

NATIONAL BRAIN RESEARCH CENTRE



ANNUAL REPORT

2007 – 2008

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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 interdisciplinary 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.

RESEARCH REPORTS

Molecular Mechanism of the Pathogenesis of the CAG Repeat Neurodegenerative Diseases

Principal Investigator: Dr. Nihar Ranjan Jana

Research Fellows: Anand Goswami, Priyanka Dikshit, Amit Mishra

Technical Assistant: D. Narender

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, dominantly inherited, generally starts 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 generation 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 transgenic animal studies have supported a toxic gain-of-function mechanism that leads to neuronal dysfunction and death, although recent evidence indicates that loss of normal protein function might also have a role in the disease pathogenesis. The formation of neuronal intranuclear inclusions or aggregates of the disease protein is the major cytopathological hallmark of all these disorders. It has been suggested that the polyglutamine tract expansion leads to formation of misfolded conformations of the target protein. When the cells sense the misfolded polyglutamine protein, initially it tries to refold and failure to refold 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 cell's quality control system. The recruitment of molecular chaperones, UPS components to the polyglutamine aggregates could be an adaptive response of the cells to get rid from the abnormal protein deposits. But, how the expanded polyglutamine proteins or their aggregates elicit a complex pathogenic responses in the neuronal cells are not fully understood.

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

This year we have extensively characterized the role of E6-AP in the degradation of expanded polyglutamine proteins and its neuroprotective role in the cellular model of HD. We have found that over expression of E6-AP suppresses while knockdown promotes the expanded polyglutamine protein-induced cell death. Overexpression of E6-AP also decreases the SDS-insoluble high-molecular-weight expanded polyglutamine protein complex retained in the stacking gel. Since E6-AP interacts and associates with the polyglutamine aggregates in the cellular models, we further tested its recruitment to the nuclear aggregates in the HD transgenic mice brain. In the control mice brain, the E6-AP was distributed primarily in the cerebellum, hippocampus and cerebral cortex. The striatum showed comparatively low levels of expression. E6-AP was also localized mostly in the nucleus with diffuse cytoplasmic staining in the Purkinje cells, hippocampal and cortical neurons. In the transgenic mice brain, we observed clear recruitment of E6-AP to the nuclear aggregates particularly in the cerebellum, cerebral cortex and hippocampus. The double immunofluorescence staining further confirmed that the E6-AP co-localized with the ubiquitin positive aggregates. About 80-90% of ubiquitin positive nuclear aggregates in the Purkinje cells were E6-AP positive and about 30-40% of ubiquitin positive nuclear aggregates in the cortex and hippocampus were E6-AP positive. The redistribution of E6-AP to the aggregates often caused decrease in the E6-AP staining in the nucleus and cytoplasm. Immunoblotting experiment further confirmed that the soluble pool of E6-AP was relatively lower in the different parts of the transgenic mice brain compared to control. Our result suggests that the loss of E6-AP function might contribute to the HD pathogenesis.

Publications:

Jana, N. R. (2008) NSAIDs and apoptosis. **Cellular and Molecular Life Sciences**, 65(9): 1295-1301.

* Dikshit, P. and **Jana, N. R.** (2008) Role of ubiquitin protein ligases in the pathogenesis of polyglutamine diseases. **Neurochemical Research**, 33: 945-951.

Mishra, A., Dikshit, P., Purkayastha, S., Sharma, J., Nukina, N. and **Jana, N. R.** (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:

N. R. Jana: Protein aggregation in neurodegenerative diseases. Invited talk at Department of Biochemistry, Moulana Azad Medical College, Delhi, March 2008.

N. R. Jana: Role of intracellular protein degradation pathways in neurodegenerative diseases. Invited talk in the 2nd National Medical Students Research Conference, Pune, Feb. 2008.

N. R. Jana: Modulation of polyglutamine neurodegeneration by ubiquitin protein ligases. Invited talk at RIKEN Brain Science Institute, Japan. Sept. 2007.

Funding:

This work is supported by NBRC Core funds.

Collaborator:

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

Degrees Awarded (Ph.D.):

Priyanka Dikshit
Anand Goswami

Understanding the Pathogenic Mechanism of Angelman Mental Retardation Syndrome

Principal Investigator: Dr. Nihar Ranjan Jana

Research fellows: Amit Mishra, Swetha K. Godavarthi

Technical assistant: D. Narender

Angelman mental retardation syndrome (AS) is a neurodevelopmental disorder characterized by severe mental retardation, ataxia, easily provoked smiling and laughter and seizure. The disease is caused primarily by maternal deletion of chromosome 15q11-q13, which encompasses the *UBE3A* locus, and also by paternal uniparental disomy of chromosome 15, imprinting defects or loss of function mutation of the *UBE3A* gene. All of these mechanisms lead to absence of functional copy of *UBE3A* gene. Although the deletion of other genes in chromosome 15q11-q13 may also be associated to AS, the identification of loss of function mutation in *UBE3A* gene in AS patients provides the most compelling evidence that the disease is caused primarily by maternal deficiency of *UBE3A* gene. *UBE3A* gene encodes E6-AP ubiquitin protein ligase, an enzyme involved in the intracellular protein degradation through ubiquitin proteasome system (UPS). E6-AP 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 cell's 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 of 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. 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.

In addition to its ubiquitination activity, E6-AP also functions as a transcriptional coactivator for steroid hormone receptors (6-9). 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.

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.

This year we have extensively characterized the functional significance of the interaction of E6-AP with Hsp70. Our finding suggests that E6-AP is involved in the degradation of misfolded protein with the help of Hsp70 and hence probably functioning as a cellular quality control ligase. We have found that E6-AP ubiquitinates heat denatured luciferases that are captured by Hsp70 in an *in vitro* ubiquitination assay. E6-AP also promotes the degradation of misfolded luciferase, CFTR and polyglutamine proteins (demonstrated in project I). Interestingly, we have also observed that heat stress, ER stress and proteasomal stress causes up-regulation of E6-AP along with Hsp70. Analysis of upstream promoter region of E6-AP revealed several HSF1 consensus binding sites. The increase in the expression of E6-AP in stressed cells could also be an adaptive response in order to get rid of the misfolded and damaged proteins and suggests that both E6-AP and Hsp70 may be working together to achieve this goal. Recently, we have received E6-AP-maternal deficient mice (model mice for Angelman syndrome) and we are now characterizing them and expanding the colony. This mice model will be used to further characterize the interacting protein as well as to identify the defective signalling pathways in order to understand the disease pathogenic mechanisms.

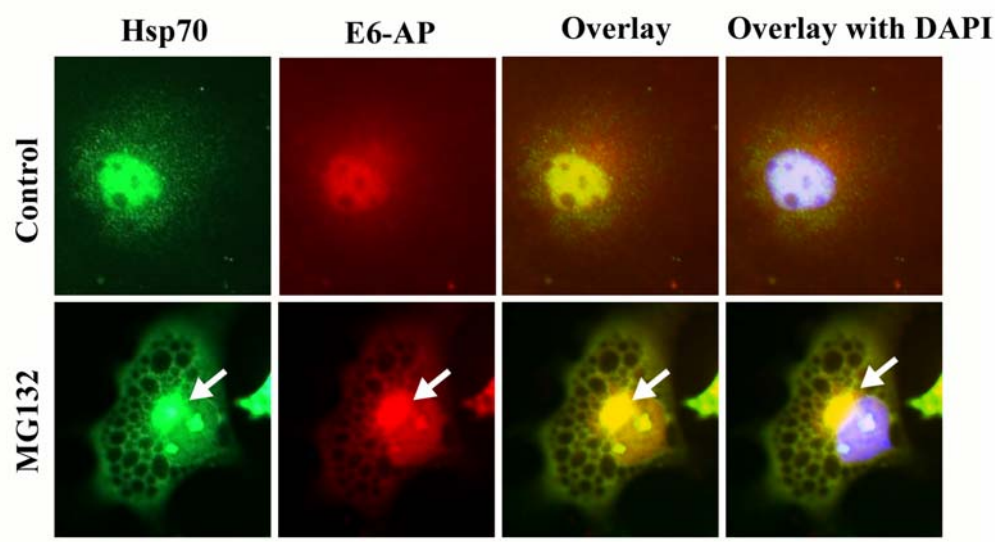


Figure: Localization of E6-AP and Hsp70 in Cos-7 cells before and after proteasome inhibition.

Cos-7 cells were plated onto 2-well chamber slides and on the following day, cells were treated with proteasome inhibitor MG132 (10 μ M) for 8 h. The cells were then subjected to double immunofluorescence staining using Hsp70 and E6-AP antibody. FITC-conjugated secondary antibody was used to label Hsp70 and Rhodamine-conjugated secondary antibody was used to stain E6-AP. Nuclei were stained with DAPI. Arrow indicates redistribution of E6-AP and Hsp70 around the MTOC.

Publication:

Mishra, A. and **Jana, N.R.** (2008) Regulation of turnover of tumor suppressor p53 and cell growth by E6-AP, a ubiquitin protein ligase mutated in Angelman mental retardation syndrome. **Cellular and Molecular Life Sciences**, 65: 656-666.

Presentations:

N. R. Jana: Understanding the functional role of E6-AP – an ubiquitin protein ligase and steroid receptor coactivator implicated in Angelman mental retardation syndrome. Invited speaker in the Asia and Oceania Society for General and Comparative Endocrinology, North Bengal University, Dec. 2007.

Funding:

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

Regulation of Neurogenesis in the Cerebellum.

Principal Investigator: Dr. Shyamala Mani

Research Fellows: Rashmi Mishra, Shailesh Kumar Gupta,
Parthiv Haldipur

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 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.

Our first achievement this year is to show that GAP-43 is important for the patterning of the normal cerebellum. We have characterized in detail the GAP-43 homozygous knockout [GAP-43 (-/-)] mice cerebellar phenotype to show decreased cerebellar size and reduced and abnormal foliation pattern. In addition we are interested in the role of extracellular cues in regulating neuronal polarity. We used the GAP-43 knockout mouse to study the link between centrosome positioning and neuronal polarization in cerebellar granule neurons. Our second important achievement this year has been to

use the technique of microcontact printing of proteins to provide directional cues to cerebellar granule neurons in culture. Using this technique we have been able to show that E-cadherin provides an extrinsic signal to the granule neurons whose centrosome and process outgrowth then orient towards this signal. We also showed that this response requires the presence of GAP-43. The significance of this result is that understanding cell polarity in zones of secondary proliferation such as the external granule cell layer would give us insight into how this may process occurs during neurogenesis in areas such as the subgranular zone of the hippocampus.

Our future goal is to dissect the signaling pathway leading from the extracellular signal to the putative movement of the centrosome. To this end we are transfecting cerebellar granule neurons with GFP constructs and performing live cell imaging.

Publications:

* Mishra, R., Gupta, S.K., Meiri, K.F., Fong, M., Thstrup P., Juncker, P.D., and **Mani S.** (2008) GAP-43 is key to mitotic spindle control and centrosome-based polarization in neurons. **Cell Cycle**, 7(3): 348-57.

* Shen, Y.\$, Mishra\$, R., **Mani, S.** and Meiri, K. (\$joint first authors) GAP-43 is required for normal patterning of the cerebellum in vivo, and its absence affects cerebellar learning in a sex-specific fashion. **Cerebellum** (In Press).

Presentations:

Shyamala Mani: Filling a GAP in the understanding of neuronal polarity - 'Model Organisms and Stem Cells in Development, Regeneration and Disease' symposium, NCBS, Bangalore, India, Feb. 2008.

Funding:

This work is supported by a FIRCA-NIH grant as well as NBRC Core funds.

Collaborators:

Karina Meiri, Tufts University, USA.

David Juncker, McGill University, Canada.

Degree Awarded (Ph.D.):

Rashmi Mishra

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

Principal Investigator: Dr. Shyamala Mani

Research Fellows: Manoj Kumar, Rupali Srivatsava

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.

Our major achievement this year is to define the role of Neuronal Restrictive Silencing Factor/ RE1-silencing transcription factor (NRSF/REST) during embryonic stem cell differentiation into neurons. To do this an ShRNA construct was used to downregulate NRSF in undifferentiated ES cells. We showed that although control ES cells required induction by retinoic acid (RA) to differentiate efficiently into neurons, down-regulation of NRSF was sufficient to drive the ES cells down the neuronal lineage even in the absence of retinoic acid. This down-regulation also led to increased expression of mature neuronal markers, and concomitantly decreased Glial Fibrillary Acidic Protein (GFAP) expression. Our results suggest that NRSF down-regulation increases the population of mature neurons at the expense of GFAP positive cells. The significance of this result is that this may give us a way of differentiating ES cells into a more homogenous neuronal lineage. Then depending on the expression of bHLH factors we would be able to perhaps direct these cells down different sublineages.

Our future goal is to be able to create cell lines that conditionally express different bHLH factors at different times during the differentiation of ES cells. For achieving this we are using an inducible lentiviral system to express our gene of interest.

Publications:

Gupta, S.K., Gressens, P. and **Mani, S.** NRSF down-regulation induces neuronal differentiation in mouse embryonic stem cells. **Differentiation** (In Press).

Kumar, M., Kaushalya, S. K., Gressens, P., Maiti, S. and **Mani, S.** Optimized derivation and functional characterization of 5-HT neurons from human embryonic stem cells. **Stem Cells and Development** (In Press).

Presentations:

Shyamala Mani: 5th ISSCR Annual Meeting in Cairns, Australia. Differentiation into serotonergic neurons of neural progenitor cells derived from human embryonic stem cells (July 2007).

Funding:

This work is supported by a grant from DBT as well as NBRC Core funds.

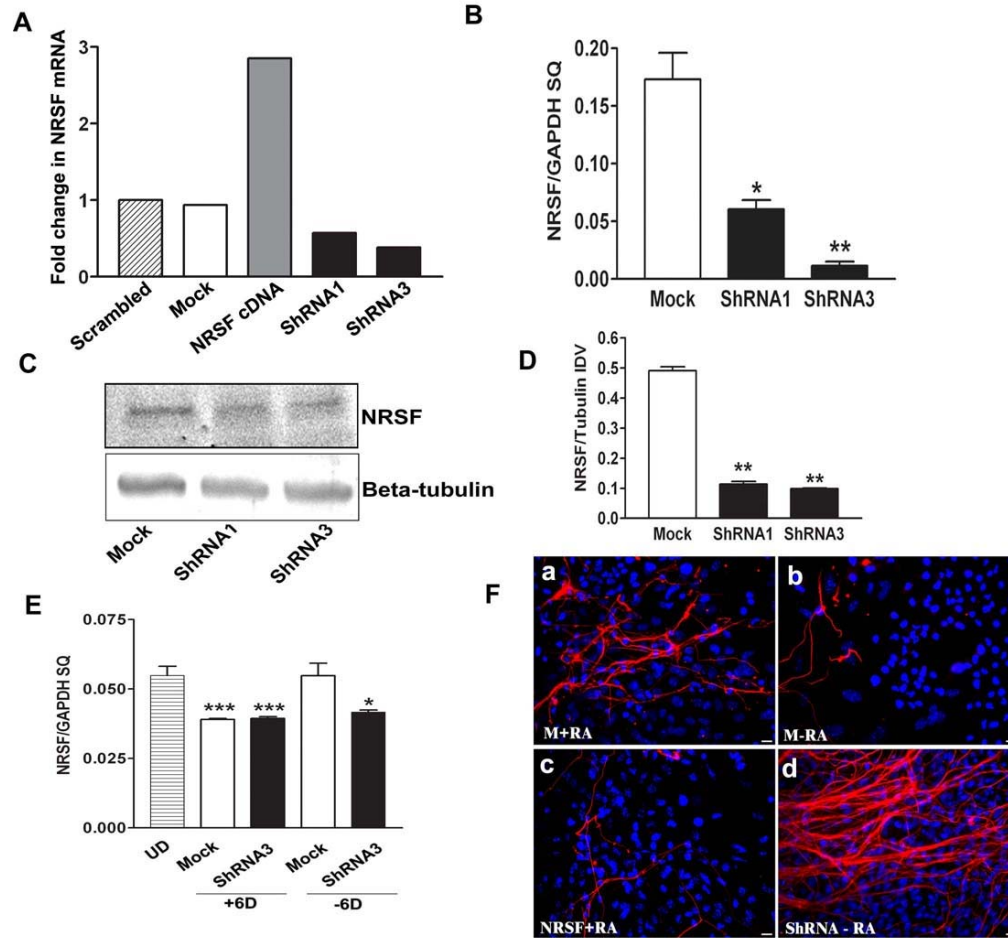


Figure: A) Real time PCR for NRSF mRNA 48 hours after transfection with scrambled vector, empty vector, NRSF cDNA and vector containing SiRNA sequences. Levels are normalized to GAPDH. Fold change over empty vector is shown. B) Real time PCR for NRSF mRNA 48 hours after transfection with empty vector and vector containing 2 different SiRNA sequences. Levels are normalized to GAPDH. C) Western blot of NRSF normalized to β -tubulin. EGFP expression in Mock (a, b, c) and ShRNA (d, e, and f) cultures. Low magnification view of ES-D3 colonies 48 hours after transfection (a and d), +6d EB (b and e) and -6d EB (c and f). D) Integrated density value (IDV) of the NRSF/Tubulin ratio. E) Real time PCR for NRSF RNA at the end of 6 days. F) β -III tubulin expression in differentiated cultures, mock transfected and exposed to RA (a), mock transfected cells and not exposed to RA (b), NRSF cDNA transfected and exposed to RA(c) and ShRNA3 transfected and not exposed to RA (d) Error bar = mean Starting Quantity (SQ) value $\pm$ S.E.M for 3 independent experiments. Values of asterisks indicate statistically significant difference from mock transfected controls (* $p < 0.05$, *** $p < 0.001$ in Dunnett's Multiple Comparison Test). Scale bar: 25 μ m.

Maternal Malnourishment and its Effect on Brain Development

Principal Investigator: Dr. Shyamala Mani

Post Doctoral Fellow: Sayali Ranade

We focus on maternal malnutrition and its effect on brain development of the fetus, an issue of great societal importance and impact. Several studies using animal models have suggested that the effects of nutritional insult on the developing brain are long-lasting and lead to permanent deficits in learning and behavior. Malnutrition can refer to the availability of all the nutrients but in insufficient quantities or it may imply that one or more of essential nutrients is either missing or is present, but in the wrong proportions in the diet. The hypothesis we wish to address is that different domains of cognitive functioning can be affected by malnutrition and this can be related to the type of nutritional deficiency that the brain has been exposed to during development. To study the effect of nutritional deprivation during brain development, a paradigm of maternal malnutrition during the period of both gestation and lactation will be used and its effects studied on the F1 offspring. Three different types of malnutrition are used, that involve, caloric restriction, inadequate amount of protein in the diet and condition of low iron content.

Our major achievement this year is to show that the domain of spatial memory affected in the F1 generation depended on the kind of malnutrition that the mother was subjected to. The significance of our results is to highlight the importance of qualifying the kind of malnutrition that is suffered by the mother during the period of gestation and lactation as it has consequences for the cognitive domain affected in the offspring. Awareness of this should inform prevention strategies in trying to reverse the effects of adverse maternal nutrition during critical periods in brain development.

Our future goal would be to now separate the effects of maternal malnourishment during gestation for malnourishment during lactation. By doing so we hope to narrow the window that would define a critical time period within which reversal of cognitive deficits is achievable.

Publication:

Ranade, S.C., Rose, A., Rao, M., Gallego, J., Gressens, P. and **Mani, S.** (2008) Different types of nutritional deficiencies affect different domains of spatial memory function checked in Radial Arm Maze. **Neuroscience**, 152: 859-866.

Funding:

This work is supported by CEFIPRA, Indo-French Grant and is being carried out under the INSERM-NBRC International Associated Laboratory.

Collaborator:

Dr. Pierre Gressens, INSERM, France.

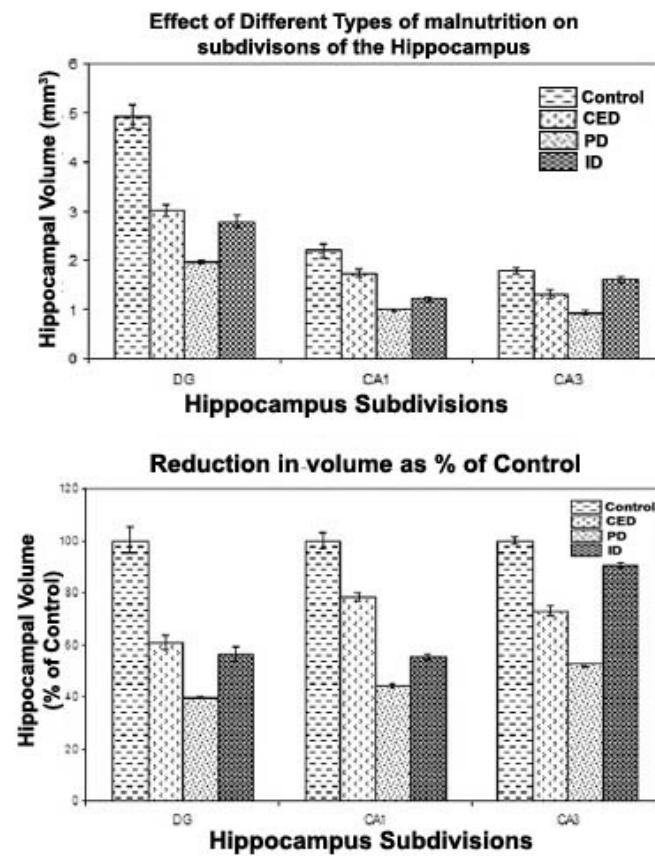


Figure: The effect of different types of nutritional deficiencies on volume of different subdivisions of hippocampus. (A) The changes in the hippocampal subdivision volume due to maternal malnutrition in the F1 pups is shown. The x axis shows different malnutrition groups. The y axis shows corrected volumes of different subdivisions of hippocampus in cubic microns. Each column represents mean value of the volume of particular subdivision for that particular group. The S.E. is plotted as error bars. (B) The percent changes in hippocampal subdivision volume of malnourished brains with respect to control brains is shown. The x axis shows different malnourished groups. The y axis shows percent changes in the volume of different subdivisions of the hippocampus. CED=chronic energy deprivation; PD= protein deficiency; ID= iron deficiency.

Cytochromes P450 Dependent Metabolism of Drugs in Brain

Principal Investigator: Prof. V. Ravindranath

Research Fellow: Varsha Agarwal

Technical Assistance: R. Khader Valli, Shankar Dutt Joshi

Cytochrome P450 (P450) is a super-family of drug metabolizing enzymes. P450 enzymes have dual function; they can metabolize drugs to pharmacologically inactive metabolites facilitating their excretion or biotransform them to pharmacologically active metabolites which may have longer half-life than the parent drug. The variable pharmacological response to psychoactive drugs typically seen in population groups is often not accountable by considering dissimilarities in hepatic metabolism. Metabolism in brain specific nuclei may play a role in pharmacological modulation of drugs acting on the CNS and help explain some of the diverse response to these drugs seen in patient population. P450 enzymes are also present in brain where drug metabolism can take place and modify therapeutic action of drugs at the site of action.

Our working hypothesis is that brain cytochromes P-450 play an important role in the pharmacological modulation of drugs acting on the CNS as well as in the metabolism of critical endogenous substrates such as, arachidonic acid and their metabolites and it is therefore important to understand major P-450-mediated biotransformation and characterize the enzymes mediating such reactions in the human brain. The long-term objective of the proposed project is to understand the role of *in situ* cerebral metabolism of drugs and endogenous substrates in the pharmacological action of psychoactive drugs and modulation of physiological function.

CYP4F family of P450 enzymes has a dual role in modulating inflammation and metabolizing of clinically used drugs. They were first discovered for their involvement in the inactivation pathway of leukotriene B₄ (LTB₄), a powerful mediator of inflammation. LTB₄ is metabolized *in vivo* by multiple pathways, one of the pathway proceeds via ω -oxidation of LTB₄ to form 20-OH LTB₄, which is mediated by CYP4F family. The CYP4F subfamily comprises of 15 genes in human, rat and mouse. There are 5 functional genes of Cyp4f in mouse, Cyp4f13, Cyp4f14, Cyp4f15, Cyp4f16 and Cyp4f18. We have amplified, cloned and expressed the above 5 isoforms of Cyp4f and studied their role in LTB₄ metabolism. Of the 5 Cyp4fs enzymes, Cyp4f14, CYPf15 and Cyp4f18 efficiently metabolized LTB₄ to 20-OH LTB₄. We then studied the constitutive mRNA expression of these 5 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 reducing LTB₄ mediated inflammation. During acute inflammation caused by LPS treatment the expression of Cyp4f15, 16 and 18 was significantly up-regulated in the cortex, while Cyp4f13 and 14 remained unaffected indicating a compensatory response to the inflammatory stimuli. The effect of Cyp4f inhibitor on the inflammatory response in the brain is currently being examined with a view to determine their contribution to the inflammation. If indeed, inflammation is aggravated by inhibiting Cyp4f enzymes, we will then study the Cyp4f promoter region to discover ways to induce the expression of Cyp4f enzymes.

Publications:

*Kommaddi, R.P., Turman, C.M., Moorthy, B., Wang, L., Strobel, H.W. and **Ravindranath, V.** (2008) An alternatively spliced cytochrome P4501A1 in human brain fails to bioactivate polycyclic aromatic hydrocarbons to DNA-reactive metabolites. **J. Neurochem.**, 102:867-77.

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(6): e2337.

Presentations:

Varsha Agarwal, Reddy P. Kommaddi, Khader Valli R and V. Ravindranath: Differential expression of CYP3A enzymes in human brain and functional significance in relation to metabolism of the anxiolytic drug, Alprazolam. Cytochrome P450 meeting in Bled, Slovenia, June 17-21, 2007.

Varsha Agarwal, Reddy P. Kommaddi, Khader Valli R and V. Ravindranath: Differential expression of CYP3A enzymes in human brain and functional significance in relation to metabolism of the anxiolytic drug, Alprazolam, Gordon Research Conference, Boston, USA from July 8-13, 2007.

Varsha Agarwal, Reddy P. Kommaddi, Khader Valli, and V. Ravindranath: Drug metabolizing enzyme, CYP3A43 is expressed in higher amounts in human brain in contrast to liver leading to increased production of the pharmacologically active metabolite of the anxiolytic drug alprazolam at the site of action at Society for Neuroscience, 3rd to 7th Nov, 2007.

Funding:

This work is supported by NIH-RO1 grant.

Collaborator:

Henry Strobel, University of Texas Medical School, Houston, USA.

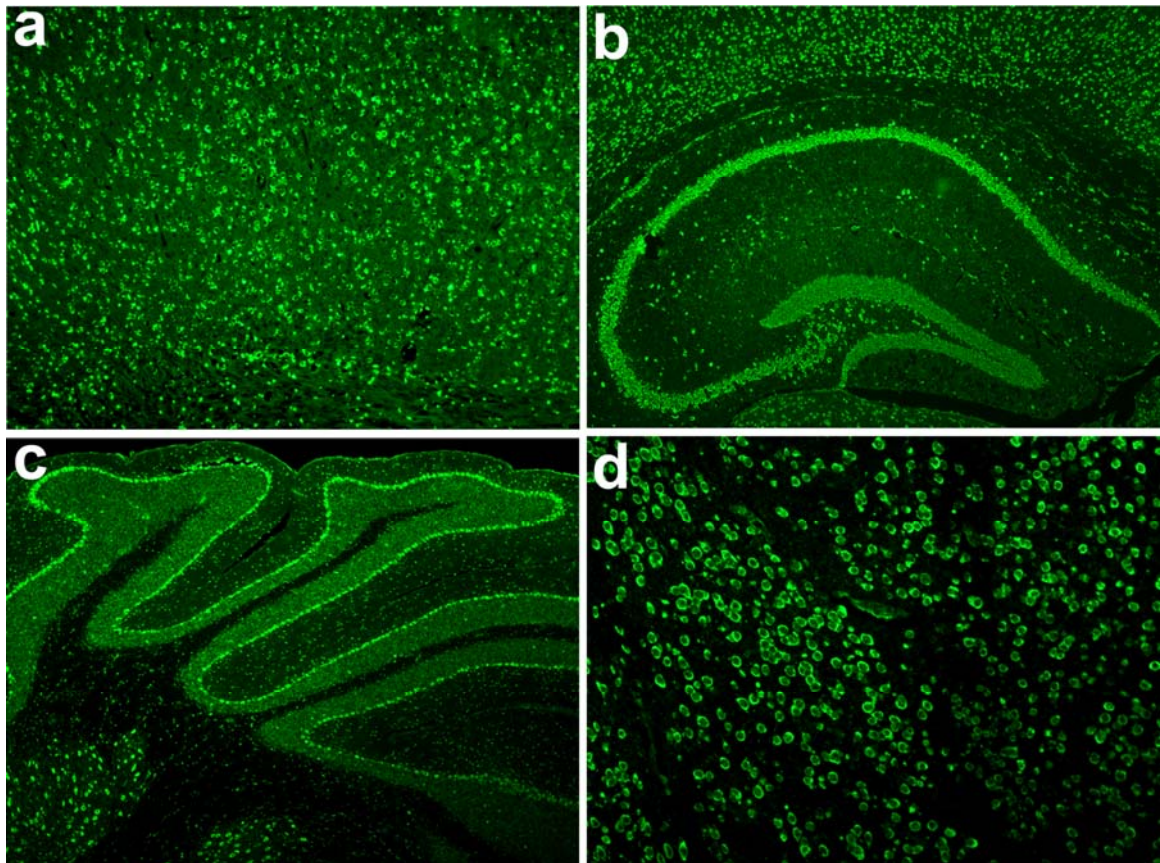


Figure: Localization of Cyp4f15 mRNA in mouse brain: (a) Cortex, (b) hippocampus, (c) cerebellum, and (d) striatum using fluorescence in situ hybridization showing constitutive expression of Cyp4f15 in mouse brain.

