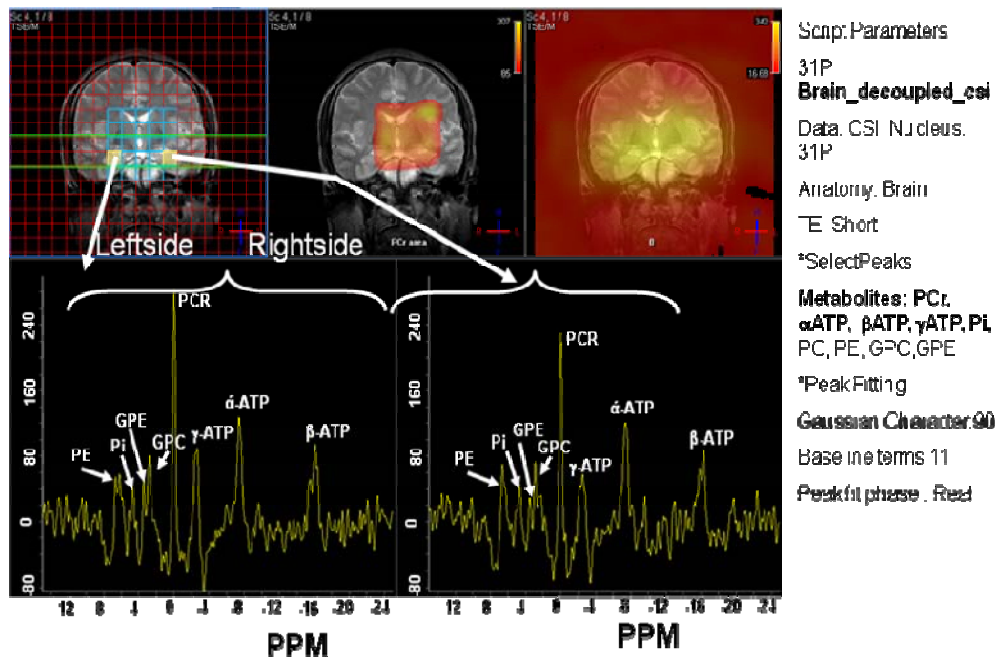


Figure 1 ^{31}P MRS data collected using ^1H decoupled dual tuned head coil (Transmit and Receive). This experiment was specifically designed to obtain spectra from hippocampus both left and right marked by yellow color. The dimension of the each voxel was 13.3 mm X 13.3 mm X 25 mm and number of scans were 24. Data Acquisition time was ~25 minutes. MRS data was processed using Philips software.

The Speech and Language Laboratory (SALLY) at NBRC is interested in studying the cortical pathways underlying reading. Researchers from SALLY laboratory are currently focused on studying word reading in Hindi-English

bilinguals. The figure 2 shows the different brain areas involved in reading words aloud in Hindi.

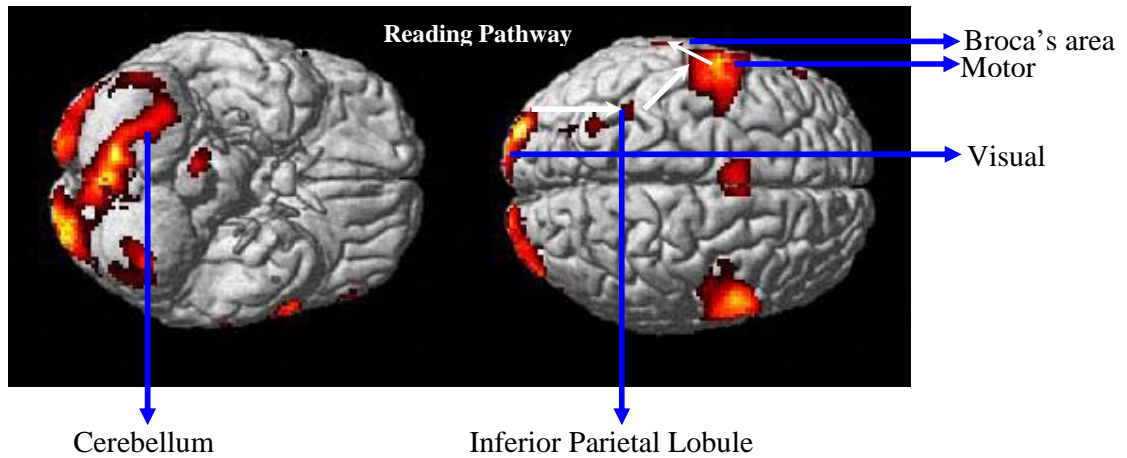


Figure 2. The left rendering depicts a ventral view while the right rendering depicts a dorsal view of the brain. Different brain areas involved in reading have been shown

