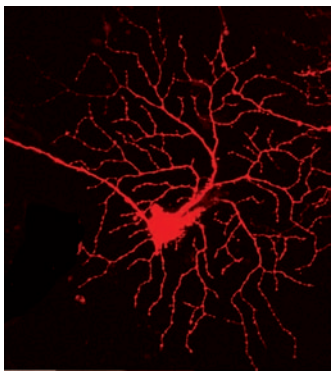
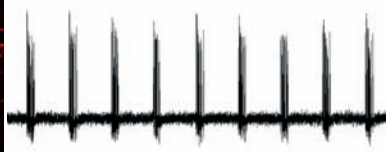
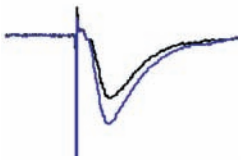
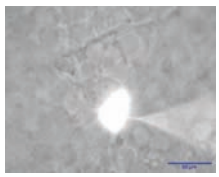


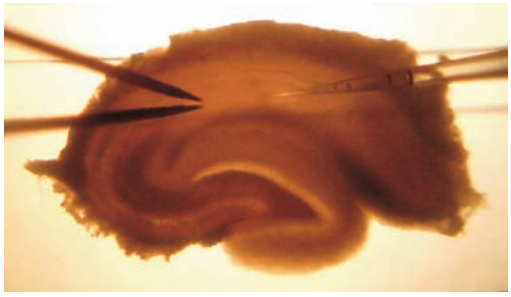


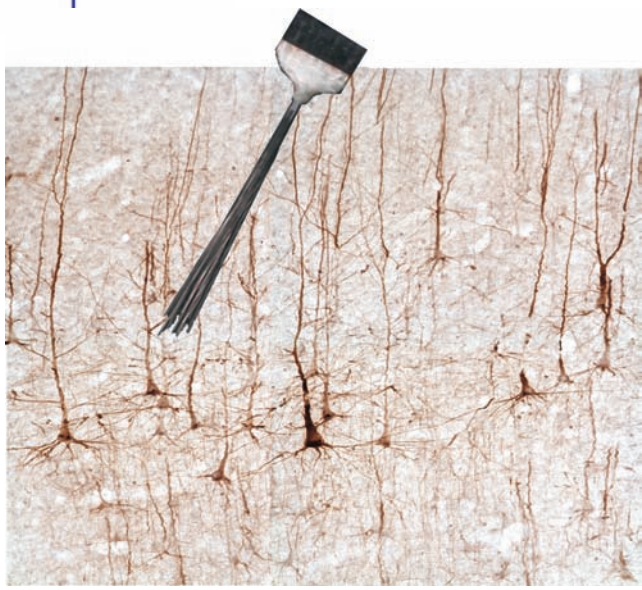
National Brain Research Centre

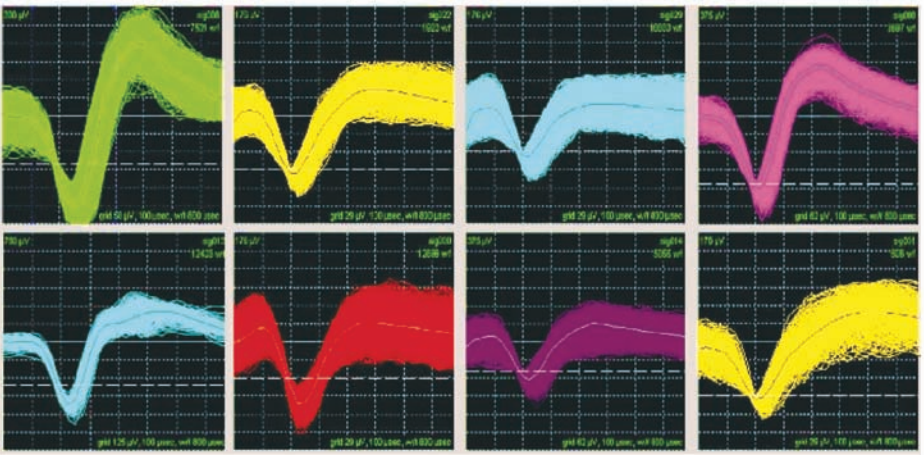
NBRC











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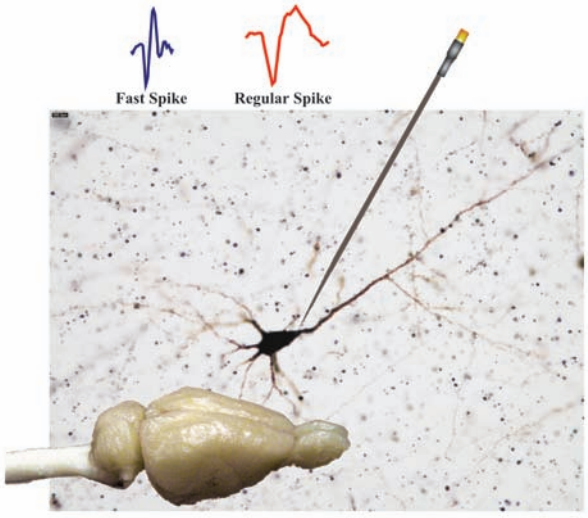
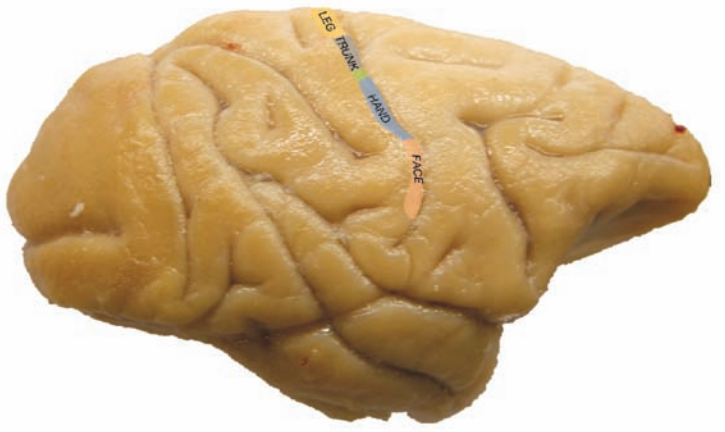




NATIONAL BRAIN RESEARCH CENTRE

Manesar, Haryana, INDIA

About the cover

Neurophysiology at NBRC: Scientists at NBRC use many different in vivo and in vitro neurophysiological techniques to unravel the brain function. Neeraj Jain uses extracellular multiunit recordings to map the brain organization. He also uses arrays of electrodes implanted at multiple sites in the brain to simultaneously record from a large number of neurons in the brains of behaving animals to understand the neural code and computational principles of information processing. Yoganarasimha uses in vivo multi-tetrode electrophysiological techniques to understand how the brain processes and encodes information about our location in the environment. Rema Velayudhan performs single neuron recordings to determine mechanisms of brain plasticity. Shiv Kumar Sharma records from hippocampal slices to understand the brain mechanisms of learning and memory. Narender Dhingra uses patch clamp techniques to understand information processing in the retina. For details of these & other exciting projects please see inside or visit the NBRC web site, www.nbrc.ac.in.

Annual Report
2009-10

National Brain Research Centre
Manesar, Haryana, INDIA

CONTENTS

MANDATE & OBJECTIVES

MANDATE

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

OBJECTIVES

- To undertake, aid, promote, guide and coordinate research of high caliber in basic and clinical neuroscience related to diseases and disorders of the nervous system.
- To develop NBRC as the national apex centre for neuroscience research and promote neuroscience research at different centres in the country and to provide consulting services to other institutions, agencies and industries.
- To promote, encourage and augment effective linkages, alliances and affiliations between the Centre and National and International Scientific and Research Institutions, bodies, agencies/laboratories and other organizations working in the field of brain and neurosciences research.
- To establish one or more satellite centers to serve different regions of the country for efficient achievement of the objectives of the Center.
- To collect, assimilate, publish and disseminate data and information on aspects relevant to neuroscience to the scientific community.
- To establish, operate and maintain state-of-the-art facilities and database for carrying research and development activities and make such facilities and database available to scientists and researchers from all over the country and abroad;
- To provide for instructions and training in such other branches of learning as the Centre may deem fit.
- To provide facilities for the advancement research and development for advancement of learning and for dissemination of knowledge.
- To undertake extramural studies, extension programmes and field outreach activities to contribute to the development of society.
- To promote, develop, collaborate or otherwise assist in providing services of research, training, consulting or guidance related to neurosciences activities comprising biological, psychological, sociological and clinical aspects; and
- To do all such other acts and things as may be necessary or desirable to further the objectives of the Centre.

From the Director's Desk

It is the brain and its emergent process, the mind, which is the basis of all that is truly human and the wellspring of all our deepest abilities and desires, ranging from consciousness and cognition to communication and creativity. Often described as the final frontier for scientific enquiry, the study of the brain is probably the only subject that needs the full gamut of human knowledge for its comprehension, spanning across biology, medicine, computing and the humanities. Not only does the brain challenge the intrepid molecular biologists into deciphering the labyrinthine pathways that exist only in the brain, but also defies the abilities of an ingenious electronics engineer who attempts to develop an intelligent supercomputer that would recognize a human face which an infant can effortlessly do.

In the current year, NBRC, true to its founding vision, has scaled further heights in its quest for excellence across its four main areas of activity: Molecular and cellular neuroscience, Systems and cognitive neuroscience, Computational neuroscience and neuroimaging, and Translational and clinical neuroscience. Across the years, the centre has evolved a unique endeavour towards unity in diversity in both research and teaching, namely striving to show the broad unifying theme of integrative neuroscience, that ties the different components of the discipline together, from the ion-channel to neuron to behavior to language. Needless to say, we have given emphasis to both aspects of NBRC's mandate, academic research as well as educational training in neuroscience, both of which will play its part to enable the ushering of a talented and trained pool of young researchers in neuroscience in the country. Harnessing the unique opportunity afforded by the institute, these researchers have been nurtured in the fertile soil of interdisciplinary training across the breadth of the different areas relevant to neuroscience, ranging from fundamental genetics to behavioral psychobiology.

In the Indian scenario, two pertinent fields demand immediate attention, namely basic and applied research pertaining to neuroinfection and neurodegeneration. Amongst infections afflicting the brain, Japanese encephalitis is a critical problem in several parts of India, especially the northern and north eastern, accounting for several thousand deaths and many more individuals with

residual deficits, during the monsoon season every year, mostly amongst children. NBRC is initiating a clinical trial on Japanese encephalitis using a polycyclic antibiotic, on which the faculty is having an active research program for several years, besides securing the patent therein. On the other hand, degenerative conditions of the brain, such as Alzheimer's disease and other dementia-like conditions, are a precipitously looming health problem in India, that would be affecting about 8 million Indians in the year 2040 according to WHO estimates. Our faculty has pursued incisive investigations into indigenous plant extracts that can markedly diminish the cerebral amyloid plaques, the hallmark of Alzheimer's disease, whenceforth the intellectual property rights have been obtained by NBRC, along with the collaborating institutions involved.

A new area of synthesis of neuroscience and computer engineering has been ushered in worldwide under the name of neuroinformatics and brain machine computation. It is here that neurobiologists and technologists challenge each other to develop the next generation of brain-inspired devices and neuromorphic systems. Our faculty have also developed a brain computer interface device that can decode electrical signals from the brain and accordingly instruct a robotic arm to move as intended by the brain. It is a fascinating sight to discern how a mere wish or intention can be made to actuate a complex moving machine. Neurorobotics is actually a decisive area in the emerging interdisciplinary fields of neuroengineering and neuroprosthetics, and has seminal implications for rehabilitation measures in brain or spinal cord damaged individuals and disabled subjects.

To be at the forefront of facilities required for advanced research in neuroscience, the Institute is establishing more advanced microscopy setups, including additional functionalities in the neuroimaging systems and hippocampal neuronavigation facility. To assure full utilization of these infrastructures, NBRC has seamless collaboration with other National Institutes/Universities and leading clinical centers of the region, thereby promoting active cooperative research, training and sharing of resources. A workshop on Perception Engineering under the auspices of the Ministry of Communications & Information Technology was held in the centre in November 2009 to brainstorm on developing an approach program for harnessing neurophysiological and neurocomputational methodologies to spawn the newer generation of perceptual systems. The institute's scientists were joined by premier research groups in the country, as that from IITs, IIIT and some universities and centres, and NBRC has been partnered as the resource centre from the neuroscience sector, in this national-level initiative.

This year has seen NBRC mature into a complete campus. The honourable Minister of Science and Technology Mr Prithviraj Chavan inaugurated the residential complex at NBRC in December. As necessary, the campus now provides accommodation to staff, officers and some faculty members. Additionally, we have two other buildings

to provide accommodation to students, project assistants and research associates. These measures do increase the bonding of the employees with the institute, considering the relative isolation of the campus. In keeping with the current practice of regular performance monitoring, committees from the Planning Commission and University Grants Commission visited the institution for assessment, and NBRC was also evaluated by the Ministry of Human Resource Development, Government of India. The NBRC Translational & Clinical unit at the Gurgaon Government Hospital has now blossomed across the full gamut of clinical neuroscience: neurology, neuropsychiatry, neuro-surgery and neuropsychology. Additional consultant faculty have joined the unit.

Fulfilling its national and international obligations, our institution has been an active collaborator to the Biennial Congress of the Federation of Asian and Oceanian Neuroscience Societies, which is to be held for the first time in India, and NBRC is organizing the accompanying event, a School of Neuroimaging, with sponsorship from International Brain Research Organization. Besides, NBRC has catalyzed Indian participation in International Neuroinformatics Coordinating Facility and the International Human Frontier Science Organization, and related meetings in India are soon in the offing. To showcase Indian neuroscience research to prospective applicants to Indian institutions, NBRC co-organized the India Neuroscience Satellite Symposium, at the Society for Neuroscience annual meeting, in Chicago last November. NBRC had an active group participation through its various faculty members and students, who had a productive interaction with leading international peers in the field. A series of meeting at twelve different cities across the country was organized by NBRC, during the Brain-Awareness Week on the month of March.

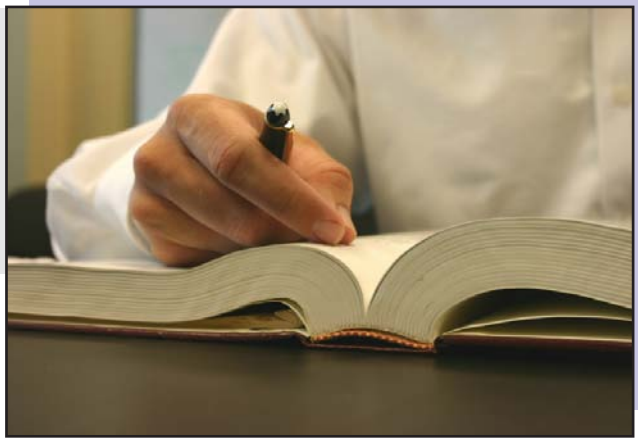
As a member of the University system in India, the institute is on a continuous monitoring and feedback mode for enhancement of the integrated MSc-PhD program as well as the regular PhD program. Indeed, several new curricular topics have been introduced or consolidated, such as Neuroimaging, Computer programming (Matlab) and Animal Handling. Furthermore, we have undertaken further broadening of the scope of student rotationships to include more laboratories, so that the students can sample more fields of neuroscience, before embarking on their thesis area. To entice the best students towards brain research, the NBRC faculty has participated in the student selection process of the summer fellowship scheme of the three science academics, whose program has been further actively consolidated. This investment of the faculty are paying off, indeed some of these talented scholars are joining NBRC for their doctoral programs.

As the centre now completes a decade of its existence, it is now time to reminisce our growth. From its initial establishment in 2000 at the ICGEB campus in New Delhi, to its interim premises at Gurgaon, and then through the inauguration of its idyllic Manesar campus by the President of India, the institute has

grown from two students to almost a hundred, from one lab to fourteen, from six network centres to forty eight, and from a couple of employees to now about a hundred and fifty. The number of publications, projects and presentations undertaken by the researchers has grown accordingly. The institute has graduated out five batches of doctorates, a couple of batches of Masters, and a steady stream of other alumni, such as post-doctoral fellows and research associates. As teachers, we find it indeed a rewarding experience to know that the institute is spawning second-generation students, a few of our alumni have matured as faculty members elsewhere, and their own students are in the process of graduating. As the centre grows into the adolescence of its second decade, we are increasingly confident that NBRC would be able to tactically reinforce its niche well in basic and applied neuroscience, and consolidate its contribution towards the building a critical mass of neuroscientists so necessary in the country.

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

RESEARCH REPORTS

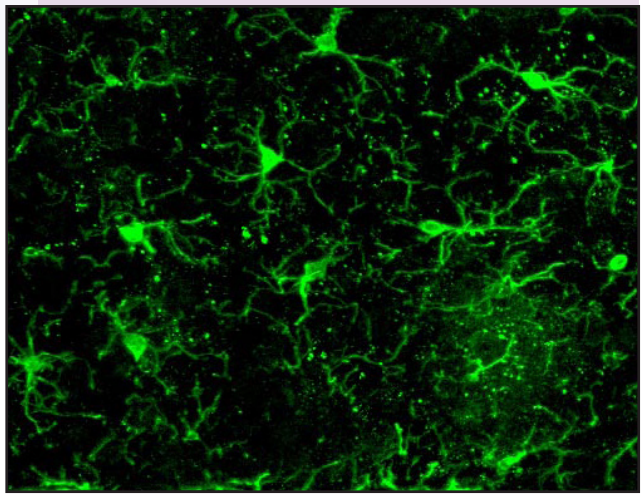


Molecular and Cellular Neuroscience

Systems and Cognitive Neuroscience

Computational Neuroscience and Neuroimaging

Molecular & Cellular Neuroscience



- Dr. Nihar Ranjan Jana
- Dr. Shyamala Mani
- Prof. V. Ravindranath
- Dr. Pankaj Seth
- Dr. Ellora Sen
- Dr. Shiv Kumar Sharma
- Dr. Anirban Basu
- Dr. Ranjit Kumar Giri

Understanding The Function Of The Autism And Autism Spectrum Disorders Associated Ubiquitin Ligase, Ube3a/E6-AP

Principal Investigator

Dr. Nihar Ranjan Jana

Research Fellows

Shalaka Mulherkar, Swetha K. Godavarthi, Megha Maheswari

Project Assistants

Parthanarayan De, Anannya Samanta

Technical Assistants

Ankit Sharma, Mahendra Singh

The gene product of Ube3a called E6 associated protein (E6-AP) belongs to the HECT (Homologous to E6-AP C-terminus) domain family of E3 ubiquitin ligases. E6-AP, the best characterized protein in this family, tags ubiquitin molecules to proteins that are destined to be degraded through the proteasome. Loss of function mutations or deletions of maternal Ube3a is known to cause Angelman syndrome (AS). Recently copy number variation of this gene is also reported in autism. Characteristics of the syndrome include motor dysfunction, seizures and mental retardation. In the brain, the maternal allele of Ube3a is predominantly expressed as a result of tissue specific imprinting. Mature neurons exhibit maternal allele-specific expression although traces of paternal allele-specific expression are also detected. Biallelic expression is restricted to GFAP positive cells lining the ventricles and absent from GFAP positive astrocytes in other regions of the brain. In the brain, Ube3a predominantly expresses in the cerebellar Purkinje cells, neurons in the hippocampus and the cortex. At the cellular level, E6-AP is localized in the nucleus as well as in the cytoplasm. Expression of E6-AP was also found in both presynaptic and postsynaptic compartments in cultured of hippocampal neurons Ube3a maternal deficient mice ($Ube3a^{m-/p+}$) exhibit learning and memory deficits as well as motor abnormalities. The motor abnormalities in these $Ube3a^{m-/p+}$ mice are so far been shown due to dysfunction of the cerebellum. Paternal deficient Ube3a mice ($Ube3a^{m+/p-}$) fail to show these typical characteristics.

Since E6-AP is an ubiquitin ligase, it is hypothesized that the AS or autistic 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 novel substrates of E6-AP, (2) study the altered gene expression profile and signaling cascades in the E6-AP deficient mice, (3) study the molecular mechanism of cognitive impairment using mice model.

Recently we have published a series of papers that suggest E6-AP might function as a cellular quality control ligase. It enhances the clearance of expanded polyglutamine proteins and also mutant α-synuclein. Now we are studying the role of E6-AP in the progression of Huntington's disease using transgenic mice. This year we have found that maternal loss of Ube3a (Ube3a$^{m-/p+}$) in the mouse model leads to motor deficits that could be attributed to the dysfunction of the nigrostriatal pathway. The number of tyrosine hydroxylase positive neurons in the substantia nigra was significantly reduced in Ube3a$^{m-/p+}$ mice as compared to the wild type counterparts. The Ube3a$^{m-/p+}$ mice performed poorly in behavioral paradigms sensitive to nigrostriatal dysfunction. Even though the tyrosine hydroxylase staining was apparently same in the striatum of both genotypes, the presynaptic and postsynaptic proteins were highly reduced in Ube3a$^{m-/p+}$ mice. These findings suggest that the abnormality in the nigrostriatal pathway along with the cerebellum produces the observed motor dysfunctions in Ube3a$^{m-/p+}$ mice.

This year we have also found that E6-AP interacts with and promotes proteasome-mediated degradation of cyclin-dependent kinase inhibitor p27. E6-AP also directly ubiquitinates p27 in an in vitro ubiquitination assay. Partial knockdown of E6-AP increases the level of p27 leading to cell cycle arrest. Interestingly, partial knockdown

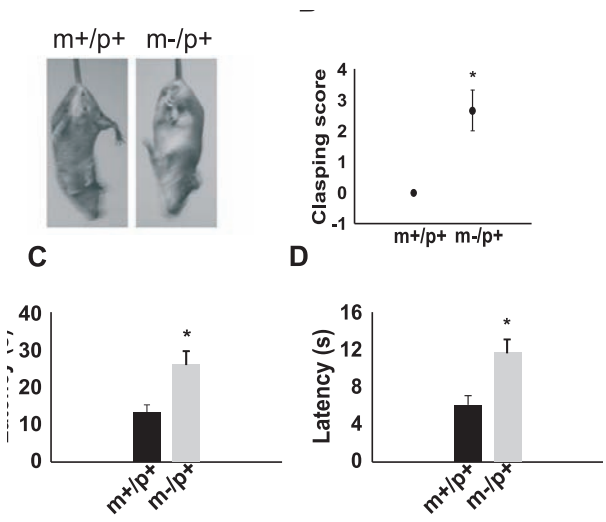


Figure. Motor deficits in Ube3a$^{m-/p+}$ mice due to nigrostriatal dysfunction.
A,B) Ube3a$^{m-/p+}$ mice showed hind limb clasping while Ube3a$^{m+/p+}$ mice held their hind limbs outwards when suspended by the tail. C) Pole test. Mice were placed on a 50 cm vertical pole and the time taken to descend was recorded. Ube3a$^{m-/p+}$ mice took significantly longer to descend from the pole than the wild type mice. D) For adhesive removal test, small adhesive tape was put on the snout of the animals and the time to remove the tape was recorded. The Ube3a$^{m-/p+}$ mice took longer to remove the adhesive than the Ube3a$^{m+/p+}$ mice. Data represented as mean ± SEM; (n=6). *p<0.05 in comparison with the wild type mice.

also increases the transcription of p27. Finally, we have demonstrated the increased levels of p27 in E6-AP-maternal deficient and null mice brain. Our result suggests that E6-AP not only enhances the degradation but also regulates the expression of p27 and its loss of function in Angelman syndrome might cause cell cycle alteration leading to disease pathogenesis.

Publications:

1. S. Mulherkar and **N. R. Jana** (2010). Loss of dopaminergic neurons and resulting behavioural deficit in mouse model of Angelman syndrome. **Neurobiology of Diseases**. (In Press)
2. **N. R. Jana** (2010). Role of ubiquitin-proteasome system and autophagy in polyglutamine neurodegenerative diseases. **Future Neurology**, 5, 105-112.
3. R. Maity, J Sharma and **N. R. Jana** (2010). Capsaicin induces apoptosis through ubiquitin-proteasome system dysfunction. **Journal of Cellular Biochemistry,** 109, 933-942.
4. S. Mulherkar, J. Sharma and **N. R. Jana** (2009). The ubiquitin ligase E6-AP promotes degradation of α-synuclein. **Journal of Neurochemistry,** 110, 1955-1964.
5. Mishra, S. K. Godavarthi and **N. R. Jana** (2009). UBE3A/E6-AP regulates cell proliferation by promoting proteasomal degradation of p27. **Neurobiology of Diseases,** 36, 26-34.

Presentations:

1. S. Godavarthi and N. R. Jana: Angelman Syndrome Candidate Protein-E6AP, is a Coactivator of Glucocorticoid Hormone Receptor, IAN, Jaipur, 2009.

2. N. R. Jana: Toxic protein aggregation in neurodegenerative diseases. National Institute of Advanced Research, Ahmedabad, 2010.

3. N. R. Jana: Understanding the functional role of E6-AP – an ubiquitin protein ligase and steroid receptor coactivator implicated in Angelman mental retardation syndrome. AOSCE, JNU, New Delhi, 2010.

4. N. R. Jana: Toxic protein aggregation in polyglutamine neurodegenerative diseases. DRDO, New Delhi, 2009.

5. N. R. Jana: Suppression of polyglutamine neurodegeneration by ubiquitin protein ligases. IGIB, New Delhi, 2009.

Funding:

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

2) Study the defect in neurogenesis and initial synapse formation in mouse model of Angelman mental retardation syndrome (CSIR).

3) Role of E6-AP in the progression of Huntington's disease (DBT Career Development Award)

Collaborator:

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

Understanding the Physiological Function of Malin, A Ubiquitin Ligase Mutated in Lafora's Progressive Myoclonus Epilepsy

Principal Investigator

Dr. Nihar Ranjan Jana

Research Fellows

Jaiprakash Sharma, Dr. Sudheendra Rao

Project Assistants

Diptendu Mukherjee

Technical Assistants

Ankit Sharma, Mahendra Singh

Lafora disease (LD) is a neuro degenerative epilepsy, characterized by progressively worsening seizure, myoclonus, dementia and ataxia without any gender preference. The onset of the disease typically between 12-17 years of age and patient usually dies within 10 years of first seizure. One of the characteristic features of LD is the cytoplasmic accumulation of Lafora inclusion bodies containing polyglucosan in various organs including brain, liver and axillary skin. It is an autosomal recessive disease caused by mutations in either at least two genes EPM2A and EPM2B. EPM2A gene encodes laforin, a dual specificity phosphatase with a carbohydrate binding domain and EPM2B gene encodes malin, an E3 ubiquitin ligase of the ubiquitin proteasome system. Patients with mutations in malin or laforin are phenotypically indistinguishable and Lafora bodies are found across all LD patients. Current understanding suggests that both laforin and malin regulate the glycogen metabolism and therefore their loss of function might lead to the accumulation of Lafora bodies through deranged glycogen metabolism. But how mutation in these two proteins induces neurodegeneration and whether Lafora bodies play any role in this process is not known.

Since malin is an E3 ubiquitin ligase and its mutation causes LD, it is hypothesized that the improper degradation and accumulation of substrates of malin might lead to disease pathogenesis. Therefore, identification of substrates of malin could open a new avenue in understanding the pathogenic mechanism of LD.

In the proposed project, we plan to identify and characterize the new substrates of malin. Additionally, we will also study the involvement of

molecular chaperones and ubiquitin-proteasome system in the pathogenesis of LD.

This year we have found that malin is spontaneously misfolded and tends to be aggregated, degraded by proteasome and forms not only aggresomes but also other cytoplasmic and nuclear aggregates in all transfected cells upon proteasomal inhibition. Malin also interacts with Hsp70. Several disease causing mutants of malin are comparatively more unstable than wild type and form aggregates in most transfected cells even without the inhibition of proteasome function. These cytoplasmic and nuclear aggregates are immunoreactive to ubiquitin and 20S proteasome. Interestingly, progressive proteasomal dysfunction and cell death is also most frequently observed in the mutant malin over-expressed cells compared to wild type counterpart. Finally, we demonstrate that the co-chaperone CHIP stabilizes malin by modulating the activity of Hsp70. All together, our result suggests that malin is unstable and aggregate prone protein and co-chaperone CHIP can modulate its stability.

This year we have also observed that the Lafora bodies in axillary skin and brain stain positively for the ubiquitin, the 20S proteasome and the molecular chaperones Hsp70/Hsc70. Interestingly, mutant malins that are misfolded also frequently colocalizes with Lafora bodies in skin biopsy sample

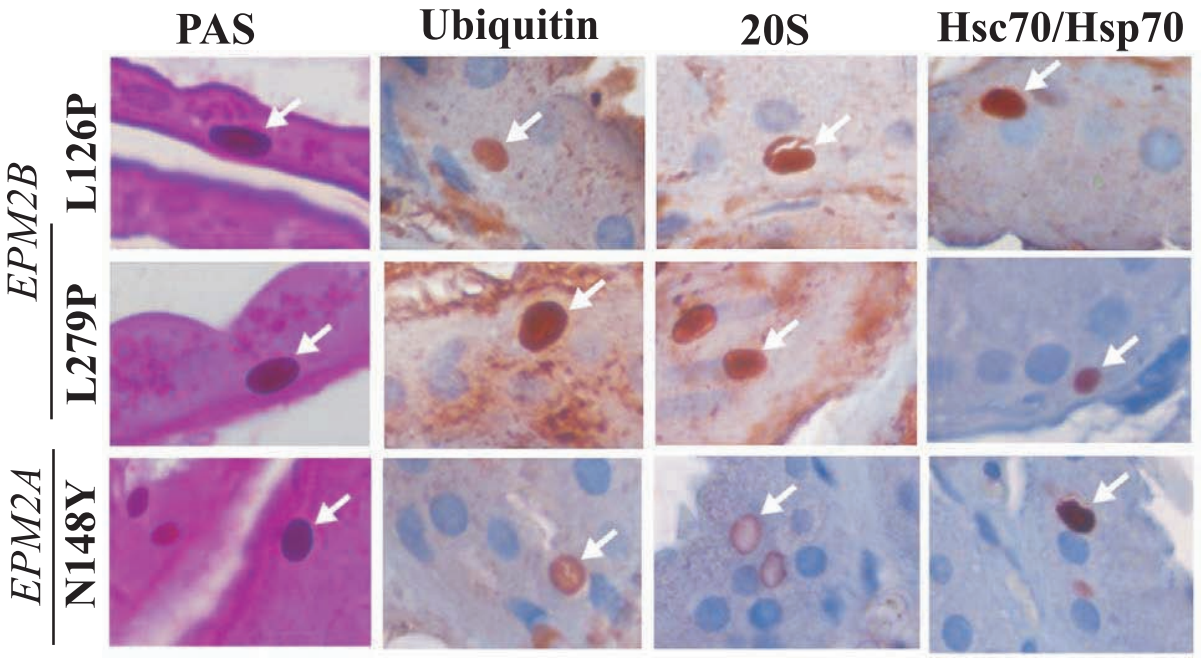


Figure Localization of ubiquitin, 20S proteasome and Hsc70/Hsp70 chaperones into Lafora bodies. Axillary skin biopsy samples from the clinically and genetically confirmed cases of LD were either processed for PAS staining or immunohistochemically stained with antibodies against ubiquitin, 20S proteasome and Hsc70/Hsp70. Arrow indicates PAS positive Lafora bodies that are also positively stained with ubiquitin, 20S proteasome and Hsc70/Hsp70 in both EPM2A (laforin) and EPM2B (malin) mutant LD patients.

of respective LD patient. The expression of disease causing mutations of malin in Cos-7 cells results in the formation of profuse cytoplasmic aggregates that colocalize with Hsp70/Hsc70 chaperones and 20S proteasome. The mutant malin expressing cells also exhibit proteasomal dysfunction and cell death. Overexpression of Hsp70 decreases the frequency of mutant malin aggregation and protects from mutant malin-induced cell death. These finding suggest that Lafora bodies are consisting of abnormal proteins including mutant malin, targeted by chaperones or proteasome for their refolding or clearance, and failure of these quality control systems could lead to LD pathogenesis. Our data also indicates that the Hsp70 chaperone could be a potential therapeutic target of LD. Currently, we are actively involved in identifying the novel substrates of malin.

Publication:

1. Rao S. N., Sharma J., Maity R. and **Jana N. R.** (2010). Co-chaperone CHIP stabilizes aggregate prone malin, an ubiquitin ligase mutated in Lafora disease. **Journal of Biological Chemistry,** 285, 1404-1413.

Presentations:

1. S. Rao, J. Sharma, R. Maity. S.K. Shankar. P. Satishchandra and N. R. Jana. Lafora disease and ubiquitin-proteasome dysfunction, PME Conference, Venice, Spain, 2010.
2. J. Sharma and N. R. Jana. Lafora disease associated ubiquitin ligase, malin interacts with and promotes proteasome-mediated degradation of neuronatin. IAN, Jaipur, 2009.
3. S. Rao, J. Sharma and N. R. Jana. CHIP stabilizes aggregate prone malin, an ubiquitin ligase mutated in Lafora disease. IAN, Jaipur, 2009.

Collaborators:

Drs. S. K. Shankar and P. Satishchandra, National Institute of Mental Health and Neurosciences, Bangalore.

Development of the cerebellum

Principal Investigator

Dr. Shyamala Mani

Research Fellows

Parthiv Haldipur, Rupali Srivastava, Pavan Kumar Rambatla

The cerebellum is a part of the hindbrain that accounts for more than half of the neurons of the brain. It helps in the integration of sensory information, coordination and motor control. Although considerable amount of work has been done on cerebellum development in several animal models, very little is known about the mechanisms involved in human cerebellum development. Previous studies in mice have implicated sonic hedgehog (Shh) signalling as a major contributor to cerebellum development. Therefore we set out to characterize this signaling pathway in human cerebellum development. We carried out the study in cerebellar autopsy samples obtained from Army Base Hospital and the All India Institute of Medical Sciences, New Delhi. Our results indicate a similar pattern of development as seen during mouse cerebellum development. During the gestational period between the 14th week to term, Shh is detected predominantly in the PL, while its downstream components are detected in the outer EGL. Sonic hedgehog continues to express itself in the PL even postnatally, until the 8-12th month. The decrease in expression coincides with the obliteration of the EGL. We also looked carefully at the cases of gestational age 10-13 weeks. The histogenic profile seen during this period is unique to humans. During the 10-13th week, there is no conspicuous purkinje layer, although the EGL is formed. Such a stage is not seen in the rodent model. We found that during the 10-13th week, Shh was produced by the EGL itself, which possibly acted in an autocrine manner. This continued till a distinct PL was formed, following which the purkinje cells took over the task of Shh release. This is an important finding in the context of medulloblastomas, where the exact reason behind the origin is unknown. Our results comparing mouse and human medulloblastomas seem to indicate that in humans following birth although the EGL does disappear over time, in some individuals, in some regions of the cerebellum EGL proliferation may continue to persist.

Persistent autocrine Shh signalling of the EGL or recapitulation of Shh dependent ontogeny, in the postnatal cerebellum could possibly be one of the reasons why medulloblastomas occur. It is hence a befitting example of ontogeny gone wrong, leading to oncogeny.

We have also studied how the normal developmental program of the cerebellum is modified by change in the environment due to preterm delivery. We addressed the changes at the level of individual cell types that cannot be detected by MRI analysis. To address the issue of how the normal developmental program is perturbed due to premature birth, several morphological parameters and molecular markers were analyzed in the cerebellum of preterm infants who had survived in an ex-utero environment and compared with controls in which the development of the cerebellum has taken place in-utero. The study reports a selective change in the differentiation of granule cells and the Bergmann glia due to the ex-utero environment that could have major consequences for later outcomes.

Embryonic stem cell differentiation into cerebellar granule neurons

Principal Investigator
Dr. Shyamala Mani

During development of nervous system, a vast array of neurons and glia form in appropriate number and at desired positions. This process depends both on the cell's intrinsic programming and the environment in which it is present. Proneural genes are one of the most important classes of genes coding for the basic helix-loop-helix containing transcription factors, which are both necessary and sufficient to initiate neural lineage and to promote generation of progenitors committed to differentiate from the ectoderm. They also integrate positional information into the neurogenesis process and contribute to the specification of progenitor-cell identity during neurogenesis. The genes have also been shown to specify neuronal subtypes. MATH-1, a bHLH gene, has been shown indispensible for the development of one of the most abundant cells of the brain, cerebellar granule cells (CGC). Cerebellum is important for various functions like movement coordination and balance, sensory discrimination, cognitive processing and others. Many cerebellar disorders are associated with progressive loss of its neurons. For treatment of such disorders, cell replacement therapy seems to be an important approach.