Redox Driven Apoptotic Signaling in Parkinson's Disease

Principal Investigator: Prof. V. Ravindranath

Research Fellows: Smitha Karunakaran, Lalitha Durgadoss,
Uzma Saeed, Ajit Ray

Project Assistant: M. Durga Praveen

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.

Loss of the thiol anti-oxidant, glutathione (GSH) is seen as an early event in animal models of PD and in substantia nigra of PD patients obtained at autopsy. Exposure to 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) results in loss of dopaminergic neurons in substantia nigra and is considered a good animal model of PD. MPTP treatment results in loss of GSH and increased formation of protein glutathione mixed disulfides (PrSSG) indicating the oxidative modification of cysteine residues in proteins. The redox status of proteins regulates 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 pathways.

Our overall aim is to understand differential vulnerability of selective cell populations, such as the dopaminergic neurons of substantia nigra to neurodegeneration.

Reactive oxygen species can activate several signaling pathways in cells including those that regulate cell death. An important signaling pathway that is activated by ROS is the MAP kinase pathway. The mitogen-activated protein kinases (MAPKs) family comprises of extracellular signal-regulated kinases (ERKs) and stress-activated protein kinases (SAPKs), c-Jun N-terminal kinases (JNKs) and p38 kinases. We reported that in the ventral midbrain, exposure to MPTP activates a redox-sensitive death signaling cascade initiated by apoptosis signal regulating kinase 1 (ASK1), which is followed by the activation of stress activated protein kinases (SAPK/MAPK). These events culminate in the activation of caspase 3 selectively in midbrain but not in striatum.

Dopaminergic neurons undergo apoptosis in animal models of PD, which has led to considerable interest in targeting the c-Jun N-terminal kinase (JNK) pathway for slowing down the progression of the disease. Several reports have earlier suggested the activation of the c-Jun N-terminal kinase (JNK) pathway in models of PD. Prior treatment with JNK inhibitor(s) offered neuroprotection in vitro in cultured cells and in vivo in animal models of Parkinson's 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 observed that there is selective phosphorylation of p38 MAP kinase within the dopaminergic neurons in SNpc while the activation of the JNK occurs predominantly in the microglia. In order to discern if the activation of p38 was indeed linked to the demise of the neurons, we examined the effect of p38 inhibitor on MPP⁺ mediated toxicity in vitro in dopaminergic neurons derived from human neural progenitor cells and observed complete neuroprotection. In vivo, in the ventral midbrain, treatment with p38 inhibitor, SB239063 prevented the downstream phosphorylation of p53 and its translocation to the nucleus as seen after MPTP treatment alone. Thus, our results point to the selective activation of p38 in dopaminergic neurons of SNpc and its role in the downstream phosphorylation of p53 leading to increased p53 mediated transcription of Bax, Noxa and Puma. The increased staining of phosphorylated p38 in the surviving neurons of SNpc but not in the pars reticulata in human brain sections of patients with PD provides further evidence suggesting a role for p38 in the degeneration of dopaminergic neurons of SNpc. One of the compelling questions in understanding the pathogenesis of neurodegenerative diseases in general and PD in particular is the vulnerability of selective cell population to neurodegeneration. The results described herein demonstrating the selective activation of JNK and p38 in distinct cell populations within the SNpc, namely the microglia and the dopaminergic neurons, is a case in point. Further studies are being carried to understand this selectivity in the activation of the MAPK pathways.

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V. Ravindranath: "Role of Glia in Neurolathyrism" Plenary lecture on Symposium on Glial Neurobiology, Gwalior on 23rd Oct., 2007.

Smitha K., Uzma Saeed and V. Ravindranath: Cell-specific activation of redox – apoptotic signaling in MPTP mouse model of Parkinson's disease. 15th Euroconference on Apoptosis, Oct. 26-31, 2007, Portoroz, Slovenia.

V. Ravindranath: "Redox driven apoptotic signaling in Parkinson's Diseases at Linus Pauling Institute, Oregon State University, USA on 30th Oct. 2007.

Uzma Saeed, Smitha Karunakaran, Ajit Ray, Latha Diwakar, Sujanitha Ramakrishnan, Ratnacaram Chandrashaas Koumar, and V. Ravindranath: Activation of apoptosis signal regulating kinase 1 in male but not female mice in animal model of Parkinson's disease: role of thiol disulfide oxidoreductase(s) at National Parkinson Foundation 10th International Symposium on Parkinson Research from Nov. 1st and 2nd, 2007, San Diego, USA.

Uzma Saeed, Smitha K, Mamata Mishra, P. Seth and V. Ravindranath: Activation of stress activated protein kinase is a critical event in 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine toxicity: kinase inhibitors as potential drug target at Society for Neuroscience, 3rd to 7th Nov, 2007, San Diego, USA.

Lalitha D., Uzma Saeed, Smitha K. and V. Ravindranath: Redox modification of protein kinase B: Implications for Neurodegenerative Disorders in Parkinson's Diseases, at the XVII WFN world congress on Parkinson's disease and related disorders, Amsterdam, The Netherlands, 9th to 13th Dec. 2007.

V. Ravindranath: G.P. Chatterjee Award Lecture, Science Congress from 3rd to 5th Jan. 2008.

L. Diwakar, Smitha K., Uzma Saeed, S. Ramakrishnan, S. Iyengar and V. Ravindranath: Thiol antioxidant affords neuroprotection against MPTP mediated death signaling pathway at International Brain Research Organization (IBRO), Melbourne, Australia from 13 to 15 July, 2007.

Collaborators:

Dr. Pankaj Seth, NBRC.

Mamata Mishra, NBRC.

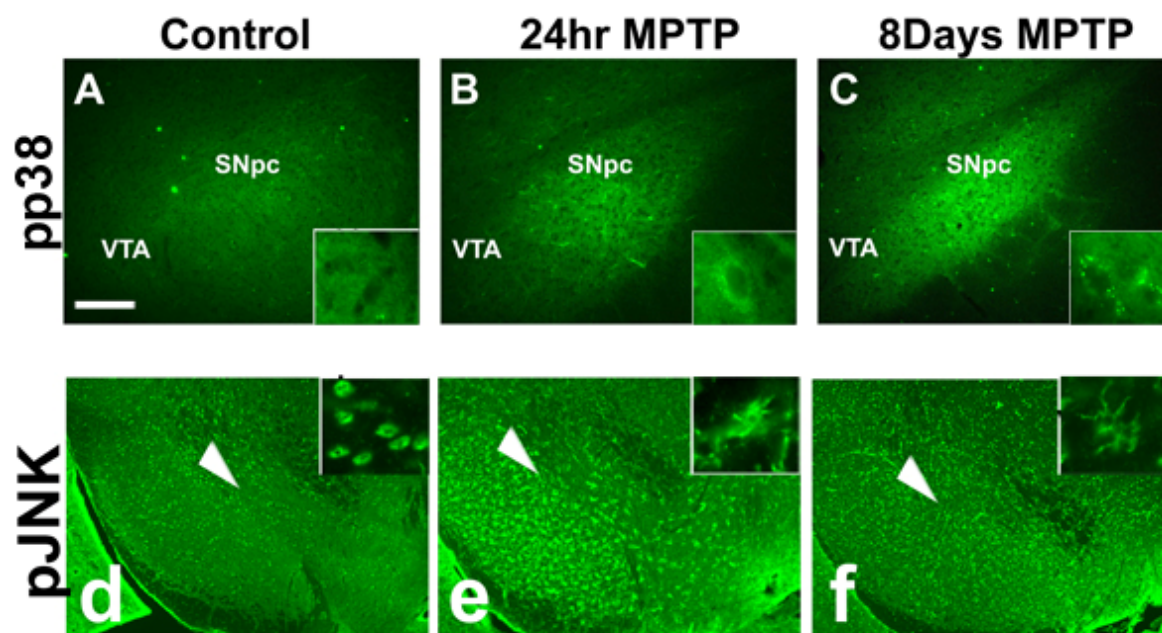


Figure: Selective activation of JNK and p38 in distinct cell populations within SNpc. Animals were treated with a single dose of MPTP and sacrificed 24 hr later or a daily dose of MPTP for 8 days and sacrificed on the 9th day. Immunohistochemical localization revealed the presence of pp38 in the neuronal soma and pJNK in the microglia of the SNpc after MPTP exposure. (A) pp38 is present at low levels in the SNpc neurons of control animals while not detectable in ventral tegmental area (VTA) neurons. (B) Following single dose of MPTP for 24 hr there was an increase in pp38 in the SNpc but not VTA. (C) pp38 level is higher in the surviving neurons of SNpc after sub-chronic exposure to MPTP for 8 days. pJNK is evenly activated throughout the brain in (d) the vehicle treated animals (control). JNK activation was observed specifically in microglia in SNpc, substantia nigra pars reticulata (SNR) and ventral tegmental area (VTA) of the ventral midbrain following (e) single dose and (f) 8 days of MPTP treatment. The inset in each panel shows magnified representative images of cells indicated in each panel. Scale Bar = 25 μ m. Scale Bar represent 10 μ m for the magnified the images.

Cellular and Molecular Mechanisms of HIV-1 Neuropathogenesis

Principal Investigator: Dr. Pankaj Seth

Research Fellows: Mamata Mishra and Dr. Nitin Koul

Project Assistant: Hena Khalique

Technical Assistant: Durga Lal Meena

The central nervous system (CNS) is vulnerable to infection by retroviruses of various species, particularly by members of the lentivirus family. Human nervous system infection with HIV-1 has been demonstrated in microglial cell, the immune effector cells of the brain that can result in irreversible damage to neuronal cells and subsequently to a range of clinical disorders that are debilitating. Such disorders develop in advanced stages of HIV infection and are collectively referred to as HIV associated dementia (HAD) or AIDS dementia complex (ADC). These are characterized by neurodegeneration resulting in progressive cognitive and motor impairments that may lead to a vegetative/mute state in extreme cases. HIV-1 virus enters the CNS at very early stages of infection and resides in brain cells that serve as viral reservoirs, as latent infections. Detailed studies regarding the molecular and cellular events during the course of HIV-1 neuropathogenesis are lacking.

The HIV-1/AIDS pandemic is attributed to its different subtypes (A-K) of HIV-1 that are unequally distributed around the world. In India, HIV-1 subtype C accounts for over 95% of HIV-1 infection. Worldwide HIV-1 subtype C is implicated in more than 50% of the cases of HIV infection. In western countries, HIV-1 subtype B is more prevalent and HAD is common in HIV infected adults having incidence up to 40%. Interestingly, the incidence of HAD in India is believed to be very low compared to western countries which may be attributed to a different subtype, HIV-1C, though there are no experimental studies to prove that. Detailed studies to understand the neurobiology of HIV-1C are warranted. Prevalence of HIV-1 related complications is reported to be more in pediatrics cases as compared to HIV-1 infected adults. It has been observed that children born with vertical transmission of HIV-1 from their mother or those that contract HIV infection during childhood falter in their developmental milestones. Autopsies of pediatric AIDS patients in western countries have revealed that they usually have a smaller brain size as compared to their age matched controls, which raises a question if the proliferation and differentiation of neural stem cells is affected due to presence of the virus in the developing brain.

The research progress in the neuroAIDS field has been significantly limited due to lack of animal models for HIV-1 infection. Globally, few cell culture systems derived from human fetal brain cells have been used in studies involving viral-cell interactions, as well as other cellular and molecular events during the course of neuropathogenesis. At National Brain Research Centre, our laboratory has established a novel cell culture system of human CNS progenitor cells in India to be used as a tool to investigate virus-induced neuropathogenesis.

We have two main aims under this project-

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

Several investigators have confirmed the damage to CNS cells by HIV-1 virus and its proteins such as gp120 and Tat. The trafficking of HIV-1 into brain parenchyma is through monocytes. The chemokine monocyte chemoattractant protein-1 (MCP-1)/CCL2 has been implicated in recruiting activated and potentially neuropathogenic immune cells (monocytes) into brain. Level of MCP-1/CCL2 has been correlated with degree of neurological deficits observed in AIDS patients. Although there are over 2.6 million HIV-1 positive individuals in India, the incidence of HAD is reported to be low in India. Hence detailed investigations into subtype specific differences in HIV-1 neuropathogenesis are necessary.

Our laboratory used cell culture models and assays for various pathways to study the effect of HIV-1 Transactivating protein Tat on astrocyte and neuronal cell functions and survival. It has been previously reported that the 101 amino acid Tat B and Tat C protein have a 69% sequence homology. However the significance of this difference at cellular and molecular level is largely unknown. The differences in protein sequence are scattered over the length in Tat C. Isogenic mutants of Tat C were used as a molecular tool to probe into the role of dicysteine motif (CC) at position 30-31 in the cysteine rich domain of the Tat protein that is conserved in all subtypes of HIV-1 except HIV-1 Tat C, where the cysteine at position 31 is naturally mutated to serine forming a CS motif instead of CC.

We studied subtype specific differences in neurotoxicity following exposure to HIV-1 Tat protein in human fetal CNS progenitor derived astrocytes and neurons, and observed that HIV-1 Tat C is less neurotoxic than Tat B. Previous studies have suggested that damage to neurons by HIV virus is by direct and indirect pathway, hence experiments simulating direct and indirect pathways were designed. Primary cultures of human astrocytes were transfected with expression vectors for Tat B and Tat C and supernatants collected from these cultures were added to primary cultures of human

neurons in various formats to assess neuronal damage by MTT assay, TUNEL assay, Caspase-3 activation and depolarization in mitochondrial membrane potential. Our experimental data confirmed that supernatants collected from astrocytes transfected with Tat B expression vectors were more neurotoxic as compared to those from Tat C transfected astrocytes, similar to our observations with Tat B protein treatments in human neuronal cultures.

Experiments were carried out with expression vectors of Tat B and C along with mutant Tat C. Interestingly we observed that supernatants from astrocytes transfected with mutant Tat C (with C-C linkage at 31 position) were also neurotoxic to neurons like Tat B. These observations provide experimental evidence that the natural alteration in amino acid sequence at position 31 in Tat C is responsible for differences seen in neurotoxicity. These novel observations of subtype specific differences in neurotoxicity of human neurons have provided new insights into the neurobiology of HIV-1C.

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

The advancement in neuroAIDS field in delineating cellular and molecular pathways involved in HIV neuropathogenesis has been greatly limited due to lack of good animal models for HIV-1 and limited access to autopsy brain samples at different stages of HIV infection or AIDS. Use of an *in vitro* human fetal brain cell culture system offers a great tool for studying the modulations at cellular and molecular levels following exposure to viral protein, particularly when animal models for studying HIV-1 neuropathogenesis are not available.

Establishing a novel cell culture model of human fetal CNS progenitor cells to be used as a tool for our ongoing studies involving primary cultures of human astrocytes and neuron was mandatory for us. We have successfully isolated and cultured several lines of human fetal CNS progenitor cells in our laboratory and have been constantly engaged in characterization of these cells. Besides different markers and receptors that we have shown previously, during characterization of human CNS progenitor cells it was observed that these express chemokine co-receptor CCR5 that is essential for the HIV-1 infection along with CD4 receptor of a human cell.

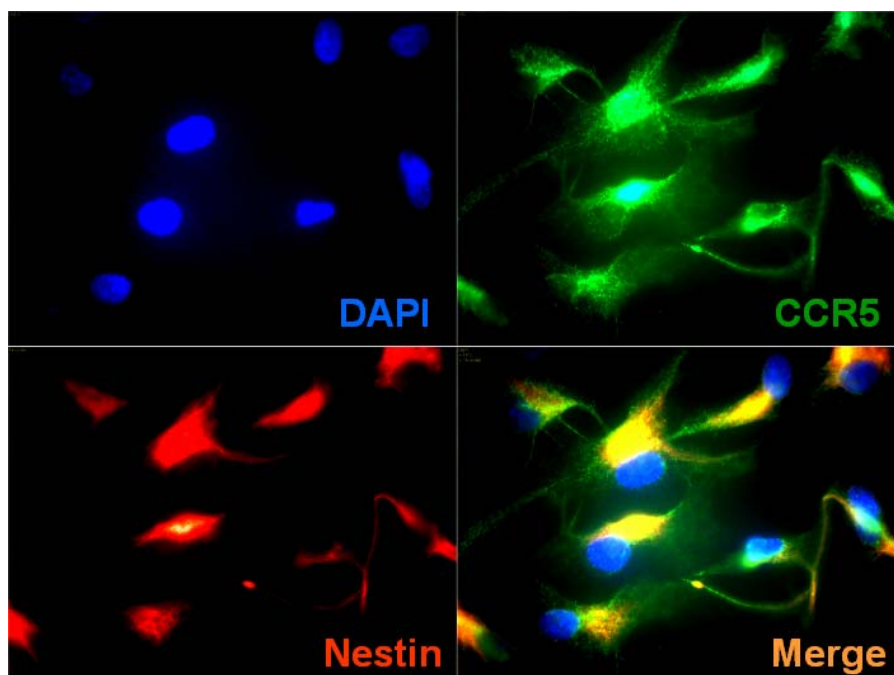


Figure: Human CNS progenitor cells express HIV-1 chemokine co-receptor CCR5. Human fetal brain derived CNS progenitor cells immunostained for HIV-1 chemokine co-receptor CCR5 (seen in GREEN) and CNS progenitor cell marker Nestin (seen in RED). Composite depicts cells that most of the cells show co-localization of the CCR5 and Nestin (seen in BRIGHT YELLOW / ORANGE). Cell nuclei are stained with nuclear stain DAPI (seen in BLUE).

Recently it has been reported that HIV-1 is present in nestin positive cells in autopsy brains sections from pediatric AIDS patients, suggesting that human neural stem/precursor cells may harbour HIV-1, it is hence important to understand the effect of the HIV-1 and its viral protein on properties of human neural stem/precursor cells. In addition to the studies of subtype specific effects of HIV-1 Tat, we carried out some preliminary experiments to investigate the effect of HIV-1 Tat protein on properties of human neural precursor cells. We observed that presence of HIV-1 Tat in culture media significantly affected their growth as well as proliferation of human neurospheres in a time and concentration dependent manner. The effect of Tat was seen in both neurospheres as well as monolayer cultures. Work is in progress to understand the mechanistic pathways that may affect the proliferation and differentiation of human neural precursor cells.

We believe our observations provide new insights into the effect of HIV-1 on human neural precursor cells there by acting as a double-edged sword, i.e the HIV infection not only irreversibly damages the neurons, but also diminishes the chance of neurogenesis that may help in replenishing the virus induced damaged neurons.

Publications:

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P. Seth: Deriving human neurons and astrocytes from human fetal brains. International Conference of Current Advances in Molecular Biochemistry, Lucknow, Dec. 2007.

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P. Seth: Deriving human astrocytes from human fetal brains. Invited Speaker, National Symposium on Glial Neurobiology, Jiwaji University, Gwalior Oct 2007, India.

P. Seth: Neural Stem Cells. Organized by Haryana State Council for Science and Technology, Bhiwani, India, Aug. 2007 (Science Popularization Series Lecture).

P. Seth: Clade Specific Differences in HIV-1 Tat Induced Neurotoxicity: Importance of Dicysteine motif at position 3031 in HIV-1 Tat. Invited Speaker, NeuroAIDS in Asia and Pacific Rim, Sponsored by and National Institute of Neurological Disorders and Stroke, National Institute of Mental Health (National Institutes of Health, USA), At Garvan Institute, Sydney, Australia, July 2007.

P. Seth: HIV-1 Tat Derived from Clade B and C Induce Neurotoxicity in Human Neuronal Cells. Invited Speaker, Neurobiology and Neuroinformatics 2007 meeting, Cheju National University, Jeju City, South Korea, July 2007.

Funding:

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

Collaborators:

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Dr. UK. Ranga, JNC SAR, Bangalore, India.

Understanding Aberrant Signaling Cascades in Glioblastoma Multiforme

Principal Investigator: Dr. Ellora Sen

Research fellows: Vivek Sharma and Dr. Nitin Koul

Technical Assistant: Uttam Kumar Saini

Glioblastoma multiforme (GBM) represents one of the most malignant brain tumors characterized by intense proliferation, widespread invasion of poorly differentiated cells and poor prognosis. Tumor initiating cancer stem cells (CSC), endowed with all the cardinal features of neural stem cells such as self-renewal and multipotency have been found within GBM. Accumulating evidence suggests that GBM may arise from the inability of these CSCs to differentiate. Thus, differentiation and glioma formation appear to be integrally related.

Neural Stem Cells (NSCs) are regulated by the same cellular pathways that are active in gliomas. Hypoxia appears to maintain stem cells in a state where a limited proliferation is allowed but not its differentiation towards committed progenitors. Hypoxia has also been implicated in maintaining NSC in a proliferative stage by preventing its differentiation towards committed progenitors. The presence of hypoxic regions within GBM is associated with increased malignancy and poor prognosis. As hypoxia is known to regulate the balance between differentiation and proliferation of stem cells and since differentiation of CSCs and glioma formation is integrally related, the focus of the laboratory is to investigate whether hypoxia modulates signaling pathways and chromatin modifiers that regulate proliferation and survival of both CSCs as well as glioma cells grown as monolayer cultures.

Objectives of this project:

1. To evaluate whether hypoxia modulates proliferation of CSC at the expense of differentiation.
2. Hypoxia Inducible Factor (HIF) is a critical regulatory factor in the tumor microenvironment because of its central role in promoting oxidative stress. As GBM are resistant to apoptosis, developing strategies that modulate susceptibility to apoptosis by modulating oxidative stress was also investigated.

We have been successful at isolating stem like cancer cells from glioblastoma cell lines that express neural stem cell markers. These stem like cells were able to differentiate into both neuronal and glial lineages. On investigating the role of hypoxia on glioma cell proliferation, we observed

that exposure of stem-like cancer cells to hypoxia alters the expression of molecules associated with cell cycle progression such as cyclin E, p21, and p27. Similar investigation to delineate the effect of hypoxia on glioma cells grown as monolayer cultures, have revealed that hypoxia increases both HIF-1 α expression and transcriptional activity in GBM cell lines. This increase in HIF-1 α activity is dependent on NF κ B expression, as inhibition of NF κ B abrogates HIF-1 α reporter activity. Interestingly, an elevation in the expression of pro-inflammatory cytokine and mediator interleukin-1 (IL-1) and cyclooxygenase -2 (COX-2) respectively, was observed in glioma cells exposed to hypoxia. As exposure of cells to inflammatory cytokines induces oxidative stress through the production of reactive oxygen species (ROS) and since ROS is known to induce oxidative damage to DNA directly, we investigated the effect of ROS on glioma cell migration, proliferation and resistance to chemotherapy. Based on our findings, we have documented that apoptosis can be induced in glioma cells through elevation of intracellular oxidative stress.

Publications:

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

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E. Sen: Kaempferol induces apoptosis in glioma cells through oxidative stress. Society for Neuroscience, San Diego, Nov. 2007.

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E. Sen: Tumor microenvironment: Role in glioblastoma progression. Jiwaji University, Gwalior, Jan. 2008.

E. Sen: Inflammation and glioblastoma: A deadly nexus. Rohtak Medical College, Rohtak, Haryana, Jan. 2008.

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E. Sen: Inflammation and cancer: Two to Tango!!! Deshbandhu College, New Delhi, Dec. 2007.

E. Sen: Epigallocatechin 3-gallate inhibits HIF-1 α accumulation, HIF-1 α target gene expression and invasiveness in human Glioblastoma cells. International Symposium on Translational Research, Lonavala, Dec. 2007.

E. Sen: Tumor microenvironment and inflammation: role in glioblastoma progression. Ranbaxy Foundation, New Delhi, Jan. 2008.

Funding :

This work is supported by grants from DBT and DRDO, India.

Collaborator:

Dr. V. S. Mehta, Paras Hospital, Gurgaon, India.

Degree Awarded (M.Sc.):

Anindita Agarwal

Involvement of Lipid Rafts in Signal Transduction Events in Glioblastoma Multiforme

Principal Investigator: Dr. Ellora Sen

Research fellows: Richa Tewari

Progression of GBM is associated with alterations in growth promoting and cell cycle control pathways. The signal to divide is typically provided by growth factors and interaction of such ligands to its respective receptors modulates signal transduction cascades whose activity is linked with cellular processes such as mitosis and invasion. Most receptors are known to be associated with lipid rafts (subdomains of the plasma membrane rich in cholesterol and glycosphingolipids). By assembling a spectrum of signaling molecules, lipid raft facilitates cross talk between different signaling pathways. Although Fas, a member of the tumor necrosis factor involved in signaling apoptotic cell death in susceptible target cells is expressed in majority of glioblastoma; GBMs are resistant to death from Fas pathway activation. Therefore, inducing GBM cell death by targeting death receptor pathways is considered as an attractive therapy. As Fas mediated apoptosis requires clustering of the receptor in the lipid raft and since modulation of lipid rafts can be achieved with cholesterol modulating agents, the feasibility of suppressing aberrant signaling through lipid rafts in GBM by agents that affect cellular cholesterol level is being investigated.

Objectives of this project:

- To investigate whether lipid rafts functions as an organizing platform crucial for cell signaling events.
- To identify novel therapeutics that can induce GBM cell death through raft intervention.

We evaluated the efficacy of Miltefosine (Hexadecylphosphocholine - an Alkyl-lysophospholipids (ALPs) analogue) on GBM. ALPs with potent antiproliferative and antitumor activities have shown promise in clinical trials. As ALPs modulate signal transduction pathways originating at the membrane level and since lipid raft facilitates cross talk between different signaling pathways in glioma, we investigated whether Miltefosine could induce apoptosis in GBM by altering signaling events originating at the cell membrane. Fas interacts with FADD to recruit procaspase-8 resulting in the formation of death-inducing signaling complex (DISC); and activation of caspase-8 further activates caspase-3 that initiates apoptosis. Our studies have suggested that treatment with Miltefosine increases the distribution of apoptotic molecules Fas into Caveolin rich raft microdomains from the non raft fraction. This altered clustering is accompanied by the increased

interaction of Fas with FADD and procaspase-8 resulting in DISC formation and Caspase 3 activation. Thus, Fas aggregation and recruitment of apoptotic molecules in Fas-enriched raft microdomains by Miltefosine seems to be an effective mechanism of triggering Fas mediated apoptosis in glioma cells

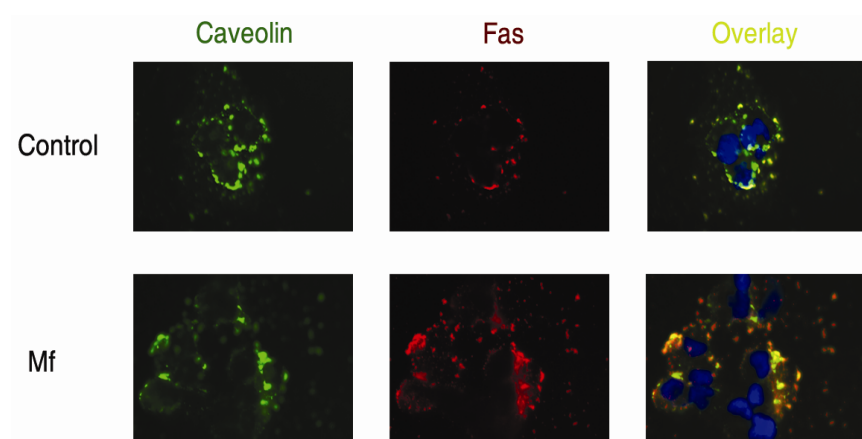


Figure: Miltefosine increases co-localization of Fas with Caveolin in glioma cells.