The Computational Neuroscience and Neuroimaging Laboratory works on diagnostic and therapeutic applications with a translational medicine aspect. The unit works on imaging-based diagnosis of neurodegenerative disease and pulsed radiotherapy and chemotherapy planning for brain tumour. In collaboration with clinical centres and medical institutes, the lab also pursues delineation of flow dynamics of blood, CSF and progenitor cells in brain, as well as localization of electrogenic focus in refractory epilepsy using EEG, ERP, fMRI, MRS and DTI (diffusion tensor imaging) (figure 3).

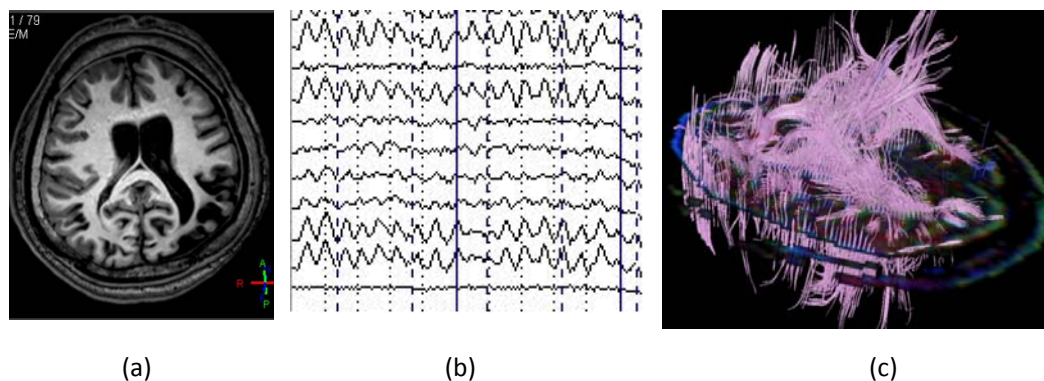


Figure 3 (a) Structural MRI scan of brain with dysplasia in epileptic patient. **(b)** EEG recording of the brain using which enables one to obtain more accurate localization of the electrical foci **(c)** Diffusion tensor image (DTI) of the brain of epileptic patient from which the conductivity tensor image (CTI) of the brain is obtained, the latter image enables accurate localization of the electrogenic epileptic focus in brain tissue, based on the conductivity image obtained earlier.

At the imaging facility, Prof Partha Raghunathan is the Consultant Professor while Mr Ashish Upadhyay and Mr Jitender Ahlawat are MRI Operation staff

**TRANSLATIONAL RESEARCH:
CLINICAL UNIT**



Translational Research

Translational research aims to connect basic research to patient care-‘from lab bench to bedside’. The Clinical Research Unit of NBRC has a tri-weekly, morning outpatient facility, at the Government Civil Hospital, Gurgaon. Till 30th June 2009, 899 newly registered patients and 1,221 review cases have received neurological attention at this out patient (OP). About 65% to 70% of the patients suffer from headache or seizure disorder, 5% have neuroses/psychoses and the remaining belong to a miscellany group of peripheral neuropathies, Bell’s palsy, sciatica, trigeminal neuralgia, old stroke, mental retardation and other common neurological disorders.

The follow up by the patients is about 90%. Male to female ratio is almost equal. Paediatric group patient attendance is mainly for management of seizure disorder of the mentally challenged. There are very few elderly patients attending, partly due to poor transport facilities, but more due to lack of awareness. Patients attending the OPD at Civil Hospital come from old Gurgaon township and the villages and towns in the surrounding districts of Haryana, while some come from neighbouring states.

Routine blood tests, X-ray, and ECG are available at Civil Hospital, Gurgaon at affordable rates. MRI brain/spine is also an available service. CT scan and EEG at moderate concession rates have been made available with private labs near Civil Hospital. Patients requiring specialist neurology in-patient care are referred to Safdarjang Hospital or AIIMS, New Delhi or rarely, to a hospital of their choice.

