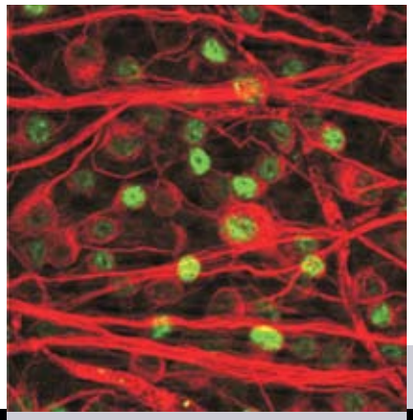

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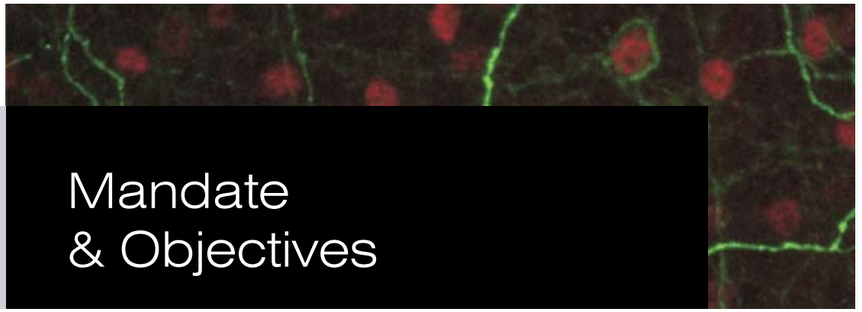


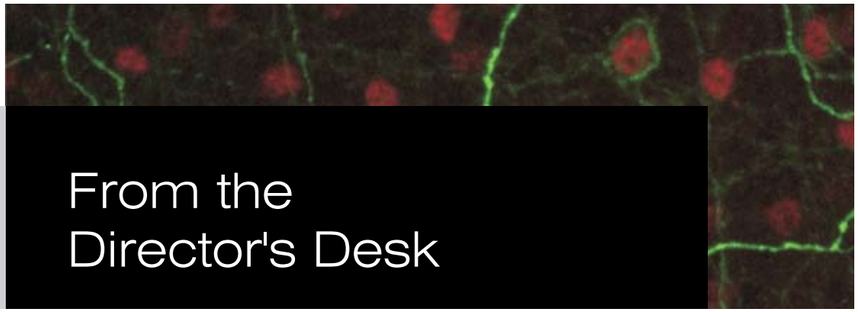
Mandate & Objectives

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.



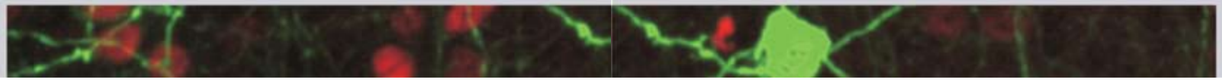
From the Director's Desk

That the brain is the last frontier is a cliché that is as old as our knowledge of organ anatomy and function. From the realm of consciousness studies, where the metaphysical brushes on to the corporeal world, to animal behavior and to molecular and supramolecular structures, neuroscience is all encompassing. More and more our technological capabilities are pushing us towards that limitless horizon where the sea and sky are supposed to meet. Also, science is, as so beautifully expressed by Sir Peter Medawar, the 'art of the possible'. This 'possible' pushes our frontiers and our technology and thoughts move forward in an ever-accelerating spiral. At NBRC, a multi-disciplinary group of scientists, encompassing molecular, systems, cognitive and computational neuroscience as well as clinical neuroscience, are working on the physiological processes that underpin the normal functioning of the brain as well as major classes of brain disorders, such as neurodegenerative, neuro-oncological, infective, developmental and neuropsychiatric ones. Infections of the brain are associated with major neurological problems in tropical countries as India. It was heartening to note that as a result of the efforts of the faculty, students and staff of NBRC, the institute ranked first in India in the number of publications in Basic Neuroscience during the last five years (2006-2010, www.scopus.com (February 23, 2011).

NBRC scientists have been conducting research on infectious agents including Japanese encephalitis, HIV and Prion diseases. As neuron-glia crosstalk is recognized to be pivotal to normal brain functions, the NeuroAIDS laboratory has broken new ground by establishing a well characterized human neuron-glia co-culture system that is used for unraveling intricacies of neuron-glia communication. It is expected that with this advancement in our capabilities with human brain cell culture system, we will be able better understand how HIV-1 proteins modulate neurocognitive functions in HIV/AIDS patients. Importantly, NBRC's endeavor from the "the bench to the bedside" has finally become a reality. One of our scientists' discoveries that minocycline can be used for the treatment of Japanese Encephalitis has been cleared by the Drug Controller General of India for a Phase II clinical trial at CSM Medical University, Lucknow.

A research group investigating the pathogenesis of Angelman's syndrome has found that chronic stress due to altered glucocorticoid receptor signalling might lead to cognitive deficits and anxiety-like behavior in a mouse model of Angelman's syndrome. Further, they have identified neuronatin, a novel substrate of malin, might be involved in Lafora disease pathogenesis. Studies from the neuro-oncology lab have dissected signaling circuitries associated with transcriptional regulation of genes associated with survival in glioblastoma and highlighted inflammation as an indispensable participant in the progression of this most malignant of brain tumors. Research carried out on understanding memory formation and mechanisms that go wrong in Alzheimer's disease has shown an activity-dependent increase in histone acetylation in the hippocampus and that a metabolite of curcumin confers neuronal protection against amyloid beta-induced toxicity. Work on the in vitro models of prion disease and protein aggregation is now at a stage where biological questions are being answered in depth. A start has also been made with a Drosophila model of neurodegeneration.

Work on systems neuroscience encompasses research on the somatosensory, motor, visual and auditory



systems as well as that underlying learning and memory. The research group which is interested in the organization and plasticity of the sensorimotor system in mammals has explored the internal organization of the hand representation in monkeys, both electrophysiologically and anatomically. They have shown that the architecture of the information processing networks in the somatosensory cortex correlates with the behaviorally advanced use of the hand. Other experiments performed by this group have shown that sensory loss due to spinal cord injuries leads to subtle but critical changes in the motor cortex besides the previously reported large-scale changes in the somtatosensory cortex. Their experiments have, for the first time, provided definitive evidence of a second motor representation in the rat motor cortex. Another group working on understanding the mechanisms underlying learning and memory has established a state-of-the-art multitetrode electrophysiological recording system to record in-vivo neural activity from different brain areas simultaneously from freely moving rodents. Research on the human auditory system has shown that axonal connections in the auditory cortex develop by the beginning of the third trimester of pregnancy, rather than during postnatal development which was based on earlier studies. Studies on the normal functioning of retinal circuitry and its responses to photoreceptor degeneration have recently identified the preferential expression of transcription factor Brn3b in retinal ganglion and its involvement in image-forming vision.

A group which focuses on translational neuroscience and computational neuroimaging has developed new methodologies including energy flow mapping and thermal conduction tensor imaging to predict the occurrence of Alzheimer's disease, and has optimized image-guided therapy of stroke and vascular dementia. Our work on Neurospectroscopy has broken new ground in the measurement of metabolites in the brain as regards sensitivity and specificity and is being used to answer questions of biological relevance. The Speech and Language Laboratory (SALLY), which has been investigating the development of cortical circuits for reading two languages (English and Hindi) that differ in script and orthography (sound-letter mapping), has shown the existence of distinct reading circuits for the two languages

NBRC is very pleased to welcome into its fold Professor Mriganka Sur, Newton Professor of Neuroscience and Head, Department of Brain and Cognitive Sciences, MIT, USA as Visiting Professor and Distinguished Biotechnology Chair, NBRC. He is an authority on plasticity, or the adaptive response of the brain to changes in inputs which is essential to brain development and function. In collaboration with scientists at NBRC, he will be setting up a state-of-the-art facility for two-photon imaging which can be used for high-resolution imaging of cells, synapses and molecules in vivo. The projects envisaged include understanding the role of cell-specific circuits in information processing and plasticity in the visual cortex, revealing the role of astrocytes in cortical processing and hemodynamics, understanding mechanisms of synaptic development and plasticity in visual cortex, studying mechanisms of synaptic dysfunction in animal models of autism, and developing human stem cell models of brain disorders and diseases, using two-photon imaging techniques.

In addition to research carried out on the campus at Manesar, the NBRC Translational & Clinical unit at the Gurgaon Government Hospital continues to make our research clinically relevant and to provide much-needed services in neurology, neuropsychiatry, neurosurgery and neuropsychology. The 'Glue Grant Scheme' of the Department of Biotechnology has further strengthened the bonds between the two institutions. There has also been an increase in the number of referrals from other centers and local hospitals. New facilities such as electromyography, neurometry and a nerve conduction study facility have recently been added to the gamut of services already being provided by the NBRC Translational and Clinical Unit.

On the academic front, NBRC, the first DBT institute to have been awarded the status of a Deemed University in 2002 by the Ministry of Human Resource Development, Government of India has been assessed by Committees from the University Grants Commission and the Ministry of HRD. Both have placed it under the highest category for its excellence in providing education. In addition to its own students, NBRC also educated a number of summer trainees (selected by the Indian Academy of Science, Bangalore, Indian National Science Academy, New Delhi and National Academy of Sciences, Allahabad in how to conduct research in the lab. Besides academics, our students are encouraged to take part in extra-curricular activities, which are held in the month-long annual festival Tantrika. This event was organized by the students with its customary gaiety, with a number of sports events, followed by various competitions on arts and crafts. The festival culminated with a cultural evening with musical and dance performances, and the enthusiastic participants also included staff and faculty members.

Other important academic activities include a 15-day IBRO-APRC School of Neuroimaging was held at NBRC from in November 2010. This workshop was sponsored by the renowned neurophysiologist and Nobel Laureate, Prof. Torsten Wiesel who addressed the faculty and students of NBRC and the participants of the school, selected from amongst candidates from India, China, Bangladesh, Nepal, Sri Lanka and Iran. Experts from India, the USA, Australia, Japan, China and Switzerland introduced students to the topic of magnetic resonance imaging and discussed the latest developments in the field. Besides providing the theoretical basis of MRI, the workshop also provided hands-on training to the students to enable them to use these techniques for their own research.

The Fourth DST-SERC School on Systems and Cognitive Neuroscience (co-sponsored by NBRC, the Department of Science and Technology and the Indo-US Science and Technology Forum) was held at NBRC in February, 2011. Experts in the field of neurosciences from India and the US gave lectures for 15 days to the participants (graduate students, postdoctoral students and junior faculty from different centres in India) on Systems and Cognitive Neuroscience. The workshop also included hands-on training and demonstrations on selected topics. One of the key features of the workshop were the informal interactive sessions between the speakers and students which were held almost daily, so that they could learn more about different areas of systems and cognitive neuroscience in an informal setting.

Besides the specialized workshops to promote neuroscience, NBRC continued its tradition of inviting students from five schools from Gurgaon and Manesar to participate in its 7th Foundation Day (16th Dec, 2010). A poster session, demonstrations, lab visits and a quiz were organized at NBRC to celebrate its foundation and dedication to the nation. To further commemorate its foundation day, NBRC organized a public lecture on 'Preparing the Brain for School' by Professor Michael Posner (Professor Emeritus, University of Oregon and Adjunct Professor, Weill Medical College, New York, USA) an eminent scientist who works on the development of attentional networks in infants and young children. In addition, students of NBRC introduced students of the Govt. Higher Secondary School, Pachgaon district in Gurgaon to neuroscience to celebrate the National Science Day on the 28th of February, 2011.

NBRC has also sponsored the Brain Awareness Week in institutions at different geographical locations across the country. At each of these institutions, a

number of talks, poster sessions and demonstrations were held to make the students and general public aware about normal brain functions as well as the mechanisms underlying different brain diseases. These have generated an extraordinary degree of interest especially in school and college students, who are the future of all our endeavors.

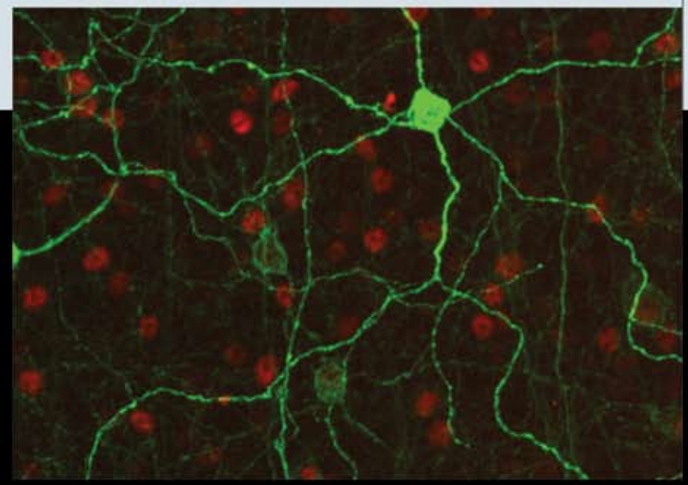
This year we look forward to building on the firm foundations of NBRC that have been laid down by our Founder-Director, Professor Vijaylakshmi Ravindranath. We will also work forward towards positioning ourselves as a leading Neuroscience institution both for research and teaching in India. We hope that the new initiatives on the substrate of an excellent foundation will make our work insightful and relevant and contribute the richness of concept that experimentation that defines the frontiers of this field.

Prof. Subrata Sinha
Director, NBRC

Research Reports

National Brain Research Centre

NBRC



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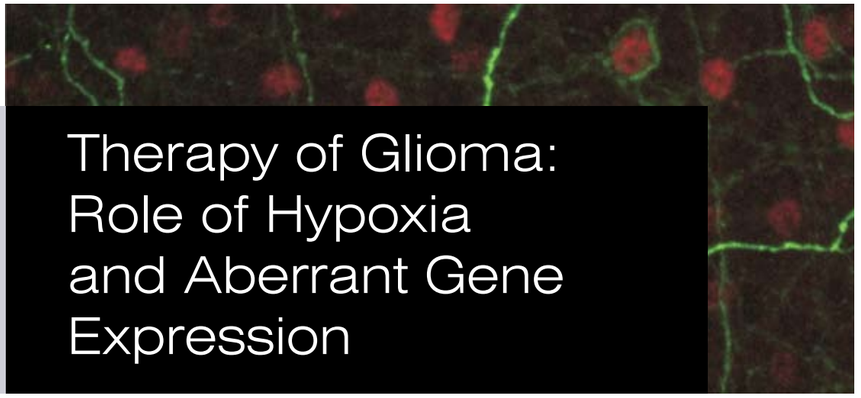

Principal Investigator
Subrata Sinha

Therapy of Glioma: Role of Hypoxia and Aberrant Gene Expression

Glioma are among the the most hypoxic tumours and the the hypoxia-necrosis cycle is a hallmark of Glioblastoma multiforme, the most malignant of glial tumours. It is also well known that many therpareutic modalities, chemotherapy as well as radiotherapy are comparatively less effective in hypoxia. To add to this difficulty of studying agents of inducing cell death and reducing cell proliferation is the artificially high degree of oxygen tension in which cells are usually cultured. No tissue interior, including that of the normally well perfused normal brain, ever approaches an oxygen tension of 20% oxygen. As far as tumours go, the oxygen tension in the interiors is close to 1-2%, whereas some areas may be profoundly anoxic, at 0.1 to 0.2%. Hence it is imperative that the properties of tumour cells and their response to chemotherapeutic drugs are studied under conditions that resemble the interiors of tumours. The aim of this work is to first study the responses of cells to short term and long term hypoxia and then to identify agents or combinations of drugs that are more likely to be effective under hypoxic conditions. As the molecular alterations in a tumour cell are key features in determining the nature of the cell response, it is important that this too be taken into account. Therefore the initital studies are being done using U87MG (wild type p53), U877MG cells transfected with a dominant negative mutant of p53 and U373 cells (mutant p53). It is expected that would provide a basis for the rational chemptherapy of glioma.

Aberrant gene expression can also provide a basis for tumour therapy. Transcriptional Gene Silencing (TGS) provides a way for long term silencing of oncogenes, unlike the more commonly used Post Transcriptional Gene Silencing by siRNA, which results in the degradation of already synthesized transcript. In an attempt to silence relevant oncogene, siRNA was directed to the c-myc promoter in U87MG glioma cells, resulting in hypermethylation and reduced c-myc expression. As a consequence, there was reduced cell proliferation and increased apoptosis, as well as increased expression of senescence markers. A similar approach has been also successful with the E6/7 oncogenes of Human Papilloma Virus.

Publications**

Mehndiratta M, Palanichamy JK, Pal, A; Bhagat M, Singh A, **Sinha S**, Chattopadhyay, P. **(2011)** CpG hypermethylation of the c-myc promoter by dsRNA results in growth suppression. **Mol Pharmaceutics**. (In Press)

Palanichamy JK, Mehndiratta M, Bhagat M, Ramalingam P, Das B, Das P, **Sinha S**, Chattopadhyay P. **(2010)**. Silencing of integrated human papillomavirus-16 oncogenes by small interfering RNA-mediated heterochromatization. **Mol. Cancer Ther**. 9(7):2114-22.

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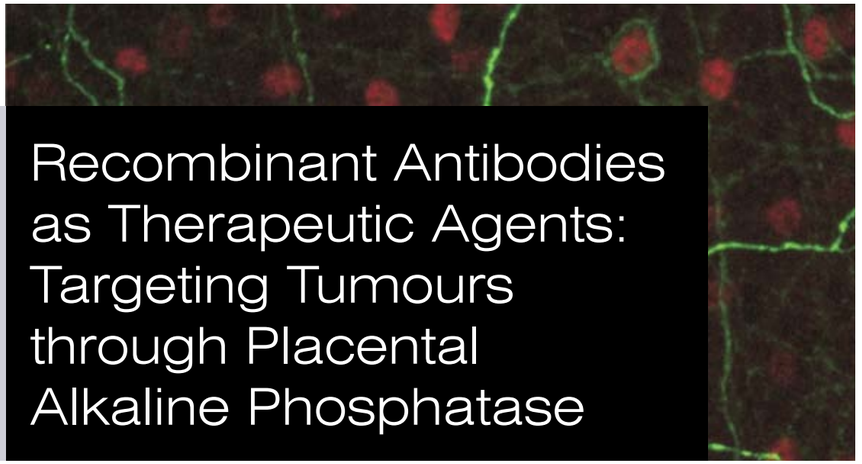
** Work done at AIIMS initially but to be continued at NBRC



Recombinant Antibodies as Therapeutic Agents: Targeting Tumours through Placental Alkaline Phosphatase

Principal Investigator
Subrata Sinha

The quest for specificity in tumour cell targeting could utilize one or more specific features of cancers that are unique to cancer cells. In our lab, we have used two modalities for this purpose. An oncoplacental antigen, the placental isozyme of alkaline phosphatase (PAP) that is ectopically expressed in several cancers, including glioma has been studied as a target for recombinant antibodies that bind to it in an isozyme specific manner. This is now sought to be developed to deliver a vector with a promoter/enhancer system that is preferentially activated in tumours. This would be used for expressing prodrug metabolizing enzymes, as also RNA complementary to the c-myc promoter for achieving Transcriptional Gene Silencing (TGS).

Recombinant scFv fragments (comprising of only the fused variable region of the light and heavy chains of an antibody molecule) that bound specifically to PAP and not to the other commonly expressed isozymes of AP, were selected form a human antibody library. The selection of isozyme specific antibodies that distinguished PAP from the other remarkably homologous isozymes that are expressed in normal cells, necessitated the use of several strategies that could bias the selection in favour of PAP binding scFv. After checking for binding and specificity, the scFv was fused to a portion of the F protein of the Sendai virus. The Sendai virus system has been extensively developed by one of us (DS) as a means of efficient particulate delivery, which has high efficiency and low immunogenicity. The scFv targeted Sendai virosome has been checked in various cell lines that are positive for PAP expression, with appropriate negative controls, including PAP negative lines that were transfected with PAP. It shows specificity in binding only to PAP expressing cell lines, and can deliver a pyload of a chemotherapeutic drug, doxorubicin, very effectively resulting in increased cell death.

Recombinant antibodies are also being used for generating antibodies to the hepatitis B surface antigen. Hepatitis encephalopathy is a major cause for admission in ICUs, and it is expected that recombinant, neutralizing antibodies to the surface antigen, including the preS1 region would help in providing an additional therapeutic modality for this disease, as the current antiviral drugs used have the problems of drug resistance and toxicity.

Publications**

Tiwari, A., Sankhyan, A., Khanna, N. and **Sinha, S (2010)**. Enhanced periplasmic expression of high affinity humanized scFv against Hepatitis B surface antigen by codon optimization. **Protein Expression and Purification**. 74, 272-279.

Ongoing Funded Project (As Co PI)

1. Therapy of infectious and chronic diseases: Targeted gene delivery & long-term specific modulation of gene expression (DBT – COE)) Was PI and project Coordinator, currently Co-PI . Current Project CoOrdinator, Prof Debi Sarkar, Dept of Biochemistry, University of Delhi , South Campus, PI for AIIMS component, Dr Parthaprasad Chattopadhyay
2. A comparison of gene expression in glioablastoma cell lines under short and long term exposure to hypoxia with reference to the key cellular regulatory and adaptive pathways ICMR) was PI, currentl PI Dr Kunzang Chosdol
3. An in-vitro study of the role of FAT, a Drosophila tumor suppressor gene homologue, in human glial tumorigenesis . (DRDO), PI: Dr Kunzang Chosdol , AIIMS
4. Hypoxia and Notch signaling in Glioblastoma: Implications for an adverse phenotype (DBT) PI Dr. Kunzang Chosdol
5. Hypoxia and p53-HIC1 axis in stemness of glial tumors and cell lines (DBT) PI Dr Parthaprasad Chattopadhyay
6. Promoter mediated tumor cell targeting by siRNA mediated gene silencing (DBT)PI Dr Parthaprasad Chattopadhyay

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** Work done at AIIMS initially but to be continued at NBRC

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Understanding the function of the Autism and Autism spectrum Disorders Associated Ubiquitin Ligase, UBE3A/E6-AP

Angelman syndrome (AS) is a neurodevelopmental disorder characterized by severe mental retardation, susceptibility to seizures, speech impairment, ataxia and unique behavioral features such as inappropriate laughter and autistic features. Most cases of AS are caused by deletion of maternal copy of the *UBE3A* gene(present within 15q11-q13). The loss-of-function mutations in maternally inherited UBE3A also have been identified in a subset of affected individual. Interestingly, the UBE3A gene is imprinted in the brain with preferential maternal-specific ex pression particularly in neurons but not in glia. Recently, copy number variation of the UBE3A gene (duplication) also has been shown to be associated with autism.

The *UBE3A* gene encodes a 100 kDa protein (also known as E6 associated protein; E6AP) that is functionally characterized as a HECT (homologous to E6AP C-terminus) domain family of E3 ubiquitin ligase involved in targeting proteins for their multi-ubiquitination and subsequent degradation by proteasome. Ube3a also function as a transcriptional co-activator of steroid hormone receptors. Mice deficient for maternal Ube3a exhibit many features of AS, including learning and memory impairment and motor dysfunction. These mice also exhibit defects in hippocampal long-term potentiation, altered function of hippocampal calcium/calmodulin-dependent protein kinase II and abnormal dendritic spine morphology. Further studies in these mice provided evidence that Ube3a is required for experience-dependent cortical plasticity and maturation of neocortex. A recent study showed that Ube3a regulates synaptic function by ubiquitinating and degrading Arc, which is involved in AMPA receptor trafficking. All these findings indicate that ubiquitin ligase function of Ube3a is crucial in regulating synaptic function. This is further supported by the fact that many of the AS-associated loss-of-function mutations of *UBE3A* result in disruption of ubiquitin ligase activity. However, this does not rule out the involvement of coactivator function of Ube3a in AS pathogenesis, because, majority of AS cases are due to loss of expression of Ube3a in the brain. The Ube3A knockout mice show defects in reproductive function and tissue-specific steroid hormone resistance, which could be attributed to the loss of its coactivator function. But, whether the loss of coactivator function of Ube3a is associated with any defects in brain function leading to AS are not known. 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.

Last year we have shown the loss of dopaminergic neurons and resulting behavioural abnormalities in AS mice. We have also reported that E6-AP interacts with and promotes proteasome-mediated degradation of cyclin-dependent kinase inhibitor p27. This year we have observed that Ube3a not only coactivates glucocorticoid receptor (GR) but also promotes its proteasome-mediated degradation in a ligand-dependent manner and the GR signalling pathway is disrupted in Ube3a-maternal deficient mice brain. AS mice show a significantly higher level of blood corticosterone, selective loss of GR and reduced number of parvalbumin-positive inhibitory interneurons in their hippocampus leading to hyperactivity of hypothalamus-pituitary-adrenal axis. These mice also exhibited increased anxiety-like behaviour, which could be due to chronic stress. Altogether, our findings suggests that chronic stress due to altered GR signalling might lead to cognitive deficits and anxiety-like behaviour in AS.

This year, we have also found that the Ube3a, which is implicated in synaptic plasticity and involved in the clearance of misfolded polyglutamine protein, strongly recruits to the mutant huntingtin nuclear aggregates resulting in significant loss of its functional pool in different regions of Huntington's disease (HD) mice brain. Interestingly, the Arc, one of the substrates of Ube3a linked with synaptic plasticity is also associated with nuclear aggregates, although its synaptic level seems to be increased in the hippocampus and cortex of HD mice brain. Different regions of HD mice brain also exhibits decreased levels of AMPA receptors and various pre and post synaptic proteins, which could be due to the partial loss of function of Ube3a. These results suggest that the loss of function of Ube3a might be associated with the synaptic abnormalities and the cognitive and motor deficits observed in HD.

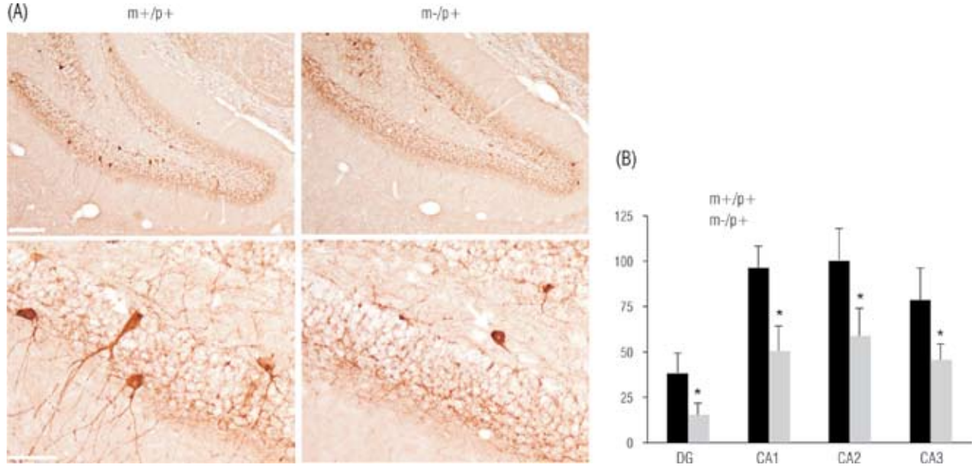


Figure 1
A) Comparison of immunohistochemical staining of parvalbumin in the DG of hippocampus of wild type and Ube3a-maternal deficient mice brain. Four months old male mice in both groups were used for the experiment. Scale bar represents 200 µm in top panel images and 50 µm and in botom panel images. Arrow indicate the parvalbumin immunostained cells. **B)** The PV-stained cell bodies in the different regions of hippocampus (at least two areas of 0.200 mm^2 in DG, CA1, CA2 and CA3 of both hemispheres) were counted and plotted as the number of PV-immunoreactive cells/mm^2 area. Values are mean ± SD of four different animals in each group.

Publications

S. Mulherkar and **N. R. Jana** (2010). Loss of dopaminergic neurons and resulting behavioural deficit in mouse model of Angelman syndrome. Neurobiology of Disease, 40, 586-592.

Presentations

N. R. Jana. Understanding the physiological function of autism and autism spectrum disorder associated ubiquitin ligase. Neurocon, Kolkata, 2011.

N. R. Jana. Evaluation of abnormal protein aggregation in neurodegenerative diseases. PGIMER, Kolkata, 2011.

N. R. Jana. Modulation of Huntington's disease pathogenesis by ubiquitin protein ligases. Indo-US workshop on aging, Hyderabad, 2011.

N. R. Jana. Understanding the function of autism and autism spectrum disorder associated ubiquitin ligase, Ube3a/E6-AP. SBCI, Bangalore, 2010.

S Godavarthi, P. N. Dey and **N. R. Jana** Defective glucocorticoid hormone receptor signaling in Ube3a-maternal deficient mice brain. SBCI, Bangalore, 2010.

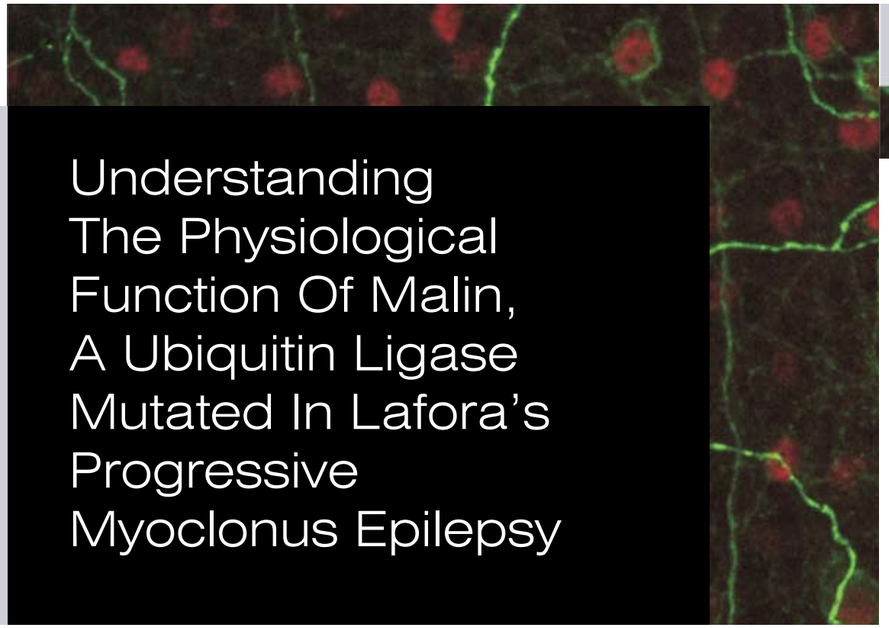
M. Maheshwari and **N. R. Jana.** Down-regulation of ubiquitin ligase E6-AP and various synaptic proteins in transgenic mice model of Huntington's disease, SBCI, Bangalore, 2010.