Embryonic stem cells are the pluripotent cells derived from the blastocyst of the developing embryo. They hold a big significance because of their two important properties, firstly they can be maintained in their undifferentiated state for technically unlimited time period, and secondly because of their potential to differentiate in almost any type of body cell. Due to these properties, they are visioned as clinically important for the cell replacement therapies. Also, they hold significance in the field of research to understand the development process during early stages, which is very difficult otherwise due to limited model systems

The project in our lab aims

- To generate a mouse stem cell line which could conditionally overexpress MATH-1 gene
- To study the effect of transient MATH-1 overexpression on the fate of cells obtained by differentiation of the cell line

Conditional MATH-1 expressing cell line was made with TET-ON system of expression, in which the gene of interest (MATH-1) is only expressed upon Doxycycline addition . To study the effect of MATH-1 overexpression during differentiation, Doxycycline induction was given transiently at one of the stages of differentiation. Various stages of differentiation were characterized by using general neuronal markers like Nestin, Tuj1, Map2, GFAP and a battery of granule cell markers like Tag1, Zic1, Zic2, Pax6, En1, Meis1 using real time PCR method and immunohistochemistry. Our results suggest that the timing of Math-1 induction is crucial in the extent and number of granule neurons that are induced. Math-1 was induced at various times during the differentiation of ES cells and we found that Math-1 was most efficient in inducing genes of the granule neuron lineage when it was induced during the period of embryoid body formation it is.

Publications:

1. Shailesh Kumar Gupta, Karina Meiri2, Kashif Mahfooz1, Upasna Bharti1 and **Shyamala Mani**. (2010) Coordination between extrinsic extracellular matrix cues and intrinsic responses to orient the centrosome in polarizing cerebellar granule neurons. **Journal of Neuroscience,** 30(7): 2755–2766.
2. Angela M. Kaindl, Sandrine Passemard Pavan Kumar, Benedicte Gerard, Alain Verloes, **Shyamala Mani** and Pierre Gressens (2010). Many roads lead to primary autosomal recessive primary microcephaly. **Progess in Neurobiology**, 90(3): 363-83.
3. Jennifer L. Moran, Emily T. Shifley, John M. Levorse, **Shyamala Mani**, Kristin Ostmann, Ariadna Perez, Dawn M. Walker, Thomas F. Vogt, and Susan E. Cole (2009). Expression and deletion analyses of Manic fringe indicates that it is not required for embryonic development, and that FRINGE proteins are not functionally redundant. Developmental Dynamics, **Developmental Dynamics,** 238(7): 1803-1812.
4. Kim-Da Destot-Wong, Kun Liang, Shailesh Kumar Gupta, Géraldine Favrais, Leslie Schwendimann, Michael Spedding, Vincent Lelièvre, **Shyamala Mani** and Pierre Gressens (2009). The AMPA receptor positive allosteric modulator, S18986, is neuroprotective against neonatal excitotoxic and inflammatory brain damage through BDNF synthesis. **Neuropharmacology**, 57: 277-286.

Presentations:

Parthiv Haldipur, Upasna Bharti, Chitra Sarkar, Corinne Alberti, Soumya Iyengar, Pierre Gressens, Shyamala Mani: Preterm delivery alters the developmental program of the cerebellum. Frontiers in Organogenesis, Kobe, Japan. 23rd – 25th March 2010

Funding:

NBRC Core funds

Department of Biotechnology, India

Principal Coordinator 2006-2009: Basic Biology of Neural Stem Cells.

A program grant under which there are 8 sub-projects that deal with various aspects of understanding basic stem cell biology and applications in retinal, spinal and stroke injury models in rodents.

Indo–French Centre for the Promotion of Advanced Research

Principal Investigator; 2009-2012: Neural differentiation of embryonic stem cells.

The major goal of this project is to study the directed differentiation of human embryonic stem cells into neurons.

Collaborator:

Prof. Pierre Gressens, INSERM U676, France

Degrees Awarded (Ph.D.):

Manoj Kumar 2009

Cytochromes P450 dependent metabolism of drugs in brain

Prof. V. Ravindranath

Research Fellows

Varsha Agarwal, Neha Sehgal

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

Cytochrome P450 (P450), a superfamily of heme proteins is involved in the metabolism of xenobiotics and endogenous compounds. While liver is the major organ involved in P450-mediated biotransformation, functional P450 enzymes are also present in the brain wherein they metabolize a variety of compounds. The P4504F subfamily comprises of 7 functional enzymes in humans, 4 in rat and 5 in mice. All of the enzymes of the P450 4F family (Cyp4f) catalyze at varying rates the hydroxylation of the inflammatory cascade prompt leukotriene B4 (LTB4) to its inactive 20-hydroxylated product. LTB4 is a product of action of 5-lipoxygenase on arachidonic acid, while another class of inflammatory prompts, the prostaglandins are formed from arachidonic acid by cyclo-oxygenases to epoxy products. The Cyp4f subfamily can also metabolize hydroxyeicosa-tetraenic acid (HETE) and hydroperoxyeicostetraenoic acid (HPETE), which are also metabolic signals for vasoconstriction/dilation

or other functions. Cyp4fs thus play a significant role in modulating the inflammatory cascade by hydroxylating and inactivating both leukotrienes and prostaglandins. While Cyp4f enzymes have previously been shown to be present in human and rat brain, what is less clear is whether the Cyp4fs play a neuroprotective role in brain during an inflammatory insult. Our working hypothesis is that brain cytochromes P-450 4Fs play an important role in the metabolism of endogenous compounds and therefore can influence the inflammatory response. The long-term objective of the proposed project is to understand the role of in situ metabolism in the brain in determining the pharmacological response to psychoactive drugs as well as endogenous compounds that regulate important cellular responses, such as inflammation.

Inflammatory processes are involved in pathogenesis and progression of CNS disorders, such as infection, traumatic brain injury, and neurodegenerative diseases. Eicosanoids including leukotrienes, particularly leukotriene B4 (LTB4) mediate inflammatory response by initiating and amplifying generation of cytokines and chemokines. Cytochrome P450 (Cyp), a family of heme proteins mediate metabolism of xenobiotics and endogenous compounds, such as eicosanoids. We demonstrate that mouse brain Cyp4fs are expressed ubiquitously in several cell types in the brain including neurons and microglia, and modulate inflammatory response triggered by LPS, in vivo and in microglial cells, in vitro through metabolism of LTB4 to the inactive 20-hydroxy LTB4. Chemical inhibitor or shRNA to Cyp4fs enhance inflammatory response, while PPARα agonist, fenofibrate induces Cyp4fs and attenuates it. Thus, catalytic activity of Cyp4fs is a novel target for modulating neuroinflammation and we identify a new application for the well-known drug, fenofibrate.

Funding:

This work is supported by NIH-RO1.

Collaborator:

Henry Strobel, University of Texas Medical School, Houston

Cell specific redox driven apoptotic signaling in Parkinson's disease

Prof. V. Ravindranath

Research Fellows

Lalitha, Uzma Saeed, Ajit Ray

Parkinson's disease (PD), a neurodegenerative disorder is characterized by loss of dopaminergic neurons in the substantia nigra pars compacta. Idiopathic Parkinson's disease (PD) as opposed to heritable forms of Parkinson's disease (PD) accounts for greater than 90% of the Parkinson's disease incidence world over. One of the compelling questions in understanding the pathogenesis of neurodegenerative disorders is the selective vulnerability of specific cell types to neurodegeneration. The redox status of proteins regulate signaling pathways that govern both cell survival and death. It is our hypothesis that protein thiol modification, occurring as a result of oxidative stress results in mitochondrial dysfunction and altered redox signaling leading to activation of cell death and suppression of survival pathways. Our overall aim is to understand differential vulnerability of selective cell populations, such as the dopaminergic neurons of substantia nigra to neurodegeneration.

Impairment of Akt phosphorylation, a critical survival molecule has been implicated in the degeneration of dopaminergic neurons in Parkinson's disease (PD). However, the mechanism underlying pAkt loss is unclear. We have demonstrated the selective loss of pAkt in the ventral midbrain in mice treated with the dopaminergic neurotoxin, MPTP and showed that the primary mechanism of pAkt loss is due to increased association of oxidatively modified Akt with the phosphatase, PP2A resulting in enhanced dephosphorylation of Akt. Mice treated with MPTP show oxidation of cysteine residue(s) in Akt both after single and chronic exposure that is reversed by pretreatment with thiol antioxidants. Maintaining the protein thiol homeostasis prevents the loss of reduced Akt and eventually predserves pAkt levels. Further, overexpression of glutaredoxin in human primary neurons helps maintain the redox status of Akt and abolishes pAkt loss caused by MPP+ exposure. We demonstrate that oxidative stress, a critical mediator of dopaminergic cell death in PD downregulates Akt cell survival pathway through

redox modification of Akt, while PTEN, the redox sensitive upstream phosphatase that antagonizes Akt survival pathway is not modified. Maintenance of redox homeostasis by thiol antioxidants and enhanced expression of Grx1 could slow down the progress of Parkinson's disease by preventing the dysregulation of the pAkt cell survival pathway.

Evaluation of the molecular basis of the pharmacological action of traditional medicinal preparations used in the treatment of dementia

Prof. V. Ravindranath

Research Fellows

Neha Sehgal, Alok Gupta

Traditional systems of medicine such as, Ayurveda offer a knowledge base that can be utilized for development for therapeutic intervention strategies for treatment of neurodegenerative disorders, such as Alzheimer's disease. Neuropharmacological effects of plants, which are used in traditional system of medicine for treatment of age-related dementia including Alzheimer's disease are being examined in animal models of Alzheimer's disease and the molecular mechanisms underlying their action are being identified.

Oral administration of semi-purified plant extract reversed behavioral deficits, accumulation of plaques and oligomers, and lowered levels of β-amyloid peptides 40/42 (Aβ40/42) in brain of both middle-aged (9-10 months) and old (22-24 months) Alzheimer's disease Tg mice (APPswe/PS1ΔE9). Decrease of Aβ42 monomers in brain and increase in plasma Aβ42 was seen after 7 days indicating increased transport of Aβ peptides from brain to the periphery. Increase in brain low-density lipoprotein receptor-related protein (LRP), which is involved in transport of Aβ42/40 from brain to the periphery was seen at 14 days and was restricted to microvessels. Increase in neprilysin (NEP), the Aβ degrading protease was seen much later at 21 days. However, substantial increase in liver LRP and NEP was seen earlier at 7 days. Increase in liver LRP was accompanied with enhancement of plasma sLRP that is known to act as a peripheral sink for brain Aβ40/42. Further, in WT mice, the extract induced liver but not brain LRP and NEP expression, which was accompanied by decrease Aβ40/42 in serum and brain indicating that the increase in liver LRP and plasma sLRP, occurring independent of the concentration of Aβ40/42, results in clearance of Aβ from the brain in WT mice. The remarkable therapeutic effect of the extract mediated through up-regulation of LRP and NEP indicates that targeting the periphery offers a novel mechanism for elimination of Aβ42 and reverses the behavioral deficits and pathology seen in Alzheimer's disease models.

Funding:

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PCT has been filed for the above

Collaborators:

S.C. Jain, Delhi University,
P. Balaram, IISc

Presentations

1. N. Sehgal, V. Agarwal, K. Valli, L. Antonovic, H. Strobel, V.Ravindranath. Neuroprotective role of cytochrome P4504f in resolution of inflammation in brain. Presented at the the 39th annual meeting of the Society for Neuroscience, Chicago, USA. October 17–21, 2009.
2. Ray A, Saeed U, Valli RK, Kumar AMRK, Karunakaran S and Ravindranath V: Perturbation of protein thiol homeostasis through downregulation of glutaredoxin, a protein disulfide oxidoreductase, results in loss of DJ-1 through proteolysis; Poster presented at the XVIII WFN World Congress on Parkinson's Disease and Related Disorders, Miami Beach, USA. December 13-16, 2009.

Publications

1. Saeed, U., Ray, A., Valli, R.K. and **Ravindranath, V** (2010) DJ-1 loss by glutaredoxin but not glutathione depletion triggers Daxx translocation and cell death. **Antioxidants & Redox Signaling**, 13(2): 127-144.
2. Karunakaran, S. and **Ravindranath, V** (2009) Activation of p38 MAP kinase in substantia nigra leads to nuclear translocation of NF-kB in MPTP treated mice: Implication in Parkinson's disease. **J. Neurochem,** 109: 1791-9.

Patent

Withania somnifera plant extract and method of preparation thereof. Joint patent with University of Delhi and Indian Institute of Science-Bangalore.

Cellular and Molecular Mechanisms of HIV-1 Neuropathogenesis

Principal Investigator

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Project Assistants

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Research in neurosciences and more so in the area of neurovirology was stimulated to great extent following designation of 1990s as "Decade of the Brain" by National Institutes of Health. During that period clinicians were struggling with an entirely new immune compromising disease, the acquired immunodeficiency syndrome (AIDS) caused by human immunodeficiency virus-1 (HIV-1). One of the major challenges of that era, and even today, is to find answers for significant neurological deficits presented in patients suffering from this dreaded disease.

Neurological deficits in HIV/AIDS patients are characterized by neurodegeneration in frontal cortex, basal ganglion and brain stem region of human brain. Progressive cognitive and motor impairments involving behavioral abnormalities, deficits in executive functions and dementia are common in AIDS patients. These disorders appear in advanced stages of HIV-1 infection due to irreversible damage to neurons by HIV or its viral proteins gp120 and Tat. Such neurological deficits are collectively referred to as HIV-1 associated dementia (HAD) or AIDS dementia complex (ADC). Advent of combinatorial anti-retroviral therapy (cART) has given a new lease of life to most of the HIV/AIDS patients who have access to this "wonder drug-cocktail". In last five years or so, severe HAD or ADC is not common anymore though a milder form of dementia known as HIV associated neurocognitive disorder (HAND) is becoming more prevalent among such patients. The prevalence of HAND is believed to increase further

as HIV/AIDS patients are now living longer due to successful anti-retroviral therapy. Moreover, human brain serves as a "safe heaven" for the HIV-1, where most of these drugs have very poor penetration due to blood brain barrier. Despite the success of cART, the central nervous system infection with HIV-1 and subsequent development of mild to severe neurological disorders remain a challenge for investigators working in neuroAIDS field. Basic neuroscientists and neurologists are working together to get to the crux of these brain disorders in AIDS patients.

Neural stem/precursor cells replenish ageing or damaged brain cells till late in life by forming new neurons or neurogenesis. Neurogenesis occurs throughout adulthood in the dentate gyrus of hippocampus, the center for learning and memory, unfortunately HIV-1 has been reported to infect these important areas of brain. In addition to its presence in astrocytes and microglial cells, HIV-1 virus is reported in areas of neurogenesis in autopsy brain sections from pediatric AIDS patients, suggesting that HIV-1 can infect and thrive in human neural stem/precursor cells. Several investigators, including our group have shown that HIV-1 can affect neural stem/precursor cell functions in in vitro models.

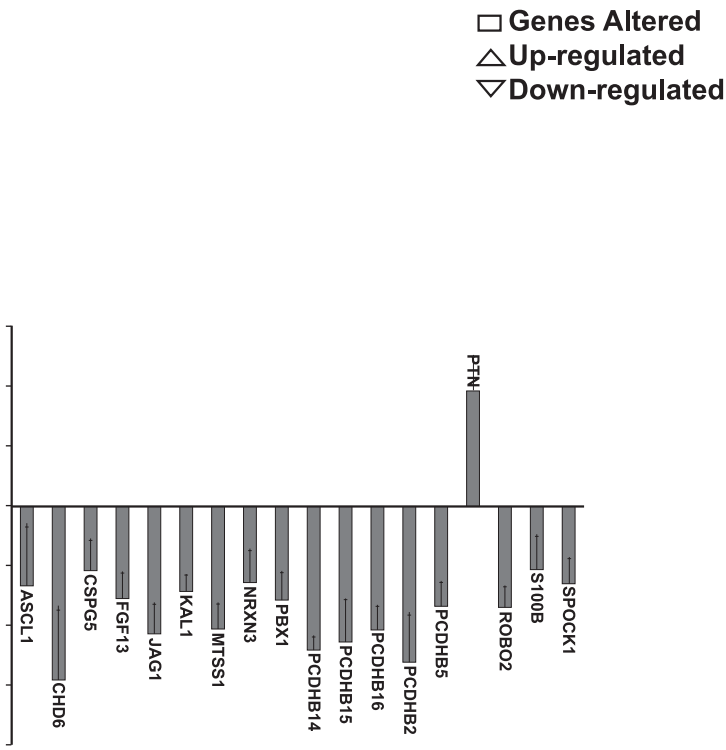

Figure 1: HIV-1 Tat Modulates Expression Profile of Genes Important for Human Neurogenesis and Neural Stem Cells. A) Tat treated hNPCs show decreased expression levels of several of the neurogenesis and neural stem cell genes (downward arrowhead). **B)** Quantitative assessment of intensity of the expressed genes normalized with house keeping genes. Genes with alterations of 20% or more over respective control are represented in the figure.

We used a well characterized cell culture model of human neural precursor cells established by us. These neural precursors grow as undifferentiated, highly proliferative, adhered monolayers cultures. We cultured these cells in presence or absence of HIV-1 transactivating protein Tat. HIV-1 Tat attenuated the growth, proliferation and differentiation capabilities of human fetal brain derived neural stem/precursor cells.

The major steps involved in process of regulation of neural precursor cells and neurogenesis are - proliferation, migration, differentiation and axonal guidance, so we used a pathway specific cDNA microarray comprising 263 genes specifically related to these functions rather than a global gene expression profile. Total RNA isolated from hNPCs undergoing differentiation/ neurogenesis in presence and absence of HIV-1 Tat for 5 days were used for cDNA microarray.

At Day 5 post differentiation, Tat resulted in down regulation of genes crucial for regulation of cell differentiation (ASCL1, JAG1), cell signaling genes involved in neurogenesis (JAG1), cell proliferation (JAG1, S100 beta, PTN, SPOCK1), regulation for cell motility and migration (KAL1, MTSS1), cell adhesion (KAL1, MTSS1, SPOCK1, PCDHB-2,-5,-14,-15 and -16, ROBO2), synaptic function (S100 beta, PCDHB-2,-5,-14 and -16), regulation of transcription (ASCL1, CHD6 and PBX1), cell cycle regulation (MTSS, PTN, KAL-1 and SPOCK1) and growth factors and cytokines (CSPG5, FGF13, JAG1, NRG1 and PTN). These findings suggest that HIV-1 Tat affects at various levels of neural stem cell functions which affects its stemness as well as the neurogenesis related genes.

Mounting evidence suggests that drugs of abuse accelerate the incidence and progression of HIV-1 induced neurological complications in AIDS patients. Drug abusing HIV-1 positive individuals exhibit more severe cognitive impairment compared with the non-drug-abusing HIV-positive counterparts. Hence there is an urgent need to investigate the underlying mechanisms and pathways that may lead to increased neuronal damage. We are actively engaged in another research project to dissect out molecular mechanisms that may be involved in neuronal damage by co-exposure of human neurons to HIV-1 Tat and morphine. Our preliminary results suggest that presence of morphine with HIV-1 Tat significantly augments the neuronal cell death. Detailed investigations are in progress to investigate the signaling mechanisms for these observations and to trace the molecular signatures that mark this event. We are also exploring if platelet derived growth factor (PDGF) can be helpful in abrogating the co-morbidity of these two agents on human neurons.

These findings provide a new facet to HIV-1 neuropathogenesis and provide the cellular and molecular basis of HIV-1 Tat induced changes on neurogenesis as well as how drugs of abuse aggravate the HIV-1 induced damage to human brain.

Presentations:

1. P. Seth: **Invited Speaker**, Brain Awareness Week, Banaras Hindu University, Varanasi, India, March 2010.
2. P. Seth: **Guest Speaker**, National Science Day, Kendriya Vidyalaya, Manesar, India, February 2010.
3. P. Seth: **Guest Faculty**, Jawaharlal Nehru University Academic Staff College Lecture series for college teachers, New Delhi, India, January 2010.
4. P. Seth: **Invited Speaker & Convener International Symposia,** Annual Meeting of Indian Academy of Neurosciences, NIIMS Univ, Jaipur, India, Dec 2009.
5. P. Seth: **Invited Speaker,** Annual meeting of International Society of Neurovirology (USA), Miami, USA, June 2009.
6. P. Seth: **Invited Speaker,** International NeuroAIDS Research Meeting organized by HIV Neurobehavioral Research Center (HNRC), Miami, USA, May 2009.
7. P. Seth: **Invited Speaker,** Annual meeting of Society of Neuroimmunopharmacology (USA) at Wuhan, China, held in April 2009.

Funding:

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Collaborators:

V Ravindranath, S K. Sharma, N. Dhingra and N Jain, NBRC, India.

N. Thapar and A. Singh, Civil Hospital, Gurgaon, India.

U. K. Ranga, JNCSAR, Bangalore, India.

A Nath, Johns Hopkins University, Baltimore, USA.

Understanding aberrant transcriptional circuitries and signaling cascades in Glioblastoma multiforme

Principal Investigator

Dr. Ellora Sen

Research Fellows

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

Objectives

1. Dissecting the role of cytokines and growth factors in the transcriptional regulation of genes involved in resistance to apoptosis, proliferation, survival and evasion of immune response in glioma cells is an active area of research in the lab.
2. Understand mechanisms that confer resistance of GBM to apoptosis and identify new treatment strategies that can manipulate the aberrant signaling pathways to induce apoptosis.

Inflammation which is an indispensable participant in tumor progression is intricately linked with redox modulation.

The pro-inflammatory cytokine Tumor Necrosis Factor (TNFα) elevates reactive oxygen species (ROS) in GBM. TNFα also elevates Akt phosphorylation in glioma cells. We have observed that increase in Akt phosphorylation was concurrent with decrease in ROS scavenger superoxide dismutase (SOD-1) levels. TNFα mediated increase in pAkt was dependent on oxidative stress as pAkt levels was abrogated in the presence of ROS inhibitor N-acetylcysteine (NAC) and elevated in cells transfected with SOD-1 siRNA. TNFα altered actin cytoskeletal organization and increased Cdc42 levels. This increase in Cdc42 was concomitant with its increased interaction with scaffold protein IQGAP-1. Also, we have reported for the first time a ROS dependent interaction between pAkt and IQGAP-1 in TNFα treated cells. Importantly, Akt inhibition not only reversed TNFα mediated changes in actin cytosketal organization but also abrogated anchorage independent growth. Together, these results suggest that TNFα induced oxidative stress affect Akt activation to regulate actin `organization and growth of glioma cells.

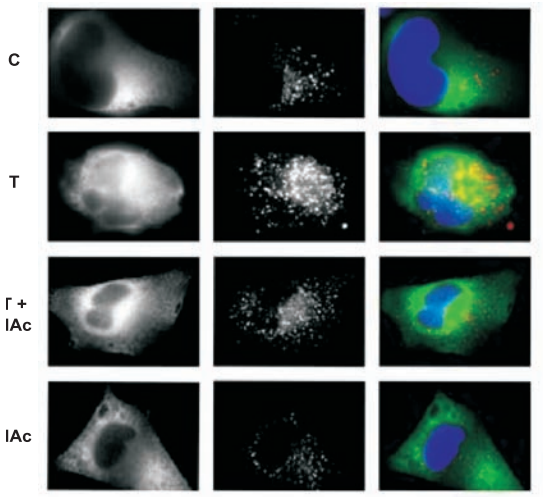

Figure: TNFα increases the colocalization of Akt with scaffold protein IQGAP-1 in glioma cells in a ROS dependent manner. C, T and NAC denote Control, TNFα and N-acetylcysteine respectively.

We also identified a novel mechanism of induction of apoptosis in glioblastoma cells by Scriptaid- an HDAC inhibitor. Scriptaid reduced glioma cell viability by increasing JNK activation and decreasing telomerase activity. Though Scriptaid induced activation of both p38MAPK and JNK, it was the inhibition of JNK that attenuated Scriptaid-induced apoptosis significantly. Scriptaid also increased the expression of (i) p21 and p27 involved in cell cycle regulation and (ii) γH2AX and MLH1 associated with DNA double stranded break and mismatch repair response respectively, in a JNK dependent manner. Treatment with Scriptaid increased Ras activity in glioma cells and transfection of cells with constitutive active RasV12 further sensitized glioma cells to Scriptaid induced apoptosis. Scriptaid mediated inhibition of telomerase activity was independent of JNK activation. Taken together, our findings indicate that HDAC inhibitor Scriptaid induces glioma cell apoptosis by elevating JNK activation and decreasing telomerase activity.

Since the farnesyltransferase inhibitor Manumycin is known to induce ROS generation, we evaluated the effect of Manumycin on glioma cells. Manumycin induced glioma cell apoptosis by elevating ROS generation. Treatment with ROS inhibitor N-acetylcysteine (NAC) blocked Manumycin induced apoptosis, caspase-3 activity and PARP

expression, indicating the involvement of increased ROS in the proapoptotic activity of Manumycin. This heightened ROS level was accompanied with concurrent decrease in antioxidants SOD-1 and thioredoxin (TRX-1). SOD-1 overexpression protects glioma cells from Manumycin induced apoptosis. In addition, siRNA mediated knockdown of SOD-1 and TRX-1 also increased ROS generation and sensitivity of glioma cells to Manumycin-induced cell death. Interestingly, suppressing ROS generation prevented Manumycin induced Ras inhibition. We report for the first time that (i) Ras inhibition by Manumycin is due to heightened ROS levels (ii) Manumycin inhibits the phosphorylation of signal transducer and activator of transcription 3 (STAT3) and telomerase activity in ROS dependent manner which plays a crucial role in glioma resistance to apoptosis. In addition Manumycin also induced DNA damage repair response, affected cell cycle regulatory molecules, impaired colony forming ability of glioma cells in a ROS dependent manner.

Publications:

1. Ghosh S, Tewari R, Dixit D, **Sen E** (2010) TNFα induced oxidative stress dependent Akt signaling affects actin cytoskeletal organization in glioma cells. **Neurochemistry International** 56(1):194-201.
2. Sharma V, Koul N, Joseph C, Dixit D, S Ghosh and **Sen E** (2010) HDAC inhibitor Scriptaid induces glioma cell apoptosis through JNK activation and inhibition of telomerase activity. **Journal of Cellular and Molecular Medicine**. 14(8):2151-61.
3. Dixit D, Sharma V, Ghosh S, Koul N, Mishra PK and **Sen E** (2009) Manumycin inhibits STAT3, telomerase activity and growth of glioma cells by elevating intracellular reactive oxygen species generation. **Free Radic Biol Med.** 47(4):364-74.

Book Chapter

Sharma V and **Sen E** (2009) Tumor microenvironment and inflammation: role in glioblastoma progression. Editors: GP Talwar and OP Sood (Narosa Publishing house).

Sen E and Ravindranath V (2010) Neurobiology. 'Science in India. Achievements and Aspirations'. Editors: HY Mohan Ram and PN Tandon. Indian National Science Academy, New Delhi.

Patent:

"Bicyclic triterpenoid Iripallidal as a novel anti-glioma and anti-neoplastic therapy in vitro". Filed for Indian patent through Department of Biotechnology (#2915/DEL/2008) and International patent (PCT/IN09/000336).

Presentations:

1. Vivek Sharma*, Nitin Koul, Veer Singh Mehta and Ellora Sen: Interleukin-1β induced HIF-α transcriptional activity in glioma cells is regulated by Ras via NF-κB. Frontiers in Basic Cancer Research Meeting. Boston, October 2009.

2. Ellora Sen: Inflammation and Cancer: Romancing death. West Bengal State University, Calcutta, August, 2009

3. Deobrat Dixit*, Vivek Sharma and Ellora Sen: Casein Kinase 2 inhibition induces SOCS-1 expression and sensitizes glioblastoma cells to Tumor Necrosis factor (TNFα) induced apoptosis. Indian Academy of Neuroscience, Jaipur December, 2009.

4. Nitin Koul*, Vivek Sharma, Deobrat Dixit, Sadashib Ghosh and Ellora Sen: Bicyclic triterpenoid Iripallidal induces apoptosis and inhibits Akt/mTOR pathway in glioma cells. International Symposium on Cancer Chemoprevention and Translational Research, New Delhi, December, 2009.

5. Vivek Sharma, Nitin Koul, Veer Singh Mehta and Ellora Sen*: 3rd International Symposium on Translational Cancer Research, Bhubaneswar, December, 2009

6. Vivek Sharma, Nitin Koul, Veer Singh Mehta and Ellora Sen*: Macbeth's three witches in glioma: IL-1β, Ras and NFκB. Molecular Immunology Forum. Calcutta, January, 2010

*Presenting author

Funding:

i. Innovative Young Biotechnologists Award (IYBA, 2007), to Ellora Sen by Department of Biotechnology

ii. Defence Research & Development Organization, Ministry of Defence. (DLS/81/48222/LSRB-140/EPB/2007)

iii. Department of Biotechnology, (BT/PR/7407/Med/14/934/2006).

Collaborator:

Dr. VS Mehta, Paras Hospitals, Gurgaon

Award:

NASI–SCOPUS Young Scientist Award conferred jointly by National Academy of Science and Elseviers 2010.

Signaling cascades regulating the differentiation of glial progenitors along specific lineages

Principal Investigator

Dr. Ellora Sen

Project Assistants

Sk. Sudipta Shaheen

Neural stem cell (NSCs) in the mammalian central nervous system (CNS) possess the ability to self-renew as well as to maintain the potential of generating all three major cell types of the CNS: neurons, astrocytes and oligodendrocytes. Differentiation of neural precursors into neurons, astrocytes and oligodendrocytes takes place sequentially and extrinsic factors play pivotal role in specifying cell lineages in the developing brain. The decisive instructive and permissive signals, that govern these developmental choices, are provided by cell external cues and cell intrinsic programs. Recent advances in understanding NSC differentiation into glial lineages have revealed the importance of growth factors and relevant downstream transcription factors. These factors working through their respective downstream transcription factor combinatorially induce the preferential differentiation of one cell lineage while suppressing another. Recent studies suggest that hypoxia promotes the survival and proliferation of NSCs. We are investigating whether hypoxia regulates the transcriptome of bipotential glial progenitors in the subventricular zone (SVZ), - a region of the brain that harbors the multipotential neural stem cells/ progenitors, to induce preferential differentiation towards one lineage at the expense of another.

Objectives

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

We hypothesized that there is aberrant glial cell generation from the subventricular zone (SVZ) after neonatal hypoxia ischemia (H/I) that contributes to an increased astrogliogenesis with concomitant oligodendroglial insufficiency. Microarray and qRT-PCR analyses of the damaged SVZ of rat pups subjected to hypoxia/ischemia (H/I) showed increased expression of several cytokines and receptors that are known to promote astrocyte differentiation, such as EGF, LIF and TGFß signaling

components. Using gliospheres to model the neonatal SVZ, we evaluated the effects of these cytokines on signal transduction pathways regulating astrocyte generation, proliferation and differentiation. These studies demonstrated that combinations of EGF, LIF and TGFß1 reconstituted the increased astrogliogenesis. TGFß1-induced Smad 2/3 phosphorylation and the combination of EGF, LIF and TGFß1 synergistically increased STAT3 phosphorylation over single or double cytokine combinations. Pharmacologically inhibiting ALK5 signaling in vitro antagonized the TGFß1-induced increase in astrocyte generation, and antagonizing ALK5 signaling in vivo similarly inhibited astrogliogenesis within the SVZ during recovery from H/I. Our studies suggest that aberrant specification of glial precursors within the neonatal SVZ during recovery from neonatal H/I is a consequence of altered cytokine signaling.

Publication:

1. Bain JM, Ziegler A, Yang Z, Levison SW*, **Sen E*** (2010) TGFβ1 stimulates over-production of white matter astrocytes from glial precursors of the "brain marrow" in a rodent model of neonatal encephalopathy. **PLoS One,** 5; 5(3):e9567.

*** Co-corresponding Authors**

Funding:

Department of Biotechnology (BT/PR6615/MED/14/857/2005).

Collaborator:

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

Principal Investigator

Dr. Shiv K Sharma

Research Fellows

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Project Assistant

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Narayanan

The overall goal of my lab is to investigate the molecular mechanisms of synaptic plasticity and memory, and the mechanisms that may contribute to cell death and deficits in synaptic plasticity and memory in the Alzheimer's disease. In this regard, we are working on two related projects.

The investigation of molecular and synaptic mechanisms of memory has received considerable attention. Activity-dependent molecular and synaptic changes play important roles in memory formation. Long-term potentiation (LTP), a persistent increase in the synaptic strength is widely studied as a putative cellular mechanism of memory formation. Despite extensive investigation, the molecular changes involved in LTP and memory are far from understood. Activity-dependent changes in the signaling molecules play crucial roles in LTP and memory. In addition, changes in protein synthesis and transcription are involved in these processes.

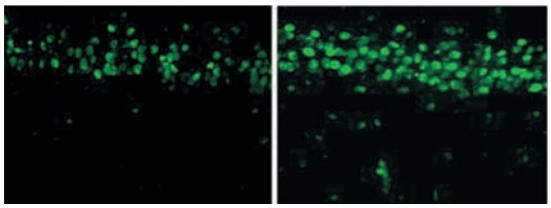
(I) Activity-dependent regulation of histone acetylation:

Given the requirement of RNA synthesis in LTP and memory, we are investigating how activity leads to changes in chromatin modifications which may be involved in RNA synthesis during LTP and memory. For these molecular studies, we prepare slices from the rat hippocampus and stimulate them with KCl. KCl treatment leads to depolarization in the cells and Ca++ influx. Ca++ influx is a primary requisite for different kinds of LTP and memory formation. Importantly, KCl can induce LTP in the hippocampus and this effect requires the activity of NMDA type of glutamate receptors. The NMDA receptor activity is critical for many forms of LTP and memory.

These studies would enhance our understanding of the mechanisms that contribute to the regulation of gene expression during LTP and memory.

In the nucleus, DNA is packaged with histones into nucleosomes. Histone modifications play crucial roles in regulating the state of chromatin, and thus transcription. Acetylation of histones is associated with transcriptional activation. Earlier, we reported activity-dependent regulation of histone H2B. During the year, we have performed additional experiments on H2B acetylation that have strengthened the findings. KCl depolarization leads to increase in histone acetylation in the CA1 region of the hippocampus (Fig. 1).

Since depolarization leads to Ca++ influx and CaMK is one of the kinases activated by Ca++ influx and known to play crucial roles in LTP and memory, we examined whether CaMK activity is required for H2B acetylation. We found that when CaMK activity was inhibited using its pharmacological inhibitor (KN-93), depolarization-induced H2B acetylation was abolished. On further examination, extracellular signal-regulated kinase (ERK) activity was found to be critically required for depolarization-induced H2B acetylation. Our results combined with other studies point to a critical role of ERK in activity-dependent histone modifications. Thus, ERK activity which is critical for synaptic plasticity and memory regulates histone modifications in addition to regulating protein synthesis and transcription factors. Furthermore, our studies reveal a critical role for CaMK in activity-dependent histone acetylation. In addition, we found that DNA methyltransferase activity is also important for depolarization-induced H2B acetylation in the hippocampus Taken together with earlier studies, our results suggest a cross talk between DNA methylation and histone acetylation. Thus H2B acetylation is regulated by events that play crucial roles in LTP and memory.



Control KCI

Figure 1 KCl depolarization enhances histone H2B acetylation in the hippocampal slices. Control or KCl treated acute hippocampal slices were processed for immunohistochemistry using acetyl-H2B antibody. KCl treatment enhanced H2B acetylation in the slices. CA1 region of the hippocampus is shown.

The physiological significance of depolarization-induced H2B acetylation is currently not understood. It is known that cbp+/- mice show impairment in LTP and memory along with deficits in histone H2B acetylation. Importantly, histone deacetylase inhibitors which increase the levels of acetylation including H2B acetylation can ameliorate impairment in LTP and memory. These results suggest that H2B acetylation may be important for LTP and memory. We have now started experiments to examine activity-dependent regulation of other histones of the nucleosome.

(II) Characterization of Acetyl-p55 in the Hippocampus

The level of acetylation in a cell is regulated by the relative activities of histone acetylases and deacetylases. We had found that treatment of the hippocampal slices with a histone deacetylase (HDAC) inhibitor leads to an increase in acetylation of a protein with a molecular weight of about 55 kDa. HDAC inhibition enhances LTP and memory, and increases acetylation of a p55 in the insular cortex, a brain region involved in taste memory formation. Importantly, p55 acetylation is regulated during taste memory formation. Considering these observations, we characterized p55 protein in more detail, in the hippocampus. We found that the mobility of p55 is different from p53, the anti-oncogene. In addition, p55 is a non-nuclear protein as opposed to p53. We further found that (1) p55 has identical mobility as alpha tubulin, (2) conditions leading to polymerization of tubulin, decrease acetyl-p55 levels in the remaining fraction, (3) sodium butyrate, which does not inhibit tubulin deacetylase, does not affect p55 acetylation, and (4) both acetyl-p55 and alpha tubulin produce same pattern in two-dimensional gel electrophoresis. These results strongly suggest that p55 is alpha tubulin. We next examined whether alpha tubulin acetylation is regulated by activity. We found that depolarization of cells with KCl increases acetylation of alpha tubulin in the CA1 region of the hippocampus. We are now examining the mechanisms of depolarization-induced alpha tubulin acetylation.

Publications:

1. Maharana C, Sharma KP, **Sharma SK** (2010). Depolarization induces acetylation of histone H2B in the hippocampus. **Neuroscience,** 167:354-360.
2. **Sharma SK** (2010). Protein acetylation in synaptic plasticity and memory. **Neurosci Biobehav Rev.,** 34:1234-40.