Publication:

Tewari, R., Sharma, V., Koul, N. and **Sen, E.** (2008). Involvement of Miltefosine mediated ERK activation in glioma cell apoptosis through Fas regulation. **Journal of Neurochemistry** (In Press).

Funding:

This work is supported by the Innovative Young Biotechnologist Award to Ellora Sen by DBT, India (IYBA, 2007).

Signaling Cascades Regulating the Differentiation of Glial Progenitors Along Specific Lineages

Principal Investigator: Dr. Ellora Sen

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. Perinatal Hypoxic/Ischemic (H/I) brain injury is a major cause of morbidity resulting from premature birth. One of the histopathological hallmarks of perinatal hypoxic injury is permanent deficit in white matter oligodendrocyte. This decrease in oligodendrocyte is commensurate with increased astrocytogenesis.

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. Recent advances in understanding neural stem cell differentiation into glial lineages have revealed the importance of growth factors and relevant downstream transcription factors. Transcription factors that regulate NSC fates, act either positively or negatively, and some transcription factors induce the differentiation of one cell lineage while suppressing another. Thus the spectrum of cell types produced during differentiation of NSCs can be understood as the output of combinatorial transcription factor actions. We hypothesize that certain inducers of astrocyte differentiation are elevated following perinatal H/I and these factors working through their respective downstream transcription factor combinatorially causes the preferential differentiation of bipotential glial progenitors in the subventricular zone (SVZ), - a region of the brain that harbors the multipotential neural stem cells/progenitors, towards astrocytes and away from the oligodendrocyte lineage.

Objectives of this project:

- To investigate whether hypoxia directly regulates the differentiation potential of glial precursors.
- To identify whether the transcription factors known to be trigger astrocytic differentiation are elevated in neural stem cells upon exposure to hypoxic environment.

To investigate the responsiveness of neural precursors to hypoxia, neurospheres isolated from the subventricular zone of rat pups were

subjected to hypoxia. Western blot analysis revealed an increase in the expression of astrocyte specific glial fibrillary acidic protein (GFAP) in neurospheres exposed to hypoxia, as compared to the untreated control. Since the phosphorylation of transcription factor STAT3 is known to promote astroglialogenesis, we determined phosphorylation status of STAT3 in neurospheres exposed to hypoxia. An increase in STAT3 phosphorylation concomitant with the increased GFAP expression was observed in neural precursors. Our preliminary findings indicate that hypoxia increases astrocytogenesis in neural precursors.

Funding:

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

Molecular Mechanisms of Synaptic Plasticity and Memory: Activity-Dependent Changes in Regulatory Molecules

Principal Investigator: Dr. Shiv Kumar Sharma

Research Fellows: Chinmoyee Maharana, Kaushik Pramod Sharma

Project Assistants: Vivek Mahadevan, Seethalakshmi

Lab Attendant: Narayan

How we make new memories has been one of the areas of immense investigation in neuroscience. Activity-dependent molecular and synaptic changes play a deterministic role in memory formation. Activation of several signalling cascades including the extracellular signal-regulated kinase (ERK) pathway has been shown to be important for synaptic plasticity and memory in several different model systems that are used for memory analyses. In addition to the regulation of signalling pathways, long-term potentiation and long-term memory involve changes at the translational and transcriptional levels. We are investigating activity-dependent regulation of ERK activation, and the regulation of translational and transcriptional components. We use adult rat hippocampal slices for our studies since hippocampus is one of the regions important for several different forms of memories.

While some studies have been carried out, the mechanisms of activity-dependent protein and RNA synthesis are far from clear. Most of the protein synthesis in a cell is cap-dependent and is regulated at the initiation step. Phosphorylation of the initiation factor, eIF4E, is correlated with enhanced protein synthesis. We find that depolarization of hippocampal slices leads to an increase in the phosphorylation of translational components. We are now examining the mechanism that initiates with Ca^{++} influx and leads to translational regulation.

It is well known that histone modifications play a deterministic role in the regulation of transcription. One such histone modification is acetylation of its lysine residue(s) that serves to neutralize the charge and hence, leads to opening of the chromatin making it accessible to transcriptional machinery. Our results suggest that depolarization leads to enhanced acetylation of histone, a modification that is correlated with enhanced rate of transcription in several cell types.

Thus, activity-dependent regulation of components involved in protein and RNA synthesis may serve to increase translation and transcription that are required for long-term forms of synaptic plasticity and memory.

Funding:

This work is supported by a grant from DBT and also by NBRC Core funds.

Neurodegeneration and Impairment in Synaptic Plasticity and Memory by Oligomeric Form of Amyloid Beta

Principal Investigator: Dr. Shiv Kumar Sharma

Research Fellow: Shilpa Mishra

Project Assistant: Prakash Mishra

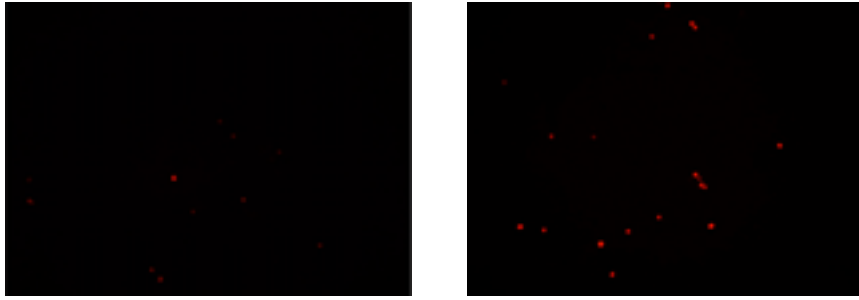
Lab Attendant: Narayan

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. The amyloid plaques consist mainly of fibrils. And hence, the fibrillar form of amyloid beta was initially thought to be the major causative agent in AD. Recent studies, however, suggest that the oligomeric form of amyloid beta (A-beta) is more relevant than the fibrillar form as far as the synaptic loss, synaptic plasticity and memory impairment, and neuronal cell death is concerned.

In this project we are examining the mechanisms of neurodegeneration and the role of protective agents. We are also investigating the mechanisms of synaptic plasticity and memory impairment caused by oligomeric A-beta.

We are using primary neurons for these studies. We find that low micromolar concentrations of A-beta oligomers cause toxicity to human neurons (see figure). We examined also the protective effects of a flavonoid. Our results show that this flavonoid has protective properties towards direct neuronal toxicity induced by A-beta oligomers. We have characterized the A-beta oligomers that were prepared in vitro using published protocols with minor modifications. Our preparation also contains different species of oligomers including dimers and high molecular weight oligomers.

Thus, a flavonoid displays protective activity towards direct neuronal cell death induced by oligomeric A-beta. Currently, we are examining whether it offers protection towards indirect neuronal toxicity caused by inflammation. We would then examine the mechanisms involved in the protective action of this flavonoid.



Control

Oligomeric A-beta

Figure: TUNEL assay showing toxicity of A-beta oligomers to human neurons. Neuronal culture treated with A-beta oligomers shows more number of TUNEL positive cells than the control culture, indicating DNA fragmentation.

In order to examine the mechanisms of synaptic plasticity and memory impairment caused by A-beta oligomers, we have standardized conditions for primary hippocampal culture from embryonic rats. We will now examine the effects of A-beta oligomers on regulatory molecules involved in long-term potentiation and memory.

Funding:

This work is supported by NBRC Core funds.

Collaborator:

Dr. Pankaj Seth, NBRC.

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

Principal Investigator: Dr. Anirban Basu

Research Fellow: Manoj Kumar Mishra, Rachna Duseja, Sulagna Das

Project Assistant: Debapriya Ghosh

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. So far one project has been initiated to understand the molecular mechanism of inflammation in Japanese Encephalitis (JE). JE is an acute viral infection of the CNS caused by a mosquito-borne flavivirus called Japanese encephalitis virus (JEV). JEV targets the CNS, clinically manifesting with fever, headache, vomiting, signs of meningeal irritation and altered consciousness leading to high mortality and neurological sequelae in some of those who survive. Despite the clinical importance, little is known about the cellular and molecular events of inflammation that underlie the host defense during JEV infection. Rapid microglial and astroglial activation could play a crucial role in the inflammatory processes of the disease. Moreover proinflammatory mediators produced by activated microglia contribute to great extent in the progression of damage at the time of disease. So proper understanding of the “cascade of events” that occur during Japanese encephalitis will help us to develop disease modifying therapies.

We have showed that *in vitro* JE virus infection i) modulates the induction of TNFR-1 associated proteins (TNFR-1, TRAF-2 and TRADD) in Neuro2a cells in time dependent fashion, ii) up regulates several signaling molecules (pASK-1, p38 MAPK, pJNK, p53) which directly regulate apoptosis, iii) modulates the induction of pro and anti apoptotic molecules (Bax, Bcl-2, Cleaved PARP and Caspase-3). We have further showed that siRNA against TRADD inhibit neuronal apoptosis following JE virus infection. Using an *in vivo* model of JE we have also showed that i) TNFR-1 is expressed predominantly in neurons, but not in microglia or in astrocytes, ii) there is a modulation of anti apoptotic and pro apoptotic proteins and signaling molecules which are related to cell death, iii) administration of TRADD siRNA increases the rate of survival in animal. We have further documented that SK-N-SH, a human neuroblastoma is also susceptible to JEV induce

neuronal apoptosis, and transfection with siRNA against TRADD confers protection from virus induced apoptosis.

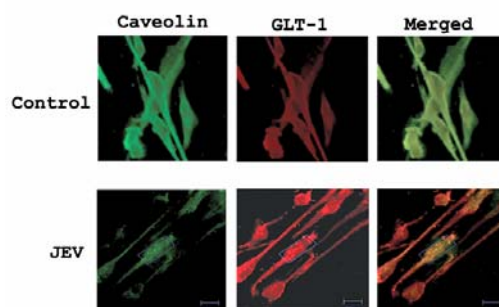


Figure 1: Colocalization of Caveolin (marker for Lipid Raft) and Glutamate Transporter (GLT-1) in primary mice astrocytes following JEV infection. Primary mice astrocyte cells were plated on cover-slips in 12-well plate at a density of 5×10^4 cells/well in 1ml of medium and were cultured for 18 hrs. Cells were then incubated with JEV (multiplicity of infection=5) for 1 hr. The virus was removed and the plates were then washed with 1X PBS to remove the unbound virus particles. The plates were kept in serum-free media at 37°C and after 24 hours processed for immunocytochemical staining for Caveolin (marker for Lipid Raft) and GLT-1 (Glutamate Transporter). Images were captured by confocal microscope (Zeiss, Germany). Coculture of JEV with primary mice astrocytes decreases the Caveolin expression in the cell, whereas GLT-1 expression was up-regulated. Colocalization (in the merged image) of Caveolin and GLT-1 indicates the close association of glutamate transporters with lipid raft in viral infection. Bar = 20µm

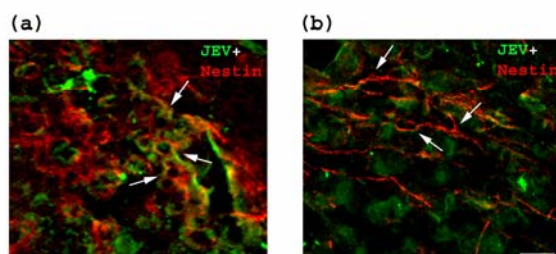


Figure 2: Colocalisation of JEV antigen with Neural Progenitor cells (NPCs) in Subventricular zone. Double immunohistochemistry was performed on JEV infected brain sections for anti-JEV (green) and anti-Nestin antibody (red). Colocalisation of JEV antigen with the Nestin positive cells (a) has been indicated by white arrows, thus indicating the infection of NPCs by JEV *in vivo*. However, uninfected Nestin positive cells were also observed in the same JEV infected brain (b), indicated by white arrows, with morphological characteristics different from JEV infected NPCs. Scale bar corresponds to 25 microns.

In continuation of our earlier work we have further demonstrated that in experimental model of JE *in vivo* administration of siRNA against TRADD i)

inhibited neuronal death ii) abated astroglial response iii) diminished activation of resting microglia toward a reactive state iv) diminished levels of proinflammatory mediators v) reduced recruitment of leukocytes vi) attenuated expression of cell adhesion molecule and chemokine receptors, and vii) down regulated MMP-9 and VEGF.

Recently we have reported that following JEV infection 1) there is an upregulation of IL-18 and IL-1 β in brain 2) both microglia and astrocytes differentially produce IL-18 and IL-1 β , 3) IL-18 and IL-1 β differentially modulate microglia and astrocytes to release cytokines and chemokines. We have also demonstrated following IL-18 and IL-1 β treatment to microglia and astrocytes produce mediators, which are capable of modulating neuronal survival. Recently we had also initiated our work on how inflammation following JEV infection modulates neurogenesis and gliogenesis. At this point of time we found that JEV infection causes a profound loss in number of neuronal stem cells as well as number of immature neurons. Neurospheres isolated from the SVZ of JEV infected animals has 1) less potential to form multipotential neurospheres and, 2) their average diameter is smaller when compared to a neurosphere isolated from the SVZ of uninfected animals. Furthermore, we had also initiated a work to understand the molecular mechanism of innate immune response in brain following JEV infection.

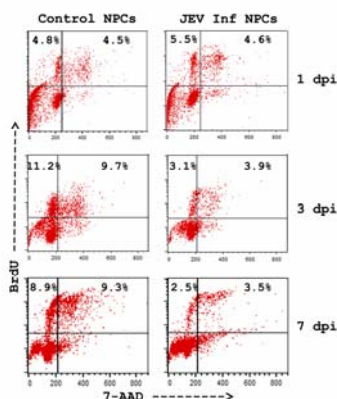


Figure 3: JEV infection decreases the proliferation of Neural Progenitor cells in vitro. Control and JEV infected NPCs were pulsed with BrdU for 6 hours, then stained for BrdU and detected by FACS. The percentage of BrdU positive cells (both 2n and 4n DNA content state) have been indicated at different days post infection (dpi). A significant decrease in BrdU positive cells upon JEV infection was observed at 3 dpi and 7 dpi. The total percentage of BrdU labeled cells underwent a significant 3 fold reduction in JEV infected NPCs than control NPCs ($p < 0.05$).

Increasing experimental, clinical, and epidemiological studies point to the pivotal role of inflammation in the pathogenesis of acute and chronic neurodegenerative diseases and to the protective effects of anti-inflammatory drug therapies. Given the potential therapeutic role of these compounds in

neuro-inflammation, we have initiated a project to evaluate the role of understanding the molecular mechanisms of action of both known and newly synthesized chemical entity in conferring protection from CNS inflammation and infection. Work in our laboratory for last one year identified the neuroprotective role of minocycline in JE. Our findings clearly indicates that minocycline 1) reduce enhanced microgliosis 2) decrease the elevated level of proinflammatory cytokine and 3) enhance neuronal survival by reducing the severity of apoptotic cascades following JE. Recently we have identified Arctigenin, a lignan isolated from plant, as a potent anti viral agent against Japanese Encephalitis.

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A Basu: Japanese Encephalitis: from Neuropathology to therapeutic intervention. B C Guha Center for Genetic Engineering & Biotechnology and Department of Biochemistry, Ballygunge Science College, University of Calcutta, 5th March, 2008.

A Basu: Japanese Encephalitis: from basic research to therapeutic intervention. Presidency College, Kolkata, 4th March, 2008.

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V Swarup, J Ghosh A Basu: Novel strategy for treatment of Japanese Encephalitis using Arctigenin, a plant lignan. 2nd International Symposium on Translational Research. Dec. 9-12, 2007, Lonavala.

J Ghosh, V Swarup and A Basu: Novel strategy for treatment of Japanese Encephalitis using Arctigenin, a plant lignan. International Conference on Emerging and Re-emerging Viral Diseases in the Tropics and Sub-Tropics, Indian Agricultural Research Institute, 11-14th Dec., 2007.

S Das and A Basu: Japanese encephalitis virus abrogates neural stem cell proliferation but fails to induce cell death. International Conference on Emerging and Re-emerging Viral Diseases of the Tropics and Sub-Tropics, Indian Agricultural Research Institute, 11-14 Dec. 2007.

R Duseja, M K Mishra, and A Basu: TLR signaling following JEV infection. Annual Meeting of Indian Academy of Neurosciences, Banaras Hindu University, Varanasi, 22-25 Nov. 2008.

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S Das, A Ghoshal and A Basu: Inflammation, a key modulator of neuronal death and neurogenesis pattern in an experimental model of Japanese encephalitis. Society for Neuroscience (SFN) Meeting, San Diego, 3rd-7th Nov. 2007.

V Swarup, S Das and A Basu: Japanese encephalitis virus infection induces Tumor-Necrosis Factor receptor-1 mediated neuronal apoptosis. Society for Neuroscience (SFN) Meeting, San Diego, 3rd -7th Nov. 2007.

A Basu: Microglial madness: when friend turns to foe. National Symposium on Glial Neurobiology, Center for Neurosciences, Jiwaji University, Gwalior, 23rd Oct. 2007.

A Basu: Molecular Mechanism of Neuronal death in Japanese Encephalitis. IMTECH, Chandigarh, 24th Aug. 2007.

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A Basu: Inflammation and Neuronal Apoptosis in Japanese Encephalitis. Chittaranjan National Cancer Research Institute, Kolkata, 17th July, 2007.

Funding:

This work is supported by grants from DBT and CSIR, India

Patent Applied:

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

Degree Awarded (M.Sc.):

Vivek Swarup

Understanding the Molecular and Cellular Pathology of Alzheimer's and Prion Disease using CNS Stem Cell Cultures

Principal Investigator: Dr. Ranjit Kumar Giri

Technical Assistant: Sanjay Kumar

Lab Attendant: Pankaj Chopra

Both prion and Alzheimer's diseases are progressive neurodegenerative diseases. Although rare, prion disease itself includes varieties of 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 that contains the infectivity for which prion diseases are special type of infectious disease, devoid of any live pathogens. Replication of this defective protein and its subsequent accumulation with the patho-progression of prion disease made it a unique disease in medical science. 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. Alzheimer's disease on the other hand is the most frequent cause of dementia affecting more than 5% of the population over the age 65 years and is caused due to the mutation/s in various genes that ultimately increase the production of beta amyloid peptide. Both these diseases consist of accumulation of multimerization of misfolded protein. In prion disease, the normal cellular prion protein (PrP^C) is converted post-translationally to pathological, infectious and alternatively folded isoforms (PrP^{Sc}). In Alzheimer's disease, Amyloid precursor protein is favorably cleaved to generate beta sheet rich beta amyloid peptides which have a tendency to aggregate. Accumulation of these proteins is the hallmark pathology of these diseases. How these events cause neurodegeneration is not known. Both human diseases and animal models of these diseases have not been able to differentiate the effect of prion protein or beta amyloid peptide on various brain cell types including CNS stem cells and their direct toxic affect on mature neuronal cells. Cell culture systems those have been used to study these issues 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 posses the power to differentiate into adult brain cell types such as, neurons, astrocytes and oligodendrocytes. Recently, we reported the prion infectivity can be propagated in neurosphere

cultures similar to the mice from which they were derived. Development of such a valuable tool can also be tested in Alzheimer's disease. Most importantly, CNS stem cells also offer opportunity to address genetic contributions towards Alzheimer's diseases.

Although extensive research has been performed for several decades on these two neurodegenerative diseases, yet there is no therapy. It could be partially due to the complexities posed by the brain. *In vivo* models contribute such challenges as various cellular and molecular networks co-exist for any specific diseased condition. Neurosphere culture will minimize such complexities as these cells can be differentiated towards specific brain cell types to specific differentiation condition. Based on these hypothesis our objectives are,

- To study cellular pathology of prion disease using neurosphere cultures that support prion replication.
- To develop a new *in vitro* cell culture model to study beta amyloid-mediated pathogenesis.
- To study the alteration in the cell cycle events, cell lineage specification and, genetic and epigenetic programs that govern normal function of various brain cells including CNS stem cells.
- To determine the effect of microglia on neuronal loss to prion and beta amyloid aggregation.

As both these diseases start with the accumulation of a defective protein/peptide, progress slowly with a long incubation time and eventually lead to neuro-degeneration, the results from both these models will complement each other and might provide insight into the mechanisms that will lead to the identification of a common network that regulate neurodegeneration.

Currently, our lab is working towards establishing CNS stem cells containing neurosphere cultures expressing either prion protein or human amyloid precursor protein containing Swedish mutation (APPswe) along with human mutated Presenilin-1 gene (PS1 δ E9). Initially, we have developed two independent neurosphere lines positive for both huAPPswe and huPS1 as shown in figure. Two separate wild type neurosphere lines are also established as a control. Similarly, we have also established CD-1 neurosphere lines for mouse prion replication.

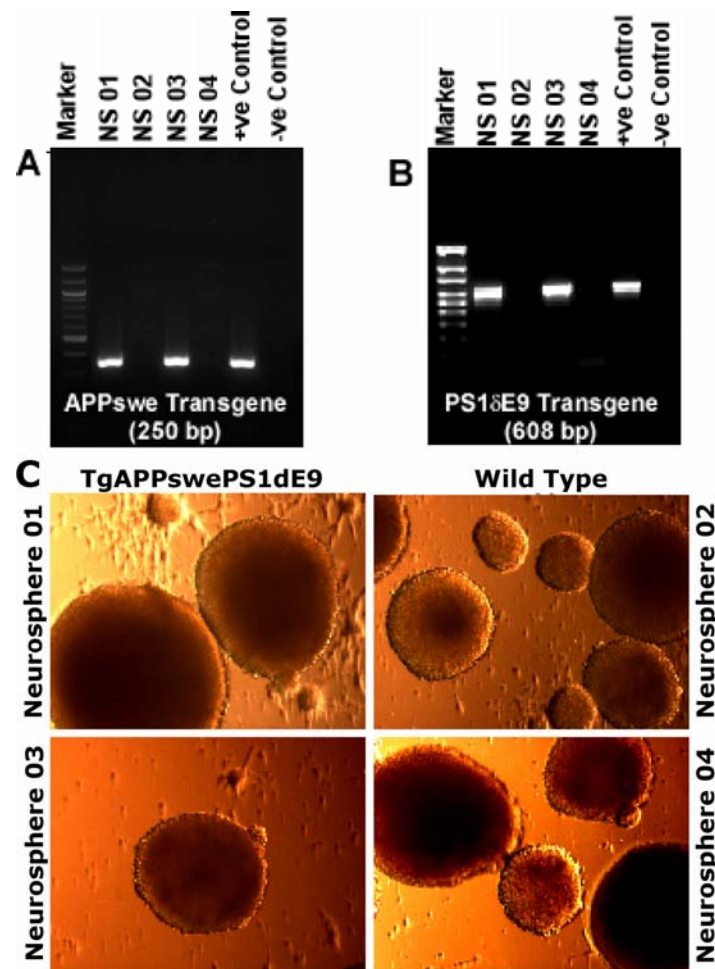


Figure: Development of Neurosphere lines for an *in vitro* model of Alzheimer's disease. PCR amplification of 350bp DNA fragment of mouse/human APPswe transgene (A) and 608 bp DNA fragment of human PS1 transgene (B) demonstrate the neurosphere (NS) line 1 and 3 as positive for transgenes and line 2 and 4 as wild type. C) Free floating spheroidal cultures was obtained from E13 embryos that are either positive for APPswe and PS1 Δ E9 genes or without transgenes (wild type), magnification 100X and bright field images.

In future, various neurosphere cultures replicating mouse prion protein along with our recently developed lines will be employed to characterize the pathology of prion disease at various brain cells level. Similar to prion disease, the neurosphere lines obtained from double transgenic mice (TgAPPswePS1 Δ E9) will be characterized for the synthesis of beta amyloid peptide, the initial step in the pathogenesis of Alzheimer's disease.

Funding:

This work is supported by NBRC Core funds.

Probing the Control of Action Using Saccadic Eye Movements

Principal Investigator: Dr. Aditya Murthy

Research Fellows: Arjun Ramakrishnan, Sharika K.M.

Because the density of photoreceptors decrease rapidly from the fovea, our visual sensitivity rapidly declines centrifugally from the centre of gaze. As a consequence objects in the periphery cannot be identified clearly. To deal with this problem our brains have evolved an oculomotor system that uses fast almost ballistic eye movements called saccades followed by fixation. 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. Since perceptual processes do not strictly dictate such behavior, the role of cognition must also be factored in. The conceptual challenge is therefore to understand the representations of the image that guides orienting responses and the nature of computations that sub-serve and link visual and cognitive processing, and eye movement programming. The long term goals of this project are to understand how vision and cognition together guide action. These questions will be approached through studies of visually-guided saccades in novel paradigms designed to probe the oculomotor control in normal human subjects.

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.

Behavioral evidence of chunking of saccades

To examine the nature of saccadic programming in the follow task 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 found this latter case to be true in many trials with the second saccades directed towards the old final target position, the new information available regarding the final target's location notwithstanding.

Serial programming of saccades

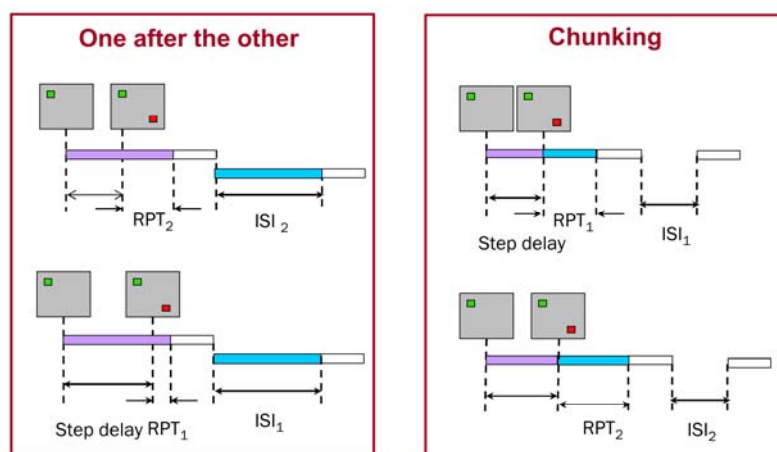


Figure: Conceptual framework to understand how sequential saccades maybe programmed. In the left panel saccades are programmed one after another. In the right panel saccade programming is chunked together as a single packet with the execution of each saccade occurring sequentially.

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Presentations:

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A. Murthy and Vishal Kapoor: Does covert inhibition potentiate online inhibitory control? Neuro2007 meeting, Yokohama, Japan, 2007.

Funding:

This work is supported by NBRC Core funds.

Brain Mechanisms of Action Control in Humans

Principal Investigator: Dr. Aditya Murthy

Research Fellow: Neha Bhutani

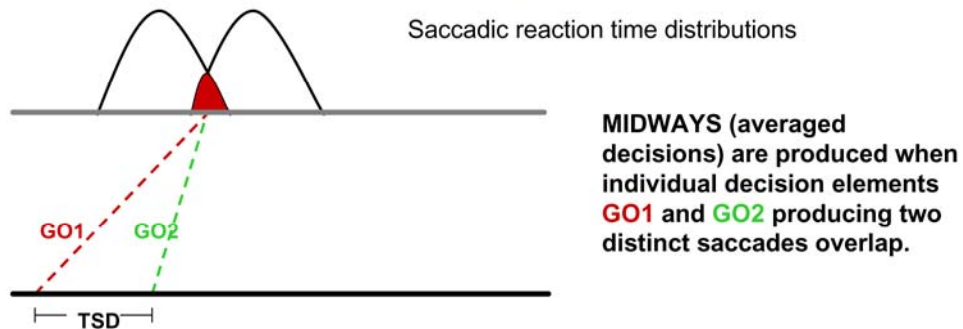
Because eye movements can provide a behavioral measure of sensorimotor processing and cognitive functions of the brain, their study can provide an elegant and simple system to understand the neural basis of voluntary control. From animal, human lesion and neuroimaging studies, the major brain areas underlying 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.