Funding

1. Understanding the functional role of E6-AP - a putative ubiquitin protein ligase implicated in Angelman mental retardation syndrome. BT/PR7744/Med/14/1094/2006 dt. 29-05-2007. (DBT, India)
2. Study the defect in neurogenesis and initial synapse formation in mouse model of Angelman mental retardation syndrome. 37(1408)/10/EMR-II dt. 25-06-2010. (CSIR, India)
3. Role of E6-AP in the progression of Huntington's disease. BT/HRD/34/18/2008 dt. 16-04-2010. (National Bioscience Award for Career Development, DBT, India).
4. Understanding the role of ubiquitin-proteasome system dysfunction in the pathogenesis of Huntington's disease. DST/INT/JAP/P-71/2009 dt. 16-09-2009. (DST, India , Indo-Japan cooperative science program)

Collaborator

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



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Understanding The Physiological Function Of Malin, A Ubiquitin Ligase Mutated In Lafora's Progressive Myoclonus Epilepsy

Lafora disease (LD) is a fatal form of progressive myoclonus epilepsy and inherited as an autosomal recessive disorder. The disease usually manifests in early adolescence with stimulus-sensitive grand mal, tonic-clonic, absence, visual and myoclonic seizures and rapidly progressing to severe myoclonic seizures, psychosis, cerebellar ataxia, dementia, muscle wasting and respiratory failure. Death usually occurs within 10 years of disease onset. One of the common pathological features of LD is the accumulation of glycogen-like intracellular inclusions named Lafora bodies in many organs including brain, liver, heart, skeletal muscle and skin. In the brain, Lafora bodies are seen predominantly in neuronal perikarya and dendrites

Mutations causing LD have been identified in two genes, *EPM2A* and *EPM2B (NHLRC1)*, although there is evidence for a third locus. 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 either *EPM2A* or *EPM2B* genes are phenotypically indistinguishable and Lafora bodies are observed in every case indicating strongly that these two gene products regulate some common physiological pathways. In fact, malin has been found to interact with laforin and malin-laforin complex promotes the degradation of muscle glycogen synthase (MSG) and protein targeting to glycogen (PTG) that are required for glycogen synthesis. Therefore, loss of function of laforin or malin would result in increased levels of MGS and PTG, leading to the formation of Lafora bodies. 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 expected that the improper clearance malin substrates 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.

Last year we have also shown that the Lafora bodies in axillary skin and brain are ubiquitinated and associates with proteasome components and molecular chaperones. The transient expression of disease causing mutations of malin in the Cos-7 cell results in the formation of cytoplasmic aggregates that associates with Hsp70/Hsc70 chaperones and 20S proteasome. The mutant malin expressing cells also exhibit proteasomal malfunction and cell death. Overexpression of Hsp70 reduces the frequency of mutant malin aggregate formation and protects from mutant malin-induced cell death. These finding indicate that Lafora bodies are consisting of abnormal proteins, targeted by chaperones or proteasome for their refolding or degradation, and failure of these quality control systems could lead to LD pathogenesis. Our data also suggests that the Hsp70 chaperone could be a potential therapeutic target of LD.

This year we demonstrate for the first time that neuronatin is a novel substrate of malin. Malin interacts with neuronatin and enhances its degradation through proteasome. Interestingly, neuronatin is an aggregate prone protein, forms aggresome upon inhibition of cellular proteasome function and malin recruited to those aggresomes. Neuronatin is found to stimulate the glycogen synthesis through the activation of glycogen synthase and malin prevents neuronatin-induced glycogen synthesis. Several LD-associated mutants of malin are ineffective in the degradation of neuronatin and suppression of neuronatin-induced glycogen synthesis. Finally, we demonstrate the increased levels of neuronatin in the skin biopsy sample of LD patients. Overall, our results indicate that malin negatively regulates neuronatin and its loss of function in LD results in increased accumulation of neuronatin, which might be implicated in the formation of Lafora body or other aspect of disease pathogenesis.

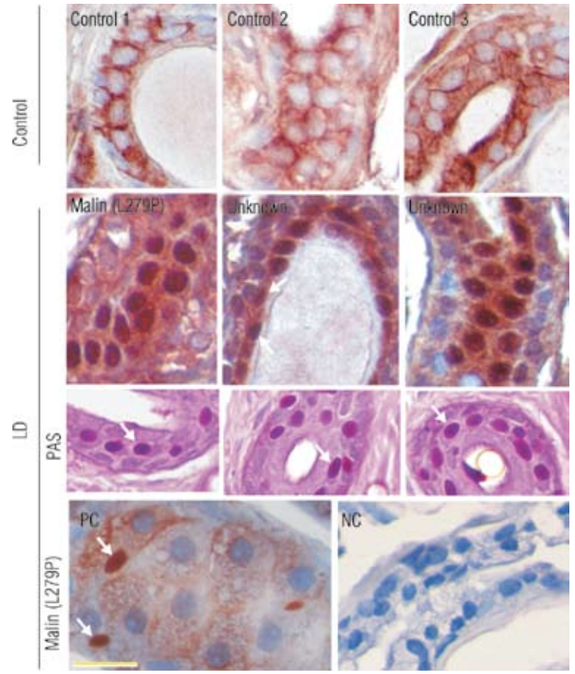

Figure
Immunohistochemical localization of neuronatin in the axillary skin biopsy samples collected from three controls and three LD patients. PAS staining was used to confirm the presence of Lafora bodies in each LD skin sample. In positive control (PC), antibody against Hsc70/Hsp70 was used to detect Lafora bodies. NC, negative control (without rabbit-specific primary antibody). Arrow indicates Lafora bodies. Scale bar; 20 μm.

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N. R. Jana. Understanding the physiological function of malin and pathogenesis of Lafora disease. SNCI, Hyderabad, 2010.

S. N. Rao, J. Sharma, R. Maity, S. K. Shankar, P. Satishchandra and **N. R Jana**. Ubiquitin proteasome system dysfunction in Lafora disease. International Symposium on Progressive Myoclonus Epilepsies, Venice, Italy, 2010.

Funding

Understanding the physiological function of malin, a ubiquitin ligase mutated in Lafora's Progressive Myoclonus Epilepsy. BT/PR13590/Med/30/286/2009 dt. 17-09-2010. (DBT, India)

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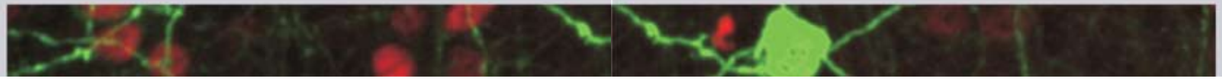
Cellular and Molecular Mechanisms of HIV-I Neuropathogenesis

The field neuroAIDS investigates neuro-cognitive deficits arising amongst HIV/AIDS patients as a consequence to HIV-1 induced neuropathogenesis. Among several leads gathered in last decade, one of the most striking observations of the field is that abuse of drugs by AIDS patients leads to more severe damage to brain cells and augmented neurocognitive deficits. Enhanced neurocognitive deficits due to co-morbidity of HIV-1 and drugs of abuse have been confirmed by several experimental and clinical studies, however the detailed investigations into cellular and molecular mechanisms are lacking. Data emerging from post-mortem studies in neuroAIDS patients suggest that HIV-1 induced damage to neuronal architecture and neuronal functions is more elaborate in drug abusers as compared to non-drug abusers. This is perhaps due to increased neurotoxicity due to co-morbid effects of neurotoxic viral proteins and drugs of abuse such as morphine, cocaine, methamphetamine etc., and warrants further investigation. Morphine and cocaine make the brain more susceptible to HIV infection by facilitating macrophage infiltration into brain parenchyma via increased chemokine expression from activated astrocytes and resident microglia. Increase in virus entry into the brain is also mediated by morphine induced changes in expression of various tight junction proteins, leading to altered blood-brain barrier permeability.

Our laboratory continues to actively pursue detailed investigations into neurotoxic effects of HIV-1 transactivating (Tat) protein on brain cells derived from human neural precursor cells (hNPCs). These hNPCs are isolated from telencephalon regions of brain of aborted fetuses of first trimester pregnancies with mother's informed consent and after clearance of institutional human ethics committee. Feeling the need for better understanding of the co-morbid effects of HIV-1 Tat and drugs of abuse, we extended our investigations to look for cellular and molecular pathways that may play pivotal role in enhanced toxicity of these two agents, which are common among the HIV/AIDS population.

Using human neurons differentiated from human neural precursor cells and human neuroblastoma cells, our research group first observed that co-exposure of neuronal cells to HIV-1 B-Tat and morphine resulted in a dose dependent increase in mortality of cells, confirming clinical observations made earlier by other investigators in the field. These were confirmed by cell viability assay as well as apoptosis assays. Following these observations, we designed experiments to look into the mechanisms that may underlie increased mortality due to HIV-1 Tat and morphine. As morphine was used in our experiments, we first confirmed the presence of mu-opioid receptors on these cells by immunostaining and also used nalaxone to confirm that the effects of morphine were indeed mediated through the mu-opioid receptors. Pre-



treatment of neuronal cells with nalaxone blocked the morphine mediated neurotoxicity in our culture systems, as evidenced by a widely used apoptosis assay, the TUNEL assay. Detailed investigations into the apoptotic pathways led to the observation that morphine exacerbated the HIV-1 Tat neurotoxicity by disturbing the delicate balance of pro- and anti-apoptotic genes leading to triggering the caspase cascade. The co-exposure of morphine with HIV-1 Tat resulted in enhanced reactive oxygen species (ROS) production which was NADPH oxidase dependent as apocynin pretreatment prevented ROS generation and subsequent neurotoxicity. The co-exposure of these agents led to increased perturbation of mitochondrial membrane potential leading to depolarized mitochondrial membranes that also contributes to neuronal damage.

The widespread use of highly active anti-retroviral therapy (HAART) has modified the nature of neurocognitive impairments categorized in HIV/AIDS patients. Although the incidence of most severe manifestation of HIV associated dementia (HAD) has decreased significantly, a milder form of HAD, called HIV-1 associated neurocognitive disorders (HAND) has surfaced and is prevalent in 40-50% of HIV/AIDS patients. Complications arising due to resistance and toxicities of highly active anti-retroviral therapy in HIV/AIDS patients necessitated search for neuroprotectants that could be used as adjuncts to the current HAART to lower their doses. In this context several anti-inflammatory compounds, anti-oxidants, NMDAR antagonists and calcium channel blockers had been tried with limited success. Neurotrophins such as Brain Derived Neurotrophic Factor (BDNF), Nerve Growth Factor (NGF) and Glial cell line-derived Growth Factor (GDNF) also offer protection against various neurotoxins and are speculated for their possible use as neuroprotective-adjuncts for HAART. On these lines, we explored the possibility of Platelet Derived Growth Factor-BB (PDGF-BB) as a neuroprotectant against co-morbid effect of HIV proteins Tat and morphine.

In addition to cellular and biochemical pathways, we probed into the signaling mechanisms involved in morphine-induced exacerbation of HIV-Tat induced toxicity in human neurons and human neuroblastoma cells. Our data suggests involvement of MAPK ERK1/2 and JNK pathways in mediating the toxicity induced by Tat and morphine. It was confirmed by use of pharmacological inhibitors specific to these pathways that abrogated the co-morbidity of Tat and morphine on neuronal cells. Furthermore, we observed significant neuroprotective effects of PDGF-BB at various levels that were mediated by PI3K/Akt pathways.

In addition to the HIV-1 and drug abuse work, recently we have initiated work in area of neuron-glia biology with an attempt to investigate intricacies of neuron-glia crosstalk during HIV-1 pathogenesis. Previous studies have reported an increase in Connexin-43 expression upon exposure of primary human astrocytes with live HIV virus which may have implications in HIV neuropathogenesis. However, the underlying signaling pathways and the consequences of the augmented gap junction communication remains poorly understood. We have established human neuron-astrocyte co-culture system using cells differentiated from human fetal brain derived neural precursor cells, to closely mimic the *in vivo* conditions of human brain. Gap Junction Channels (composed of connexins as their key proteins) are known to be one of the major mode of intercellular communication as they allow the passage of various ions and second messengers, thereby regulating signaling pathways. We have some interesting leads that we are actively pursuing to gain novel insights into role of neuron-glia crosstalk in HIV-1 neuropathogenesis.

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S. Mishra, M. Mishra, **P. Seth**, S. Sharma **(2010)**. Tetrahydrocurcumin confers protection against amyloid ß-induced toxicity. **Neuroreport**, 22: 23-27.

S. Malik, H. Khalique, S. Buch and **P. Seth (2011)**. A Growth Factor Attenuates HIV-1 Tat and Morphine Induced Damage to Human Neurons: Implication in HIV/AIDS-Drug Abuse Cases **PLoS One**, 6 (3): e18116.

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P. Seth. Glia-Neuronal Cell Culture Model to Study Neurodegenerative Disorders. Glia Symposia Health and Disease on Jiwaji University, Gwalior, India, December 2010 (Invited Speaker).

P. Seth. Human Fetal Brain Derived Neural Stem Cell: An *in vitro* Model. 5th Congress of Federation of Asian Oceanic Neuroscience Society, Lucknow, November 2010. (Convener, Session Speaker and Co-Chair of symposium on Neural Stem Cell: Potential and Challenges).

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S. Malik and P. Seth. A Growth Factor Attenuates HIV-1 Tat and Morphine Induced Damage to Human Neurons: Implication in HIV/AIDS-Drug Abuse Cases, at the XXVIII Annual Conference of Indian Academy of Neuroscience, Lucknow, India, November 2010.

P. Garg, S. Singh and P. Seth. HIV - 1 Tat Mediated Modulations in Intercellular Communication In Human Fetal Brain Derived Cells, presented at 5th Congress of Federation of Asian and Oceanian Neuroscience Societies (FAONS) XXVIII Annual Meeting of Indian Academy of Neurosciences (IAN), Lucknow, India, November 2010.

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Awards

P. Garg. IBRO Travel Grant 2011, for Gordon Research Conference (Registration Fee) March 2011.

P. Garg. DBT Travel Support for attending International Conference/ Seminar/Symposium, March 2011

P. Garg. Recipient of IBRO-APRC Alumni Best Poster Award held at 5th Congress of Federation of Asian and Oceanian Neuroscience Societies (FAONS) XXVIII Annual Meeting of Indian Academy of Neurosciences (IAN), Lucknow, India, December 2010.

S. Malik. DST Travel Support for attending International Conference, 10th International Symposium on NeuroVirology, Milan, Italy, October, 2010.

P. Garg. IBRO Travel award for attending International Brain Research Organization (IBRO) School of Neuroscience held at Hong Kong from June 2010.

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Understanding aberrant transcriptional circuitries and signaling cascades in Glioblastoma multiforme

Glioblastoma multiforme (GBM) represents one of the most malignant brain tumors characterized by intense proliferation, widespread invasion of poorly differentiated cells and poor prognosis. As inflammation is an indispensable participant in tumor progression, 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 survival, resistance to apoptosis and evasion of immune response. The aim is to understand how aberrant transcriptional circuitries and signal transduction pathways contribute to the progression GBM. The highly resistant nature of GBM to chemotherapy has also prompted us to identify new treatment strategies.

Objectives

A. Dissecting the role of cytokine and growth factors in the transcriptional regulation of genes involved in immune responses

Involvement of TNFα induced TLR4-NFκB and TLR4-HIF-1α feed-forward loops in the regulation of inflammatory responses in glioma

The precise role of different toll-like receptor (TLR) superfamily members is just beginning to get elucidated in Glioblastoma multiforme (GBM). In this study, we observed heightened TLR4 in GBM tumor samples as compared to adjacent normal tissue. Since the pro-inflammatory cytokine TNFα induces NFκB activation in GBM, and as several common signaling mediators are involved in TNFα and TLR4 mediated NFκB activation, we investigated the role of TLR4 in the regulation of NFκB activation and inflammatory responses in TNFα treated glioma cells. TNFα elevated TLR4 expression and inhibition of TLR4 signaling by either signaling inhibitor, neutralizing antibody or siRNA attenuated TNFα induced NFκB activation. TLR4 mediated NFκB activation was independent of canonical myeloid differentiation factor 88 (MyD88) signaling but involved toll/IL-1R homology (TIR)-domain-containing adaptor protein-inducing interferon-α (TRIF). Inhibition of TLR4 signaling abrogated TNFα induced increase in (i) transcription factors IFN-regulatory factor 3 (IRF3) and STAT-1 and (ii) IFNα and inflammatory cytokines/ chemokines expression. Furthermore, TNFα induced TLR4 dependent increase in AKT activation and HIF-1α transcriptional activation

suggested the existence of TLR4-AKT-HIF-1α axis. Importantly, TNFα induced TLR4 was abrogated in cells transfected with DN-IκB and HIF-1α siRNA. Our studies indicate that TNFα triggered TLR4-HIF-1α and NFκB-TLR4 feed-forward loops act in tandem to sustain inflammatory response in glioma.

IGF-1 induced HIF-1α-TLR9 cross talk regulates inflammatory responses in glioma

The insulin-like growth factor (IGF-1) induces hypoxia inducible factor (HIF-1α) regulated genes in GBM. As HIF-1α links inflammatory and oncogenic pathways in GBM, we investigated whether IGF-1 affects HIF-1α to regulate inflammatory response in glioma cells under normoxia. IGF-1 induced Ras and Calmodulin-dependent kinase II (CaMKII) regulated HIF-1α transcriptional activity in glioma cells. Increase in HIF-1α was concurrent with decreased Toll-like receptor (TLR9) and CXCR4 expression and elevated suppressor of cytokine signaling (SOCS3) levels. Interestingly, while synthetic CpG containing oligodeoxynucleotide TLR9 agonist (CpG DNA) decreased IGF-1 mediated increase in HIF-1α activity, siRNA mediated knockdown of HIF-1α decreased TLR9 levels. This suggested that IGF-1 induced HIF-1α-TLR9 axis is regulated by both positive and negative feedback loops. Importantly, TLR9 agonist reversed the effect of IGF-1 on CXCR4 and SOCS3 expression. While knockdown of HIF-1α abrogated IGF-1 mediated increase in SOCS3 it elevated IGF-1 induced decrease in CXCR4 levels. Thus HIF-1α positively and negatively regulates SOCS3 and CXCR4 expression respectively, in glioma cells. Though TLR9 agonist had no additive effect on IGF-1 mediated increase in pro-inflammatory cytokines IL-1β, IL-6 and IL-8, treatment with TLR9 agonist alone elevated expression of these pro-inflammatory cytokines. Our studies indicate that a complex HIF-1α-TLR9 cross-talk sustains a self-regulating cycle of inflammatory response through intrinsic negative and positive feedback mechanisms.

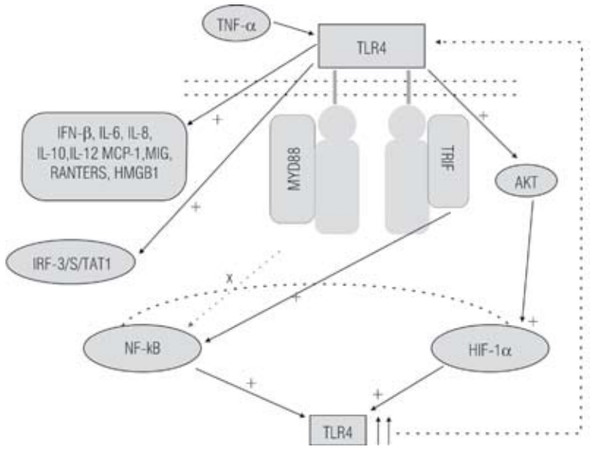

Figure A
Proposed model indicating that TLR4 activation induces NFkB through a MyD88-independent and TRIF-dependent pathway. TNFa induces a TLR4-STAT1 and TLR4-AKT-HIF-1 axis. TNFa triggers the NFkB-TLR4 and TLR4-HIF-1a feed-forward loops that operate concurrently to sustain TLR4 mediated release of inflammatory mediators.

B. Survival and resistance to apoptosis

COX-2 regulates the proliferation of glioma stem like cells independent of p53

Cancer stem-like cells (CSC) possessing features of neural precursor cells (NPC) influence initiation, recurrence and chemoresistance of GBM. As inflammation is crucial for glioblastoma progression we investigated the effect of chronic IL-1β treatment on CSCs derived from glioblastoma cell line U87MG. Exposure to IL-1β for 10 days increased (i) accumulation of 8-OHdG- a key biomarker of oxidative DNA damage, (ii) DNA Damage Response (DDR) indicators γH2AX, ATM and DNA-PK (iii) nuclear and cytoplasmic p53 and COX-2 levels and (iv) interaction between COX-2 and p53. Despite upregulating p53 expression IL-1β had no effect on cell cycle progression, apoptosis or self renewal capacity of CSCs. COX-2 inhibitor Celecoxib reduced self renewal capacity and increased apoptosis of both control and IL-1β treated CSCs. Therefore the ability of COX-2 to regulate proliferation of CSCs irrespective of exposure to IL-1β warrants further investigation of COX-2 as a potential anti- glioma target.

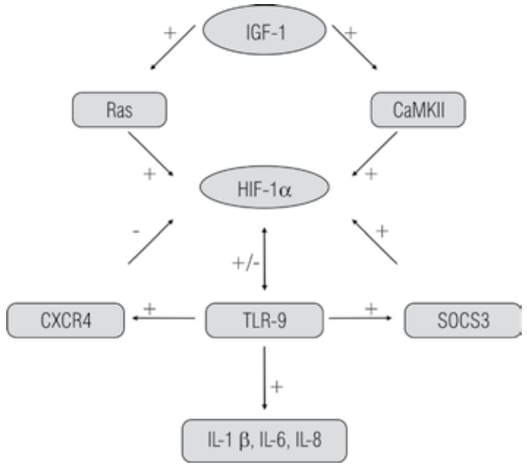

Figure B
Proposed model for IGF-1 triggered HIF-1 dependent regulation of inflammatory response in glioma cells.

C Understanding mechanisms that confer resistance of GBM to apoptosis and identify new treatment strategies that can manipulate the aberrant signaling pathways to induce apoptosis.

Farnesyltransferase inhibitor Manumycin targets IL1β-Ras-HIF-1α axis in tumor cells of diverse origin

We have recently reported that Ras acts an intermediate coactivator in IL-1β-mediated HIF-1α activation in GBM. Since HIF-1α plays a crucial role in linking inflammatory and oncogenic pathways, we investigated whether this IL1β-Ras-HIF-1α signaling axis observed in GBM, also exists in other tumors of diverse origin under normoxia. Treatment with IL-1β induced Ras in non GBM cell lines A549 (lung), HeLa (cervical) and HepG2 (liver); and inhibition of Ras activity attenuated HIF-1α activity. Our findings suggest that Ras links IL-1β and HIF-1α in tumors of diverse origin. As we have previously reported that the farnesyltransferase inhibitor Manumycin decreases Ras activity in glioma cells, we investigated whether Manumycin could regulate IL-1β-mediated HIF-1α activation. Manumycin abrogated IL-1β induced HIF-1α activation, in both glioma and non-glioma tumor cells. In addition, Manumycin also decreased IL-1β induced pro-inflammatory responses in tumor cells.

Bicyclic triterpenoid Iripallidal induces apoptosis and inhibits Akt/mTOR pathway in glioma cells

The highly resistant nature of GBM to chemotherapy prompted us to evaluate the efficacy of bicyclic triterpenoid Iripallidal against GBM in vitro. The effect of Iripallidal on proliferation and apoptosis on glioma cell lines was evaluated. Iripallidal (i) induced apoptosis, (ii) inhibited Akt/mTOR and STAT3 signaling, (iii) altered molecules associated with cell cycle and DNA damage, (iv) inhibited telomerase activity and colony forming efficiency of glioma cells. In addition, Iripallidal displayed anti-proliferative activity against non-glioma cancer cell lines of diverse origin. This ability of Iripallidal to serve as a dual-inhibitor of Akt/mTOR and STAT3 signaling warrants further investigation into its role as a therapeutic strategy against GBM.

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

(iii) Department of Biotechnology, (BT/PR12924/Med/30/235/2009).

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Activity-Dependent Protein Modifications: Implications for Synaptic Plasticity and Memory

The work in our lab is directed towards two related projects. In the first project, the long-term goal is to examine the molecular and cellular mechanisms that may contribute to memory formation. In the second project, we aim to understand the mechanisms of cell death, neuroprotection, and impairment in synaptic plasticity and memory in the Alzheimer's disease.

The examination of molecular and synaptic mechanisms that may contribute to memory formation has received considerable attention. Several different levels of analyses including molecular, cellular and systems approaches are used to study the properties of synaptic plasticity and memory. One type of synaptic plasticity, long-term potentiation (LTP) is widely considered as cellular mechanism of memory formation. Activity-dependent molecular changes in the cells are known to play critical roles in LTP and memory. Although different levels of analyses have tremendously contributed to our current understanding of synaptic plasticity and memory, the mechanisms involved in these processes are not clearly understood. Our work has focused on activity-dependent changes which may be involved in synaptic plasticity and memory formation.

Mechanisms of ERK Activation

Protein phosphorylation plays crucial roles in different processes including synaptic plasticity and memory. The extracellular signal-regulated kinase (ERK) is known to play critical roles in these processes. This has been established in several different systems including Drosophila, Aplysia and mammals. ERK is activated by stimuli relevant for synaptic plasticity. In addition, ERK is activated by memory training. Furthermore, blocking ERK activity inhibits synaptic plasticity and memory. However, the mechanisms of ERK activation are not completely understood. To examine the mechanisms involved in activity-dependent ERK activation, we use hippocampal slices from adult rats and stimulate them with KCl. KCl treatment results in depolarization of the cells and Ca^{++} influx. The increased intracellular Ca^{++} is required for development of LTP and memory. In addition, KCl induces LTP in the hippocampal slices. Importantly, KCl-induced LTP requires the activity of NMDA type of glutamate receptors. The activity of NMDA receptors is critical for LTP and memory. Thus, KCl serves as an in vitro analog of activity generating cellular changes which are involved in LTP and memory.

We found that KCl treatment of the hippocampal slices enhanced ERK activation. This was done using antibodies that recognize ERK when phosphorylated and the antibodies that recognize ERK independent of its phosphorylation state. This observation has been made by us and others previously. Interestingly, we found that ERK was activated for a long duration after the stimulus. This is refereed as sustained ERK activation. Having shown that KCl induces sustained ERK activation, we then asked: how is ERK activation sustained? One of the properties of long-lasting forms of synaptic plasticity and memory

is that it requires new RNA and protein synthesis. Thus, we next investigated whether the sustained ERK activation requires protein synthesis. We found that pharmacological inhibition of protein synthesis blocks sustained ERK activation. We then looked at the requirement of transcriptional activity for sustained ERK activation. Our results showed that the sustained ERK activation is critically dependent upon transcriptional activity since blocking transcription inhibited sustained ERK activation. Importantly, the immediate ERK activation was unaffected by protein synthesis or transcriptional inhibitors. These interesting results show that there are different mechanisms of immediate and sustained ERK activation.

The requirement of RNA and protein synthesis for sustained ERK activation raises the possibility of a factor that may be synthesized in response to KCl depolarization which then keeps ERK activated beyond the duration of the stimulus. Further investigation on the mechanisms of sustained ERK activation has suggested that a growth factor is synthesized after depolarization which keeps ERK activation sustained.

Synaptic Mechanism of Memory: Long-Term Potentiation in the Hippocampus

We have started experiments aimed at examining the synaptic mechanisms of memory. As mentioned earlier, LTP, a long-lasting increase in synaptic strength is considered a promising candidate for synaptic mechanism of memory. We perform LTP experiments on the acute adult rat hippocampal slices. In these experiments, the CA3 region is stimulated and the response is recorded in the CA1 region of the hippocampus. We apply tetanic stimulation in either massed or spaced pattern. As shown by others, we also found that different patterns of stimulations induce different extent of LTP. We are now conducting experiments to examine whether the LTP induction pattern can be changed by pharmacological manipulations.

Pattern-Dependent Memory Formation

Behavioral studies of memory have shown that memory formation is critically dependent on the pattern of training. In a multi-trial task, memory is more robust if the trials during training are applied with wide inter-trial interval (spaced training) than when they are applied with little or no inter-trial interval (massed training). The superiority of spaced training over massed training in inducing long lasting memory has been observed in several different model systems used to study memory. We use Morris water maze system to study spatial memory in rats. In this task, using spatial cues, the animal has to find an escape platform that is hidden under water. To force the animal to use spatial cues to learn the location of the platform, the water is made opaque. Consistent with findings by others, our results show that spatial memory formation is sensitive to the pattern in which the trials are applied during training. The animals that received spaced training showed better long-term spatial memory than the animals that had received same number of trials but in a massed pattern. We are now exploring ways to find out whether this pattern dependence of memory can be altered by different treatments.

Funding

This work is supported by NBRC core.

Publication

Pandey K, Sharma SK (2011). Activity-dependent acetylation of alpha tubulin in the hippocampus. J Mol Neurosci. 2011 Mar 12. PubMed PMID: 21400108.

Awards

Chinmoyee Maharana received the Young Scientist award from Indian Science Congress.