Presentations:

1. Shiv K Sharma, Kiran Pandey, Chinmoyee Maharana and Kaushik Sharma: Histone deacetylase inhibitor- and activity-induced acetylation of p55: relevance for synaptic plasticity and memory. Poster presentation at the Society for Neuroscience Conference, Chicago, USA, Oct. 17-21, 2009.
2. Chinmoyee Maharana, Kaushik P Sharma and Shiv K Sharma: Depolarization induces histone H2B acetylation in the hippocampus. Poster presentation at the XXVII Conference of Indian Academy of Neurosciences, Jaipur, Dec. 18-20, 2009.
3. Kiran Pandey, Chinmoyee Maharana, Kaushik Sharma and Shiv K Sharma: Activity-dependent regulation of alpha tubulin acetylation. Poster presentation at the XXVII Conference of Indian Academy of Neurosciences, Jaipur, Dec. 18-20, 2009.

Funding:

DBT and NBRC core.

Amyloid Beta and Neurodegeneration: Identification of a Curcumin Metabolite as a Neuroprotective Agent

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Narayanan

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and a common form of dementia among the elderly. Pathologically, it is characterized by the presence of amyloid plaques and neurofibrillary tangles in different brain regions. The amyloid plaques are extracellular deposits, whereas the neurofibrillary tangles are intracellular. Amyloid beta (A-beta) is a primary component of the plaques. A-beta is produced by the proteolytic processing of a larger intramembrane peptide, amyloid precursor protein. A-beta exists in several forms such as monomeric, oligomeric and the fibrillar form. Several studies show that A-beta oligomers cause synaptic dysfunction and neuronal cell death. In addition, these toxic species cause impairment in long-term potentiation (LTP). LTP is considered a putative cellular mechanism of memory. Furthermore, injection of A-beta oligomers in the brain causes memory deficit. Despite extensive research, the mechanisms of neurodegeneration and the impairment in synaptic plasticity and memory are not clearly understood. In this project, currently we are focusing on identifying agents that can protect neurons from A-beta oligomer induced toxicity, and examine the mechanisms of neuroprotection.

Cell death is a common feature in many neurodegenerative diseases including AD. Several studies have shown that A-beta is toxic to the neurons. This effect of A-beta is brought about in two ways: (1) A-beta acting on the neurons and affecting their survival (direct toxicity), and (2) A-beta acting on the glial cells leading to the release of toxic substances including cytokines (indirect toxicity). Thus, significant efforts are directed towards identifying compounds especially from herbs and dietary sources that can protect neurons against A-beta-induced direct

and indirect cell death. Curcumin is one of the neuroprotective agents that has received considerable attention due to its antioxidant activity and safety profile. Using primary hippocampal cultures prepared from rat embryos, we earlier reported that a metabolite of curcumin showed neuroprotective property against oligomeric A-beta-induced cell death and the possible mechanisms involved in neuroprotection. During the year, we have performed more experiments to strengthen the findings on the curcumin metabolite. A-beta treatment of the hippocampal cells leads to cell death. Initially we used MTT reduction assay and found that the curcumin metabolite reduced oligomeric A-beta-induced toxicity. This finding was confirmed using another assay, the TUNEL staining (Fig. 2). Treatment of hippocampal cells to A-beta led to enhanced production of reactive oxygen species, reduction of mitochondrial membrane potential and caspase activation.

The curcumin metabolite showed protective effects in all these measures. In addition to rat primary hippocampal neurons, curcumin metabolite showed protective effects in human primary neurons also against A-beta-induced toxicity. These results suggest that the curcumin metabolite protects neurons by affecting the machinery involved in apoptotic neuronal cell death, and the antioxidant property of THC may contribute to its protective property. As mentioned earlier A-beta acts on the glial cells and increases the production of substances such as chemokines, cytokines, ROS and NO. These toxic substances are involved in indirectly causing neuronal cell death. We have started experiments to examine indirect toxicity caused by A-beta and neuroprotection. We have obtained some promising results in this direction which we are pursuing in more detail.

Publication:

Sharma S (2010) Hepatocyte growth factor in synaptic plasticity and Alzheimer's disease. **Scientific World Journal,** 10:457-61.

Funding:

NBRC core.

Collaborator:

Dr. Pankaj Seth, NBRC.

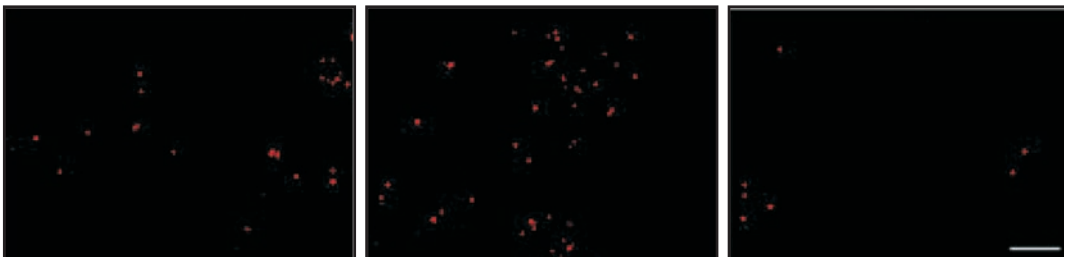

Figure 2. Curcumin metabolite shows protection against oligomeric A-beta-induced cell death. Cultured rat primary hippocampal neurons were untreated (control, left panel), treated with oligomeric A-beta (middle panel) or with oligomeric A-beta and curcumin metabolite (right panel). TUNEL staining shows that oligomeric A-beta induced cell death which was prevented by the curcumin metabolite.

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

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Manish Dogra

The focus of our laboratory is to understand the pathophysiology and pharmacology of infection and inflammation in CNS. Chronic microglial activation is an important component of neurodegenerative diseases, and this chronic neuroinflammatory component likely contributes to neuronal dysfunction, injury, and loss (and hence to disease progression) in these diseases. The recognition of microglia as the brain's intrinsic immune system, and the understanding that chronic activation of this system leads to pathologic sequelae, has led to the modern concept of neuroinflammation.

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

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

We have earlier showed that JE Virus can infect neural stem cells/ progenitors (NSPs) and harbor in them. Interestingly, the virus does not induce robust NPC death, but with progressive infection arrests their proliferative ability. This eventually culminates in depletion of NPC pool upon JEV infection, which could lead to long-term neurological sequel in JE survivors. We have also initiated work to investigate whether JE virus infection induce immunogenecity in NSPs. Recently we have reported that Japanese encephalitis virus induce immuno-competency in neural stem/ progenitor cells. The key finding of this study is: 1) The NPC residing in the subventricular zone of the JEV infected brains showed a prominent expression of MHC-I and the costimulatory molecules CD40, CD80, and CD86. 2) We have observed increased surface expression of co-stimulatory molecule and MHC class I antigen in NPC upon progressive JEV infection. 3) Moreover, significant production of pro-inflammatory cyto/chemokines was detected in JEV infected NPC by Cytokine Bead Array analysis on Flow cytometry. 4) Interestingly, NPCs were capable of providing functional costimulation to allogenic T cells and JEV infection resulted in increased proliferation of allogenic T cells, as detected by Mixed Lymphocyte reaction and CFSE experiments. 5) We have also reported IL-2 production by NPC upon JEV infection, which possibly provides mitogenic signals to T cells and trigger their proliferation.

Regarding our work with virus entry into neural stem/progenitor cells (NSPs) we have found that lipid rafts play a critical role in JEV entry into neural stem cells (C17.2 cells) in at least two ways: (i) association of the virus envelope proteins with the lipid rafts (which possibly helps to concentrate the virus receptors present on the host cell membrane) and (ii) activation of SFKs and downstream PI3K/Akt pathway which maintain host cell survivability in the initial stages of infection. Interestingly, we also found that though JEV utilises the rafts, however, internalisation into C17.2 occurs by clathrin-mediated endocytosis and do not involve caveolae which are mostly associated with the rafts. The importance of the lipid rafts in other stages of the JEV life cycle was observed, specially in virus replication as shown by the association of the

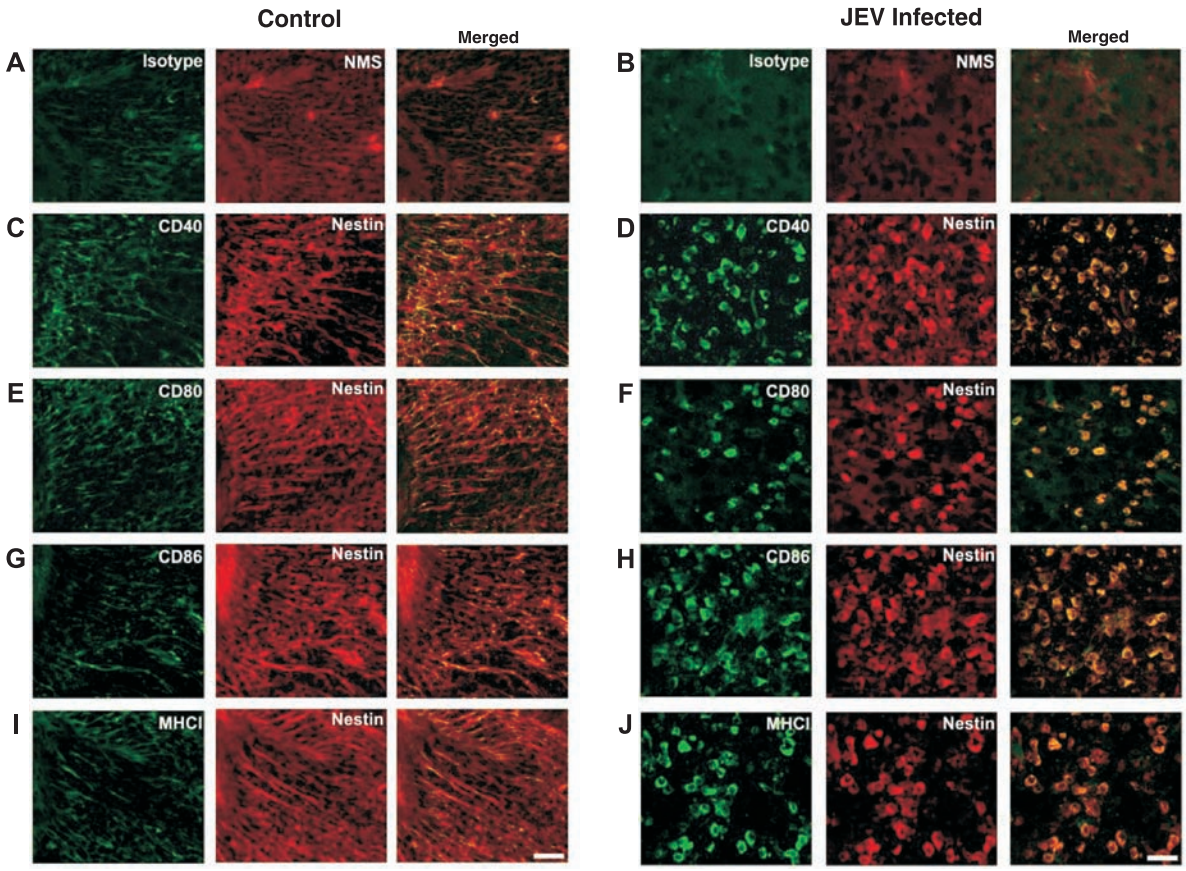

Figure1 ***Upregulation of costimulatory molecules and MHC class I in Nestin-positive cells in SVZ during JEV infection.*** Brain cryosections from control and JEV infected animals were stained with antibodies against CD40, CD80, CD86, and MHC class I molecules and Nestin. Isotype staining using rat IgG2a□ (for costimulatory molecules and MHC class I) and normal mouse serum (NMS; for Nestin) was performed on both control **(A)** and JEV infected brain sections **(B)**. Co-localization of Nestin (red) with the costimulatory molecules and MHC class I (green) was performed using confocal microscopy. Isotype staining on both control and JEV infected sections show no detectable fluorescence **(A-B)**. The Nestin +ve cells show a distinctive morphological change following infection from process bearing cells to round/oval shaped cells. Nestin positive cells in control sections show very less co-localization with all the costimulatory molecules and MHC class I **(C, E, G, I)**. JEV infected SVZ show complete and increased co-localisation of Nestin positive cells with CD40 **(D)**, CD80 **(F)**, CD86 **(H)**, and MHC class I **(J)**. Scale bar corresponds to 20 microns.

different components of the replication complex (NS1, and NS3) with the rafts at later time points of infection (24 hour post infection).

In continuation of our earlier work with minocycline, recently we have showed that minocycline plays a pivotal role in regulating peripheral immune response following JE virus infection. Persistence of internalized virus within macrophages was visualized by immunofluorescent staining. Cytotoxicity assay revealed that there was no significant cell death

after 24h and 72h infection with JEV. Proinflammatory cytokine levels were elevated in cells that were infected with JEV but it was abrogated following minocycline treatment. Reactive oxygen species level was also increased after JEV infection. Nitric oxide level was found to increase after 72h post infection but remained unchanged after 24h. The cellular levels of signaling molecules such as PI3 kinase, phophoAkt and phospho p38MAP kinase were found to be altered after JEV infection and minocycline treatment. JEV infection also affected the VEGF-MMP pathway. Increased activity of MMP-9 was detected from JEV-infected macrophage culture supernatants after 72h; minocycline treatment resulted in reduced activity. Thus it seems that minocycline dampens peripheral immune reactions by decreasing proinflammatory cytokine release from infected macrophages and the virus survives within macrophages long enough to be carried into the CNS, even though minocycline inhibits cell survival. We have further shown that the levels of T cell activating cytokine IL-12 and MCP-1 levels were significantly elevated in JEV-infected tissue samples in a time dependent manner. Corresponding to this increase was the increase in number of CD3 and CD11b positive cells in the tissues of infected animals. Minocycline treatment abrogated these changes. Minocycline treatment also resulted in gradual decrease in the number of CD11b (but not CD3) positive cells in the lymph node and in spleen, even though the virus persisted in these organs. We also observed structural changes in the spleen following minocycline treatment.

From these studies we have found that minocycline has differential activities on different organs of the body that are infected by JEV. In the brain it serves as a protective agent by reducing the release of proinflammatory cytokines and preventing the accumulation of cells of monocyte/macrophage lineage. In the periphery minocycline stimulates the generation of immune response within the spleen that is targeted towards the virus, but is not sufficient to prevent its spread into the CNS, in our experimental model. Apart from this preliminary study, the role of minocycline in modulation of peripheral responses needs to be studied in detail for a better understanding of its anti-JEV activities.

Based upon our findings recently NBRC decided to fund JE-Minocycline clinical trial at Dept of Pediatrics, CSM Medical University (Erstwhile King George Medical College), Lucknow. This clinical trial will be supervised by Prof Rashmi Kumar, Head of the department, Pediatrics. The trial protocol is currently under consideration of Drug Controller General of India.

Earlier we have initiated a work to study the role of different environmental pollutant in neuroinflammation and subsequent neuro-degeneration. Recently we have showed that a common carcinogen Benzo[a]pyrene (B[a]P) causes neuronal death in mouse via microglial cctivation. Using neuroblastoma cell line and primary cortical neuron culture, we demonstrated that B[a]P has no direct neurotoxic effect. We utilized both in vivo and in vitro systems to demonstrate that B[a]P causes microglial activation. Using microglial cell line and primary

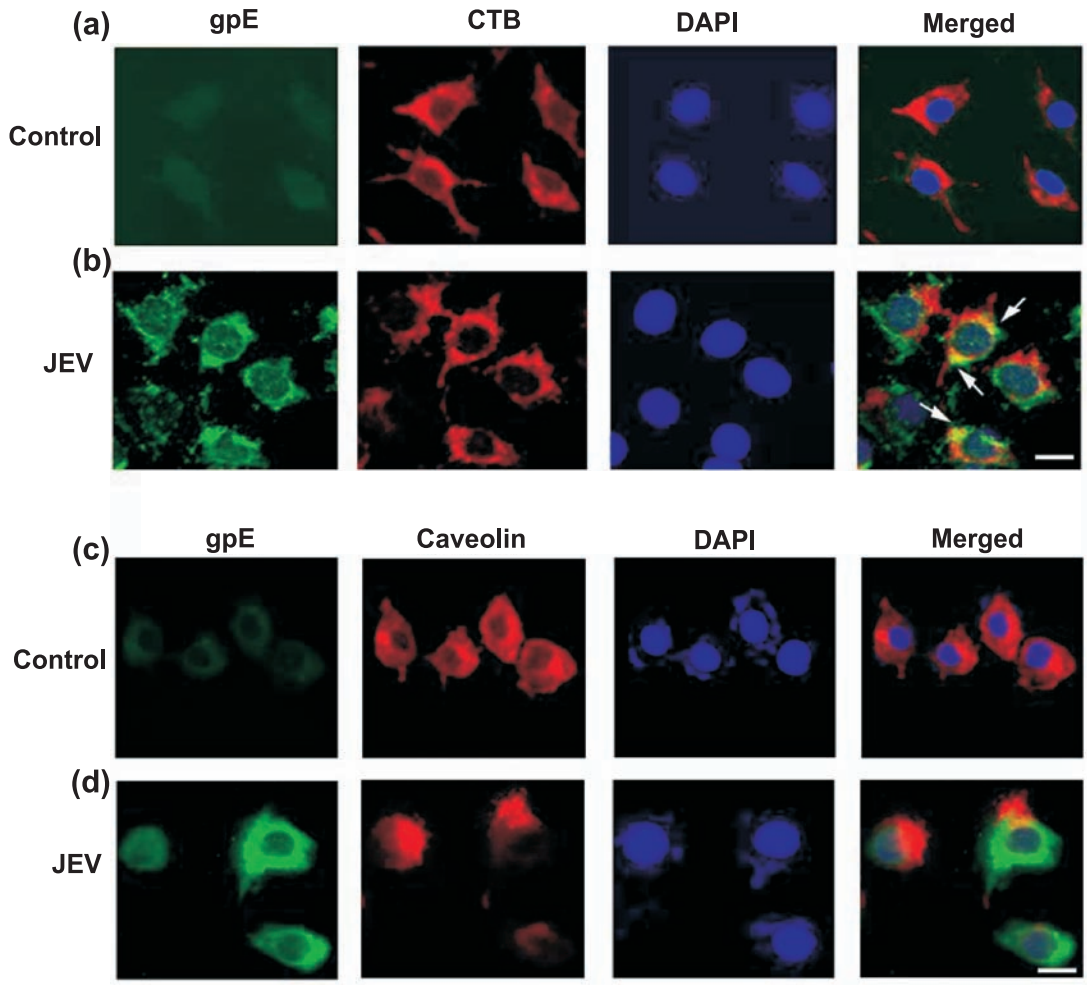

Figure2 ***JEV gpE co-localise with CTB, but not with caveolin at the plasma membrane***
C17.2 cells grown in 8-well chamber slides were infected JEV at 5 MOI and incubated with 10ug/ml of biotin-conjugated CTB for 45 mins at 4°C. Cells were shifted to 37°C for 30 mins and then fixed with 2% PFA. Streptavidin-Alexa 594 was added to detect CTB, followed by staining with JEV gpE (FITC). Both control (a) and infected cells (b) show CTB expression. Discrete areas of co-localisation of gpE with CTB were observed (b). Similarly, control (c) and JEV infected cells (d) were also double-stained for gpE (FITC) and caveolin-1 (Alexa 594) or CD71 (Alexa 594, red). Cells were counterstained with DAPI and visualised under 40X magnification of Zeiss Apotome microscope. No co-localisation of gpE with caveolin-1 in JEV infected cells (d) was observed. Scale bar corresponds to 20 microns.

microglial culture, we showed for the first time that B[a]P administration results in elevation of reactive oxygen species within the microglia thereby causing depression of antioxidant protein levels; enhanced expression of inducible nitric oxide synthase, that results in increased production of NO from the cells. Synthesis and secretion of proinflammatory cytokines were also elevated within the microglia, possibly via the p38MAP kinase

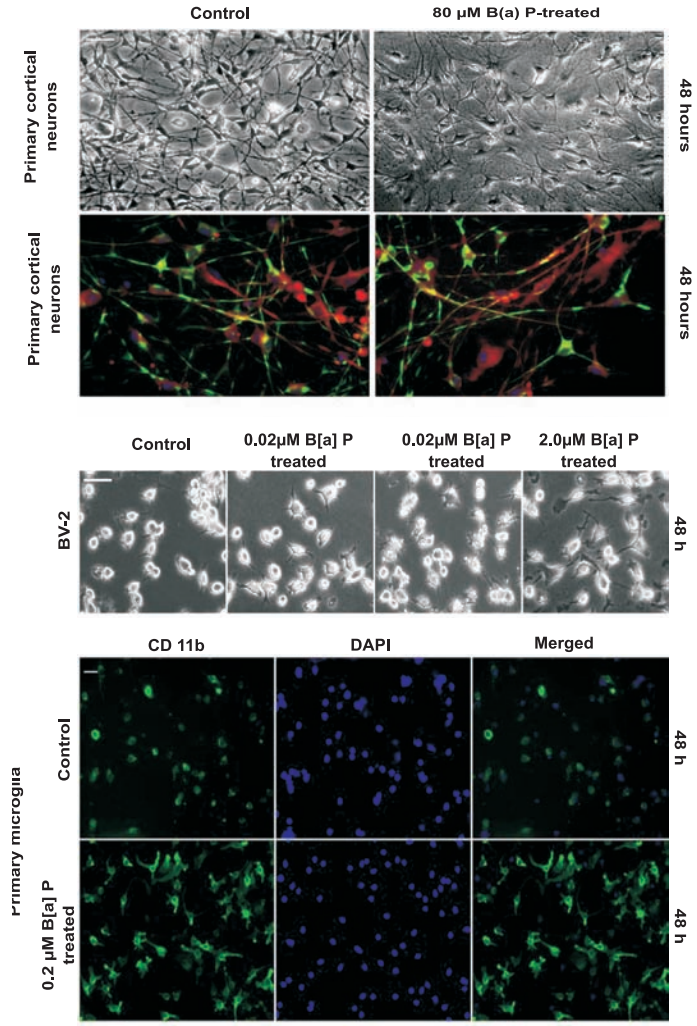

Figure3 ***Photomicrographs showing effect of B[a]P treatment on N2a, primary neurons, BV-2 and primary microglia.*** Light microscopic images of primary cortical neurons, grown in poly-D-lysine coated chamber slides that were treated with 80 µM of B[a]P, did not reveal any significant morphological alterations when compared to control (A). To confirm this finding, immunofluorescent staining of the B[a]P treated primary neurons were done. The slides were stained for beta III tubulin, a primary neuronal marker, and glial acidic fibrilary protein (GFAP), a marker for activated astrocytes, followed by mounting with DAPI. The image shows that no significant change can be visualized in the B[a]P treated neurons when compared to control (B). The scale bars correspond to 50 µ and magnification is 20×.

Light microscopic images of BV-2 after treatment with varying doses of B[a]P for 48 h shows morphological signs of activation at all three doses (C). To see whether primary microglia also became activated due to B[a]P, cells were culture and then seeded onto chamber slides and treated with 0.2 µM B[a]P for 48 h. The slides were then processed to be stained with anti-CD11b antibody and mounted with DAPI. Images were captured using Zeiss Axioplan 2 fluorescence microscope. Figure S1D clearly shows morphological difference between B[a]P treated and untreated cells. Scale bar correspond to 50 µ in both (C) and (D). Magnification is 20× in both figures.

pathway. All these factors contributed to bystander death of neurons, in vitro. When administered to animals, B[a]P was found to cause microglial activation and astrogliosis in the brain with subsequent increase in proinflammatory cytokine levels.

Publications:

Research article:

1. K Dutta, M K Mishra, A Nazmi, K L Kumawat and **A Basu** (2010) Minocycline Differentially Modulates Macrophage Mediated Peripheral Immune Response Following Japanese Encephalitis Virus Infection. **Immunobiology**. (In Press)

2. K Dutta, D Ghosh, A Nazmi, K L Kumawat , and **A Basu** (2010) A Common Carcinogen Benzo[a] pyrene Causes Neuronal Death in Mouse via Microglial Activation **PLoS One**, 5(4): e9984.

3. D Nandi, M K Mishra, **A Basu,** and B Bishayi (2010) Protective effects of Interleukin-6 in Lipopolysaccharide (LPS) induced experimental endo-toxemia are linked to alteration in hepatic anti-oxidant enzymes and endogenous cytokines. **Immunobiology,** 215: 443-451.

4. R Mukhopadhyay, M K Mishra, **A Basu,** and B Bishayi (2010) Effect of particular antigenic stimulation or in vivo administration of Interleukin-6 on the level of steroidogenic enzymes in adrenal glands and lymphoid tissues of mice with parallel alteration in endogenous inflammatory cytokine level. **Cellular Immunology,** 261 (2010) 23–28.

5. S Das, D Ghosh, and **A Basu** (2009) Japanese encephalitis virus induce immuno-competency in neural stem/progenitor cells. **PLoS One,** 4(12): e8134.

6. *M K Mishra, K Datta, S K Saheb, and **A Basu** (2009) Understanding the molecular mechanism of blood brain barrier damage in an experimental model of Japanese Encephalitis: Correlation with minocycline administration as a therapeutic agent. **Neurochemsitry International**, 55(8):717-233.

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Review:

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9. S Chakraborty, D K Kaushik, M Gupta, and **A Basu** (2010) Inflammasome Signaling At The Heart of Central Nervous System Pathology. **J Neurosci Res.**, 88:1651-1631.

10. S Chakraborty, A Nazmi, K Dutta, and **A Basu** (2010) "Neurons Under Viral Attack: Victims Or Warriors?" **Neurochemsitry International,** 56:727-735.

11. K Dutta, P N Rangarajan, S Vrati, and **A Basu** (2010) Japanese Encephalitis: Pathogenesis, Prophylactis and Therapetucis. **Current Science,** 98 (3): 22-30. (Special section: Biology and pathogenesis of Virus)

12. *D Ghosh and **A Basu** (2009) Japanese Encephalitis - A Pathological and Clinical Perspective **PloS Neglected Tropical Diseases,** 3(9) e437.

**In press last year*

Presentations:

1. S Das, and A Basu: Japanese Encephalitis Virus arrests Neural stem cell proliferation and confers them with immunogenic properties. 2nd Bangalore Microscopy Course, NCBS, Bangalore, 21st-28th February, 2010.

2. A Basu: Immuno-competency of Neural stem cells: Neuro-tropic Viral infection as a model system. Molecular Immunology Forum meeting. Fort Radisson, Raichak (Near Kolkata), 15-17th January, 2010.

3. A Basu: Japanese Encephalitis Virus causes "double trouble" to brain. Guha Research Conference. Summer Sand Beach Resort, Ullal, Mangalore. 19th -23rd December, 2009.

4. K Dutta, K L Kumawat, M K Mishra, and A Basu: Minocycline modulates Japanese Encephalitis Virus entry in the central nervous system. XXVII Annual conference of Indian Academy of Neuroscience. NIMS University, Jaipur, 18-20 December, 2009.

5. S Chakraborty, S Das, and A Basu: Lipid rafts play a critical role in Japanese Encephalitis Virus entry into neural stem cells. XXVII Annual conference of Indian Academy of Neuroscience. NIMS University, Jaipur, 18-20 December, 2009.

6. D K kaushik, S Das, M Gupta, and A Basu: To elucidate the role of Kruppel like factor 4, a novel transcription factor in neuroinflammation. XXVII Annual conference of Indian Academy of Neuroscience. NIMS University, Jaipur, 18-20 December, 2009.

7. S Das, and A Basu: Infection of neural stem cells by Japanese Encephalitis Virus: Implications in long-term viral neuropathogenesis. XXVII Annual conference of Indian Academy of Neuroscience, NIMS University, Jaipur, 18-20 December, 2009.

8. A Basu: Japanese Encephalitis: from neuropathology to therapeutic intervention. West Bengal State University, Barasat, North 24 Paraganas, 23rd October, 2009.

9. A Basu: Japanese Encephalitis Virus infects Neural Stem Cells and decreases their proliferation. Biology and Pathogenesis of Viruses: Molecular Insights, IISC, Bangalore, 4-5th May, 2009.

10. A Basu: The brain's response to Japanese Encephalitis virus infection: Do neural stem cells play a role? 15th SNIP Conference, Wuhan, China, 21st-24th April, 2009.

11. A Basu: Host pathogen interaction in Japanese Encephalitis Virus

infection: from bench to bedside; Department of Physiology, University of Calcutta, 6th April, 2009.

Fundings:

1. To elucidate the role of inflammasome and other molecular events leading to Hypoxia induced neuro inflammation [Funded by Life science Research Board, DRDO (No LSRB-213/EPB/2010)]
2. Dissecting molecular circuitries that regulate Progenitors Cell Response to Japanese Encephalitis Virus. (Funded by Department of Biotechnology, BT/PR8682/Med/14/1275/2007)
3. Evaluation of Minocycline as a neuroprotective and/or anti-inflammatory and/or anti viral drug in Japanese Encephalitis [Funded by CSIR, (27(0173)/07/EMR-II)]

Degrees Awarded (Ph.D.):

Manoj Kumar Mishra.

Development of a Novel *in vitro* Model of Alzheimer's Disease Employing Neurosphere Culture from TgAPP$_{swe}$PS1ΔE9 mice

Principal Investigator

Dr. Ranjit Kumar Giri

Research Fellows

Pankaj Ghate

Technical Assistant

Sanjay Kumar

Lab Attendant

Lalit Bidla

Alzheimer's disease (AD) is a progressive and irreversible neurodegenerative disorder. It is the most common cause of dementia worldwide. AD can be classified either as sporadic Alzheimer' disease (SAD) or familial Alzheimer's disease (FAD). Genetic studies of early onset FAD have identified three causative genes: amyloid precursor protein (APP), Presenilin 1 (PSEN1) and presenilin 2 (PSEN2). Mutation/s in these genes affect the stability or increase formation of Aβ peptides, specifically the more fibrillogenic Aβ_{1-42} peptides that forms the backbone of the amyloid (Aβ) cascade hypothesis. However, very little is known about exact role of beta amyloid peptides towards neurotoxicity. In order to study the mechanisms in AD associated neurodegeneration in humans, transgenic lines expressing human FAD genes were developed. Though these transgenic mice show beta amyloid deposits, astrogliosis, impaired learning processes and mild cognitive impairement, exact role of beta amyloid peptides towards neurotoxicity remains puzzled. Moreover, the effect of beta amyloid on various mature brain cells is not known. Therefore, an alternative model that retains the capacity to generate major cell types of brain and generates human beta amyloid peptides endogenously is needed. No such model is available to date.

Extensive researches have pointed out the presence of neural stem cells in adult and embryonic brain both in animals and in humans. These CNS stem cells posses the potential to differentiate towards major cell types of brain except microglia *in vitro* and *in vivo*. It is not clear why these cells fail to replenish the neuronal cell loss seen in AD, especially in hippocampus where CNS stem cells are enriched. Thus, we hypothesize that beta amyloid peptides might be affecting the normal

functioning of CNS stem cells. So, to recapitulate most of the pathological features of AD, such as, de novo beta amyloid production and to study its effect on major cell types of brain, my lab is working towards developing an alternative *in vitro* model employing CNS stem cells. According to Aβ cascade hypothesis, Aβ peptide is the central and key molecule in the development of AD. Therefore, endogenous production and multimerization of human Aβ peptides are essential features in developing AD model *in vitro*.

As shown in previous annual report, we have developed 4 separate neurosphere lines. Two of these were positive for HuAPPswe and HuPS1ΔE9 gene (Tg +ve) and two are negative (Tg –ve) which served as control. We have shown that Tg +ve lines express HuAPPswe and HuPS1ΔE9 transgenes at mRNA level (by RT-PCR) which is not present in Tg -ve neurosphere lines.

Previously, we have also shown the expression of human APP protein and its fragments in all transgenic positive neurosphere lines but not in transgenic negative lines by western blot analysis of neurosphere lysates and by immunohistochemistry (IHC). However, presence of beta amyloid peptides was not detected in any transgenic positive line. We speculated

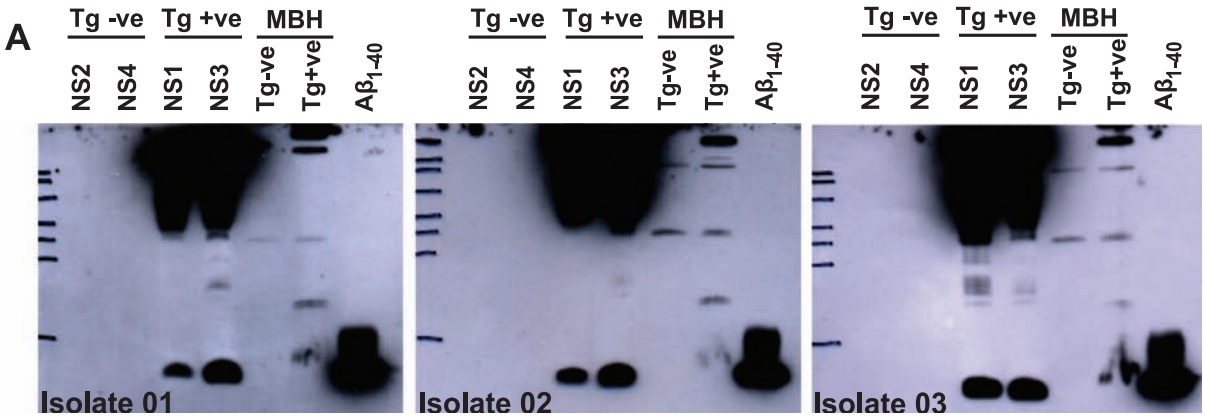

Figure1 Western blot analysis of Aβ peptides from culture supernatants (A). 60μg of total protein from Tg -ve and Tg +ve neurosphere culture supernatant was size fractionated in 16% Tris-tricine gel along with mouse brain homogenates (MBH) from Tg -ve and Tg +ve animals and 25 ng of beta amyloid peptide as positive control. Proteins were transferred onto a nitrocellulose membrane and immunoblotted with 6E10 antibody specific for human APP and its proteolytic peptides including Aβ peptides. The result indicates the presence of Aβ peptides only in Tg +ve but not in Tg -ve neurosphere culture supemantants. The densitometric analysis also confirmed the increased presence of Aβ peptide only in Tg +ve neurosphere cultures significant over Tg -ve neurosphere cultures (B)

that, intracellular beta amyloid pool might not be within detectable range by western blotting or Aβ peptides might have been released to extracellular space, the culture media. Therefore, we wanted to detect human Aβ peptides from culture supernatants of both Tg –ve and Tg +ve active neurosphere cultures. Interestingly, the western blot analysis of media concentrate indicated the presence of human Aβ peptides in all Tg +ve neurosphere lines but not at all in Tg -ve lines as shown in Figure 01. Moreover, these Aβ peptides are seen both as monomers as well as oligomers (seen as high molecular weight smear).

It is also known extensively that in AD brain, Aβ peptides accumulate extracellularly as senile plaques. Since neurospheres grow as three dimensional spheres and are actively secreting Aβ peptides, we wanted to explore this additional pathological feature in our proposed *in vitro* model of AD. Detection of $A\beta_{1-42}$ is the major step in addressing this issue as extracellular senile plaques in AD brain consists mostly of $A\beta_{1-42}$. In physiological condition $A\beta_{1-42}$ has a tendency to form beta sheet structure there by hindering its interaction with antibodies specific for $A\beta_{1-42}$. However, we utilized conformation dependent immunocytochemistry to unfold beta sheet structure of $A\beta_{1-42}$. Formic acid (FA) has been utilized previously to unfold $A\beta_{1-42}$ beta sheet structures. Therefore, it is speculated that neurosphere expressing Aβ peptide upon FA treatment will have more immunoreactions over untreated counterparts. As to our expectation, the intensity of Tg +ve neurosphere section is significantly higher in FA treated neurosphere

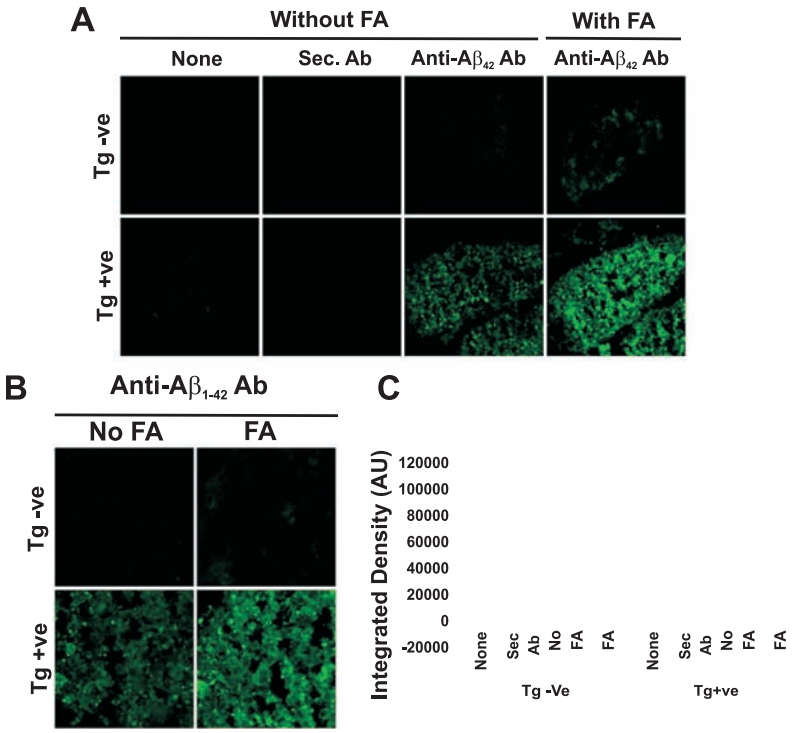

Figure 2 Immunohistochemical analysis of $A\beta_{1-42}$ in neurosphere sections. 10 µm sections were obtained from Tg –ve and Tg +ve neurospheres. Sections were treated with FA to unford β-sheet rich $A\beta_{1-42}$. Immunostaining was performed using antibody specific for $A\beta_{1-42}$. Result indicated vere high level of expression in Tg +ve neurospheres than in Tg –ve neurospheres (A, 20X). Moreover, Tg +ve neurospheres treated with FA have significantly more immunoreaction than without FA treated neurospheres (B, 63X; C). FA: Formic Acid, Ab: Antibody

sections than untreated counterparts. Furthermore, Tg +ve neurosphere has far more immunoreactions towards antibody specific for $A\beta_{1-42}$ than Tg –ve neurosphere sections as depicted in Figure 02. Thus, the results strongly indicate the expression, protein misfolding and accumulation of human $A\beta_{1-42}$ peptides in Tg+ve neurosphere cultures in parallel with transgenic mice brain. Collectively, it indicates the genesis of a newer *in vitro* model for AD that has the potential to address other pathological effect of Aβ peptides on various adult brain cells like neurons, astrocytes, oligodendrocytes and CNS stem cells.

