

ANNUAL REPORT

2003-2004



National Brain Research Centre

Manesar, India

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MANDATE

Pursuing basic research to understand brain function in health and disease.

Generating trained human resources with the capability to carry out inter-disciplinary research in neuroscience.

Promoting neuroscience in India through networking among institutions across the country.

OBJECTIVES

To undertake, aid, promote, develop, guide and coordinate research of high caliber in basic and clinical neurosciences related to diseases and disorders of the nervous system.

To develop the centre 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 centres to serve different regions of the country for efficient achievement of the objectives of the centres.

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 advanced 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 neuroscience 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 centres.

From the Director's Desk

In the annals of NBRC, the past year will go down as a great year—one of consolidation, expansion transition and accomplishment. During the past year, NBRC has undergone tremendous growth in terms of its research and teaching activities, reflecting the vitality and dynamism of a growing organization and the excitement of neuroscience as a discipline. No challenge would be beyond our reach if we truly understood how we learn, remember, think, and communicate. If we can fathom how children learn, our education policy could be strengthened with a new understanding. Better understanding of brain in health & disease would invigorate industry. Thus, major advances in neuroscience would have profound effects on most aspects of human progress and health. The creation of a Brain Research Centre in India has been a dream of the neuroscience community of the country for many years. It was a day of celebration and hope when NBRC was dedicated to the nation on December 16, 2003 by H.E. Dr. A.P.J. Abdul Kalam, the Hon'ble President of India.

It is appropriate that NBRC is situated at Manesar – which translates as “the Lord of the Mind”. The study of brain, mind and consciousness has intrigued philosophers, psychologists, biologists and physical scientists & mathematicians for centuries and remains the last frontier. Now that the map of human life, the genome, has been unraveled, it is time to turn our attention to that which makes human life unique: the mind. A concerted effort involving several groups of investigators is needed to explore the human brain from molecule to behaviour and this has been the inspiration behind the inter-disciplinary research at NBRC, which is indeed a unique example in this country. Although the question of the relation between brain and mind has occupied a central position in man's quest to understand the universe, it is only at the turn of the twentieth century that it has become possible to address this issue at the scientific level. This new science—‘Cognitive Neuroscience’—is more than just an amalgamation of psychology, biology, computer science, and philosophy, but now exists as a discipline in its own right with the onerous task of understanding of how mind arises from brain. In other words we need to understand how patterns of electrical activity distributed across neural circuits, consisting of billions of neurons and trillions of synapses, process information that leads to our thoughts, actions and memories.

To address these complex issues cognitive neuroscientists use a variety of different approaches, some of which are being used by NBRC scientists. In one such approach, in collaboration with neurologists and neurosurgeons at AIIMS, patients with focal brain lesions and neurodegenerative disorders that compromise circumscribed brain circuits, are being quantitatively tested to understand how neural circuits, particularly those involving the frontal cortex and basal ganglia, are involved in controlling our actions. Another approach that is being used is to record the activity of individual neurons while experimental animals perform cognitively demanding tasks. An understanding of the patterns of electrical activity that occur during the control of action may provide new insights into the causes and treatment of various psychopathologies and motor abnormalities where there is a failure of control as seen in Parkinson's and

Huntington's disease. While we have initiated research in the study of brain functions, which underlies our ability to see, perceive and think; the reductionist approach has to be broadened to include a holistic approach. Modern technology, such as functional imaging offers a new window to re-explore the brain in a holistic manner. NBRC would soon be acquiring a state-of-art functional imaging facility to address the question of brain-mind relationship in a more meaningful manner.

Today, biological research in general, and brain research in particular, is multidisciplinary. Therefore, it is very important that students with backgrounds ranging from psychology, mathematics, engineering, and computer science, apart from life sciences, be trained in neuroscience. In order to facilitate such inter-disciplinary human resource development, NBRC was formally awarded Deemed University status in May 2002 by the Ministry Human Resources Development on the recommendation of the UGC and is the first Institute of the Department of Biotechnology to achieve this status. Recognizing that understanding brain function requires integration of knowledge from multiple disciplines, the Ph.D. programme in Neuroscience has been initiated at NBRC with students from diverse background, including M.Sc in mathematical, physical and life science, M.B.B.S., B.E., or B.Tech. The goal is to train human resource who can bridge the barriers across disciplines as diverse as molecular biology, psychology (cognitive neuroscience) and computer science and integrate information across traditional boundaries.

As neuroscientists, we understand the power of networking – it is after all the neural circuits generated through networks, which provide us with enormous capabilities. Thus, the fundamental ethos of NBRC has been to bring together neuroscientists and create a network of neuroscience laboratories in the country where sharing of knowledge is encouraged. Out of these interactions new directions of research can be initiated simultaneously minimizing the duplication of research across the country. It is in this atmosphere that we see NBRC and its network of 44 centres in the country growing together.

From its inception when we had only a handful of people at NBRC till today, we have functioned not as employees but as a family. This centre could not have been built without the commitment and dedication our staff has brought where every individual has played a very significant role in putting together this centre. We hope that in the years to come NBRC would function as the brain does – a dynamic ever-changing entity that transforms itself to meet the needs and challenges. An epidemiological transition is occurring in developing countries as disease burden shifts from communicable to non-communicable disorders. At this point of time it is imperative that we have better understanding of the how the brain functions and what happens when it is diseased or injured. In order to realize the dream of a developed India, we need healthy minds. Through the study of the normal brain and its diseases and disorders, we can improve the development of children, enrich adult life, and age gracefully.