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

Using the well-known double-step task a number of studies have provided evidence that the preparation of two sequential saccades may overlap in time. One consequence of parallel preparation is saccade averaging, which is thought to result from the collision of two saccade decision processes aimed at stimuli at close spatial and temporal proximity. To test this notion we recorded subjects on a FOLLOW task where they had to follow the sequence of the appearance of two targets with two saccadic eye movements. The results showed that on 1.84% ($\pm 0.98\%$) of such trials gaze landed between the two targets. Further, the propensity to produce averaging was highest at the shortest temporal delays. Using Monte Carlo simulations we used the LATER model (Linear Accumulation to Threshold with Ergodic Rate) to predict the frequency of saccade averaging as a function of target step delay and found that although the simulations were successful at predicting the occurrence and pattern of midways, the LATER model consistently overestimated the extent of saccade averaging. These observations suggest that the brain must have mechanisms that actively prevent the averaging of saccadic decisions processes. Because the basal ganglia have been

implicated in response selection, we hypothesized a role for basal ganglia in the gating of responses during sequential saccades production. To test our hypothesis we recorded 10 PD patients and 5 age-matched controls in the FOLLOW task and observed a significantly higher percentage of midways in PD patients ($9.37\% \pm 2.79\%$) compared to controls ($2.35\% \pm 1.57\%$; $p < 0.05$). These results taken together suggest that the basal ganglia help maintain distinct representations of concurrently evolving decisions ensuring the correct execution of sequential movements.

RACE MODEL explanation for averaged decisions



Hypothetical control of averaged decisions

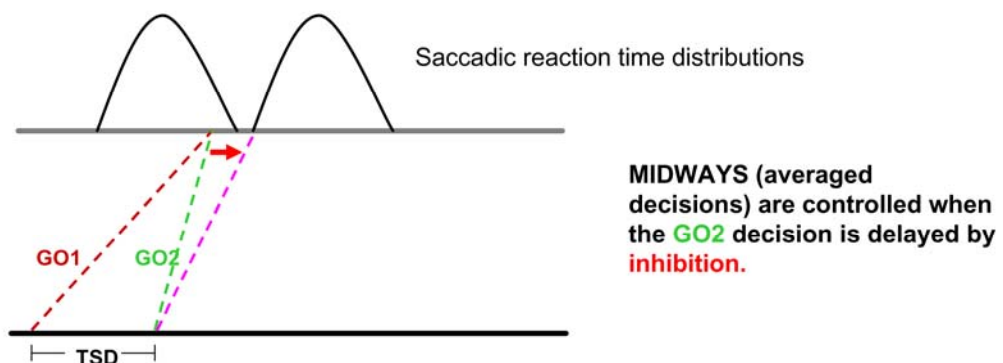


Figure: Proposed race model to understand the how averaged saccades (midways) are produced by the overlap of individual saccadic decision elements. We propose that inhibition between decision elements limit the extent of temporal overlap causing fewer averaged saccades.

Funding:

This work is supported by NBRC Core funds.

Collaborators:

Prof. Madhuri Behari (AIIMS), Prof. Vinay Goyal (AIIMS).

Neural Control of Action by Frontal / Basal Ganglia Networks

Principal Investigator: Dr. Aditya Murthy

Research Fellows: Supriya Ray, Arjun Ramakrishnan,
Neha Bhutani, Sharika K.M.

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 frontal/basal ganglia network. 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. 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.

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 study the temporal evolution of the control of decision-making in a double-step task. In the future we hope to insert our electrodes in basal ganglia to study their role in the control of saccadic decision-making as well.

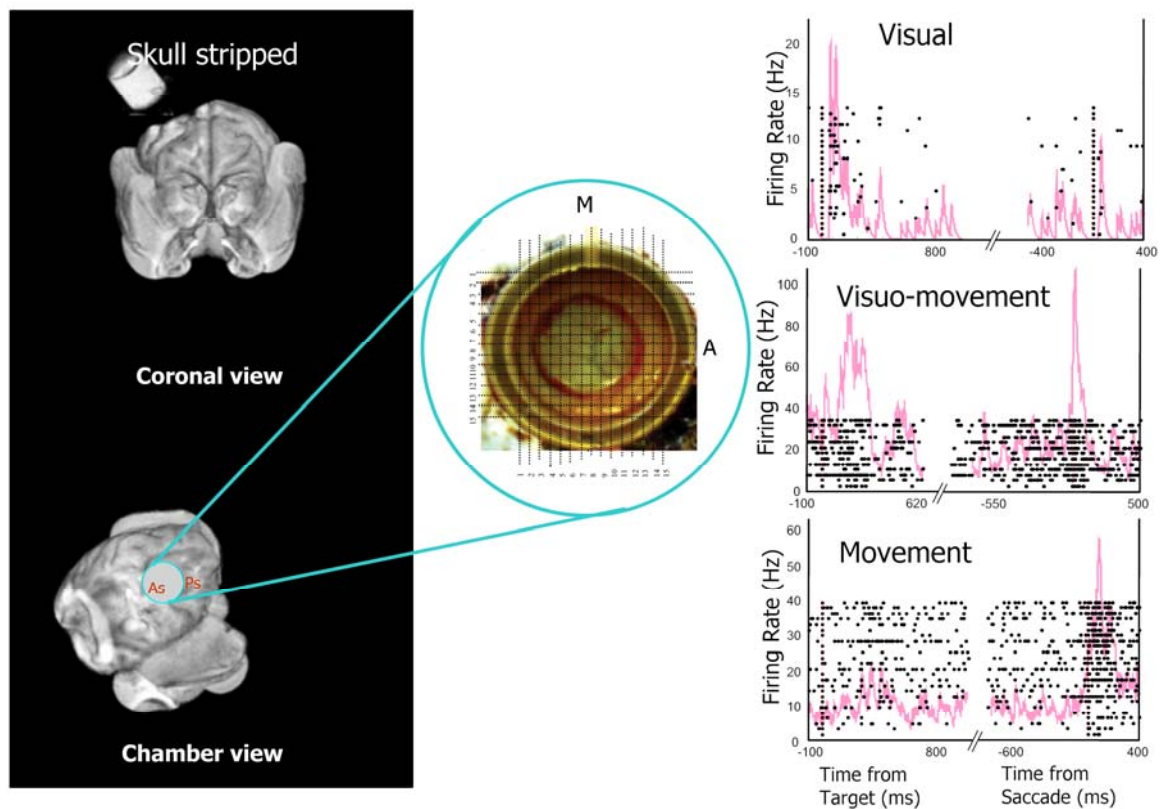


Figure: (Left) MRI guided localization of frontal eye fields in the craniotomy. (Right) Neurophysiological recording of single neurons in macaque frontal cortex during a memory-guided task. Neurons are classified as visual, visuomovement and movement depending on whether they are driven by the stimulus or the saccade response.

Funding:

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

Degree Awarded (Ph.D.):

Supriya Ray

Processing and Integration of Tactile Information in the Somatosensory Cortex

Principal Investigator: Dr. V. Rema

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

Project Assistant: K. Praveen

The focus of our laboratory is to understand the mechanisms by which tactile sensation is transduced and processed in the cerebral cortex of normal brain and in brains with injury. The questions we are addressing are the follows: (i) How are patterns of tactile stimuli acquired and how is this information encoded and integrated with motor performance. (ii) How does lesions or stroke-like injuries modify sensory processing in the somatosensory cortex. (iii) What are the mechanisms that cause functional deficits in lesioned cortex. We are using electrophysiological and behavioural methodology to study somatosensory functioning of the adult rats and how it is affected by cortical injuries. Tactile stimulus is acquired by moving the 25 large whiskers on each side of snout across an object at different frequencies. The neurons in the barrel cortex of the rat process the sensory information. In addition, the neurons within the barrel column also integrate sensory information from adjacent barrel columns and from the contralateral sensory cortex. In our earlier studies we have shown that an injury to a small area of the somatosensory cortex affect the neuronal activity in the contralateral intact hemisphere. We see reduction of spontaneous activity of the neurons. The neurons decrease their ability to respond the sensory stimulation and also show impairment in achieving experience-dependent plasticity.

During this year our studies were directed towards understanding the mechanisms of this injury-induced plasticity and addressed the following hypotheses: (1) Deficits in experience-dependent plasticity in the somatosensory cortex of the intact hemisphere are due to alterations in synaptic activity resulting from loss of input from the lesioned region in the contralateral hemisphere. (2) Lesions in one hemisphere will result in modifying the excitability of neurons in the intact hemisphere by altering the levels of molecules that regulate neuronal activity. To test these hypotheses we did experiments addressing questions: (a) Is the reduction in evoked responses and experience-dependent plasticity due to the effect of lesion on thalamo-cortical processing? Neurons in layer 4 of somatosensory cortex receive major sensory input from the thalamus. We recorded from somatosensory cortical neurons in layer 4 to examine thalamocortical processing in lesioned animals. We found that these neurons did not show significant changes in either spontaneous or stimulus evoked activity during

the initial hours following lesion. However at longer post-lesion times of four months and above there is significant reduction in the responses. These observations lead us to conclude that the long-term reduction in neuronal activity and in experience-dependent plasticity in layer 4 might not be due to immediate remodeling of thalamocortical synaptic inputs but is due to changes in neurotransmitters and their receptors. Preliminary experiments based on this conclusion indicated that the reduction in neuronal activity in layer 4 might be due to the lessening in excitability of the neurons resulting from reduction in level of NMDAR1 and increase in GAD 65.

(b) Is the decrease in evoked responses and experience-dependent plasticity due to the effect of lesion on cortico-cortical processing? For this study we recorded from neurons in layers 2/3 from the intact somatosensory cortex of the normal hemisphere opposite lesion site. These layers receive and process intracortical sensory information. We saw significant increase in both spontaneous and stimulus-driven activity over time during the initial 12 hours. These results suggested neurons in layers 2/3 are more plastic (sensitive) as compared to neurons that process thalamocortical information in layer 4. Therefore, it is possible that different mechanisms of plasticity operate on neurons in different layers. One of the mechanisms causing impairment of experience-dependent plasticity could be through synaptic modification in layers 2/3.

In the rat somatosensory cortex callosal inputs are known to reciprocally terminate in layers 2/3 on the septal neurons surrounding the barrel column. It has been suggested that these septal neurons are inhibitory interneurons which in turn terminate on barrel column neurons to regulate their activity by feedforward inhibition. Hence we hypothesized that the significant increase in both spontaneous and stimulus-driven activity during early postlesion hours in layers 2/3 is caused due to reduction in the activity of neurons in the area surrounding the lesion thereby removing inhibition exerted through the callosal inputs on somatosensory neurons of layers 2/3 in the opposite intact hemisphere. To test this hypothesis we examined the activity of neurons surrounding the lesion. Our results conclusively show that the activity of neurons remains at about 50% below prelesion (control) responses. This indicates that the alteration of synaptic activity in layers 2/3 through callosal input could be one of the mechanisms that underlie injury-induced plasticity. In addition, we have preliminary results showing layer-specific up-regulation in GABA receptor alpha 3 subunit in lesioned cortex. Inclusion of the GABA receptor alpha 3 subunit could make the GABA receptor to function as an excitatory receptor. Therefore another mechanism for up-regulation of neuronal activity after an injury could be by switching the GABA receptors from inhibitory function to excitatory function.

An important question that arises from the above mentioned studies is whether these plastic changes are specific to lesions of the somatosensory cortex? In other words, will lesion of the interconnected whisker motor cortex produce similar plastic changes in the somatosensory cortex. We lesioned the motor cortex and recorded the neuronal activity from the somatosensory cortex in the same hemisphere. Our results show that the neurons in the input layer 4 do not change significantly but there is increase in spontaneous activity of neurons in the output layers 2/3 and layer 5. In addition, these neurons show an increase in the magnitude of response to stimuli. The results of this study suggests that lesions in the motor cortex would interfere with sensory integration from all the whiskers and could cause deficit in spatial as well as temporal processing of sensory information.

Publication:

Rema, V., Bali, K.K., Ramachandra, R. Chugh, M., Darokhan, Z., Chaudhary, R. (2008). CDP-choline supplement in early life induces stable increase in dendritic complexity of neurons in the somatosensory cortex of adult rats. **Neuroscience, 155: 556-564.**

Presentations:

Z. Darokhan, M. Chugh & V. Rema: Laminar differences in response of barrel cortex neurons in the immediate hours following lesions of homotopic somatosensory cortex. Society for Neuroscience, 2007.

M. Chugh, Z. Darokhan, V. Rema: Photothrombotic lesions of motor cortex increase neuronal activity in layer 5 of whisker barrel cortex in adult rats. Society for Neuroscience, 2007.

M. Chugh, Z Darokhan & V. Rema: Differential influence of motor cortex on neuronal activity of barrel and septal domains in somatosensory cortex. Indian Academy of Neuroscience, 2007.

R. Chaudhary and V. Rema: Chronic iron deficiency impairs somatosensory behavior and alters the expression of NMDAR1 and GAD 65 in somatosensory cortex. Indian Academy of Neuroscience, 2007.

Z. Darokhan, M. Chugh & V. Rema: Lesions in the somatosensory cortex reduces activity of neurons around the lesion site in adult rats. Indian Academy of Neuroscience, 2007.

V. Rema: Invited talk "Injury-induced plasticity in the somatosensory cortex". Salk Institute, 31 Oct. 2007.

V. Rema: Invited talk "Modulation of sensory information processing following lesion of motor cortex." Indian Academy of Neuroscience, 22 Nov. 2007.

V. Rema: Invited talks in the lecture Workshop “Frontiers in Neuroscience” at Sophia College, 4-5 Jan. 2008: Basic lecture: “Techniques for studying sensory processing in rats”.

V. Rema: Invited talks in the lecture Workshop “Frontiers in Neuroscience” at Sophia College, 4-5 Jan. 2008: Research lecture: “Plasticity in the rat somatosensory cortex”.

Funding:

This work is supported by:

1. International Senior Research Fellowship from Wellcome Trust, UK.
2. A grant from DBT, 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: Devesh Kumar

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

We perform unilateral lesions of the dorsal columns of the spinal cord leaving spinothalamic and other ascending and descending pathways intact. Using multiunit mapping and intracortical microstimulation techniques we are determining the effects of these injuries on the somatosensory and motor areas of the brain. These plastic changes in the brain organization are then related to the behavioural effects of the injuries in order to understand the mechanisms of recovery of behaviour following such spinal injuries and to develop interventions for better recoveries. We use both primate as well as rodent model for our studies due to specific advantage of each system. Work done during the year is described below.

Representations of the neck and the whiskers in the rat motor cortex and its mutability following dorsal spinal lesions. Our experiments, reported last year showed that in the motor cortex of normal adult rats when mapped under low anaesthetic levels, the medial most eye movement region in M1 is bordered laterally by whisker movement zone, followed even more laterally by a small area with representation of movement of the neck muscles. However, in rats mapped under deep anesthesia the neck movement region expanded medially into the whisker region. We have further investigated this phenomenon taking into account the movements evoked at suprathreshold currents. Based on results from these experiments we propose that in parts of what was believed to be the whisker region of the rat motor cortex there is a dual representation of the neck and whiskers. A detailed analysis of the data showed that only the caudal whisker region has the dual representation, perhaps reflecting the combined use of whiskers and the neck movements by rats for the exploratory behaviour.

We mapped the somatosensory and motor cortices of rats with unilateral lesions of dorsal columns in order to understand how reorganizations in the sensory and motor cortices are related. The rats were mapped between 4 – 15 months after the lesion. The results show that the deafferented parts of the S1 remain largely unresponsive to stimulation of skin of any part of the body. There was no large-scale reorganization in the somatosensory cortex. In the motor cortex of rats with complete lesions no movement of the contralateral arm was observed when stimulated by intracortical microstimulation. Instead there was an expansion of the whisker movement region or the neck movement region into the de-efferented cortex. In some of the rats we could also evoke movements of the ipsilateral arm. The results show emergence of new movement fields in the primary motor cortex of adult rats as a result of the spinal injury.

Brain reorganization following dorsal spinal cord injuries in primates. We determined how organization of the somatosensory area S2/PV of adult monkeys is affected by unilateral lesions of the dorsal columns at upper cervical levels. We found that neurons in the hand region in area S2/PV become unresponsive to stimulation of the deafferented parts of the contralateral hand following lesions of the dorsal columns. In addition, as for area 3b, there is emergence of face responsive regions in the part of the cortex where hand inputs are normally observed. In case the dorsal columns lesions are partial, parts of area S2/PV continue to respond to stimulation on the hand as seen for area 3b. The results show that area S2/PV undergoes reorganization similar to that for area 3b, and alternate spinal inputs are not able to preserve normal topography in these somatosensory areas. The results point to a common underlying substrate for brain plasticity across different somatosensory areas.

We have also determined effects of lesions of the dorsal columns on the organization of the motor cortex. These new series experiments are designed to determine if a partial sensory deprivation that leads to large-scale plasticity in the somatosensory cortex also leads to reorganization of the primary motor cortex, an area that has interconnections with the somatosensory cortex. Our results from a monkey with partial lesion show that although area 3b shows massive medial expansion of the face inputs, the primary motor cortex is very normal-like in its organization.

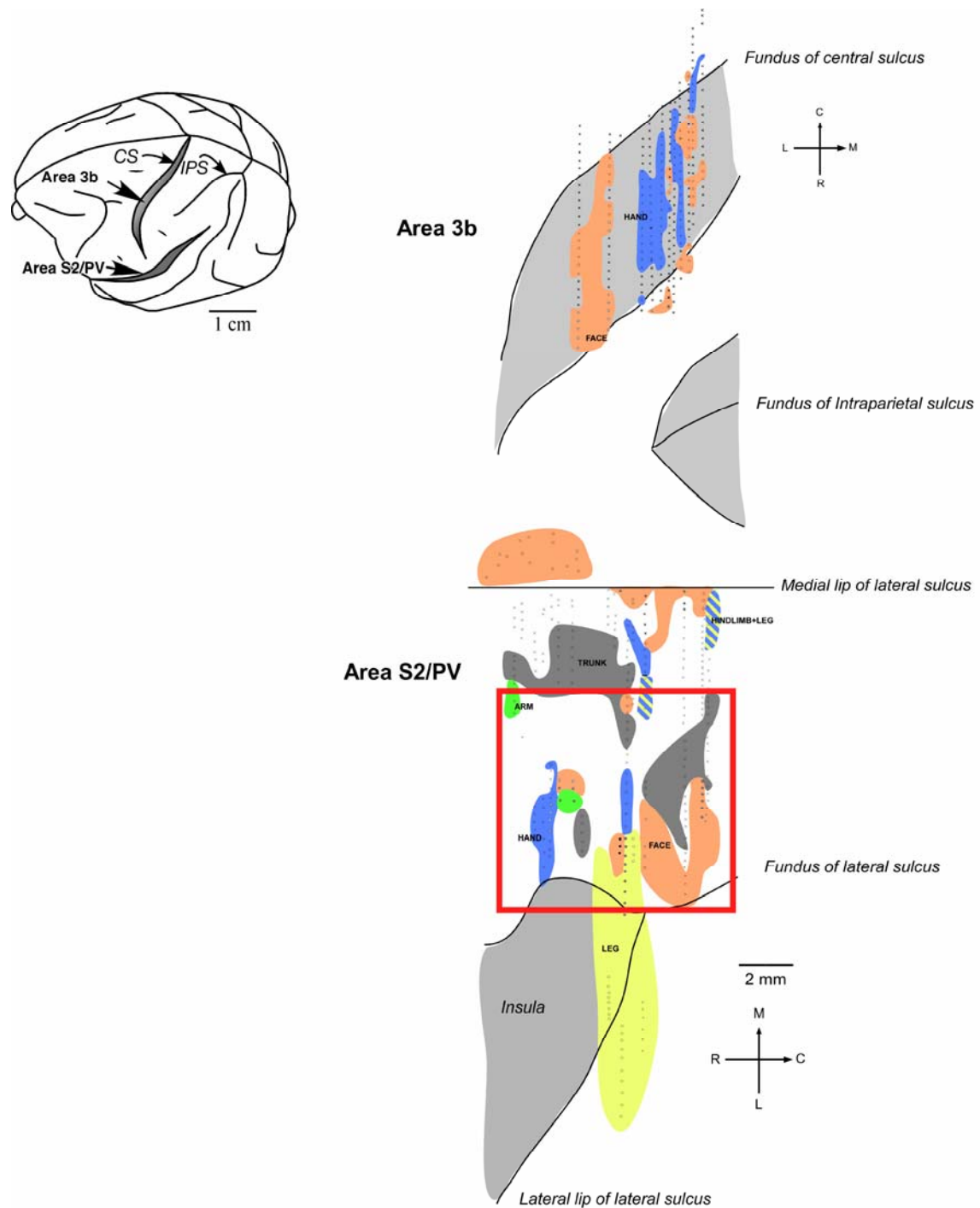


Figure: Reorganization of area 3b and S2/PV in a monkey after chronic, unilateral lesion of the dorsal columns of the spinal cord. The figure shows a part of the parietal cortex that has been unfolded and aligned to the medial lip of the lateral sulcus. Note the expanded face responsive region (pink) in both area 3b (intermingled with the hand representation) and in area S2/PV (bounded by the red square). The other face regions are at the expected normal location. Responses to the stimulation of the hand are seen due to partial nature of the lesion.

Publication:

Tandon, S., Kambi, N. and **Jain, N.** (2008) Overlapping representations of the neck and whiskers in the rat motor cortex revealed by mapping at different anesthetic depths. **Eur. J. Neuroscience.** 27: 228-237.

Presentations:

S. Tandon, N. Kambi and N. Jain: Anesthetic depth affects observed topography in the motor cortex of rats. Neuroscience 2007, Annual Meeting of the Society for Neuroscience, San Diego, CA, USA, Nov 3-7, 2007.

N. Jain: 'Organization of the Brain' and 'The Plastic Brain' at 'Workshop on Mathematical Aspects of Neuroscience'. Department of Mathematics, Indian Institute of Science, Bangalore, Jul 9 – 14, 2007.

N. Jain: 'Brain' at orientation course for undergraduate college lecturers from Haryana State'. Govt. College, Sector 14, Gurgaon, Oct 1-21, 2007.

N. Jain: 'Functional Anatomy of the Brain' and 'Reorganization of the Brain after Injuries' at the workshop 'Frontiers in Neuroscience'. Sophia College, Mumbai, Jan. 4-5, 2008.

Funding:

This work is supported by:

1. International Senior Research Fellowship from Wellcome Trust, UK.
2. Defense Research and Development Organization, India.
3. Department of Biotechnology, India.
4. Department of Science and Technology, India under Indo-Russian ILTP program.

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

Principal Investigator: Dr. Soumya Iyengar

Project Assistants: Souvik Kar, Senthil Krishnasamy

Technical Assistants: OP Sharma, Arvind Singh Pundir

Functional imaging studies in adult humans have shown that specialized foci within the larger auditory association areas (TA, TB and TD) process complex sounds including environmental sounds, and speech. These specialized foci can also be delineated in postmortem brain samples, by staining for calcium binding proteins and enzyme histochemistry for cytochrome oxidase. It is possible that the specialized auditory foci may be present in fetuses near term, since third trimester fetuses and newborns can discern their mothers' voices from those of strangers and even discern pitch and prosody in speech. Given the difficulties of imaging third trimester fetuses or newborns, we decided to study the development of auditory association areas in postmortem brain tissue, using histological methods. Our objectives were therefore to study the cytoarchitecture of the developing human auditory cortex and its subdivisions by using histological and histochemical methods. We also wanted to study the expression of the calcium binding proteins (calbindin, calretinin and parvalbumin) in auditory cortical areas responsible for identifying and localizing sound during development.

We had earlier shown that whereas the calcium binding proteins calretinin (CR) and calbindin (CB) were present throughout the auditory cortex before birth, the third calcium binding protein parvalbumin (PV) was present at negligible levels in neonates.

Earlier research has shown that the expression of PV generally follows that of CR and CB in different parts of the brain, and it has been associated with an increase in neural activity and the maturation of synapses. Interestingly, PV is expressed at higher levels in the smallest auditory cortical areas in adults. These earlier studies therefore suggest that the expression of PV can indicate when the specialized auditory foci become functionally active. Using a larger sample of brains, we have confirmed that the levels of parvalbumin increased in Layer 4 of the auditory cortex by birth, although they still do not demarcate the smallest auditory areas. We have also found that parvalbumin is present in well-differentiated neurons in the striatum and insula at term, in contrast to the auditory cortex. Our findings suggest that

the association of auditory cortex is relatively immature at term and becomes fully mature during postnatal development.

In addition to studying when the smallest auditory foci develop in the brain, we also wanted to study whether they were more specialized than the surrounding areas in terms of the density of neurons. For this study, the density of CR and CB positive cells was measured in Layers 2-6 of one of the smaller auditory areas (AA) in serial sections of the auditory cortex and compared with those in the surrounding rostral TA region (Figure). Our results demonstrated that there were no significant differences in the number of neurons expressing CB or CR in rostral TA and AA in adults or at term. Further, the average number of neurons in rostral TA and AA which were positive for CB or CR was similar at term and adulthood. These results suggest that although AA is involved in processing complex sounds (such as environmental noise), compared to the surrounding auditory association area TA, there is no difference in neuronal density between these areas. We have earlier shown that the size of neuronal somata in Layers 3 and 5 were smaller in AA compared to those in rostral TA. Perhaps other parameters such as the number of dendrites or axonal connections also differ between AA and rostral TA, and need further study.

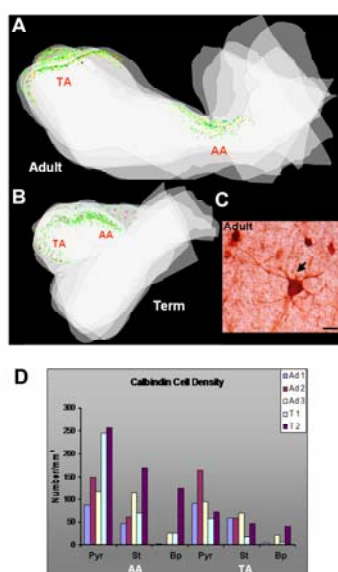


Figure: Stellate, pyramidal and bipolar neurons positive for the calcium binding protein calbindin were counted in serial coronal sections of area AA and the surrounding rostral TA region of the auditory association cortex in an adult (**A**) and at term (**B**). (**C**) An example of a calbindin-positive stellate neuron in an adult. (**D**) There was no significant difference in the density of calbindin positive cells in area AA and rostral TA in adulthood (n = 3) or at term (n = 2) in humans.

Funding:

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

Collaborators:

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Dr. K Joshi, PGIMER, Chandigarh.

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Dr. S. Bishnoi, Gurgaon Civil Hospital, Gurgaon.

Dr. N. Thapar, Gurgaon Civil Hospital, Gurgaon.

Dr. S. Sharma, Gurgaon Civil Hospital, Gurgaon.

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

Neurogenesis in the Song Control System of Zebra Finches

Principal Investigator: Dr. Soumya Iyengar

Research Fellow: Nazia Khurshid

Project Assistants: Naveen Jayaprakash, Anushree Tripathi

Technical Assistants: Arvind Singh Pundir, Shalini Sharma

The upregulation of endogenously occurring neurogenesis for repairing the damage caused by lesions or neurodegeneration in adult brains continues to remain an intriguing possibility. One of the best model systems to study various factors underlying adult neurogenesis is a species of songbirds, namely zebra finches. Earlier studies have shown that new neurons are added to neural circuits in the brains of these birds throughout their adulthood. Interestingly, new neurons also become incorporated within specialized circuits which are important for the production of songs in male zebra finches, which are used to court females. We are interested in studying the factors underlying the regulation of adult neurogenesis. Our objectives were to localize the opioid receptors in different brain regions including the ventricular and subventricular zone (VZ and SVZ) of adult male zebra finches. Further, we would like to examine whether increasing the levels of neurogenesis in adult male zebra finches would change their songs, which are normally highly stereotyped. Our immediate aim is to increase the levels of neurogenesis in these birds by blocking opioid receptors expressed by the VZ which is known to increase cell proliferation in other species. Since little is known about the opioid system in zebra finches, we also decided to confirm the expression of opioid receptors in the song control system of adult male zebra finches. Further, since the opioid system is known to modulate several behaviors in addition to social behaviors in other species of birds and mammals, we decided to study the effects of the opioid system on food and water intake, movement and stereotyped behaviors.

We had earlier studied the expression of opioid receptors in song control nuclei which are involved in song learning and singing, as well as the VZ and SVZ, which contain neural stem cells. These findings were confirmed by performing in situ hybridization on sections of the zebra finch brain, using primers specific to the zebra finch μ - and δ -ORs. Further, we have used RT-PCR and qRT-PCR to confirm that both μ - and δ -OR RNA is present in song control nuclei, the VZ and SVZ and that higher levels of μ -OR RNA was expressed compared to δ -OR RNA in the zebra finch brain.

We had also shown earlier that systemic injections of the opioid antagonist naloxone upregulate cell proliferation in adult male zebra finches. However, we needed to ascertain if cell proliferation was increased directly by the action of naloxone on ORs expressed by the VZ and SVZ of adult males or whether changes in testosterone levels brought about by naloxone treatment (reported by other studies) mediated this increase. In order to answer this question, we administered naloxone systemically to adult female birds. Our results suggest that sex hormones were not responsible for the increase in cell proliferation after naloxone treatment, since naloxone-induced cell proliferation was also observed in females.