The NBRC Clinical Research Unit has integrated well with the Civil hospital medical team and there is an increasing number of referrals from other in-house departments and local hospitals. As part of the major plans for renovation of Civil Hospital, the Neurology OP rooms will be refurbished and three rooms will be allotted for NBRC in the outpatient area, which can accommodate other members of our team when they join.

Outpatient case records in neurology are maintained from the outset, aside from relevant entry into the patient OP case sheets, which the patients keep in their possession. A comprehensive Neurology case sheet has been formulated and formatted by DIC of NBRC. With the appointment of an Assistant Medical Officer, we hope to prospectively enter all the medical data of new patients, to create computer database with relevant patient data along with any planned neuroimaging/molecular studies at the NBRC labs, thus creating a well documented ‘clinical window’ for our research institute. In this effort to narrow the gap between Basic Neuroscience and Clinical Neurology, an ethics committee protocol has been formulated and the scientific question will focus on a single neurological disorder, to start with – probably epilepsy seizure disorder, the commonest neurological condition in India.

An informal tie up with HelpAge India, Delhi chapter from November 2008 has resulted in the NBRC Consultant joining the HelpAge medical team weekly/bimonthly on their outreach programmes to specific locations in old Gurgaon town and the surrounding hinterland. This interaction promises to grow to the mutual benefit of both institutions concerned primarily with the common goal of elder care in its varied aspects. Besides medical and neurological health conditions, one is exposed to the psychosocial and public health problems of the ageing populace in their home environment. NBRC has been able to generate significant data for a poster presentation at the 1st TS Srinivasan Neuroscience forum held at Delhi on 15th Feb, 2009, based on Quality of Life in the elderly population. (WHO QoL-BREF)-I

The association of NBRC with ARDSI, Delhi Chapter, which was established 5 years ago, continues. The NBRC neurologist gave a talk on the 'Caregiving aspects of Alzheimer's disease' under the ARDSI auspices at Delhi, in Sept. 2008, which was well received. After this event, a number of patients with AD caregivers, based in Gurgaon, requested house visits for the severe and the bed-bound patients. The 'bedside end of the NBRC Translational Research Unit has been initiated and established.

Dr. Subbulakshmy Natarajan runs the Civil Hospital Neurology OPD and is the Clinical Neurology Research Consultant, Translation Research Unit, NBRC.

A photograph of a large audience seated in a conference hall. The audience is diverse in age and appearance, and they are all looking towards the front of the room. The room has dark wood paneling and a balcony level above the main seating area. The text "MEETINGS & WORKSHOPS" is overlaid in the center of the image in a bold, black, sans-serif font.

MEETINGS & WORKSHOPS

Cognitive Neuroscience Workshop 2009

In recognition of the rapid growth of the Indian neuroscience community, and the concomitant need to establish and reinforce international connections, the National Brain Research Centre conducted an intensive two-week workshop on cognitive neuroscience research, concepts, and techniques in Manesar, India, during January of 2009 (January 5-16, 2009). The workshop was held on the campus of the National Brain Research Center (NBRC). The purpose of the workshop was two-fold. First, cognitive neuroscience in India is at a critical point in its evolution and NBRC in conjunction with Indian and international neuroscientists wished to offer its collective expertise to aid in the training of Indian students. Second, the workshop would serve as an outstanding mechanism to facilitate scientific interchange between India and North America.

The workshop was directed by Professor Vijayalakshmi Ravindranath, Director of the NBRC in collaboration with Dr. Thomas Albright (Professor of the Salk Institute, USA) and Dr. Aditya Murthy of the NBRC. The workshop accommodated about 35 students who were recruited from various universities throughout India. These students were chosen from a variety of fields ranging from psychology to engineering and medicine, keeping in mind the interdisciplinary nature of modern neuroscience research. This workshop was also unique in that efforts were made to draw students pursuing their bachelors, masters and Ph.D degrees. The workshop faculty was composed of approximately 30 distinguished neuroscientists drawn, from NBRC various universities and research institutes in India and abroad.