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Alzheimer's Disease: Neuroprotection Against Amyloid Beta-Induced Toxicity

Alzheimer's disease (AD) is the most common form of dementia amongst the elderly. The number of patients suffering from this disease is projected to increase in the coming years. The brains of AD patients show extracellular plaques and intracellular tangles. Amyloid beta (A-beta), a small peptide generated after proteolytic processing of the amyloid precursor protein, is a primary component of the plaques and is considered a causative agent in AD. A-beta exists in different forms including the oligomeric and the fibrilar forms. It has become clear now that the oligomeric form of amyloid beta causes neuronal cell death, synaptic impairment and memory loss. In this project, we are exploring ways by which neuronal protection can be obtained against A-beta-induced toxicity. In addition, we are examining the effects of amyloid beta on the processes that are important for synaptic plasticity and memory.

Effects of an Alkaloid on Amyloid Beta-Induced Indirect Neurotoxicity

Neuronal cell death is a common feature in AD. Thus, prevention of cell death is considered one of the promising therapeutic approaches in AD. There are two ways by which A-beta causes neurotoxicity: direct toxicity and indirect toxicity. In the direct toxicity, A-beta causes neuronal cell death by directly acting on neurons. In the indirect toxicity, A-beta acts on the glial cells and releases toxic and inflammatory molecules. We earlier showed that one of the metabolites of curcumin confers protection against direct neurotoxicity by A-beta. In the current study, we have examined whether sinomenine confers neuroprotection against indirect toxicity caused by A-beta. As shown by others, we also found that treatment of microglial cells with oligomeric A-beta causes the release of reactive oxygen species (ROS) and nitric oxide (NO). In both the assays, sinomenine inhibited the release of ROS and NO from the A-beta treated microglial cells. In addition, A-beta treatment led to enhanced release of inflammatory molecules from the microglial cells. But, sinomenine was able to reduce the release of inflammatory molecules from A-beta treated microglial cells.

Having shown that sinomenine inhibits the release of toxic and inflammatory molecules from the A-beta treated microglial cells, we next asked whether sinomenine prevents indirect toxicity to the neurons. To examine the indirect neurotoxicity, we first used a hippocampal cell line that has extensively been used for toxicity studies by different agents. We found that whereas the conditioned medium from the A-beta treated microglial cells led to cell death in the hippocampal neurons, the conditioned medium from microglial cells that were treated with A-beta and sinomenine did not cause cell death. The protective effect of sinomenine was confirmed in two different assays that measure toxicity. We next asked whether sinomenine confers protection against indirect toxicity to primary hippocampal neurons. Primary hippocampal neuronal cultures were prepared from embryonic rats. We found

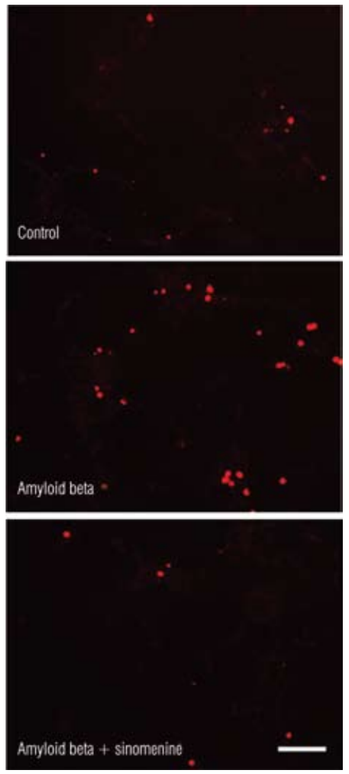


Figure 1
HT22 cells were treated with different conditioned medium and processed for TUNEL staining.The conditioned medium from oligomeric amyloid beta treated BV2 cells increased the number of TUNEL positive cells, but the conditioned medium from BV2 cells that were treated with oligomeric amyloid beta and sinomenine did not increase the number of TUNEL positive cells.

that whereas the conditioned medium from the A-beta treated microglial cells caused cell death to the primary hippocampal neurons, the alkaloid prevented cell death. Thus, this alkaloid was able to prevent indirect cell death of neurons caused by A-beta treated microglial cells. We found also that the level of toxic and inflammatory molecules was reduced in the microglial conditioned medium after treatment with sinomenine.

Effects of Amyloid Beta on Growth Factor Signaling

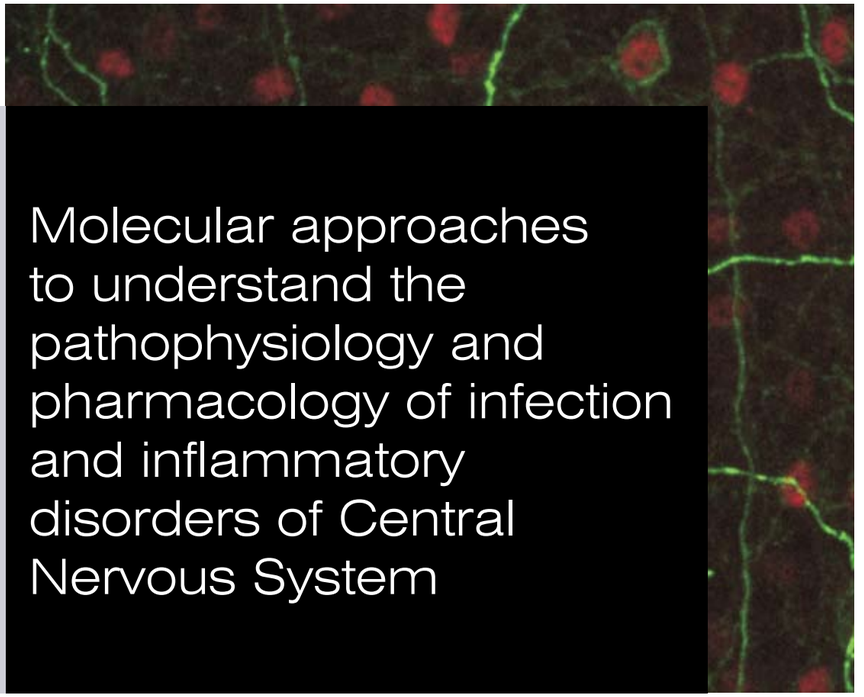
Alzheimer's disease is a memory impairment condition. Studies have shown that growth factor signaling critically contributes to synaptic plasticity and memory in different systems including Aplysia and mammals. As mentioned earlier, amyloid beta is considered a primary causative agent in the development of AD pathology. In this project, our aim is to understand how growth factor signaling is affected by amyloid beta. For these experiments, we use primary hippocampal cultures prepared from embryonic rats. We treat these differentiated cultures with oligomeric amyloid beta and examine its effects on growth factor signaling. Our results suggest that growth factor signaling is impaired by amyloid beta. These results raise the possibility that one of the mechanisms by which A-beta impairs synaptic plasticity and memory is due to its effects on growth factor signaling. We are now examining the mechanisms by which A-beta affects growth factor signaling.

Publication

Mishra S, Mishra M, Seth P, **Sharma SK (2011)**. Tetrahydrocurcumin confers protection against amyloid β-induced toxicity. **Neuroreport**, 22(1):23-7.

Funding

This work is supported by Council of Scientific and Industrial Research and NBRC core.



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

Microglia are seen as the sentries in the CNS who provide a first line of defense whenever there is injury or disease. Microglia and related perivascular macrophages perform various functions, ranging from immunological surveillance to neuroprotection. 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.

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. 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. An acute inflammatory milieu is created in the subventricular neurogenic niche following Japanese encephalitis (JE) and a resultant impairment in neurogenesis occurs, which can be reversed with minocycline treatment. Immunohistological studies showed that proliferating cells were replenished and the population of migrating neuroblasts were restored in the niche following minocycline treatment. In vitro, we checked for the efficacy of minocycline as an anti-inflammatory compound and cytokine bead array showed that production of cyto/chemokines decreased in JEV-activated BV2 cells. Furthermore,

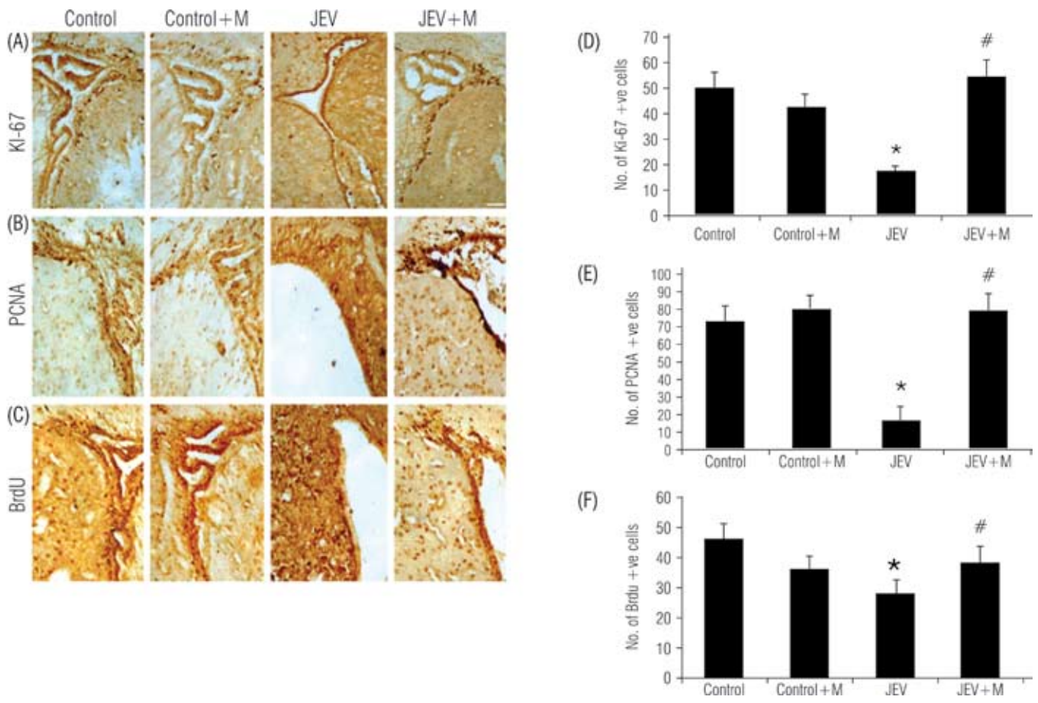


Figure 1
Replenishment of proliferating cells in the infected adult SVZ by minocycline administration Cryostat sections of brains from control, control + M, JEV and JEV+M animal groups were stained for markers of proliferation- Ki-67 **A)** and PCNA **B)** and developed using DAB substrate. BrdU was also administered to animals for 5 days at 50mg/kg body weight and then animals were sacrificed 6h after the last BrdU injection. Cryostat sections from BrdU administered animals from all groups were stained using anti-BrdU antibody **C)** Discrete population of cells in control SVZ show localisation of all the antigens. While reduced population of all three cell types were observed in JEV-infected SVZ, however, they were replenished in the SVZ from JEV+M animals. The graphs represent the number of Ki-67 **D)** PCNA **E)** and BrdU **F)** positive cells in the SVZ from the different treatment groups. Cell counting was done using5 serial sections from 3 animals with Leica IM50 software. Values represent means ± SEM from three animals in each group (* significant change from control, $p<0.05$; #significant change from JEV-infected animals, $p<0.05$); scale bar is 50µ.

mouse neurospheres grown in the conditioned media from JEV-infected microglia exhibit arrest in both proliferation and differentiation of the spheres compared to conditioned media from control microglia. These effects were completely reversed when conditioned media from JEV-infected and minocycline treated microglia was used.

An effective way to counter the virus would be to inhibit viral replication by using anti-sense molecules directed against the viral genome. Octaguanidiniumdendrimer-conjugated Morpholino (or Vivo-Morpholino) are uncharged anti-sense oligomers that can enter cells of living organisms by endocytosis and subsequently escape from endosomes into the cytosol/nuclear compartment of cells. Mice were infected with JEV (GP78 strain) followed by intraperitoneal administration of Morpholinos (5 mg/kg body weight), daily upto five treatments.

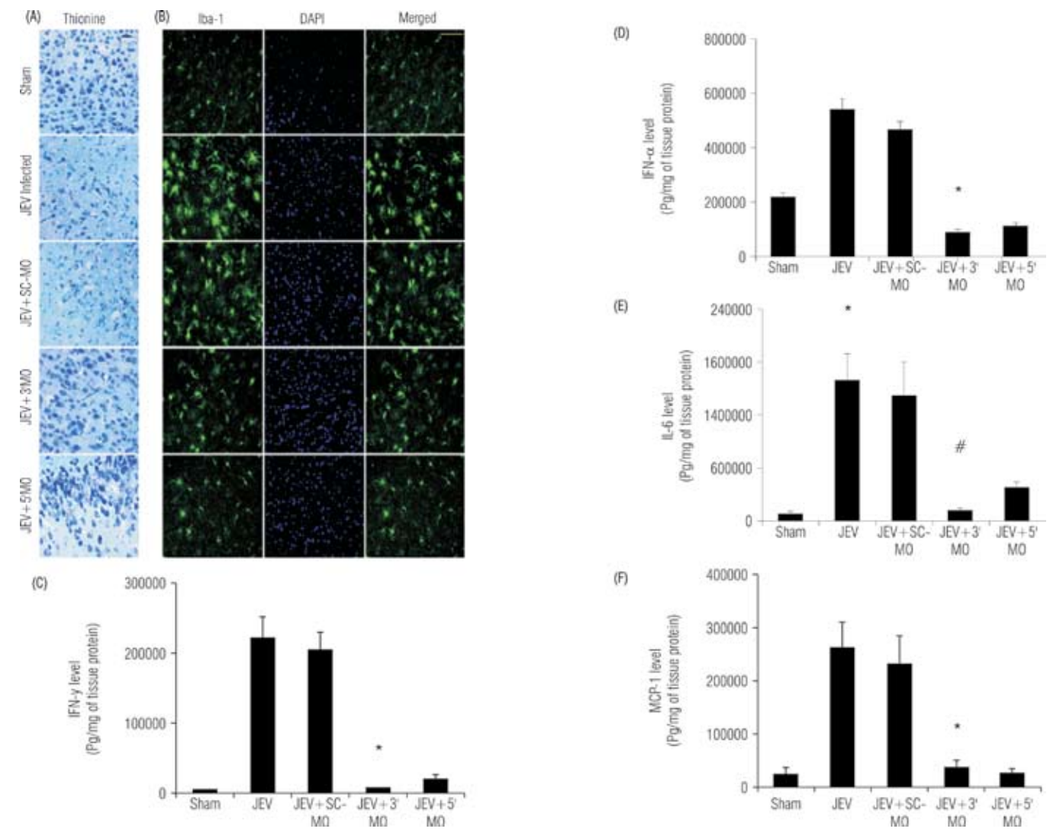


Figure 2
Morpholino oligomers (MO) neuroprotect, reduces microglial activation and inhibits proinflammatory cytokines production in brain. Thionin staining of brain sections from all the treatment groups showed neurons with distinct morphology in Sham-treated, JEV+3' MO and JEV+5' MO groups. However in sections from JEV-infected and JEV+SC-MO groups showed damaged neurons with altered morphology. Magnification ×20; scale bar correspond to 50m **A)** Immunofluorescent staining for microglia-specific Iba-1 performed in brain sections of all groups showed that number of activated (star shaped) microglia appeared to be more frequent in JEV-infected and JEV+SC-MO groups as compared to compared to sections belonging to Sham, JEV+3' MO and JEV+5' MO groups. Magnification ×20; scale bar correspond to 50m **B)** Photomicrographs shown here in this figure are representative of three individual animals from each group. CBA showed levels of MCP-1, IFN-g, TNF-a, and IL-6 were increased significantly in both JEV-infected and JEV+SC-MO groups when compared to Sham treated groups. The elevated levels of these proinflammatory cytokines were then significantly reduced with 3' and 5' MO treatments (* $p < 0.01$ for JEV and JEV+SC-MO when compared to Sham; # $p < 0.01$ for JEV+ 3'MO and JEV+ 5' MO when compared to only JEV-infected group) (C-F).

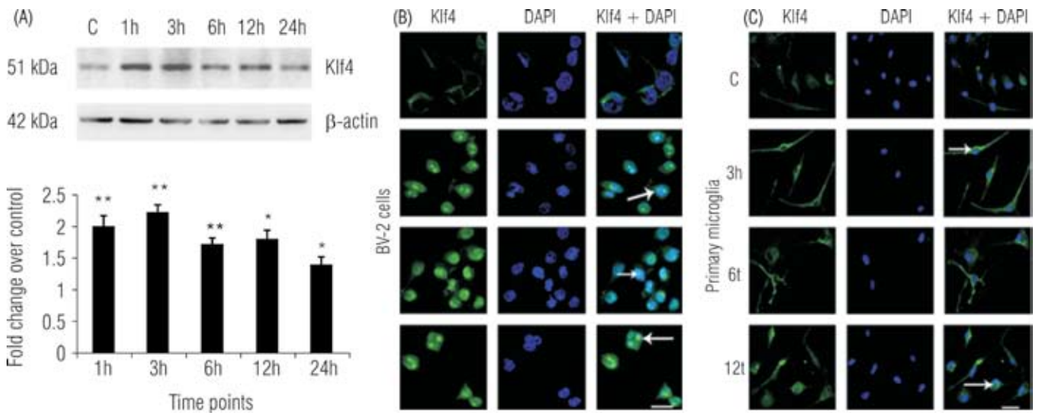


Figure 3
Nuclear expression and translocation of Klf4 in response to LPS. Immunoblotting was carried out for nuclear extracts from LPS-treated BV-2 cells in a time-dependent manner. **A)** A significant increase is observed in Klf4 levels in nuclear extracts at the 1h and 3h time points. The graph represents nuclear Klf4 protein levels relative to untreated controls. *, **, Statistical differences in comparison to control values (* p< 0.05; ** p < 0.01). For nuclear translocation studies, immunofluorescence for Klf4 was carried out in BV-2 cells and primary microglia. **B)** Increased expression and nuclear translocation of Klf4 in BV-2 cells at 3h, 6h and 12h time points, indicated by arrows. **C)** Increased expression of Klf4 in mouse primary microglia cells and nuclear localization of Klf4 at the 12h time point are indicated by arrows. Scale bar: 20μm

Survivability of the animals was monitored for 15 days (or until death) following which they were sacrificed and there brains were processed either for immunohistochemical staining or protein extraction. Plaque assay and immunoblot analysis performed from brain homogenates showed reduced viral load and viral protein expression, resulting in greater survival of infected animals. Neuroprotective effect was observed by thionin staining of brain sections. Cytokine bead array showed reduction in the levels of proinflammatory cytokines in brain following Morpholino treatment, which were elevated after infection. This corresponded to reduced microglial activation in brain. Oxidative stress was reduced and certain stress-related signaling molecules were found to be positively modulated following Morpholino treatment. In vitro studies also showed that there was decrease in infective viral particle production following Morpholino treatment. Administration of Vivo-Morpholino effectively resulted in increased survival of animals and neuroprotection in a murine model of JE. Hence, these oligomers represent a potential antiviral agent that merits further evaluation.

Based upon our previous findings recently Drug Controller General of India approved a Phase II clinical trial in JE patients, using minocycline as a drug. This clinical trial will be supervised by Prof Rashmi Kumar, Head of the department, Pediatrics. CSM Medical University(Erstwhile King George Medical College), Lucknow. The initial preparatory work has already commenced after the requisite approvals.

Alongside with neurobiology of JE, our laboratory is also deeply engaged in basic research to understand the transcriptional regulation of microglial activation. We have identified a novel transcription factor Krüppel-like factor 4, which regulates microglial activation and subsequent neuro-inflammation. Our findings suggest that Klf4 expression and nuclear translocation increased in microglial cells in response to lipopolysaccharide (LPS). Promoter binding assays and knockdown studies revealed that Klf4 binds to iNOS and Cox-2 promoters and upregulates their levels in microglia upon LPS stimulation. Klf4 is also important in upregulating key proinflammatory cytokines including TNF-α, MCP-1 and IL-6. This novel transcription factor promises to be a potent target for therapeutic agents aiming to alleviate inflammation in brain

Publications

Research articles

A. Nazmi, K. Dutta, S. Das, and **A. Basu (2011).** Japanese Encephalitis Virus Infected Macrophages Induces Neuronal Death **J Neuroimmuno Pharmacology.** 6(3): 420-33

S. Das, K. Dutta, K. L. Kumawat, A. Ghoshal, D. Adhya, and **A. Basu (2011)**. Abrogated Inflammatory Response Promotes Neurogenesis in a Murine Model of Japanese Encephalitis. **PLoS One,** 6(3); e17225

A. Nazmi, K. Dutta, and **A. Basu (2010)**. Antiviral and Neuroprotective Role of Octaguanidinium Dendrimer-Conjugated Morpholino Oligomers in Japanese Encephalitis. **PLoS Neglected Tropical Diseases**, 4(11) e892

D. K. Kaushik, M. Gupta, S. Das, and **A. Basu (2010)**. Krüppel-like factor 4, a novel transcription factor regulates microglial activation and subsequent neuroinflammation. **Journal of Neuroinflammation**, 7 (1):68

S. Das, S. Chakraborty, and **A. Basu (2010)**. Critical role of lipid rafts in virus entry and activation of Phosphoinositide 3' Kinase / Akt signaling during early stages of Japanese Encephalitis Virus infection in neural stem/progenitor cells. **J Neurochem**, 115 (2): 537-549

U. K. Misra, J. Kalita, R. Srivastava, P.P. Nair, M.K. Mishra and **A. Basu (2010)**. A Study of cytokines in tuberculous meningitis: clinical and MRI correlation. **Neurosci Lett**, 483 (1): 6-10.

K. Dutta, K.L. Kumawat, A. Nazmi, M.K. Mishra, and **A. Basu (2010)**. Minocycline Differentially Modulates Viral Infection And Persistence In An Experimental Model Of Japanese Encephalitis. **J Neuroimmuno Pharmacology**, 5(4):553-65

* 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**, 215: 884-893

Reviews

S. Das, and **A. Basu (2011)**. Viral Infection and Neural Stem/Progenitor Cell's fate: Implication in brain development and neurological disorders. **Neurochemistry International** (in press) Invited review for a special issue 'The potential of Stem Cells for 21st Century Neuroscience'. 59 (3): 357-66

D. Adhya and **A. Basu (2010)**. Epigenetic Modulation of Host: New Insights into Immune Evasion by Viruses. **Journal of Bioscience** 35(4):647-663

*In press last year

Presentations

A. Basu. Host pathogen interaction in Japanese encephalitis virus infection: from bench to bedside. 2nd Annual Conference of International Association of Medical and Pharmaceutical Virologists, organized by Vallabhai Patel Chest Institute, University of Delhi, 3rd-5th March, 2011. [Plenary talk].

D. K. Kaushik, M. Gupta, and A. Basu. NALP3 inflammasome mediates the production of IL-1α and IL-18 upon Japanese encephalitis virus infection: 37th Annual Conference of the Indian Immunology Society (IMMUNOCON 2011), 7th - 9th February 2011, Jammu University, Jammu.

K. Dutta, A. Nazmi and A. Basu. Japanese encephalitis virus infected peripheral macrophages mediate neuronal death. 37th Annual Conference of the Indian Immunology Society (IMMUNOCON 2011), 7th - 9th February 2011, Jammu University, Jammu.

A. Nazmi, K. Dutta and A. Basu. RIG-I mediates innate immune response in Japanese encephalitis. 37th Annual Conference of the Indian Immunology Society (IMMUNOCON 2011), 7th - 9th February 2011, Jammu University, Jammu.

A. Nazmi, K. Dutta and A. Basu. Therapeutic implications of octaguanidinium dendrimer-conjugated morpholino oligomers in an experimental model of Japanese encephalitis. 37th Annual Conference of the Indian Immunology Society (IMMUNOCON 2011), 7th - 9th February 2011, Jammu University, Jammu.

A Basu. Transcriptional regulation of microglial activation. Neurocon 2011, organized by IPGME&R and Indian Institute of Chemical Biology, Kolkata, 29-31st January, 2011. [Invited speaker]

D. K. Kaushik, M. Gupta, and A. Basu. Role of NLRP3 Inflammasome in Japanese Encephalitis Virus Mediated Neuro-inflammation. 36th Mahabaleshwar Seminar on infection and pathology organized by the institute of fundamental research (TIFR), 8th - 13th January 2011, Mahabaleshwar.

A. Basu. Kruppel-like factor 4, a novel transcription factor regulates microglial activation. Glial Cells in Health and Disease, Satellite Symposia of 5th Congress of FAONS, School of Studies in Neurosciences, Jiwaji University, Gwalior, 30th November, 2010. [Invited speaker]

A. Basu. The innate immunity of the central nervous system in viral encephalitis Central India Institute of Medical Sciences, Nagpur 6-7th August, 2010. [Invited speaker]

Funding

To study the role of Neuronal innate immune response in Japanese encephalitis virus infection [Funded by CSIR (27(0238)/10/EMR-II)]

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)]

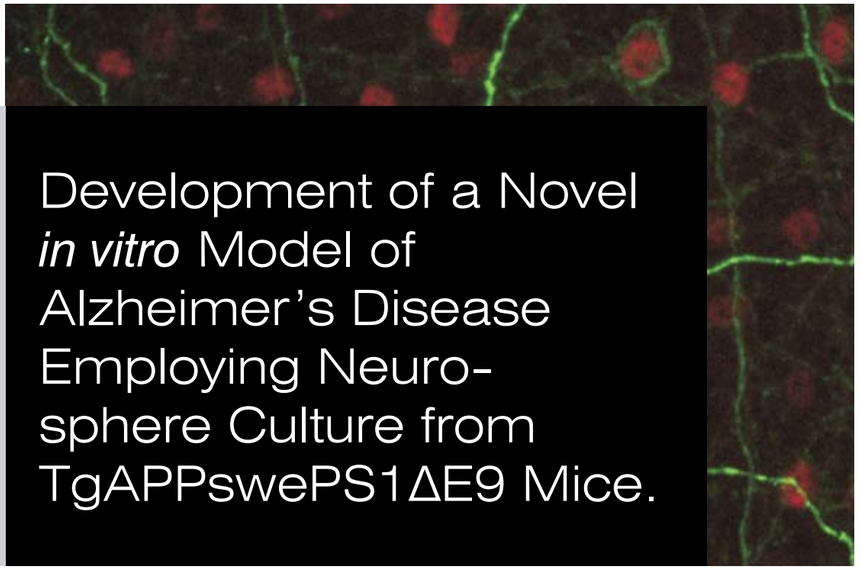
Dissecting molecular circuitries that regulate Progenitors Cell Response to Japanese Encephalitis Virus. (Funded by Department of Biotechnology, BT/PR8682/Med/14/1275/2007)

Awards

National Bioscience Award for Career Development-2010 (Department of Biotechnology, Government of India)

Degree Awarded

Ph.D. Sulagna Das (2010)



Development of a Novel *in vitro* Model of Alzheimer's Disease Employing Neuro-sphere Culture from TgAPPswePS1ΔE9 Mice.

Principal Investigator
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Alzheimer's disease (AD) 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 $A\beta_{1-42}$ peptides that forms the backbone of the amyloid (Aβ) cascade hypothesis. However, very little is known about the exact role of beta amyloid peptides towards neurotoxicity. In order to study the mechanisms associated with AD neurodegeneration in humans, transgenic animals expressing human FAD genes were developed. Though these transgenic mice show beta amyloid deposits, astrogliosis, impaired learning abilities and mild cognitive impairment, 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 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 cell types 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*.

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 wild type controls. Our results demonstrated that, Tg +ve lines express huAPPswe and huPS1ΔE9 transgenes at mRNA level (by RT-PCR) which are not present in Tg -ve neurosphere lines.

Western blot analysis of neurosphere lysates and immunofluorocytochemistry (IFCC) analysis indicated the expression human APP protein and its fragments only in Tg +ve neurosphere lines but not in transgenic negative lines. However, presence of beta amyloid peptides in neurosphere lysates was not detected in any transgenic positive neurosphere lysates. This could be because of release of Aβ peptides to extracellular space, the culture media. Western blot analysis of human Aβ peptides from culture supernatants of both Tg –ve and Tg +ve active neurosphere cultures indicated the presence of human Aβ peptides in all Tg +ve neurosphere lines but not at all in Tg -ve lines. These Aβ peptides are seen both as monomers as well as oligomers. Moreover, resolution of Aβ peptides in Tris-Bicine Urea gel followed by western blot analysis clearly demonstrated the presence of human Aβ40 and Aβ42 in Tg +ve (NS1 and NS3) but not in Tg -ve NS lines and Aβ42 to Aβ40 ratio is higher than any other *in vitro* model of AD.

Intracellular Aβ load is another pathological feature of various cells in AD brain. Immunofluoroscence staining of adherent cells from neurosphere cultures demonstrated Tg +ve neurosphere lines have significant increased immunosignal towards 6E10 antibody than Tg -ve neurosphere lines without Formic acid (FA) treatment. Upon FA treatment, Tg +ve cells showed dramatic increased immunosignal over non-treated counterparts, whereas Tg -ve cells showed little increased signal than non-treated cells. Increased immunosignal in Tg +ve neurosphere cultures might be due to the presence of Aβ peptides in beta-sheet isoforms that required epitope retrieval by FA prior to its interaction with 6E10 antibody. Taken together, the results strongly indicate the expression, protein misfolding and accumulation of human Aβ 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 as well.

Presentations

R. K. Giri and P. S. Ghate. Utilization of CNS Stem Cells as a Tool to Model Neurodegenerative Diseases in vitro; a High Throughput Assay System to Screen Novel Therapeutic Molecules. Invited oral presentation at the 25th Annual Meeting of Society for Neurochemistry and International Symposium on Metabolic Signalling in Brain in Health and Diseases, University of Hyderabad, India, 2011.

R. Giri. Neurosphere cultures are superior in vitro tool to model neurodegenerative diseases. Invited oral presentation at the International Conference on Molecular Medicine, CHARUSAT, Gujrat, India, 2011.

R. Giri. Neurosphere cultures are superior in vitro tool to model neurodegenerative diseases. Invited oral presentation at Biosparks, School of Life Sciences, JNU, New Delhi, India 2011.