In addition to studies on cell proliferation in the brain, we have found that the short term treatment of adult male zebra finches with naloxone significantly decreased the frequency of female-directed songs and calls. However, this treatment had no effect on any of the other behaviors studied, including food and water intake, movement, pecking and preening. The lack of a significant effect of naloxone treatment on food and water intake suggests that the dose of naloxone used in our studies acted only on singing and calling and did not interfere with ingestion of food and water. Our results suggest that the decrease in singing after short term administration of naloxone results from a decrease in the motivation of the birds to sing female-directed songs.

Publication:

Tripathi, A., Khurshid, N., Kumar, P., and **Iyengar, S.** (2008) Expression of δ - and μ -opioid receptors in the ventricular and subventricular zones of the developing human neocortex. **Neurosci. Res.**, 61: 257–270.

Presentations:

S. Iyengar: Development of the Human Auditory Cortex – Neuroanatomical Studies. Presented at the symposium on Brain, Cognition and Behaviour organized by the School Of Language, Literature and Culture studies, Jawaharlal Nehru University, New Delhi, March 14 –15, 2008.

S. Iyengar: The expression of different markers and changes in cytoarchitecture in the developing human auditory cortex. Presented at the symposium Current Trends in Auditory Research organized by the Maulana Azad Medical College, New Delhi, Sept 21-22, 2007.

S. Iyengar: The development of the human auditory cortex. Presented at the 9th Karnataka Chapter of Anatomists, Conference and Workshop (Special theme: Recent Advances in Neuroanatomy) organized by JSS Medical College, Mysore, May 25-27, 2007.

A. Tripathi, S. Iyengar: Expression of opioid receptors in the human ventricular and subventricular zones during the first and second trimester of gestation. Indian Association of Neurology, Annual Meeting, 2007.

P.V. Haldipur, C. Sarkar, S. Iyengar, S. Mani: Role of Sonic Hedgehog signalling in human cerebellum development. Indian Association of Neurology, Annual Meeting, 2007.

N. Khurshid, S. Iyengar: Effects of blocking opioid receptors on the proliferative neuroepithelium of adult male zebra finches. Annual Meeting of Society for Neuroscience, San Diego, CA, USA, 2007.

Funding:

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

Degree Awarded (M.Sc.):

Anushree Tripathi

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

Principal Investigator: Dr. Narender K. Dhingra

Research Fellows: Varsha Jain, Saumya Nagar,
Pitchaiah Cherukuri

Project Assistants: K Vidhyasankar, Orthis Saha, Santhosh
Sethuramanujam, Sonia Baloni

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. Even though photoreceptors progressively degenerate, 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 treatment strategies have been tried in animal models and in human patients, but have produced only limited clinical outcome thus far. We believe that the success of these strategies depends on our understanding of the retinal circuitry, the factors that regulate retinal synaptogenesis, and how information is transmitted through retinal neurons. Our lab is interested in addressing these fundamental questions, and in testing some of these treatment approaches in animal models.

One project in our lab envisages to understand the structure and function of a class of retinal ganglion cells (RGC) that express a POU-IV transcription factor, Brn3. We are characterizing these cells using electrophysiology, immunocytochemistry and morphometric analysis. We have previously reported the morphology, dendritic arborization and distribution of Brn3-positive RGCs in mouse retina. In our recent co-localization studies we have found that only some of the RGCs that express nonphosphorylated neurofilaments (positive for SMI-32 antibody) also express Brn3 while most of the Brn3-positive RGCs do not express nonphosphorylated neurofilaments (Fig. 1A). Similarly, when we looked at the co-localization of Brn3a and

Brn3b in mouse retina, we found that these two populations overlap, but only partially (Fig. 1B).

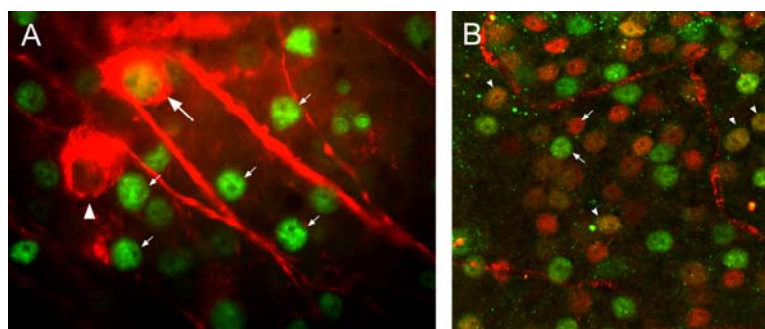


Figure 1: Characterization of Brn3-positive retinal ganglion cells by co-localization **A)** Co-localization of Brn3 (green) with SMI-32 (red) showed that most of the Brn3-positive RGCs (small arrows) do not express nonphosphorylated neurofilaments (SMI-32). Similarly, many of the SMI32-positive cells did not express Brn3 (arrowhead), but there were some cells that expressed both. **B)** Co-localization of Brn3a (green) and Brn3b (red) showed a partial overlap of expression (arrowheads) in addition to cells that exclusively expressed Brn3a or Brn3b (arrows).

We have also been studying an inducible animal model of retinal degeneration where selective and progressive photoreceptor degeneration is induced with a single systemic injection of N-methyl-N-nitrosourea (MNU). We have found evidence that the induced photoreceptor degeneration leads to retinal remodeling. Particularly, second-order neurons, i.e., horizontal cell and rod bipolar cell progressively retract their dendrites in the absence of presynaptic input, whereas the inner retinal neurons and circuitry apparently remains intact. We have quantified not only the progressive photoreceptor degeneration by measuring a photoreceptor-specific protein, *PSD-95*, but also the ensuing retinal remodeling by measuring several cell-specific retinal proteins, including calbindin and by studying the visual behavior of MNU-injected animal (Fig. 2).

We have previously developed a novel method for labeling cone photoreceptors in a live animal by peanut agglutinin (PNA). To further investigate its potential for human application for early diagnosis of degenerative diseases, we have studied the reversibility of *in vivo* PNA binding, the effect of PNA on other retinal neurons and on visual behavior, and demonstrated that this method does not cause any gross adverse effects.

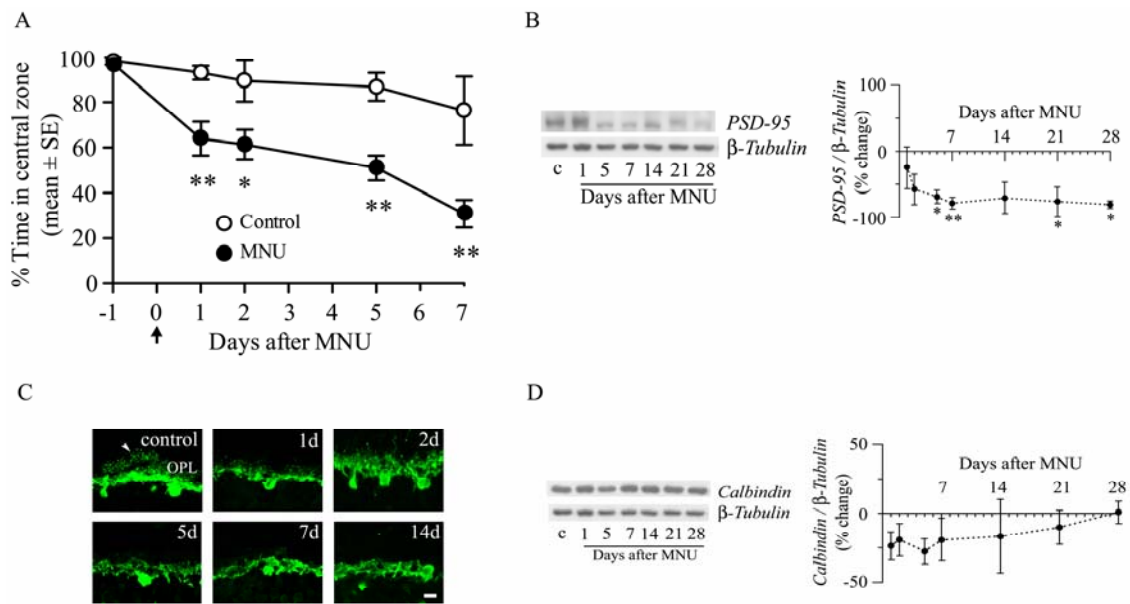


Figure 2: Quantification of MNU-induced photoreceptor degeneration and the ensuing remodeling of horizontal cell dendrites, using behavioral and immunoblot analyses. **A)** Visual behavior of an animal in a Cliff test, measured as time spent in "safe" zone, deteriorated progressively by ~70% during the first week after MNU treatment. **B)** Quantification of a photoreceptor-specific protein, PSD-95 by immunoblot analysis showed a large reduction during the first week after MNU, which was maintained through next 3 weeks. **C)** Horizontal cells, immunostained for calbindin showed progressive disappearance of their dendrites (bright green puncta; arrowhead in control) over 2 weeks after MNU injection. Scale bar: 10 μ m. **D)** Quantification by immunoblot analysis showed ~25% reduction in calbindin levels during the first week, but they recovered over the next 3 weeks.

Publication:

Krishnamoorthy, V., Jain, V., Cherukuri, P., Baloni, S., **Dhingra, N.K.** (2008) Intravitreal injection of fluorochrome-conjugated peanut agglutinin results in specific and reversible labeling of mammalian cones in vivo. **Invest Ophthalmol Vis Sci**, 49: 2643-2650.

Presentations:

N.K. Dhingra: Understanding Information Processing in Retina - Critical for Treating Retinal Degenerative Diseases? 9th China-India-Japan-Korea joint workshop on Neurobiology and Neuroinformatics (NBNI-2007) in Jeju Island, S. Korea, July 5-7, 2007.

K. Vidhyasankar, C. Pitchaiah, S. Baloni, N.K. Dhingra: In Vivo Labeling of Mammalian Cone Photoreceptors by Intravitreal Injection of Fluorescently Tagged Peanut Agglutinin – A Potential Tool for Assessing Photoreceptor Degeneration in Humans. OSA Fall Vision Meeting in Berkeley (Sep. 16-19, 2007) Journal of Vision 7, 75a, 2007 <http://journalofvision.org/7/15/75>.

N.K. Dhingra, P. Cherukuri, V. Krishnamoorthy, S. Baloni, S.K. Jose: Morphological and behavioral characterization of N-methyl N-nitrosourea-induced mouse model of retinal degeneration. 37th annual meeting of the Society for Neuroscience in San Diego (Nov. 3-7, 2007). Soc Neurosci Abs 699.19/S19.

N.K. Dhingra: The Power of Brain. Popular science lecture for high school students on 22nd National Science Day at Kendriya Vidyalaya (Sector 14) Gurgaon, Feb. 28, 2008.

Funding:

This work is supported by grants from DBT, India.

Patent:

In Vivo Staining of Cone Photoreceptors by a Fluorescently Labeled Compound (PCT filed, Pending).

Degree Awarded (M.Sc.):

Pitchaiah Cherukuri

Articulation Maps for Spoken Language

Principal Investigator: Dr. Nandini Chatterjee Singh

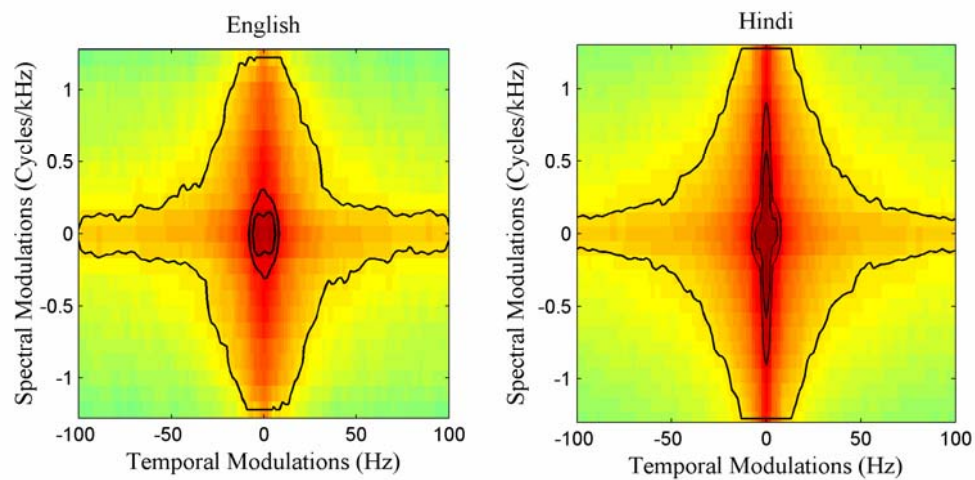
Research Fellows: Latika Singh, Tanusree Das

Our current focus is on the study of spoken language, also called speech. Spoken language, when analyzed from a signal processing perspective, can be described as a signal with information at multiple time scales. This information is embedded in the form of amplitude fluctuations, which are at different time scales and encode various features of language. For example, fluctuations at 200-400 milliseconds encode speech/language rhythm, whereas fluctuations at 10-20 milliseconds encode place of articulation.

Based on fluctuation rates of amplitude, spoken language can be classified into four abstract features namely, rhythm, formant transitions, place and manner of articulation, and voiced pitch. Each of these features interestingly is associated with a different time scale and is currently investigated using a different technique. For example, rhythm also called syllabicity is investigated using tedious measurements of syllable durations, place of articulation is studied using careful measurements voice onset times. In the current scenario each of these features is estimated using a different measurement technique, and all these techniques are rather laborious. Using advanced techniques of spectral analysis, we have developed a novel computational tool called the Speech Modulation Spectrum (SMS) provides information on all four articulatory features at the same time quite easily. The SMS provides information on the distribution of energy in the different articulatory features of any given language.

Figure shows the articulation maps for adult speakers of Hindi and English. The figure clearly shows similarities between the two languages, in that energy is seen at all the time scales. However at a more subtle level, it is also possible to study the differences between languages. The articulation maps have numerous applications. They can be used to classify languages on the basis of articulatory features. They also enable comparisons between different languages and could provide information on how the articulatory features of various languages could be similar or dissimilar.

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



Publication:

*Das, T., Singh, L. and **Singh, N.C.** (2007) Rhythmic structure of English and Hindi – new insights from a computational analysis, **Prog. in Brain Research**, 168, 207-214.

Presentation:

N.C. Singh: Speech rhythms in bilinguals, Abstract, Society for Neuroscience, San Diego, USA, Nov. 2007.

Funding:

This work is supported by NBRC Core funds.

The Development of Articulatory Features in Children

Principal Investigator: Dr. Nandini Chatterjee Singh

Research Fellow: Latika Singh

Project Assistant: T. Padma Subhadra

There is little information on the development of different articulatory features in typically developing children. These are important in order to set milestones for development of speech motor skills in children. We use the articulation map to study the development of different articulatory features in children of different age groups in a population. Using the speech modulation spectrum analysis, we are able to capture all the four articulatory signatures in adult speech. We obtain speech productions from typically developing children between 4-13 years of age on a series of common tasks. We make comparisons with adult speech and find age dependence in the appearance of these features. In our earlier reports we have shown how various articulatory features mature between 4-8 years. We had also shown that children do not achieve adult-like maturity even at 8 years. We have extended our study to older children. We now have the developmental pattern of articulatory features in children from 4 years to 13 years wherein we are now able to report that adult-like maturity in speech motor articulation is achieved between 11-13 years of age. Our results indicate that as children get older they exhibit increasingly more power in features associated with shorter time scales, thereby indicating the maturation of fine motor control in speech.

Publications:

*Singh, L. and **Singh, N.C.** (2008) The development of articulatory signatures in children, **Developmental Science**, Vol.11 (4):467-73.

T., Padma, Das, T., and **Singh, N.C.** (2008), Speech rhythms in children learning two languages: From Heart to Brain, **Life Sciences Series**, Springer (In Press).

Presentations:

N.C. Singh: Invited talk - Speech and Hearing Impairments in Children, National Seminar on empowering the differently abled, Feb. 9-11th 2008.

N.C. Singh: Invited talk – Speech rhythms in bilingual children, Indian Association of Neuroscience, Varanasi, Nov. 2007.

N.C. Singh: Invited talk – Patterns of speech in children with autism, Indo-US Symposium on Autism, 28-29th Sept. 2007.

N.C. Singh: Invited talk - Development of articulatory features in children and those with cochlear implants, MAMC, Sept. 2007.

Funding:

This work is supported by a grant from the Ministry of Communications and Information Technology, India.

The Neural Organization of Language in Bilinguals

Principal Investigator: Dr. Nandini Chatterjee Singh

Research Fellow: Tanusree Das

Post Doctoral Fellow: Uttam Kumar

Most of our understanding on the organization of language has come from studies of single language users also called monolinguals. A majority of the world's population is however language bilingual or multilingual. Studying and characterizing the neural concomitants of multiple language users is not only interesting but also important for narrowing this gap. From a broader perspective, this is also necessary to understand language disorders in multilingual populations. The third objective of our laboratory is to study the organization of language in bilinguals and multilinguals using a combination of the spectral analysis described earlier with functional neuroimaging.

We use functional imaging to study speech articulation patterns during reading in two different languages. Previous research has shown that age of acquisition and proficiency in a language are two important factors that determine the neural organization of language. There have however been limitations to studying this paradigm in overt speech i.e. spoken language because of the lack of objective measures to determine spoken language fluency. With the help of the speech modulation spectrum we are able to quantify speech fluency in a behavioral paradigm. We are now attempting to correlate this with the neural activation patterns invoked during the performance of this task in the scanner.

Twelve late adult bilinguals, native speakers of Hindi and moderately fluent speakers of English were asked to read passages in Hindi and English. A standard passage that was balanced for articulation features and semantically matched for number of words was used. Two measures were used to determine language fluency, namely mean reading time in each language and the speech articulation map. The measures showed increased articulation space and shorter reading times for the more fluent language.

Subjects were then scanned while reading sentences from the same passage in the scanner. Brain activation patterns reveal *reduced activation* in articulatory motor areas in the more fluent language. We therefore conclude that reading in a less proficient language requires greater articulatory effort and a smaller articulation space.

We also see effects of different scripts, wherein reading in Hindi shows greater visuo-spatial processing as compared to reading in English. We

attribute this to Devnagari being a more complex spatial script as compared to Hindi. We are now investigating this in greater detail.

We would now like to start collecting data from infants and children in the age group (newborn – 4 years) to study how various articulatory features begin to emerge from babbling sounds in children. This would be a novel set because there is very little information regarding early language acquisition skills in bilingual children.

Since our analysis is able to capture the development of fine speech motor control we are now interested in using this analysis to study motor speech disorders, particularly in children.

With our advent into fMRI analysis we would now like to use an approach wherein we can combine all the behavioral and spectral analysis with functional MRI. In this context we would now like to initiate experiments with children using functional MRI in order to correlate our spectral analysis results with fMRI.

Funding:

This work is supported by NBRC Core funds.

Collaborators:

Dr. R S Bapi, Dept of Computer and Information Sciences, University of Hyderabad.

Dr. S. Charavarthy, Dept. of Biotechnology, Indian Institute of Technology, Madras.

Spatiotemporal Neural Processing and Information Transmission

Principal Investigator: Dr. Prasun Kumar Roy

Research Fellow: Kh. Budhachandra

Technical Assistant: Ashish Upadhyay

A fundamental challenge in neuroscience is understanding how information transmission, volume conduction and connectivity occurs across the layered or anisotropic brain. One needs quantitative tensor models that can account for information transmission and its neuromodulation across the brain. We have delineated the approach of dynamic functional tensor neuroimaging and elucidated tensor images to describe flow and deformation processes, information flux or connectivity in brain. The research has considerable potentiality for clinical applications, in diagnosis and therapy. The objective is to understand the physiological or pathological dynamics of transport or flow processes in the brain, whether that of fluids, tissue, energy or information.

Stress Imaging: The requisite MRI pulse sequences and algorithm needed for fluidic stress imaging has been elucidated. Tensor algorithms have been studied computationally using our MRI scanner on normal volunteers and the stress image has been reconstructed by 2^4 point simulation, namely for (i) CSF flow in ventricles (ii) blood flow in heart and aorta (fig. 2a-c). This tensorial image can provide a new window to study the pathophysiology and therapeutic monitoring of fluid flow under strain and shear, such as CSF in obstructive encephalopathy, or blood stream irregularity in cerebral vessel stenosis or aneurysms.

Cortical Deformation & Conductivity Imaging: We also delineated the other transport or mobility tensors of the brain, such as the deformation tensor, as well as thermal conductivity tensor imaging, a new neuroimaging approach. We also elucidated the deformation mapping of the brain using Alzheimer patient images (using processing platform courtesy MNI) and this gave an accurate representation of quantitative distortion and atrophy of patient brains when compared to normal brains (fig. 2d). A cortical connectivity mapping of the brain, based on small world networking, is generated for Alzheimer brain scans. One obtains a clinically useful and accurate visualization of structural elastoplastic distortion of brain atrophy seen in such patients.

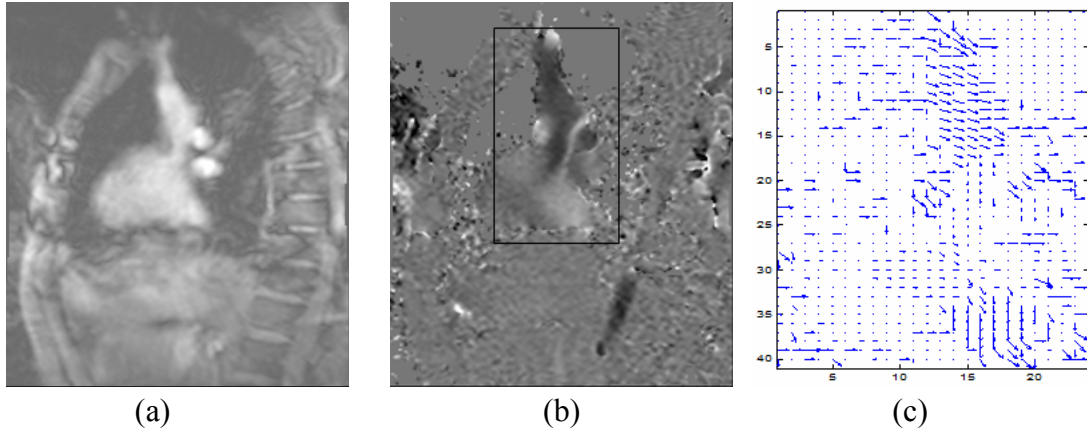


Figure: 2(a-c). Strain Image of blood flow in aorta and carotid arteries serving the brain: (a) Structural image (b) Phase image (c) Vector image.

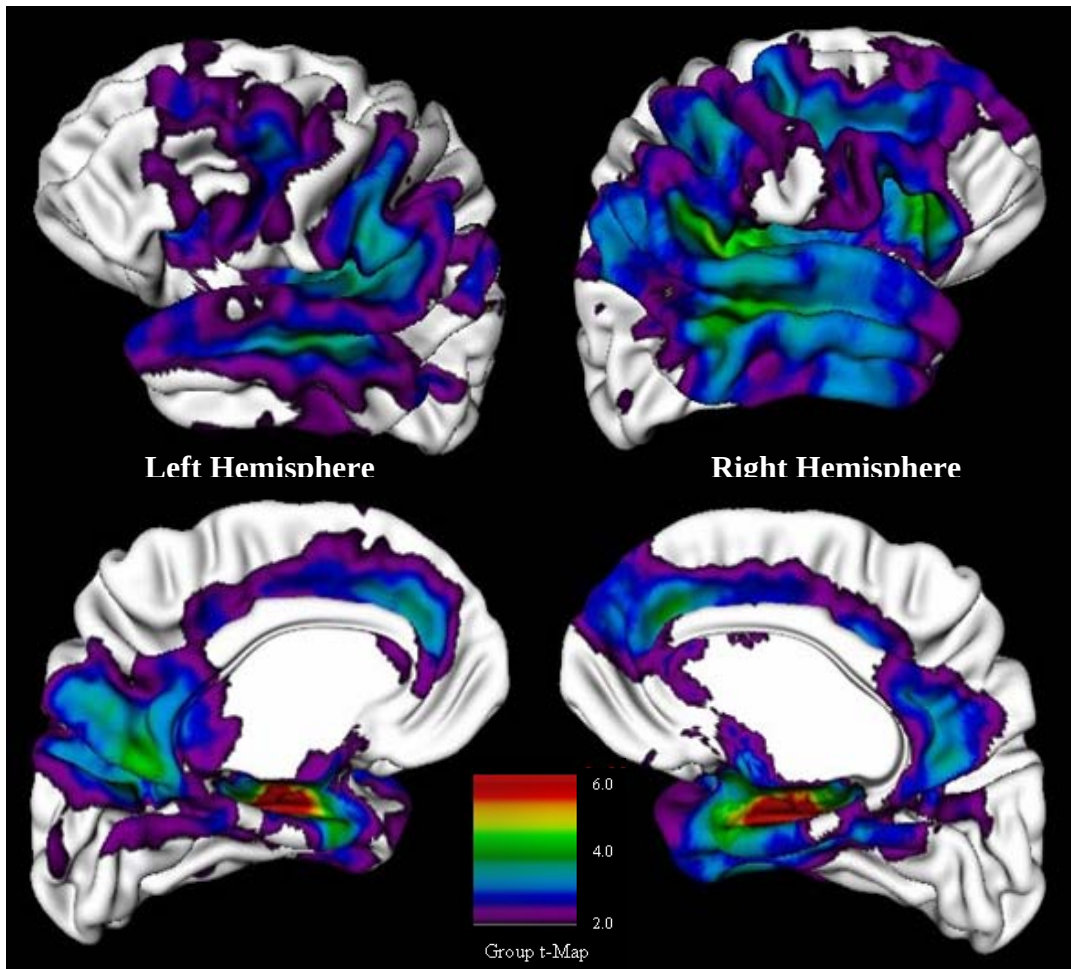


Figure: 2d. Cortical Orthogonal Distortion in Alzheimer's disease, colour-coded as per intensity of distortion.

fMRI, Language Structuration & Bimodal Cognitive Processing: Another transport tensor, namely information flux tensor image, of the brain has also been elaborated, where information transmission occurs via two multiplexed modes, a first-order mode and a second-order mode. In language

communication, the two modes are syntagmatic word output (primary process) and the paradigmatic word output (secondary process). We performed fMRI studies using linguistic word association tests to delineate the differential brain areas responsible for syntagmatic-syntactic processing vis-à-vis paradigmatic-semantic processing. This is thus a direct instrumental observation of the fundamental biphasic modes of human cognition (syntagmatic vis-à-vis paradigmatic operations).

Publications:

Subramanyam, V.P., Upadhyay, A., Budhachandra, Kh. and **Roy, P.K.** (2008) The Self and Its Brain: A Symbiotic Integration of Functional Mapping and Tensor Imaging Strategy for a Neuroinformatics initiative, **Computer Society of India Communications**. 32(3), 27-31.

Budhachandra, Kh. and **Roy, P.K.** Informational Tracking of Epileptic Focus in the Brain. **Developmental Neurobiology and Neuroimaging** (edited volume) (In Press).

Presentations:

A. Upadhyay and P.K. Roy: Towards a Dynamic Analysis of Brain and Language, Conference on Auditory Development, Maulana Azad Medical College, Delhi University, April 2007.

P.K. Roy and Kh. Budhachandra: A Tensorial Approach to Perfusion Flux Imaging, Humboldt University, Berlin, May 2007.

P.K. Roy: Brain Imaging: Looking at Nerve Fibres, Haryana State Govt. Council of Science & Technology, Jind, Aug. 2007.

A. Upadhyay and P.K. Roy: Multiplexed Information Processing in Human Neurocognitive System: fMRI, Annual Meeting of Indian Academy of Neuroscience, B.H.U., Banaras, Nov 2007.

Kh. Budhachandra and P.K. Roy: Dynamic Functional Tensor Neuroimaging: A Multimodal Analysis, Annual Meeting of Society of Neuroscience, San Diego, Nov 2007.

P.K. Roy and Kh Budhachandra: Dynamic space-time representation in the Neural system, Silver Jubilee Symposium of Indian Academy of Neuroscience, B.H.U., Banaras, Nov 2007.

P.K. Roy and A. Upadhyay: Neurodynamic Basis of Adaptation, Cognition, Language, International Conference on Cognitive Psychology, Indian Statistical Institute, Calcutta, Dec 2007.