The faculties were chosen based on expertise in targeted areas of cognitive neuroscience and on their interest and commitment to achieving the stated purposes of the workshop. The workshop itself had three basic educational components: lectures, lab practicum, and discussion groups. These components were interleaved with other group activities that were largely social in nature and intended to promote discussion and informal interactions between students and faculty. At the close of the workshop, all students were asked to complete a workshop evaluation form, which assessed the quality and effectiveness of (1) each of the educational components of the workshop, and (2) the workshop faculty, and (3) the workshop administration. Based on the feedback received it appears that the workshop was an astounding success. NBRC hopes that such workshops would become a regular part of its activities contributing to the growth of neuroscience research in the country.



**INTERNATIONAL COLLABORATIONS &
NETWORKING**

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

NIH-RO1 grant has been awarded to Dr. Pankaj Seth in collaboration with Prof. A.Nath of the Johns Hopkins University. This NIH-RO1 grant proposes to study the “Role of CNS opportunistic infections in subsequent development of HIV dementia”.

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

The Italian Ministry for University and Research funded a project to Dr.Pravat K.Mandal, NBRC in collaboration with Prof.Vincenzo Fodale of University of Messina, Italy to study “Characterization of the molecular interactions of anesthetics with the beta-amyloid”.

The Ministry of Education & Research, Italian Govt. under program of European Commission, has funded a project for collaboration between Prof Prasun Roy and Prof. Patrizia Baraldi, University of Modena & Reggio Emilia, for functional and tensorial neuroimaging approach to cortical information transmission (training project).

The Netherlands

A project of high field neuroimaging methodology development, for collaboration between Prof Prasun Roy and Prof. Peter Luijten, Utrecht Medical Centre, has been sponsored by The Utrecht University Foundation & Philips Research (research projects of students).

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. Nizam's 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.
48. Vision Research Foundation, Chennai



INVITED LECTURES

Invited Lectures

Sr. No.	Name of the Speaker	Title of the Lecture	Date
1.	Dr. Vijayaraghavan Rangachari Dept of Neuroscience, Mayo Clinic College of Medicine Jacksonville, FL-32224	Amyloid β -peptides in Alzheimer's Disease: Interfacial Aggregation and Rational Design of Anti-amyloid Agents	April 10 th 08
2.	Mr. Suryadeep Dash University of Teubingen, Germany	The role of cerebellar complex spikes in motor learning	April 17 th 08
3.	Dr. Sheeba Vasu D310, Medical Sciences 1, University of California, Irvine, CA	Of Clocks and Flies - Investigating the Neural Circuit That Regulates Circadian Rhythms in Drosophila	April 23 rd 08
4.	Dr. N.B. Siddappa Post Doctoral Fellow, Dana- Farber Cancer Institute, Harvard Medical School	Microglial adapted novel SHIV model to study HIV associated neuropathogenesis	April 25 th 08
5.	Dr. Ritu Kulshreshtha Postdoctoral Research Fellow, Dana Farber Cancer Inst., Harvard Medical School, Boston, MA, USA	Hypoxic Regulation of microRNAs: Implications for Cancer Biology	May 14 th 08
6.	Dr. Gaiti Hasan NCBS, Bangalore	Invertebrate odor detection - new paradigms in sensory transduction	May 22 nd 08
7.	Prof. Avindra Nath Director of Neuroimmunology and Neurological Infections, Department of Neurology, Johns Hopkins University, USA	Neurodegeneration in HIV dementia and drug abuse	May 28 th 08
8.	Dr. Vikas Goel Research Associate Molecular Oncology Research Institute, Tufts-New England Medical center	Modelling human melanoma: the V6t00E mouse	June 24 th 08
9.	Dr. Angela M. Kaindl Laboratoire de Neurologie du Développement, UMR 676 , Inserm, PARIS	Somatostatin receptor 2A function in the brain	July 17 th 08
10.	Dr. Niloy Choudhury Oregon Health University	Measurement of volumetric blood flow using FD-OCT	July 21 st 08