Funding

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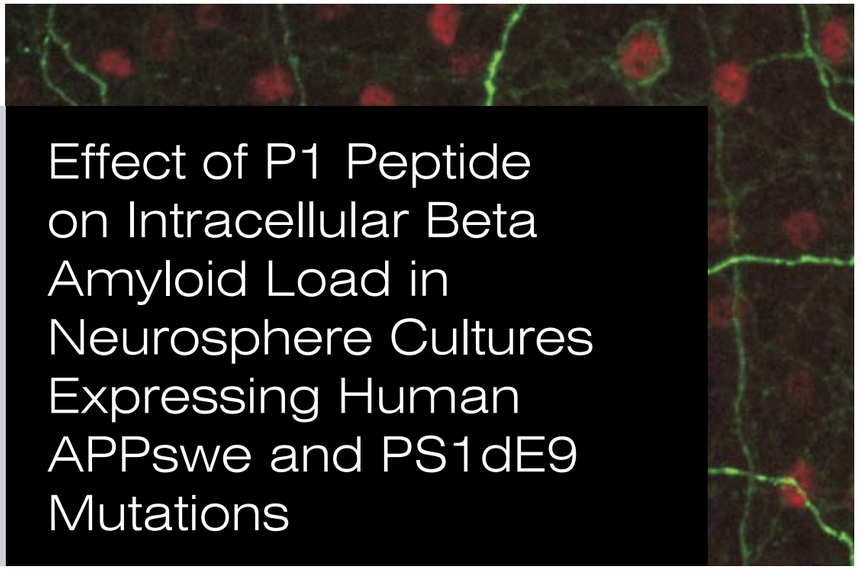

Effect of P1 Peptide on Intracellular Beta Amyloid Load in Neurosphere Cultures Expressing Human APPswe and PS1dE9 Mutations

Principal Investigator
Ranjit Kumar Giri
Lab Attendant
Lalit Bidla

Accumulation of beta amyloid peptides is the first and key event in the pathoprogression of Alzheimer's disease (AD). Beta amyloid peptides undergo post-translational modification to form beta-sheet structure which favors its oligomerization and subsequent fibrillization. In India, more than a million people are suffering from this disease and the number will increase dramatically in coming decade as per the WHO projection. No therapy is available to combat this disease. A variety of compounds have been proposed as potential therapeutics for the treatment of Alzheimer's diseases. However, none of these compounds are effective in actively progressing AD. Therefore, novel molecules those could reduce beta amyloid load either by inhibiting beta amyloid synthesis or enhancing beta amyloid degradation need to be studied. Molecules with beta-sheet breaking activity were of high importance. Recently Prof. Rani Gupta at Delhi University has found P1 peptide has been found to accelerate the enzymatic degradation of fibrillar feather protein, beta amyloid plaques on AD brain sections and prion plaques on prion diseased brain sections by substilisin. However, in the absence of P1 peptide the degradation was minimal. In addition, P1 peptide had no effect on the proteolysis of a globular protein such as, casein. The result indicates that the P1 peptide might have altered the conformation of keratin from protease resistant to protease sensitive keratin. Based on this information, I hypothesize that, P1 peptide might be acting as a beta-sheet breaker and might reduce the beta amyloid load in *in vitro* and *in vivo* models of Alzheimer's disease by enhancing its proteolysis.

To test the hypothesis, we initially employed our recently developed neurosphere based model of AD. We also employed conformation dependent immuno-cytochemistry to detect the reduction of intracellular beta amyloid load by P1 peptide.

Our preliminary result indicated that P1 peptide treated neurosphere cultures expressing human APPswe and human PS1dE9 mutation have similar immuno-reaction to 6E10 antibody specific for human APP and its processed product in formic acid untreated cells but dramatic reduction in formic acid treated samples than P1 untreated transgenic positive cells. Among all the processed product of APP, beta amyloid peptide rapidly forms beta-sheet structure and oligomerization in physiological condition and demands epitope retrieval by FA. Furthermore, cells treated with P1 peptide have longer processes and more number of branches per cell indicating a favorable condition for CNS stem cell survival and differentiation (see figure 1). Taken together, P1 peptide may act as beta amyloid lowering molecules.

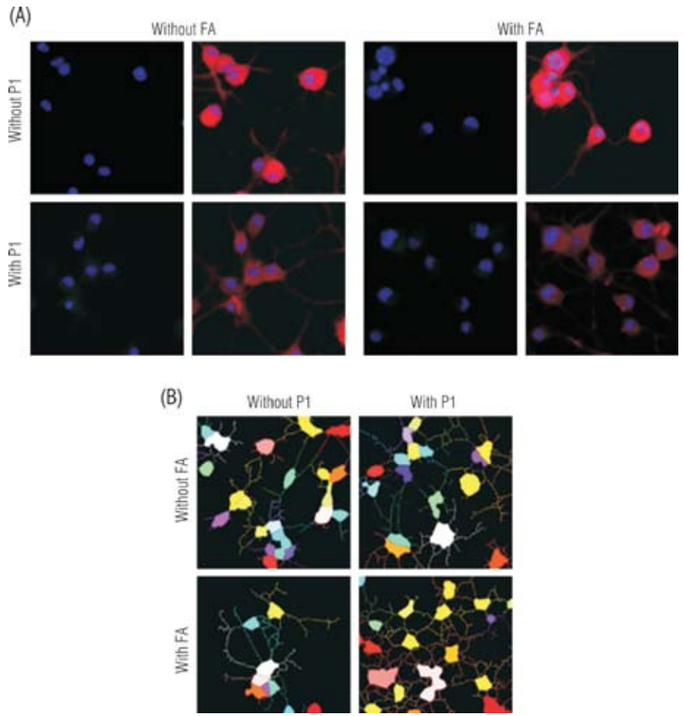

Figure 1
Effect of P1 peptide on intracellular beta amyloid load by conformation dependent immunocytochemistry.
A) P1 peptide reduced the formic acid sensitive beta amyloid pool in transgenic positive neurosphere culture.
B) P1 peptide favors the development of cellular processes.

Presentations

R. K. Giri. Development of a novel in vitro model of prion disease and it's possible application on anti-prion drug screening and discovery. Invited oral presentation for UGC networking summer course on the Emerging Trends in Drug Discovery and Development, University Institute of Pharmaceutical Sciences, Panjab University, Chandigarh, India, 2010.

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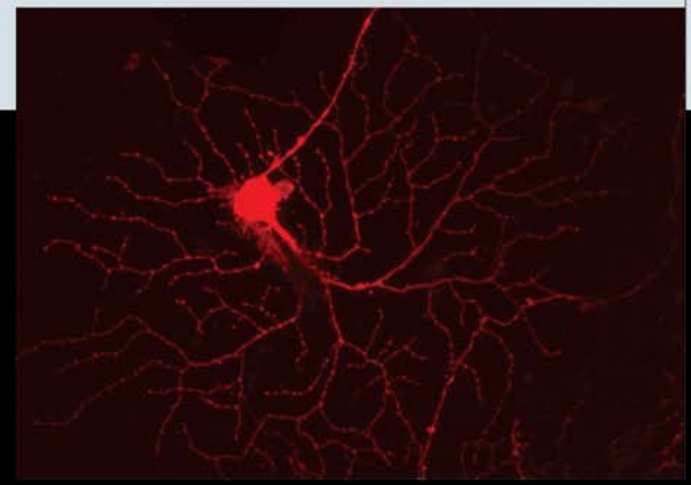

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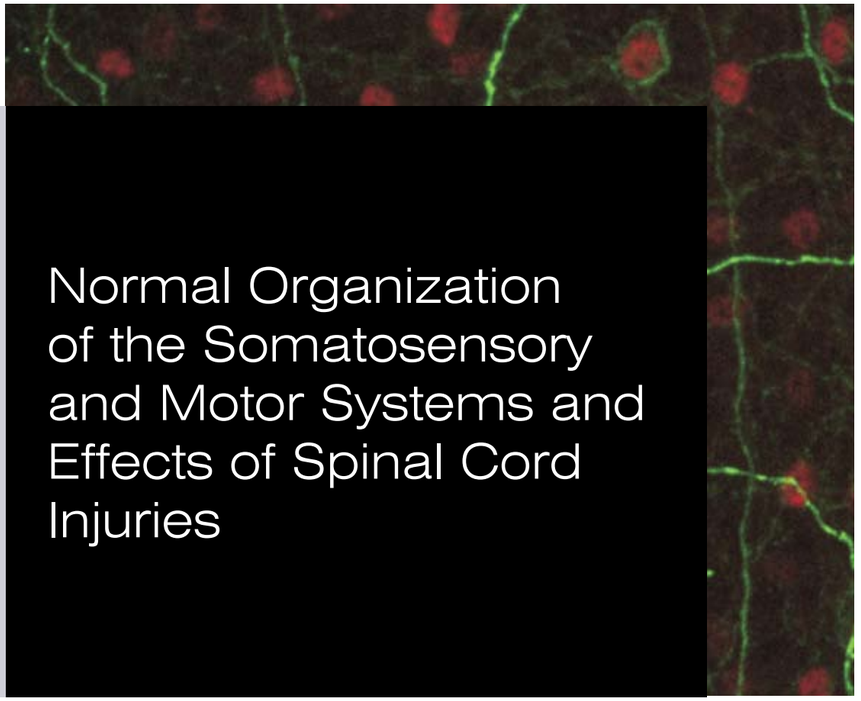

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Normal Organization of the Somatosensory and Motor Systems and Effects of Spinal Cord Injuries

Tactile inputs are processed in multiple cortical and subcortical areas of the brain to enable tactile perception and planning, initiation and control of movements. We are interested in understanding the organization and information processing in the somatosensory and motor areas of mammalian brains. Another major goal of the laboratory is to understand how injuries, particularly the spinal cord injuries, affect the organization and information processing in these systems. We use a combination of neurophysiological, neuroanatomical and behavioural tools in our laboratory.

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. The behavioural effects of these lesions are restricted to inability of the monkeys to form a precision grip. We use both primate and rodent models for our studies because each model system offers specific advantages. The work done during the year is described below.

Information processing in the hand area of the primary somatosensory cortex of monkeys

Hand is the most important tactile organ for humans and other primates. In area 3b (the primary somatosensory cortex), inputs from the hand have a large representation. This map has an orderly topographic representation of the digits and the palm.

We are interested in understanding how the somatosensory cortex processes information from the hand for perception and behaviour. Last year we reported our results from experiments where we determined response properties of neurons in different parts of the hand representation in area 3b following stimulation on a particular location on the skin of the hand. The goal was to understand how neurons in the hand representation integrate sensory inputs from different parts of the hand. We reported that neurons in the D1 (digit 1 or the thumb) representation of area 3b respond to the stimulation of the skin on D1, and rarely to a stimulation on other digits. Neurons in representations of digits D2, D3, D4 and D5 showed maximal response to

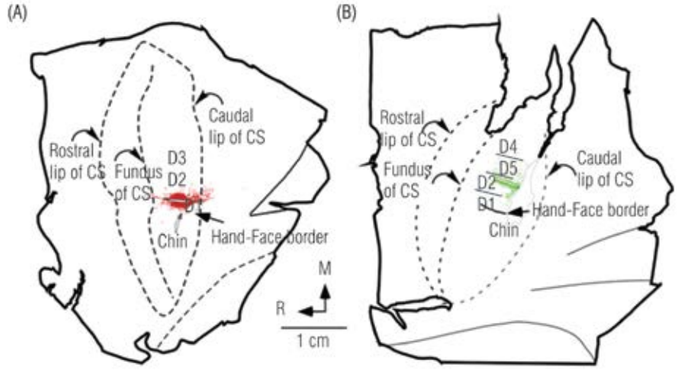

Figure 1
Labeled axons following injections of fluorescent tracers in **A)** D1, and **B)** D3 representations in the somatosensory area 3b of monkeys. Note that after injection of the tracer in D1 most of the spread of horizontal connections is confined to D1, while after the D3 injection the spread is wider, primarily in D2, D3, D4 and D5 representations. Stippled regions are the site of injections showing the zone of uptake of the tracers. The hand-face border, and the border between digits are drawn from adjacent sections stained for myelin substance. The part of the cortex shown here has been flattened to open the centras sulcus CS, central sulcus; M, medial; R, rostral.

stimulation in the classical receptive field; however, responses were also noted when any of the other three digits were stimulated. Neurons in the representations of these digits generally did not respond to the stimulation of D1.

During the last year we carried out experiments to determine if there is a neuroanatomical substrate underlying the neurophysiological observations described above. Specifically we determined if horizontal connections in the hand representation have evolved to reflect the altered use of the digits due to an opposable thumb. We injected small amounts of neuroanatomical tracers in identified locations in the hand representation of area 3b. The locations were identified by neurophysiological mapping. The labeled axons and cells were plotted to determine the spread of horizontal connections. The data showed that if the tracer was injected in D1 (thumb) representation, its spread in area 3b was largely limited to the D1 representation. However, when the tracers were injected in the representation of D2-D5, the labeled axons were more widespread and extended over the representation of all the digits except D1 (Fig. 1). The results suggest that intracortical interactions could provide an anatomical substrate for the neurophysiological observations of the receptive field properties of neurons in the hand representation in area 3b.

Normal organization of the motor cortex in rats

Primates and many other mammalian species have multiple motor areas for initiating, controlling, coordinating and executing movements. In the rat cortex only one motor area has been clearly delineated. Although it has been suggested that there is an additional rostral motor area, there is no definitive proof of the existence of a second representation of any body part except for forelimb, called in the rostral forelimb area (RFA).

Based on differences in the nature of 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

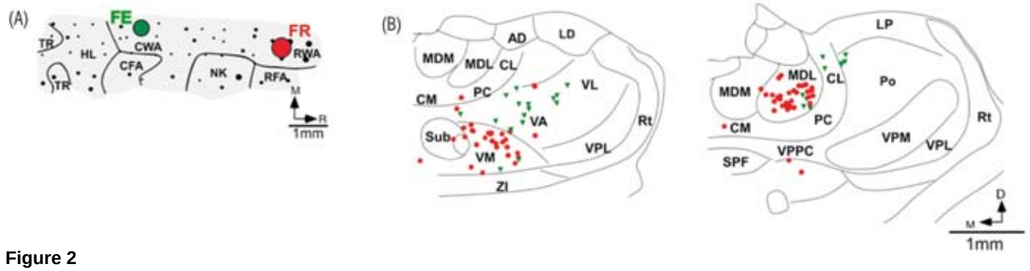

Figure 2
Thalamocortical connections of the caudal whisker area (CWA, green) and the rostral whisker area (RWA, red) in a rat. **A)** Organization of the motor cortex and the sites of injections of neuroanatomical tracers fluororuby (FR, red) and fluoroemerald (FE, green). **B)** Drawings of two sections through the thalamus showing various nuclei and the neurons labled after injections of the tracers in CWA (green triangles) and RWA (red dots). Clear differences can be seen in the sources of the thalamic inputs to these areas. Please see text for details. Abbreviations (for A): HL, hindlimb; NK, neck; RWA, rostral whisker area; RFA, rostral forelimb area; TR, trunk. In B thalamic nuclei are: AD, anterodorsal; CM, central medial; CL, centrolateral; LD, laterodorsal; LP, lateral posterior; MDM, mediodorsal medial; MDL, mediodorsal lateral; Po, posterior thalamic nucleus; PC, paracentral; Rt, thalamic reticular nucleus; Sub, Submedius nuclei; SPF, subparafascicular nuclei; VPM, ventroposteromedial; VPL, ventroposterolateral; VM, ventromedial; VA, ventral anterior; VL, ventrolateral; VPPC, parvicelular subdivision of ventroposterior medial nucleus; ZI, zona incerta.

cortex has two separate representations of the whiskers (Tandon et al., Eur J Neurosci. 27:228, 2008). We suggested that the rostral whisker area (RWA), along with RFA might be part of a rostral motor area. We have sought further experimental proof of the presence of two motor areas in rats. Last year we reported our results from experiments where 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 showed that sources of inputs to RWA and CWA were different. Moreover, the connection pattern of RWA was similar to that of RFA, and the connection pattern of CWA was similar to that for CFA. Further continuing these experiments, we determined sources of thalamic inputs to CWA, RWA, CFA and RFA. The data show that although there are many common sources of thalamic inputs, there are specific differences in the input patterns to the caudal and rostral motor representations. The lateral subdivision of the mediodorsal nucleus (MDL) projects to RWA and RFA, but only very sparsely to CWA and CFA. Similarly, the ventromedial nucleus (VM) projects strongly to the rostral motor representations, but only weakly to the caudal areas. Conversely, the ventral anterior (VA) and the ventral lateral (VL) nuclei project strongly to CWA and CFA, but only weakly to the rostral areas. Thus CWA and RWA are two different motor areas with distinct corticocortical and thalamocortical input patterns, which are similar to those for CFA and RFA respectively. The results strongly suggest that as for the higher mammals, the rat motor cortex also has at least two motor areas.

Publications

N. Kambi, S. Tandon, H. Mohammed, L. Lazar and **N. Jain (2011)**. Reorganization of the primary motor cortex of adult macaque monkeys following sensory loss due to partial spinal cord injuries. **Journal of Neuroscience**, 31: 3696-3707.

N. Jain and S. Tandon (2011). Plasticity of the somatosensory system following spinal and peripheral injuries. In **Expanding Horizons of the Mind Sciences** In Press.

N. Jain (2010). Brain-machine interface: The future is now. (An invited Editorial). **The National Medical Journal of India**. 23: 321-323.

Presentations

N. Jain. 'Effects of spinal cord injuries on the brain – interventions using brain machine interface devices.' Science Awareness Workshop, Indian Statistical Institute, Systems Science and Informatics Unit, Bangalore. March, 2011

N. Jain. (i) Brain – an introduction, (ii) The somatosensory system – from periphery to brain, (iii) The somatosensory system – the cortical somatosensory areas and their role, (iv) Plasticity of the adult brain. 4th DST-SERC School on Systems and Cognitive Neuroscience, National Brain Research Centre, Manesar. February - March , 2011.

H. Mohammed, M. K. Singh and N. Jain. Corticocortical connections of the motor cortex in rats: Evidence for two separate motor areas. Annual Meeting of the Society for Neuroscience, USA, San Diego, USA. November 2010,

Funding

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Development of the Human Auditory Cortex

We have been studying the development of primary and surrounding non-primary (association) auditory cortical areas in humans. Studies using functional magnetic resonance imaging in adult subjects have demonstrated that small foci within the auditory association areas TA and TB process complex sounds including environmental sounds and speech. It has also been shown that these areas can be delineated by staining for the enzyme acetylcholinesterase and calcium binding proteins (calretinin, calbindin and parvalbumin) in postmortem brain tissue. Earlier studies have shown that of the three calcium binding proteins, parvalbumin is associated with an increase in activity and maturation of synapses during development, suggesting that its expression in the developing brain can be used as a marker for maturation. Since hearing begins in utero and the human fetus can discern speech sounds in the last few weeks before birth, we wanted to study whether the specialized auditory areas for discerning complex sounds could be delineated before birth in postmortem brain tissue, using immunohistochemistry to visualize calretinin, calbindin and parvalbumin. We found that whereas calretinin and calbindin were expressed as early as ~15GW (gestation weeks) in the developing auditory cortex, parvalbumin was expressed in the auditory cortex at ~ 33GW. Even at this stage, there was no cellular label and parvalbumin was expressed only in the neuropil in some parts of the auditory cortex. Interestingly, scattered parvalbumin-positive stellate cells appeared for the first time in the Heschl's gyrus at 37GW, where the primary auditory cortex is located. However, there were no parvalbumin-positive cells

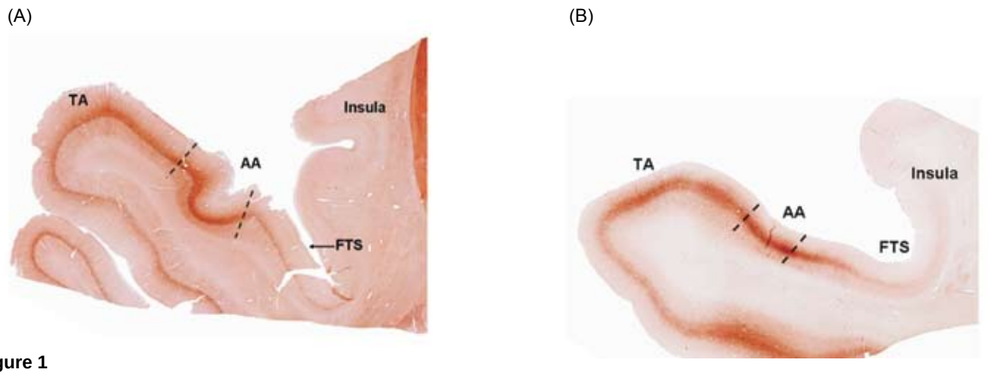

Figure 1
Low levels of parvalbumin are expressed in neurons throughout the auditory cortex before and at birth. Parvalbumin is present in the neuropil as well as neurons in area AA which is nested in the auditory association area TA (A) 9 months after birth. The expression of parvalbumin in the auditory cortex at 9 months was similar to that in an adult (B). Scale bar = 1mm.

in any of the areas which process complex sounds (TA or TB). By the 9th postnatal month, staining for parvalbumin in both primary and auditory association areas resembled the adult pattern, with high levels of parvalbumin immunopositivity in the neuropil and the presence of a number of stellate cells which are intensely immunoreactive for parvalbumin in layer IV (Fig. 1). Our data suggest that amongst the auditory areas in humans, the primary auditory cortex matures earlier than the auditory association areas in terms of immunoreactivity for parvalbumin (~37GW).

Presentations

L. S. Hameed, A. S. Pundir, B. Radotra, P. Kumar, S. Mohan, P.C. Dikshit, S.K. Shanker, A. Mahadevan and S. Iyengar. Development of Connectivity in the human auditory cortex. Poster presented at the Annual meeting of the Indian Association of Neurology, Lucknow, November 2010

S. Iyengar. Introduction to the Human Brain. IBRO-APRC (Asia Pacific Regional Committee) School of NeuroImaging organized at the National Brain Research Centre, Manesar, Nov-Dec, 2010.

Funding

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The Role of the Opioid System in Neurogenesis and Behaviour in Adult Zebra Finches

Songbirds such as zebra finches are excellent models to study the phenomenon of adult neurogenesis as well as song behaviour. New cells are continuously born in the ventricular zone in these birds after which they migrate into the brain parenchyma, differentiate into neurons and become incorporated into neural circuits which are important for singing. 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. We are also interested in studying the effects of opioid modulation on behaviour, since our previous results showed that there was widespread expression of the opioid receptors throughout the brain.

We had earlier found that there was an increase in cell proliferation in cultures of the zebra finch VZ after naloxone administration. Further, we also found that some of these cells differentiated into neurons. Recently, we have found that there is a marginal decrease in cell proliferation in VZ cultures treated with naltrindole, compared to saline-treated controls. We have also confirmed that treatment of VZ cultures with the δ-opioid agonist SNC-80 leads to an increase in neurite length, suggesting that the δ-ORs and their endogenous ligands may modulate neuronal differentiation. Our results suggest that the endogenous opioids may have opposing effects on cell proliferation in zebra finches, with the μ-opioids decreasing and δ-opioids increasing cell proliferation in the adult brain.

Our earlier research had shown that both μ- and δ-OR subtypes were present throughout the brain of zebra finches including song control areas and the hypothalamus. Results from our experiments had also revealed systemic administration of the general opioid antagonist naloxone led to a decrease in the number of songs sung by adult male birds either directed to females or in isolation and that the spectral and temporal properties of songs were also altered. However, stereotyped behaviours such as pecking and preening were not affected following naloxone injections.

Although naloxone is a non-specific OR antagonist, it has higher affinity for μ-ORs compared to δ-ORs. Since our earlier results have demonstrated that the expression of μ-ORs is higher than that of δ-ORs in the adult male zebra finch brain, it is possible that the effects of systemic administration of naloxone could be attributed mainly to μ-ORs. In order to test whether δ-ORs also play a role in modulating song and other behaviours, we systemically injected adult male zebra finches with different doses of the selective δ-OR antagonist naltrindole (1mg, 2.5 mg and 5 mg/kg body weight) for a period of four days. We found that there was a significant decrease in the number of songs and calls directed towards females but there were no changes in the spectral and temporal features of song following naltrindole injections. We also found

that there was a decrease in pecking and increase in preening behaviours following administration of naltrindole. Our results suggest that whereas systemic injections of low doses of δ-OR and μ-OR antagonists lead to a decrease in directed song, only μ-OR antagonists appear to affect the quality of song. Further, low doses of naltrindole appeared to affect stereotyped behaviours, suggesting that the δ-ORs may play a larger role in these behaviours compared to μ-ORs.

Publications

S. Iyengar (2011). Comparative and Evolutionary Aspects of Cognition. In **Expanding Horizons of the Mind Sciences**. edited by Prof. PN Tandon, RC Tripathi, and N. Srinivasan, Nova Science Publications, Inc., New York. USA.(In Press)

N. Khurshid, L.S. Hameed, S. Mohanasundaram and **S. Iyengar (2010)**. Opioid modulation of cell proliferation in the ventricular zone of adult zebra finches (Taenopygia guttata). **FASEB J**., 24: 3681 - 3695.

Presentations

S. Iyengar: Basics of the Auditory System. Fourth DST-SERC school in Neuroscience (Systems and Cognition), National Brain Research Centre, Manesar, Feb – March, 2011.

S. Iyengar: 'Bird Brains' and Mammalian brains – Comparative Aspects. Fourth DST-SERC school in Neuroscience (Systems and Cognition), National Brain Research Centre, Manesar, Feb – March, 2011.

S. Iyengar: The Opioid System in Zebra Finches. Fourth DST-SERC school in Neuroscience (Systems and Cognition), National Brain Research Centre, Manesar, Feb – March, 2011.

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Opioid Modulation of song in Male zebra finches awarded in 2010. This work is supported by NBRC Core and DST funds.

Neurobiology and Understanding the Circadian System Linkage of Cognitive Performance in an Avian Model System awarded in 2010. This work is supported by NBRC Core and DST funds.

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Ph.D. Nazia Khurshid: Role of Opioid System in Behavior and Cell Proliferation in Adult Male Zebra finches (Taenopygia guttata) Awarded July 15th, 2010.

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Retinal Circuitry: in health and in disease

Retinal degenerative diseases such as Retinitis Pigmentosa and Age-Related Macular Degeneration have high incidence rates, and are among the leading causes of blindness. These diseases have varied etiology but are characterized by degeneration and loss of photoreceptors. 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

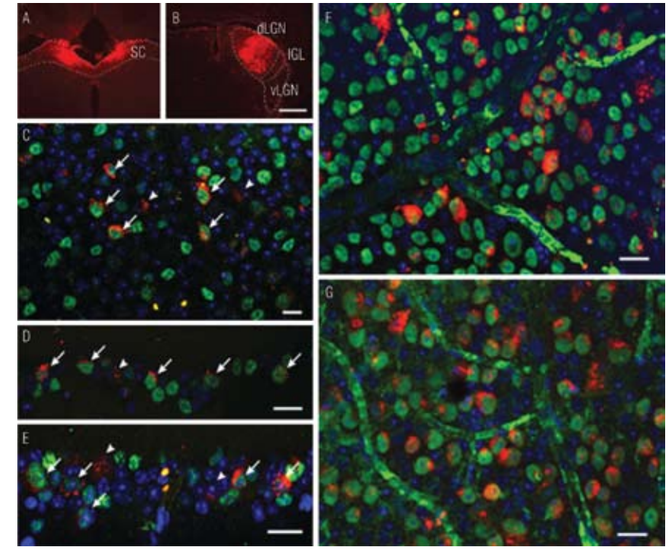

Figure 1
Retinal ganglion cells that projected to SC or dLGN expressed Brn3a or Brn3b or both.
A) A representative coronal section of a mouse brain showing bilaterally injected fluorescent dye, micro-ruby into superior colliculi. Dashed lines define superior colliculus boundaries. **B)** A representative coronal section of a mouse brain showing unilaterally injected micro-ruby into the left LGN. Dashed lines define dorsal and ventral LGN and intergeniculate leaflet (IGL). **C)** A representative field from a flat-mount retina removed four days after bilateral micro-ruby injection in SC and immunolabeled for Brn3b (green) shows several dye-filled RGCs (red) that are also Brn3b-positive (arrows). Note some dye-filled cells that are negative for Brn3b (arrowheads). **D)** Same as in C, but in a vertical section from another retina. **E)** A section from the right retina removed four days after micro-ruby injection in the left dLGN and immunolabeled for Brn3b, shows several dye-filled cells that are Brn3b-positive (green; arrows), but also some that are Brn3b-negative (arrowheads). **F)** A representative field from a flat-mount retina removed four days after unilateral micro-ruby injection in SC and immunolabeled for Brn3a and Brn3b (both green) shows several dye-filled RGCs (red) almost all of which are positive for Brn3a or Brn3b. **G)** A representative field from a flat-mount retina removed four days after unilateral micro-ruby injection in dLGN and immunolabeled for Brn3a and Brn3b (both green) shows several dye-filled RGCs (red), almost all of which are positive for Brn3a or Brn3b. Scale bar (**A** and **B**): 500 μm. (**C** to **G**): 20 μm.