P.K. Roy and Kh. Budhachandra: Multimodal Tensor Imaging, Workshop on Computational Neuroscience, Delhi University, Dec 2007.

Kh. Budhachandra and P.K. Roy: Neural Causality Analysis: Transformational Invariance of the Hodgkin-Huxley Equation, International Biophysics Congress, Los Angeles, Feb 2008.

Funding:

This work is supported by a grant from the Ministry of Education & Research, Italian Govt. under a program of the European Commission and from the Biophysical Society of America (exchange program: support for student's collaborative research project).

Collaborators:

Dr Alan Evans, Montreal Neurological Institute (MNI), McGill University.

Dr Patrizia Baraldi, University of Modena/CNRS-Rome.

Dr T R Seshadri, Delhi University.

Dr Peter Luijten, Utrecht University Radiology and Radiotherapy Centre.

Dr Bapi Raju, Central University of Hyderabad.

Patent:

Rapid Automated Screening for Diagnosis and Classification of Alzheimer's Disease using Magnetic Resonance Imaging signal (Filed).

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

Principal Investigator: Dr. Prasun Kumar Roy

Research Fellow: Subhadip Paul

R&D Engineer: V.P. Subramanyam Rallabandi

Project Assistant: Vinay Shukla

For improving the efficiency of neuroradiological processes, whether diagnostic or therapeutic, an innovative approach is offered by adding small perturbation to the signal, utilizing the principles of nonlinear dynamics and computational biology. This procedure, referred to as stochastic activation or noise-aided resonance, is a general principle of complex systems applicable to various levels of functioning, from molecular to behavioural, and occurs basically due to the statistical collective behaviour of the functional components of the system. Stochastic activation has been used to enhance various processes relevant to neurobiologists, such as cellular information processing or temporal signal transmission. Nevertheless the clinical application of stochastic activation effect as a novel technique in neuroimaging or therapy has not been systematically pursued, and exploring such applications is our main objective.

Diagnostic Radiology: We have generalized the stochastically activated radon transform to generate the stochastically activated integral transform, so as to be more effective for the intrinsic harmonic space/k-space geometry of the image. Furthermore, when the procedure is applied to a CT/MRI tumour image, we can discriminate various zones of a gliomatous tumour, such as necrotic and proliferative zones based on contrast agent uptake parameters (fig. 1a-d). We also used the method for tissue differentiation as in discriminating cytotoxic edema from vasogenic edema in cerebral infarction. Knowledge of the differential edema zones is of great help in optimizing therapy in cerebrovascular accidents.

Therapeutic Radiology: Furthermore, our stochastic activation approach has also been pursued to enhance the efficiency of therapeutic radiology, with particular application to brain tumours. We investigated the effect of radiotherapy photon on the alteration of the DNA double-strand, and the outcome of temporally perturbing the radiotherapy beam is studied. The major disadvantage of radiotherapy or chemotherapy is that the therapy agent eliminates both malignant tissue and normal tissue (though to somewhat different degrees). We have shown how selecting proper perturbation parameters of the beam flux can increase the therapeutic

differential considerably, so that more malignant cells and less normal cells are eliminated.

Image Interpretation in Neurodegenerative disease: We have elucidated a rapid automated technique to use nonlinear dynamics analysis to differentiate MR images of the Alzheimer disorder spectrum. We characterized the stochastic perturbation of image scale geometry by 1st & 2nd order topological metric indices. Based on machine intelligence and learning theory approaches, our computational classifier differentiates between the three important classes: Normals, Mild cognitive deficit and Mild Alzheimer disease (fig 1e-g). We performed trial of the methodology on images of 200 subjects (with known diagnosis), and then a blinded analysis. The correct classification rate was 96-98%, this accuracy is significantly higher than usual procedures followed by radiologists which have 83-95% precision.

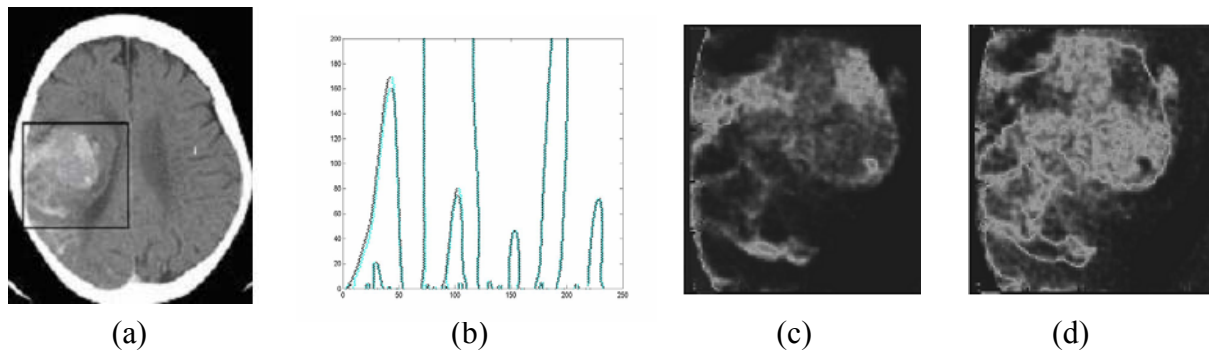


Figure: (a-d) Image enhancement and identification of Tissue type. (a). Malignant glioma image under contrast agent uptake. (b) Scale-space segmentation of stochastically activated image to generate mask to differentiate various tissues of lesion (c, d) proliferative region and hypoxic region respectively of lesion.

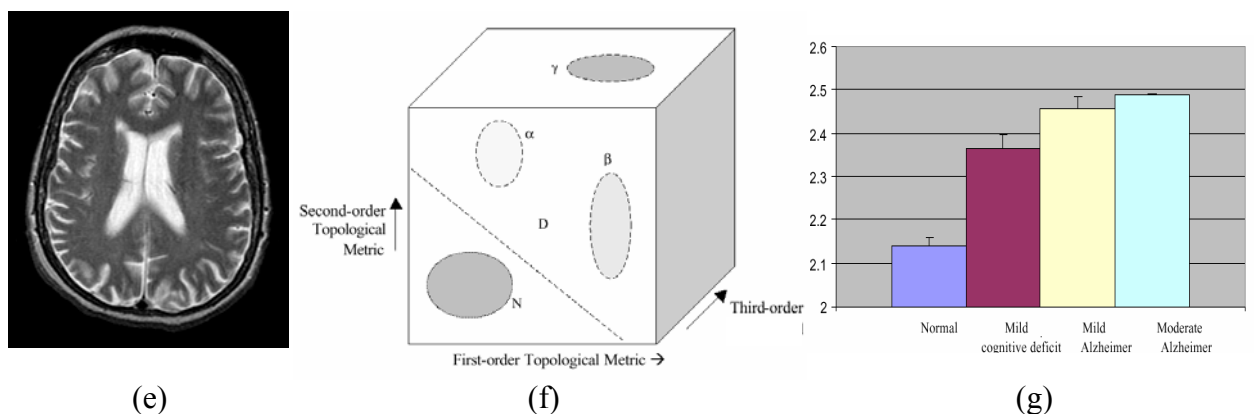


Figure: (e) Transcallosal MRI image of patients of Alzheimer's Disease used for analysis, (f) Scheme of increasing higher-order feature vectors to increase power of classification, N = zone of Normal controls, D = zone of Demented individuals that consists of Mild cognitive deficit, Mild Alzheimer's disease and Moderate Alzheimer's

disease, respectively denoted by the clusters α , β , and γ . (g) Automated identification of Normal subjects, and patients of Mild cognitive deficit, Mild Alzheimer's disease and Moderate Alzheimer's Disease, using first order topological metric on vertical axis.

Publication:

Subramanyam, V.P. and **Roy, P.K.** (2008). Stochastic Resonance-based Tomographic Transform for Image Enhancement of Brain Lesions, **J. Computer Assisted Tomography**, 32(5), 675-683.

Presentations:

V.P. Subramanyam and P.K. Roy: Stochastic Resonance as a Novel Enhancement Technique in Neuroscience, D.R.D.O., Defense Ministry, New Delhi, April 2007.

P.K. Roy: The Fractal Landscape Behind Cognition, International Conference on Mathematical Neuroscience, I.I.Sc, Bangalore, June 2007.

S. Paul and P.K. Roy: Effect of Stochastic Fluctuation on Radiosurgical Efficiency: International Workshop on Recent Advances in Radiosurgery, A.I.I.M.S., New Delhi, June 2007.

S. Paul and P.K. Roy: Application of Stochastic Modeling in Radiobiology, International Conference on Mathematical Neuroscience, I.I.Sc., Bangalore, June 2007.

P.K. Roy: Fractal analysis for Differential Diagnosis in Dementia Imaging, Meeting on Dementia, National Institute of Immunology, New Delhi, Aug 2007.

P.K. Roy: Presentation at Discussion Meeting on New Topics in Biotechnology, Anna University, Madras, Sept 2007.

P.K. Roy: Application of Stochastic Processes in Neuroimaging, Montreal Neurological Institute, McGill University, Nov. 2007.

S. Paul: Scale-space Segmentation of Tumour Tissue: Prospects for Image Guided Radiotherapy, University of Modena & Reggio Emilia, Dec 2007.

V.P. Subramanyam and P.K. Roy: Neurophysics: The Newest Frontier of Physics, I.I.T., Bombay, Feb 2008.

Funding:

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

Collaborators:

Dr Paul Thompson, University of California – Los Angeles.

Dr James Becker, University of Pittsburg.

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

Dr Manjari Tripathi, All-India Institute of Medical Sciences, New Delhi.

Dr T. Kataria, Artemis Medical Linear Accelerator Centre, Gurgaon.

Patents:

A Medical Image Enhancement Device based on Image Transform Resonance, using an Embedded System (filed).

A Technique to Enhance the Clinical Efficiency of Radiotherapy and Radiosurgery using Perturbative Beaming and Tissue-specific Radiobiology (Accepted).

PUBLICATIONS

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1. **Jana, N. R.** (2008) NSAIDs and apoptosis. **Cellular and Molecular Life Sciences**, 65(9): 1295-301.
2. * Dikshit, P. and **Jana, N. R.** (2008) Role of ubiquitin protein ligases in the pathogenesis of polyglutamine diseases. **Neurochemical Research**, 33: 945-951.
3. Mishra, A., Dikshit, P., Purkayastha, S., Sharma, J., Nukina, N. and **Jana, N. R.** (2008) E6-AP promotes misfolded polyglutamine proteins for proteasomal degradation and suppresses polyglutamine protein aggregation and toxicity. **Journal of Biological Chemistry**, 283: 7648-7656.
4. Mishra, A. and **Jana, N.R.** (2008) Regulation of turnover of tumor suppressor p53 and cell growth by E6-AP, a ubiquitin protein ligase mutated in Angelman mental retardation syndrome. **Cellular and Molecular Life Sciences**, 65: 656-666.
5. * Mishra, R., Gupta, S.K., Meiri, K.F., Fong, M., Thostrup P., Juncker, P.D., and **Mani S.** (2008) GAP-43 is key to mitotic spindle control and centrosome-based polarization in neurons. **Cell Cycle**, 7(3): 348-57.
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7. Gupta, S.K., Gressens, P. and **Mani, S.** NRSF down-regulation induces neuronal differentiation in mouse embryonic stem cells. **Differentiation** (In Press).
8. Kumar, M., Kaushalya, S. K., Gressens, P., Maiti, S. and **Mani, S.** Optimized derivation and functional characterization of 5-HT neurons from human embryonic stem cells. **Stem Cells and Development** (Accepted).
9. Ranade, S.C., Rose, A., Rao, M., Gallego, J., Gressens, P. and **Mani, S.** (2008) Different types of nutritional deficiencies affect different domains of spatial memory function checked in Radial Arm Maze. **Neuroscience**, 152: 859-866.
10. * Kommaddi, R.P., Turman, C.M., Moorthy, B., Wang, L., Strobel, H.W. and **Ravindranath, V.** (2008) An alternatively spliced cytochrome P4501A1 in human brain fails to bioactivate polycyclic aromatic hydrocarbons to DNA-reactive metabolites. **J. Neurochem.**, 102:867-77.
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23. Ghosh, J., Swarup, V., Saxena, A., Das, S., Hazra, A., Paira, P., Banerjee, S., Mondal, N.B. and **Basu, A.** 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** (In Press).
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41. Subramanyam, V.P., Upadhyay, A., Budhachandra, Kh. and **Roy, P.K.** (2008) The Self and Its Brain: A Symbiotic Integration of Functional Mapping and Tensor Imaging Strategy for a Neuroinformatics initiative, **Computer Society of India Communications. Vol 32(3), 27-31.**
42. Budhachandra, Kh. and **Roy, P.K.** Informational Tracking of Epileptic Focus in the Brain, Developmental **Neurobiology and Neuroimaging** (edited volume) (In Press).
43. Subramanyam, V.P. and **Roy, P.K.** (2008) Stochastic-Resonance-based Tomographic Transform for Image Enhancement of Brain Lesions, **J. Computer Assisted Tomography**, 32(5), 675-683.

* Reported as “In Press” last year

PRESENTATIONS

International Presentations:

1. N. R. Jana: Modulation of polyglutamine neurodegeneration by ubiquitin protein ligases. Invited talk at RIKEN Brain Science Institute, Japan, Sept. 2007.
2. N. R. Jana: Understanding the functional role of E6-AP – an ubiquitin protein ligase and steroid receptor coactivator implicated in Angelman mental retardation syndrome. Invited speaker in the Asia and Oceania Society for General and Comparative Endocrinology, North Bengal University, Dec. 2007.
3. S. Mani: 5th ISSCR Annual Meeting in Cairns, Australia. Differentiation into serotonergic neurons of neural progenitor cells derived from human embryonic stem cells, July 2007.
4. V. Agarwal, R.P. Kommaddi, Khader Valli R and V. Ravindranath: Differential expression of CYP3A enzymes in human brain and functional significance in relation to metabolism of the anxiolytic drug, Alprazolam. Cytochrome P450 meeting in Bled, Slovenia, June 17-21, 2007.
5. V. Agarwal, R.P. Kommaddi, Khader Valli R and V. Ravindranath: Differential expression of CYP3A enzymes in human brain and functional significance in relation to metabolism of the anxiolytic drug, Alprazolam, Gordon Research Conference, Boston, USA, July 8-13, 2007.
6. V. Agarwal, R.P. Kommaddi, Khader Valli, and V. Ravindranath: Drug metabolizing enzyme, CYP3A43 is expressed in higher amounts in human brain in contrast to liver leading to increased production of the pharmacologically active metabolite of the anxiolytic drug alprazolam at the site of action at Society for Neuroscience, 3rd to 7th Nov, 2007.
7. V. Ravindranath, L. Diwakar, U. Saeed, R. Kenchappa: Mitochondrial Dysfunction Mediated Through Protein Thiol Modification in Neurolathyrism, a Chemically Induced Motor Neuron Disease New York Academy of Sciences, New York, 20 to 29th Sept., 2007.
8. S. Karunakaran, U. Saeed and V. Ravindranath: Cell-specific activation of redox – apoptotic signaling in MPTP mouse model of Parkinson's disease. 15th Euroconference on Apoptosis, Oct. 26-31, 2007, Portoroz, Slovenia.
9. V. Ravindranath: Redox driven apoptotic signaling in Parkinson's Diseases at Linus Pauling Institute, Oregon State University, USA on 30th Oct., 2007.
10. U. Saeed, S. Karunakaran, A. Ray, L. Diwakar, S. Ramakrishnan, R.C. Koumar, and V. Ravindranath: Activation of apoptosis signal regulating

kinase 1 in male but not female mice in animal model of Parkinson's disease: role of thiol disulfide oxidoreductase(s) at National Parkinson Foundation 10th International Symposium on Parkinson Research, Nov. 1st and 2nd, 2007, San Diego, USA.

11. U. Saeed, S. Karunakaran, M. Mishra, P. Seth and V. Ravindranath: Activation of stress activated protein kinase is a critical event in 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine toxicity: kinase inhibitors as potential drug target at Society for Neuroscience, 3rd to 7th Nov, 2007, San Diego, USA.
12. L. Durgados, U. Saeed, S. Karunakaran and V. Ravindranath: Redox modification of protein kinase B: Implications for Neurodegenerative Disorders in Parkinson's Diseases, at the XVII WFN world congress on Parkinson's disease and related disorders, Amsterdam, The Netherlands, 9th to 13th Dec., 2007.
13. L. Diwakar, S. Karunakaran, U. Saeed, S. Ramakrishnan, S. Iyengar and V. Ravindranath: Thiol antioxidant affords neuroprotection against MPTP mediated death signaling pathway at International Brain Research Organization (IBRO), Melbourne, Australia from 13 to 15 July, 2007.
14. M. Mishra and P. Seth: Clade Specific Variation in HIV-1 Transactivating Protein (Tat) Induced Neurotoxicity in Human Neurons, Oral presentation in a special session "Investigators in Training" organized by International Society of Neurovirology, 8th International Symposia on Neurovirology, San Diego, USA, Oct 29th to Nov 2nd 2007.
15. M. Mishra and P. Seth: Apoptosis by HIV-1 B and C Tat protein in Human Neurons is clade specific, Presented poster at the annual meeting of Society for Neuroscience, San Diego, USA, Nov. 2007.
16. P. Seth: Clade Specific Differences in HIV-1 Tat Induced Neurotoxicity: Importance of Dicysteine motif at position 3031 in HIV-1 Tat. Invited Speaker, NeuroAIDS in Asia and Pacific Rim, Sponsored by and National Institute of Neurological Disorders and Stroke, National Institute of Mental Health (National Institutes of Health, USA), At Garvan Institute, Sydney, Australia July 2007.
17. P. Seth: HIV-1 Tat Derived from Clade B and C Induce Neurotoxicity in Human Neuronal Cells. Invited Speaker, Neurobiology and Neuroinformatics 2007 meeting, Cheju National University, Jeju City, South Korea, July 2007.
18. P. Seth: Clade Specific HIV Tat Induced Neurotoxicity in human neurons. International Conference on Opportunistic Pathogens in AIDS, New Delhi, India, Jan. 2008.

19. E. Sen: Inflammation and oxidative stress: Indispensable participants in glioblastoma progression. Becton Dickinson, La Jolla, San Diego, CA, Nov. 2007.
20. E. Sen: Kaempferol induces apoptosis in glioma cells through oxidative stress. Society for Neuroscience, San Diego, Nov. 2007.
21. A. Basu: Viral Induction of Central Nervous System Innate Immune Responses. BD Pharmingen R&D Center, San Diego, 8th Nov. 2007.
22. S. Das, A. Ghoshal and A. Basu: Inflammation, a key modulator of neuronal death and neurogenesis pattern in an experimental model of Japanese encephalitis. Society for Neuroscience (SfN) Meeting, San Diego, 3rd-7th Nov. 2007.
23. V. Swarup, S. Das and A. Basu: Japanese encephalitis virus infection induces Tumor-Necrosis Factor receptor-1 mediated neuronal apoptosis. Society for Neuroscience (SfN) Meeting, San Diego, 3rd -7th Nov. 2007.
24. Ramakrishnan and A. Murthy: Neural Control of saccadic decision-making Neuro2007 meeting, Yokohama, Japan, 2007.
25. K.M. Sharika and A. Murthy: Predictive oculomotor control during errors. Neuro2007 meeting, Yokohama, Japan, 2007.
26. A. Murthy and V. Kapoor: Does covert inhibition potentiate online inhibitory control? Neuro2007 meeting, Yokohama, Japan, 2007.
27. Z. Darokhan, M. Chugh & V. Rema: Laminar differences in response of barrel cortex neurons in the immediate hours following lesions of homotopic somatosensory cortex. Society for Neuroscience, 2007.
28. M. Chugh, Z. Darokhan, V. Rema: Photothrombotic lesions of motor cortex increase neuronal activity in layer 5 of whisker barrel cortex in adult rats. Society for Neuroscience, 2007.
29. V. Rema: Invited talk "Injury-induced plasticity in the somatosensory cortex". Salk Institute, 31 Oct. 2007.
30. S. Tandon, N. Kambi and N. Jain: Anesthetic depth affects observed topography in the motor cortex of rats. Neuroscience 2007, Annual Meeting of the Society for Neuroscience, USA, Nov 3-7, San Diego, CA, USA, 2007.
31. N. Khurshid and S. Iyengar: Effects of blocking opioid receptors on the proliferative neuroepithelium of adult male zebra finches. Annual Meeting of Society for Neuroscience, San Diego, CA, USA, 2007.
32. N.K. Dhingra: Understanding Information Processing in Retina - Critical for Treating Retinal Degenerative Diseases? 9th China-India-Japan-Korea joint workshop on Neurobiology and Neuroinformatics (NBNI-2007) in Jeju Island, S. Korea, July 5-7, 2007.

33. K. Vidhyasankar, C. Pitchaiah, S. Baloni, N.K. Dhingra: In Vivo Labeling of Mammalian Cone Photoreceptors by Intravitreal Injection of Fluorescently Tagged Peanut Agglutinin – A Potential Tool for Assessing Photoreceptor Degeneration in Humans. OSA Fall Vision Meeting in Berkeley (Sep. 16-19, 2007) Journal of Vision 7, 75a, 2007 <http://journalofvision.org/7/15/75>.
34. N.K. Dhingra, P. Cherukuri, V. Krishnamoorthy, S. Baloni and S.K. Jose: Morphological and behavioral characterization of N-methyl N-nitrosourea-induced mouse model of retinal degeneration. 37th annual meeting of the Society for Neuroscience in San Diego (Nov. 3-7, 2007). Soc Neurosci Abs 699.19/S19.
35. N.C. Singh: Speech rhythms in bilinguals, Abstract, Society for Neuroscience, San Diego, USA, Nov. 2007.
36. N.C. Singh: Invited talk – Patterns of speech in children with autism, Indo-US Symposium on Autism, 28-29th Sept. 2007.
37. P.K. Roy and Kh. Budhachandra: A Tensorial Approach to Perfusion Flux Imaging, Humboldt University, Berlin, May 2007.
38. Kh. Budhachandra and P.K. Roy: Dynamic Functional Tensor Neuroimaging: A Multimodal Analysis, Annual Meeting of Society of Neuroscience, San Diego, Nov. 2007.
39. Budhachandra Kh and P.K. Roy: Neural Causality Analysis: Transformational Invariance of the Hodgkin-Huxley Equation, International Biophysics Congress, Los Angeles, Feb. 2008.
40. P.K. Roy: Application of Stochastic Processes in Neuroimaging, Montreal Neurological Institute, McGill University, Nov. 2007.
41. S. Paul and P.K. Roy: Scale-space Segmentation of Tumour Tissue: Prospects for Image Guided Radiotherapy, University of Modena & Reggio Emilia, Dec. 2007.

National Presentations:

1. N. R. Jana: Protein aggregation in neurodegenerative diseases. Invited talk at Department of Biochemistry, Moulana Azad Medical College, Delhi, March 2008.
2. N.R. Jana: Role of intracellular protein degradation pathways in neurodegenerative diseases. Invited talk in the 2nd National Medical Students Research Conference, Pune, Feb. 2008.
3. S. Mani: Filling a GAP in the understanding of neuronal polarity - 'Model Organisms and Stem Cells in Development, Regeneration and Disease' symposium, NCBS, Bangalore, India, Feb. 2008.
4. V. Ravindranath: "Role of Glia in Neurolathyrism" Plenary lecture on Symposium on Glial Neurobiology, Gwalior on 23rd Oct. 2007.
5. V. Ravindranath: G.P. Chatterjee Award Lecture, Science Congress from 3rd to 5th Jan. 2008.
6. P. Seth: Human Neural Stem Cells As A Model to Study HIV-1 Induced Dementia Invited Speaker, Organized by Uttar Pradesh Association of Science and Technology Advancement and National Academy of Sciences (Local Chapter), Lucknow, March 2008.
7. P. Seth: Deriving human neurons and astrocytes from human fetal brains. International Conference of Current Advances in Molecular Biochemistry, Lucknow, Dec. 2007.
8. P. Seth: Invited Speaker, International Meeting of Association of Clinical Biochemists of India, New Delhi, Dec. 2007.
9. Mamata Mishra and P. Seth: Neuronal Apoptosis By HIV-1 Tat Protein Derived From Clade B And C, Oral presentation at the mini-symposium on 11th July 2007, "AIDS in India: A Regional Workshop-symposium to enhance HIV/AIDS Research Capacity" jointly organized by Albert Einstein's AIDS International Training and Research Program (AITRP), the Einstein/MMC CFAR and the Jawaharlal Nehru Center for Advanced Scientific Research (JNCASR), Bangalore, India.
10. P. Seth: HIV-1 Tat Modulates Human Fetal Brain Derived Neuronal Progenitor Cell Proliferation, Indian Academy of Neuroscience, Varanasi, India, Nov. 2007.
11. P. Seth: Deriving human astrocytes from human fetal brains. Invited Speaker, National Symposium on Glial Neurobiology, Jiwaji University, Gwalior, India, Oct. 2007.
12. P. Seth: Neural Stem Cells. Organized by Haryana State Council for Science and Technology, Bhiwani, India, Aug. 2007 (Science Popularization Series Lecture).

13. E. Sen: Microenvironment & Tumor aggressiveness: Dial M for Murder. Biosparks, JNU, New Delhi, March 2008.
14. E. Sen Inflammation and cancer: A destructive affair! Chittaranjan National Cancer Institute, Kolkata, Aug. 2007.
15. E. Sen: Tumor microenvironment: Role in glioblastoma progression. Jiwaji University, Gwalior, Jan. 2008.
16. E. Sen: Inflammation and glioblastoma: A deadly nexus. Rohtak Medical College, Rohtak, Haryana, Jan. 2008.
17. E. Sen: Inflammation and cancer: The flame within!!! TRendys, Rajiv Gandhi Centre for Biotechnology, Trivandrum, Sep. 2007.
18. E. Sen: Inflammation and cancer: Two to Tango!!! Deshbandhu College, New Delhi, Dec. 2007.
19. E. Sen: Tumour microenvironment and inflammation: role in glioblastoma progression. Ranbaxy Foundation, New Delhi, Jan. 2008.
20. E. Sen: Epigallocatechin 3-gallate inhibits HIF-1 α accumulation, HIF-1 α target gene expression and invasiveness in human Glioblastoma cells. International Symposium on Translational Research, Lonavala, Dec. 2007.
21. V. Swarup, J. Ghosh and A. Basu: Novel strategy for treatment of Japanese Encephalitis using Arctigenin, a plant lignan. 2nd International Symposium on Translational Research. Dec. 9-12, 2007, Lonavala.
22. J. Ghosh, V. Swarup and A. Basu: Novel strategy for treatment of Japanese Encephalitis using Arctigenin, a plant lignan. International Conference on Emerging and Re-emerging Viral Diseases in the Tropics and Sub-Tropics, Indian Agricultural Research Institute, 11-14th Dec. 2007
23. S. Das and A. Basu: Japanese encephalitis virus abrogates neural stem cell proliferation but fails to induce cell death. International Conference on Emerging and Re-emerging Viral Diseases of the Tropics and Sub-Tropics, Indian Agricultural Research Institute, 11-14 Dec. 2007.
24. A Basu: Brain's immune system: From molecules to mind. Society for Young Scientist, AIIMS, 4th April 2008.
25. A Basu: Japanese Encephalitis: from Neuropathology to therapeutic intervention. B C Guha Center for Genetic Engineering & Biotechnology and Department of Biochemistry, Ballygunge Science College, University of Calcutta, 5th March 2008.
26. A Basu: Japanese Encephalitis: from basic research to therapeutic intervention. Presidency College, Kolkata, 4th March 2008.