11.	Dr. Vatsala Thirumalai Cold Spring Harbor Laboratory, Cold Spring Harbor, New York	The Net Inside the Fish: Development of Neural Networks Controlling Locomotion in Zebrafish	Aug 5th 08
12.	Dr. Madhavi Rangaswamy Assitant Professor, Henri Begleiter Neurodynamics Laboratory, Dept. of Psychiatry and Behavioral Science, Downstate Medical Center, State University of New York	Brain oscillations underlying cognitive operations and their utility in psychiatric research	Aug 6 th 08
13.	Dr. Yoganasimha Doreswamy Dept. of Neurobiology & Anatomy, University of Texas Medical School at Houston, Houston, TX 77225	Neural Network Mechanisms For Spatial Learning And Navigation	Aug 21 st 08
14.	Prof. Rakesh Kumar Dept. of Molecular and Cellular Oncology, MD Anderson Cancer Centre, University of Texas USA	MTA family of Master Coregulators in Biology	Aug 29 th 08
15.	Dr. Shubha Tole Tata Institute Of Fundamental Research, Mumbai	Building the nervous system: signals from the edge in the middle of the brain	Sept 11 th 08
16.	Dr. Ahalya Viswanathan Graduate Student (Ralph Freeman's lab), UC-Berkeley	Neurometabolic coupling is not uniform in cerebral cortex	Sept 15 th 08
17.	Dr. Karan Aggarwal SUNY, New York	Chromatic Cues for Visual Accommodation	Sept 18th 08
18.	Dr. Siddharath Ramakrishnan UCLA, Los Angeles, California USA	Exploring the Gonadotropin Releasing hormone neuroendocrine circuit: Development, Disruption and Behavioral Connections	Oct 20 th 08
19.	Prof. Anirvan Ghosh Professor, Chair, Neurobiology Section, Director, Neurosciences Graduate Program, University of California San Diego, La Jolla, CA 92093-0366	On the emergence of synaptic specificity in developing neural circuits	Nov 18 th 08
20.	Dr. Sovan Sarkar Research Associate, Cambridge Institute for Medical Research, University of Cambridge	Small molecule enhancers of autophagy for neurodegenerative disorders	Dec 1 st 08

21.	Dr. Kumar Sambamurti Associate Professor, Neuroscience Institute, Medical University of South Carolina	Alzheimer's disease and Retinal degeneration: Is there a common pathway?	Dec 2 nd 08
22.	Prof. Inder Verma Salk Institute		Dec 9 th 08
23.	Prof. Smita Deshpande Head, Department of Psychiatry, Ram Manohar Lohia Hospital, New Delhi	Psychiatric disorder in particular to Schizophrenia	Dec 11 th 09
24.	Dr. Ranu Jung Co-Director, Center for Adaptive Neural Systems, Associate Professor of Bioengineering and Electrical Engineering, Arizona State University	Promoting Plasticity	Dec 18 th 08
25.	Dr. Suresh Tyagi University of Louisville	Homocysteine an Excitatory Neurotransmitter Contributes to Alzheimer's disease	Dec 22 nd 08
26.	Dr. Deepak Kumar Saini Dept. of Anesthesiology, Washington University School of Medicine, St. Louis, USA	Spatio & Temporal Dynamics of G Protein Signaling in Living Cells : From Outside to Inside	Jan 14 th 09
27.	Prof. R. K. Padhi Control Systems Division, Indian Institute of Science, Bangalore	Automated Therapy Systems using Neural Network based Adaptive Control Analysis	Jan 15 th 09
28.	Dr. Kamala Dutt Morehouse School of Medicine, Atlanta, Georgia.	Human Ocular Cell Line: Model for Disease and Therapeutics	Jan 23 rd 09
29.	Dr. GuruPrasad Medigeshe Vaccine and Gene Therapy Institute, Oregon Health and Science University, USA	Understanding virus-host interactions: a shifting paradigm in antiviral target identification	Jan 29 th 09
30.	Dr. Avi Choudhary James McGill Professor, Director, Behavioural Neuroscience Training Program, Department of Psychology, McGill University, Canada	Neural Substrates of Face Perception in Monkeys	Feb 2 nd 09

31.	Dr. Subhendu Ghosh Professor, Dept of Biophysics, University of Delhi South, Campus	Noise in Cells, Membranes and Neurons	Feb 4 th 09
32.	Dr. Koel Das University of California, Santa Barbara	Pattern classifiers in computational neuroscience	Feb 20 th 09
33.	Dr. Chandan Goswami Max Planck Institute for Molecular Genetics, Berlin, Germany	Cell biology of pain: bidirectional regulation of TRPV channels with cytoskeleton	Feb 24 th 09

The image features a stack of several books with light-colored covers, some showing signs of wear. A white scroll is rolled up and placed on top of the books. The scroll is partially unrolled, revealing a colorful, abstract painting with shades of yellow, green, blue, and purple. The entire scene is set against a soft, light-colored background, creating a warm and scholarly atmosphere.