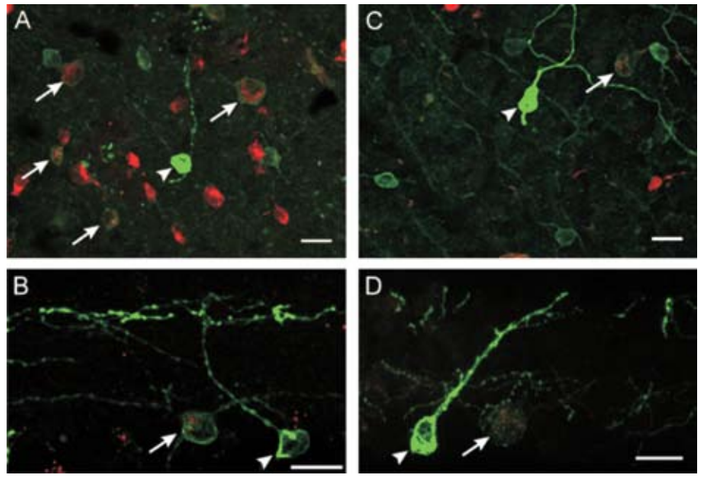

Figure 2
Melanopsin cells that projected to SC or dLGN were non-M1 type. A fluorescent dye, micro-ruby (red) was injected bilaterally or unilaterally in SC or dLGN, and after four days of survival the retinas were flat-mounted or sectioned and immunolabeled for melanopsin (green). **A)** A representative field of flattened retina retrogradely labeled from SC, shows several faintly-labeled, likely non-M1 melanopsin cells that are also filled with micro-ruby (arrows), and a brightly-labeled, likely M1 melanopsin cell which is not filled with micro-ruby (arrowhead). **B)** A section from a retina retrogradely labeled from SC, shows a M2 cell that stratifies in inner IPL (arrow) and a M1 cell that stratifies in outer IPL (arrowhead). The M2 cell, but not the M1 cell is filled with micro-ruby. **C)** A representative field of retina retrogradely labeled from contralateral dLGN, shows a faintly-labeled, likely non-M1 melanopsin cell which is filled with micro-ruby (arrow), and a brightly-labeled, likely M1 cell which is not filled with micro-ruby (arrowhead). **D)** A section from retina retrogradely labeled from contralateral dLGN, shows a M2 cell that stratifies in inner IPL (arrow) and a M1 cell with its processes in outer IPL (arrowhead). The M2 cell, but not the M1 cell is filled with micro-ruby. Scale bar: 20 µm.

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 as electrical stimuli which will be transferred to specific retinal neurons, and thus produce artificial vision in blind patients. Similarly, the transplanted stem cells are expected to differentiate into photoreceptors which would functionally integrate with the host neurons. Both of these approaches have shown great promise in recent years, but are yet to produce the desired clinical outcome. The clinical success of these treatment approaches is linked to our understanding of how the retinal circuitry develops and functions, normally as well as in retinal degeneration. Our lab is interested in addressing these fundamental questions, with emphasis on their relevance to treatment of the retinal degenerative diseases.

We have been studying a specific group of RGCs which express Brn3 transcription factors. Our working hypothesis is that these cells form a suitable target for electrical stimulation by an epiretinal prosthetic device after photoreceptor degeneration. Previously we found that Brn3 transcription factors are differentially expressed by intrinsically-photosensitive (ip)RGCs. We have continued to explore this further and found that while ipRGCs do not express either Brn3a or Brn3c, non-M1 type of ipRGCs express Brn3b. We have also found that nearly all RGCs that project to superior colliculus or dLGN, the brain areas involved in image-forming vision, express Brn3a, Brn3b or both (Fig. 1). Furthermore, we found that nearly all melanopsin cells that projected to these brain areas were of non-M1 type (Fig. 2). Together, these findings support the view that RGCs that express Brn3 transcription factors are responsible for image-forming vision.

Many RGCs exhibit rhythmic spike bursting at 5-10 Hz after photoreceptor loss. However, the mechanism underlying the bursting is not clear. We are testing the hypothesis that the bursts originate in and are intrinsic to bipolar cells, which are revealed and transferred to amacrine cells and RGCs in the absence of photoreceptor input. We have found increased synaptic activity in the inner retina after photoreceptor loss. Furthermore, using pharmacological interventions, we have found evidence that the neurotransmitter GABA plays an important role in producing the spike bursts in RGCs. Understanding the mechanism underlying the aberrant firing in RGCs after photoreceptor loss will help in designing optimal electrical stimulation protocols.

Publications

A. Mathur, C.M. Markan and N.K. Dhingra (2010) Retinal prosthetic interfaces using conducting polymeric thin films. Proc Nanosci and Technol Chem, Hlth, Environ Energy (NATCHEE). Pg 80-84.

Presentations

V. Jain, E. Ravindran and N.K. Dhingra. M2-type, but not M1-type of intrinsically-photosensitive retinal ganglion cells express Brn3 transcription factors. 13th Annual Vision Research conference, Retinal Ganglion Cells. Fort Lauderdale, FL (USA); April-May, 2010.

V. Jain, D. Poria, O. Saha and N.K. Dhingra. Expression of specific ganglion cell proteins by Brn3-positive retinal ganglion cells in mouse. ARVO. Fort Lauderdale, FL (USA); May, 2010.

N.K. Dhingra, S. Nagar, V. Jain, M. Goel and P. Cherukuri. Photoreceptor degeneration upregulates GABA signaling in inner retina. Saxtons River, VT (USA); July, 2010.

N.K. Dhingra. Remodeling of second-order and third-order retinal neurons after photoreceptor degeneration. 18th Annual meeting of the Indian Eye Research Group (IERG). Hyderabad; July 2010.

N.K. Dhingra Three lectures on 1) Membrane biophysics, 2) Retina and 3) Retinal ganglion cells. Fourth DST-SERC School in Neurosciences, Systems and Cognitive Neuroscience. Manesar; February, 2011.

E. Ravindran, V. Jain and N.K. Dhingra. Brn3 transcription factor: a molecular marker of image-forming retinal ganglion cells. 5th Federation of Asian and Oceanian Neuroscience Societies (FAONS) Congress. Lucknow; November, 2010.

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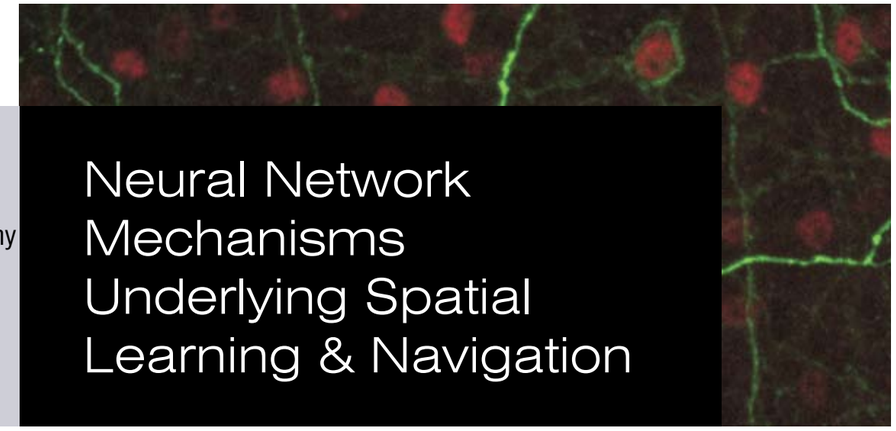

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Neural Network Mechanisms Underlying Spatial Learning & Navigation

Main research focus of our laboratory is to understand how the brain constructs higher-order representations of experience and how those representations are stored and recalled as conscious memories. Place cell of the hippocampal formation and head direction cell system plays a very critical role in spatial memory and navigation. Place cells and head direction cells are an outstanding model system for deciphering the neural network mechanisms by which the brain constructs these cognitive representations from multimodal inputs. The hippocampus is critically involved in learning and memory and has been suggested to play a major role in episodic-memory, context-dependent learning, learning of spatiotemporal sequences, which requires integration of spatial and nonspatial representations. Spatially active place cells selectively fires at specific location in an environment, indicating that the hippocampus may form the locus of a "cognitive map" of the surrounding environment. Previous studies have shown that place cells are controlled by a complex interaction between self-motion cues and salient landmarks in the environment, and it has been suggested that the place cell firing may also reflect encoding of behaviourally salient nonspatial information onto the spatial framework provided by place cells. Head direction cells (cells encoding heading direction present in anterodorsal & laterodorsal thalamic nuclei, lateral mamillary nucleus, post-subiculum and retrosplenial cortex) fire selectively when the animal's head is pointed in a particular direction in allocentric space, regardless of its location and serve as internal compass for the animal. These cells are also controlled by a complex interaction between idiothetic cues and external landmarks. Further, close coupling between head direction cells and place cells have been reported, and the preferred firing locations/directions of place cells and head direction cells remain strongly coupled to each other even when they become completely uncoupled from external landmarks. Thus, the head direction system is suggested to govern the orientation of the hippocampal spatial representation relative to the external environment. However, understanding the precise computations performed by the hippocampus has been limited due to paucity of knowledge on representations from all of its input brain areas. In order to identify specific role played by the hippocampus in learning and memory, it is critical to understand the nature of neural representations already formed in inter-related brain areas in the hippocampal formation, which sheds light on how these representations are processed within the hippocampus and in its afferent and efferent structures.

Hippocampus receives major inputs from two parallel processing streams, the lateral and medial entorhinal cortex, involved in processing of non-spatial and spatial information, respectively, and then creates a conjunctive representation of the external environment. 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. 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 postrhinal cortical neurons are weakly spatially modulated, indicating that other brain areas may be involved in transfer of spatial information to the entorhinal cortex. Based on anatomical connectivity, subiculum has been regarded as both an afferent and efferent area of the hippocampus. Subicular complex neuons receives projections from the hippocampus; also it connects to superficial layers of the entorhinal cortex, which are the input layers to different subfields of the hippocampus. Subicular complex, consisting of subiculum proper, presubiculum, postsubiculum and parasubiculum, receives sensory inputs from different cortical areas and connects to the hippocampus and entorhinal cortex, two major brain areas involved in processing of spatial information. Subicular complex neurons show directional and locational correlates and 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 subicular 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. Further, postsubiculum is connected to anterodorsal thalamic nuclei, containing head direction cells which encode the current heading direction. Thus, the subiculum may act as an interface between these brain areas in the integration of spatial and directional information. 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 complex neurons to elucidate exact role of various brain regions during spatial memory and navigation. Our lab is currently interested in understanding the network properties of subicular complex neurons, that give rise to the spatial tuning and other properties of place cells and to determine the neural basis of learning and memory processes. We have established state of the art in vivo neurophysiology laboratory to study information processing in rodent brain with 96-channel high density electrophysiology system, which allows recording of neural activity as well as local field potentials at specific brain areas in awake freely behaving animals, through multitetrode recording technique.

Publications

D. Yoganarasimha, G. Rao, J.J. Knierim **(2010)**. Lateral entorhinal neurons are not spatially selective in cue-rich environments. **Hippocampus** Article first published online: 20 SEP 2010 DOI: 10.1002/hipo.20839

S.S. Deshmukh, **D. Yoganarasimha**, H. Voicu, J.J. Knierim **(2010)**. Theta modulation in the medial and the lateral entorhinal cortices. **Journal of Neurophysiology** 104(2):994-1006.

Work done elsewhere

Presentations

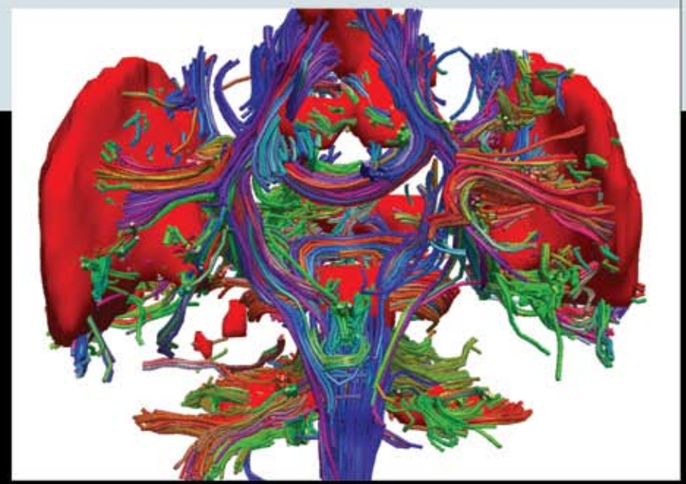
D. Yoganarasimha: Invited lecture on "Spatial Cognition" at DST-SERC School in Neuroscience (21 February to 6 March 2011), NBRC, Manesar, India.

Funding

Department of Biotechnology, Govt. of India. NBRC Core funds.

National Brain Research Centre

NBRC

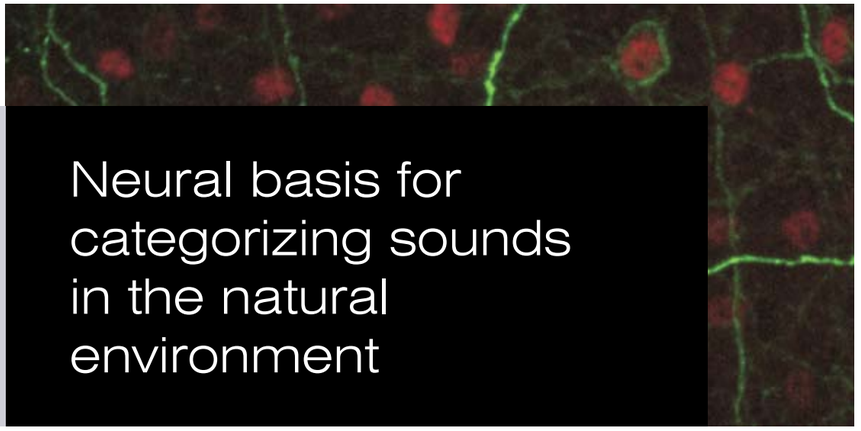


Computational Neuroscience & Neuroimaging Division

Dr. Nandini Chatterjee Singh

Prof. Prasun Kumar Roy

Dr. Pravat Kumar Mandal



Neural basis for categorizing sounds in the natural environment

Principal Investigator
Nandini Chatterjee Singh
Research Fellow
Megha Sharda

Background

The perception of sounds by the human auditory cortex is a rather complex feat. We hear all kinds of sounds from various sources, locations and of varying acoustic parameters like temporal and spectral structure. Yet our brain is able to simplify the task rather easily. We can identify sounds from different categories, classify them with ease, discriminate between loud and soft, pleasant and unpleasant, natural or man-made. However, we still do not fully understand the mechanisms, which enable our brain to solve this seemingly simple problem. Our attempt is to use a multidisciplinary approach to a supposedly physical problem. Using a combination of behaviour, signal processing and functional neuroimaging, to identify a possible basis for the categorization of sounds by the human brain.

We used a series of natural sounds belonging to three categories defined by source – animal vocal sounds (A), human vocal non-speech sounds(V) and environmental sounds, both natural and man-made (NV), which were simultaneously heterogeneous in their distribution of acoustic structure, covering a whole range in each category, yet homogenous enough to be similar across categories. We developed a novel measure of spectral dynamics called the Spectral Structure Index (SSI) to describe the spectral dynamics of sounds.

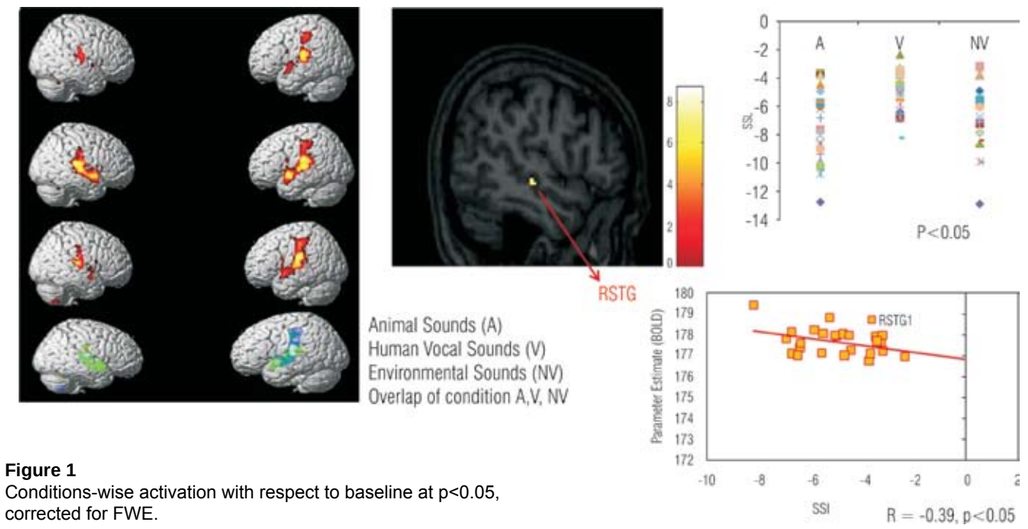


Figure 1
Conditions-wise activation with respect to baseline at p<0.05, corrected for FWE.

A behavioral task, which required loudness matching was developed and tested on 20 participants with normal hearing across sounds of all three categories using a structural and functional MRI protocol. The SSI was successful in categorizing human vocal non-speech sounds as distinct from animal and environmental sounds. The functional neuroimaging results revealed an auditory-brain network (Fig.1(a)) comprising of the bilateral superior temporal gyri, superior temporal sulci, bilateral insulae, cerebellum and thalamus, for each category. Condition specific activations using a conjunction analysis revealed selectivity only for human Vocal sounds but not for any other category where the level of activation in the Superior Temporal Gyrus response correlated with the SSI values (Fig 1(b)). Our results suggest that a lower order acoustic feature in terms of rate of change of spectral dyamics (SSI) might contribute to the behavioural relevance of species-specific vocalizations.

Principal Investigator
Nandini Chatterjee Singh
Research Fellow
Anya Chakraborty

Compensatory mechanisms for naming pictures in patients with frontal lobe tumours

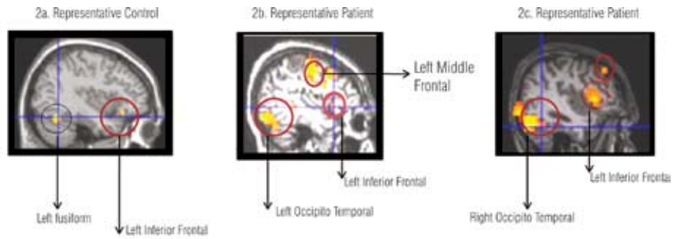
Background

Functional magnetic resonance imaging (fMRI) as a non-invasive technique has become increasingly popular for the pre-surgical evaluation of patients with brain pathology. The particular advantages of fMRI are (1) Providing information prior to surgery (2) Information at both individual and group levels thereby providing us an opportunity to study and understand cortical processing in a compromised brain.

The process of naming pictures is one of the simplest processes in the use of language and we propose it as an essential component in task batteries for pre-surgical assessment since it is largely independent of subject's literacy, education and proficiency levels. Picture naming is elementary, in that while it only requires the production of speech sounds associated with a visual stimulus, it involves distinct cognitive processes, which begin with visual identification of a known concept, lexical retrieval, access to the phonological word form and finally motor articulation. Evidence from a number of neuroimaging studies has shown that naming a particular picture requires the recruitment of occipital, temporal and frontal brain regions.

The development of an intraparenchymal brain tumor or brain lesion in any of the above mentioned cortical areas might disrupt the process of naming pictures. We studied picture - naming and the underlying neural network in 10 patients with a tumor in the left frontal lobe and compared them with those of 9 normal right-handed controls. Patients were between 18 – 65 years and participated in the study prior to their surgery. Clinical examination did not reveal any speech defect in any of the patients. Patients were scanned in a 3T Philips Achieva scanner while they named aloud picture stimuli of common objects and animals like bottle, leaf, baby, bird.

All subjects named pictures with near 100% accuracy, suggesting that naming of simple pictures is preserved in patients with a tumour in the frontal lobe. The functional MRI analysis revealed a distributed picture naming network with a larger number of activated clusters in the patient group involving both the hemispheres (as seen in representative patient activations in Fig. 2(b) and 2(c) as compared to discrete left hemisphere activation loci in the control group (Fig. 2 (a)). Combining data across all patients, we found that patients showed activations in significantly greater number of clusters in frontal areas



of both hemispheres, as compared to controls. Our results therefore suggest compensatory mechanisms in the form of additional activation sites in the frontal lobe of the ipsi and/or contralateral hemispheres in patients. Our results suggest that when confronted by a slowly evolving brain pathology like that caused by a brain tumor, the brain is capable of reorganizing in order to compensate for loss of function. One such compensatory mechanism is in terms of distributed activation in neighboring regions of both the ipsi and contralateral hemispheres.

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N. C.Singh. Neural and oral representations of language, Invited talk at Haskins Laboratories, Yale University, New Haven, Connecticut, USA, May 2010

N. C.Singh. Categorization of sounds in the natural environment, Invited talk at the conference on Perspectives in nonlinear dynamics, Indian Institute of Science, Bangalore, July, 2010

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N. C. Singh. 'Practice makes perfect' - cortical reading networks in second language learners – Invited talk at the conference on IIT Cognition, Experience and Creativity, IIT Gandhinagar, Gandhinagar, October 2010.

N. C.Singh. Sorting sounds in the brain, Keynote speaker at GHC, India for Women in Computing, December 2010.

N. C.Singh. Reading patterns in children learning two scripts, Invited talk, International Conference on Cognitive Development, Allahabad, December 2010.

N. C.Singh. How the brain learns to read, Invited talk at Maharashtra Dyslexia Association, Mumbai, February 2011.

N. C.Singh. Language processing in the brain, Invited talk at International workhop on Cognitive and Systems Neuorscience, February 2011.

N. C.Singh. Reading in the brain, Invite talk at Science Festiva, St. Stephens College, New Delhi, March 2011.

Funding

Research grant from language and brain organisation in normative multi lingualism, a functional imaging study of Dyslexia in biscriptal Indian Children, Department of Science and Technology. Research grant from Department of Biotechnology Cortical processing of natural sounds using functional neuroimaging, Research grant from Department of Information Technology. Research grant from Department of Science and Technology Development of computational model of parkinson disease based on handwriting and speech

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Spatiotemporal Processing and Information Transmission in Brain

A basic problem in neuroscience, both basic and applied, is comprehending how flow processes occur, whether that of energy, information, electrical current, drugs, cells or tissue displacement, across the layered brain extent. Customary scalar quantitative models of flow processes, or its biochemical/pharmacological neuromodulation, have difficulty in accounting for experimentally-observed preferential flow in one direction vis-à-vis another, in the oriented tissue. Hence, one needs a quantitative computational approach that can clarify and predict the various transport processes and their modulation across the brain, vis-à-vis direction. The recent advance of tensor neuroimaging, beyond simply scalar imaging, implies a broad general perspective towards pathophysiological processes,

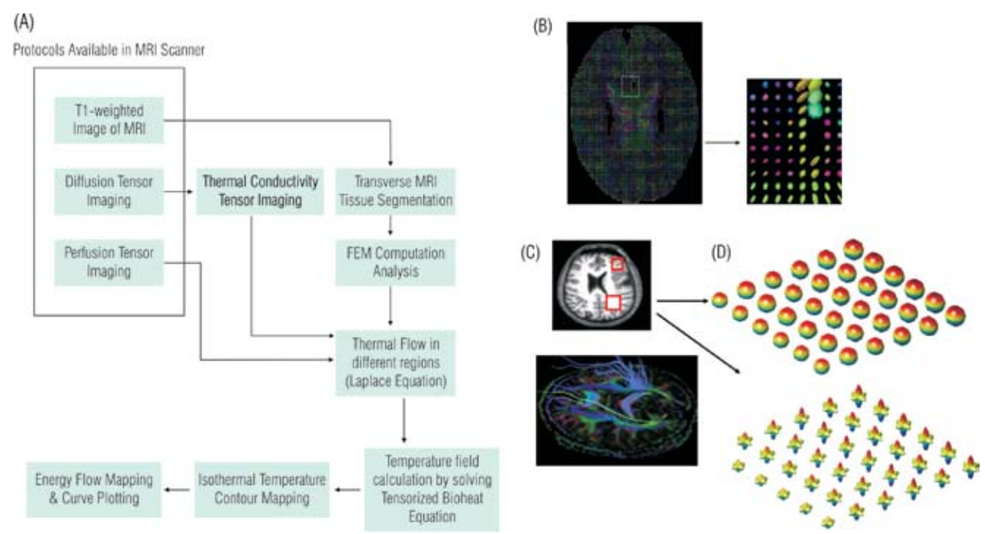
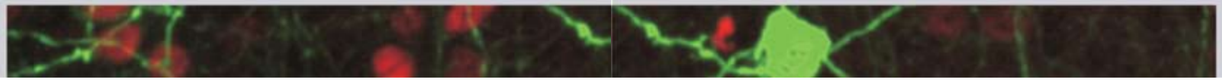


Figure 1
A) MRI methodology for Perfusion Tensor Imaging and Energy Flow analysis, **B)** Thermal conductivity tensor imaging of the brain, the inset shows the individual high-resolution 3D ellipsoids of the heat flow tensors voxel-by-voxel. **C)** Structural image of malignant brain tumour, glioma (upper panel), whose conventional tensor imaging does not show crossing tracts (lower panel). **D)** If there are multiple fibre orientations, the directions are not distinct if conventional 2nd order tensor imaging is used, here a spherical diffusion tensor results (upper panel). In contrast, if higher-order tensor imaging procedure is used, the different fibre directions are obtainable (lower panel) for each voxel.



wherein one can study the various transport processes or flow parameters in the layered anisotropic brain, as chemical diffusion, cellular permeation, electrical conduction and information transmission. The research has considerable potentiality of applications to clinical medicine as well as to biological engineering, especially for diagnosis, therapy and neurophysiological investigations. The overall objective of this program is to comprehend the physiological or pathological dynamics of the various transport or flow processes in the brain, with deeper implications for both primary and translational research.

Perfusion Tensor Imaging and Thermal Mapping for Hypothermic Therapy in Cerebral Ischaemia

Infant Mortality by neonatal hypoxia/cerebral ischemia is a major preventable public health problem worldwide, with 4 million deaths yearly, and incidence of 1.1% of births, the main cause being metabolic secondary energy failure. Being validated clinically, a readily implementable device is presently available from the NIH-NICHD study, namely a water-cooled head cap, to empirically treat the condition by cooling the brain to 34.5°C. The main problem of therapeutic hypothermia is an optimization one, namely the balancing of neuroprotection by increased brain cooling (occurring through heat conduction through brain tissue), vis-à-vis minimizing cardiac arrythmia due to body cooling (taking place via heat convection through cerebral blood perfusion).

We approach the problem by developing the technique of optimization of Functional Energy Flow Mapping of brain, by orchestrating two MRI-based methods (i) Perfusion Tensor Imaging (Fig.1A), and (i) Tissue Thermal Conductivity Tensor Imaging (Fig.1B). Using a MiniMax algorithm, more efficient localization and scheduling of scalp cooling tubes is designed, so that there is maximal conductivity-based heat transport (ensuring higher neuroprotection) and minimal convectivity-based heat transport (ensuring lower cardio-toxicity). Thus one optimizes the outcome of hypothermic therapy on hypoxic infants. An optimally designed head-cap cooler, if formalized, may have considered implications towards the challenge of infant mortality.

Multi-directional Crossing Tracts and 3D Profile of Tumour Cell Invasion in Glioma:

It is well know that conventional diffusion tensor imaging, using 2nd order tensors, gives only the single fibre direction passing through a voxel, and does not show the other tracts in the voxel, particularly if there are joining/crossing/originating fibres. This is a major drawback of conventional tractography and brain connectivity approaches (Fig.1C). Generalizing the Stejskal-Tanner approach to NMR signature of diffusion, we delineated the construction of higher-order tensor imaging architecture of the brain that can determine the directions of multiple tracts as they pass through a voxel (Fig.1D). We have developed the acquisition model and planned the administration of RF pulse sequence in the Philips 3 tesla scanner, using multioriented motion probing fields. Our results suggest that 4th order tensor imaging significantly better represents the template of aqueous diffusion and cellular invasion in high grade glioma tissue compared to the conventional 2nd order diffusion tensor model which fails to provide 3D distribution of tumour spread from a voxel of neoplastic tissue.

We also come across an unexpected and fortuitous result: there is no significant efficiency in tissue characterization increasing the tensorial order above 4. This indicates that 4th order tenor computation is sufficient, extra processing time and computational power for calculating higher orders are not warranted. Further, the 4th order field maps well visualize and quantify the multi-modal nature of water diffusion in high grade glioma tissue, while 2nd order maps are unsatisfactory. Higher-order Tensor Tractography can provide unique understanding and prediction of the directional propensity of glioma invasion, which will enable the oncologist to avoid diffuse radiotherapy and give a focussed treatment field.

Collaborators

Dr Alan Evans, Montreal Neurological Institute, McGill University

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Dr Shinjini Bhatnagar, Translational Health Science & Technology Institute, Gurgaon.

Funding

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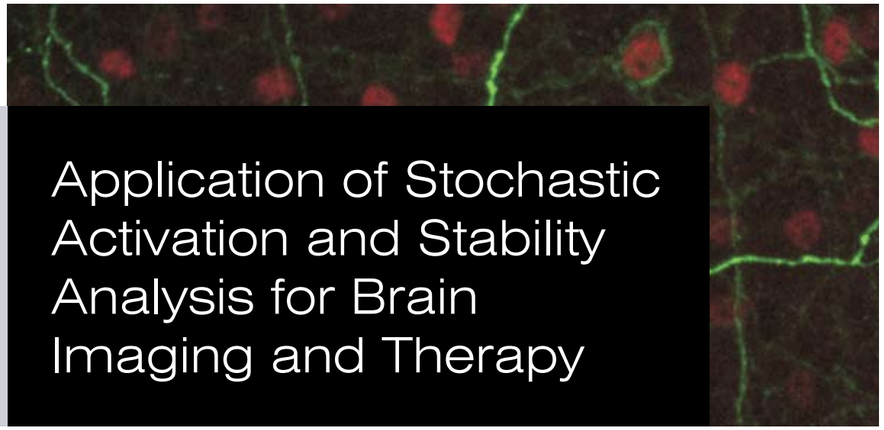
Dept. of Biotechnology, Govt. of India (collaborative project with AIIMS).