27. A Basu: Japanese Encephalitis: from Neuropathology to therapeutic intervention. Ranbaxy Research Laboratory, Gurgaon, 10th Jan. 2008.
28. A Basu: Aberrant microglial response in Japanese Encephalitis: from mechanism to intervention. Indian Institute of Chemical Biology, Kolkata, 24th Dec. 2007.
29. R Duseja, M K Mishra, and A Basu: TLR signaling following JEV infection. Annual Meeting of Indian Academy of Neurosciences, Banaras Hindu University, Varanasi, 22-25 Nov. 2008.
30. A Basu: Minocycline confers complete protection against Japanese Encephalitis: Correlation with microglial activation and neuronal protection. Symposium on Science of Life: The New Horizon, Miranda House, University of Delhi, 22nd Nov. 2007.
31. A Basu: Microglial madness: when friend turns to foe. National Symposium on Glial Neurobiology, Center for Neurosciences, Jiwaji University, Gwalior , 23rd Oct. 2007.
32. A Basu: Molecular Mechanism of Neuronal death in Japanese Encephalitis. IMTECH, Chandigarh, 24th Aug. 2007.
33. A Basu: The secret life of the brain. Senior Secondary School, Tauru, Mewat, Haryana, 4th Aug. 2007 (Science Popularization lecture).
34. A Basu: Inflammation and Neuronal Apoptosis in Japanese Encephalitis. Chittaranjan National Cancer Research Institute, Kolkata. 17th July, 2007.
35. A. Murthy: The control of saccadic decision-making. Indian Academy of Neuroscience, Banaras Hindu University, India, 2007.
36. A. Murthy and K.M Sharika: Predictive oculomotor control during error correction. Soc. for Neuroscience Abstract, 2007.
37. M. Chugh, Z. Darokhan & V. Rema: Differential influence of motor cortex on neuronal activity of barrel and septal domains in somatosensory cortex. Indian Academy of Neuroscience, 2007.
38. Rahul Chaudhary and V. Rema: Chronic iron deficiency impairs somatosensory behavior and alters the expression of NMDAR1 and GAD 65 in somatosensory cortex. Indian Academy of Neuroscience, 2007.
39. Ziauddin Darokhan, Manisha Chugh & V. Rema: Lesions in the somatosensory cortex reduces activity of neurons around the lesion site in adult rats, Indian Academy of Neuroscience, 2007.
40. V. Rema: Invited talk "Modulation of sensory information processing following lesion of motor cortex." Indian Academy of Neuroscience, 22 Nov. 2007.

41. V. Rema: Invited talks in the lecture Workshop "Frontiers in Neuroscience" at Sophia College 4-5 Jan. 2008: Basic lecture: "Techniques for studying sensory processing in rats".
42. V. Rema: Invited talks in the lecture Workshop "Frontiers in Neuroscience" at Sophia College 4-5 Jan. 2008: Research lecture: "Plasticity in the rat somatosensory cortex".
43. N. Jain: 'Organization of the Brain' and 'The Plastic Brain' at 'Workshop on Mathematical Aspects of Neuroscience'. Department of Mathematics, Indian Institute of Science, Bangalore, Jul 9 – 14, 2007.
44. N. Jain: 'Brain' at orientation course for undergraduate college lecturers from Haryana State'. Govt. College, Sector 14, Gurgaon. Oct 1-21, 2007.
45. N. Jain: 'Functional Anatomy of the Brain' and 'Reorganization of the Brain after Injuries' at the workshop 'Frontiers in Neuroscience'. Sophia College, Mumbai, Jan. 4-5, 2008.
46. S. Iyengar: Development of the Human Auditory Cortex – Neuroanatomical Studies. Presented at the symposium on Brain, Cognition and Behaviour organized by the School Of Language, Literature and Culture studies, Jawaharlal Nehru University, New Delhi, March 14 -15, 2008.
47. S. Iyengar: The expression of different markers and changes in cytoarchitecture in the developing human auditory cortex. Presented at the symposium Current Trends in Auditory Research organized by the Maulana Azad Medical College, New Delhi, Sept 21-22, 2007.
48. S. Iyengar: The development of the human auditory cortex. Presented at the 9th Karnataka Chapter of Anatomists, Conference and Workshop (Special theme: Recent Advances in Neuroanatomy) organized by JSS Medical College, Mysore, May 25-27, 2007.
49. A. Tripathi and S. Iyengar: Expression of opioid receptors in the human ventricular and subventricular zones during the first and second trimester of gestation. Indian Association of Neurology, Annual Meeting, 2007.
50. P.V. Haldipur, C. Sarkar, S. Iyengar, and S. Mani: Role of Sonic Hedgehog signalling in human cerebellum development. Indian Association of Neurology, Annual Meeting, 2007.
51. N.K. Dhingra: The Power of Brain. Popular science lecture for high school students on 22nd National Science Day at Kendriya Vidyalaya (Sector 14) Gurgaon, Feb. 28, 2008.

52. N.C. Singh: Invited talk - Speech and Hearing Impairments in Children, National Seminar on empowering the differently abled, Feb. 9-11th 2008.
53. N.C. Singh: Invited talk – Speech rhythms in bilingual children, Indian Association of Neuroscience, Varanasi, Nov. 2007.
54. N.C. Singh: Invited talk - Development of articulatory features in children and those with cochlear implants, MAMC, Sept. 2007.
55. A. Upadhyay and P.K. Roy: Towards a Dynamic Analysis of Brain and Language, Conference on Auditory Development, Maulana Azad Medical College, Delhi University, April 2007.
56. P.K. Roy: Brain Imaging: Looking at Nerve Fibres, Haryana State Govt. Council of Science & Technology, Jind, Aug. 2007.
57. A. Upadhyay and P.K. Roy: Multiplexed Information Processing in Human Neurocognitive System: fMRI, Annual Meeting of Indian Academy of Neuroscience, B.H.U., Banaras, Nov. 2007.
58. P.K. Roy and Kh. Budhachandra: Dynamic space-time representation in the Neural system, Silver Jubilee Symposium of Indian Academy of Neuroscience, B.H.U., Banaras, Nov. 2007.
59. P.K. Roy and A. Upadhyay: Neurodynamic Basis of Adaptation, Cognition, Language, International Conference on Cognitive Psychology, Indian Statistical Institute, Calcutta, Dec. 2007.
60. P.K. Roy and Kh. Budhachandra, Multimodal Tensor Imaging, Workshop on Computational Neuroscience, Delhi University, Dec. 2007.
61. V.P. Subramanyam and P.K. Roy: Stochastic Resonance as a Novel Enhancement Technique in Neuroscience, D.R.D.O., Defense Ministry, New Delhi, April 2007.
62. P.K. Roy: The Fractal Landscape Behind Cognition, International Conference on Mathematical Neuroscience, I.I.Sc, Bangalore, June 2007.
63. S. Paul and P.K. Roy: Effect of Stochastic Fluctuation on Radiosurgical Efficiency: International Workshop on Recent Advances in Radiosurgery, A.I.I.M.S., New Delhi, June 2007.
64. S. Paul and P.K. Roy: Application of Stochastic Modeling in Radiobiology, International Conference on Mathematical Neuroscience, I.I.Sc., Bangalore, June 2007.
65. P.K. Roy: Fractal analysis for Differential Diagnosis in Dementia Imaging, Meeting on Dementia, National Institute of Immunology, New Delhi, Aug 2007.

66. P.K. Roy: Presentation at Discussion Meeting on New Topics in Biotechnology, Anna University, Madras, Sept. 2007.
67. V.P. Subramanyam and P.K. Roy: Neurophysics: The Newest Frontier of Physics, I.I.T., Bombay, Feb. 2008.

DISTINCTIONS, HONOURS AND AWARDS

Prof. V. Ravindranath

Awards

- (1) J.C. Bose Fellowship.
- (2) G.P. Chatterjee Memorial Lecture Award presented by Science Congress.

Member of Committees

- (1) Member, Governing Council of International Brain Research Organization.
- (2) Council Member, Federation of Asian and Oceanian Neuroscience Societies.
- (3) Member, Asia Pacific Regional Council, IBRO.
- (4) Council and Sectional Committee Member, National Academy of Sciences, India.
- (5) Council and Sectional Committee member, Indian National Science Academy, New Delhi.
- (6) Member Sectional Committee (Neuroscience), TWAS.
- (7) Chairman, Expert Committee for Senior Research Fellow, CSIR, New Delhi.
- (8) Member, Medical Sciences Research Committee, CSIR, New Delhi.
- (9) Member Research Advisory Council (RAC) of the Human Resource Development Group, CSIR.
- (10) Member, Standing Committee for Emeritus Scientists and One Time Grant Research Committee, CSIR.
- (11) Member, Programme Advisory Committee for Medical Sciences, Department of Science and Technology.
- (12) Member, Task Force on Chronic Disease Biology (TFCDB), Dept. of Biotechnology.
- (13) Member, Life Sciences Research Development Board (LSRDB), Department of Biotechnology.
- (14) Member, Scientific Advisory Committee to Cabinet.
- (15) Chairman, Building Committee, Institute of Life Sciences, Bhubaneswar.
- (16) Member, Advisory Committee of Special Centre for Molecular Medicine, Jawaharlal Nehru University.
- (17) Member of the Senate, Indian Institute of Technology, Delhi.

Membership of Editorial Board of Journals:

- (1) Member, Editorial Board, Progress in Neurobiology, USA.
- (2) Member, Editorial Board of the International Journal, "Neurotoxicity Research", USA.
- (3) Member, Editorial Board, Neuroscience Research, Japan.

Dr. Anirban Basu

Member, National Academy of Sciences, India.

Dr, Ellora Sen

- (1) Innovative Young Biotechnologist Award (2007): Awarded by the Department of Biotechnology (DBT), Government of India. Through this she will undertake a project (2008-2011) that will investigate the "Role of lipid rafts in epigenetic silencing and immune cell signaling: Implication in the aggressiveness of glioblastoma multiforme".
- (2) EC member, Neuro-Oncology Society of India (NOSI).
- (3) Nominated Associate Member, American Association for Cancer Research.

Dr. Aditya Murthy

Member, National Academy of Sciences, India.

Student Awards:

- (1) Smitha Karunakaran: "Marie Curie Scholarship" to attend 15th Euro Conference on Apoptosis & 4th Training course on 'Concepts and Methods in Programmed Cell Death' Portoroz, Slovenia, Oct. 26-31, 2007.
- (2) Lalitha Durgadoss: "Travel Award from the Melvin Yahr International Parkinson's Disease Foundation" for participation at the XVII WFN World Congress on Parkinson's Disease and Related Disorders in Amsterdam 2007.
- (3) Shailesh Kumar Gupta: "APDBN Travel Award" to attend Centre for Developmental Biology meeting, Kobe, Japan 21st-24th March 2008.
- (4) Mamata Mishra: "Investigator in Training Travel Award" by International Society of Neurovirology to attend 8th International Symposia on Neurovirology held on Oct 29th to Nov 2nd 2007 at San Diego, USA.
- (5) Mamata Mishra: "The Hilary Koprowski 2004 ISNV Pioneer in Neurovirology Lectureship Award" for Oral presentation organized by

8th International Symposia on Neurovirology held on Oct 29th to Nov 2nd 2007 at San Diego, USA.

- (6) Kh. Budhachandra: International Student Award, Biophysical Society of America, Washington DC, Nov 2007.
- (7) V.P. Subramanyam Rallabandi: Best Participant Award, Training Workshop on NMR: From Molecules to Mind, Society of Magnetic Resonance, Indian Institute of Science-Bangalore, May, 2007.
- (8) Subhadip Paul: Young Researcher Award on Neuroinformatics, Ministry of Education, Govt. of Italy, Oct 2007.
- (9) Vinay Shukla: Nonlinear Dynamics Training Award, Indian Institute of Science, Bangalore, March, 2008.
- (10) Ashish Upadhyay: Parmer Award, Silver Jubilee Conference of Indian Academy of Neuroscience, Banaras Hindu University, Varanasi, Nov. 2007.
- (11) Subhadip Paul: Mathematical Neuroscience Travel Award, Indian Institute of Science, Bangalore, June 2007.
- (12) V.P. Subramanyam Rallabandi: Medical Physicist Fellowship Award, International Medical Physics Collegium, International Centre of Theoretical Physics, Trieste and Bhabha Atomic Research Centre, Bombay, Dec. 2007.
- (13) Kh. Budhachandra: Visiting Trainee program, Laboratory of Neuro-Imaging, University of California-Los Angeles, and Montreal Neurological Institute, McGill University, Montreal, Feb 2008.

**EXTERNALLY FUNDED
RESEARCH PROJECTS**

Dr. Nihar Ranjan Jana

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

Dr. Shyamala Mani

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

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

Maternal Malnourishment and its Effect on Brain Development - CEFIPRA, Indo-French Grant

Prof. V. Ravindranath

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

Dr. Pankaj Seth

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

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

Role of CNS Opportunistic Infections in Subsequent Development of HIV encephalitis (NIH, USA).

Dr. Ellora Sen

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

Modulation of oxidative stress and hypoxia by inflammation: Implication in the pathogenesis of glioblastoma (DRDO).

Role of lipid rafts in epigenetic silencing and immune cell signaling: Implication in the aggressiveness of glioblastoma multiforme. (Innovative Young Biotechnologists Award 2007, DBT).

Oligodendrocyte Differentiation from Neural Stem Cells: Implication in CNS repair (DBT).

Dr. Shiv Kumar Sharma

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

Dr. Anirban Basu

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

Dissecting Molecular Circuitries that regulate Progenitors Cell Response to Japanese Encephalitis Virus (DBT).

Evaluation of Minocycline as a neuroprotective and/or anti-inflammatory and/or anti viral drug in Japanese Encephalitis (CSIR).

Dr. Aditya Murthy

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

Brain Mechanisms of Action Control in Humans (DBT).

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

Dr. V. Rema

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

Recovery of neuronal and behavioural functions with embryonic stem cell therapy following brain injury (DBT).

Dr. Neeraj Jain

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

Spinal cord plasticity and rehabilitation after spinal cord injuries (In collaboration with Pavlov Institute, Russia; Department of Science and Technology, India under Indo-Russian ILTP Program).

Autonomous Navigation using Brain-Machine Interface (BMI) (in collaboration with IISC, Bangalore, CAIR, Bangalore and MIT, USA; Defence Research and Development Organization, India).

Transplantation of Stem Cells for Recoveries from Spinal Cord Injuries (DBT).

Dr. Soumya Iyengar

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

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

Dr. Narender K. Dhingra

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

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

Dr. Nandini Chatterjee Singh

Articulation maps for spoken language (DST).

The development of articulatory features in children (The Ministry of Communications and Information Technology).

Dr. Prasun Kumar Roy

Spatiotemporal Neural Processing and Information Transmission (Ministry of Education & Research, Italian Govt. under a program of the European Commission. & Biophysical Society of America (exchange program: support for student's collaborative research project).

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

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:

The e-campus at NBRC continues to be upgraded using latest technology multicore fiber optics, Network Connection between Campus buildings, WiFi connection within buildings. DIC has upgraded internet bandwidth from 2 to 4 Mbps on the lease line connectivity. In order to provide back-up in case of landline breakdown DIC has also implemented RF link connectivity for high-speed internet to the scientific community. As part of infrastructure expansion DIC has established video conferencing for conducting lectures and seminars and to enable interactions with eminent scientists across other centres and universities. High speed computing is available in the form of a The IBM and SUN servers, which provides Active Directory Services, Mail Services, DNS Services and Web services that runs by the SUN Solaris 10, Linux and Windows 2000/2003/2008 Server operating system. A tape drive for data backup has also been installed and weekly backup schedules have been implemented. All the servers and personal computers are integrated with 11 TB Centralized Network Attached Storage, which is used as a repository for neural data and high-resolution graphics. DIC has balanced manpower with 2 system manger handling the servers and 3 computer operators assisting in technical problems in addition to helping the scientists. NBRC having two mailservers for ease the communication with the scientific community both server having around 200 mailboxes which is fully secured by firewall one mail server recently shifted from HCL these servers are managing and maintaining by DIC.

Research Support:

In lieu of the recently setup Neuroimaging facility at NBRC, DIC personnel have started to help in paradigm design and set up for experiments. The computing facilities at the fMRI have been integrated into the existing network and new software and machines have been procured to handle increased storage. DIC is also making efforts to develop new computational techniques for faster and efficient analysis of neural data and signal processing which would benefit the neuroscience community.

New Initiatives:

In order to deal with the increasing fMRI data, DIC is currently setting up a High performance-computing cluster for faster and efficient data analysis in

functional MRI data. Implementing Disaster recovery to protect important aspect of computing hardware and critical research data this DR will be installed on fMRI building.

Animal Facility

NBRC animal facility procures and breeds a wide variety of species of laboratory animals to meet requirements of investigators in the institute. It adheres to the highest standards of laboratory animal care and ensures compliance with all the regulations regarding the care and use of animals in research. Staff at the animal facility 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 are available for sterilization of cages, water bottles, bedding and feed. There is a hot vapour jet machine for cleaning rabbit and monkey cages. Animal house staff also takes shower and changes clothing before entering the animal rooms. It is mandatory to 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 optimizing enrichment and social interactions. 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 transgenic, knock out and mutant mice are housed under strict clean conditions in filter top cages and individually ventilated cage system (IVC). All animal manipulations are done in laminar hoods and cages are changed in cage changing stations under Hepa filtered air.

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 sterilizer and ethylene oxide gas sterilizer.

Animal facility has separate necropsy room, a 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. It is mandatory for all personnel who handle animals to have a current tetanus vaccination. Those who handle non-human primates are screened for tuberculosis and are trained to provide initial first aid in case of animal bite or scratch. Close circuit cameras have been installed at various locations in the facility for security and effective monitoring of 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 mice(Alzheimer disease model) UBC-GFP mice (Green fluorescent protein)
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 and Sprague Dawley.
Rabbits	:	New Zealand white
Guinea pigs	:	Duncan Hartley
Non-human primates	:	Macaca mulatta and Macaca radiata, 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 specialized 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. It also provides facilities and support to the Scientists, researchers, students, staff and its networked centers.

The NBRC library has good collection of Journals, books and other relevant research materials on Neuroscience, Biochemistry, Genetics, Molecular Biology, Immunology & Microbiology, Pharmacology and Toxicology, Psychology, Physics, Mathematics, Computer Science and General Subjects. NBRC Library is currently subscribing to 532 journals among of them 448 are online (including some free journals) and others are in the printed hard copy format. Library is also subscribing Newspapers and News Letters. The Collection of NBRC Library is growing rapidly in view of the extensive research and knowledge in the field of Neuroscience and related areas.

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

The NBRC Library has setup 22 IBM PC-Pentium-IV Computers with ISDN Internet facility in the common room to provide services for use of researchers and students at NBRC. The Library provides access to the most current reference sources available in order to assure the accuracy of information. The Library has been providing electronic access to the subscribed journals within campus portal.

A total of 245 registered users including Scientists, Researchers, students and other staff use the NBRC library facilities. The NBRC Library also provides the services of “Inter Library Loan” to the 48 Networked Centres all over India. The researchers, scientists and students send their requirement for research material or journal articles through email to NBRC Library (library@nbrc.ac.in) and staff of library download the articles / papers / information and send the same to the requestors free of cost. The library entertains an average of approximately 458 articles every year and such requests are increasing.

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

The Main Activities of NBRC Library

- Book Acquisition
- Periodicals Acquisition
- Selective Dissemination Information (SDI)
- Current Awareness Services (CAS)
- Inter Library Loan
- Resource Sharing
- Circulation services
- Reference services, Bibliographic services
- Indexing and Special services
- Collect, maintain, store and retrieve information and data keeping in view the evolving needs of researchers.
- Help to Networked Centres.

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

NATIONAL NEUROIMAGING FACILITY

National Neuroimaging Facility

The discovery that magnetic resonance imaging can be used to map changes in brain hemodynamics that correspond to brain function extends the possibilities of traditional anatomical imaging to now include maps of human brain function. The ability to observe both the structures that participate in different brain functions is due to a new technique called functional magnetic resonance imaging also called fMRI. fMRI provides high resolution, noninvasive reports of neural activity detected by a blood oxygen level dependent signal also called the hemodynamic response. Understandably, its advent has brought about a revolution in the field of neuroscience and has opened up an array of new opportunities to advance our understanding of brain organization, as well as a potential new standard for assessing neurological status and neurosurgical risk.

The National Neuroimaging Facility set up at NBRC consists of a 3 Tesla Phillips whole body MRI system and is housed on the NBRC campus. The facility has capability for performing structural and functional MRI, MR spectroscopic imaging, diffusion tensor tractography, arterial spin labeling and multinuclear chemical shift imaging. There is also a high-resolution 64-channel EEG system that can be used to monitor electrical activity in the brain while the subject is being scanned for MRI and is performing demanding cognitive tasks therein. This enables simultaneous measurements of recording brain reactivity, such as evoked potentials and contingent variation. This MRI/fMRI facility, the first of its kind in India, is a National Facility and is open to researchers from across the country. In addition to understanding brain function, the center also is closely interacting closely with researchers worldwide to develop new and better methods to image brain function.

In addition to the basic machine the National Neuroimaging Facility has also acquired state-of-art software and hardware for the delivery of auditory and visual stimulation, (NEUROSCAN, 'Eloquence' and E-prime systems) to programme proper sophisticated sequencing and timing of such cognitive tasks. In order to enhance its capabilities the NEUROSCAN system can be run in conjunction with the fMRI, enabling the simultaneous measurement of electrical activity and blood flow changes non-invasively from human brains performing cognitive tasks. At NBRC, fMRI is currently being used to provide insights on how the brain areas interact to enable complex functions such as decision-making and object perception as well as studying the organization of language in multilingual populations. We hope that the use of such state-of-art technology will help us develop novel diagnosis, therapeutic monitoring and evidence-based treatment planning in brain dysfunction, characteristic of a host of neurological and psychiatric disorders.

Further, in the field of structural imaging, the investigations focus on localization of primate cortical processing areas, an MRI/EEG study of decision making and control (to provide spatial and temporal resolution), as well as harnessing newer image processing techniques for proper diagnoses of brain tumours and neurodegenerative diseases as dementia. The National Neuroimaging Facility actively encourages researchers from across the nation to make use the imaging center to fully utilize its potential.

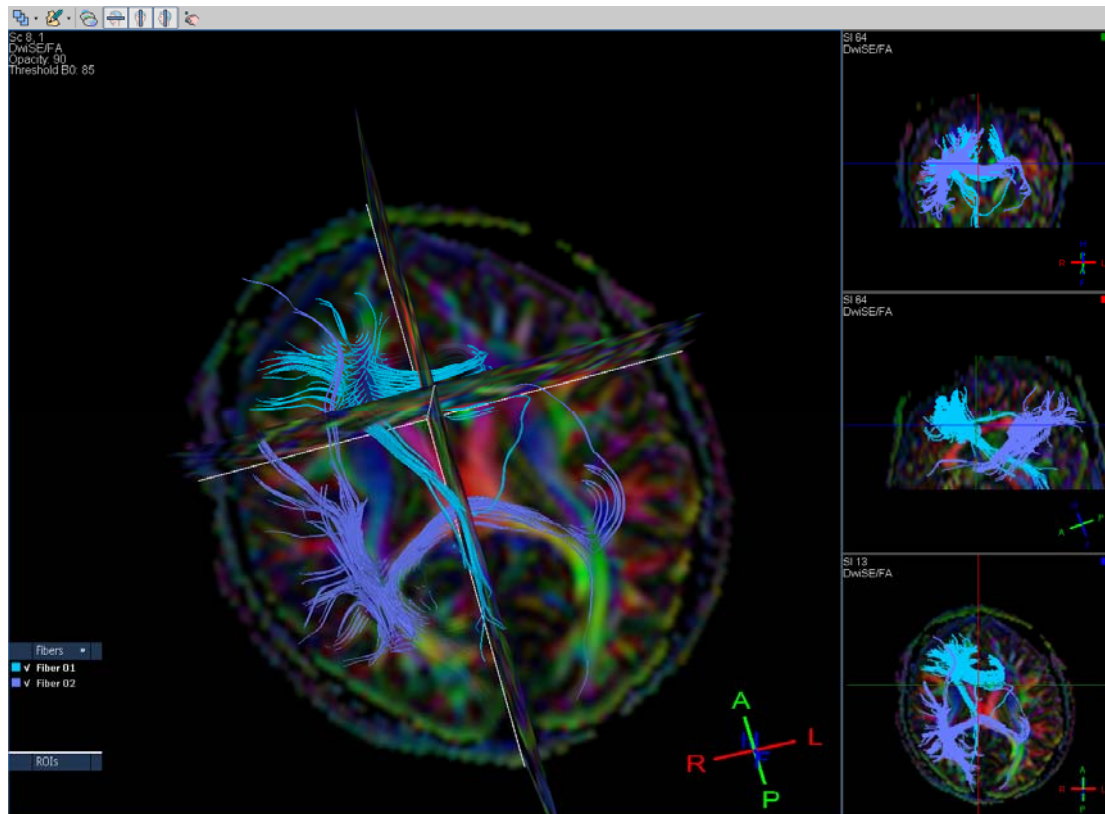


Figure: An MRI image of human brain depicting fibre tracts.

TRANSLATIONAL RESEARCH

Translational Research at NBRC

Translational research aims to more directly connect basic research to patient care-‘from (lab) bench to bedside’ as it is popularly referred to, and it has been adopted globally over the past several years to bring the right perspective and mutual motivating force to both disciplines.

The Clinical Research Unit of NBRC, a thrice a week, morning outpatient facility, at the Civil Hospital, Gurgaon was started on Jan. 28th, 2008 to take a first step in translational research. It is envisaged that this unit would open a ‘clinical window’ for the basic scientists to peer through, even as the clinician looks through from his/her side of the tinted glass, to catch a glimpse of what appears to be the ‘magic wand’ wielded by the basic scientist. Mutual respect and intermingling of the disciplines will hopefully help achieve common goals.

The Clinical Unit has in this short period managed to reach out the message to the surrounding semi-urban and rural communities, that effective medical intervention is possible in many neurological and psychiatric disorders. Patient rapport shows an encouraging trend. At present, 75% of the patients who attend NBRC Clinical Unit, report headache or seizure disorder, 15% have neuroses/psychoses, the remaining 10% having a diagnosis of peripheral neuropathies, Bell’s palsy, sciatica, trigeminal neuralgia and other common neurological disorders. There is the occasional Guillain-Barré syndrome or neurosurgical case, which requires to be referred to the, appropriate, urgent inpatient facility. It is hoped that this clinical unit will provide the scope to recruit patients for research studies, including clinical trials.

Dr. Subbulakshmy Natarajan, Consultant Clinician is running the facility.

MEETINGS & WORKSHOPS

Workshop on Identification of Priorities for Clinical and Basic Research in Dementia Including Alzheimer's Disease

Brain related disorders are known to contribute up to one-third of the total disease burden in both developed and developing countries. Among these, a cause of serious concern, are the age-related disorders such as senile dementia, Alzheimer's disease and Parkinson's disease etc. These disorders are progressive and irreversible, and currently no cure is available since the etiopathogenesis of these disorders is poorly understood. The number of people suffering from dementia slowly increases from the age of 65 onwards. It affects 0.5% of those aged 65-70, 20% of those aged over 80, and 30% of those aged over 90. Alzheimer's disease accounts for about 60-70% of dementia cases. About 15% of sufferers have a family member who has also suffered from the disease.

A one-day workshop was organized on August 10, 2007 to discuss different issues and to develop multi-institutional programmes for both clinical and basic research initiatives in dementia. Several neurologists from various Centres in the country participated in the meeting along with the basic scientists. The primary aim of the meeting was to discuss the state of knowledge, identify future goals and prioritize research initiatives based on the needs of the country and the niche areas. The presentations were made in different areas related to dementia. After the presentations, the participants had a discussion to identifying the research priorities. It was decided to focus on (1) development of clinical research protocol including tools for monitoring incidence of dementia including Alzheimer's disease, (2) identifying protective factors, and (3) invite individual investigator as well as multi-institutional grant proposals in basic, translational and clinical research. This would be taken up as an extramural research effort of NBRC.

A follow-up meeting was held in Dec. 2007 in which Prof. Sangram Sisodia was also present. Prof. Sisodia made several recommendations for the success of this important endeavour.

Meeting for establishing A National Research Initiative on Language

A two day meeting to initiate a national research effort on language under Department of Science & Technology Cognitive Science Initiative in the 11th five-year plan was organized at the National Brain Research Centre was organized on 12-13th Oct. 2007. Twenty experts from various domains such as Linguistics, Cognitive Neurologists, Psychologists, Speech Pathologists and Computational Modelers from different parts of the country attended and participated in the meeting.

On the first-day, a series of presentations were made which comprised of the state-of-the-art theories and models extant in the three domains, namely, the clinical, the linguistic and the computational. The second day was devoted to brainstorming on specific problems that were relevant for the Indian context and approaches that may be taken. Strengths in terms of domain-specific expertise, experimental and infrastructural resources and access to patient registry were identified. This was followed by two subsequent meeting by the Department of Science and Technology and has resulted in a program grant for National Research initiative on Language under Department of Science & Technology Cognitive Science Initiative in the 11th five-year plan.