ACADEMIC PROGRAMMES

Academic Programmes

Deemed University Status

NBRC was awarded Deemed University status (de-novo category) in 2002 under Section 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.

On completion of 5 years period from the time NBRC has given de-novo deemed University status, a panel of 6 member committee (duly constituted by UGC) chaired by Dr.P.K.Banerjee, visited NBRC for reviewing the Deemed to be University status and for recommending further extension. The report / notification for further extension of Deemed to be University status is still awaited.

Courses Offered:

Ph.D. in Neuroscience

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

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.12,000/- per month and for Senior Research Fellows is Rs.14,000/- (which may change as per their educational background).

Integrated-Ph.D in Neuroscience

NBRC has 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 PhD. programme from diverse backgrounds including Bachelor's degree in any branch related to Neurosciences, M.B.B.S., B.E., 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 are paid fellowship at 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 through three National Science Academies viz: (1) Indian Academy of Science, Bangalore (2) Indian National Science Academy, New Delhi (3) National Academy of Sciences, Allahabad. The summer training was for a period of 8 weeks. The Trainees were provided with shared 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 encourage them to consider it as a future career option.

A science awareness camp for students from 5 schools selected by Haryana State Council for Science and Technology was organized at NBRC in December, 2008. Participation certificates were issued to the students who attended the programme

National science day celebration was also conducted at Kendriya Vidyalaya, NSG Campus, Manesar on 27th February, 2009 and 13 students / project Assistants and 1 faculty of NBRC participated in the celebration.

Also science popularisation lectures were conducted at Faridabad and Gurgaon located in Haryana and 2 Scientists visited the respective places to deliver the lectures.

GENERAL ADMINISTRATION

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 and he is responsible for overall management of 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, and he is responsible for the students' administration, project co-ordination, new students' admissions, course co-ordination etc.

During the year under review, the administration wing strived hard in providing support services and in carrying out the following activities

- The first cultural festival of NBRC, 'TANTRIKA 2008' was organized within the campus which included a variety of cultural and sports events. students, officers, and staff of NBRC participated in the event.
- Making due diligence and compliance to the Right to Information Act, 2005 including compilation and updating of the required disclosure data on the website.
- A 12-day international workshop, "The Making of Mind" a Cognitive Neuroscience was organized in NBRC campus. In house arrangements were made to visiting faculties and students for their stay. The workshop was designed to introduce students to cognitive neuroscience and laboratory demonstrations of the latest techniques in the field.
- Making major imports from different countries in terms of equipments and other consumables with a meticulous planning and precise schedule.
- The new hostel building for housing various students and research assistants was taken over from DAE.
- All the students who were residing in a rented building at Gurgaon were shifted to the new hostel building, after taking over of the new hostel building at NBRC campus, Manesar.
- A blood donation camp was facilitated in the campus through the student organisation called "Tantrika".
- New items of equipment were installed at the gymnasium for the benefit of users.

Implementation of Official Language

NBRC, though a scientific research organization, is making effort to implement 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 official language committee with its members taking keen interest and 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, rubber stamps (seals) Boards etc. A proposal for creation of posts for Hindi officer/Assistant and other positions is under consideration of the Department of Biotechnology.

Officers, staff and students of NBRC participated in various activities, programmes / competitions such as Essay writing, Debating etc. which were held at various occasions.

RTI Act

The provisions of RTI Act are being followed in NBRC in letter and in spirit. During 2008-09, six RTI applications were received seeking information on various matters concerning NBRC. All six applicants were provided the requisite information within the prescribed time-limit.

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 committee for redressal of sexual harassment of women at NBRC and grievances, if any, from aggrieved girl students/women employees of NBRC. 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 the help of the said committee constituted for this purpose.

Reservations and concessions in Employment & Admission of students

NBRC follows reservations & concessions as per rules of Government of India in Employment and in students admission the provision of exemption as provided in Gazette Notification No. 5 dated 4th January 2007 is implemented.

Vigilance

The Institute has a Chief Vigilance Officer. As per the guidelines of DBT, one of the Officer /Scientists of NBRC has been nominated as Chief Vigilance Officer of the Centre.

**INSTITUTIONAL GOVERNANCE STRUCTURE
&
PEOPLE AT NBRC**



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