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

A promising prospect to enhance the efficiency of neuroscience applications, whether diagnostic or therapeutic, is offered by perturbation-induced activation, an emerging research field in computational neuroscience and bioengineering. Stochastic activation, noise-aided resonance or fluctuation-induced transition, is a general principle of nonlinear biological systems, and occurs basically due to the statistical kinetic nature of the components that exhibits probabilistic fluctuations of parameters. However the practical application of the stochastic activation effect as a novel technique in diagnostic or therapeutic radiology, has not been systematically pursued, and the applicability is the aim of our project. As an example, our laboratory has developed the method of Stochastic Resonance Imaging as a general radiological technique 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, whereby the image performance augments to 150%-180% of the pre-enhancement value. Applications range for differential diagnosis, from benign to malignant foci and from developmental lesions to cerebrovascular incidents. With patent being in progress, the imaging procedure furnishes more efficient pathognomic characterization of tissue or lesion signals across a broad-spectrum of pathologies.

MRI and Systems Biology based Platform for Regenerative Intervention in Stroke

For treatment of cerebral stroke there is a seminal need of developing a quantitative model to optimize the performance of a translational neuroregenerative intervention. We have elucidated an endogenous neural stem cell based therapeutic approach using differential equations by incorporating the principles of Michaelis-Menten kinetics and chemotactic gradient-caused cell mobility to delineate cellular renewal and stochastic diffusion. Utilizing MRI-based finite element analysis of brain parenchyma, the study of spatiotemporal mobility of endogenous reparative neuroblasts across the brain, followed by synapse formation on reaching the target site, is a promising area for regenerative therapy in stroke and vascular dementia. We develop a quantitative analysis of neurogenesis and its migration from subventricular zone (SVZ), and thereafter synaptogenesis and its stabilization in target tissue, under the augmented influence of drugs as erythropoietin and atorvastatin that can be enabled to cross blood-brain barrier (Fig. 2A). A main problem is efficient synaptotropic conversion of individual neurones to functionally behaving neurons with synaptic/dendritic stabilization.

Using systems biology analysis and relevant bioinformatics techniques, we have developed a quantitative model of synaptotrophic efficiency under pharmacological action. We observe a strong peak of maximal transformation of migrated neurons into synapsed neurons at specific dose combination of the drugs (Fig.2A). These are optimal dosing profile, other combination of dosing will reduce the synaptogenesis. The procedure is validated by empirical data on animal studies of a

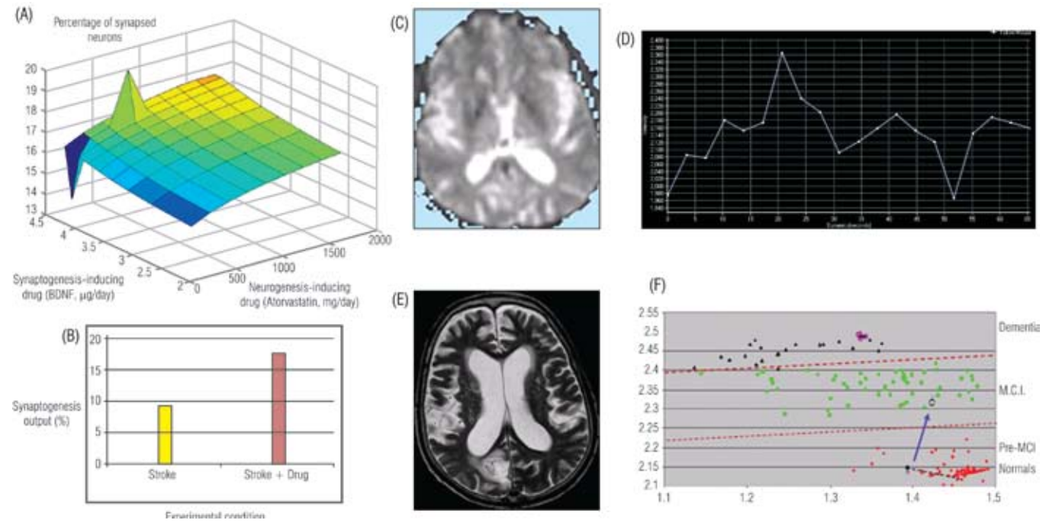

Figure 2
A) Maximizing the functional yield and performance efficiency as induced by combined stage-wise administration of pharmacological agents for neurogenesis (Atorvastatin) and synaptogenesis (BDNF). Note the parabolic shaped response surface indicating optimization of the yield output at specific combination of doses of the agents inducing the successive stages of neurogenesis and synaptogenesis. **B)** Validation by experimental data where synapse formation is gauged by from synaptophysin immunochemistry, the yield value predicted by the mathematical model differs only by 6%. **C)** MRI spin labeling to estimate neurovascularization and neurovascular coupling in stroke patient. **D)** Recording the cerebral perfusion dynamics to estimate functional recovery in stroke after pharmacological intervention; x-axis = dynamics (time), y- axis = perfusion intensity. **E)** Transcallosal MRI image for textural analysis for developing algorithm to enable automated diagnosis of images of Normal subjects, Mild Cognitive Impairment, and Alzheimer's Disease. **F)** Longitudinal study to develop subalgorithm to predict the conversion of Normal subjects to Mild Cognitive Impairment. The x-axis and y-axis are textural indices characterizing the MRI image, while the arrow shown the conversion of a subject from normal condition to Mild Cognitive Impairment, the two data points being separated by 3 years.

collaborating laboratory where stroke is induced by occlusion of middle cerebral artery (Fig. 2B). Clinical applicability of the approach is being explored in collaboration with investigators of All-India Institute of Medical Sciences-Delhi. Utilizing MRI Flowmetric procedure of Spin Labelling (Fig.2C), we have performed perfusion imaging of stroke patients, and have enabled the method to estimate the functional recovery with pharmacological treatment, after stroke (Fig.2D).

Prediction of Mild Cognitive Impairment and progression to Alzheimer's Disease

As per the Revised Criteria-2011 released by the NIH-Alzheimer Associations's Workgroup for determining very early stages of Alzheimer's disease, one of the most important problems is to predict those normal individuals who would later convert to the precursor transition stage, Mild Cognitive Impairment, so that disease-modifying or disease-delaying measures could be instituted early. Hence, it is increasingly essential that a rapid screening and grading technique be developed that can predict which normal individuals would convert to Mild Cognitive Impairment (MCI). Using MRI-based stochastic scaling dynamics and elastometric tissue textural analysis, we have developed an algorithm, to diagnose images of brain, classifying them into

Normal subjects, MCI, and Alzheimer's disease, with 96% accuracy, which has been patented (Fig.2E). As normal subjects undergo ageing, the majority do not deteriorate (the stable subgroup), but a portion converts to MCI (the labile subgroup). What is important is to predict whether an apparently normal subject belongs to the labile subgroup, who would undergo the neurodegenerative process later.

We have adapted the MRI algorithm to explore the possibility of predicting the 'conversion process', i.e, forecast the labile subgroup who would convert from Normal stage → MCI stage (Fig.2F). We then desired to test the predictive power of the algorithm. Using statistical modelling and image processing methodology, we constructed a sub-algorithm to enable the original algorithm to separate the Normal population into two groups. We used the longitudinal study approach, utilizing images of 36 subjects of initially normal subjects, who had scanning done twice, separated by 3 years, and during the interval some converted to MCI and some remained normal. We tested the subalgorithm to separate the 36 subjects into two classes, and then matched with the follow-up clinical and imaging data of the subjects after 3 years. The algorithm could correctly predict which of the normal subjects would later convert to MCI, with 76% accuracy. It would still be desirable that if this accuracy is further increased by using other feature vectors, which we are currently pursuing.

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S. Kapoor, V.P.S Rallabandi and P.K. Roy. New Horizons in Brain Disorders: A Systems Biology perspective to Degeneration and Regeneration, National Conference on Medical Biotechnology: Vision 2010. Postgraduate Institute of Medical Education & Research, M. D. University, Rohtak, April, 2010.

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P. Roy, A. Evans and B. Singh. The Indian Challenge of Gracefully Ageing. National Knowledge Network Seminar, Office of the Principal Scientific Adviser, Govt. of India, New Delhi, June 2010.

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Dr R. K. Padhi, Indian Institute of Science, Bangalore.

Dr Paul Thompson, University of California – Los Angeles.

Dr Sashi Bala Singh and Dr Sunil Hota, Defence Research & Development Organization, Delhi.

Dr Santanu Chaudhuri and Dr Raj Khanna, Indian Institute of Technology – Delhi.

Awards

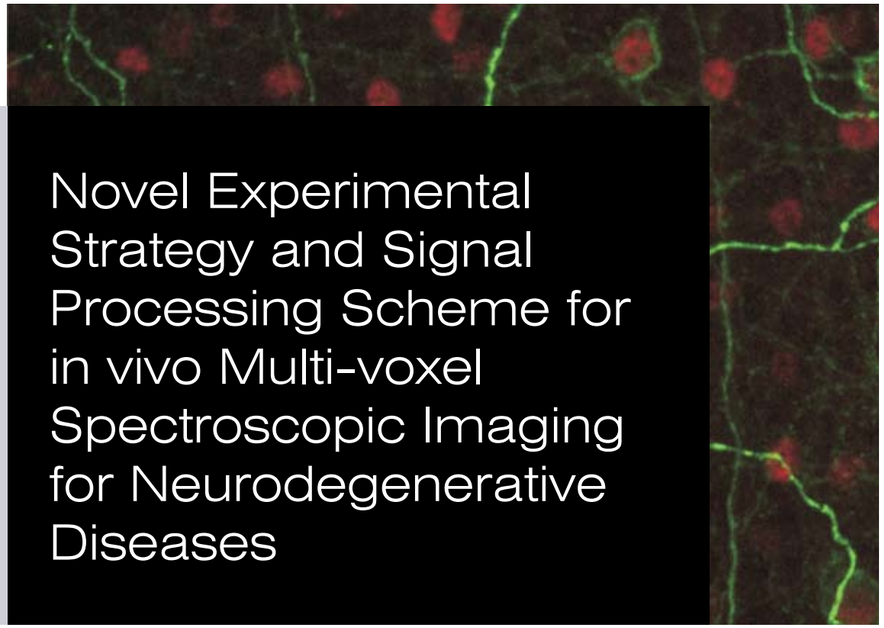
S. Kondra. Traineeship participation award, HBM-2011, International Society of Human Brain Mapping, USA, March 2011.

V. Shukla. Selected as Young researcher participant, International Summer School on Multimodal Approaches in Neuroscience, Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany, May 2010.

V.P.S. Rallabandi. Paper selected as among the most topical paper in Magnetic Resonance Imaging, by Elsevier Press, USA, Dec 2010.

Degree Awarded

Ph.D. Budhachandra Singh Khundrakpam, for the thesis on A Generalized Tensor Approach to Brain Imaging (2010).



Novel Experimental Strategy and Signal Processing Scheme for in vivo Multi-voxel Spectroscopic Imaging for Neurodegenerative Diseases

Principal Investigator
Pravat Kumar Mandal
R&D Engineer
Himanshu Akolkar,
M. Tech

Non-invasive detection and subsequent quantitative estimation of different neurochemicals provide important information for various molecular processes involved in neurodegenerative disorders. In the brain, the available concentrations of these important neurochemicals are in the range of 1-6 millimolar. Hence detecting such small amount brain neurochemicals in shortest possible time using noninvasive MRS technique is a major challenge in clinical setting. Major focus of our laboratory is to develop experimental strategy for high quality data generation as well as efficient signal processing scheme development for the quantitation of brain neurochemicals. We are also focused to correlate clinical status of the patients with the detected amount of these neurochemicals. The long-term aim of our group is to investigate the causal molecular process using this state-of-the-art imaging technology for neurodegenerative disorders that will help to monitor disease progression as well as therapeutic development.

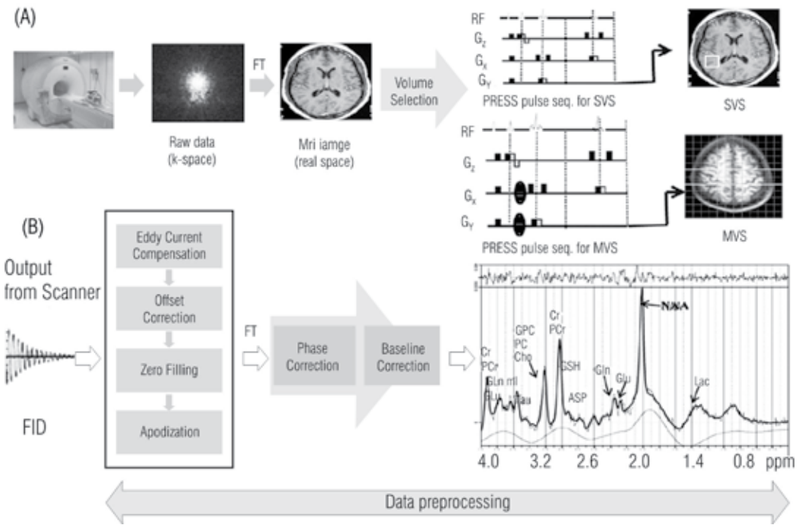


Figure 1
Diagrammatic representation of MRS data generation **A)** and data processing in MRS. SVS and MVS refer to single voxel and multi-voxel spectroscopy **B)**. For the sake of simplification, the output from the time domain data is shown as free induction decay (FID) only.

Peak #	Peak	Freq (ppm)	T2 (ms)	Amplitude	SD (Amp)
1.	Cr/PcR	3.954	23.1	5.273 e-3	4.295 e-4
2.	Gln/Glu	3.790	25.8	2.380 e-3	6.075 e-4
3.	mI	3.665	28.9	1.620 e-3	6.084 e-4
4.	Tau	3.571	54.4	1.103 e-3	2.997 e-4
5.	GPC/PC/Cho	3.235	45.6	2.278 e-3	1.904 e-4
6.	Cr/PcR	3.045	52.6	3.152 e-3	1.811 e-4
7.	Gln	2.373	54.4	8.569 e-4	2.373 e-4
8.	Glu	2.283	39.7	9.447 e-4	2.831 e-4
9.	NAA	2.026	30.8	7.428 e-3	2.300 e-4
10.	Lac	1.313	16.9	1.772 e-3	3.627 e-4
11.	Lipid	0.872	9.0	3.339 e-3	4.857 e-4

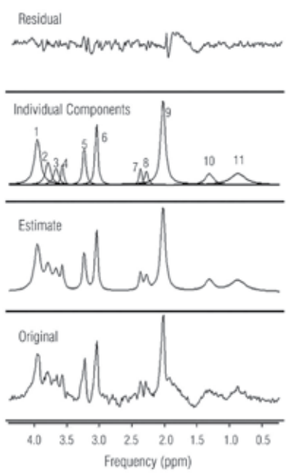


Figure 2
Multi-voxel MRS data was collected using 3T Philips scanner and processed by jMRUI program. We have used jMRUI (AMARES) package for the quantitation of the metabolites.

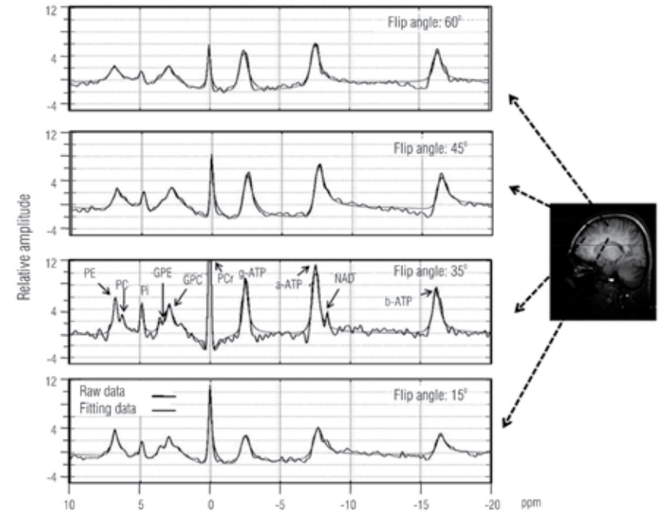


Figure 3
Stack plot of original spectra collected using excitation angle 250, 350 and 450 and 600 (marked in black color), and respective fitted spectra are marked in red color. For all the excitation angles, the simulated data fitted well with the respective experimental data. The abbreviation for different neurochemicals are as follows: Phosphomonoester (PME), phosphoethanolamine (PE), phosphocholine (PC), phosphodiesters (PDE), glycerophosphocholine (GPC), glycerophosphoethanolamine (GPE) and adenosine triphosphate (ATP).

We have generated high quality 1H MRS and 31_P *in vivo* data from the hippocampal area and other brain regions of age-matched normal subjects and from patients (Alzheimer, Parkinson etc.). We have also shown that application of excitation pulse of smaller flip angle (35^0) has significant effect to generate overall well resolved 31_P spectra in

particular to the membrane building blocks (PC/PE) and membrane breakdown products (GPC/GPE). General MRS experimental strategy is presented in Figure 1.The proton and phosphorous data processing results are provided in Figure 2 and Figure 3 respectively.

Publications

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P. K Mandal and Himanshu Akolakar (2011). A new experimental approach and signal processing scheme for the detection andquantitation of 31P brain neurochemicals from in vivo MRS studies. Biochemical and Biophysical Research Communications

Funding

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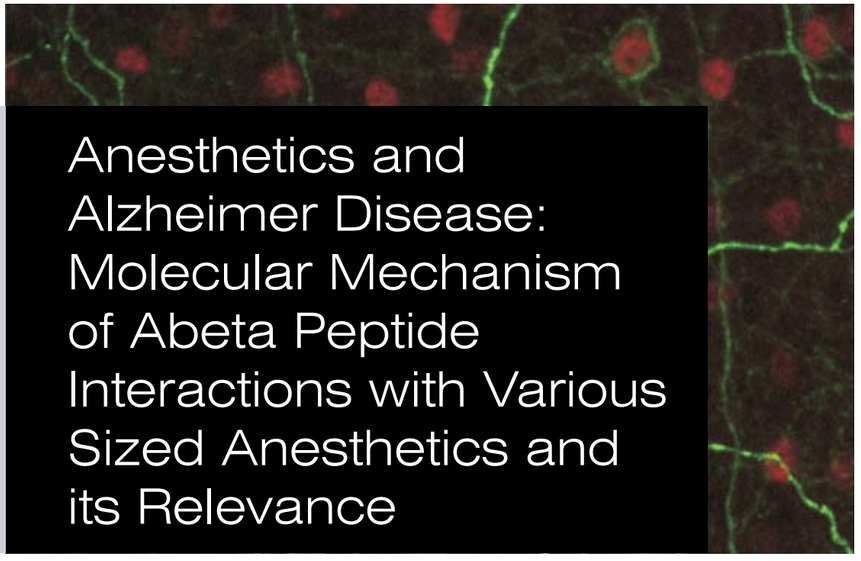

Anesthetics and Alzheimer Disease: Molecular Mechanism of Abeta Peptide Interactions with Various Sized Anesthetics and its Relevance

Principal Investigator
Pravat Kumar Mandal

Project Assistant
Sashirekha Sahoo,
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Advancement of modern science and technology has improved the quality of living and the average age of life expectancy has increased substantially. Number of aged people undergoing surgery for different purpose has also increased. Numerous reports suggest that elderly persons undergoing long surgical procedures may experience long term cognitive impairment with clinical features similar to those in patients with dementia. Hence, the question of any relationship of dementia to anesthesia requires through investigation at molecular level, animal model and possible human studies before any definitive conclusions can be drawn. This area of research is highly important and timely as evidenced by a publication of a special issue on "anesthetics and Alzheimer disease" in the leading journal, Journal of Alzheimer Disease, under the Guest Editorship of Dr. Pravat Kumar Mandal and Dr. Vincenzo Fodale.

Anesthetic induced structural changes of amyloid beta (Aβ) peptide from normal monomeric α-helix to the toxic oligomeric β-sheet form is a significant area of research to the scientific community as Aβ oligomerization is a crucial event in Alzheimer disease pathogenesis. Based on extensive studies on

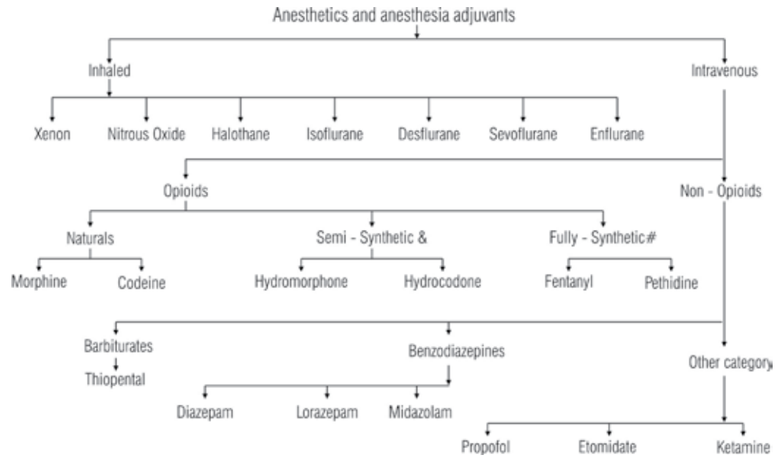

Figure 1
Detailed overview of anesthetics and anesthesia adjuvants. Two representative substances of each group of opioids are shown due to space limitations. Further members of the respective groups are abbreviated as follows: $ thebaine; &oxycodone, oxymorphone, desomorphine, diacetylmorphine (heroin), and nicomorphine; # methadone, tramadol, and dextropropoxyphene. Analogues fentanyl compounds are sufentanil, alfentanil, and remifentanil.

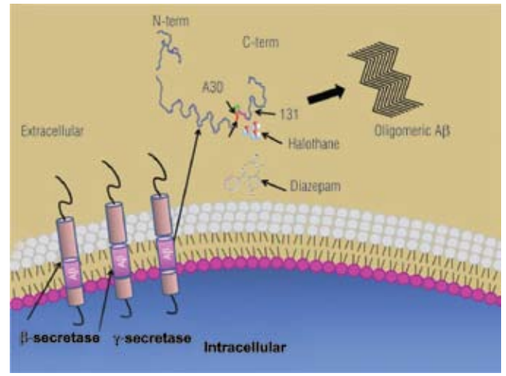

Figure 2
Schematic diagram for interaction studies of Abeta peptide with bigger sized anesthetic (e.g. diazepam) co-administered with smaller sized anesthetic (e.g. halothane). Due to steric hindrance, diazepam could not access the helix loop helix region containing critical residues G29, A30 and I31. Diazepam also could not block the entry of the smaller sized halothane. Hence Abetaoliogomerization was initiated when halothane is co-administered with diazepam. This model works in a same fashion with inhaled anesthetics alone or other bigger sized anesthetics (e.g. thiopental and propofol) when halothane is co-administrated with them separately.

Aβ and various anesthetics using state-of-the-art Nuclear Magnetic Resonance studies (NMR), we first provide the molecular pathway for the smaller sized anesthetic induced Aβ oligomerization. We present a list of anesthetics and anesthesia adjuvants (Figure 1) generally used in surgery.

Our continued research in this area with various sized anesthetics lead to the conclusions that indeed the smaller sized anesthetics access the cavity consisting of three amino acid residues (G29, A30 and I31) of Aβ and disturb the dynamics of the Aβ structure and cause of Aβ oligomerization. The molecular pathway for anesthetic induced Aβ oligomerization based on NMR studies is provided in Figure 2. The NMR derived biophysical model is now supported from animal model studies from two research groups. The animal model studies have also proved that smaller sized inhaled anesthetics, isoflurane significantly reduce cognitive behavior of transgenic mice (Tg2576) compared to wild type.

Publications

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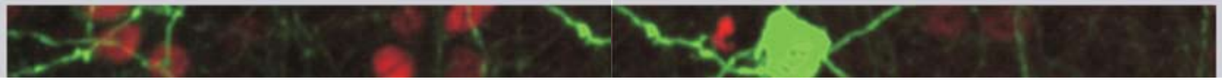
Collaborator

Dr. Vincenzo Fodale, MD (University of Mesina, Italy)

Publications



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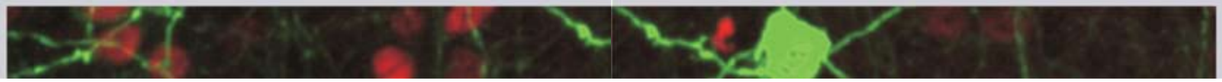

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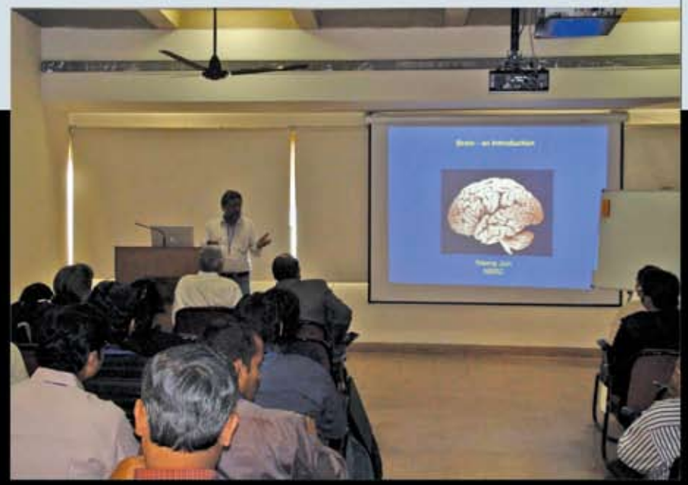
*** In press last year**

 # Work done elsewhere

National Brain Research Centre

NBRC



Presentations

Presentations

1. N. R. Jana. Understanding the physiological function of autism and autism spectrum disorder associated ubiquitin ligase. Neurocon, Kolkata, 2011.
2. N. R. Jana. Evaluation of abnormal protein aggregation in neurodegenerative diseases. PGIMER, Kolkata, 2011.
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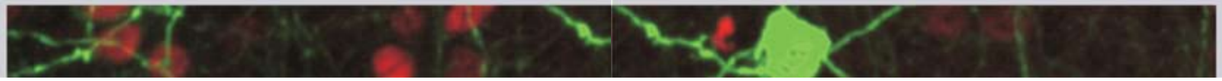
28. D. K. Kaushik, M. Gupta, and A. Basu. Role of NLRP3 Inflammasome in Japanese Encephalitis Virus Mediated Neuro-inflammation. 36th Mahabaleshwar Seminar on infection and pathology organized by the institute of fundamental research (TIFR), 8th - 13th January 2011, Mahabaleshwar.
29. A. Basu. Kruppel-like factor 4, a novel transcription factor regulates microglial activation. Glial Cells in Health and Disease, Satellite Symposia of 5th Congress of FAONS, School of Studies in Neurosciences, Jiwaji University, Gwalior, 30th November, 2010. [Invited speaker]
30. A Basu The innate immunity of the central nervous system in viral encephalitis Central India Institute of Medical Sciences, Nagpur 6-7th August, 2010. [Invited speaker]

31. R. K. Giri and P. S. Ghate. Utilization of CNS Stem Cells as a Tool to Model Neurodegenerative Diseases in vitro; a High Throughput Assay System to Screen Novel Therapeutic Molecules. Invited oral presentation at the 25th Annual Meeting of Society for Neurochemistry and International Symposium on Metabolic Signalling in Brain in Health and Diseases, University of Hyderabad, India, 2011.
32. R. Giri. Neurosphere cultures are superior in vitro tool to model neurodegenerative diseases. Invited oral presentation at the International Conference on Molecular Medicine, CHARUSAT, Gujrat, India, 2011.
33. R. Giri. Neurosphere cultures are superior in vitro tool to model neurodegenerative diseases. Invited oral presentation at Biosparks, School of Life Sciences, JNU, New Delhi, India 2011.
34. R. K. Giri. Development of a novel in vitro model of prion disease and it's possible application on anti-prion drug screening and discovery. Invited oral presentation for UGC networking summer course on the Emerging Trends in Drug Discovery and Development, University Institute of Pharmaceutical Sciences, Panjab University, Chandigarh, India, 2010.
35. N. Jain. Brain 'Effects of spinal cord injuries on the brain – interventions using brain machine interface devices.' Science Awareness Workshop, Indian Statistical Institute, Systems Science and Informatics Unit, Bangalore. March, 2011
36. N. Jain: (i) Brain – an introduction, (ii) The somatosensory system – from periphery to brain, (iii) The somatosensory system – the cortical somatosensory areas and their role, (iv) Plasticity of the adult brain. 4th DST-SERC School on Systems and Cognitive Neuroscience; National Brain Research Centre, Manesar. February - March , 2011.
37. H. Mohammed, M. K. Singh and N. Jain. Corticocortical connections of the motor cortex in rats: Evidence for two separate motor areas. Annual Meeting of the Society for Neuroscience, USA, San Diego, USA. November 2010,
38. L. S. Hameed, A. S. Pundir, B. Radotra, P. Kumar, S. Mohan, P.C. Dikshit, S.K. Shanker, A. Mahadevan, S. Iyengar. Development of Connectivity in the human auditory cortex. Poster presented at the Annual meeting of the Indian Association of Neurology, Lucknow, November 2010
39. S. Iyengar: Introduction to the Human Brain. IBRO-APRC (Asia Pacific Regional Committee) School of NeuroImaging organized at the National Brain Research Centre, Manesar, Nov-Dec, 2010.
40. S. Iyengar: Basics of the Auditory System. Fourth DST-SERC school in Neuroscience (Systems and Cognition), National Brain Research Centre, Manesar, Feb – March, 2011.
41. S. Iyengar: 'Bird Brains' and Mammalian brains – Comparative Aspects. Fourth DST-SERC school in Neuroscience (Systems and Cognition), National Brain Research Centre, Manesar, Feb – March, 2011.
42. S. Iyengar: The Opioid System in Zebra Finches. Fourth DST-SERC school in Neuroscience (Systems and Cognition), National Brain Research Centre, Manesar, Feb – March, 2011.
43. V. Jain, E. Ravindran, N.K. Dhingra. M2-type, but not M1-type of intrinsically-photosensitive retinal ganglion cells express Brn3 transcription factors. 13th Annual Vision Research conference, Retinal Ganglion Cells. Fort Lauderdale, FL (USA); April-May, 2010.
44. V. Jain, D. Poria, O. Saha, N.K. Dhingra. Expression of specific ganglion cell proteins by Brn3-positive retinal ganglion cells in mouse. ARVO. Fort Lauderdale, FL (USA); May, 2010.
45. N.K. Dhingra, S. Nagar, V. Jain, M. Goel, P. Cherukuri. Photoreceptor degeneration upregulates GABA signaling in inner retina. Saxtons River, VT (USA); July, 2010.