Workshop on Computational Neuroscience 2007

For the 7th year in succession, NBRC supported a national level workshop on course on Computational Neuroscience to provide students from the engineering, physics, computer science and mathematics community a detailed exposure to basics of neuroscience and the new computational techniques that have been developed to handle neural data. In 2007, the CNS course was conducted at the Department of Computer Science, University of Delhi from Dec. 22-31st 2007. In 2007, workshop went international, in that three international students, two from Iran and one from Bangladesh, who were supported by IBRO also attended the workshop. 50 students from different colleges in India participated and were exposed to lectures on computational models and experiments addressing information processing at various levels such as cellular, systems and cognitive levels. Additionally, related topics in Artificial neural networks, Neuroimaging, Machine learning and AI were covered. NEURON, Matlab, Genesis, and SciLab toolkits were used for demonstrations and exercises to gain a deeper understanding of the concepts and methods introduced in the course. Eminent researchers working in various institutions such as NBRC, NCBS, IIT Bombay, IIT Delhi, IIT Madras, University of Hyderabad, delivered lectures.

The course was planned with 5 theory sessions every day between 9:30 am and 4.00 pm, followed by 2 lab sessions between 4:30 pm and 6:30 pm. Thus the course comprised a total of 50 one-hour theory sessions and 20 one-hour lab sessions, adding up to a fairly workshop for the participants.

The 3rd Ramamurthy Memorial Lecture

Dr Robin Sengupta, Professor of Neurosurgery, University of Newcastle, U.K. and Chairman, National Neuroscience Centre, Calcutta, delivered the Third Ramamurthy Memorial Lecture at NBRC on 30th Jan., 2008. The topic of the lecture was on "Role of Neurosciences on Human Unity". Prof. Sengupta is an internationally acclaimed neurosurgeon who has developed

pioneering neurovascular interventions. In course of the lecture, he took the audience over an enthralling tour across the historical development of neurosurgery and clinical neuroscience over the last century, culminating in the contemporary but perplexing questions posed by neuroethics which often present real dilemma to the practicing neuroscientist. Possible future advances of neuroscience along these issues were also explored.

INTERNATIONAL COLLABORATIONS & NETWORKING

International Collaborations

International collaborations are aimed at promoting neuroscience through exchange programs. Towards this endeavour, in a very short span of time, NBRC has made great strides in establishing collaborations with various prestigious neuroscience institutions in different countries around the world. Several research projects with USA, Russia, France, Italy and Canada are being pursued.

In the current year, an INSERM-NBRC associate lab was established at NBRC. An agreement was signed between the National Brain Research Centre represented by its director Prof. V. Ravindranath and the Deputy Director of INSERM, in charge of the strategical affairs M. Thierry Damerval and The President of the University Paris Diderot- Paris VII Professor Guy Cousineau on 25th Jan. 2008 in the presence of the Hon'ble Prime Minister of India, Dr. Manmohan Singh and the President of France, Mr. Nicolas Sarkozy. The agreement pertained to the setting up of a joint DBT- INSERM Associated Laboratory known as PROTECT an acronym for Promoting Research Oriented Towards Early CNS Therapy with a view to extending and strengthening relations in the area of research on developmental brain disorders. The agreement includes a teaching element for building human capacity and exchange of research scientists from both countries. The mandate of the associated laboratory is to make contributions to basic mechanisms involved in developmental brain disorders and towards treatment of neonatal brain disorders. The laboratory will focus on maternal malnutrition and its effect on brain development of the foetus, an issue of great societal importance and impact. It will also focus on abnormal brain development and whether stem cells can be used in the context of developmental disorders. This is the first international laboratory that has been set up by INSERM in India.



Networking

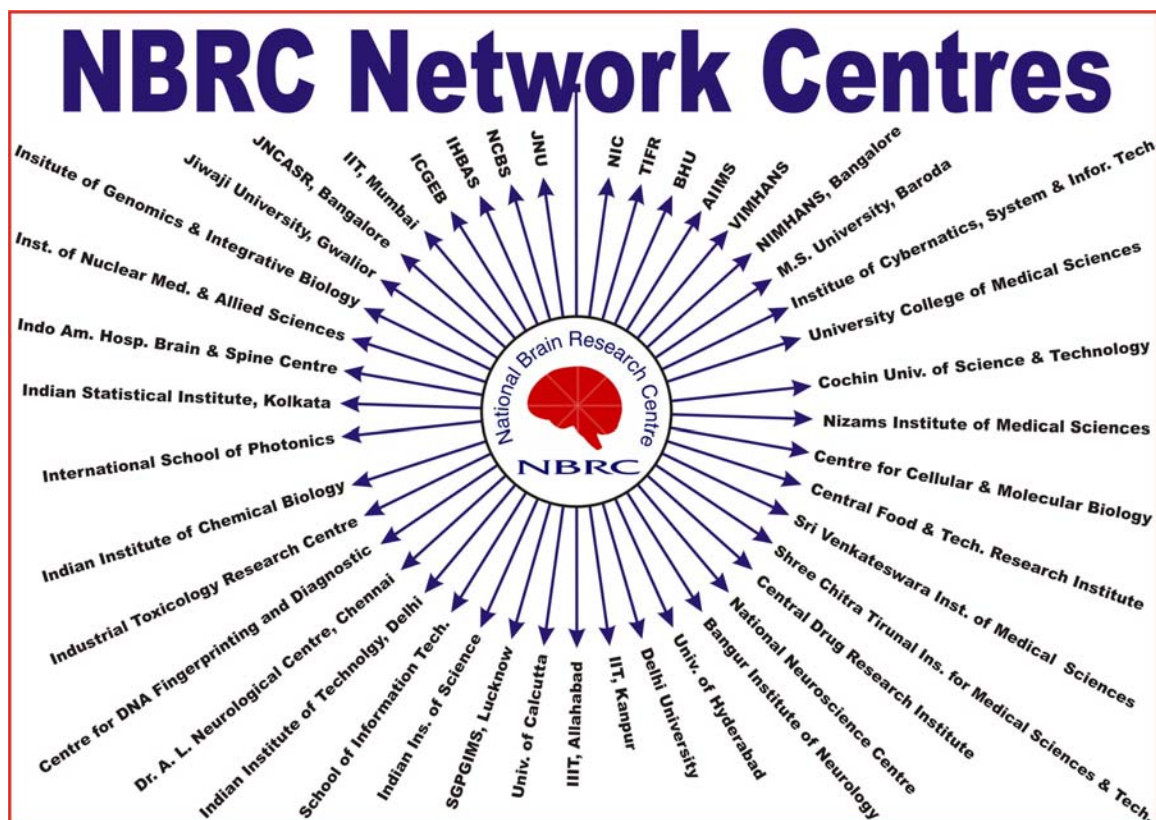
A major goal of NBRC is to network the existing neuroscience groups/institutions in the country and promote multidisciplinary research in neuroscience. This is aimed to prevent unnecessary duplication of the work and facilities already existing. It also facilitates sharing of expertise and available 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.



INVITED LECTURES

Sr. No.	Name of the Speaker	Name of the Institute	Title	Date
1.	Dr Shashi Bala Singh	Addt. Director Defence Institute of Physiology and Allied Sciences	Hypobaric hypoxia impairs spatial memory in rats	April 3 rd 07
2.	Prof. Tom Albright	Salk Institute, San Diego, USA	Contextual influences on visual motion processing	April 19 th 07
3.	Dr. Aurnab Ghose	Dept of Cell Biology Harvard Medical School, Boston , USA	Receptor Tyrosine Phosphatases in Neuronal Development	April 24 th 07
4.	Dr. Mayurika Lahiri	MGH Cancer Centre, Harvard Medical School, Boston , USA	The Damage Surveillance Pathway in human Pathologies	April 24 th 07
5.	Dr. Supratim Ray	Johns Hopkins University, USA	Effects of attention on ECoG high-gamma activity in humans and relationship of high- gamma to single-unit activity in non-human primates	May 11 th 07
6.	Dr. Sravan K Goparaju	Dept of Biochemistry and Mol. Biology, Hokkaido University Japan	The regulation of cell migration and Synaptic transmission by Sphingosine-1- Phosphate	May 14 th 07
7.	Dr. Rakesh Sharma	Florida State University, College of Engineering, Chemical/Biomedical Engineering Tallahassee, Florida	Magnetic Resonance Spectroscopic Imaging and Magnetic Resonance Imaging in Alzheimer's Disease, Epilepsy, Multiple Sclerosis and emerging microimaging techniques	June 4 th 07
8.	Dr Gaiti Hassan	Professor NCBS (TIFR)	Intracellular calcium signaling in Drosophila flight: where multiple wrongs make a right	June 7 th 07

9.	Dr. Arvind Kumar	Instructor Mol. Psychiatry Lab., Dept of Psychiatry, University of Texas Southwestern Medical Centre, Texas	Epigenetic Mechanisms In Animal Models Of Addiction And Depression	June 26 th 07
10.	Dr. Kamesh R Ayasolla		Neuroinflammatory issues in Alzheimer's Dementia (AD); Therapeutics of AICAR & Vitamin E" (b) "Redox issues in Preclampsia; Possible implications to IUGR & Cerebral Palsies	June 29 th 07
11.	Dr Manorama Patri		The Environmental Contaminants: Polycyclic Aromatic Hydrocarbons and Brain Development	July 10 th 07
12.	Prof. Partha Mitra	Cold Spring Harbour Laboratory	working memory, attention and correlated neural activity	July 20 th 07
13.	Dr Tapan Kumar Khan	Assistant Professor Blanchette Rockefeller Neurosciences Institute, Rockville, USA	Molecular convergence of memory and Alzheimer's disease pathways on PKC isozymes: Targets for therapeutics and diagnostics biomarker in human fibroblasts	Aug 3 rd 07
14.	Dr. Krishna Kumar Menon	Assistant Research Scientist, Department of Neurology, University of Iowa.	Molecular mechanisms in immune-mediated demyelination	Aug 16 th 07
15.	Prof. Claude Bernard	Associate Director, Immunology and Stem Cell Laboratories, Monash University, Australia	Understanding CNS autoimmunity: from animal models to multiple sclerosis patients	Aug 16 th 07
16.	Dr. Srivatsun Sadagopan	Graduate Student Dept. of Neuroscience, Johns Hopkins University School of Medicine, USA	Non-linear computations underlying feature selectivity in primary auditory cortex	Sept 3 rd 07

17.	Prof. Stuart Baker	Newcastle University, UK	A Functional Role for Motor Cortical Oscillations	Sept 20 th 07
18.	Dr Claire Witham	Newcastle University, UK	A Functional Role for Motor Cortical Oscillations	Sept 20 th 07
19.	Dr. Stuart A. Lipton	Scientific Director, Burnham Center for Neuroscience, Aging, and Stem Cell Research, Professor, Burnham Institute for Medical Research, The Salk Institute, The Scripps Research Institute and University of California at San Diego, USA	Free Radical-Induced Protein Misfolding and Neuroprotection in Neurodegenerative Disorders	Oct 9 th 07
20.	Dr. Subhash C. Pandey	Professor & Director Neuroscience Alcoholism Research Depts. of Psychiatry, Anatomy, and Cell Biology, University of Illinois at Chicago & Jesse, Brown VA Medical Center, Chicago IL, USA	From Genes to Neurons in Anxiety and Alcohol Abuse Disorders	Nov 20 th 07
21.	Prof. Rajesh Kalaria	Institute of Ageing & Health, University of Newcastle, England	Fronto-temporal dementia	Nov 21 st 07
22.	Dr. Ashok Kumar	Associate Professor Dept. of Anatomical Sciences & Neurobiology University of Louisville, School of Medicine, Louisville, USA	Molecular mechanism of skeletal muscle atrophy	Dec 3 rd 05
23.	Dr. Udaykumar Ranga	Associate Professor JNCASR, Bangalore.	Are HIV-1 subtype-C viruses less pathogenic?: an investigation into the neuro-pathogenic property of HIV-1	Dec 12 th 07

24.	Dr. Shrikant Bharadwaj	Indiana University School of Optometry, USA	Plasticity in the neural control of human focusing responses	Dec 14 th 07
25.	Prof. Sangram Sisodia	Director, Centre for Molecular Neurobiology, University of Chicago USA	Function and Dysfunction of Presenilins in Alzheimer's Disease	Dec 17 th 07
26.	Prof. Elisabetta Ladavas	Dipartimento di Psicologia Universita' di Bologna	Multisensory-based approach to the recovery of unisensory deficits	Dec 17 th 07
27.	Mr. Mahalingum	The Complex systems and Brain sciences Florida Atlantic University	Distinguishing neocortical pathways by dynamic latency analysis of event-related local field potentials	Dec 18 th 07
28.	Dr. Rajat N. Agrawal	Assistant Professor of Ophthalmology, and Co-director, Intraocular Implants Doheny Eye Institute, Keck School of Medicine University of Southern California Los Angeles, CA, USA	Artificial Vision: Current work and Future prospects	Dec 19 th 07
29.	Dr. Ruma Banerjee	Vincent Massey Collegiate, Professor, Department of Biological Chemistry USA	Redox Communications in Neuroprotection	Dec 28 th 07
30.	Dr. Aniruddha Das	Columbia University	Trial-linked anticipatory hemodynamic signals in V1	Dec 28 th 07
31.	Dr. Bradley Vines	University of California, Davis	Cognitive and neural processes underlying human communication: From music to stroke recovery'	Jan 8 th 08
32.	Dr. Chris Dijkerman	Dept. of Psychology, Utrecht University	Sensory processes subserving perception and action	Jan10th 08

33.	Mr. Rahul Garg	IBM TJ Watson Research Center, NY, USA	Granger Causality and other Neuroimaging Data Analysis Techniques	Jan 11 th 08
34.	Dr. Dhirendra Katti	Indian Institute of Technology(IIT) Kanpur Uttarpradesh	ECM mimicking nanofiber-based scaffolds for cartilage regeneration	Jan 29 th 08
35.	Dr. Suresh Shastry	University of Alabama, Birmingham	(I) Homocysteine induces macrophage inflammatory protein-2, apoptosis and microvessel remodeling, (II) Purification of a cell lytic enzyme	Jan 25 th 08
36.	Dr. Gwen	RNAi expert Open Biosystems USA	Expression Arrest(tm) Lentiviral shRNA - Versatile RNAi Tools advance Genome- Wide Screening and Animal Model Development	Jan 30 th 08
37.	Dr. Andrew Jennings	International Director, Open Biosystems USA	Expression Arrest(tm) Lentiviral shRNA - Versatile RNAi Tools advance Genome- Wide Screening and Animal Model Development	Jan 30 th 08
38.	Dr Pravat K. Mandal	Assistant Professor Dept of Psychiatry, Bio-engineering, and Center for Neuroscience University of Pittsburgh Medical School, Pittsburgh, PA, USA	Spectroscopic investigation of Neurodegenerative diseases (Alzheimer's, Parkinson, and Dementia with Lewy Body	Jan 31 st 08
39.	Dr Sandhitsu Das	University of Pennsylvania USA	Integrative neuroscience: from clinical to basic applications with tools from imaging to behavior	Feb 4 th 08
40.	Dr. Rathinaswamy B. Govindan	SARA Research Center, University of Arkansas for Medical Sciences USA	Objective Assessment of fetal and neonatal Auditory evoked response	Feb 6 th 08

41.	Prof. Michael J. Zigmond	Department of Neurology, University of Pittsburgh, USA	Exercise as an intervention in neurodegenerative disease: studies in models of Parkinson's disease	Feb 26 th 08
42.	Dr. Pooja Jain	Drexel University USA	Defining the Role of Dendritic Cells in HTLV-1-Associated Neuroinflammatory Disease	Feb 29 th 08
43.	Dr. Devavrata Kumar	Central Institute of Psychiatry Ranchi	Implications of cognitive impairments in schizophrenia	March 10 th 08

ACADEMIC PROGRAMMES

Ph.D. in Neuroscience

NBRC was awarded Deemed University status 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.

NBRC inducts students for its PhD. 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., or B.Tech or Psychology.

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

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

Summer Training and Short-term Programmes

NBRC conducted Summer Training Programme for the students who were in their penultimate year of their course. Students from different academic backgrounds from varied academic Institutions applied against our advertisement published in various National Dailies and in our website. The applications were screened, by a Committee constituted for this purpose, based on certain criteria and depending upon availability of vacancies in different laboratories at NBRC. The Summer training was for a period of 8 weeks (2 months). The Trainees were provided a stipend of Rs.1000/- per

month along with free 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. Students under IASC-INSA-NASI programme underwent summer training programme in NBRC.

NBRC organized a Science awareness camp for students from 8 schools selected by Haryana State Council for Science and Technology at campus in Dec., 2007. Participation certificates were issued to the students who attended the programme.

National Science Day celebration was also celebrated at Kendriya Vidyalaya, Sector-14, Gurgaon on 28th February, 2008 and three NBRC students / project assistants and one faculty of NBRC participated in the celebration.

Also Science Popularisation lectures were delivered at Faridabad, Hisar and Gurgaon located in Haryana.

GENERAL ADMINISTRATION

General Administration

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

- General Administration, headed by the Chief Administrative Officer, is responsible for Establishment, Personnel & Administration Wing, Stores & Purchase Wing, Import & Project Cell, Finance & Accounts Wing, Estate Management & Engineering Maintenance Wing – Civil, Electrical & Mechanical.

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

- Making due diligence and compliance to the Right to Information Act, 2005 including compilation and hosting of the required disclosure data on the website.
- Leave Management System (LMS) enabling employees to access on- line information related to their leave and other related details was implemented.

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, and general applications etc. The Welcome Board displays a Hindi word/line everyday. The official language committee with worthy members is actively looking into the use of Hindi and is being reviewed every quarter. Thus, the organization has manifold use of Hindi by way of nameplates, letterheads, and visiting cards, signboards etc. A proposal for creation of posts for Hindi Officer/Assistant and other positions is under consideration of the Department of Biotechnology.

‘Hindi Diwas’ was celebrated at NBRC on 14th Sept. 2007. Activities and competitions such as workshop, essay writing, poetry and debating were held on the occasion. Officers, staff and students of NBRC participated in the celebration.

RTI Act

The provisions of RTI Act are being followed in NBRC in letter and in spirit. During 2007-08, five RTI applications were received seeking information on various matters concerning NBRC. All five 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 “complaints committee” for redressal of 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, they 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 “Complaints Committee” constituted for this purpose.

Major initiatives in hand include:

- Introduction of doorstep banking services on the premises.
- Registration under section 12 A of the Income Tax Act enabling the NBRC to claim income tax exemption. A claim for refund of Rs. 36 lacs (approx.) of Income Tax already paid before grant of income tax exemption is under process with Income Tax Department.
- Continuous improvement in the Accounting systems and reporting standards.
- Adoption of user-friendly tools and techniques to reach the information through MIS for concerned users.

Hindi Day Celebration at NBRC

To promote the use of Hindi in the official work NBRC celebrated “Hindi Day” on 14th Sept. 2007.

Many activities and competitions such as workshop, essay writing, and debate competitions were held on this occasion. Many officers and staff participated in the ‘Hindi Workshop’ which was coordinated by Shri Satish Chopra and Shri Mahender Singh for Hindi Teaching and Learning Scheme on Computer. A printed Layout of Hindi Keyboard was distributed in the Hindi Workshop for convenience of the NBRC staffs.

Shri Ramesh Neel Kamal a famous poet was invited as the Chief Guest on this Occasion. Hindi Day Programme was organized by D. D. Lal, Nominated Hindi Officer who explained the implementation and development works of Hindi at the Centre. The Chief Guest and Senior Scientist Dr. Pankaj Seth appreciated the efforts regarding various activities at the Centre.

On this occasion short lectures (in Hindi) were given by Registrar (Shri K.V. S. Kameshwar Rao), Chief Administrative Officer, Administrative Officer, & Other Senior Scientists to promote the use of Hindi. The lectures delivered were very useful for the administrative staff.

Essay Writing Competition, Poem, Vad-Vivad (Hindi Debate) were also organized at the Centre. The subject of essay writing competition was “Human Brain Versus Computer and the subject of Lecture was Importance of Science in our Life”. First, second and third prizes were given by Shri Ramesh Neel Kamal Chief Guest and Dr. Pankaj Seth, Senior Scientist of the Centre.

The first, second and third prizes of Essay competition were given to the following:

Ms. Kiran (Student)	First
Ms. Pooja Gosain (Staff)	First
Shri Arvind Pundir (Staff)	Second
Shri Brijpal Singh (Staff)	Third

The first, second and third prizes of Lecture competition were given to the following:

Shri Mithlesh Kr. Singh (Staff)	First
Shri Alok Gupta (Student)	Second
Shri Brijpal Singh (Staff)	Third

The Hindi Day celebration was made full success by students, staff and participants.



INSTITUTIONAL GOVERNANCE STRUCTURE
&
PEOPLE AT NBRC

NBRC Society

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1.	Prof. V. Ravindranath	1.	Ms. Rashmi Mishra
2.	Dr. Shobini L. Rao (till 30 th June'07)	2.	Mr. Anand Goswami
3.	Dr. Neeraj Jain	3.	Ms. Latika
4.	Dr. Rema Velayudhan	4.	Mr. Sandeep Kumar
5.	Dr. P.K. Roy	5.	Ms. Priyanka Dikshit
6.	Dr. Narender K. Dhingra	6.	Mr. Manoj Kumar
7.	Dr. Pankaj Seth	7.	Ms. Smitha Karunakaran
8.	Dr. Shiv Kumar Sharma	8.	Mr. Ziauddin
9.	Dr. Shyamala Mani	9.	Mr. Shashank Tandon
10.	Dr. Aditya Murthy	10.	Ms. Uzma Saeed
11.	Dr. Nihar Ranjan Jana	11.	Mr. Amit Kumar Mishra
12.	Dr. Anirban Basu	12.	Ms. Varsha Agarwal
13.	Dr. Ellora Sen	13.	Ms. Manisha Chugh
14.	Dr. Nandini C. Singh	14.	Mr. Shailesh K.Gupta
15.	Dr. P. K. Swain (till 24 th July'07)	15.	Ms. Chinmoyee Maharana
16.	Dr. Soumya Iyengar	16.	Mr. Alok Gupta
17.	Dr. Ranjit Kumar Giri	17.	Mr. Leslee Lazar
Post Doctoral Fellows		18.	Ms. Nazia Khurshid
1.	Dr. K.Vani	19.	Ms. Shalaka Mulherkar
2.	Dr. Madhumita Ghosh	20.	Mr. Kh.Budhchandra Singh
3.	Dr. Uttam Kumar	21.	Dr. Raka Maitra
4.	Dr. Ugir Hossain	22.	Ms. Mamata Mishra
5.	Dr. Sayali Ranade	23.	Mr. Arjun
Research Associates		24.	Mr. Manoj Kumar Mishra
1.	Mr. Supriya Ray	25.	Mr. Niranjana A.Kambi
2.	Dr. Kamlesh Kumari Gulia	26.	Mr. Anshul Shrivastava
R & D Engineer		27.	Mr. Patel Dharmeshkumar
1.	Mr. V.P.Subramanyam Rallabandi	28.	Ms. Sulagna Das

29.	Ms. Rupali Srivastava	Integrated Ph.D. Students	
30.	Ms. Neha Sehgal	1.	Ms. Saumya Nagar
31.	Mohammad Hisham P.M	2.	Ms. Swetha Kameswari
32.	Ms. D.Lalitha	3.	Ms. Deepti Chugh
33.	Mr. Vivek Sharma	4.	Ms. Varsha Jain
34.	Ms. Richa Tewari	5.	Mr. Ajit Ray
35.	Ms. Tanushree Das	6.	Ms. Shaily Malik
36.	Ms. Radhika Rajan	7.	Mr. Sadashib Ghosh
37.	Mr. Nitin Koul	8.	Ms. Megha Maheswari
38.	Ms. Shilpa Mishra	9.	Ms. Pooja Vishwanathan
39.	Mr. Subhadip Paul	10.	Mr. Deepak Poria
40.	Mr. Parthiv Haldipur	11.	Ms. Manvi Goel
41.	Mr. Jai Prakash Sharma	12.	Mr. Pavan Kumar
42.	Ms. Rachna Duseja	13.	Mr. Atul Gopal P.A
43.	Mr. Kaushik Pramod Sharma	14.	Ms. Megha Sharda
44.	Ms. Neha Bhutani	15.	Ms. Suhela Kapoor
45.	Ms. K.M.Sharika	Project Assistants	
46.	Dr. Sudheendra Rao N.R	1.	Mr. Kailash Tiwari
47.	Mr. Rahul Chaudhary	2.	Mr. K.Vidya Sankar
48.	Ms. Shilpa Harshan	3.	Ms. Suhela Kapoor
49.	Ms. Monika Gothwal	4.	Mr. Chetan Nagaraja
50.	Mr. Pranav Oberoi	5.	Mr. S.Vetrivel
51.	Mr. Madhusudhana Rao	6.	Ms. Anushree Tripathi
52.	Mr. Pankaj S.Ghate	7.	Ms. P.M.Rubeena
53.	Mr. Deepak Kumar Koushik	8.	Mrs. T. Padma Subhadra
54.	Mr. Kashif Mahfooz	9.	Mrs. Kumari Anjusha
55.	Mr. Deobrat Dixit	10.	Mr. Naveen Jayaprakash
56.	Ms. Kiran	11.	Mr. Christy Joseph
57.	Ms. Subhashree Mahapatra	12.	Mr. Souvik Kar

13.	Mr. Arindam Das	37.	Mr. Debapriya Ghosh
14.	Mr. Joydeep Ghosh	38.	Mr. Vinay Kumar Shukla
15.	Ms. Sonia Baloni	39.	Mr. Prakash Kumar Mishra
16.	Ms. Hema Nawani	40.	Ms. Upasna Bharti
17.	Mr. M. Vivek	41.	Mr. Abhishek Ghosh
18.	Ms. H. Seethalakshmi	42.	Ms. Hena Khaliq
19.	Ms. Suhela Kapoor	43.	Mr. Senthil Krishnaswamy
20.	Mr. Yathi Raj	44.	Ms. Dipanwita Ghose
21.	Mr. Anoop Raj. K.	45.	Ms. Sarah Dalpa
22.	Mr. K. Praveen	46.	Md. Sarfaraz Nawaz
23.	Dr. Shilpa Shree Balakrishnan	47.	Mr. N.Prakash
24.	Ms. Anuradha Sharma	48.	Ms. Praseeda Venugopalan
25.	Ms. Applonia Josephine Rose		
26.	Ms. Priyanka Agarwal		
27.	Mr. Nilabh Anand		
28.	Mr. Vijander Singh		
29.	Mr. Ausaf A.Farooqui		
30.	Mr. Chandra Mouli		
31.	Ms. Soumya K.		
32.	Mr. Devesh Kumar		
33.	Mr. Santhosh Sethuramanujam		
34.	Mr. Durga Praveen		
35.	Mr. S.Ramakrishnan		
36.	Mr. Orthis Saha		

Other Staff

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1.	Dr. A.R. Subramanian (till 28 th Jan'08)	13.	Mr. Deepak Jain (till 29 th June'07)
2.	Sh. K.V.S. Kameswara Rao	14.	Ms. Bandita Bagchi (till 18 th Jan'08)
3.	Mr. Santosh Kumar (till 14 th Sept'07)	15.	Mr. Arvind Singh Pundir
4.	Ms. Neena Kapoor	16.	Mr. Kanhaiya Lal Kumawat
5.	Mr. Surya Narayan Mishra	17.	Mr. Ankit Sharma
6.	Mr. P.K. Srivastava	18.	Mr. D. Narender
7.	Mr. Immanuel Alexander (till 20 th Apr'07)	19.	Mr. Mithlesh Kumar Singh
8.	Mr. Debashish Bhattacharjee	20.	Mr. Sanjay Kumar
9.	Ms. Beena (till 11 th Mar'08)	21.	Mr. Dil Bahadur Karki
10.	Ms. Pooja Gosain	22.	Mr. Durgalal Meena
11.	Mr. Anuj Kumar Gupta	23.	Mr. P. Manish
12.	Mr. Anoop Singh	24.	Mr. Rammehar
13.	Mr. Bhupender Pal Sharma	25.	Md. Irshad Alam
14.	Mr. Surender Kumar	26.	Mr. Mahendra Singh
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5.	Mr. Jothibas V.	4.	Mr. Bhupender Singh
6.	Mr. R. Khader Valli	DIC STAFF	
7.	Mr. Hariharakrishnan S.	1.	Mr. Ashish Kumar Upadhyay
8.	Mr. Jitender Ahlawat	2.	Ms. Manjubala Bansal (till 21 st June'07)
9.	Mr. Mahender Kumar Singh	3.	Ms. Reema Saxena
10.	Ms. Pooja Sethi	4.	Mr. Sanjeev Bhardwaj
11.	Mr. Kedar Singh Bajetha	5.	Mr. Venkata Srinivas B. (till 28 th May'07)

6.	Mr. Punit Kumar		
7.	Mr. Gyanendra Vicky (till 5 th Sept'07)		
8.	Mr. Sanjay Kumar Gupta		