Funding:

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

Principal Investigator

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Prion Diseases are a group of rare neurodegenerative disorders that include Kuru, Cruetzfeldt-Jakob Disease (CJD), Gerstmann-Straussler-Scheinker syndrome (GSS) and fatal familial insomnia (FFI) in humans; scrapie in sheep and goat, and bovine spongiform encephalopathy (BSE) in cattle. The main causative agent is an infectious protein which replicates by using cellular isoform of a membrane anchored glycoprotein (PrP^{C}) as substrate and converting it into disease causing isoform (PrP^{Sc}). Though the mechanism of conversion of PrP^{C} to PrP^{Sc} is yet to be unveiled but it has been reported that replication and subsequent aggregation and accumulation of PrP^{Sc} in brain parenchyma causes the neuropathological changes characteristic of prion diseases. The neuropathological features of prion diseases include amyloid plaque formation, spongiform degeneration of brain parenchyma, reactive astrogliosis and neurodegeneration. Various *in vivo* and *in vitro* models have been developed to have better insight to prion propagation but no model so far have been able to address effect of prion replication on various mature brain cell types including CNS stem cells. Neurosphere cultures containing CNS stem cells can be isolated from embryonic and adult mouse brain and can be cultured over several passages. Moreover, they are multi-potent, and can be differentiated to various brain cell types like neurons, astrocytes and oligodendrocytes. Therefore, this culture model provides opportunity to study the pathological effect of prion replication on different brain cell types separately or in combination. Furthermore, using this model, we also aim to address the effect of prion replication on CNS stem cells. Therefore, the immediate goals of the project are

1. Replication of mouse prion protein in CD1 and C57BL/6J mice neurosphere culture.
2. To study cellular pathology of prion disease using neurosphere cultures supporting prion replication.
3. To study the effect of prion replication on CNS stem cells fate determinants.

Last year, we had established neurosphere cultures from CD1 mouse embryos and shown the replication of prion protein in those neurosphere cultures. To validate the findings, in the current year we have extended the replication of prion protein in neurosphere cultures established from C57BL/6J mice. Both CD1 and C57BL/6J mice express wild type level of PrP^{C} and are homozygous for $PrnP^{a/a}$ allele. At present, we have established CNS stem cell lines from C57BL/6J mouse embryos. Two CNS stem cell lines have been isolated from C57BL/6J E15 embryos (Figure 1, A). Similar to CD1 mouse neurosphere cultures, these cell lines express PrP^{C} protein as shown in western blot analysis (Figure 1, B) and Immunohistochemistry (Figure 1, C). Since these cell lines express the PrP^{C}, substrate for PrP^{Sc} replication, we anticipate, they may support mouse prion replication. Once the neurosphere cell culture model for prion disease is established, we would like to address the 2nd and 3rd objectives using immunocytochemistry, protein biology and high-through-put gene expression and regulation systems.

Funding:

This work is supported by a grant from DBT (No.BT/PR10721/Med/30/105/2008) and NBRC core fund.

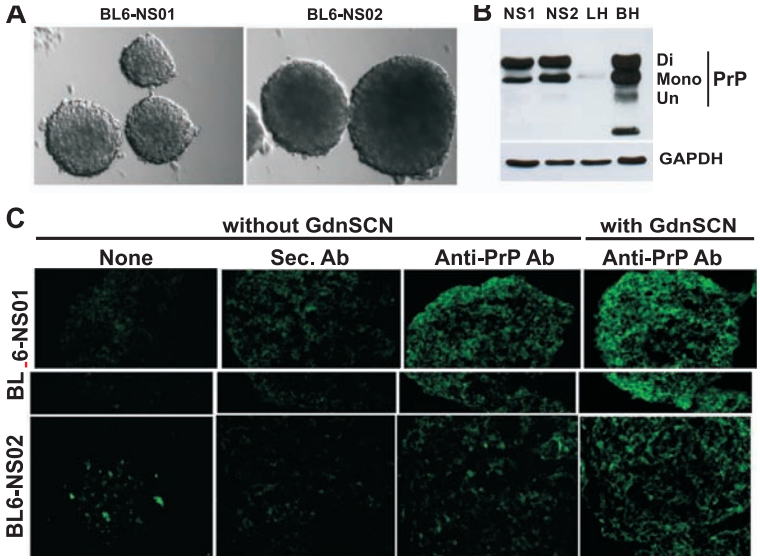
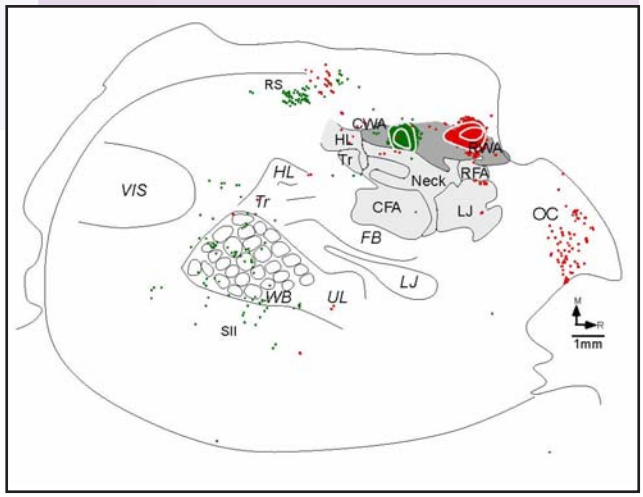


Figure 1: Expression of PrP^{c} in CNS stem cell cultures. A) Two independent neurosphere cultures were established from C57BL/6J mouse embryos. B) Western blot analysis demonstrating the expression on PrP^{c} in these cultures. Mouse liver homogenate (LH) and brain homogenate (BH) are negative and positive controls respectively. C) Immunohistochemical analysis indicates PrP^{c} expression in neurosphere sections of both the cell lines. However, exposure to GdnSCN has little effect on epitope retrieval of PrP^{c}. Un: unglycosylated; Mono: monoglycosylated; Di: Diglycosylated.

Systems & Cognitive Neuroscience



- Dr. Aditya Murthy
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Probing the control of action using saccadic eye movements

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

OBJECTIVES

Spatial programming of double-step saccades.

Saccades are goal directed movements that direct the fovea to points of interest in a visual scene. Being easily accessible and simple, with well-defined neural substrates, the saccadic system is a popular model to study sequential movements in goal directed behavior. A longstanding question in understanding the planning of sequential saccades is how the brain prepares a saccade to the second stimulus when the retinal vector to the second target becomes different from the saccadic vector needed to capture it following the first eye movement.

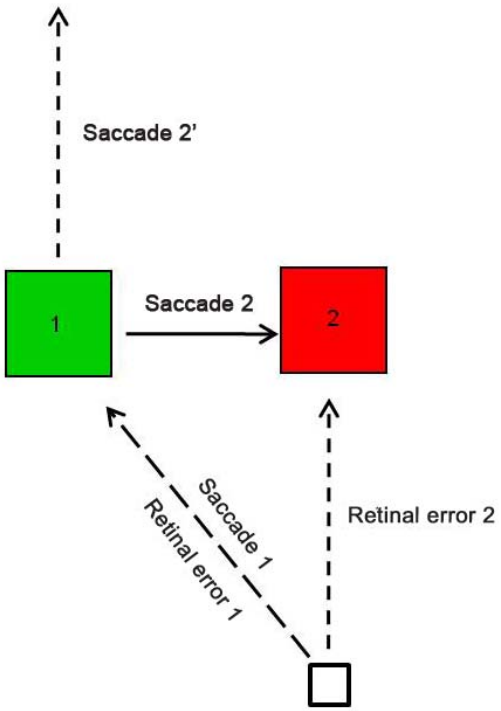

Figure 1

In a typical double-step task (Fig. 1), there are two possible solutions. The allocentric solution is to store in memory the spatial relationship between A and B, which can provide the vector A→B. The egocentric solution is to sum the retinal coordinates of stimulus B (retinal vector 2) with the coordinates of the effected eye displacement to A (saccade 1) to provide the coordinates of stimulus B in space. There is good psychophysical evidence for the existence of an internal signal of eye position or eye displacement in the brain that could help in computing the latter. However, how exactly the computation that involves an eye-position signal is implemented is unclear. We have examined the nature of this process at play in the computation and preparation of the second saccade motor vector.

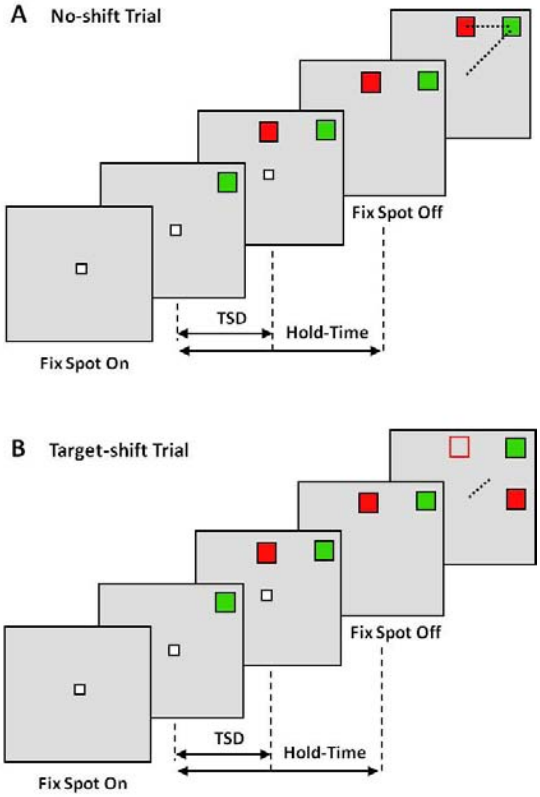

Figure 2

1. Planning of the second saccade before the end of first saccade

We used the Target-Shift (see Fig. 2) trials to determine if the motor preparation of the second saccade can occur before the end of the first saccade. The logic used was as follows: if the second saccade motor preparation cannot occur before the end of the first saccade and commences only after the first saccade, they should always be directed to the new, shifted position of the final target. However, if the second saccade motor preparation can begin before the end of the first saccade, one should find instances when these saccades end up at the old position of the final target. Across subjects we found that while in some trials the

second saccades landed up in the new position of the final target, in others, they were directed at the old location of the final target, consistent with the second alternative proposed above that motor preparation of the second saccade may begin before the end of the first saccade itself.

2. Preparation of the second saccade motor command – Feedback or Feedforward?

We examined if the preparation of the second saccade's motor command involves continuous updating of the retinal error of the final target with information about the ongoing first saccade (dynamic feedback) or relies on the efference copy of the planned first saccade before its initiation (predictive remapping). For this, we shifted the initial target in a fraction of trials to a new location (about 60 ms before the fixation spot disappears), while maintaining the retinal error of the final target. In half of such trials, the final target is then shifted during the execution of the first saccade, like in a normal Target-shift trial, to examine the effect of the initial target shift in the frequency of second saccades to the old. If the preparation of the second saccade's motor command occurs via dynamic feedback, shifting the initial target shouldn't affect the frequency of saccades to the old in these trials (when compared to their frequency in normal Target-shift trials) since the retinal error of the final target remains the same. On the other hand, if the preparation of the second saccade's motor command relies on the predictive remapping of the first saccade, then shifting the initial target, and thereby, changing the first saccade vector, would make the predictive signal ineffectual and hence, decrease the percentage of second saccades to the old. Nine out of ten subjects show the latter effect (overall, $P < 0.025$) suggesting the role of predictively remapped visual signal in the preparation of the second saccade motor command.

Brain Mechanisms of Action Control in Humans

Principal Investigator
Dr. Aditya Murthy

Because eye movements can provide a behavioral measure of sensorimotor processing and cognitive functions of the brain, their study can provide an elegant and simple system to understanding the neural basis of voluntary control. From animal, human lesion and neuroimaging studies, the major brain areas underlying saccadic eye movements have been identified. These include the parietal cortex, the dorsolateral prefrontal cortex, the frontal eye fields, the supplementary eye fields, the anterior cingulate cortex, the basal ganglia, the superior colliculus and the brainstem. Since goal directed eye movements involve participation of a number of different brain areas a conceptually challenging question is to understand how computations done locally in one area integrate or affect the computations performed elsewhere and how these computations contribute to goal directed behaviors. Last year we have used a new approach called Transcranial magnetic stimulation to study the role of the medial frontal cortex (supplementary eye fields) in collaboration with Dr. S. Neggers, Utrecht University, Netherlands.

OBJECIVES

TMS on the supplementary eye fields during a delayed saccade double-step task

Neurons in the supplementary eye fields (SEF) are known to be active during associative learning of saccades, during a shift of the current plan to a novel one based on visuo-motor associations, performance monitoring as well as for executive control. Based on these studies, we examined the role of SEF by reversibly disturbing its function while normal, healthy volunteers performed the delayed saccade task (with 40% Target-shift trials). As a control, the vertex was stimulated on a different session. Perturbing SEF function was hypothesized to compromise the ability for controlled behaviour i.e. the ability to switch to new plans when required, thereby facilitating the programming of saccades to the old final target position.

Disruption of 'controlled' behaviour by TMS on the supplementary eye fields

The percentage of trials in which the

second saccade went to the old position of the final target was significantly higher ($P < 0.05$) in case of TMS on SEF as compared to that on the vertex for seven out of ten subjects (Fig. 3). We also examined the second saccades that landed in a location mid-way to the old and new position of the final target (referred to as 'mid-way' trials from hereafter). Since the shift in the final target position is essentially a vertical one, I plotted the y-coordinates of the end-points of all second saccades in mid-way trials to find that the median of eye-positions showed a significant shift ($P < 0.025$) towards the old target for midways in TMS on SEF as compared to that on Vertex.

The above results show that TMS on SEF facilitated not only the total outcome of the decision process by increasing the frequency of second saccades to the old, but influenced the process itself on the whole by weighing the mid-ways more towards the old. This is consistent with the role of SEF in proactive executive control of action and suggests that its disruption can facilitate uncontrolled, almost 'automatic' behavior borne out of practice.

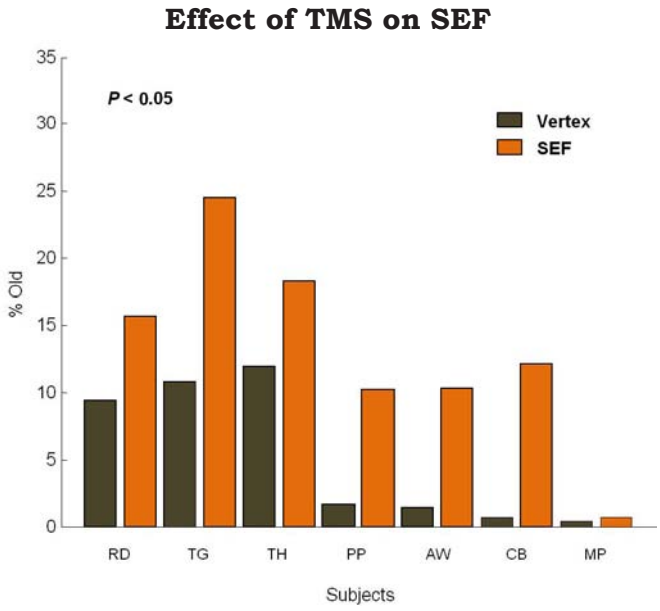

Figure 3

Neural control of action by frontal /basal ganglia networks

Principal Investigator
Dr. Aditya Murthy

To understand how neural networks instantiate saccade control we use the non-human primate model to study how the pattern of electrical activity in single neurons can be related to the computational models that we have proposed to account for behavior. In these series of experiments we train monkeys on similar tasks that human subjects have performed and record/ stimulate/microinject drugs onto single/groups of neurons in frontal cortex and basal ganglia to understand information processing in the so-called oculomotor loop in which information from the frontal eye fields (FEF), is relayed to the basal ganglia, processed and sent to the mediodorsal nucleus of the thalamus and sent back to the FEF. Here we propose to study the sensorimotor transformations in this loop in the context of how basal ganglia thalamocortical circuitry initiates actions, how actions maybe cancelled and reprogrammed by this circuit and how this circuit may help in the correction of erroneous actions. The long term goal of this project is to understand the neural representations that control our actions in basal ganglia/frontal cortex.

OBJECIVES

Control of decision-making by frontal cortex

Actions are typically made in dynamic environments, which occasionally force a reconsideration of planned actions. Instantiating such online control raises an interesting problem for the brain since interruption of the current motor program must occur by a competing motor program that begins later and is weaker in strength. To understand how changes of mind get expressed at the behavioral level we used a redirect task that entailed monkeys to change a planned saccade after suddenly presenting a second stimulus. Using intracortical microstimulation in macaque frontal eye field we have shown how we can track a changing action by measuring the systematic deviations from the evoked saccade during redirect behavior. We tested the predictions from three race models (GO-GO model; GO-STOP-GO and GO-GO+STOP) of redirect behavior. The GO-GO+STOP model that incorporated an active and spatially specific inhibitory mechanism to suppress the first

saccade could best predict the pattern of the deviation. The time to inhibit, as estimated from the deviation profiles, also matched that predicted from such a race model. Thus it appears that changes of mind require a covert short-acting but potent inhibitory process to inhibit the current inappropriate action, allowing the expression of the new action.

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1. **Murthy, A.,** Shorter-Jacobi, S.M., Thompson, K.G. and J. D. Schall (2009) Neural control of visual search by frontal eye field: Effects of target displacement on visual selection and saccade preparation. **Journal of Neurophysiology,** 101: 2485-2507.
2. K.M. Sharika, Supriya Ray and **A. Murthy** (2009) Attention for Action during Error Correction. **Progress in Brain Research**. 176: 227-244.
3. Ramakrishnan, A., Chokandre, S. and **A. Murthy** (2010) Voluntary control of multi-saccade gaze shifts during movement preparation and execution. **Journal of Neurophysiology** 103:2400-16.

Presentations:

1. Ramakrishanan, Ramakrishnan S. and A. Murthy. Tracking the decision as it changes: Supra-threshold microstimulation in macaque frontal eye field reveals how decisions are controlled. Soc. for Neuroscience Abstract (USA) 2009.
2. Gopal, P. Vishwanathan, A. Murthy. The Control of Eye Hand Coordination in a Redirect Task. Indian Academy of Neuroscience, Jaipur, India. 2009.
3. N. Bhutani, Ramakrishnan S., A. Murthy. Basal Ganglia and the Control of Sequential Eye Movements. Indian Academy of Neuroscience, Jaipur, India. 2009.

Funding:

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Collaborator:

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Prof. Madhuri Behari and Prof. Vinay Goyal, Dept. of Neurology AIIMS, New Delhi.

Injury induced plasticity in the cerebral cortex

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Ankit Sharma

We are interested in the neuronal plasticity of the cerebral cortex in response to injuries. Brain injuries have many ramifications, which could be due to alterations in neuronal activity, metabolism and blood flow at the site of injury. Apart from changes at the site of lesion, distant areas that are anatomically connected to the injured region fall into the realm of secondary reactions in the aftermath of an injury. All these changes could transform behaviour. The amount and nature of the ensuing behavioural impairment is determined by the size and location injury and also could influence post-injury recovery of behavioural functions. The multifaceted reactions that result from cortical injuries could be attributed to the ineffectiveness of most interventions. Loss of tissue could limit the extent of recovery at the site of impact. However, an in depth understanding of the ongoing cellular reactions becomes necessary for identifying effective therapy to prevent or reduce the severity of deficits at distant regions connected to the injured site. Our research attempts to understand the neuronal changes that occur at a region of cerebral cortex that is reciprocally connected to an injured area. We are examining the effect of stroke-like injuries of the motor cortex on neuronal functions of the reciprocally connected somatosensory cortex in adult rats.

Rats acquire somatic sensation by rhythmic movement of the large facial whiskers (~25-30 whiskers) over objects in the environment. Each whisker primarily projects to a group of neurons in the cortex and is the “principal whisker” for those neurons. Stimulation of the principal whisker generates the “centre receptive field”. These neurons also receive tactile information from

other whiskers which contribute to establishing "surround receptive field". Thus computing the nature of an object necessitates integration of the centre and the surround receptive fields. In the rat somatosensory cortex the various features of tactile sensation are transduced and processed in two main functional domains: the barrel column and the septal column. Various lines of evidence suggest that the barrel and its related circuits are involved in processing the spatiotemporal aspect of sensory information, whereas the septa and their related circuits are involved in the processing of temporally encoded information. In addition, there is also layer-specific processing of sensory information such that the layer 4 receives sensory input from the thalamus which is then transferred to output layers 2/3 (supragranular) and layer 5 (infragranular). We therefore examined the layer-specfic changes following stroke-like lesions of motor in neurons within the barrel column and the septal column of somatosensory cortex.

Photothrombotic lesions were produced in the whisker motor cortex of adult rats to mimic stroke. At post lesion day 7, the effects of lesion on neurophyisological and behavioural functions of whisker representation area of ipsilateral somatosensory cortex (barrel cortex) were determined. We recorded the spontaneous activity and stimulus evoked responses of neurons from layers 2/3, layer 4 and layer 5 from the barrel column and from the septal column. The centre receptive field for the neurons was determined by estimating the response magnitude to stimulation of the principal whisker. The responses to stimulation of the whiskers adjacent to the principal whisker generated the surround receptive field. The major findings of these experiments show that lesion in the whisker motor cortex produce differential effect on centre receptive field of neurons in barrel and septal columns of the somatosensory cortex. In lesioned animals, neurons within the barrel column showed higher spontaneous and evoked activities in comparison to controls. Whereas, in the septal columns the spontaneous activity of neurons did not differ significantly, but there was a reduction in the evoked responses of lesion animals in comparison to controls. Most significant changes in spontaneous and evoked activities of barrel and septal column neurons were observed in supra and infragranular layers. Lesions in the whisker motor cortex modified the surround receptive field of neurons in the somatosensory cortex. There is increase in the responses of neurons to stimulation of surround whiskers in all layers of both septal and barrel columns, suggesting that there is a change in excitation and inhibition of these neurons. These results imply that lesions in the motor cortex could result in interference with spatio-temporal aspects of somatosensation and hence affect the somatosensory behavioural functions. We therefore examined somatosensory behaviour in rats with motor cortex lesions. The lesioned animals showed sensory deficits in performance of a whisker-dependent tactile task called "Gap-crossing task". This study shows that focal lesions in a part of cortex does not produce generalized effect on neuronal activity of all functional columns in

anatomically connected intact regions. Rather, the lesion had specific effects on neurons belonging to different layers and different columns within the cortex. The atypical neuronal activity could be the reason for the deficits seen in the behavioural functions following stroke-like injuries in the cortex.

Presentations:

1. Rahul Chaudhary, Praseeda Venugopalan & V. Rema. Unilateral barrel cortex lesion results in long-lasting deficits in somatosensory behavior of adult rats. Society for Neuroscience Annual Meeting. Chicago, Illinois, October, 2009.
2. Sakthikumar M, Ethiraj Ravindran, Rahul Chaudhary and V. Rema. Effect of focal injury on distant, anatomically connected brain regions. Indian Academy of Neuroscience. Jaipur Dec. 2009.

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Brain Reorganization following Spinal Cord Injuries

Principal Investigator

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Research Fellows

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Project Assistants

Vishalini Sivarajan, Kanchan Bisht

The information-processing networks of the somatosensory areas of the brain involve both serial and parallel pathways. Any perturbation results in widespread effects throughout the system. Research interest in my laboratory centres around understanding the organization and information processing in the somatosensory and motor systems, and determining how these systems are affected by spinal cord injuries. We are also interested in developing technologies for recoveries from spinal cord injuries.

To understand the effects of spinal cord injuries on the brain, we perform unilateral lesions of the dorsal columns of the spinal cord, leaving spinothalamic and other ascending and descending pathways intact. As a result of these lesions the animals loose their fine tactile discrimination abilities. Using multiunit mapping and intracortical microstimulation techniques we determine the effects of these injuries on the somatosensory and motor areas of the brain. We use both primate as well as rodent models for our studies, because each model system offers specific advantages. The work done during the year is described below.

Brain reorganization following dorsal spinal cord injuries in primates. We have previously shown that the primary somatosensory area 3b and the somatosensory areas of the lateral sulcus (area S2, the secondary somatosensory area, and area PV, the parietal ventral area) undergo large–scale reorganization after unilateral lesions of the dorsal columns at cervical levels. In these somatosensory areas the intact face inputs expand into the deafferented hand regions. Since motor system depends on the sensory feedback for control of movements, we determined if long-term abnormal inputs from the somatosensory cortex affect the functional organization

of the motor cortex. Last year we reported our first results after mapping the motor cortex in monkeys with chronic lesions of the dorsal columns. We had reported that many months after unilateral lesions of the dorsal columns, the overall organization of the motor cortex remained normal, with face to hindlimb representations in a lateral to medial sequence. The threshold currents required to evoke movements were largely same as in the normal animals.

Our further experiments done during the year, and analysis of the data show that the relative area of representations of different body parts in the primary motor cortex of monkeys with the lesions does not change (Fig. 1). However, we found a significant difference in the nature of the movements of digit 1 (D1) or the thumb that are evoked from the motor cortex of the lesioned animals. In normal animals, at nearly all the stimulation sites the evoked D1 movement is flexion-

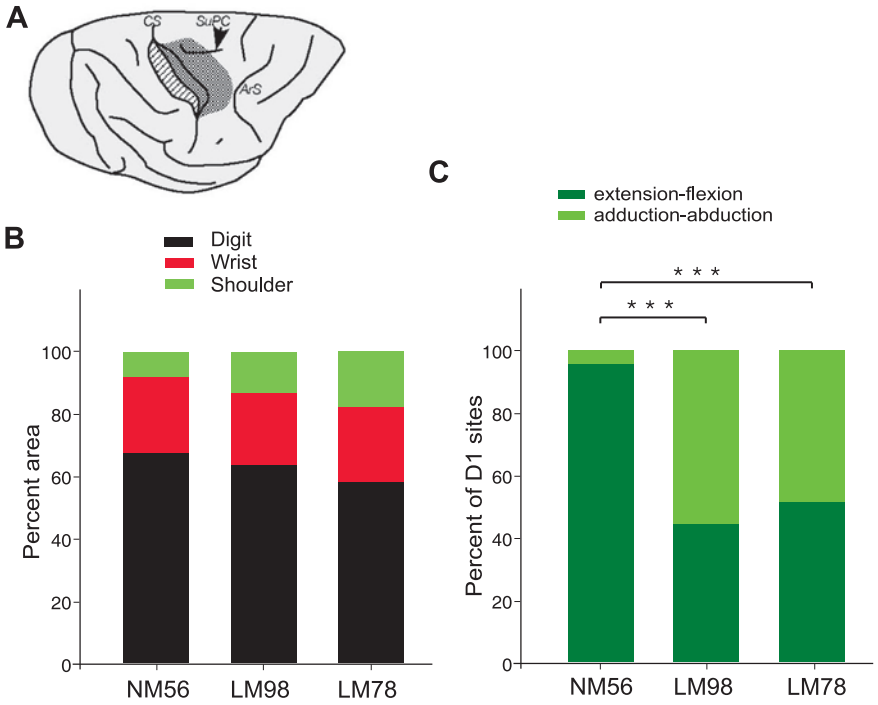

Figure1 (A) A dorsolateral view of the macaque monkey brain. The stippled region corresponds to the primary motor cortex and the rostrally adjacent motor areas; the hatched region shows the location of the primary somatosensory area. The central sulcus has been shown opened to illustrate these areas in the pre-central and post-central cortex. ArC, arcuate sulcus; CS, central sulcus; SuPC, superior pre-central dimple. (B) Relative area of representation of the digits, wrist and shoulder as a percentage of total area of these representations in a normal monkey NM56, and two monkeys with lesions of the dorsal columns - LM98 and LM78. The differences between the normal monkey and the lesioned monkeys were not significant. (C) The percentage of D1 movement sites from which flexion-extension, and adduction-abduction movements of the digit 1 (thumb) were evoked in the primary motor cortex of a normal monkey NM56, and two monkeys with lesions of the dorsal columns - LM98 and LM78. The differences between the normal monkey and the lesioned monkeys were highly significant ($P<0.001$).

extension. In the lesioned animals, the adduction-abduction movement is evoked at significantly larger number of sites, while there is a reduction in the percentage of sites from which extension-flexion is evoked (Fig. 1). These differences reflect the inability of the lesioned monkeys to use their deafferented hand for precision grip, which requires flexion of D1. Thus abnormal sensory feedback, which leads to altered behavioural use of the hand results in reorganization of the primary motor cortex of macaque monkeys.

Information processing in the hand area of the primary somatosensory cortex of monkeys. We are interested in determining how injuries to the spinal cord affect information processing and connectivity in the somatosensory cortex. We determined response properties of neurons in different parts of the hand representation in area 3b (the primary somatosensory cortex), when a particular location on the skin of the hand is stimulated. The data show that in normal animals, nearly all of the neurons in the D1 representation of area 3b primarily respond to the stimulation of the skin on D1; whereas, neurons in D2, D3, D4 and D5 representations respond to stimulation on any of these four digits, but rarely to the stimulation of D1 (Fig. 2). The results show that evolutionary advanced behavioural use of the increasingly opposable thumb in Macaca, an Old World monkey, has lead to concomitant changes in the intrinsic connections in the cortex.

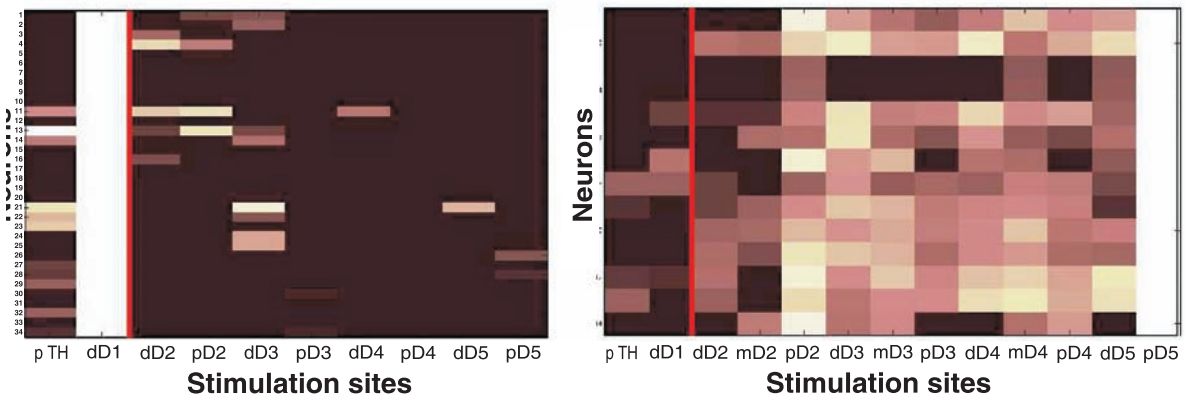

Figure 2. Activation of neurons in different parts of the hand representation in area 3b when different locations on the skin of the hand are stimulated at 1Hz. Each row in the panels shows normalized firing rate (see scale on the right) of a single neuron when stimulated at locations marked along the x-axis. The left panel shows activity of neurons whose receptive field was on the distal part of D1 (digit 1 or thumb), and the right panel shows activity of neurons whose receptive field was on the proximal part of D5 (digit 5 or little finger). Red lines separate D1 and the thenar pad (pTH) from rest of the digits for ease of visualization. Note that neurons in the D1 representation generally do not get activated when the hand is stimulated elsewhere. The neurons in D5 representation show activation when digits D2 to D5 are stimulated, but very little activity when D1 or pTH is stimulated. d, distal; m, middle; p, proximal.

Normal organization of the motor cortex in rats. In our previously published report (Tandon et al., Eur J Neurosci. 27:228, 2008), based on differences in the movements evoked by electrical stimulation of neurons in the motor cortex of rats under different depths of anesthesia, we have argued that the rat motor cortex has two separate representations of the whiskers. We suggested that the rostral whisker area (RWA), along with previously described rostral forelimb area (RFA) might be part of a second motor area. Based on these observations, we sought further experimental proof for the existence of two motor areas in rats. We used neuroanatomical tracers to determine cortico-cortical connections of the two whiskers areas, RWA and CWA (caudal whisker area), and compared the pattern of these connections to that of the two forelimb areas, RFA and CFA (caudal forelimb area). The results show that the sources of inputs to RWA and CWA are different (Fig. 3). Moreover, the connection pattern of RWA is similar to that of RFA, and the connection pattern of CWA is similar to that for CFA. The results strongly suggest that as for higher mammals,

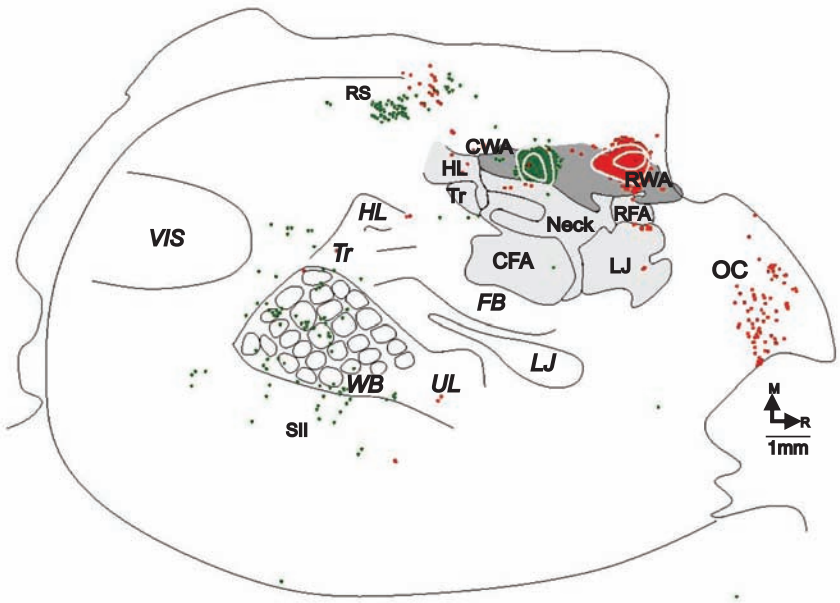

Figure 3. Ipsilateral cortical inputs to the caudal whisker area (CWA) and the rostral whisker area (RWA) of the rat motor cortex (shown in grey). Injections of fluoroemerald (green) and fluororuby (red) were made in these two areas, and the retrogradely labeled cells were plotted. Note that inputs to these two areas are different, supporting the proposition that these are two distinct areas. The major sources of inputs to the CWA area are the whisker barrel somatosensory cortex (WB) and the retrosplenial cortex (RS), whereas the RWA does not get many inputs from WB cortex. The inputs to RWA are from RS, orbital cortex (OC), and the CWA. Visual cortex (VIS) is shown for reference. UL upper lip; LJ, lower jaw; FB, forepaw barrels; Tr, trunk; HL, hindlimb; RFA, rostral forelimb area; SII, second somatosensory area, M, medial; R, rostral. The representations shown in italics are in the primary somatosensory cortex.

the rat motor cortex also has multiple motor areas.