46. N.K. Dhingra. Remodeling of second-order and third-order retinal neurons after photoreceptor degeneration. 18th Annual meeting of the Indian Eye Research Group (IERG). Hyderabad; July 2010.
47. N.K. Dhingra. Three lectures on 1) Membrane biophysics, 2) Retina and 3) Retinal ganglion cells. Fourth DST-SERC School in Neurosciences, Systems and Cognitive Neuroscience. Manesar; February, 2011.
48. E. Ravindran, V. Jain, N.K. Dhingra. Brn3 transcription factor: a molecular marker of image-forming retinal ganglion cells. 5th Federation of Asian and Oceanian Neuroscience Societies (FAONS) Congress. Lucknow; November, 2010.
49. D. Yoganarasimha: Invited lecture on "Spatial Cognition" at DST-SERC School in Neuroscience (21 February to 6 March 2011), NBRC, Manesar, India.
50. N. C. Singh. Sounds of Melody - Pitch patterns in children with autism, Poster at International Meeting for Autism Research, Philadelphia, USA, May, 2010
51. N. C. Singh. Neural and oral representations of language, Invited talk at Haskins Laboratories, Yale University, New Haven, Connecticut, USA, May 2010
52. N. C. Singh. Categorization of sounds in the natural environment, Invited talk at the conference on Perspectives in nonlinear dynamics, Indian Institute of Science, Bangalore, July, 2010
53. N. C. Singh. An fMRI study of picture naming in patients with frontal lobe tumor - Abstract, Human Brain Mapping, Barcelona, Spain, July 2010
54. N. C. Singh. 'Practice makes perfect' - cortical reading networks in second language learners – Invited talk at the conference on IIT Cognition, Experience and Creativity, IIT Gandhinagar, Gandhinagar, October 2010.
55. N. C. Singh. Sorting sounds in the brain, Keynote speaker at GHC, India for Women in Computing, December 2010.
56. N. C. Singh, Reading patterns in children learning two scripts, Invited talk, International Conference on Cognitive Development, Allahabad, December 2010.
57. N. C. Singh. How the brain learns to read, Invited talk at Maharashtra Dyslexia Association, Mumbai, February 2011.
58. N. C. Singh. Language processing in the brain, Invited talk at International workhop on Cognitive and Systems Neuorscience, February 2011.
59. N. C. Singh. Reading in the brain, Invite talk at Science Festiva, St. Stephens College, New Delhi, March 2011.
60. S. Kapoor, V.P.S Rallabandi, P.K Roy. New Horizons in Brain Disorders: A Systems Biology perspective to Degeneration and Regeneration, National Conference on Medical Biotechnology: Vision 2010. Postgraduate Institute of Medical Education & Research, M. D. University, Rohtak, April, 2010.
61. P. Roy and U. Bhalla. Neuroinformatics in India: Building Academic and Research Excellence in the Developing World. Neuroinformatics Nodes Workshop, International Neuroinformatics Coordinating Facility, Karolinska Institute, Stockholm, April 2010.
62. B. Singh and P. Roy. Neural Basis of mapping the Spatiotemporal Representation in Perception: A Systems Engineering Approach, National Workshop on Perception Engineering, Jadavpur University, Calcutta, May 2010.
63. V.P.S. Rallabandi and S. Kapoor, P. Roy, Ageing Gracefully Across the Life-span: What Materials Science Can Offer Neuroscience, Condensed Matter Physics Days, University of Kalyani, Nadia, May 2010.
64. P. Roy, A. Evans and B. Singh. The Indian Challenge of Gracefully Ageing. National Knowledge Network Seminar, Office of the Principal Scientific Adviser, Govt. of India, New Delhi, June 2010.
65. B. Singh, V. Shukla and P. Roy. Perfusion Tensor Imaging and Energy Flow Mapping of the Brain, International Workshop on Medical Imaging: Perspectives in Perception & Diagnostics, Indian Institute of Technology, New Delhi, Sept. 2010.
66. P. Roy, S. Kapoor and V.P.S. Rallabandi. Harnessing the Self-Repair Potentiality of the Brain in Dementia: New Horizons of Neuroregenerative Therapy using Molecular Radiology, National Dementia Strategy Summit, Alzheimer's and Related Disorders Society of India, New Delhi, Sept. 2010.
67. B. Singh, V. Shukla and P. Roy. Imaging the Energy Flow Landscape of the Brain: From Valleys to Vortices, International Conference on Emerging Trends in Basic and Clinical Neuroscience, Federation of Asian & Australasian Neuroscience Societies, Lucknow, Nov. 2010.
68. V.P.S Rallabandi, S. Paul, A. Upadhyay and P. Roy. From Information Technology to Neuroinformatics: Harnessing the Digital Revolution & Brain Research for Human Wellbeing, National Seminar on Brain Awareness, Indian Institute of Information Technology, Allahabad, March 2011.
69. S. Paul, V. S. Mehta and P. Roy. Harnessing Molecular-domain Fluctuation to Enhance Diagnostic and Therapeutic Neuro-oncology: Crossing-tract Tensor MRI and Perturbative Radiotherapy, Neuro-oncological Society of India, Calcutta, March 2011.

Distinctions, Honours & Awards

Dr. Anirban Basu

National Bioscience Award for Career Development-2010 (Department of Biotechnology, Government of India)

Students Awards

P. Garg. IBRO Travel Grant 2011, for Gordon Research Conference (Registration Fee) March 2011.

P. Garg. DBT Travel Support for attending International Conference/ Seminar/Symposium, March 2011

P. Garg. Recipient of IBRO-APRC Alumni Best Poster Award held at 5th Congress of Federation of Asian and Oceanian Neuroscience Societies (FAONS) XXVIII Annual Meeting of Indian Academy of Neurosciences (IAN), Lucknow, India, December 2010.

S. Malik. DST Travel Support for attending International Conference, 10th International Symposium on NeuroVirology, Milan, Italy, October, 2010.

P. Garg. IBRO Travel award for attending International Brain Research Organization (IBRO) School of Neuroscience held at Hong Kong from June 2010.

C. Maharana. Received a Young Scientist award from Indian Science Congress.

S. Kondra. Traineeship participation award, HBM-2011, International Society of Human Brain Mapping, USA, March 2011.

V. Shukla. Selected as Young researcher participant, International Summer School on Multimodal Approaches in Neuroscience, Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany, May 2010.

V.P.S. Rallabandi. Paper selected as among the most topical paper in Magnetic Resonance Imaging, by Elsevier Press, USA, Dec 2010.

National Brain Research Centre

NBRC

Externally Funded Research Projects

Dr. Nihar Ranjan Jana

1. Understanding the functional role of E6-AP - a putative ubiquitin protein ligase implicated in Angelman mental retardation syndrome. BT/PR7744/Med/14/1094/2006 dt. 29-05-2007. (DBT, India)
2. Study the defect in neurogenesis and initial synapse formation in mouse model of Angelman mental retardation syndrome. 37(1408)/10/EMR-II dt. 25-06-2010. (CSIR, India)
3. Role of E6-AP in the progression of Huntington's disease. BT/HRD/34/18/2008 dt. 16-04-2010. (National Bioscience Award for Career Development, DBT, India).
4. Understanding the role of ubiquitin-proteasome system dysfunction in the pathogenesis of Huntington's disease. DST/INT/JAP/P-71/2009 dt. 16-09-2009. (DST, India , Indo-Japan cooperative science program)
5. Understanding the physiological function of malin, a ubiquitin ligase mutated in Lafora's Progressive Myoclonus Epilepsy. BT/PR13590/Med/30/286/2009 dt. 17-09-2010. (DBT, India)

Dr. Pankaj Seth

1. Characterization of Human Fetal Brain Derived Neural Stem Cells as a Model for Studying Neurodegenerative Diseases. BT/PR6615/MED/14/857/2005, date: Dec 2006. (DBT, India)
2. AIDS and its Effect on Nervous System. date: June 2008 (AIDS Research, NIH, USA)
3. Role of CNS opportunistic infections in subsequent development of HIV dementia. 1 R01 NS055628-01A3 date: July 2008. (NINDS, NIH,USA)

Dr. Ellora Sen

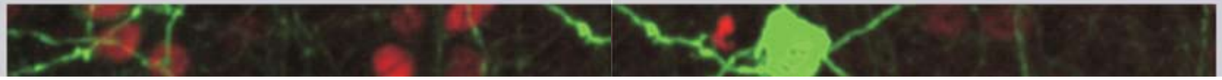
1. Oligodendrocyte Differentiation from Neural Stem Cells: Implication in CNS repair. BT/PR6615/MED/14/857/2005, date: 22nd December, 2006. (DBT, India).
2. Modulation of oxidative stress and hypoxia by inflammation: Implication in the pathogenesis of glioblastoma. DLS/81/48222/LSRB-140/EPB/2007, date: 20th Nov, 2007. (LSRB DRDO, India)
3. Role of lipid rafts in epigenetic silencing and immune cell signaling: Implication in the aggressiveness of glioblastoma multiforme. Innovative Young Biotechnologist Award 2007 (IYBA), date: 6th May, 2008. (DBT, India)
4. Understanding signaling circuitries involved in transcriptional regulation of genes associated with survival and immune response in an inflammatory environment: Implications in glioblastoma progression. BT/PR12924/MED/30/235/2009, date: 18th March, 2010. (DBT, India)

Dr. Shiv Kumar Sharma

1. Effects of amyloid beta on growth factor signaling in the hippocampus: implications for the Alzheimer's disease. 27(0196)/09/EMR-II, date: March 09, 2009. (CSIR, India)

Dr. Anirban Basu

1. To study the role of Neuronal innate immune response in Japanese encephalitis virus infection. 27(0238)/10/EMR-II, date: 28th december, 2010. (CSIR, India)
2. To elucidate the role of inflammasome and other molecular events leading to Hypoxia induced neuro inflammation. LSRB-213/EPB/2010, date: 2nd August, 2010, (Life science Research Board, DRDO, India)
3. Dissecting molecular circuitries that regulate Progenitors Cell Response to Japanese Encephalitis Virus. BT/PR8682/Med/14/1275/2007, date: 1st April 2007. (DBT, India)



Dr. Ranjit Kumar Giri

1. Understanding the cellular pathogenesis of Alzheimer's disease employing CNS stem cell cultures: Development of a novel model of Alzheimer's disease. 102/IFD/SAN/758/2007-08, date: 12/08/2008. (DBT, India)

Prof. Neeraj Jain

1. Brain Mechanisms of Tactile Perception. DIT/R&D/TDC/13(7)/2010, date: 22 February 2011. (DIT, India)
2. Transplantation of Stem Cells for Recoveries from Spinal Cord Injuries. BT/PR/6615/MED/14/85782005, date: 22 December 2006. (DBT, India)
3. Autonomous Navigation using Brain-Machine Interface (BMI). ERIP/ER/0501094/M/01/1248/D(R&D), date: 26 April 2006. (DRDO, India)

Dr. Soumya Iyengar

1. Effects of altering the levels of neuronal proliferation on the learning and production of song behavior in male zebra finches. BT/PR6615/MED/14/857/2005, date: 22 December 2006. (DBT, India)
2. Opioid modulation of song in male zebra finches. SR/SO/AS-39/2009, date: 10 June, 2010. (DST, India)

Dr. Narender Dhingra

1. Replacement of Degenerating Retinal Neurons by Electronic Prosthesis: A Study on Parameter Optimization of Electrical Stimulus and Signal Processing in Different Types of Retinal Ganglion Cells. BT/PR6410/MED/14/801/2005, date: 16 December 2005. (DBT, India)
2. 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. BT/PR6615/MED/14/857/2005, 22 December 2006. (DBT, India).

Dr. Yoganarasimha Doreswamy

1. Neural Network Mechanisms In Subicular Complex Neurons During Spatial Navigation And Learning In Awake Behaving Rats. BT/PR14057/Med/30/352/2010, Grant award date: 21 January 2011. (DBT, India)

Dr. Nandini Chatterjee Singh

1. A functional imaging study of dyslexia in biscriptal Indian children. BT/PR14046/Med/30/341/2010, date: 22nd September 2010. (DBT, India)
2. Perception Engineering Programme - Understanding auditory perception. DIT/R&D/TDC/13(7)2010, date: 22nd February 2011. (DIT, India)

Prof. Prasun Kumar Roy

1. Tensorial analysis of brain connectivity in functional neuroimaging with clinical applicability. DIT/R&D/TDC/13(7)/2010, date: 22 Feb 2011. (DIT, India)
2. Linking basic science and clinical centres in inter-institutional linkages. (DBT, India)
3. National facility for Epilepsy research (co-investigator). (DBT, India)
4. Indian integration with international imaging system: A multi-zone Study using Neuroinformatics and Telemedicine. MPEC/NKN/2011, date: 31 March 2011. (DIT, India)

Dr. Pravat Kumar Mandal

1. Brain Imaging, Neurochemical Analysis of Alzheimer's, Parkinson's and other Neurodegenerative diseases using in-vivo Magnetic Resonance Spectroscopy (MRS). DBT/44/2010, 18 January 2010. (DBT, India)
2. A-beta peptide interactions with anesthetics. PRIN/PKM/India/209, date: March 30th 2009. (Italian Ministry for University and Research Program (Multi-center Grant))
3. Functional MRI and perception. DIT/percept/PKM/2011, date: April 2011.(DIT, India)

National Brain Research Centre

NBRC

Core Facilities

Distributed Information Centre (DIC)

Animal Facility

Digital Library

Distributed Information Centre

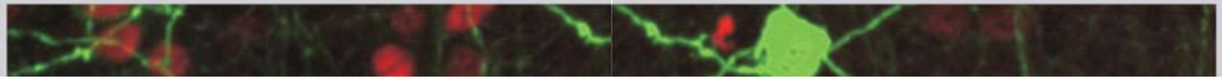
Objectives

The Distributed Information Centre (DIC) manages the Computational and Information technology activities of the institute. Apart from providing e-services and aiding in the research activities, it also constantly updates the digital environment with new and existing resources which are in sync with the growing requirements of the centre.

Infrastructure & Services

NBRC has a modest IT setup managed and maintained by the DIC, some of which are listed as under:

- Campus wide LAN spanning 10 Gbps fibre optic backbone and integrated with robust Wi-Fi network spreading through the entire campus. The network is running on manageable Layer-3 Switches for security and manageability.
- The network is connected with National Knowledge Network (NKN) with gigabit connectivity from National Informatics Centre, apart from another 10 Mbps radio link for redundancy. The network is secured by dedicated firewall clusters.
- Centralized data storage to the tune of 50 TB with multiple levels of redundancy is centrally maintained, it is also provided with a robotic tape library for further backups.
- DIC also hosts and manages critical servers which includes web servers, 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 for computational requirements of researchers running on windows and Linux are also centrally maintained and are accessible through thin client systems/terminals. The performance and uptime of servers are monitored round the clock and up-gradation, server consolidation, virtualization are done as and when required.
- The servers and core network infrastructure are housed and maintained in the central data centre facility that is provided with precision cooling and multiple levels of power backups.
- State-of-the-art video-conferencing facility for collaborating, research and teaching.
- DIC also provides technical support to users in their routine requirements and also undertakes in-house development of softwares, web-tools and web servers for aiding in the research and teaching activities of the centre.



Animal Facility

NBRC has a modern animal facility to meet the requirements of the scientists for advanced neuroscience research. The Animal Facility procures and breeds a wide variety of species of laboratory animals and supplies quality animals to in-house researchers, which are used as animal models for understanding the human brain in health and disease. The Institute recognizes that the use of laboratory animals in research is an important privilege, which should be accompanied with a great ethical responsibility to ensure the humane care and use of these valuable subjects. To ensure appropriate care and use, detailed programs of excellent veterinary and husbandry care, and programs for the peer-reviewed evaluation of all protocols prior to the use of any animal in research are in place. NBRC is committed to the highest standards of research and recognizes that laboratory animals must receive the best possible care, not only to obtain valid research data, but also to ensure the health and safety of animals, researchers, and animal caretakers. The Animal Facility is registered with the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Ministry of Environment and Forests, Government of India, New Delhi. All activities of the Laboratory Animal Facility are carried out as per standard operating procedures (SOPs). The Animal Facility maintains records of day-to-day activities as well as breeding, maintenance and experimentation as per the statutory requirement of CPCSEA. 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 staff of the animal facility ensures humane and appropriate animal care.

A high degree of hygiene is 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 showers before changing to work-overalls before entering the animal rooms, and again in the evening after finishing work. The animals are maintained under controlled environmental conditions as specified in the CPCSEA guidelines, with temperature between 22 $\pm$ 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.

All animals are housed in species-appropriate cages, which are designed as per the CPCSEA guidelines or exceed them. 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, knockout 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 then moved to fresh cages in the cage-changing station under hepa-filtered air. 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 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 monitor, pulse-oximeter and rectal thermometer. For cleaning and sterilization of the surgical instruments there is an ultrasonic instrument cleaner, autoclave, 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 animal carcasses.

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 the animals are required to have a current tetanus vaccination, and those who handle non-human primates (NHP) are screened annually for tuberculosis. Everyone handling NHPs are especially trained in the procedures for the first-aid in case of an injury from an animal bite or scratch.

The Veterinary staff of the Animal Facility also conducts a training course for Integrated M.Sc.-PhD and PhD students, and Project Assistants on laboratory animal science, principles of three R's, ethics, laws and guidelines on the regulation of scientific experiments on animals, general biology and reproduction of the laboratory animals, animal identification techniques, husbandry and care, sex differentiation, handling and restraint, and approved techniques for blood collection, injections, anesthesia and monitoring, humane euthanasia, etc

The animal facility currently maintains 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: Long Evans, Sprague Dawley

Rabbits: New Zealand white

Guinea Pigs: Duncan Hartley

Non-human primates

- Rhesus Monkeys (Macaca mulatta)
- Bonnet Monkeys (Macaca radiata)

Birds

- Zebra finches (Taenopygia guttata)
- House crows (Corvus splendens)
- Jungle crows (Corvus levaillantii)

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 also provides facilities and support to the scientists, researchers, students, staff and NBRC's networked centers.

The NBRC library has a large 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. The NBRC Library currently subscribes to 18 journals and 917 online journals through the DBT e-Library Consortium (DeLCON). It also maintains digital archives and news clips about the centre and subscribes to Newspapers and News Letters. The collection of the NBRC Library is growing day-by-day along with new developments in research and knowledge in the field of Neuroscience and related areas.

To provide optimum service to all users, the NBRC library is currently digitizing its list of collections using the LSEASE software, to which all users will have full access. A barcode technology has been installed for accurate and speedy circulation and the management of all library documents. The new software will also help in efficient library operations viz. administration, acquisition, circulation, serial control, cataloguing and information retrieval.

The Library has set up 22 IBM PC-Pentium-IV Computers with ISDN Internet facility to provide services for use of researchers and students in the NBRC Common room and has been providing electronic access to the subscribed journals within the campus portal.

A total of 132 registered users including scientists, researchers, students and other staff used the NBRC library facilities in the past year. The NBRC Library also provides "Inter Library Loan" services to NBRC's 48 networked centres all over India. Researchers at different centres send their requirement for research material or journal articles through email to NBRC Library (library@nbrc.ac.in) or to the librarian Mr. DD Lal (ddlal@nbrc.ac.in), which are then downloaded and sent to them free of cost. The library entertains an average of approximately 448 requests for articles and this number is increasing every year.

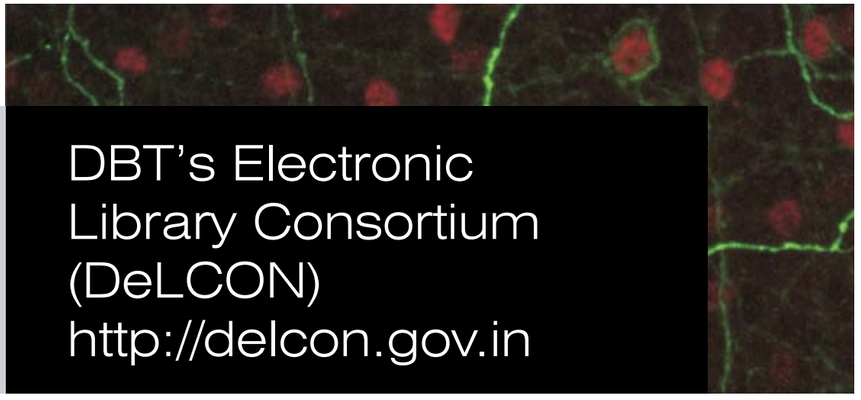
The NBRC Library regularly evaluates its information services to ensure that the Institution's requirements are met. It promotes resource sharing and cooperation activities among libraries by providing the inter library loan for the maximum use of resources, by providing copies of documents which are not available to researchers at centres outside the institute.

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 under construction, which will have the providing for reading room, reference room, video conferencing, online journal access facility, book section, Internet access facility and reprographic facilities. The main aim of the NBRC Library staff is to provide excellent services to users in NBRC and all centers associated with the institute.

DBT's Electronic Library Consortium (DeLCON)



DBT's Electronic Library Consortium (DeLCON) http://delcon.gov.in

Introduction

The primary purpose of establishing a consortium is to share physical resources including Journals/periodicals and books amongst members. However, the mode of cooperation has undergone a transformation with the shift from the traditional print-based environment to a digital environment. The emergence of the Internet, particularly the World Wide Web (WWW) as a new medium of delivering information has triggered the proliferation of Web-based full-text online resources. An increasing number of publishers have begun widely using the Internet to offer their publications to the international community of scientists. On the one hand, shared subscription or consortia-based subscription to electronic resources, permits easy access to electronic resources at highly discounted rates of subscription and on the other, meets with the increasing pressures of diminishing budgets, an increasing number of users and the rising cost of journals. The library consortia, on the basis of sheer strength of th e number of institutions involved, offer healthy business opportunities to the electronic publishers and thus attract the best possible price and terms of agreement.

About the 'DeLCON Consortium'

The 'DeLCON Consortium' (Department of Biotechnology's Electronic Library 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 DeLCON is a major initiative to bring a qualitative change in the research institutions under the aegis of the DBT. 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 the DBT institutional community. It facilitates access of DBT research institutions in the country to high quality e-resources 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 and aggregators. The access to all major e-resources was given to 10 institutions in the beginning of the year 2009. It has been extended to 17 institutions in the year 2010 and 7 more institutions in the beginning of year 2011.

Currently, DeLCON comprises the following member institutions:

DeLCON Phase-I members

- National Brain Research Centre (NBRC), Manesar
- Department of Biotechnology (DBT), New Delhi
- National Institute of Plant Genome Research (NIPGR) - New Delhi
- National Institute of Immunology (NII) - New Delhi
- National Centre for Cell Science (NCCS) - Pune

- Institute of Life Sciences (ILS) - Bhubaneshwar
- Institute of Bioresources and Sustainable Development (ISBD) - Imphal
- Centre for DNA Fingerprinting and Diagnostics (CDFD) - Hyderabad
- Rajiv Gandhi Centre for Biotechnology (RGCB) - Thiruvananthapuram
- International Centre for Genetics and Engineering Biotechnology (ICGEB), New Delhi

DeLCON Phase-II members

- The Wellcome Trust-DBT India Alliance, Hyderabad
- Dibrugarh University, Assam
- Assam University, Silchar
- North Eastern Regional Institute of Science & Technology, Arunachal Pradesh
- North East Institute of Science & Technology, Assam
- Mizoram University, Mizoram
- D. M. College of Science, Manipur
- Sikkim University, Gangtok
- College of Veterinary Science, Assam Agricultural University, Guwahati
- St. Anthony's College, Meghalaya
- Biotechnology Industry Research Assistance Program (BIRAP), New Delhi
- Gauhati University, Assam
- Manipur University, Imphal
- College of Veterinary Science & Animal Husbandry Central Agricultural University, Mizoram
- Rajiv Gandhi University, Arunachal Pradesh
- Nagaland University, Nagaland
- North-Eastern Hill University, Shillong

DeLCON Phase-III members

- Indian Institute of Technology Guwahati, Guwahati, Assam
- National Agri-Food Biotechnology Institute, Mohali, Punjab
- National Institute of Biomedical Genomics, Kalyani, Kolkata
- Regional Centre for Biotechnology, Gurgaon
- Tezpur University, Tezpur, Sonitpur, Assam
- Transnational Health Science & Technology, Institute, Gurgaon
- Sikkim State Council of Science and Technology, Gangtok, Sikkim

In terms of the number of users, DeLCON is the largest Consortium in India for disseminating literature on Life Sciences and Biotechnology to all DBT Institutions, Research Institutions, Universities, and their colleges affiliated to the DBT.

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.

Importance & Benefits of the 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;
- Members of the DeLCON Consortium have the benefit of a cap on the annual increase in the rates of subscription. While the usual increase in price of e-resources varies from 15 % to 20%, DeLCON consortium members enjoy a cap on increase in price ranging from 5% to 7%;
- The DeLCON Consortium has 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 are 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.

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,

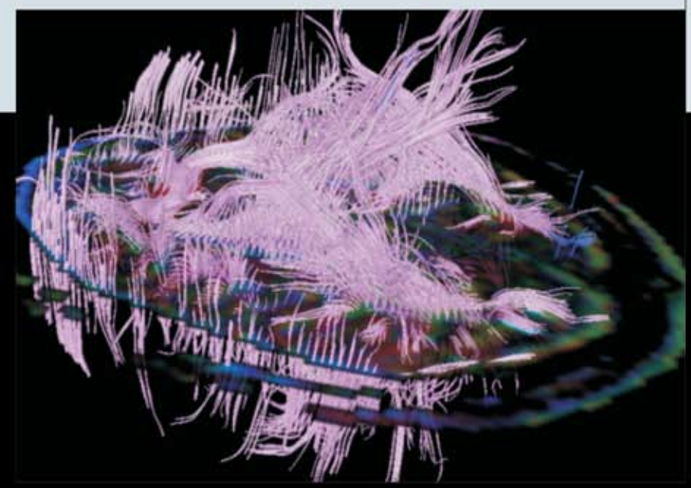
Radiology, Medicines, Computational Biology, Cell Biology, Cell Sciences, Molecular biology, Molecular and Cellular Biology, Computational Neuroscience, System Neuroscience etc.

DeLCON Electronic Resources

The DeLCON Consortium subscribes to electronic resources covering all major Life Science & Biotechnology disciplines being taught at the DBT research Institutions, Universities & Colleges. It includes a 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 one bibliographic database from 20 renowned foreign publishers, societies and aggregators. The DeLCON has added 18 new e-resources in the year 2010. 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 the following table:

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	Mary 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 Biologists	http://www.aspb.org/	(2 Journals)
19	American Association of Immunologists	http://www.aai.org/	(1 Journals)
20	Scopus Database	http://www.scopus.com	(1 Database)



National
Neuroimaging Facility

National Neuroimaging Facility

The National Neuroimaging Facility, sponsored by the Department of Biotechnology, Govt. of India, came into existence in the year of 2006. The main purpose of this National Facility is to facilitate/support cutting edge brain imaging research. The facility is equipped with four state-of-the-art equipments including:

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)

MRI provides much greater contrast between the different soft tissues of the body compared to computed tomography (CT), making it especially useful in neurological (brain), musculoskeletal, cardiovascular. Various imaging modalities also play important role providing crucial information which can aid diagnostic processes. The various imaging modalities are:

(1) MR Spectroscopy (MRS) provides non-invasive neurochemical level estimations and enables clinical correlation.
(2) Functional MRI (fMRI) correlates functional (haemodynamics) activity with images of brain activation

The3 Tesla Phillips whole body MRI scanner at our Facility is equipped with state-of-the-art hardware, software and data processing software 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 closely interacts with leading imaging centers within the country and across the globe.

Electroencephalography (EEG)

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

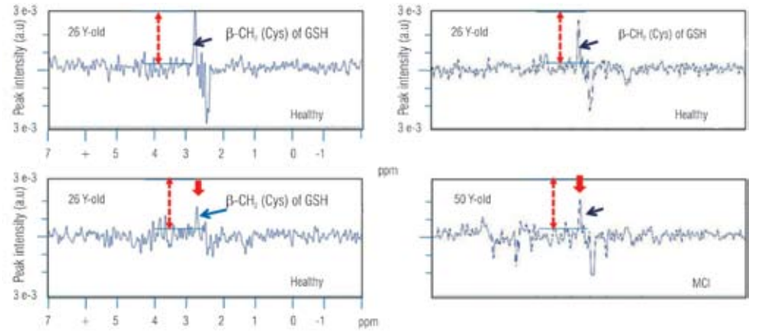


Figure 1
GSH level in right frontal cortex in various cases:
A) healthy female (26Y old);
B) healthy female (56Y old);
C) MCI female (50Y old) and
D) Probable AD female patient (62Y old) using MEGA-PRESS pulse sequence in a 3T MRI scanner. The decrease of GSH content is indicated by red arrow.

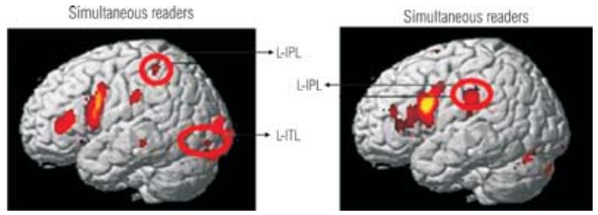


Figure 2 shows how skilled readers using different cortical networks.

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 and quantitative stress measurement from age-matched normal persons and diseased persons using novel MRS pulse sequences and signal processing. Figure 1 shows a gradual decrease of glutathione molecule, an important anti-oxidant in the brain, with aging and in different clinical conditions. This is the first report of quantitative measurement of oxidative stress using non-invasive state-of-the-art technique

The Speech and Language Laboratory (SALLY)

Research in the Speech & Language. SALLY is focused on unraveling the cortical pathways involved in Hindi-English biscriptal adults and children (Figure 2).

The Computational Neuroscience and Neuroimaging Laboratory

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

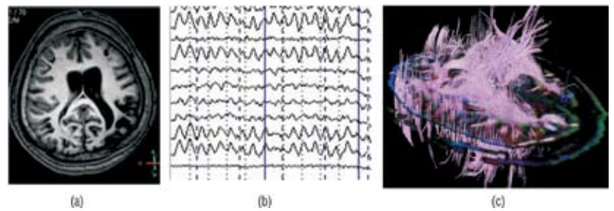
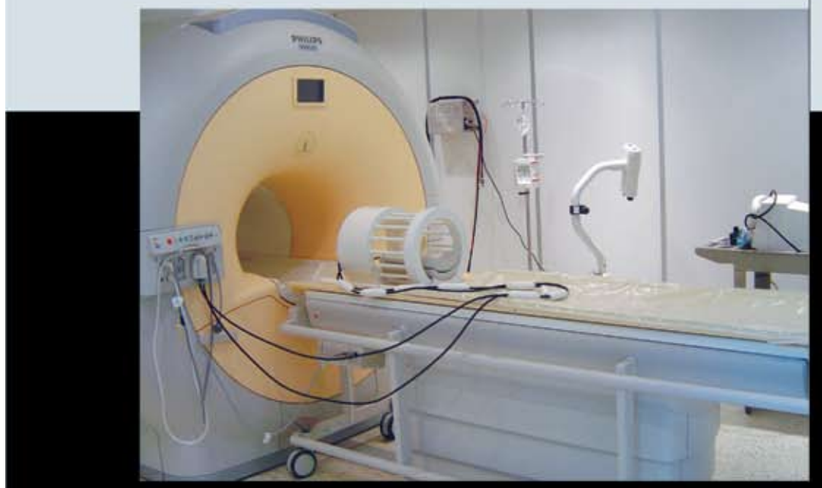


Figure 3
(a) Structural MRI scan of brain with dysplasia in epileptic patient. **(b)** EEG recording of the brain using which enables one to obtain more accurate localization of the electrical foci **(c)** Diffusion tensor image (DTI) of the brain of epileptic patient from which the conductivity tensor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



Translational Research: Clinical Unit

Translational & Clinical Neuroscience Unit

Translational research aims to connect basic research to patient care: "From the Bench lab to the Bedside patient". The Clinical Research Unit of NBRC covers the full spectrum of clinical neuroscience: neurology, neurosurgery, neuropsychology, neuropsychiatry, and psychometry. The unit has a tri-weekly, morning outpatient facility, at the Government General Hospital, Gurgaon, each of the consultant clinical faculty is available on one of the designated days. The NBRC Unit has integrated well with the Civil hospital medical team and there is an increasing number of referrals from other in-house departments and local hospitals. If a patient of the unit requires indoor treatment or observation, then, with courtesy of neuropsychiatrists and other specialists of the General Hospital, the patient is taken care of. The out-patient facility is busy, and on some days attendance can exceed forty patients. The main disease spectrum comprise epilepsy, peripheral neuropathies, neuralgia, cerebrovascular disease, stroke sequelae, refractory migraine, and neurodegenerative diseases as Parkinsonism, Alzheimer's disease and vascular dementia.

The follow up for 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, as well as cerebral palsy and asphyxia. There are also elderly patients attending, and movement disorders are an important cause of attendance. Patients attending the OPD at Civil Hospital come from old Gurgaon township and the villages and towns in the surrounding districts of Haryana, while some come from neighbouring states as Rajasthan, Uttarkhand, Delhi and Uttar Pradesh.

Patients requiring advanced specialist neurology in-patient care are referred to the 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 he so desires. As part of the major plans for renovation of Civil Hospital, the Neurology OPD rooms have been refurbished and electrophysiological facilities as Electromyography, Neurometry and Nerve Conduction study facility have been installed.

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. As different investigative studies in the unit progress, we plan to create a computer database with relevant patient data along with any planned neuroimaging/ molecular/neurophysiological studies at the NBRC labs, thus creating a well documented "clinical window" for our research institute. In this effort to narrow the gap between Basic Neuroscience and Applied Neuroscience, an ethics committee protocol has been formulated that includes representation of the Government Hospital.

The association of NBRC with Alzheimer's & Related Disorders Society of India (ARDSI) which has continuing from 2005 onwards has been further fostered. This interaction promises to grow to the mutual benefit of both institutions concerned primarily with the common goal of advancing neurological management and research in its varied aspects. Besides medical and neurological health conditions, one is exposed to the milieu of psychosocial and public health problems of the ageing populace in their home environment.

For proper functioning and further clinical support, the Unit receives the fullest cooperation of the Ministry of Health - Government of Haryana, and the Deputy Commissioner - Gurgaon, as well as from the Civil Surgeon and the Principal Medical Officer of the Hospital.

The specialists and personnel involved with the unit comprise of:

Consultant Clinical Professor: Dr. V. S. Mehta

Consultant Clinical Assistant Professor:
Dr Kapil Agarwal

Consultant Clinical Assistant Professor:
Dr Rajnish Kumar

Clinical Neuropsychiatrist (of Government Hospital): Dr Bramhadeep Sindhu

Clinical Neuropsychologist: Krishan Kumar

Clinic Assistant: H. Singh

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; Nerve Conduction velocity analysis.

Neuromyological study:
EMG, Neurometry.

X-ray and Contrast imaging.

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

Meetings & Workshops

IBRO

Prof. Ramamurthi Memorial Lecture

Fourth DST-SERC School

International workshop on Neuroimaging

The IBRO-APRC School of Neuroimaging workshop was held at the National Brain Research Centre from the 29th of November to the 10th of December, 2010. This workshop was sponsored by the International Brain Research Organization and was inaugurated by the neurophysiologist Prof Torstein Wiesel, Nobel Laureate. The workshop provided a platform to bring together some of the experts from India (including NBRC), USA, Australia, Japan China, and Switzerland for detailed discussion on magnetic resonance methodologies, their applications and the latest developments in this emerging field. An important objective of this workshop was to provide a solid theoretical basis of magnetic resonance imaging and also to provide 'hands-on' experience with this novel technology enabling students to carry this back to their laboratories. Students from China, Bangladesh, Nepal, Sri Lanka and Iran as well as from different Indian institutes participated this international meeting.

A cultural programme depicting the diversity of Indian culture was also organized during the course of the workshop to entertain the participants.

The late Dr. B. Ramamurthi Memorial Lecture (31st January, 2011)

The sixth late Dr. B. Ramamurthi Memorial Lecture was delivered by Prof. Govardhan Mehta on 31th January 2011, at the premises of the National Brain Research Centre in Manesar. Initiated in 2006, this lecture series commemorates his immense contribution role in setting up this centre.

Prof. P.N. Tandon, the Chairman of the NBRC Society presided over the function. Prof. Tandon and Prof. Sinha, the director of the institute both reminded the gathering about the strong and important role played by the late Prof. B. Ramamurthi in the setting up of a centre devoted to research in Neuroscience.

In his scientific oration, Prof. Mehta, National Research Professor and holder of the Lilly Grantee and Jubilant-Bhartia Chair from the School of Chemistry, University of Hyderabad, enlightened the audience on 'Higher Education and Research Landscape : Quest for a new trajectory'.

The lecture was widely attended by staff and students of the Institute.

Fourth DST-SERC School on Systems and Cognitive Neuroscience, Feb 21st – Mar 6th, 2011.

The Department of Science and Technology (Science and Engineering Research Council) has been sponsoring a series of schools focused on different areas of Neuroscience across the country, with a view to generate motivated and skilled man-power in the subject. The Fourth DST-SERC School, co-sponsored by DST, the Indo-US Science and Technology Forum (IUSSTF) was held at the National Brain Research Centre, Manesar from the 21st of February to the 6th of March, 2011 with a focus on Systems and Cognitive Neuroscience. Twenty three experts in systems and cognitive neurosciences from India and the US were invited to give lectures and demonstrations for the twenty five young researchers who were selected from different parts of India. The first week of the school was

mainly devoted to systems neuroscience, including introductory lectures and demonstrations to provide the basics of neuroscience. Lectures on speech and language, the olfactory, motor, somatosensory and auditory systems and an introduction to magnetic resonance imaging (MRI) were included in this week. The participants visited the MRI centre in AIIMS, New Delhi over the weekend for a detailed demonstration of MRI-related techniques. The second week focused on cognitive neurosciences with experts in the field speaking about attention, language processing, electroencephalography (EEG), memory, executive functions, cognitive disorders and cognitive retraining. Lectures on the visual system and brain plasticity were also delivered in this week, in addition to a demonstration of the Morris Water maze and EEG. Besides the lectures, interactive sessions were organized almost everyday so that participants could interact with the speakers on an informal basis. The fact that the participants were from vastly different backgrounds helped foster even more interactions between students of different disciplines than had been earlier envisaged.

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. The 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".

Japan

Dr. Nobuyuki Nukina and Dr. Nihar Ranjan Jana have been awarded a JSPS-DST collaborative grant to study the role of ubiquitin-proteasome system dysfunction in the pathogenesis of Huntington's disease.

Italy

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

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

The Netherlands

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

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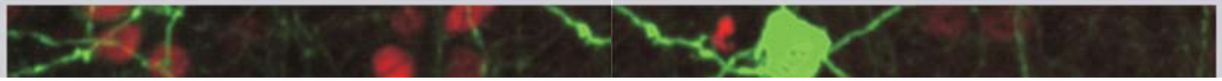
Canada

A neuroinformatics project on Indian integration with international imaging systems and networks, has been undertaken by Prof. Prasun Roy and Prof. Alan Evans, Montreal Neurological Institute, McGill University. The Indian inftrastucture is supported by the Office of the Principal Scientific Adviser, Govt. of India, and the Canadian infrastructure by the Canadian Advanced Research and Innovation Initiative, Govt. of Canada.

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 members 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

Sr. No.	Name of the Speaker	Title of the Lecture	Date
1.	Prof. Vinod Kumar Department of Zoology, University of Delhi	Timekeeping in Animals: The Story from Birds	April 13, 2010
2.	Dr. Sharmila Bapat National Centre for Cell Sciences Pune	Ovarian Cancer Stem Cells	May 5, 2010
3.	Dr. Vipin Verma Application Scientist- Discovery Labware BD Biosciences	Importance of cell culture surfaces for successful tissue culture	May 20, 2010
4.	Prof. Ford F Ebner Vanderbilt University, Nashville, TN, USA	The effect of early sensory deprivation on multisensory cortical responses	June 4, 2010
5.	Dr. Rohit Joshi Department of Biochemistry and Molecular Biophysic Columbia University Medical Center, New York	Molecular basis of Hox specificity	June 21, 2010
6.	Prof. Shilpa Buch, Professor and Vice Chair for Research at Dept. of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, USA	NEUROAIDS: A Tango of HIV and the Host	June 28, 2010
7.	Mr. Garga Chatterjee Doctoral student of Cognition Brain and Behavior at the Vision Science Lab Department of Psychology Harvard University, USA)	Perceptual and cognitive processes in face recognition deficits: the case of prosopagnosia	July 1, 2010
8.	Dr. Baskaran Thyagarajan, Dept of Pharmacology and Physiology, New Jersey Medical School, UMDNJ, Newark, New Jersey	TRPV1 - Lipid Microdomains - BoNT/A - A cross talk that modulates neuronal exo-endocytosis	July 14, 2010
9.	Mr. Karan Behar Ohio University, Athens, OHIO, USA	Reverse Engineering of the Neo-cortex: Rise of (Intelligent) Machines	July22, 2010
10.	Dr. Sanjiv Bhatia, MD Associate Professor of Clinical Neurosurgery, University of Miami Florida 33136	Integration of Technologies for the Management of Epilepsy	July 26, 2010

Sr. No.	Name of the Speaker	Title of the Lecture	Date
11.	Prof Mriganka Sur Newton Professor of Neuroscience, Head, Department of Brain and Cognitive Sciences, MIT	'Cell Specific Circuits in Cerebral Cortex'	August 19, 2010
12.	Prof. Kiyohiro Houkin, M.D. Professor and Chair Department of Neurosurgery Hokkaido University Graduate School of Medicine, Japan	Bone Marrow Stem Cell (BMSC) Treatment for Cerebral Infarction	Sept 20, 2010
13.	Prof. A. Ruiz i Altaba Department Genetic Medicine and Development, University of Geneva Medical School, Switzerland	Stemness in human brain and other cancers	Nov 18, 2010
14.	Dr. Nobuyuki Nukina the RIKEN Brain Science Institute, Japan	The pathomechanism of polyglutamine diseases and the strategy for the treatment	Nov. 23, 2010
15.	Mahak Sharma Postdoctoral Research Fellow, Brigham and Women's Hospital Research Fellow, Harvard Medical School, Boston, USA	Multiple Roles of an Arf-like Small G Protein, Arl8b, at the Lysosomes	Dec 10, 2010
16.	Dr. Tora Mitra Ganguli, Postdoctoral research associate Massachusetts Institute of Technology 77 Massachusetts Avenue, Cambridge, MA 02139	Role of Voltage-gated Calcium Channels in Neuromodulation and Neuroplasticity	Dec 13, 2010
17.	Dr Haritha Sanapala Technical Sales Director, The European Collection of Cell Culture (ECACC), UK	Cryo preservation and long time storage of Animal/Human Cell lines Mycoplasma testing, Authentication and Characterisation of Cell lines	Dec 14, 2010
18.	Dr. Hari Eswaran Associate Professor and SARA Scientific Director, College of Medicine University of Arkansas for Medical Sciences, 4301 W Markham St. Slot 518, Little Rock, AR 72205	Magnetic Encephalography and its Applications	Dec 21, 2010
19.	Dr. Sunil Kumar Dept. of Psychiatry & Behavioral Sciences Duke University Medical Center 333, Bryan Research Building Duke University, Durham, North Carolina 27705, USA	Top down control of global brain neural circuit dynamics	Dec 22, 2010

Sr. No.	Name of the Speaker	Title of the Lecture	Date
20.	Prof. Dipankar Dasgupta, Dept. of Computer Science University of Memphis, Memphis Tennessee, USA	Information Processing in the Immune System	Dec 23, 2010
21.	Dr. Joseph Mathew Antony Post-doctoral fellow, Sunnybrook Hospital, Toronto, Canada	Retroviruses in the Brain: Boon or Bane	Jan 7, 2011
22.	Dr Budhachandra Khundrakpam McConnell Brain Imaging Centre Montreal Neurological Institute McGill University, Montreal, Canada	Developmental Changes in Structural Brain Networks of Children and Adolescents	Jan 7, 2011
23.	Prof. Hari Shanker Sharma Professor of Neurobiology, University Hospital, Uppsala University, Sweden.	Nanoneuroprotection and Nanoneurotoxicology in CNS Injury and Repair	Feb 3, 2011
24.	Prof. Muresanu Dafin Fior Professor in Neurology, University of Medicine and Pharmacy, Romania.	Brain Protection and Recovery. Current Status and Future Perspectives	Feb 3, 2011
25.	Dr. Arun Chaudhary Harvard Medical School	A Longshoreman in gut nerve terminal	Feb 10, 2011
26.	Dr. Prem N. Yadav Research Associate University of North Carolina at Chapel Hill, Chapel Hill, USA	Designer Receptor Exclusively Activated by Designer Drug (DREADD): A Chemogenitc Approach for Deconstructing Neurocircuitry	Feb 17, 2011
27.	Professor Ralph Martins, Sir James McCusker Alzheimer's Disease Research Unit, Edith Cowan University, Nedlands, Perth, Australia	Towards Developing Early Diagnosis and Effective Treatments for Alzheimer's Disease	Feb 17, 2011
28.	Dr Sanjay Kumar Research fellow School of Psychology, University of Birmingham, UK	Object and Action	March 9, 2011
29.	Dr Sharba Bandyopadhyay Assistant Research Scientist Institute for Systems Research and Department of Biology, University of Maryland, College Park	Functional Micro-Organization of the Auditory Cortex and its Modulation by the Orbito-Frontal Cortex	March 30, 2011

National Brain Research Centre

NBRC

Academic Programmes

Ph.D. in Neuroscience

Integrated Ph.D. in Neuroscience

Summer Training & Short term Programme

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 the completion of 5 years period from the time NBRC had been given de-novo deemed University status, a Committee (duly constituted by UGC) visited NBRC for reviewing the 'Deemed to be University' status and recommended further extension. The deemed university status has also been reviewed by an independent Committee constituted by Ministry of HRD. The Committee gave NBRC an excellent report and placed this University / Institute under the highest category.

Further, UGC desired to re-assess and review the deemed university status and a duly constituted Committee visited NBRC again and gave it 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. 16,000/- per month and for Senior Research Fellows it is Rs.18,000/-

Integrated-Ph.D. in Neuroscience

NBRC is one of the first Institutes in the country to develop an integrated multidisciplinary teaching programme in Life Sciences. The institute has initiated 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. 5000/- 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. programme, the students will be awarded a dual degree (M.Sc. and Ph.D.).

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

Summer Training and Short-term Programmes

NBRC conducted a 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. Trainees were provided with shared accommodation in the NBRC hostel during the 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 encourages them to consider it as a future career option.

NBRC celebrated its 7th Foundation Day on 16th

December 2010. Five schools from Gurgaon / Manesar participated in the open exhibition and quiz, held at NBRC in connection with the Foundation Day celebrations. The events included Lab visits and poster viewing by students, a lecture in the Seminar Hall (given by senior students) and a Quiz.

NBRC celebrated the National Science Day on 28th February, 2011. In this connection, senior students participated in a presentation at Govt. Higher Secondary School Pachgaon, dist. Gurgaon, for the benefit of school children.

General & Academic Administration

General & Academic Administration – A Profile

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

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

During the year under review, the Administration achieved par excellence in execution of following activities at NBRC:

- The cultural festival of NBRC, 'TANTRIKA 2010' was organized within the campus which included a variety of cultural and sports events. Students, officers, and staff of NBRC participated in the event.
- Provided necessary logistics in conducting international conference/seminar organized in the campus as well outside of the campus.
- Complied with the Right to Information Act, 2005 which includes compilation and updating the required disclosure data on the website.
- Made major imports from different countries in terms of equipments and other consumables with meticulous planning and a precise schedule.

Implementation of Official Language

NBRC Administration has given due importance for the implementation of Hindi as the Official Language at this centre and has made full efforts to implement the use of Official Language in all the administrative jobs such as internal official meetings, interviews, debates, general applications etc. It is to be noted that even though NBRC has not been sanctioned any vacancy for a Hindi cell, the centre has implemented using the Official Language in all official correspondence. However, a proposal for creation of posts for a Hindi Cell is under consideration in the Department of Biotechnology. NBRC Administration has received a letter of appreciation from the 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 Reports" are being sent to Official Language Department, Ghaziabad, Department of Biotechnology, New Delhi and Nagar Rajbhasha Vibhag, Gurgaon. The official language committee takes keen interest in the use of Hindi at the centre and is being reviewed every quarter. Staff and students of NBRC participated enthusiastically in the "Bhashan Pratiyogita' which was organized on the occasion of Hindi Diwas for promoting the official language. The Rajbhasha Sansthan, New Delhi has awarded NBRC with a shield in recognition of its efforts made towards the implementation of Hindi as the official language.

RTI Act

The provisions of RTI Act are being followed at NBRC in letter and in spirit. General information pertaining to NBRC has been disclosed on our website as per RTI Act 4 (I) (b). All RTI applications received during 2010-11 seeking information on various matters concerning NBRC 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 in all its committees 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. Any lady/ woman of NBRC, among the Students/ Employees who 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 the 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

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

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

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

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

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

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

7 Prof. Samir K. Brahmachari
Director General CSIR
Institute of Genomics & Integrative Biology,
Mall Road,
Delhi

8 Ms. Sheila Sangwan (IRS)
Additional Secretary &
Financial Advisor
Department of Science & Technology,
New Delhi

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

10 Dr. L.M. Patnaik
Vice-Chancellor
Defence Institute of Advance Technology
Pune, Maharashtra

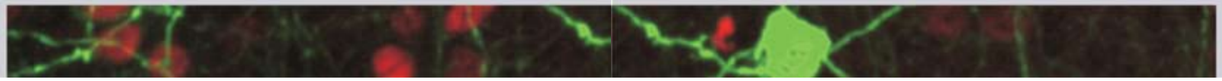
11 Prof. Kalluri Subba Rao
Hon. Professor. & INSA-Senior Scientist Centre
for Biotechnology, (IST)
Jawaharlal Nehru Technological University
Hyderabad , Andhra Pradesh

12 Prof. Gomathy Gopinath
Flat # 001, Kanchanjunga Apartments,
122/2, Nagavarapalaya,
Varthur Road,
Bangalore, Karnataka

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

14 Prof. P.K.Roy (Member Secretary)
Director (I/C),
National Brain Research Centre,
Manesar,
Haryana
(Upto 28th June, 2010)

15 Prof. Subrata Sinha (Member Secretary)
Director,
National Brain Research Centre,
Manesar, Haryana
(From 28th June, 2010)



Members of the Governing Council

1 Dr. M.K. Bhan (Chairperson)
Secretary
Department of Biotechnology, New Delhi

2 Prof. P.N. Tandon
No. 1, Jagriti Enclave,
Vikas Marg, New Delhi

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

4 Ms. Sheila Sangwan (IRS)
Additional Secretary & Financial Advisor
Department of Science & Technology,
New Delhi

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

6 Dr. Ashok Mishra
Chairman
Intellectual Ventures India,
Bangalore, Karnataka

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

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

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

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

11 Dr. V. Rajshekhar
Neuro Surgeon
CMC
Vellore, Tamil Nadu

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

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

14 Prof. P.K.Roy (Member Secretary)
Director (I/C),
National Brain Research Centre,
Manesar, Haryana
(Upto 28th June, 2010)

15 Prof. Subrata Sinha
(Member Secretary)
Director
National Brain Research Centre
Manesar, Haryana
(From 28th June, 2010)

Members of the Finance Committee

1 Dr. M.K. Bhan (Chairperson)
Secretary
Department of Biotechnology,
New Delhi

2 Ms. Sheila Sangwan (IRS)
Additional Secretary & Financial Advisor
Department of Science & Technology,
New Delhi

3 Dr. K. Vijayaraghavan
Director
NCBS
Bangalore, Karnataka

4 Dr. V. Rajshekhar
Neuro Surgeon
CMC
Vellore, Tamil Nadu

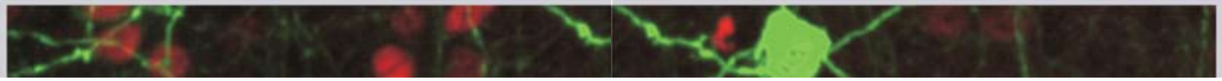
5 Dr. K.P. Singh (UGC Nominee)
Joint Secretary
University Grants Commission,
New Delhi

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

7 Prof. P.K.Roy
Director (I/C)
National Brain Research Centre,
Manesar,
Haryana
(Upto 28th June, 2010)

8 Prof. Subrata Sinha
Director
National Brain Research Centre,
Manesar, Haryana
(From 28th June, 2010)

9 Mr. Santosh Kumar Choudhary
(Member Secretary)
Offg.Finance & Accounts Officer,
National Brain Research Centre,
Manesar, Haryana



Members of the Scientific Advisory Committee

Prof. P.N.Tandon (Chairperson)
No. 1, Jagriti Enclave
Vikas Marg Ext.
Delhi

Dr. Ravi Mehrotra
Scientist "G" & Head Central Computer Facility
National Physical Laboratory
New Delhi

Prof. N. K. Ganguly
Distinguished Biotechnology Fellow,
National Institute of Immunology,
New Delhi

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

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

Dr. P. Satishchandra
Director / Vice Chancellor
National Institue of Mental Health and Neurosciences (NIMHANS)
Bangalore, Karnataka

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

Dr. Satyajit Rath
Scientist
National Institute of Immunology
New Delhi

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Varthur Road, Bangalore
Karnataka

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

Prof. Basabi Bhaumik
Department of Electrical Engineering
Indian Institute of Technology
New Delhi

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

Dr. V. Mohan Kumar
Emeritus Scientist & Visiting Professor,
Sree Chitra Tirunal Institute for Medical Science & Technology, Trivandrum, Kerala

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

Prof. B. N.Gangadhar
Professor of Psychiatry, Advanced Centre for Yoga
National Institute of Mental Health and Neurosciences
(NIMHANS)
Bangalore, Karnataka

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

RAP - Research Area Panel

Dr. R. K. Gupta
Professor, MR Section
Dept. of Radio diagnosis
Sanjay Gandhi Post graduate Institute of Medical Sciences (SGPGIMS),
Lucknow, Uttar Pradesh

Dr. Rajesh Sagar
Associate Professor
Psychiatry & Dead diction Centre
All India Institute of Medical Sciences,
New Delhi

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

Prof. K. P. Mohan Kumar
Scientist "G" & Head, Cell Biology & Physiology,
Division, Indian Institute of Chemical Biology (IICB),
Kolkata, West Bengal

Dr. Shobha Srinath
Professor
Department of Psychiatry
National Institute of Mental Health and Neurosciences
(NIMHANS), Bangalore, Karnataka

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

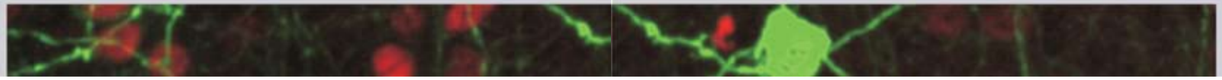
Dr. Chitra Sarkar
Department of Pathology,
All India Institute of Medical Sciences,
New Delhi

Prof. Subrata Sinha
Director
National Brain Research Centre,
Manesar, Haryana

Dr. C. L. Khetrapal
Director,
Sanjay Gandhi Postgraduate Institute of Medical Sciences
(SGPGIMS),
Lucknow, Uttar Pradesh

Dr. P. K. Roy
National Brain Research Centre,
Manesar, Haryana

Dr. Sumitra Purkayastha
Bayesian and Interdisciplinary Research Unit,
Indian Statistical Institute
Kolkatta , West Bengal



Members of the Building Committee

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

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

3 Prof. P. K. Roy
Director (I/C)
National Brain Research Centre,
Manesar, Haryana
(Upto 28th June, 2010)

4 Prof. Subrata Sinha
Director
National Brain Research Centre
Manesar, Haryana
(From 28th June, 2010)

5 Shri B. Bose
Senior Consultant
National Institute of Immunology,
New Delhi

6 Mr. K. V. S. Kameswara Rao
Registrar
National Brain Research Centre,
Manesar, Haryana

7 Mr. Kannan Kasturi N. S.
(Member Secretary)
Offg.Chief Administrative Officer
National Brain Research Centre,
Manesar, Haryana

Members of the Academic Council

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Dr. Nihar Ranjan Jana
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Prof. Basabi Bhaumik
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Indian Institute of Technology,
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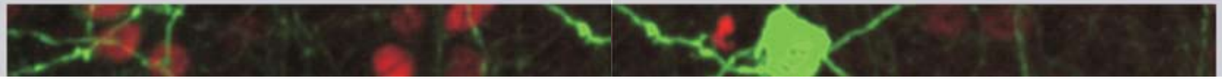

Members of the Board of Studies

Prof. Subrata Sinha (Chairman)
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Manesar, Haryana

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Manesar, Haryana

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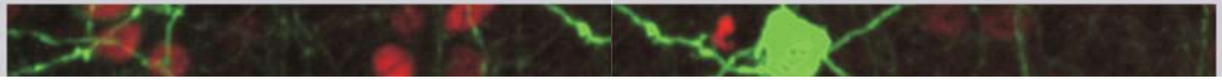
Manesar, Haryana



Technical Staff

Scientists

1 Prof. Subrata Sinha (Director)
From 28th June 2011
2 Prof. Prasun Kumar Roy
3 Prof. Neeraj Jain
4 Dr. Nihar Ranjan Jana
5 Dr. Pravat Kumar Mandal
6 Dr. Pankaj Seth
7 Dr. Narender K. Dhingra
8 Dr. Shiv Kumar Sharma
9 Dr. Ranjit Kumar Giri
10 Dr. Nandini C. Singh
11 Dr. Soumya Iyengar
12 Dr. Anirban Basu
13 Dr. Yoganarasimha Doreswamy
14 Dr. Ellora Sen
15 Dr. Rema Velayudhan (From 8th Nov, 2010)

Consultant

Prof. Partha Raghunathan

Clinical Psychologist

Mr. Krishan Kumar

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Dr. Rupanjan Mukhopadhyay
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Dr. Supriya Bhavnani
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R&D Engineer

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Mr. Deepak Kamboj (Till 24-09-10)
Ms. Sebati Ghosh (Till 28-10-10)
Mr. Rohit Yadav (Till 25-01-11)

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10 Ms. Radhika Rajan
11 Ms. Shilpa Mishra
12 Mr. Subhadip Paul
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15 Ms. Tanushree Das
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24 Mr. Deobrat Dixit
25 Ms. Kiran
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27 Mr. Apoorv Sharma
28 Ms. Pretty Garg
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7 Ms. Megha Maheswari
8 Mr. Deepak Poria
9 Mr. Manvi Goel
10 Mr. Pavan Kumar R.
11 Mr. Atul Gopal PA
12 Ms. Megha Sharda
13 Ms. Suhela Kapoor
14 Ms. Guncha Bhasin
15 Ms. Sarika Cherodath
16 Ms. Himakshi
17 Ms. Ruchi Ghildiyal
18 Ms.Piyushi Gupta
19 Ms. Avantika Mathur
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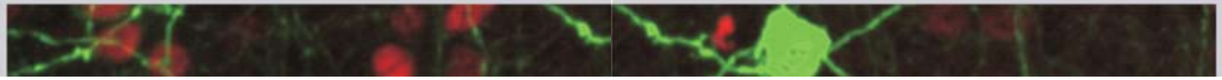

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36 Mr. Saurabh Ghosh
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