Publications:

1. Shashank Tandon, Niranjan Kambi, Leslee Lazar, Mohammed Hisham and **Neeraj Jain** (2009) Large-scale expansion of the face representation in somatosensory areas of the lateral sulcus following spinal cord injuries in monkeys. **Journal of Neuroscience**, 29: 12009-12019.
2. Aatira G Nedungadi, G Rangarajan, **Neeraj Jain** and Mingzhou Ding (2009) Analyzing multiple spike trains with nonparametric Granger causality. **Journal of Computational Neuroscience,** 27:57-64.
3. Hui-Xin Qi, **Neeraj Jain,** Christine E Collins, David Lyon and Jon H Kaas (2010). Functional Organization of motor cortex of adult macaque monkeys is altered by sensory loss occurring in infancy. **Proc. Natl. Acad. Sci., USA,** 107: 3192-3197.

Presentations:

Abstracts:

1. Niranjan A Kambi, Shashank Tandon, Hisham Mohammed, Leslee Lazar, Radhika Rajan and Neeraj Jain: Topography of primary motor cortex in monkeys with dorsal spinal injuries. Neuroscience 2009, Annual Meeting of the Society for Neuroscience, Chicago, USA. Oct 17-21, 2009.
2. Leslee Lazar, Radhika Rajan and Neeraj Jain: Focal stimulation on the skin of the hand activated neurons over large regions of the hand representation in area 3b of macaque monkeys. Neuroscience 2009, Annual Meeting of the Society for Neuroscience, Chicago, USA. Oct 17-21, 2009.

Invited Presentations:

1. 'Advances in Biological Sciences', a National Conference organized by Department of Zoology, Panjab University, Chandigarh, India. March 29-30, 2010.
2. 'Challenges in Spinal Cord Injury Repair' a seminar organized by Dr ALMPG Institute, University of Madras. March 5, 2010.

Funding:

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Department of Biotechnology.

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Emergence of Connectivity in the Developing Auditory Cortex in Humans

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Earlier studies had shown that axonal connectivity in the human auditory cortex develops over a protracted period compared to other regions of the brain. Using immunohistochemistry for phosphorylated neurofilaments (SMI-312 and SMI-31), these studies demonstrated that neither cortico-cortical nor thalamocortical axons appeared to be present in the temporal lobe (future auditory cortex) until the first postnatal year. Their studies revealed that the marginal layer (future Layer I) appeared at 22GW and continued to increase in size until 4.5 months after birth. However, no other axons appear to be present in Layers II-VI of the cortex until 4.5 months after birth. They also demonstrated that there was an increase in the number of axons in Layers IV-VI starting at 1 year after birth. Axons could be seen in supragranular layers (Layers II and III) 3 years after birth and increased to resemble adult patterns only by 12 years. These earlier results suggested that the auditory cortex had a prolonged period of development compared to other human primary sensory cortices, which mature during the first postnatal year.

Our aim was to confirm the above results not only by immunohistochemistry but also by using RT-PCR (reverse transcription polymerase chain reaction) to detect neurofilament mRNA and western blots to detect neurofilament protein. To our surprise, we found that mRNA for neurofilament H (heavy chain) was present in the human temporal lobe (presumptive auditory cortex) in the second trimester (at 15GW, 19GW, 21GW and 26GW) and during the postnatal period (1 year - 4 years). Further, western blots using specific antibodies against SMI-312 and SMI-31 confirmed the presence of medium as well as heavy chain neurofilaments in the temporal lobe at these ages. Finally, immunohistochemistry was used to detect the presence of fibers labeled with SMI-312 and SMI-31 as early as 15GW in the temporal lobe. Interestingly,

we found that a fairly well-developed plexus of axons immunoreactive for both antibodies was present in Layer I and in presumptive layers V and VI at 15GW. Additionally, we found axons in Layer II and III, running perpendicular to the pial surface, with well-developed varicosities along their lengths at this age. The complexity of axons increased from 25GW until birth (40GW) wherein numerous fibers, could be seen in all layers of the auditory cortex (Figure1). Further, we found that the density of axons in almost all layers of the auditory cortex appeared to be adult-like at 9 months after birth when visualized using immunoreactivity to SMI-312 and SMI-31. The only exception was Layer II where at 9 months (postnatal), the immunoreactivity for neurofilaments was slightly less than that seen in adults. Taken together, our results suggest that the timeline for development of the human auditory cortex may in fact, be similar to that of other sensory cortices in the brain, such as that of the visual cortex. Our results also suggest that auditory input from auditory brainstem regions and the medial geniculate nucleus may reach the auditory cortex during the second trimester itself rather than after birth.

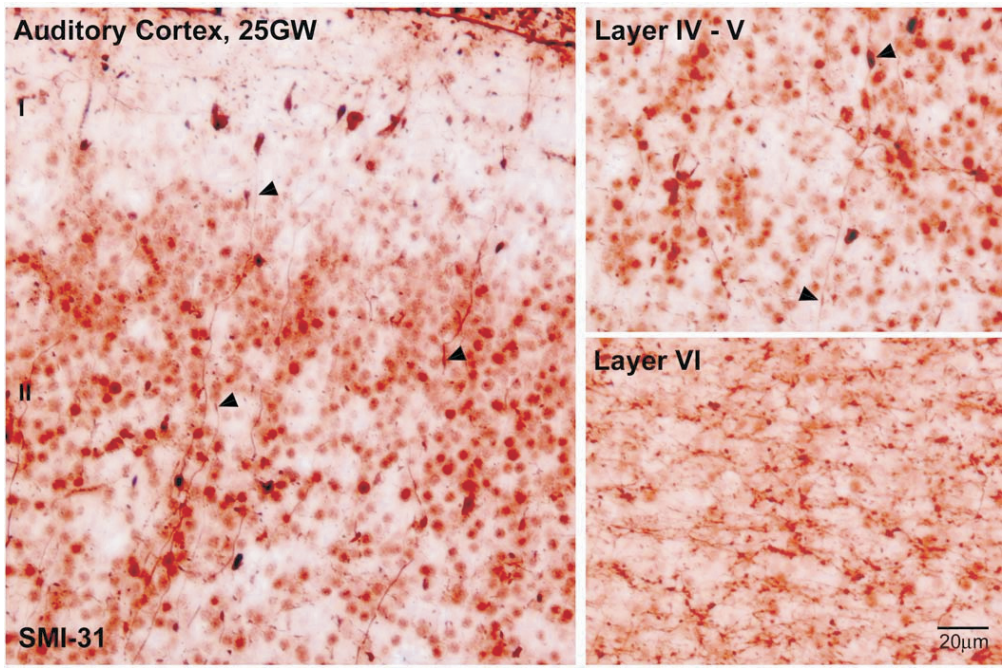

Figure1 (Left) Very fine fibers and axon terminals as well as a small number of axons oriented towards the pial surface can be seen in the deeper part of Layer I just below the dense band of fibers (arrowheads). Large varicosities are also seen along some of the fibers. Layer II consists of densely packed cells, some of which are labelled for SMI-31. **(Layer IV-V)** SMI-31-positive axons (arrowheads) are also present at the junction of Layers IV and V, interspersed between cells. **(Layer VI)** A dense plexus of SMI-31 immunoreactive fibers is present in presumptive Layer VI of HG. Scale bar = 20µm.

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Neurogenesis in the Song Control System of Zebra Finches

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An interesting research question is to attempt increasing or upregulating endogenously occurring neurogenesis in adult brains to repair damage caused by different lesions or neurodegenerative diseases. The songbird brain provides an excellent model system to study adult neurogenesis. In these species of birds (a well-studied example being zebra finches), new neurons are continuously produced in adult life by the ventricular zone and are then incorporated into discrete neural circuits, some of which are important for singing and song learning. We are interested in studying whether the opioid system (consisting of endogenous opioids and their receptors) modulates adult neurogenesis in zebra finches, since it is known to affect neuronal and glial proliferation. 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.

We used quantitative RT-PCR and in situ hybridization to demonstrate that μ and δ-opioid receptors are expressed by the VZ of adult male zebra finches, as well as other cells in the surrounding brain parenchyma. In order to confirm that cell proliferation is affected by the opioid system, primary cultures of adult zebra finch VZ cells were maintained and treated with the opioid antagonist naloxone as well as met-enkephalin (an endogenous opioid), followed by

treatment with the S-phase marker BrdU (5-bromo-2-deoxyuridine) or EdU (ethynyl deoxyuridine). Whereas naloxone treatment led to a significant increase in cell proliferation in culture, treatment with met-enkephalin decreased cell proliferation. Systemic administration of naloxone (2.5 mg/kg body weight) for four days in adult birds (both male and female) also led to a significant increase in cell proliferation in the VZ, compared with saline-treated controls. Interestingly, we also found that the highest increase in cell proliferation occurred in the ventral subdivision of the VZ at the level of the anterior commissure in zebra finches. Since this subdivision of the VZ is known to give rise to GABAergic interneurons throughout the telencephalon including song control regions, our results suggest that the endogenous opioid system may modulate the production of different cell types mainly from the ventral proliferative areas of the zebra finch brain by inhibiting cell proliferation. Our results also suggest that natural variations in the endogenous opioids in some of the song control nuclei during singing may modulate the number of cells (both neurons and glia) being produced by the VZ, which would likely influence the composition of the song control nuclei in zebra finches.

Further, preliminary data from our lab suggests that zebra finch VZ cultures treated with the δ-OR agonist SNC 80 are slightly more differentiated than saline treated controls (Figure1). That is, individual neurons in culture (which are labelled with the neuronal marker Tuj1) have a greater number of neurites compared to those from controls. There is also a small increase in cell proliferation following treatment with SNC-80, suggesting that μ- and δ-ORs may have opposite effects on cell proliferation, since met-enkephalin (which is a μ-OR agonist) decreases cell proliferation.

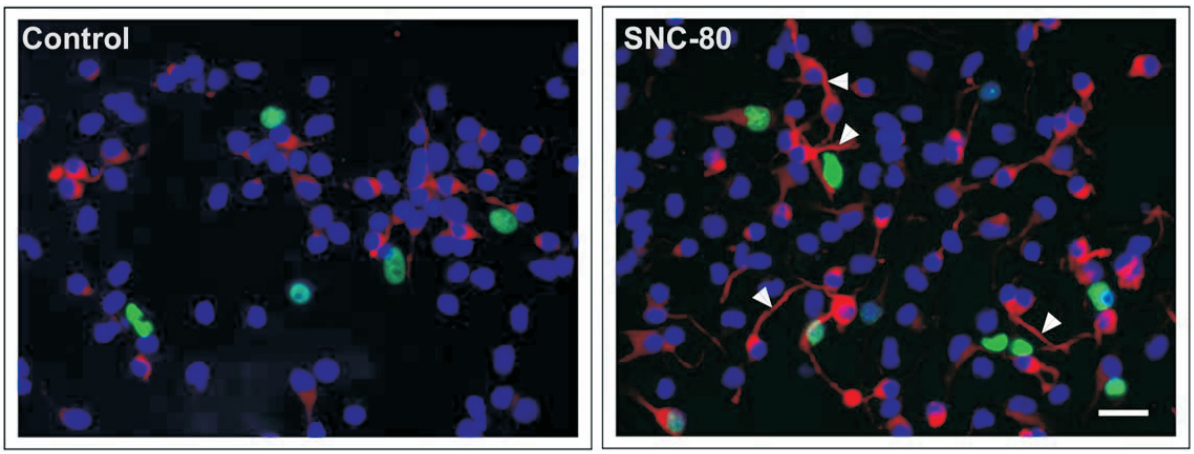

Figure1 Treatment of zebra finch VZ cultures with the δ-OR agonist SNC 80 leads to an increase in the outgrowth of neurites (arrowheads) in differentiating neurons labelled with Tuj1 (red), compared to a saline-treated control culture. Nuclei in both cases are labelled with DAPI (blue) and some of the nuclei are also labelled with the S-phase marker EdU (green) showing that they are undergoing proliferation. Scale bar = 20μm.

Publications:

1. Khurshid N, Jayaprakash, N, Hameed, LS, Mohanasundaram, S and **Iyengar S** (2010) Opioid modulation of singing in male zebra finches (*Taenopygia guttata*). **Behav. Brain Res**.208; 359–370.

Presentations:

1. Soumya Iyengar: Development of the Human Auditory Cortex – Neuroanatomical Studies. Psychology Dept., Vanderbilt University, Nashville, TN, USA. October, 2009.
2. Soumya Iyengar: The human auditory cortex – a developmental timeline. National Programme on Perception Engineering (Technical Workshop). NBRC, Manesar, December, 2009.
3. Arvind S Pundir, Senthil Krishnasamy, Souvik Kar, Bishan S Radotra, Praveen Kumar, PC Dikshit, Soumya Iyengar: The human auditory cortex during the third trimester and at term. Poster presented at the Annual Meeting of Society for Neuroscience, Chicago, IL, USA. October, 2009.
4. Arvind S Pundir, Bishan S Radotra, Praveen Kumar, PC Dikshit, Soumya Iyengar: Development of the perinatal and postnatal human auditory cortex. Poster presented at the Annual meeting of the Indian Association of Neurology, Jaipur, December 2009.
5. Parthiv Haldipur, Upasana Bharti, Chitra Sarkar, Corinne Alberti, Soumya Iyengar, Pierre Gressens, Shyamala Mani: Preterm delivery alters the developmental program of the cerebellum. Poster presented at "Frontiers in Organogenesis", a meeting organized by the Centre for Developmental Biology, Kobe, Japan, March 2010.

Funding:

1. Effects of altering the levels of neuronal proliferation on the learning and production of song behavior in male zebra finches awarded in 2007. This work is supported by NBRC Core and DBT funds.
2. Opioid Modulation of song in Male zebra finches awarded in 2010. This work is supported by NBRC Core and DST funds.`

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

Principal Investigator

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Technical Assistants

Sumit Mahapatra

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. While photoreceptors progressively degenerate, the inner retinal neurons, especially retinal ganglion cells (RGCs), which send visual signals to the brain, are relatively preserved, at least initially. Based primarily on this, several novel therapeutic strategies, such as stem cell transplantation and implantation of a prosthetic device have been designed. A retinal prosthesis is an electronic device designed to transform visual information into a spatiotemporal set of electrical stimuli which are applied to the surviving retinal neurons via an array of microelectrodes. The underlying assumption is that the information about the specific components of the visual scene would be correctly encoded in the form of electrical stimuli which will be transferred to specific retinal neurons. Similarly, the transplanted stem cells are expected to differentiate into photoreceptors which would synaptically connect to the surviving retinal neurons. These treatment approaches have shown great promise in recent years, but the clinical outcome has so far been limited. Our lab is interested in understanding normal retinal circuitry, how it is altered after photoreceptor degeneration, and how these treatment strategies can lead to better functional recovery.

We have been studying a specific group of RGCs which express brn3 transcription factors, in terms of their size, spatial distribution, dendritic arbor, projections and co-expression of other ganglion cell markers. We have found evidence that the brn3-expressing RGCs exclusively carry

image-forming visual information. We have also found that a specific subtype of intrinsically-photosensitive ganglion cells, the M1 cells do not express brn3 (Fig.1). Considering that brn3-expressing RGCs constitute only about 35% of all cells in the ganglion cell layer, they offer a more specific target for electrical stimulation for the treatment of retinal degeneration.

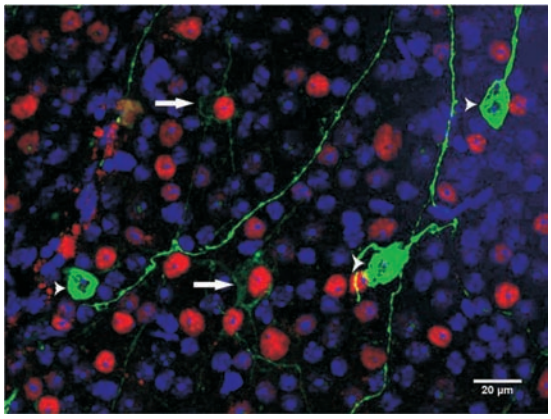

Figure1: The transcription factor brn3 is expressed by about 35% of cells (red) out of all cells in the ganglion cell layer (blue). A specific type of intrinsically-photosensitive cells, the M2 cells (light green, *arrows*), but not the M1 cells (bright green, *arrowheads*) express brn3.

We have also been studying structural and functional alterations in retinal circuitry following photoreceptor degeneration. We have recently found that loss of photoreceptors leads to upregulation of synaptic activity selectively in amacrine cells. These results have implications, not only in understanding the disease process and in improving the therapeutic strategies for retinal degeneration, but also in unraveling how adult retinal circuitry is maintained and functions normally. For example, we are testing the hypothesis that GABAc receptors on the bipolar cell axon terminal are critically required for the RGCs to be able to precisely encode and send visual signals to the brain.

In another project, we have found evidence that Mueller glial cells undergo dedifferentiation after photoreceptor degeneration and may act like stem cells. Among other cell-based therapeutic approaches we are evaluating how Mueller cells can be promoted to differentiate into rods and cones after photoreceptor degeneration.

Publications

1. Smith RG, **Dhingra NK** (2009) Ideal observer analysis of signal quality in retinal circuits. **Prog Retin Eye Res,** 28: 263-288.

Presentations

1. NK Dhingra: Remodeling in Third-Order Retinal Neurons After Photoreceptor Degeneration. Invited talk at IIT, Delhi, July 15, 2009.
2. NK Dhingra: Invited to chair a symposium on Neurophysiological Basis of Complex Behaviors, and present on Retinal Degeneration in an Inducible Animal Model – Biochemical, Morphological, Physiological and Behavioral Correlates in International Conference on Neuroscience Updates & ISN, APSN, IBRO & SNCI School, Cochin, December 7-14, 2009.
3. S. Nagar, S. Sethuramanujam, V. Jain, P. Cherukuri, NK Dhingra: Remodeling of Third-Order Retinal Neurons Following Photoreceptor

Degeneration. 27th Annual Conference of the Indian Academy of Neurosciences, Jaipur, India; December 18-20, 2009.

4. V. Jain, NK Dhingra: Expression of Melanopsin by Brn3-Positive Retinal Ganglion Cells in Mouse. 27th Annual Conference of the Indian Academy of Neurosciences. Jaipur, December 18-20, 2009.

5. NK Dhingra: Invited to present at a brainstorming meeting by Society for Biomedical Technology, DEBEL, DRDO regarding Bionic Eye in India, Bangalore, January 16, 2010.

Funding

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Neural Network Mechanisms Underlying Spatial Learning And Navigation

Principal Investigator

Dr. Yoganarasimha Doreswamy

Research Fellows

Apoorv Sharma, Guncha Bhasin

One of the fundamental challenges of neuroscience is to understand how the brain constructs higher-order representations of experience and how those representations are stored and recalled as conscious memories. Place cells of the hippocampus are an outstanding model system for deciphering the neural network mechanisms by which the brain constructs these cognitive representations from multimodal input. The discovery of hippocampal "Place cells" which selectively fires at a specific location in an environment, lead to the suggestion that the hippocampus may form the locus of a "cognitive map" of the surrounding environment. The hippocampus is critically involved in certain forms of spatial learning, context-dependent learning, and declarative memory. Despite years of research, elucidation of the precise computations performed by the hippocampus has been hampered by a limited knowledge of representations from its input brain areas. The medial entorhinal cortex receives major input from the dorsal presubiculum and retrosplenial cortex, which contain directionally and spatially tuned neurons, and from postrhinal cortex, which is connected with visuospatial regions of the neocortex and has been linked to contextual processing. The lateral entorhinal cortex receives major input from the perirhinal cortex, which is connected with unimodal sensory areas and appears to be involved in the processing of configurations of objects. Both medial and lateral entorhinal cortex provide inputs to different sub-regions of the hippocampus for creating conjunctive representation of the external environment. While, the role of perirhinal cortex in nonspatial information processing has been documented, the postrhinal cortical neurons are weakly spatially modulated, indicating that other brain areas may be involved in transfer of spatial information to the entorhinal cortex. Subicular complex (comprising of subiculum proper, presubiculum and parasubiculum), receive sensory inputs from different cortical areas and connects to the hippocampus and entorhinal cortex, two major

brain areas involved in processing of spatial information. Based on anatomical connectivity, subiculum has been regarded as both an afferent and efferent area of the hippocampus. Subiculum receives projections from the hippocampus; also it connects to superficial layers of the entorhinal cortex, which are the input layers to different hippocampal subfields. Dorsal presubiculum (also named as postsubiculum), is also connected to anterodorsal thalamic nuclei (containing head direction cells), which encode the current head direction and serve as internal compass for the animal. Thus, the subiculum may act as an interface between these brain areas in the integration of spatial and directional information.

Subicular neurons show directional and locational correlates, although the spatial tuning has been reported to be less specific than that of the hippocampal place cells. Further, theta modulated place by direction cells have been reported in postsubiculum, which may act as internal units allowing updating of position from one location to another based on the current directional heading. The subiculum neurons also encode head angular velocity and running speed, two properties that are necessary to allow self-motion information to update representation of head direction and location. Considering the anatomical connections with other brain regions involved in spatial and directional information processing, it is essential to understand the functional properties of subicular neuronal firing in order to identify the amount of processing performed by different brain areas. Our study will result in comprehensive characterization of different types of subicular complex neuronal response during spatial navigation and learning, which in turn help in determining the precise role of hippocampus in information processing. Recording of large population of neurons in vivo using multitetrode electrophysiological recording technique in different sub-areas of subicular complex simultaneously, will result in dissociating the dynamics of representations within this area and also lead to better understanding of the relative contribution of different brain regions in information processing.

Presentations:

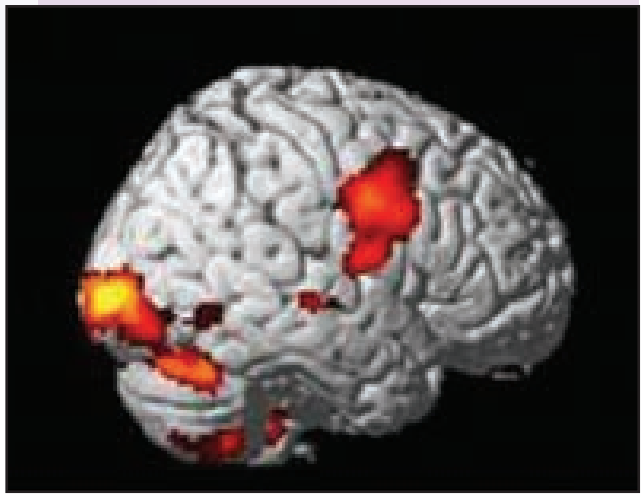
D. Yoganarasimha: Representation of external environment in place cell and head direction cell networks. Symposium on Neurophysiological Basis of Complex Behaviors. International Conference on Neuroscience Updates & ISN, APSN, IBRO & SNCI School. Centre for Neuroscience, CUSAT, Cochin, December 7-14 2009.

Funding:

This work is supported by NBRC Core funds.

Computational Neuroscience and Neuroimaging

Dr. Nandini Chatterjee Singh
Prof. Prasun Kumar Roy
Dr. Pravat Kumar Mandal



Cortical network for reading words in Devanagari

Principal Investigator

Dr. Nandini Chatterjee Singh

Research Fellow

Tanusree Das

Project Assistants

T. Sumathi

Background: The advent of functional neuroimaging has provided a unique opportunity to study the representation of different languages in the human brain. Unlike spoken language, which is acquired through immersion, reading is acquired only through instruction. Reading provides a unique example of neuroplasticity, in that brain networks meant for visualizing and hearing develop new connections in order to map units of sound onto units of a writing system. Our laboratory is currently interested in focused on understanding how this remarkable process is achieved in adults and children.

Earlier, functional neuroimaging studies have established cortical networks for reading alphabetic, scripts like English and French, syllabic scripts like Japanese and logographic scripts like Chinese. The writing system of Hindi, called Devanagari, is different from all of these in that it is an alphasyllabary, with an unusual blend of alphabetic and syllabic properties. The basic written unit in the script is an Akshara, which is either a vowel in full form or a consonant with an embedded vowel/ vowel diacritic. Hence, every akshara is a syllable, which can be broken down into constituent phonemes. Devanagari is a largely transparent script, with almost one-to-one mapping of sounds onto these units. It has a distinct orthographic layour and is non-linear in nature, with consonants arranged in left-to-right order, but vowels placed on the sides, above or below the consonant. Although about 33% of the Indian population speaks Hindi of which around 200 million use the Devanagari script (Singh, Solanki and Bhatnagar, 2008, UNDP report, 2004), very few studies have ventured to investigate the neural reading networks in Devanagari (T. Das et al, 2009). There is currently no information about the different cortical areas that participate in reading an alphasyllabary. We use functional brain imaging to study the reading network for Devanagari,

In this study we used functional neuroimaging to ascertain the cortical reading network when 10 native speakers of Hindi, read only linear words in Devanagari. As shown in Fig.1 we found that reading linear words in Devanagari exhibit activations in superior temporal gyri and occipitotemporal areas as seen in an alphabetic script like English; and left inferior parietal lobule as observed in a syllabic script like Japanese Kana. Akin to other word reading studies, we found activation in the mid-fusiform gyrus (visual word form area, BA 37). Region of interest analysis showed involvement of left superior temporal gyrus (BA 41), similar to that seen for alphabetic scripts and inferior (BA 40) and superior parietal (BA 7) lobules, similar to those seen for syllabic scripts. Our findings suggest that the reading network for an alphasyllabary includes cortical areas involved in reading both alphabetic and syllabic writing systems.

Publications:

1. T. Das, U. Kumar, R. S. Bapi, P. Padakannaya and **N. C. Singh** (2009) Neural representation of an alphasyllabary – the story of Devanagari. **Current Science,** 97, 1033.

Funding:

This work is supported by NBRC core.

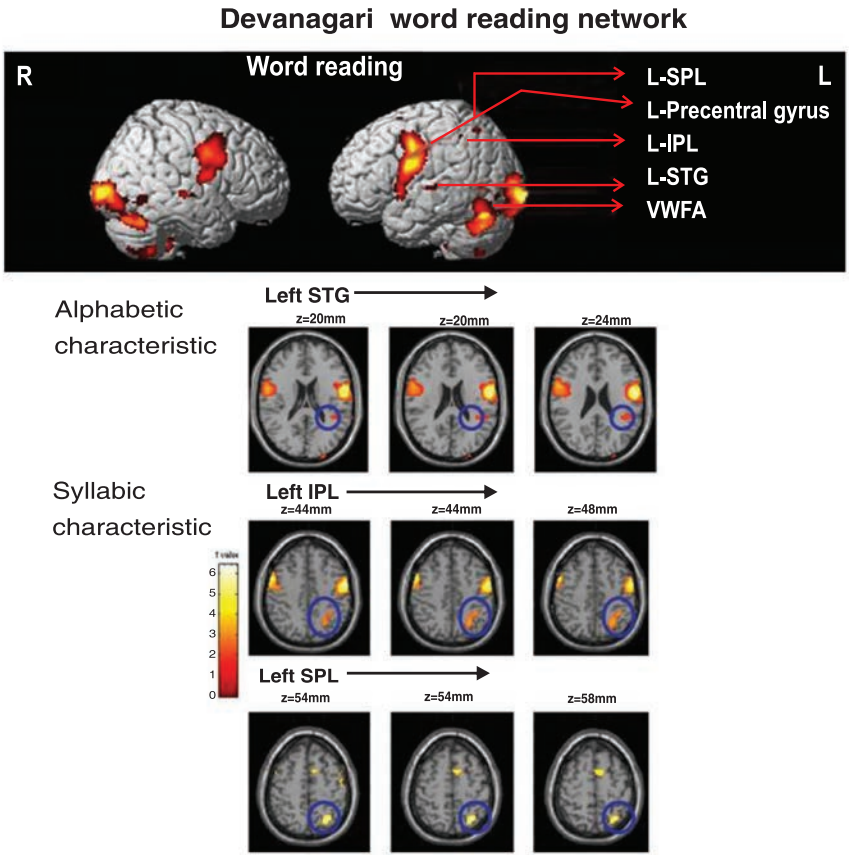


Figure 1: Cortical reading network for Devanagari shows alphabetic and syllabic features.

Distinct cortical pathways for reading distinct scripts (the case for Hindi and English)

Principal Investigator

Dr. Nandini Chatterjee Singh

Research Fellow

Tanusree Das

Background: The multilingual environment of India not only promotes learning to speak multiple languages but the educational system ensures learning to read in at least two scripts, namely one Indic language and English. Little is known about how the brain accommodates the learning of distinct scripts and our a second area of interest in our laboratory has been to study biscriptals, namely bilingual individuals reading two scripts, in particular English and Hindi and the effects of age of acquisition and proficiency in the neural pathways recruited during reading.

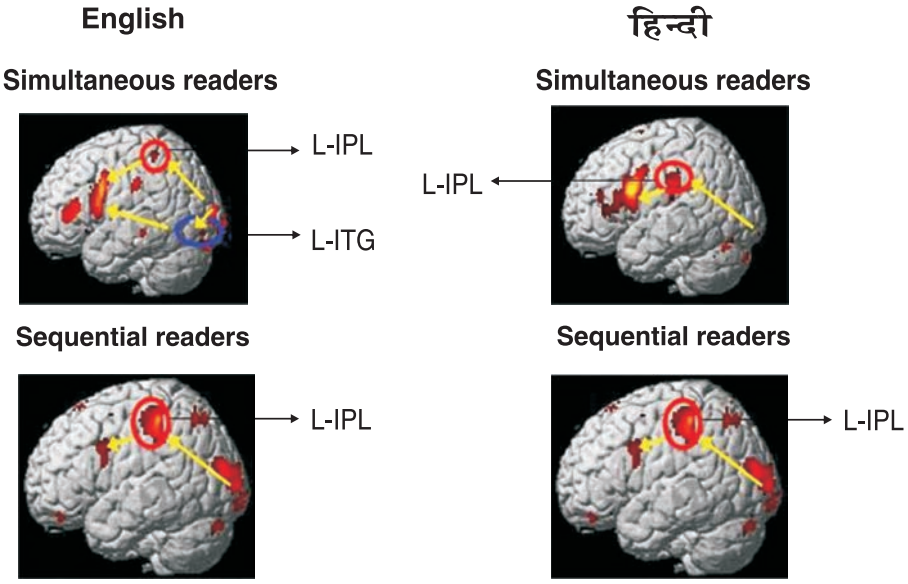
Hindi and English are not only written in different scripts but are also distinct orthographies. Orthography is sound-letter mapping. While Hindi written in Devanagari script has a transparent orthography with almost unique letter-to-sound mapping; English written in Roman script has an opaque orthography with one letter representing many sounds (eg, c/ough/, b/ough/). The acquisition of reading in populations learning to read two languages can occur in two possible ways, namely in a simultaneous manner or a sequential manner. We studied both groups of bilinguals, those who learn to read both Hindi and English simultaneously around 5 years are called simultaneous readers as opposed to sequential readers, who learn to read the native Hindi at 5 years of age and English after age 7 years of age. As shown in Fig. 2, our functional neuroimaging results showed that early simultaneous readers show distinct cortical pathways for reading distinct orthographies (namely English and Hindi) whereas the late sequential readers show a common pathway for reading both English and Hindi.

Long term goals Two new projects have been introduced in the laboratory namely

a) Identification of the neural correlates for dyslexia in Devanagari.

b) Comparing speech and music networks in children with autism spectrum disorder,

Word reading networks in Hindi and English



Publications:

1. T. Das, R. S. Bapi, P. Padakannaya, and **Nandini C Singh** (2010) Cortical network for reading linear words in an alphasyllabary. **Reading and Writing** (In Press)
2. U. Kumar, T. Das, R. S. Bapi, P. Padakannaya, R. M. Joshi and **Nandini C Singh** (2010) Reading different orthographies: An fMRI study of phrase reading in Hindi-English bilinguals. **Reading and Writing,** 23, 239-255.

Presentations:

1. N.C. Singh: Distinct Reading routes for deep and shallow orthographies in simultaneous biliterates – a functional imaging study, Abstract, Human Brain Mapping, San Francisco, USA, June 2009.
2. N.C. Singh: Influence of native language reading networks on the second language – a fMRI study, Abstract, Scientific Studies for Reading, Boston, USA, June 2009.
3. N.C. Singh: Fourier transforms, Novel applications in Neuroscience, Delhi University, March 2010.

Funding:

Research grant from Department of Science and Technology.

Collaborators:

1) D. Prakash Padakannaya, Professor & Coordinator for UGC Innovative Program on learning disability and dyslexia, Department of Psychology, University of Mysore.
2) Dr. R S Bapi, Dept of Computer and Information Sciences, University of Hyderabad.
3) Dr. Kenneth Pugh, Haskins Laboratories, New Have, CT, USA.

Spatiotemporal Processing and Information Transmission in Brain

Principal Investigator

Prof. Prasun Kumar Roy

Research Fellow

Suhela Kapoor

Project Assistant

Vinay Shukla

A seminal challenge in brain research and neuroscience is to decipher how flow processes occur, whether that of information, electrical current, drugs, cells or tissue displacement, across the layered brain extent. One needs quantitative matrix (tensor) approach that can account for, and can furnish a quantitative description, of flow processes and its neuromodulation across brain. We have developed the methodology of dynamic functional tensor neuroimaging and obtained accurate measurement of matrix-tensor maps to describe flow and deformation processes, information flux or connectivity in the brain. The research has considerable potentiality of applications to clinical medicine as well as to biological engineering, especially for diagnosis, therapy and neurophysiological investigations. For instance, the MRI tensorial imaging technique to determine the stress-strain disturbance and in obstructive blood or CSF flow has been developed, alongside patenting the procedure jointly with Delhi University. The methodology has potential applications in predicting early thrombogenesis and intracranial tension in dysfuntional flow of blood or CSF respectively. The overall objective of this program is to comprehend the physiological or pathological dynamics of transport or flow processes in the brain, whether that of fluids, tissue, energy or information.

Energy Flow Mapping and Heat Tensor Imaging:

The spatiotemporal mapping of the distribution of energy transmission across the brain, is required for some essential inputs in diagnostic and therapeutic management in neurology, oncology and radiology. Using the MRI scanner platform, we have also developed the novel technique of these tensor imaging procedures, including determination of other transport or mobility indices (matrices) of the brain, such as the conduction/ convection tensor, deformation tensor, as well as thermal conductivity tensor imaging,

a multimodal imaging approach. Conventionally, tissue heat energy flow conductivity is assumed as scalar, which induces errors in obtaining proper heat flow distribution. Using thermodynamics principles, we evolve a method for constructing heat conductivity tensor image of a spatiotemporally extended tissue or an organ, using an MRI scanner (fig. 1 a,b). Our noninvasive imaging methodology is quantitatively validated with over 90% accuracy, to the values of the transport parameters of the tissue measured directly by invasive probes. We delineate the possible applications of this novel imaging modality to clinical problems involving biological heat transfer equations, such as planning of hyperthermic treatment for paediatric hypoxia-ischemia and brain tumours, or for electrode localization in deep brain stimulation during Parkinson's disease (Fig. 1c).

Imaging-enabled Regenerative Intervention in Stroke

Utilizing MRI-based finite element analysis of brain parenchyma, the study of spatiotemporal mobility of endogenous reparative neuroblasts across the brain is a potential area for regenerative therapy in stroke and vascular dementia. We develop a quantitative analysis of neurogenesis and progenitor cell migration from subventricular zone (SVZ) under influence of erythropoietin/ IGF2-based drugs that can be enabled to cross blood-brain barrier (Fig.2 a,b). By means of the consequent NFκB pathway modulation, we develop the cellular flow dynamics using the nonlinear differential equations for neural stem cell formation in the SVZ . Thereafter we formulate the NPC migration process that is known to be thermodynamically coupled to the CSF flow dynamics, the migration occurring

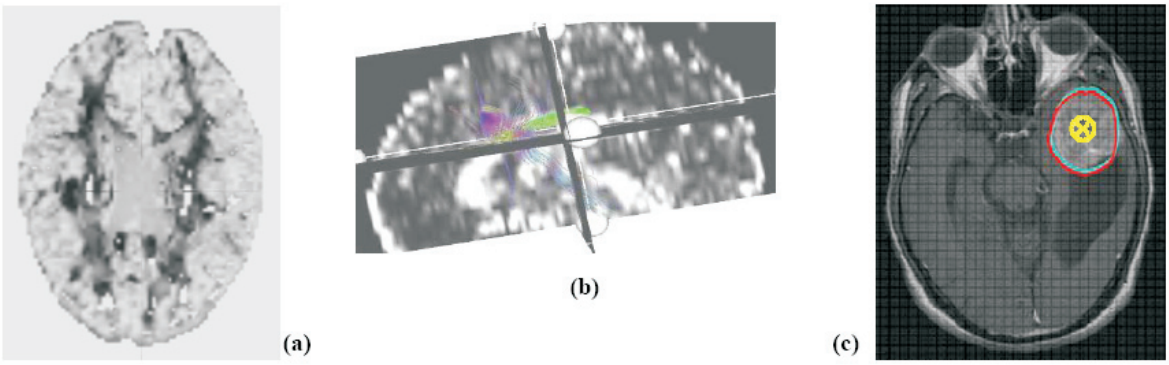


Figure1(a) Heat conductivity tensor image (trace plot) of brain; (b) Heat Tractography across brain tissue showing pathways of energy flux: saggital view; (c) Energy Flow Mapping (EFM) of brain used to determine the temperature contour and thermal dose rate of a glioma tumour due to interstitial heating by an electrode (yellow cross). The voxel-wise heat conduction tensor is measured by the MRI technique developed, and then the tensorial Bioheat equation is solved on a finite element meshwork across the brain tissue. As the mesh resolution and gradient orientations increase, the blue curve (the temperature contour predicted from the EFM method) approximates the red curve (the temperature contour obtained by direct thermometric probes), thus showing the applicability of the MRI method.

across the lateral ventricular rostral extension (MRI/CSF flow image), and then across the orthogonal fibre tracts (MRI/DTI image). We observe a strong peak of maximal production of matured neurons at specific dose rate and particular time duration (Fig.2c). These are optimal dosage and therapy duration, any other combination reduces the neurogenesis. The procedure is validated by empirical data on animal studies in a collaborating laboratory where stroke is induced by occlusion of middle cerebral artery (Fig.2d). Additional confirmation of the accuracy of the methodology is furnished by its prediction of the speed of neuroblast migration at 34 μm/ hour, which precisely corresponds to experimental values within 8% error. The clinical applicability of the procedure to optimize regenerative therapy in stroke penumbra is being now explored.

Funding:

1. Ministry of Education & Research, Italian Govt. under a program of the European Commission.
2. Dept. of Biotechnology, Govt. of India (collaborative project with AIIMS).

Collaborators:

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

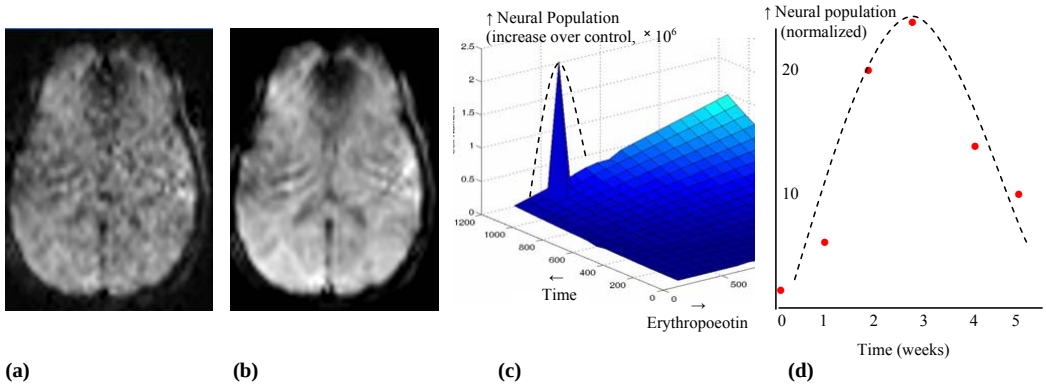


Figure 2(a) MRI structural image; **(b)** Perfusion image, both after stroke, the subtractive mismatch image obtained from the two images denotes the penumbra region that is attempted to be salvaged by regenerative intervention; **(c)** Dose-Time-Response surface of Erythropoetin-induced neuroblast population reaching the penumbra; vertical axes denotes neurogenesis in terms of cell number, the two horizontal axes stand for erythropoetin concentration and time duration since administration, respectively. Note the inverted-U shaped performance curve implying optimization of neurogenesis output at specific values of dose and duration, the curve can be widened or narrowed depending of the drug dosing and system parameters; **(d)** Validation by experimental data, x-axis is time duration in days, and y-axis implies the cell formation. Observe the inverted U-shaped optimality curve closely corresponding to the optimal curve predicted in the quantitative model shown in (c).

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

Principal Investigator

Prof. Prasun Kumar Roy

Research Fellow

Subhadip Paul

R&D engineer

VPS Rallabandi, Sripad Kondra

A fundamental quest in applied neuroscience is the enhancement of the efficiency of clinical output, such as neuroradiological processes, whether diagnostic or therapeutic. A promising approach is offered by the process of perturbation-induced activation, an emerging research field in computational neuroscience and bioengineering. This procedure of stochastic activation, noise-aided resonance or fluctuation-induced transition, is a general principle of nonlinear behaviour applicable to various systems, whether physical or biological, and takes place basically due to the statistical kinetic nature of the components that exhibits probabilistic fluctuations of parameters. The practical application of the principle of stochastic activation as a novel technique for signal enhancement, whether in diagnostic or therapeutic radiology, has not been systematically investigated. Exploring the feasibility of such applications towards clinical medicine is the aim of our program. To illustrate, we have formalized the technique of Stochastic Resonance Imaging as a general radiological methodology which can be applied in Fourier space for upgradation of the signal, the tissue-adaptive technique of how to administer the stochastic perturbation in the MRI image transform has been rigorously delineated, with the image upgradation performance increasing by 45%-85%. The procedure affords increasing characterization of tissue or lesion architecture across various pathologies, ranging from benign to malignant foci and from developmental lesions to cerebrovascular incidents.

Higher Order Tensor Imaging of Brain Tumour Invasion:

Diffusive behaviour is a most important manifestation of the process of stochastic kinetic fluctuation seen in various biological systems, whether molecular or cellular, in normality or disease. However, conflicting results are found in clinical utility of the usually available lower-order MRI diffusion tensor imaging (DTI) for characterization of the architecture

of malignant tumour tissue or cerebral stroke penumbra. As per conventional practice, the DTI based study of brain lesions use low order (2nd rank) DTI based formulation. Actually, higher-order (4th rank) DTI can furnish the architecture of multiple crossing neural tracts, which the lower-order DTI cannot provide (Fig. 3 a,b). Indeed, the error between the actual diffusion signal and the estimated diffusion signal appreciably lessens in the higher rank tensor image. Such imaging mode has not been yet explored to study brain tumours or any pathological lesion. Utilizing rapid-switching motion-probing gradients across 15 or more directions, we show for the first time that higher order diffusion tensor imaging significantly represents accurately the diffusion process in high-grade and low-grade glioma tissue when compared to conventional 2nd order DTI (Fig.3 c,d). Thereby we can delineate the brain region where the malignant cells have covertly invaded (though this cannot be found by other MRI protocols), thereby one can plan the radiotherapy beam to affect the invaded tissue, but minimize the normal tissue exposure. We are applying higher order tensor imaging to delineate brain lesions that can regenerate, as stroke penumbra.

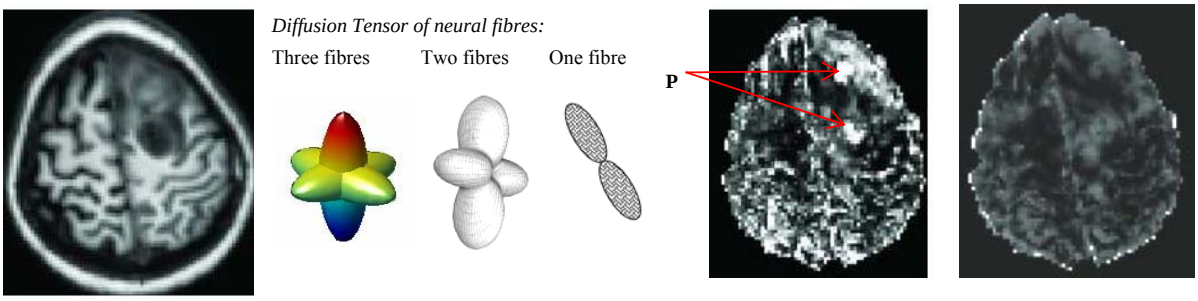
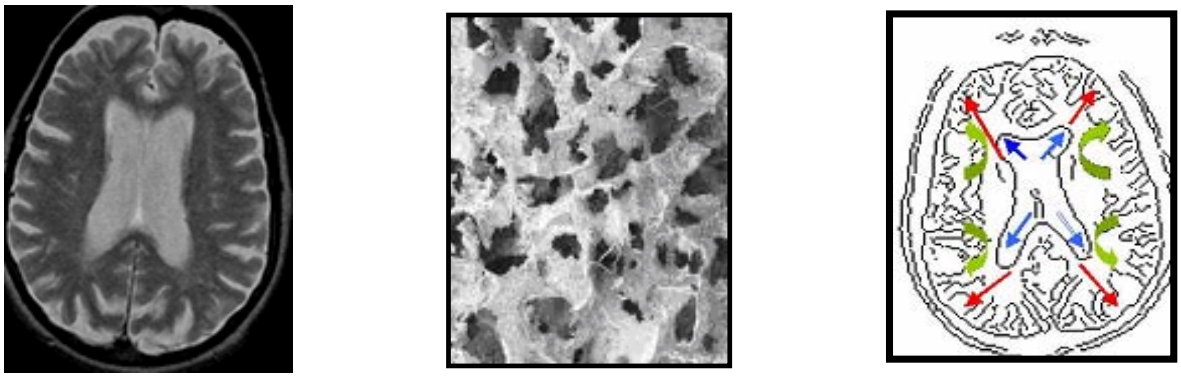


Figure 3(a) Structural image of the glioma; **(b)** Crossing nerve fibres: 2nd order tensor imaging shows only the one major fibre (right diagram), for other fibres, one needs higher order tensor imaging; both the two and three fibre architecture (left and middle diagrams) can be observed using 4th rank tensor mapping; **(c)** Error map of 2nd rank tensor image, the pixel value or whiteness intensity of each pixel denotes the error in that pixel, observe the high hyperintensity in the tumour region indicating high error behavior therein (point P); **(d)** Error map of 4th rank tensor image. Note that the image is hypointense with lesser graey values, implying considerable error reduction. The peak-error points P are absent.

Window to the Ageing process in Normality and Neurodegenerative disease.

Ageing gracefully is a coveted desire of people as they journey through life. However abnormal ageing give rise to mild cognitive impairment (MCI) heralding Alzheimer's disease or vascular dementia, a major upcoming public health problem worldwide. One ideally needs a simple quantitative formulation of normal brain ageing that would differentiate normal from very early dementic brains, when therapeutic interventions has better efficiency. Moreover, the formulation should be implementable as a simple technician-based automated technique for ready MRI screening in the public health setting. We develop a

conceptual biophysics-based model of brain ageing, treating the normal brain as a elastoplastic two-phase porous medium with stochastically generated morphometric patterning. As □-amyloid deposition increases during dementia progression, there is rising elastic shear stress due to neurodegeneration-induced reactive oxygen species which is associated with misaligned stress-strain in the cross-□-sheet, along with change of elastic modulus in brain parenchyma. Based on elastoporous characterization of MRI scans and irreversible thermodynamic analysis, we derive a quantitative linear principle of normal brain ageing. By accessing the textural strain in the MRI image, the pre-MCI stage, namely the earliest deviation from normal ageing, can be detected at an especially initial stage.



(a) **(b)** **(c)**

Figure4.(a) MRI image for accessing the 2-phase tissue-fluid medium; (b) The textural characterization of porous medium furnishes estimation of elastometric indices; (c) Elastoporous stress-strain analysis of the MRI brain image provides an window to the ageing process, as gradual temporal relaxation behaviour occurs in the elastometric indices.

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1. Kh. Budhachandra Singh, Vinay Shukla and **Prasun Roy** (2010) Thermal Conductivity Tensor Imaging and Energy Flow Mapping of Brain: An MRI Feasibility Study, **Annals of Biomedical Engineering** (in press), (DOI: 10.1007/s10439-010-9974-9).
2. Sripad Kondra and **Prasun Roy** (2010). A Mathematical Approach to Brain and Cognition. In S. Doraiswamy (ed). **Mathematics of Biological Processes,** CRC Press, (in press).
3. Partha Raghunathan and **Prasun Roy** (2010), The Neuroimaging of Cognitive processes, in VK Singh (ed). **Advances in Neuroscience, Springer-Narosa,** (accepted).

Patent:

1. A non-invasive technique to produce the stress image of fluid flow (stress tensor) with medical

applications (Assignee: NBRC, Delhi University and DBT).

Presentations:

1. Subhadip Paul: Tensor imaging of the Brain to outline hidden tumour invasion, B.H.U., Varanasi, July 2009.
2. Suhela Kapoor: Image-guided approach to therapeutic neurogenesis in stroke and vascular dementia, Indian Academy of Neuroscience, Jaipur, Dec. 2009.
3. Vinay Shukla: Pulse perturbative chemotherapy to increase cytotoxic efficiency, Indian Academy of Neuroscience, Jaipur, Dec 2009.
4. VPS Rallabandi, Prasun Roy: Glimpses to the Landscape of the Ageing Brain: A Neuroimaging Perspective, National Dementia Summit: Alzheimer's & Related Disorders Society of India, New Delhi, Sept 2009.
5. Budhachandra Singh, Vinay Shukla, Prasun Roy: Energy Flow Tensor Imaging as a Clinical Modality: A Conceptual Extension of Diffusion and Perfusion Tensor Imaging, Nuclear Magnetic Resonance-10, Sanjay Gandhi Medical Institute, Lucknow, Dec 2010.
6. VPS Rallabandi and Prasun Roy: Imaging in Neurodegenerative Disease: New Horizons for Alzheimer Disease, International Conference on Alzheimer's & Related Disorders Society of India, Calcutta, Dec 2009.
7. Suhela Kapoor, VPS Rallabandi, Prasun Roy: A Computational Neuroimaging Approach For Optimizing Therapeutic Neurogenesis and Synaptogenesis in Stroke, DST Workshop & Symposium on Mathematical Biology, IISER, Pune, Aug 2009.
8. Subhadip Paul, Prasun Roy: Higher order Tensor Imaging: New Horizons of Translational Molecular Radiology, DST-NWO Indo-Dutch Workshop on Medical Imaging & Translational Medicine, SCTIMST, Trivandrum, Jan 2010.
9. Prasun Roy: Cross-scale Integration of Information Transmission across Neuronal, Cortical and Cognitive Modes: A Systems Biology Approach, Computational Neuroscience & Neuroimaging Workshop, SCTIMST, Trivandrum, Oct 2009.
10. Prasun Roy: Multiscale Systems Approach to Brain Disorders: Towards Radiogenomics and Programmed Therapy, International Neuro-informatics Workshop on Multiscale Modelling, NCBS, Bangalore, Nov 2009.
11. Prasun Roy: A Neuroregenerative Approach to Ischaemic Cerebral Palsy using Molecular Radiology, National Institute of Mentally Handicapped, Hyderabad, Feb 2010.
12. Prasun Roy: The Self and its Brain: The Newest Frontier of Computing, IIIT, Allahabad, March 2010.

Fundings:

1. Defense Ministry (Defense Research & Development Organization).
2. NBRC Core fund.

Collaborators:

1. Dr Peter Luijten, Dutch Centre for Translational Molecular Medicine
2. Dr R. K. Padhi, Indian Institute of Science, Bangalore.
3. Dr Paul Thompson, University of California – Los Angeles.
4. Dr P. Sarat Chandra, All-India Institute of Medical Sciences, New Delhi.

Awards:

1. Subhadip Paul, SERC Student Fellowship award, Workshop on Finite Element Modelling of Fluid Flow, BHU, Varanasi, Aug 2009.
2. Suhela Kapoor, Neuroinformatics Travel Award, NCBS, Bangalore, Oct 2009.
3. Vinay Shukla, Trainee fellowship award, Advanced Workshop on Control Systems Analysis, I.I.Sc, Bangalore, May 2009.
4. Prasun Roy, Asia Partnership Professor Award in Medical Imaging, Utrecht University Medical Centre, Utrecht, The Netherlands, Nov 2009.

Biomarker for Alzheimer and other Neurodegenerative disorders using in vivo Magnetic Resonance imaging (MRI) and Spectroscopic (MRS) Techniques.

Principal Investigator

Dr. Pravat Kumar Mandal

Project Assistant

Manisha Ahuja

R&D engineer

Sebathi Ghosh, Deepak Kamboj and Rohit Jadav

Alzheimer's disease (AD) is a major neurodegenerative disorder and a worldwide serious health concern for the elderly. The cause of this disease is still not known. However, it is indicated that oxidative stress, energetic stress, and irregular membrane phospholipid metabolism play an important role in AD pathology. Among these molecular processes, which come first and causally related to the disease is a crucial area of AD research. In vivo MRI and MRS technique can provide vital information for identifying the causal molecular process in AD.

Using 3T MRI scanner, we are investigating volumetric (using 3D MRI) as well as neurochemical analysis using 1H and 31P MRS on mild cognitive impairment (MCI), AD, Parkinson disease (PD) and age/gender/education matched healthy control subjects for longitudinal analysis. We are conducting single voxel and multivoxel (1H MRS, 31P MRS MRS), MEGA-PRESS experiments. A change of N-acetylaspartate (NAA) concentration and an increment of myoinositol (mI) from normal to MCI and AD patients is found. Data are processed using different data processing software packages (LCModel, 3DiCSI and jMRUI).

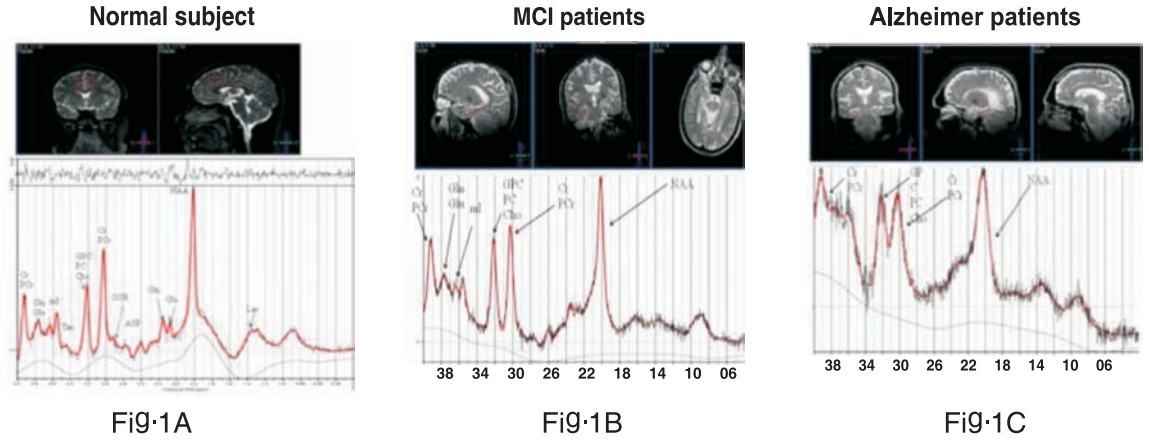
Figure 1 shows the 1H single voxel MRS spectra of three categories of subject (healthy control, MCI and AD patients). Figure 2 shows the 31P MRS spectra of same region and on same category of subject.

Funding:

Department of Biotechnology, Govt. of India

Collaboration:

1. Dr. Manjari Tripathi, MD, DM, Department of Neurology, (AIIMS)
2. Dr. Subbulakshmy Natarajan, MBBS, Ph. D
3. Dr. Sada Nand Dwivedi, Ph. D, Dept. of Biostatistics, (AIIMS)
4. Dr. Partha Raghunathan, Ph. D



Fig·1A Fig·1B Fig·1C

Figure 1 Single voxel (25mm x 25mm x 25mm) 1H MRS spectra for health control (1A), MCI (1B) and AD (1C) subjects on 3T Philips scanner at NBRC. Total experiment time 7 minutes in each case.

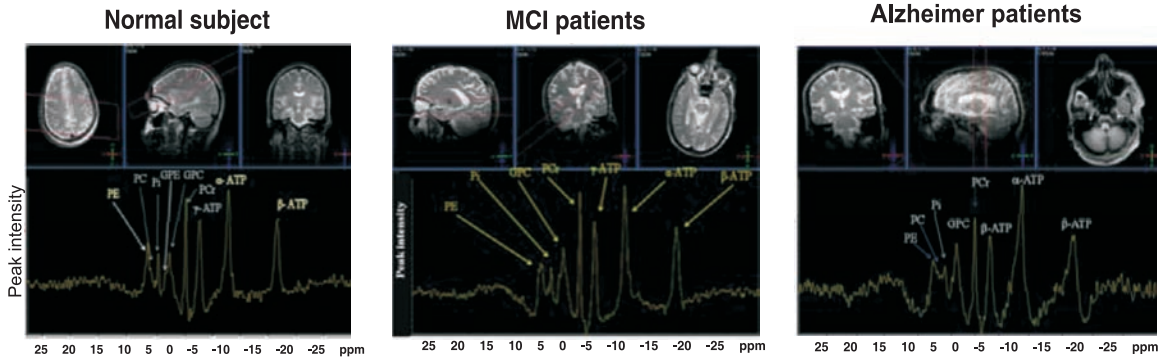


Fig. 2A Fig. 2B Fig. 2C

Figure 2: Single voxel (25mm x 25mm x 25mm) 31P MRS spectra for health control (2A), MCI (2B) and AD (2C) subjects on 3T Philips scanner at NBRC. Total experiment time 26 minutes in each case.

Smaller Sized Anesthetics Induce Amyloid beta peptide Oligomerization

Principal Investigator

Dr. Pravat Kumar Mandal

Project Assistant

Manisha Ahuja

R&D engineer

Sebathi Ghosh

Alzheimer's disease (AD) is a neurodegenerative disorder affecting millions of people worldwide and has become a major global concern. Uncontrolled oligomerization (aggregation) of Aβ peptide is the hallmark of AD and it is believed to be causally related to AD pathomechanism. Intensive research (biophysical, animal model and clinical) is underway to investigate the cause of this unexplained Aβ peptide oligomerization, which is probably triggered by some agent or process in predisposed individuals, and subsequently to trace the mol ecular pathways involved in the phenomenon.

Recently, it is reported using biophysical studies that several commonly used inhaled anesthetics induce A□ aggregation (oligomerization). Similar observations have also been found from animal model studies that smaller sized anesthetics, induce more plaque load in transgenic mice compared to non-transgenic mice (control group). But the molecular mechanism for these anesthetics induced Aβ oligimerization is unknown.

Our laboratory, using NMR spectroscopic techniques on several anesthetics, have arrived at the conclusion that smaller sized anesthetics (Figure 1) are able to access and interact with the helix-loop-helix region of Aβ peptide containing three specific amino acid residues (G29, A30 and I31); thereby causing Aβ oligomerization. The "size factor" of these anesthetics and their profound role in Aβ oligomerization is a novel and thought-provoking concept.

The molecular pathway for the smaller sized inhaled anesthetic induced halothane is shown in Figure 2

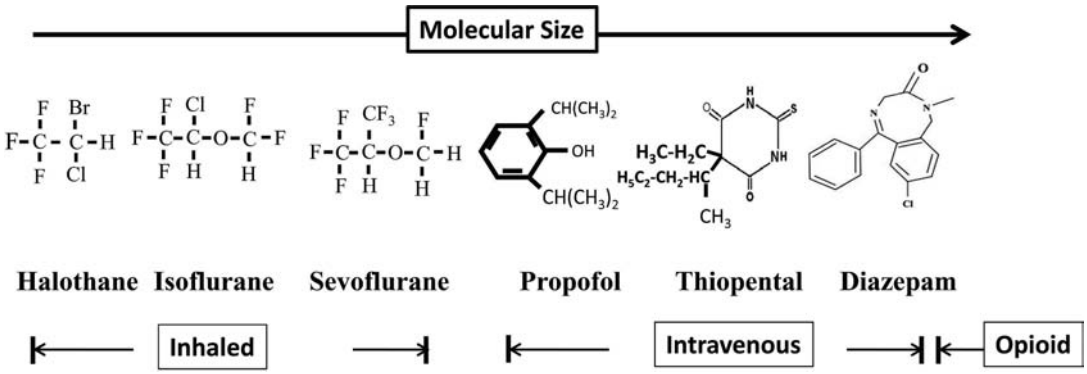


Figure1 Molecular structure of anesthetics based on molecular volume (Å3). The molecular volume of propofol is in the intermediate range between smaller (inhaled) and larger sized (intravenous) anesthetics.

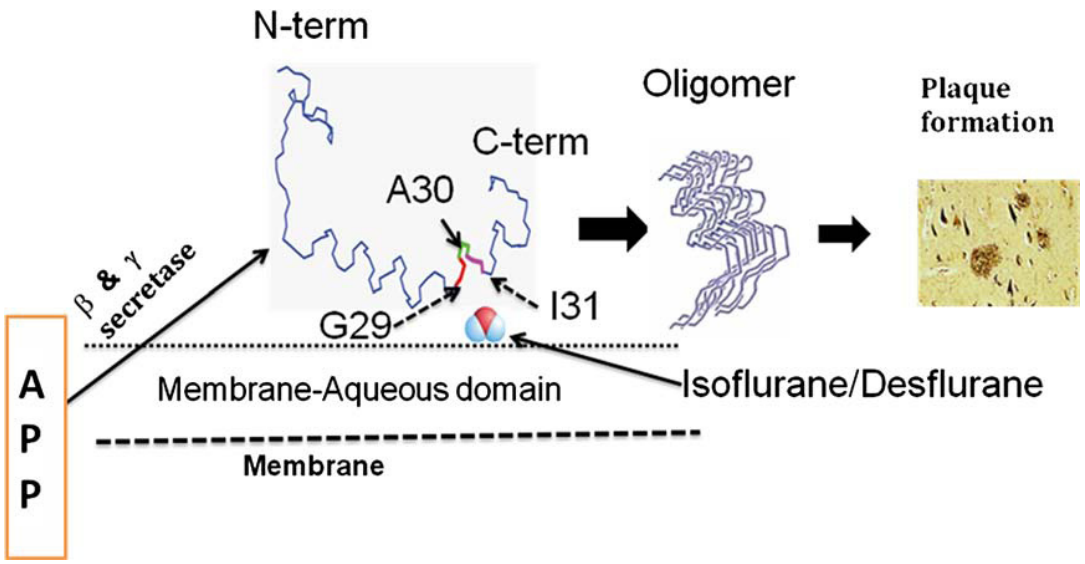


Figure2: A schematic diagram for Aβ interactions with isoflurane and/or desflurane at a clinically relevant concentration that leads to oligomeric Aβ formation. Aβ peptide is generated by the amyloid precursor protein (APP), by the action of β and γ secretase by natural process, and the inhaled anesthetic interacts with three specific residues (G29, A30 and I31) and initiates the formation of neurotoxic oligomeric Aβ formation. This oligomer may be responsible for plaque formation as seen in AD patients on biopsy

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1. **Pravat K Mandal** *, Virgil Simplaceanu and Vincenzo Fodale (2010) Intravenous Anesthetic Diazepam does not induce Amyloid beta-peptide Oligomerization but Diazepam Co-administered with Halothane Oligomerizes Amyloid Beta-peptide: An NMR study. **Journal of Alzheimer Disease**, Vol 20(1), 127-134.
2. V. Fodale, L.B. Santamaria, D. Schifilliti and **P. K. Mandal** (2010) Anaesthetics and post-operative cognitive dysfunction: a pathological mechanism mimicking Alzheimer's Disease. **Anesthesia**, Vol 65(4) 388-395.
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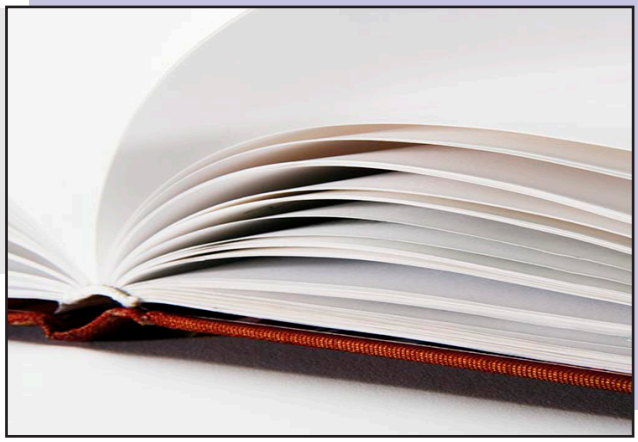
Funding:

Italian Ministry for University and Research Program (Multi-center Grant)

Collaboration:

1. Dr. Vincenzo Fodale, MD (University of Mesina, Italy)
2. Prof. Virender S. Chauhan (ICGEB), New Delhi

PUBLICATIONS & PATENTS



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2. **N. R. Jana** (2010). Role of ubiquitin-proteasome system and autophagy in polyglutamine neurodegenerative diseases. **Future Neurology,** 5, 105-112.
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(2010) Minocycline Differentially Modulates Macrophage Mediated Peripheral Immune Response Following Japanese Encephalitis Virus Infection. **Immunobiology.** (In Press)

22. K Dutta, D Ghosh, A Nazmi, K L Kumawat, and **A Basu** (2010) A Common Carcinogen Benzo[a] pyrene Causes Neuronal Death in Mouse via Microglial Activation **PLoS One,** 5(4): e9984.

23. D Nandi, M K Mishra, **A Basu,** and B Bishayi (2010) Protective effects of Interleukin-6 in Lipopolysaccharide (LPS) induced experimental endo-toxemia are linked to alteration in hepatic anti-oxidant enzymes and endogenous cytokines. **Immunobiology,** 215: 443-451.

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25. S Das, D Ghosh, and **A Basu** (2009) Japanese encephalitis virus induce immuno-competency in neural stem/progenitor cells. **PLoS One,** 4(12): e8134.

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27. *K Datta, D Ghosh, and **A Basu** (2009) Curcumin protects neuronal cells from Japanese Encephalitis virus mediated cell death and also inhibits infective viral particle formation by dysregulation of Ubiquitin proteasome system. **J Neuroimmuno Pharmacology,** 4(3): 328.

28. K Dutta, A Nazmi, and **A Basu** (2010) Chemotherapy In Japanese Encephalitis: Are We There Yet? **Infectious Disorders - Drug Targets.** (In Press)

29. S Chakraborty, D K Kaushik, M Gupta, and **A Basu** (2010) Inflammasome Signaling At The Heart of Central Nervous System Pathology. **J Neurosci Res.,** 88:1651-1631.

30. S Chakraborty, A Nazmi, K Dutta, and **A Basu** (2010) "Neurons Under Viral Attack: Victims Or Warriors?" **Neurochemsitry International,** 56:727-735.

31. K Dutta, P N Rangarajan, S Vrati, and **A Basu** (2010) Japanese Encephalitis: Pathogenesis, Prophylactis and Therapetucis. **Current Science,** 98 (3): 22-30. *(Special section: Biology and pathogenesis of Virus)*

32. *D Ghosh and **A Basu** (2009) Japanese Encephalitis - A Pathological and Clinical Perspective **PloS Neglected Tropical Diseases,** 3(9) e437.

33. **Murthy, A.,** Shorter-Jacobi, S.M., Thompson, K.G. and J. D. Schall

(2009) Neural control of visual search by frontal eye field: Effects of target displacement on visual selection and saccade preparation. **Journal of Neurophysiology,** 101: 2485-2507.

34. K.M. Sharika, Supriya Ray and **A. Murthy** (2009) Attention for Action during Error Correction. **Progress in Brain Research.** 176: 227-244.

35. Ramakrishnan, A., Chokandre, S. and **A. Murthy** (2010) Voluntary control of multi-saccade gaze shifts during movement preparation and execution. **J. Neurophysiology**

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38. Hui-Xin Qi, **Neeraj Jain,** Christine E Collins, David Lyon and Jon H Kaas (2010). Functional Organization of motor cortex of adult macaque monkeys is altered by sensory loss occurring in infancy. **Proc. Natl. Acad. Sci., USA,** 107: 3192-3197.

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41. T. Das, U. Kumar, R. S. Bapi, P. Padakannaya and **N. C. Singh** (2009) Neural representation of an alphasyllabary – the story of Devanagari. **Current Science**, 97, 1033.

42. U. Kumar, T. Das, R. S. Bapi, P. Padakannaya, R. M. Joshi and **Nandini C Singh** (2010) Reading different orthographies: An fMRI study of phrase reading in Hindi-English bilinguals. **Reading and Writing,** 23, 239-255.

43. Kh. Budhachandra Singh, Vinay Shukla and **Prasun Roy** (2010) Thermal Conductivity Tensor Imaging and Energy Flow Mapping of Brain: An MRI Feasibility Study, **Annals of Biomedical Engineering** (in press), (DOI: 10.1007/s10439-010-9974-9).

44. Sripad Kondra and **Prasun Roy** (2010). A Mathematical Approach to Brain and Cognition. In S. Doraiswamy (ed). **Mathematics of Biological Processes,** CRC Press.(in press).

45. Partha Raghunathan and **Prasun Roy** (2010) The Neuroimaging of Cognitive processes, in VK Singh (ed). **Advances in Neuroscience, Springer-Narosa,** (accepted).

46. **Pravat K Mandal***, Virgil Simplaceanu and Vincenzo Fodale (2010) Intravenous Anesthetic Diazepam does not induce Amyloid beta-peptide Oligomerization but Diazepam Co-administered with Halothane Oligomerizes Amyloid Beta-peptide: An NMR study. **Journal of Alzheimer Disease,** Vol 20(1), 127-134.

47. V. Fodale, L.B. Santamaria, D. Schifilliti and **P. K. Mandal** (2010) Anaesthetics and post-operative cognitive dysfunction: a pathological mechanism mimicking Alzheimer's Disease. **Anesthesia,** Vol 65(4) 388-395.

48. **Pravat K. Mandal*** and Vincenzo Fodale (2009) Smaller molecular-sized anaesthetics oligomerize Abeta peptide simulating Alzheimer's disease: a relevant issue. **European Journal of Anesthesiology,** Vol 26(10) 805-806. **Editorial (last year it was indicated as in press)**

Patents

P.K. Roy: A non-invasive technique to produce the stress image of fluid flow (stress tensor) with medical applications (Assignee: NBRC, Delhi University and DBT).

Ellora Sen: "Bicyclic triterpenoid Iripallidal as a novel anti-glioma and anti-neoplastic therapy in vitro". Filed for Indian patent through Department of Biotechnology (#2915/DEL/2008) and International patent (PCT/IN09/000336).

V. Ravindranath: *Withania somnifera* plant extract and method of preparation thereof. Joint patent with University of Delhi and Indian Institute of Science-Bangalore.

PRESENTATIONS

Presentations

1. S. Godavarthi and N. R. Jana: Angelman Syndrome Candidate Protein-E6AP, is a Coactivator of Glucocorticoid Hormone Receptor, IAN, Jaipur, 2009.
2. N. R. Jana: Toxic protein aggregation in neurodegenerative diseases. National Institute of Advanced Research, Ahmedabad, 2010.
3. N. R. Jana: Understanding the functional role of E6-AP – an ubiquitin protein ligase and steroid receptor coactivator implicated in Angelman mental retardation syndrome. AOSCE, JNU, New Delhi, 2010.
4. N. R. Jana: Toxic protein aggregation in polyglutamine neurodegenerative diseases. DRDO, New Delhi, 2009.
5. N. R. Jana: Suppression of polyglutamine neurodegeneration by ubiquitin protein ligases. IGIB, New Delhi, 2009.
6. S. Rao, J. Sharma, R. Maity. S.K. Shankar. P. Satishchandra and N. R. Jana. Lafora disease and ubiquitin-proteasome dysfunction, PME Conference, Venice, Spain, 2010.
7. J. Sharma and N. R. Jana. Lafora disease associated ubiquitin ligase, malin interacts with and promotes proteasome-mediated degradation of neuronatin. IAN, Jaipur, 2009.
8. S. Rao, J. Sharma and N. R. Jana. CHIP stabilizes aggregate prone malin, an ubiquitin ligase mutated in Lafora disease. IAN, Jaipur, 2009.
9. Parthiv Haldipur, Upasna Bharti, Chitra Sarkar, Corinne Alberti, Soumya Iyengar, Pierre Gressens, Shyamala Mani: Preterm delivery alters the developmental program of the cerebellum. Frontiers in Organogenesis, Kobe, Japan. 23rd – 25th March 2010.
10. N. Sehgal, V. Agarwal, K. Valli, L. Antonovic, H. Strobel, V.Ravindranath. Neuroprotective role of cytochrome P4504f in resolution of inflammation in brain. Presented at the the 39th annual meeting of the Society for Neuroscience, Chicago, USA. October 17–21, 2009.
11. Ray A, Saeed U, Valli RK, Kumar AMRK, Karunakaran S and Ravindranath V: Perturbation of protein thiol homeostasis through

downregulation of glutaredoxin, a protein disulfide oxidoreductase, results in loss of DJ-1 through proteolysis; Poster presented at the XVIII WFN World Congress on Parkinson's Disease and Related Disorders, Miami Beach, USA. December 13-16, 2009.

12. P. Seth: Invited Speaker, Brain Awareness Week, Banaras Hindu University, Varanasi, India, March 2010.
13. P. Seth: Guest Speaker, National Science Day, Kendriya Vidyalaya, Manesar, India, February 2010.
14. P. Seth: Guest Faculty, Jawaharlal Nehru University Academic Staff College Lecture series for college teachers, New Delhi, India, January 2010.
15. P. Seth: Invited Speaker & Convener International Symposia, Annual Meeting of Indian Academy of Neurosciences, NIIMS Univ, Jaipur, India, Dec 2009.
16. P. Seth: Invited Speaker, Annual meeting of International Society of Neurovirology (USA), Miami, USA, June 2009.
17. P. Seth: Invited Speaker, International NeuroAIDS Research Meeting organized by HIV Neurobehavioral Research Center (HNRC), Miami, USA, May 2009.
18. P. Seth: Invited Speaker, Annual meeting of Society of Neuroimmunopharmacology (USA) at Wuhan, China, held in April 2009.
19. Vivek Sharma *, Nitin Koul, Veer Singh Mehta and Ellora Sen: Interleukin-1β induced HIF-1α transcriptional activity in glioma cells is regulated by Ras via NF-κB. Frontiers in Basic Cancer Research Meeting. Boston, October 2009.
20. Ellora Sen: Inflammation and Cancer: Romancing death. West Bengal State University, Calcutta, August, 2009
21. Deobrat Dixit*, Vivek Sharma and Ellora Sen: Casein Kinase 2 inhibition induces SOCS-1 expression and sensitizes glioblastoma cells to Tumor Necrosis factor (TNFα) induced apoptosis. Indian Academy of Neuroscience, Jaipur December, 2009.
22. Nitin Koul*, Vivek Sharma, Deobrat Dixit, Sadashib Ghosh and Ellora Sen: Bicyclic triterpenoid Iripallidal induces apoptosis and inhibits Akt/mTOR pathway in glioma cells. International Symposium on Cancer Chemoprevention and Translational Research, New Delhi, December, 2009.
23. Vivek Sharma, Nitin Koul, Veer Singh Mehta and Ellora Sen*: 3rd International Symposium on Translational Cancer Research, Bhubaneswar, December, 2009
24. Vivek Sharma, Nitin Koul, Veer Singh Mehta and Ellora Sen*: Macbeth's three witches in glioma: IL-1β, Ras and NFκB. Molecular Immunology Forum. Calcutta, January, 2010
25. Shiv K Sharma, Kiran Pandey, Chinmoyee Maharana and Kaushik

Sharma: Histone deacetylase inhibitor- and activity-induced acetylation of p55: relevance for synaptic plasticity and memory. Poster presentation at the Society for Neuroscience Conference, Chicago, USA, Oct. 17-21, 2009.

26. Chinmoyee Maharana, Kaushik P Sharma and Shiv K Sharma: Depolarization induces histone H2B acetylation in the hippocampus. Poster presentation at the XXVII Conference of Indian Academy of Neurosciences, Jaipur, Dec. 18-20, 2009.

27. Kiran Pandey, Chinmoyee Maharana, Kaushik Sharma and Shiv K Sharma: Activity-dependent regulation of alpha tubulin acetylation. Poster presentation at the XXVII Conference of Indian Academy of Neurosciences, Jaipur, Dec. 18-20, 2009.

28. S Das, and A Basu: Japanese Encephalitis Virus arrests Neural stem cell proliferation and confers them with immunogenic properties. 2nd Bangalore Microscopy Course, NCBS, Bangalore, 21st-28th February, 2010.

29. A Basu: Immuno-competency of Neural stem cells: Neuro-tropic Viral infection as a model system. Molecular Immunology Forum meeting. Fort Radisson, Raichak (Near Kolkata), 15-17th January, 2010.

30. A Basu: Japanese Encephalitis Virus causes "double trouble" to brain. Guha Research Conference. Summer Sand Beach Resort, Ullal, Mangalore. 19th -23rd December, 2009.

31. K Dutta, K L Kumawat, M K Mishra, and A Basu: Minocycline modulates Japanese Encephalitis Virus entry in the central nervous system. XXVII Annual conference of Indian Academy of Neuroscience. NIMS University, Jaipur, 18-20 December, 2009.

32. S Chakraborty, S Das, and A Basu: Lipid rafts play a critical role in Japanese Encephalitis Virus entry into neural stem cells. XXVII Annual conference of Indian Academy of Neuroscience. NIMS University, Jaipur, 18-20 December, 2009.

33. D K Kaushik, S Das, M Gupta, and A Basu: To elucidate the role of Kruppel like factor 4, a novel transcription factor in neuroinflammation. XXVII Annual conference of Indian Academy of Neuroscience. NIMS University, Jaipur, 18-20 December, 2009.

34. S Das, and A Basu: Infection of neural stem cells by Japanese Encephalitis Virus: Implications in long-term viral neuropathogenesis. XXVII Annual conference of Indian Academy of Neuroscience,NIMS University, Jaipur, 18-20 December, 2009.

35. A Basu: Japanese Encephalitis: from neuropathology to therapeutic intervention. West Bengal State University, Barasat, North 24 Paraganas, 23rd October, 2009.

36. A Basu: Japanese Encephalitis Virus infects Neural Stem Cells and decreases their proliferation.

Biology and Pathogenesis of Viruses: Molecular Insights, IISC, Bangalore, 4-5th May, 2009.

37. A Basu: The brain's response to Japanese Encephalitis virus infection: Do neural stem cells play a role? 15th SNIP Conference, , Wuhan, China, 21st-24th April, 2009.

38. A Basu: Host pathogen interaction in Japanese Encephalitis Virus infection: from bench to bedside;Department of Physiology, University of Calcutta, 6th April, 2009.

39. Rahul Chaudhary, Praseeda Venugopalan & V. Rema. Unilateral barrel cortex lesion results in long-lasting deficits in somatosensory behavior of adult rats. Society for Neuroscience Annual Meeting. Chicago, Illinois, October, 2009.

40. Sakthi Kumar M, Ethiraj Ravindran, Rahul Chaudhary and V. Rema. Effect of focal injury on distant, anatomically connected brain regions. Indian Academy of Neuroscience. Jaipur Dec. 2009.

41. Ramakrishanan, Ramakrishnan S. and A. Murthy. Tracking the decision as it changes: Supra-threshold microstimulation in macaque frontal eye field reveals how decisions are controlled. Soc. for Neuroscience Abstract (USA) 2009.

42. Gopal, P. Vishwanathan, A. Murthy. The Control of Eye Hand Coordination in a Redirect Task. Indian Academy of Neuroscience, Jaipur, India. 2009.

43. N. Bhutani, Ramakrishnan S., A. Murthy. Basal Ganglia and the Control of Sequential Eye Movements. Indian Academy of Neuroscience, Jaipur, India. 2009.

44. Niranjan A Kambi, Shashank Tandon, Hisham Mohammed, Leslee Lazar, Radhika Rajan and Neeraj Jain: Topography of primary motor cortex in monkeys with dorsal spinal injuries. Neuroscience 2009, Annual Meeting of the Society for Neuroscience, Chicago, USA. Oct 17-21, 2009.

45. Leslee Lazar, Radhika Rajan and Neeraj Jain: Focal stimulation on the skin of the hand activated neurons over large regions of the hand representation in area 3b of macaque monkeys. Neuroscience 2009, Annual Meeting of the Society for Neuroscience, Chicago, USA. Oct 17-21, 2009.

46. 'Advances in Biological Sciences', a National Conference organized by Department of Zoology, Panjab University, Chandigarh, India. March 29-30, 2010.

47. 'Challenges in Spinal Cord Injury Repair' a seminar organized by Dr ALMPG Institute, University of Madras. March 5, 2010.

48. Soumya Iyengar: Development of the Human Auditory Cortex – Neuroanatomical Studies. Psychology Dept., Vanderbilt University, Nashville, TN, USA. October, 2009.

49. Soumya Iyengar: The human auditory cortex – a developmental

timeline. National Programme on Perception Engineering (Technical Workshop). NBRC, Manesar, December, 2009.

50. Arvind S Pundir, Senthil Krishnasamy, Souvik Kar, Bishan S Radotra, Praveen Kumar, PC Dikshit, Soumya Iyengar: The human auditory cortex during the third trimester and at term. Poster presented at the Annual Meeting of Society for Neuroscience, Chicago, IL, USA. October, 2009.

51. Arvind S Pundir, Bishan S Radotra, Praveen Kumar, PC Dikshit, Soumya Iyengar: Development of the perinatal and postnatal human auditory cortex. Poster presented at the Annual meeting of the Indian Association of Neurology, Jaipur, December 2009.

52. Parthiv Haldipur, Upasana Bharti, Chitra Sarkar, Corinne Alberti, Soumya Iyengar, Pierre Gressens, Shyamala Mani: Preterm delivery alters the developmental program of the cerebellum. Poster presented at "Frontiers in Organogenesis", a meeting organized by the Centre for Developmental Biology, Kobe, Japan, March 2010.

53. NK Dhingra: Remodeling in Third-Order Retinal Neurons After Photoreceptor Degeneration. Invited talk at IIT, Delhi, July 15, 2009.

54. NK Dhingra: Invited to chair a symposium on Neurophysiological Basis of Complex Behaviors, and present on Retinal Degeneration in an Inducible Animal Model – Biochemical, Morphological, Physiological and Behavioral Correlates in International Conference on Neuroscience Updates & ISN, APSN, IBRO & SNCI School, Cochin, December 7-14, 2009.

55. S. Nagar, S. Sethuramanujam, V. Jain, P. Cherukuri, NK Dhingra: Remodeling of Third-Order Retinal Neurons Following Photoreceptor Degeneration. 27th Annual Conference of the Indian Academy of Neurosciences, Jaipur, India; December 18-20, 2009.

56. V. Jain, NK Dhingra: Expression of Melanopsin by Brn3-Positive Retinal Ganglion Cells in Mouse. 27th Annual Conference of the Indian Academy of Neurosciences. Jaipur, December 18-20, 2009.

57. NK Dhingra: Invited to present at a brainstorming meeting by Society for Biomedical Technology, DEBEL, DRDO regarding Bionic Eye in India, Bangalore, January 16, 2010.

58. D. Yoganarasimha: Representation of external environment in place cell and head direction cell networks. Symposium on Neurophysiological Basis of Complex Behaviors. International Conference on Neuroscience Updates & ISN, APSN, IBRO & SNCI School. Centre for Neuroscience, CUSAT, Cochin, December 7-14 2009.

59. N.C. Singh: Distinct Reading routes for deep and shallow orthographies in simultaneous biliterates – a functional imaging study, Abstract, Human Brain Mapping, San Francisco, USA, June 2009.

60. N.C. Singh: Influence of native language reading networks on the second language – a fMRI study, Abstract, Scientific Studies for Reading, Boston, USA, June 2009.

61. N.C. Singh: Fourier transforms, Novel applications in Neuroscience, Delhi University, March 2010.

62. Subhadip Paul: Tensor imaging of the Brain to outline hidden tumour invasion, B.H.U., Varanasi, July 2009.

63. Suhela Kapoor: Image-guided approach to therapeutic neurogenesis in stroke and vascular dementia, Indian Academy of Neuroscience, Jaipur, Dec. 2009.

64. Vinay Shukla: Pulse perturbative chemotherapy to increase cytotoxic efficiency, Indian Academy of Neuroscience, Jaipur, Dec 2009.

65. VPS Rallabandi, Prasun Roy: Glimpses to the Landscape of the Ageing Brain: A Neuroimaging Perspective, National Dementia Summit: Alzheimer's & Related Disorders Society of India, New Delhi, Sept 2009.

66. Budhachandra Singh, Vinay Shukla, Prasun Roy: Energy Flow Tensor Imaging as a Clinical Modality: A Conceptual Extension of Diffusion and Perfusion Tensor Imaging, Nuclear Magnetic Resonance-10, Sanjay Gandhi Medical Institute, Lucknow, Dec 2010.

67. VPS Rallabandi and Prasun Roy: Imaging in Neurodegenerative Disease: New Horizons for Alzheimer Disease, International Conference on Alzheimer's & Related Disorders Society of India, Calcutta, Dec 2009.

68. Suhela Kapoor, VPS Rallabandi, Prasun Roy: A Computational Neuroimaging Approach For Optimizing Therapeutic Neurogenesis and Synaptogenesis in Stroke, DST Workshop & Symposium on Mathematical Biology, IISER, Pune, Aug 2009.

69. Subhadip Paul, Prasun Roy: Higher order Tensor Imaging: New Horizons of Translational Molecular Radiology, DST-NWO Indo-Dutch Workshop on Medical Imaging & Translational Medicine, SCTIMST, Trivandrum, Jan 2010.

70. Prasun Roy: Cross-scale Integration of Information Transmission across Neuronal, Cortical and Cognitive Modes: A Systems Biology Approach, Computational Neuroscience & Neuroimaging Workshop, SCTIMST, Trivandrum, Oct 2009.

71. Prasun Roy: Multiscale Systems Approach to Brain Disorders: Towards Radiogenomics and Programmed Therapy, International Neuro-informatics Workshop on Multiscale Modelling, NCBS, Bangalore, Nov 2009.

72. Prasun Roy: A Neuroregenerative Approach to Ischaemic Cerebral Palsy using Molecular Radiology, National Institute of Mentally Handicapped, Hyderabad, Feb 2010.

73. Prasun Roy: The Self and its Brain: The Newest Frontier of Computing, IIIT, Allahabad, March 2010.

DISTINCTIONS, HONOURS AND AWARDS

Distinctions, Honours and Awards

Dr. Ellora Sen

NASI–SCOPUS Young Scientist Award conferred jointly by National Academy of Science and Elseviers 2010.

Dr. Pankaj Seth

Dr. Seth's research was highligted by International Society of Neurovirology in newsletter in Janaury 2010.

"Best Paper Award" to Dr. Pankaj Seth, from Alumni Association of Department of Biochemistry, Lucknow University, Lucknow, Dec 2009.

Selected as Associate Editor for Journal of Neurovirology and Annals of Neurosciences.

Dr. Nandini C. Singh

Travel award from the Society of Scientific Research on Reading to attend the annual meeting from June 25-27 2009 at Boston, MA, USA

Dr. Prasun Roy

Asia Partnership Professor Award in Medical Imaging, Utrecht University Medical Centre, Utrecht, The Netherlands, Nov. 2009.

Ms. Shaily Malik

"Best Paper Award" to Ms. Shaily Malik, from the organizers at XXVII Annual Conference of Indian Academy of Neurosciences at NIMS University, Jaipur.

"Prof. R. Nath Memorial Travel Award" to attend XXVII Annual Conference of Indian Academy of Neurosciences at NIMS University, Jaipur.

Ms. Mamata Mishra

"Prof. R. Nath Memorial Travel Award" to attend XXVII Annual Conference of Indian Academy of Neurosciences at NIMS University, Jaipur.

Mr. Subhadip Paul

SERC Student Fellowship award to attend Workshop on Finite Element Modelling of Fluid Flow at Banaras Hindu University, Varanasi, August 2009.

Ms. Suhela Kapoor

Neuroinformatics Travel Award, NCBS, Bangalore, Oct 2009.

Mr. Vinay Shukla

Trainee fellowship award to attend Advanced Workshop on Control Systems Analysis at Indian Institute of Science, Bangalore, May 2009.

Mr. Parthiv Haldipur

Center for Developmental Biology travel fellowship to attend "CDB 2010 - Frontiers on Organogenesis" organized by the Center for Developmental Biology (CDB)-RIKEN, Kobe, Japan.

Mr. Niranjan Kambi

IBRO/Society for Neuroscience Travel Grants 2009 - Society for Neuroscience - May 2009

Ms. Pretty Garg

Ph.D student, has been awarded first rank certificate upon completion of course work during the year 2009.

Mr. Apoorv Shrama

Ph.D student, has been awarded second rank certificate upon completion of course work during the year 2009.

Ms. Ruchi Bansal

Integrated Ph.D student, has been awarded first rank certificate upon completion of course work during the year 2009.

Following students have been awarded Ph.D. degree from NBRC.

Name of the Student	Name of the Supervisor	Title of Ph.D. Thesis	Date of Award
Mr. Manoj Kumar	Dr. Shyamala Mani	Neuronal differentiation and subtype specification in embryonic stem cells.	12.06.2009
Ms. Latika Singh	Dr. Nandini C. Singh	Development of articulatory features in children.	01.09.2009
Ms. Mamata Mishra	Dr. Pankaj Seth	Understanding Molecular Basis of HIV-1 Tat-Induced Complications in Human Fetal Brain Cells.	12.02.2010
Mr. Manoj Kumar Mishra	Dr. Anirban Basu	To study the aberrant glial response in Japanese Enephalitits; from molecular mechanism to therapeutic intervention.	16.02.2010

EXTERNALLY FUNDED RESEARCH PROJECTS

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, India).

Understanding the role of ubiquitin-proteasome system dysfunction in the pathogenesis of Huntington's disease: Indo-Japan cooperative science program (DST, India).

Study of the neuroprotective role of ubiquitin ligase, E6-AP in the transgenic mice model of Huntington's disease: National Bioscience Awardee (DBT, India).

Dr Pankaj Seth

Characrerization of human fetal brain derived Neural Stem cells as a model for studying Neurodegenerative diseases: Basic biology of stem cells grant (DBT, India)

Role on CNS Opportunistic infection in subsequent development of HIV Dementia. (RO1, NIH, USA)

Dr. Anirban Basu

Dissecting molecular circuitries that regulate progenitors cell response to Japanese Encephalitis virus. (DBT, India)

Evaluation of Monocycline as a neuroprotective and/or anti inflammatory and/or anti viral drug in Japanese encephalitis. (CSIR, India).

Dr. Shiv K Sharma

Effect of amyloid beta on Growth factor signaling the hippocampus: Implication for the Alzheimer Disease. (CSIR, India).

Prof. V Ravindranath

Evaluation of the Molecular basis of action of an herbal extract in the treatment of Dementia Including Alzheimer's Disease. (DBT, India).

Cytochrome P-450 dependedt metabolism of drugs in brain. (RO1, NIH, USA).

Dr. Ellora Sen

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

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

Oligodendrocyte Differentiation from Neural Stem Cells - Implication in CNS repair: Basic biology of stem cells grant. (DBT, India)

Role of lipid rafts in Epigenetic lilencing and immune cell signaling: Implication in the aggressiveness of Glioblastome multiforme: Innovative Young Biotechnologist Awardee. (DBT, India)

Understanding signalling circuitaries involved in transcriptional regulation

of genes associated with survival and immune response in an inflammatory environment: Implications in glioblastoma progression. (DBT, India).

Dr. Ranjit K Giri

The Study of Molecular and cellular events in mouse CNS stem cell cultures replicating mouse prions. (DBT, India).

Understanding the cellular pathogenesis of Alzheimer's disease employing CNS stem cells cultures: Development of a novel in vitro model of Alzheimer's disease. (DBT, India).

Dr. Shyamala Mani

Neural differentiation of embryonic cells. (CEFIPRA, France).

Factors Governing Human Stem cell Differentiation Basic biology of stem cells grant (DBT, India).

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, India).

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: Basic biology of stem cells grant (DBT, India).

Prof. Neeraj Jain

Autonomous Navigation Using Brain -machine Interface. (DRDO, India).

The uses of stem cells in treating cases of spinal injury: Basic biology of stem cells grant. (DBT, India).

Dr. Soumya Iyengar

Effects of altering the level of neuronal proliferation on the learning and production of behavior in male Zebra finches: Basic biology of stem cells grant. (DBT, India).

Dr. Rema Velayudhan

Embryonic Stem Cells therapy for Brain Injury: Basic biology of stem cells grant. (DBT, India).

Dr. Sayali Ranade

Iron Deficiency memory dysfunction hippocampal development and defects: Women Scientist Awardee. (DST, India).

Dr. Pravat K Mandal

Characterization of the molecular interactions of anesthetics with the beta-amyloid. (Italian Ministry for University & Research).

The understanding of early Molecular events which initiate the Alzheimer's Disease using in vivo magnetic resonance Spectroscopy study. (DBT, India).

Prof. Prasun Roy

Stochastic Resonance Effect as a new technique for Image Processing in neuroscience. (DRDO, India).

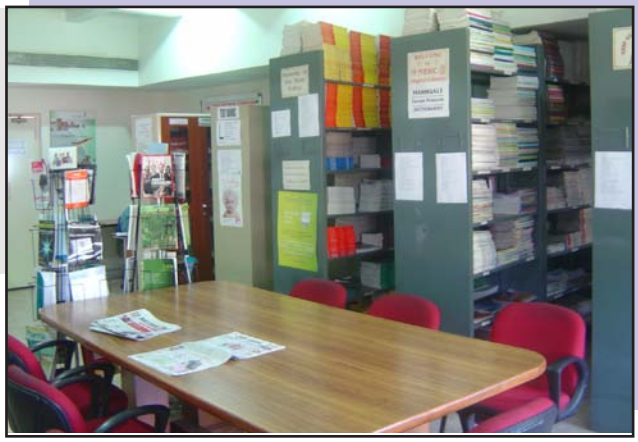
Establishment of translational research unit at NBRC. (DBT, India)

Dr. Nandini Chatterjee Singh

Parkinson Disease: Development of Computational Model Based on hand Writing and Speech for prediction and Treatment. (DST, India).

Language and brain organization in normative multilingualism. (DST, India).

CORE FACILITIES



- Distributed Information Centre (DIC)
- Animal Facility
- Digital Library

Distributed Information Centre (DIC)

The Distributed Information Centre (DIC) of the National Brain Research Centre is responsible for management of IT services of the institute. It not only provides e-services but also constantly updates the digital environment with new and existing resources which are in sync with the growing requirements of the centre.

IT Infrastructure:

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

- *Campus wide LAN over gigabit fiber backbone with wi-fi hotspots for students and faculty. The network is running on manageable Layer-3 Swithces for security and manageability.*
- *20 Mbps (1:1) Internet bandwidth (10 Mbps on fibre optic and 10 Mbps on RF) for redundancy. The network is secured by dedicated secure firewall clusters.*
- *Centralized data storage to the tune of 50 TB with multiple level of redundancy. It is further protected by automated tape library based backup solution.*
- *State-of-the-art video-conferencing facility for collaborating research and teaching.*
- *In-house hosting of critical servers which includes webservers, mail servers, dns servers etc. (http://www.nbrc.ac.in, http://neuroscienceacademy.org.in, http://snci.nbrc.res.in, http://webmail.nbrc.ac.in) primarily running on unix/linux platforms.*
- *Application servers running on windows and linux are also centrally maintained for providing services to thin client systems. The performance of the critical servers are monitored round the clock and up-gradation, server consolidation, virtualization are done as and when required.*

DIC also provides technical support to users in the routine requirement and also undertakes in-house development of softwares, web-tools and web servers for aiding in the research and teaching activities of the centre.

New Initiatives:

High performance-compute (HPC) cluster using blade servers based infrastructure for data analysis in functional MRI experiments has being initiated. The institute will also be connected under National Knowledge Network (NKN) to various universities and national institutes on a gigabit link which will open new possibilities of collaborations, aiding in research activities and knowledge sharing with other scientific institutions/ laboratories in India and abroad.

Animal Facility

NBRC has a modern animal facility to meet the requirements of the scientists for advanced neuroscience research. The animal facility of NBRC procures and breeds a wide variety of species of laboratory animals which are used as animal models for understanding the human brain in health and disease. The Animal Facility adheres to the highest standards of laboratory animal care, and complies with all the national and international regulations for the care and use of animals in research. The animal facility staff ensures humane and appropriate animal care. A high degree of hygienic conditions are maintained in the animal house by regular cleaning and sterilization of the cages, water bottles, bedding and feed. The animal rooms are also regularly disinfected. Heavy-duty steam autoclaves have been installed for these purposes. A hot vapour jet machine is used for cleaning the large rabbit and monkey cages. The staff is required to take shower, before changing to work-overalls before entering the animal rooms, and again in the evening after finishing the work. All users wear facemasks and gloves before handling animals.

All the animal species are housed in species appropriate cages, which are designed as per the CPCSEA guidelines. The outdoor play area for non-human primates has six large interconnected enclosures that provide a flexible layout for optimising enrichment and social interactions. The transgenic, knock out and mutant mice are housed under germ-free conditions in filter top cages and individually ventilated cages (IVC). Such animals are handled in laminar hoods, and the moved to fresh cages in cage-changing station under hepa-filtered air.

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

Qualified and trained veterinarians oversee all the animal health concerns, and provide all necessary veterinary care to ensure that healthy animals are available for research.

The animal facility has a state-of-art surgical suite equipped with intensity controlled surgical lights, advanced surgical microscopes, gas anesthesia machines, equipment for monitoring

the physiological state of the animals, including heart rate moniter, pulse oximeter and rectal thermometer. For cleaning and sterilization of the surgical instruments there is an ultrasonic instrument cleaner, glass bead steriliser and ethylene oxide gas steriliser.

The animal facility has a necropsy room, perfusion room with a perfusion hood, deep freezer for carcass storage, and incinerator for disposal of the animal carcass.

The animal facility has been equipped with a card reader security system. The access is restricted to the animal house staff, maintenance staff and the investigators who are listed in the IAEC approved protocols. All the personnel who handle animals are required to have a current tetanus vaccination, and those who handle non-human primates (NHP) are screened for tuberculosis. Everyone handling NHP's is trained in the procedures for the first-aid in case of an injury from a animal bite or scratch.

Close circuit monitoring cameras have been installed at various locations in the facility to help in effective monitoring of the animal facility.

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

Mice Strains

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

Transgenic Mice

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

UBC-GFP (Green fluorescent protein)

B6CBA-Tg(Hdexon1)62Gpb/3J (Huntington disease model)

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

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

Knock Out Mice

GAP-43 knock out mice,

UBE3Anull mice (Angelman syndrome model)

Mutant Mice

CBA/J mice (Retinal degeneration model)

Rat Strains

Long Evans

Sprague Dawley

Rabbits

New Zealand white

Guinea Pigs

Duncan Hartley

Non-human primates

Macaca mulata

Macaca radiata

Birds

Zebra finches

All the mice strains are maintained by inbreeding and the rat strains by out breeding. Guinea pig and zebra finch colonies are maintained by out breeding. The transgenic and knockout mice are maintained under a 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 and is also providing the facilities and support to the Scientists, researchers, students, staffs and its networked centers.

The NBRC library has good collection of Journals, books and other relevant research materials on Neuroscience, Biochemistry, Genetics, Molecular Biology, Immunology & Microbiology, Pharmacology and Toxicology, Psychology, Physics, Mathematics, Computer Science and General Subjects. NBRC Library is currently subscribing to 16 Journals and rest of 917 Online Journals covered through DBT e-Library Consortium (DeLCON). Library is also subscribing Newspapers, News Letters. The Collection of NBRC Library is growing day-by-day in the view of research and knowledge in the field of Neuroscience and related areas. These resources were kept to fully meet the present day requirements of the users such as faculty, research scholars, students and staffs.

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

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

A total of 110 registered users including Scientist, Researchers, students and other staff used the NBRC library facilities. The NBRC Library also provides the services of “Inter Library Loan” to the 48 Networked Centres at all over India. The researchers,

scientists and students send their requirement for research material or journal articles through email to NBRC Library (library@nbrc.ac.in) and staff of library download the articles / papers / information and sends the same to the requestors free of cost. The library has entertained approximately 340 PDF articles in this financial year, and the requests are increasing day-by-day.

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

The Main Activities of NBRC Library

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

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

DBT'S ELECTRONIC LIBRARY CONSORTIUM (DELCON)

DBT's Electronic Library Consortium (DeLCON)

About 'DeLCON Consortium'

The DBT's Electronic Library Consortium called as "DeLCON". The 'DeLCON Consortium' has been set up by the DBT to promote the use of electronic databases and full text access to journals by the Research and academic community in the country.

The 'DBT's Electronic Library Consortium (DeLCON)' is major initiative of the 'Department of Biotechnology (DBT)' to bring qualitative change in their research Institutions. It was launched in January, 2009 with the 10 DBT member Institutions (including DBT H.Q. & ICGEB) with a large number of high impact online journals. It is a national initiative for providing access to scholarly electronic resources including full-text and bibliographic databases in all the life science subject disciplines to DBT Institutional community. It facilitates access to high quality e-resources to DBT research Institutions in the country to improve teaching, learning and research.

The 'DeLCON Consortium' provides current as well as archival access to more than 917 core and peer-reviewed journals and one bibliographic database (SCOPUS Database) in different disciplines from 20 Foreign publishers including some of aggregators. The access to all major e-resources was given to 10 DBT Institutions in the beginning of the year 2009. It has now been extended to new 17 more DBT Institutions in 1st phase of extension in this year 2010.

The Faculties, Scientists, Research Scholars, Students and Project Assistants of Institutions covered under DeLCON are the primary beneficiaries. DBT sponsored the entire expenses for DBT organizations for providing e-Journals access through 'DeLCON Consortium'.

The DeLCON comprises the following 27 Member Institutions which are given below

DeLCON MEMBERS

1. National Brain Research Centre (NBRC), Manesar
2. Department of Biotechnology (DBT), New Delhi
3. National Institute of Plant Genome Research (NIPGR) - New Delhi
4. National Institute of Immunology (NII) - New Delhi

5. National Centre for Cell Science (NCCS) - Pune
6. Institute of Life Sciences (ILS) - Bhubaneshwar
7. Institute of Bioresources and Sustainable Development (ISBD) - Imphal
8. Centre for DNA Fingerprinting and Diagnostics (CDFD) - Hyderabad
9. Rajiv Gandhi Centre for Biotechnology (RGCB) - Thiruvananthapuram
10. International Centre for Genetics and Engineering Biotechnology (ICGEB), New Delhi

NEW DeLCON MEMBERS

1. The Wellcome Trust-DBT India Alliance, Hyderabad
2. Dibrugarh University, Assam
3. Assam University, Silchar
4. North Eastern Regional Institute of Science & Technology, Arunachal Pradesh
5. North East Institute of Science & Technology, Assam
6. Mizoram University, Mizoram
7. D. M. College of Science, Manipur
8. Sikkim University, Gangtok
9. College of Veterinary Science, Assam Agricultural University, Guwahati
10. St. Anthony's College, Meghalaya
11. Biotechnology Industry Research Assistance Program (BIRAP), New Delhi
12. Gauhati University, Assam
13. Manipur University, Imphal
14. College of Veterinary Science & Animal Husbandry Central Agricultural University, Mizoram
15. Rajiv Gandhi University, Arunachal Pradesh
16. Nagaland University, Nagaland
17. North-Eastern Hill University, Shillong

In terms of number of users, the DBT's Electronic Library Consortium (DeLCON) is the largest Consortium in India in the term of Life Sciences & Biotechnology Subject area with a vision and plan to reach out to all DBT Institutions departments, Research Institutions, Universities, and their colleges affiliated to the DBT, over a period of time.

OBJECTIVES

The main objective of the DBT's e- Library Consortium (DeLCON) is to provide access to qualitative electronic resources including full-text and bibliographic databases to DBT institutions at a lower rates of subscription. The major aims and objectives of the DBT's e- Library Consortium (DeLCON) are as follows :

- To provide access to a high-quality and scholarly electronic resources to a large number of DBT institutions including research Institutions, universities and colleges at substantially lower rates of subscription and at most favourable terms and conditions;
- To promote rapid and efficient access to scholarly content to the users and to create and promote use of DeLCON in teaching and

learning in research organizations, universities, and colleges in India;

- To extend the benefit of Consortium to its associate members
- To impart training to the users, librarians, research scholars and faculty members of the institutions in use of electronic resources with an aim to optimize their usage;
- To promote use of e-resources with gradual decrease in print subscription;
- To promote interaction and inter-library cooperation amongst the participating DeLCON members;
- To evaluate the usage of the subscribed resources and to identify new resources that are required to be subscribed under the DeLCON Consortium;
- To bring qualitative change in teaching, learning and research with an aim to meet the ever growing challenges of globalization of higher education; and
- To increase the research productivity of the institutions both in terms of quality and quantity of publications.

Benefits OF 'DeLCON CONSORTIUM'

The consortia-based subscription to e-resources is a viable solution for increasing the access to electronic resources across DBT institutions at a lower rate of subscription. Major benefits of DeLCON Consortium are as follows:

- The DeLCON Consortium acts as a single-window service for a large number of DBT Institutions with their diverse research and academic interest;
- The DeLCON Consortium, with its collective strength of participating institutions, attracts highly discounted rates of subscription with most favourable terms of agreement for a wider range of e-resources. Most of the e-publishers have responded positively to the call of the Consortium. The rates offered to the consortium are lower by 60% to 99% depending upon the category of DBT institutions;
- Users have immediate access to material previously not subscribed to, at no incremental cost for accessing back files;
- It improves the existing library services and reduced the subscription cost;
- The research productivity of DBT institutions is expected to improve with increased access to international full-text resources (Journals and database);
- The DeLCON Consortium is expected to trigger remarkable increase in sharing of electronic resources amongst participating DeLCON members
- The DeLCON Consortium has been opened-up to add more DBT institutions through its next phase of extension and other DBT institutions can also join the DeLCON Consortium and

get the benefit of not only highly discounted rates of subscription but also the favourable terms and conditions;

- The DeLCON Consortium is offered better terms of agreement for use, archival access and preservation of subscribed electronic resources, which would not have been possible for any single institutions; and
- Since the subscribed resources is accessible online in electronic format, the DBT institutions have less pressure on space requirement for storing and managing print-based library resources. Moreover, all problems associated with print media such as their wear and tear, location, shelving, binding, organizing, etc. are not an issue for electronic resources.

DeLCON Electronic Resources

The DeLCON Consortium subscribes to electronic resources covering all major Life Science & Biotechnology subject discipline being taught in the DBT research Institutions, Universities & Colleges. It includes wide variety of materials e.g. e-journals, bibliographic databases, reviews published by scholarly societies, university presses, institutional and commercial publishers. The DeLCON Consortium subscribes to 917 full-text e-resources and 01 bibliographic database from 20 renowned foreign publishers including societies and some of aggregators. The member institutions are provided differential access to these resources based on their needs and activity profile as per the recommendation of the National DeLCON Steering Committee.

The complete list of full-text resources (e-Journals) and bibliographic databases subscribed under the DeLCON Consortium is given in **Appendix I**.

Appendix I

1	American Association for Advancement of Science	http://www.sciencemag.org	(3 Journal)
2	American Association for Cancer Research (AACR)	http://www.aacr.org	(8 Journals)
3	American Chemical Society (ACS)	http://pubs.acs.org	(37 Journals)
4	Annual Reviews	http://www.annualreviews.org	(23 Journals)
5	American Society for Biochemistry and Molecular Biology	http:///www.jbc.org	(2 Journal)
6	American Society For Microbiology	http://www.asm.org/	(12 Journal)
7	Cold Spring Harbor Laboratory Press Journals	http://www.cshl.edu	(4 Journals)

8	Informa Healthcare / Taylor and Francis	http://www.informaworld.com	(7 Journals)
9	Lippincott William and Wilkins (LWW) / Wolter and Kluwer / OVID	http://ovidsp.ovid.com	(11 Journals)
10	Marry ANN Liebert	http://www.liebertonline.com	(7 Journals)
11	Nature Publications	http://www.nature.com	(40 Journals)
12	Oxford University Press (OUP)	http://www.oxfordjournals.org	(18 Journals)
13	Springer India	http://www.springerlink.com	(237 Journals)
14	Society for General Microbiology	http://mic.sgmjournals.org	(3 Journals)
15	Society for Hematology	http://bloodjournals.hematologylibrary.org	(1 Journal)
16	Wiley-Blackwell	http://www3.interscience.wiley.com/cgi-bin/home	(86 Journals)
17	Elsevier Science (ScienceDirect)	http://www.sciencedirect.com	(415 Journals)
18	American Society of Plant Biologist	http://www.aspb.org/	(2 Journals)
19	American Association of Immunologist	http://www.aai.org/	(1 Journals)
20	Scopus Database	http://www.scopus.com	(1 Database)

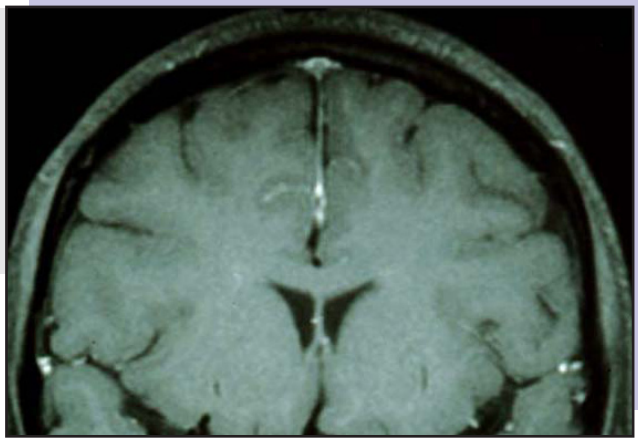
Subject Coverage Under DeLCON Consortium

The DeLCON Consortium covers all the disciplines and subjects coming under Life Sciences i.e. Biotechnology, Bioinformatics, Biochemistry, Biology, Chemical Biology, Sciences, Immunology, Neuroscience, Plant Genome, Plant Biology, Microbiology, Physiology, Psychology, Physiotherapy, Psychotherapy, Genome, Gene, Genetics, Mathematics, Physics, Chemistry, Radiology, Medicines, Computational Biology, Cell Biology, Cell Sciences, Molecularbiology, Molecular and Cellular Biology, Computational Neuroscience, System Neuroscience etc.

DBT's E-LIBRARY CONSORTIUM (DeLCON) JOURNALS are AVAILABLE to ACCESS : http://www.nbrc.ac.in/delcon/

DD Lal
DeLCON Administrator
National Brain Research Centre

NATIONAL NEUROIMAGING FACILITY



National Neuroimaging Facility

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

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

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

(1) MR Spectroscopy (MRS) which provides non-invasive neurochemical level estimations, enabling clinical correlation and early diagnosis of a disease.

(2) Functional MRI (fMRI) which, as the name suggests, correlates functional activity (haemodynamics) with anatomical images of brain.

(3) Diffusion weighted tensor imaging (DTI) is yet another specialized imaging modality.

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

Electroencephalography (EEG) is used for measuring and recording the spontaneous electrical activity of the brain caused by neuronal conduction. Special sensors/electrodes are attached to the scalp and the neural activity is recorded as oscillations of varying frequency. Various conditions like epilepsy, dementia, consciousness

and narcolepsy (sleeping disorder) can be studied by EEG.

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

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

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

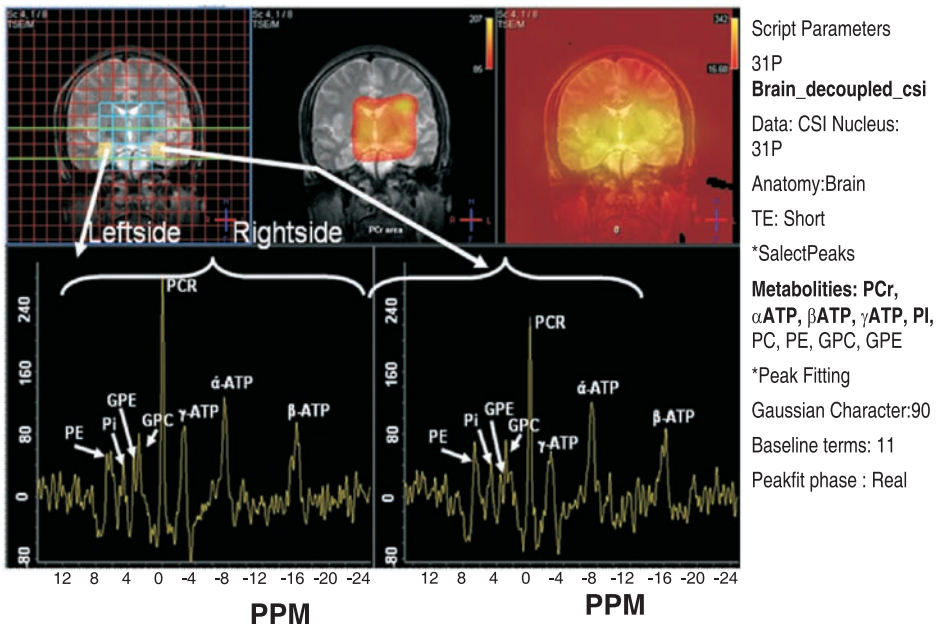


Figure1 31P MRS data collected using 1H decoupled dual tuned head coil (Transmit and Receive). This experiment was specifically designed to obtain spectra from hippocampus both left and right marked by yellow color. The dimension of the each voxel was 13.3 mm X 13.3 mm X 25 mm and number of scans were 24. Data Acquisition time was ~25 minutes. MRS data was processed using Philips software.

the hippocampus of a normal control subject for different neurochemicals containing phosphorous atom.

The Speech and Language Laboratory (SALLY) at NBRC is interested in studying the cortical pathways underlying reading. Researchers from SALLY laboratory are currently focused on studying word reading in Hindi-English bilinguals. The figure 2 shows the different brain areas involved in reading words aloud in Hindi.

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

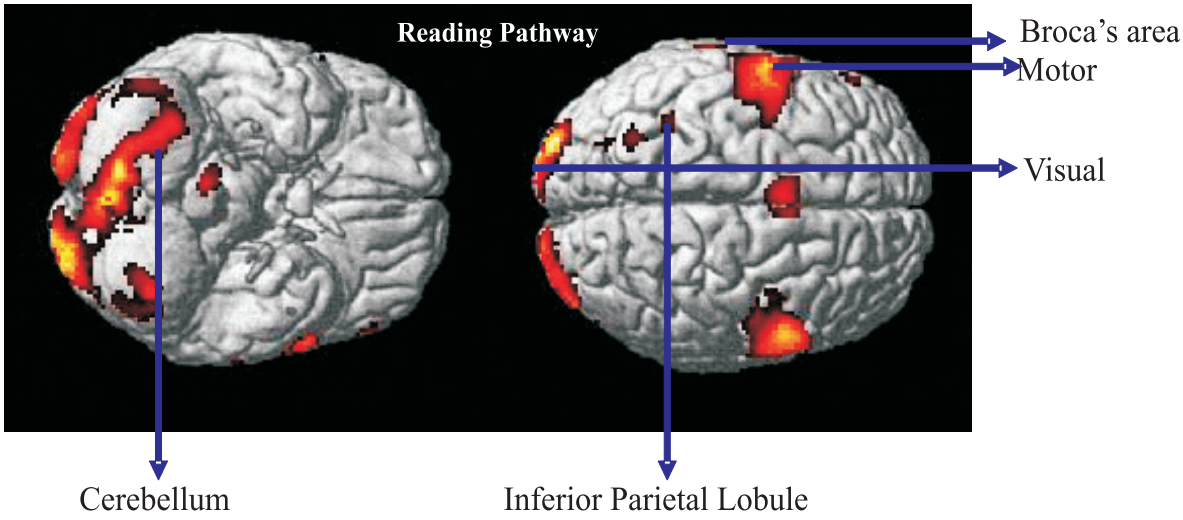


Figure2. The left rendering depicts a ventral view while the right rendering depicts a dorsal view of the brain. Different brain areas involved in reading have been shown

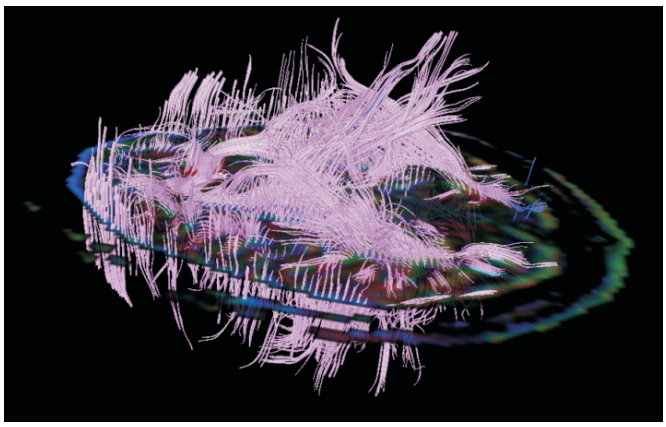


Figure3 Diffusion tensor image of the brain of epileptic patient from which the conductivity tensor image of the brain is obtained which enables more accurate localization of the electrical foci based on EEG and potential field recordings.

At the imaging facility, Prof. Partha Raghunathan is the Consultant Professor while Mr. Jitender Ahlawat is the MRI/ EEG Operation staff.

TRANSLATIONAL & CLINICAL NEUROSCIENCE UNIT

Translational & Clinical Neuroscience Unit

Translational research aims to connect basic research to patient care: From the Bench to the Bedside. The Clinical Research Unit of NBRC covers the full spectrum of clinical neuroscience: neurology, neuropsychiatry, neurosurgery, neuropsychology, and psychometry. The unit has a tri-weekly, morning outpatient facility, at the Government General Hospital, Gurgaon, one of NBRC's consultant clinical faculty is available on a designated day. The NBRC Unit has integrated well with the General hospital medical team and there is an increasing number of referrals from other in-house departments and local hospitals. The out-patient facility is busy, and on some days the attendance can be about forty patients. Around 65% to 70% of the patients suffer from headache or seizure disorder, 5% have neuroses/psychoses and the remaining belong to a miscellany group of peripheral neuropathies, Bell's palsy, sciatica, trigeminal neuralgia, old stroke, mental retardation and other common neurological disorders.

The follow up by the patients is about 90%. Male to female ratio is almost equal. Paediatric group patient attendance is mainly for management of epileptic seizure and disorders of the mentally challenged. There are also elderly patients attending, and movement disorders is an important reason of attendance. Patients attending the OPD at the General Hospital come from old Gurgaon township and the villages and towns in the surrounding districts of Haryana, while some come from neighbouring states as Rajasthan, Uttarkhand, Delhi and Uttar Pradesh.

Patients requiring advanced specialist neurology in-patient care are referred to All-India Institute of Medical Sciences (AIIMS) or Vardhaman Medical College (Safdarjung Hospital), New Delhi or to other tertiary hospital as per the choice of the patient, if they desire.

Outpatient case records in neurology are maintained from the outset, aside from relevant entry into the patient OP case sheets, which the patients keep in their possession. A comprehensive Neurology case sheet has been formulated and formatted by Distributed Information Centre of NBRC. We duly hope to prospectively enter all the medical data of new patients, to create computer database with relevant patient data along with any planned neuroimaging/ molecular/physiological studies at the NBRC laboratories, thus creating

a well documented "clinical window" for our research institute. In this effort to narrow the gap between Basic Neuroscience and Applied Neuroscience, an ethics committee protocol has been formulated.

The association of NBRC with Alzheimer's & Related Disorders Society of India (ARDSI) which has been going on from 2005, has been further fostered by the NBRC consultant faculty. This interaction promises to grow to the mutual benefit of both institutions concerned primarily with the common goal of amelioration of neurodegenenerative diseases in their varied aspects. Besides clinical neuroscience, one is exposed to the psychosocial and neuroepidemiological problems of the ageing populace in their environment.

Further expansion of the electrophysiological facility is underway, with procurement of 64-channel high density EEG/evoked potential response analysis, electrical dipole source mapping, Electromyography (EMG) and Neurophysiological studies as Nerve Conduction velocity system and neurometry.

For proper functioning and further clinical support, the Unit receives full cooperation of the Government of Haryana, and the Civil Surgeon and Principal Medical Officer of the General Hospital.

Investigation facilities:

The following facilities are available to the patients of the unit through the hospital/clinics at concessional rates:

MRI system: Siemens Magnetom 1.5 Tesla scanner with various investigation protocols

CT system & Ultrasonography

Neurophysiology: EEG and Evoked response.

X-ray and Contrast imaging.

Wetlab facilities: Biochemistry, Microbiology, Haematology, Pathology & Immunology.

Consultants:

Consultant Clinical Professor:
Dr. V. S. Mehta

Consultant Neurologist:
Dr Subbulakshmy Natarajan (till Dec. 2009).

Consultant Clinical Assistant Professor:
Dr Kapil Agarwal

Consultant Clinical Assistant Professor:
Dr Rajnish Kumar

Staff:

Resident Medical Officer:
Dr Shelly

Clinical Neuropsychologist:
Krishan Kumar

Clinic Assistant:
H. Singh

MEETINGS AND WORKSHOP

Perception Engineering Workshop 2009

Perception Engineering Workshop 2009

A workshop on Perception Engineering was held on 4-5th December 2009 at the National Brain Research Centre in coordination of the Ministry of Information Technology, Govt. of India. The workshop sessions were conducted with participation of active groups across the country on neuroscience, cognitive science, linguistics along with computer engineers and robotics researchers and artificial intelligence experts. The participants in the workshop were from IIT Delhi, IIT Bombay, IIIT, Hyderabad, Jadavpur University, Central Electronic Engineering Research Institute (CEERI), Pilani, and Centre for Development of Advanced Computing (CDAC), Kolkata, besides National Brain Research Centre.

The two day workshop, the first day of which was held at National Brain Research Centre, Manesar and the second day at Indian Institute of Delhi, New Delhi, mainly focused on information processesing in the human brain and the modelling of these processes using computational tools and machines. There were presentations of research projects on targeted areas of ranging from electrophysiology, brain machine interface and rehabilitation to neuroimaging, neuromorphic technology and pattern recognition. Research associates, and students from National Brain Research Centre, IIT Delhi, CEERI Pilani, actively participated and it was a rewarding experience for them, being exposed to a wide range of interdisciplinary endeavours. Possible areas of collaboration between NBRC laboratories and the other institutions were explored.

This is the first initiative in the country encompassing a versatile symbiosis of all the relevant disciplines cognate to the Perception Engineering field which is well on the way to transform to the critical field of neuromorphic technology in near future.

INTERNATIONAL COLLABORATIONS AND NETWORKING

International Collaborations

Networking

International Collaborations

International collaborations aimed at promoting neuroscience enabling the Centre to evolve cross border relationship for Indian Neuroscientists with the international neuroscience community through such exchange programs. Towards this endeavour of excellence in a very short span of time, NBRC has made great strides in establishing such collaborations with various prestigious neuroscience institutions in different countries around the world. Following are a few notable collaborative arrangements:

United States

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

France

Dr. Pierre Gressens and Dr. Shyamala Mani have been awarded an INSERM-ICMR collaborative grant to study the effect of maternal malnutrition on the developing brain of the fetus and also plan to use stem cells for neonatal neuroprotection.

Italy

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

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

The Netherlands

A project of high field neuroimaging methodology development, for collaboration between Prof Prasun Roy and Prof. Peter Luijten, Utrecht Medical Centre, has been sponsored by The Utrecht University Foundation.

Networking

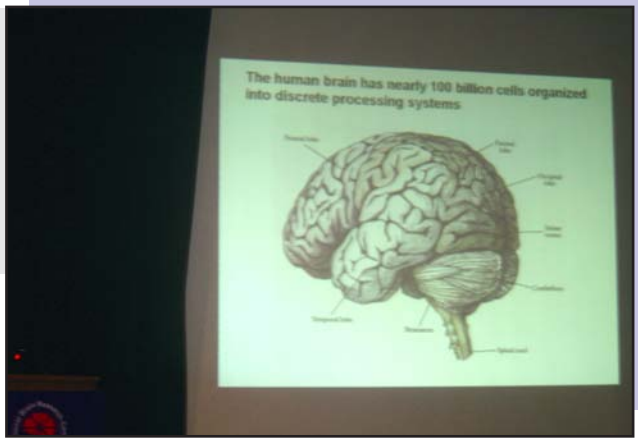
A major goal of NBRC is to network the existing neuroscience groups/ institutions in the country and promote multidisciplinary research in neuroscience. This is aimed to prevent unnecessary duplication of the work and facilities already existing. It also facilitates sharing of expertise and available 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 48 centres throughout India are networked to NBRC. The following institutions/universities are member of our network activities

List of Network Centres

1. All India Institute of Medical Sciences (AIIMS), New Delhi.
2. Banaras Hindu University (BHU), Varanasi.
3. Bangur Institute of Neurology, Kolkata.
4. Centre for Behavioural and Cognitive Sciences (CBCS), University of Allahabad, Allahabad.
5. Centre for Cellular & Molecular Biology (CCMB), Hyderabad.
6. Central Drug Research Institute (CDRI), Lucknow.
7. Centre for DNA Fingerprinting and Diagnostic, Hyderabad.
8. Central Food and Technological Research Institute (CFTRI), Mysore.
9. Cochin University of Science and Technology, Cochin.
10. Department of Biotechnology. New Delhi.
11. Delhi University, South Campus, Delhi.
12. Dr. A. L. Neurosurgical Centre, Chennai.
13. Indo American Hospital Brain and Spine Center, Kerala.
14. Institute of Cybernetics, Systems and Information Technology, Kolkata.

15. International Centre for Genetic Engineering and Biotechnology (ICGEB), New Delhi.
16. Institute of Genomics and Integrative Biology (IGIB), Delhi.
17. Institute of Human Behaviour & Allied Sciences (IHBAS), Delhi.
18. Indian Institute of Information Technology (IIIT), Allahabad.
19. Indian Institute of Technology (IIT), Mumbai.
20. Indian Institute of Technology (IIT), Delhi.
21. Indian Institute of Technology (IIT), Kanpur.
22. Indian Institute of Science (IIS), Bangalore.
23. Indian Institute of Chemical Biology (IICB), Kolkata.
24. Institute of Nuclear Medicine and Allied Sciences (INMAS), New Delhi.
25. Industrial Toxicology Research Centre (ITRC), Lucknow.
26. Indian Statistical Institute, Kolkata.
27. International School of Photomics, Cochin.
28. Jagadguru Sri Shivarathreeshwara Medical College, Mysore
29. Jawaharlal Nehru University (JNU), New Delhi.
30. Jawaharlal Nehru Centre for Advance Scientific Research (JNCASR), Bangalore.
31. Jiwaji University, Gwalior.
32. M.S. University of Baroda (Dept. of Microbiology and Biotechnology Centre), Baroda.
33. National Centre for Biological Sciences (NCBS), Bangalore.
34. National Informatics Centre (Medical Informatics and Telemedicine Division), (NIC) New Delhi.
35. National Institute of Mental Health & Neuroscience (NIMHANS), Bangalore.
36. Nizam's Institute for Medical Sciences (NIMS), Hyderabad.
37. Rajiv Gandhi Centre for Biotechnology, Trivandrum.
38. National Neuroscience Centre (NNC), Kolkata.
39. Sanjay Gandhi Post-Graduate Institute of Medical Sciences (SGPGIMS), Lucknow.
40. School of Information Technology, West Bengal University.
41. Shree Chitra Tirunal Institute for Medical Sciences and Technology, Thiruvanthapuram.
42. Sri Venkateswara Institute of Medical Sciences, Tirupati.
43. Tata Institute of Fundamental Research (TIFR), Mumbai.
44. University College of Medical Sciences (UCMS), Delhi.
45. University of Hyderabad, Hyderabad.
46. University of Calcutta, Kolkata.
47. Vidyasagar Institute of Mental Health and Neuroscience (VIMHANS), New Delhi.
48. Vision Research Foundation, Chennai

INVITED LECTURES



Invited Lectures

Sr.	Name of the Speaker	Title of the Lecture	Date
1.	Dr. Rama Jayasundar, Department of NMR All India Institue of Medical Sciences (AIIMS) New Delhi	Quantum logic in ayurveda.	April 6th 09
2.	Dr. Arpan Banerjee, NYU	'Model Based approaches for studying brain and behavior.	April 15th 09
3.	Dr. Romi Nijhawan University of Sussex	Predicting the Present: Visual-Motor Neural Delays and Compensation.	April 17th 09
4.	Dr. Beena Khurana University of Sussex	Cuing of Saccadic Orienting: Moving Eyes versus Moving Arrows.	April 17th 09
5.	Dr. Anandmohan Ghosh CNRS, France	'Noise during rest enables the exploration of the brains dynamic repertoire	April 24th 09
6.	Dr. Debabrata Chakravarti Associate Professor Northwestern University Feinberg School of Medicine	Chromatin remodeling and nuclear receptor signaling.	May 13th 09
7.	Dr. Tapas Nag, Associate Professor, Dept. of Anatomy, AIIMS, New Delhi	Selective vulnerability of cones in aging human retina.	May 25th 09
8.	Dr. Anil G. Cashikar Assistant Professor Medical College of Georgia, USA	Molecular chaperones and neurodegenerative disorders.	June 19th 09
9.	Dr Elizabeth Thomas University of Dijon Burgundy, France	The study of the neural encoding of categorization with a Kohonen network.	July 6th 09

10.	Dr. Deb Ranjan Bhattacharya Deputy General Manager- Technical & Application Support Laboratory Products Group, ThermoFisher Scientific, India	Recent Spectroscopic Detection Techniques for Bio-molecules & their Interactions.	July 30th 09
11.	Dr. Sachin Deshmukh Mind Brain Institute Johns Hopkins University Baltimore USA	Representation of Spatial and Non-Spatial Information in Lateral and Medial Entorhinal Cortex.	August 7th 09
12	Dr. Samarjit Bhattacharyya, Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine	The role of post-synaptic density proteins in AMPA receptor trafficking.	August 11th 09
13.	Dr. Susanne Reiterer The University of Tubingen, Germany	A neuro-cognitive approach to speech imitation & foreign language learning talent.	August 27th 09
14.	Dr. Sankar Venkatachalam, Department of Anatomy, Dr A.L.M. Postgraduate Institute of Basic Medical Sciences, University of Madras Tamil Nadu	Role of bone marrow and amnion derived stem cells in spinal cord injury repair research.	September 3rd 09
15.	Dr. Rashmi Bansal Associate Professor Dept. Neuroscience, MC-3401 University of Connecticut Medical School 263 Farmington Avenue Farmington CT 06030-3205 USA	Role of Fibroblast Growth Factors in Glial-Neuron Signaling.	September 29th 09
16.	Dr. Poonam Malhotra, MD Associate Professor Cardiac Anesthesia AIIMS, New Delhi	Inhaled Anesthetics and Cognitive performance of patients undergoing Coronary artery bypass surgery.	November 3rd 09
17.	Dr. Kenneth R. Pugh Associate Professor, Department of Pediatrics (Neurology), Yale University School of Medicine and President and Director of Research, Haskins Laboratories, New Haven CT. 06511	Neuroimaging studies of Reading and Language Development: An update on recent findings.	November 17th 09

18.	Mr. Sourojit Bhowmick Dept. of Microbiology and Immunology Univ. of Connecticut Health Center	The Sympathy behind immune regulation: An unique relationship between the Sympathetic Nervous System and regulatory T cells.	November 25th 09
19.	Dr Kavita Babu Department of Molecular Biology Massachusetts General Hospital	An IgSF protein RIG-3 prevents synaptic potentiation in C. elegans.	November 25th 09
20.	Dr Hatim Zariwala Allen Institute for Brain Science	Toward the genetic and cellular basis of cognition.	November 25th 09
21.	Prof. Adhip PN Majumdar DSc., Karmanos Cancer Inst., Wayne State University Detroit	Cancer Stem Cells: A New Paradigm in Aging and Gastrointestinal Carcinogenesis.	December 2nd 09
22.	Dr Pratik Mutha Penn State University NM VA Healthcare System	Visual modulation of reflex responses during movement	December 8th 09
23.	Dr Sujay Kumar Dhara Research Associate Morehouse School of Medicine, University of Georgia Atlanta, GA	Human Embryonic Stem Cells in Basic and Applied Neural Research.	December 15th 09
24.	Dr Krish Sathian Professor of Neurology Rehabilitation Medicine and Psychology Emory University, USA	Multisensory integration of vision and touch.	December 17th 09
25.	Dr. Puneet Opal Assistant Professor Davee Department of Neurology, Northwestern University Feinberg School of Medicine	Unraveling the pathogenesis of Spinocerebellar Ataxia Type 1.	January 6th 10
26.	Dr. Charanjit Kaur Associate Professor National University of Singapore	Hypoxia induced blood-brain, blood-retinal and blood-cerebrospinal fluid barrier dysfunction	January 21st 10
27.	Dr. Matthew Belmonte Department of Human Development Cornell University	Frontal Lobe Physiology and Autistic Traits within and beyond the Autism Phenotype	January 18th 10

28.	Ms. Sonia Baloni Graduate student German Primate Center, Göttingen (Germany)	Spatial and feature Based attention in area MST of macaque visual cortex	February 2nd 10
29.	Kaveri Rajaraman Dept. of Molecular and Cellular Biology Harvard University, USA	Intrinsically photosensitive ganglion cells of the tiger salamander retina	February 15th 10
30.	Mr. Sourav Banerjee Neuroscience Research Institute University of California Santa Barbara CA-93106, USA	MicroRNAs in Synaptic Plasticity: Tiny RNAs with Big Potential	February 19th 10

ACADEMIC PROGRAMMES

Ph.D. in Neuroscience

Integrated Ph.D. in Neuroscience

Summer Training and Short-term Programmes

Academic Programmes

Deemed University Status

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

On completion of 5 years period from the time NBRC has been given de-novo deemed University status, a panel of 6 Member Committee (duly constituted by UGC) visited NBRC for reviewing the 'Deemed to be University' status and for recommending further extension. The report has been received. However the deemed university status has been reviewed by an independent committee constituted by Ministry of HRD. The committee has given excellent report and placed this university as "A" category Institute.

UGC also desired to re-assess and review the deemed university status and again a duly constituted committee visited NBRC on 03rd, 04th & 05th February, 2010 and gave a very good report. The notification from Ministry of HRD is awaited.

Courses Offered:

Ph.D. in Neuroscience

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

NBRC inducts students for its Ph.D. programme from diverse backgrounds including Masters degree in any branch related to Neurosciences, Psychology or M.B.B.S., B.E., or B.Tech. NBRC recognizes that understanding brain functions requires a fusion of knowledge from multiple disciplines.

Fellowship for Junior Research Fellows is Rs.12,000/- per month and for Senior Research Fellows it is Rs.14,000/- (which may change as per extant rules and as per circulars issued time to time on the subject).

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 Ph.D. programme from diverse backgrounds including

Bachelor's degree in any branch related to Neurosciences, M.B.B.S., B.E., B.Tech. or Psychology. NBRC recognizes that understanding brain functions requires a fusion of knowledge from multiple disciplines.

Integrated Ph.D. Students are provided a fellowship of Rs. 3000/- per month for the first two years. From third year onwards they are paid fellowship on par with Ph.D. students. After completion of the Integrated Ph.D. 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 multidisciplinary teaching programme in Life Sciences.

NBRC offers certain benefits to its students in the form of fellowships, hostel accommodation, transportation facility, medical reimbursement to its students.

Summer Training and Short-term Programmes

NBRC conducted Summer Training Programme for the Students through three National Science Academies viz: (1) Indian Academy of Science, Bangalore (2) Indian National Science Academy, New Delhi (3) National Academy of Sciences, Allahabad. The summer training was for a period of 8 weeks. The Trainees were provided with shared accommodation in the Hostel of NBRC during their training period. Summer trainees were encouraged to attend seminars and journal clubs organized at the Institute.

The summer training projects give students an exposure to Neuroscience and encourage them to consider it as a future career option.

Also Science Popularisation Lectures were conducted at Faridabad and Gurgaon located in Haryana and Research Associates visited the respective places to deliver the lectures.

GENERAL & ACADEMIC ADMINISTRATION

General & Academic Administration – A Profile

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

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

During the year under review, the Administration Wing strived hard in providing support services and in carrying out the following activities.

- The cultural festival of NBRC, 'TANTRIKA 2009' was organized within the campus which included a variety of cultural and sports events. Students, officers, and staff of NBRC participated in the event.
- Making due diligence and compliance to the Right to Information Act, 2005 including compilation and updating of the required disclosure data on the website.
- Making major imports from different countries in terms of equipments and other consumables with a meticulous planning and precise schedule.
- The new hostel building for housing staff and Research Assistants was taken over from DAE.
- The staff and Research Assistants were shifted in the new hostel building at NBRC campus, Manesar.

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, general applications etc. A proposal for creation of posts for Hindi Cell is under consideration of the Department of Biotechnology. An appreciation letter had been received

by NBRC from Ministry of Home Affairs, Regional Implementation Office, Ghaziabad towards implementation of Hindi in day to day official work. The correspondence in Hindi is 76%, which is remarkable. The "Timahi Report" are used to sent to Official Language Department, Ghaziabad; Department of Biotechnology, New Delhi and Nagar Rajbhasha Vibhag, Gurgaon. The official language committee with its members taking keen interest and is actively looking into the use of Hindi and is being reviewed every quarter.

RTI Act

The provisions of RTI Act are being followed in NBRC in letter and in spirit. During 2009-10, nine RTI applications were received seeking information on various matters concerning NBRC. All applicants were provided the requisite information within the prescribed time limit.

Women Empowerment

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

Reservations and concessions in Employment & Admissions of Students

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

Vigilance

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

INSTITUTIONAL GOVERNANCE STRUCTURE & PEOPLE AT NBRC

- NBRC Society
- Governing Council
- Finance Committee
- Scientific Advisory Committee
- Research Area Panel
- Building Committee
- Academic Council
- Board of Studies
- M.Sc. Neuroscience Co-ordination Committee
- Scientific Staff
- Other Staff

Members of the NBRC Society

Prof. P.N. Tandon
(President)
No. 1, Jagriti Enclave,
Vikas Marg, New Delhi

Dr. M.K. Bhan
Secretary
Department of Biotechnology,
New Delhi

Dr. T. Ramasami
Secretary
Department of Science & Technology,
New Delhi

Dr. V.M.Katoch
Director-General
Indian Council of Medical Research,
New Delhi

Dr. Sandip K. Basu
Professor of Eminence,
National Institute of Immunology,
New Delhi

Dr. K. Vijayaraghavan
Director
National Centre for Biological
Sciences, Bangalore, Karnataka

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(Upto 31 January 2010)

Ms. Sheila Sangwan (IRS)
Additional Secretary & Financial
Advisor
Department of Science & Technology,
New Delhi (From 01 February 2010)

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Director (Retd.),
Flat –9, Doctors Apartments,
Vasundhara Enclave, Delhi

Dr. L.M. Patnaik
Vice-Chancellor
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Technology Pune, Maharashtra

Prof. Kalluri Subba Rao
Hon. Professor. & INSA-Senior
Scientist Centre for Biotechnology,
(IST) Jawaharlal Nehru Technological
University Hyderabad, Andhra Pradesh

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Advisor,
Department of Biotechnology,
New Delhi

Prof. V. Ravindranath
(Member Secretary)
Director (Upto 30 April 2009)
National Brain Research Centre,
Manesar, Haryana

Prof. P.K. Roy
(Member Secretary) Director (I/C)
(from 01 May 2009) National Brain
Research Centre, Manesar, Haryana

Members of the Governing Council

Dr. M.K. Bhan (Chairperson)
Secretary
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New Delhi

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No. 1, Jagriti Enclave,
Vikas Marg, New Delhi

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Secretary
Department. of Science & Technology
New Delhi

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Department of Science & Technology,
New Delhi (From 01 February 2010)

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National Centre for Biological
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Dr. Ashok Mishra
Chairman
Intellectual Ventures India,
Bangalore, Karnataka

Dr. Nimesh G. Desai
Medical Superintendent & Head of
the Department of Psychiatry,
Institute of Human Behavior &
Allied Sciences, New Delhi

Prof. P. Balaram
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Indian Institute of Science,
Bangalore, Karnataka

Prof. N.K. Ganguly
Advisor, THSTI
National Institute of Immunology,
New Delhi

Dr. A.K. Agarwal
Dean
Maulana Azad Medical College,
New Delhi

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Neuro Surgeon
CMC, Vellore, Tamil Nadu

Dr. V. M. Katoch
Director-General,
Indian Council of Medical Research,
New Delhi

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New Delhi

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National Brain Research Centre
Manesar, Haryana

Members of the Finance Committee

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New Delhi

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(Upto 31 January 2010)

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Bangalore, Karnataka

Dr. V. Rajshekhar
Neuro Surgen
CMC
Vellore, Tamil Nadu

Dr. K.P. Singh (UGC Nominee)
Joint Secretary
University Grants Commission,
New Delhi

Dr. T.S. Rao
Advisor
Department of Biotechnology,
New Delhi

Prof. V. Ravindranath
Director (Upto 30 April 2009)
National Brain Research Centre,
Manesar, Haryana

Prof. P.K. Roy
Director (I/C) (From 01 May 2009
National Brain Research Centre,
Manesar, Haryana

Mr. Santosh Kumar
(Member Secretary)
Offg.Finance & Accounts Officer,
National Brain Research Centre,
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Members of Scientific Advisory Committee

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Prof. N.K.Ganguly
Advisor, THSTI
National Institute of Immunology
New Delhi

Dr. W. Selvamurthy
Outstanding Scientist
Chief Controller R&D, (LS & HR)
DRDO Headquarters,
New Delhi

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Director
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Indian Institute of Technology
New Delhi

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Visiting Professor, Sree Chitra
Tirunal Institute for Medical Science
& Technology Trivandrum,
Kerala

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Professor of Psychiatry,
Advanced Centre for Yoga
National Institute of Mental Health
and Neurosciences (NIMHANS)
Bangalore, Karnataka

Dr. Ravi Mehrotra
Scientist “F”
National Physical Laboratory
New Delhi

Dr. Kanuri Venkata Subha Rao
Scientist
International Centre for
Genetic Engineering and
Biotechnology (ICGEB)
New Delhi

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Professor & Head
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National Institue of Mental Health
And Neurosciences (NIMHANS)
Bangalore, Karnataka

Dr. Satyajit Rath
Scientist
National Institute of Immunology
New Delhi

Dr. Thomas D. Albright
The Salk Institute for Biological
Studies San Diego, USA

Dr. Jean - Pierre Julien
Professor,
Laval University Research Centre of
CHUL Quebec,
Canada

Prof. Sangram Sisodia
Thomas Reynolds Senior Family
Professor of Neurosciences
Department of Neurobiology
The University of Chicago Chicago,
USA

Dr. T. S. Rao
Advisor
Department of Biotechnology
CGO Complex,
New Delhi

Members of the Research Area Panel

Dr. R. K. Gupta
Professor & Head
Dept. of Pathology
Sanjay Gandhi Post graduate
Institute of Medical Sciences
(SGPGIMS) Lucknow,
Uttar Pradesh

Dr. Shashi Wadhwa
Professor
Department of Anatomy
All India Institute of Medical Sciences
New Delhi

Dr. Shobha Srinath
Professor
Department of Psychiatry
National Institute of Mental Health
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Dr. Chitra Sarkar
Department of Pathology,
All India Institute of Medical
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Dr. Sumitra Purkayastha
Department of Theoratical Statistical
& Mathematics Unit,
Indian Statistical Institute
Kolkatta, West Bengal

Dr. Rajesh Sagar
Associate Professor
Psychiatry & De-addiction Centre
All India Institute of Medical Sciences
New Delhi

Prof. K.P.Mohan Kumar
Scientist "G" & Head,
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Indian Institute of Chemical Biology
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Jadavpur Kolkata,
West Bengal

Prof. V. Ravindranath
Director
National Brain Research Centre
Manesar, Haryana
(Has relocated to IISc, Bangalore from
NBRC w.e.f. 30th April 2009)

Dr. P.K.Roy
Director (I/C),
National Brain Research Centre,
Manesar, Haryana

Members of the Building Committee

Dr. T.S. Rao (Chairperson)
Advisor,
Department of Biotechnology
New Delhi

Dr. Satish Gupta
Scientist,
National Institute of Immunology
New Delhi

Prof. V. Ravindranath
Director (Upto 30 April 2009)
National Brain Research Centre,
Manesar, Haryana

Prof. P.K. Roy
Director (I/C) (From 01 May 2009)
National Brain Research Centre
Manesar, Haryana

Shri B. Bose
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National Institute of Immunology,
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Mr. K.V.S.Kameswara Rao
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Mr. Kannan Kasturi N.S
(Member Secretary)
Offg.Chief Administrative Officer,
National Brain Research Centre,
Manesar, Haryana

Members of the Academic Council

Prof. V.Ravindranath
(Former Director) has relocated to IISc, Bangalore from NBRC w.e.f.30th April, 2009.

Prof. P. K. Roy (Chairman)
Director (I/C)
National Brain Research Centre
Manesar, Haryana

Prof. Basabi Bhaumik
Department of Electrical Engineering
Indian Institute of Technology
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Dr. V. S. Mehta
Paras Hospitals
Gurgaon, Haryana

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University of Delhi
Delhi

Prof. Neeraj Jain
National Brain Research Centre
Manesar, Haryana

Dr. Pravat K.Mandal
National Brain Research Centre
Manesar, Haryana

Dr. Nihar Ranjan Jana
National Brain Research Centre
Manesar, Haryana

Dr. Pankaj Seth
National Brain Research Centre
Manesar, Haryana

Dr. Narender K. Dhingra
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Dr. Ranjit K. Giri
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Dr. Yoganarasimha Doreswamy
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Dr. Aditya Murthy
(Former Faculty) has relocated to IISc, Bangalore from NBRC w.e.f.19th May, 2009.

Dr. Rema Velayudhan
(Former Faculty) left NBRC w.e.f.31st August, 2009.

Dr. Shyamala Mani
(Former Faculty) has relocated to IISc, Bangalore from NBRC w.e.f.01st October, 2009.

Members of the Board of Studies

Prof. V.Ravindranath
(Former Director) has relocated to IISc, Bangalore from NBRC w.e.f.30th April, 2009.

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1 Prof. V. Ravindranath (Upto 30 April 2009)
2 Prof. Prasun Kumar Roy
3 Prof. Neeraj Jain
4 Dr. Rema Velayudhan (Upto 31 August 2009)
5 Dr. Pankaj Seth
6 Dr. Narender K. Dhingra
7 Dr. Shiv Kumar Sharma
8 Dr. Shyamala Mani (Upto 01 October 2009)
9 Dr. Aditya Murthy (Upto 19 May 2009)
10 Dr. Nihar Ranjan Jana
11 Dr. Nandini C. Singh
12 Dr. Soumya Iyengar
13 Dr. Anirban Basu
14 Dr. Ellora Sen
15 Dr. Ranjit Kumar Giri
16 Dr. Pravat K. Mandal
17 Dr. Yoganarasimha Doreswamy

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2 Dr. Subbulaxmi Natarajan (Till 31.12.2009)

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2 Dr. Sayali C. Ranade

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3 Ms. Uzma Saeed (Till 15.01.2010)

4 Mr. Shashank Tandon (Till 16.03.2010)

5 Ms. Manisha Chugh

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10 Mr. Kh. Budhachandra Singh (Till 28.10.2009)

11 Mr. Niranjan A. Kambi

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19 Ms. Radhika Rajan

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21 Ms. Shilpa Mishra

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24 Mr. Vivek Sharma (Till 26.02.2010)

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27 Ms. K.M.Sharika

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31 Mr. Deepak Kr Kaushik

32 Mr. Kashif Mahfooz (Till 04.01.2010)

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36 Mr. Apoorv Sharma

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38 Ms. Manju Pant

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23 Ms. Swarupa Chakraborty
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29. Mr. Yunis Khan

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