Intramural Research Reports

Molecular mechanism of the pathogenesis of the CAG repeats neurodegenerative diseases

Principal Investigator: Dr. Nihar Ranjan Jana

Research Fellows: Anand Goswami
Priyanka Dikshit

Technical Assistant: D. Narender

The abnormal expansion of trinucleotide repeats is now known to cause 16 neurological diseases. Among them, 9 are neurodegenerative diseases (also referred to as polyglutamine diseases) that are due to the abnormal expansion of CAG repeat in the coding region of the target genes. These include Huntington's disease (HD), Dentatorubro pallidoluysian atrophy (DRPLA), Spinobulbar muscular atrophy (SBMA) and several spinocerebellar ataxias (SCA's). All these neurodegenerative disorders are autosomal dominant (except SBMA) and progressive.

The symptoms typically begin in midlife and the patients die after 10-15 years of the onset of disease. However, the disease onset and severity directly depend on the length of the CAG repeats. The repeats show both somatic and germline instability and the successive generations of affected families experience anticipation, or earlier age of onset and more rapid disease progression. After the discovery of the disease gene, enormous progress has been made in the past few years, but the detailed mechanism of the disease pathogenesis remains largely unknown and currently there is no effective therapy for these diseases. The challenge now is to determine which cellular pathways are vulnerable to toxic insults exerted by expanded polyglutamine proteins. Also to see whether these responses account for the clinical manifestation of disease and ultimately this knowledge can then facilitate the development of drugs.

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

The mechanism of polyglutamine disease pathogenesis using HD and SCA3 as models is presently being studied. Last year the study determined that the increased glutamine repeat length and the N-terminal truncation of the mutant ataxin-3 dramatically increased the 1C2 antibody binding, misfolding, ubiquitination, aggregate formation and cell death. The search of the ubiquitin ligase specifically involved in the ubiquitination of the polyglutamine-expanded ataxin-3. This year it was identified that CHIP (C-terminus of hsp70 interacting protein) interacts specifically with the polyglutamine-expanded

ataxin-3 and associates with ataxin-3 aggregates. The specific interaction of CHIP with the polyglutamine-expanded truncated N-terminal huntingtin was also observed. Interaction is not observed with ataxin-3 or truncated N-terminal huntingtin with normal glutamine repeat length. Since CHIP is an ubiquitin ligase and interacts specifically with the expanded polyglutamine proteins, CHIP may be involved in the ubiquitination of polyglutamine-expanded proteins. Therefore, studies were conducted to see the possible role of CHIP in the ubiquitination of expanded polyglutamine proteins. The findings were that over expression of CHIP increased the ubiquitination polyglutamine-expanded ataxin-3 as well as truncated N-terminal huntingtin. Presently, investigations are underway to verify the possible role of CHIP in polyglutamine protein aggregation and polyglutamine protein induced cell death. Efforts to make the stable cell lines of the wild type and mutant ataxin-3 in a tetracycline-inducible system is also underway for further investigation of the disease pathogenesis.

Using the cellular model of HD, the investigation is on the role of oxidative and endoplasmic reticulum stress on the polyglutamine protein induced cell death. This is to determine whether those stressors modulate the cellular proteasomal function. Preliminary data suggests that the oxidative stress induced proteasomal malfunction could be linked with expanded polyglutamine protein induced cell death.

Fundings: 1) Department of Biotechnology, Government of India.
2) RIKEN Brain Science Institute, Japan.

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

Publications:

*U. Nagaoka, K. Kim, **N. R. Jana**, H. Doi, K. Mitsui, F. Oyama and N. Nukina Increased expression of p62 in expanded polyglutamine-expressing cells and its association with polyglutamine inclusions. **Journal of Neurochemistry**, 2004. (In Press).

*M. Tanaka, Y. Machida, S. Niu, T. Ikeda, **N. R. Jana**, H. Doi, M. Kurosawa, M. Nekooki and N. Nukina. Trehalose alleviates polyglutamine-mediated pathology in a transgenic mouse model of Huntington's disease. **Nature Medicine**, 10, 148-154, 2004.

N. R. Jana and N. Nukina. Assessment of impaired proteasomal function in a cellular model of polyglutamine diseases. In **Methods in Molecular Biology: Trineucleotide repeat protocols** (Y. Kohwi ed), Humana Press, vol. 277, pp 271-276, 2004.

*E. A. Zemskov, **N. R. Jana**, G. Wang and N. Nukina. Involvement of protein kinase C δ in the Huntington's disease pathogenesis. **Journal of Neurochemistry**, 87, 395-406, 2003.

N. R. Jana and N. Nukina. Recent advances in understanding the pathogenesis of polyglutamine diseases: involvement of molecular chaperones and ubiquitin-proteasome pathway. **Journal of Chemical Neuroanatomy**, 26, 95-101, 2003.

* Work done at Riken Brain Science Centre, Japan – a collaborating centre of NBRC.

Presentations:

U. Nagaoka, K. Kim, **N. R. Jana**, H. Doi, K. Mitsui, F. Oyama and N. Nukina. Identification of p62 as an increased protein in expanded polyglutamine expressing cells. Society for Neuroscience meeting, 2003.

A. Goswami, P. Dikshit and **N. R. Jana**. Alteration of cellular redox state and unfolded protein response promotes mutant huntingtin aggregation and mutant huntingtin-dependent cell death. Indo-US workshop on genomics. Bangalore, 2003.

N. R. Jana, P. Dikshit, A. Goswami and D. Narender. Possible involvement of CHIP in the misfolding-dependent ubiquitination of polyglutamine-expanded ataxin-3, the defective gene product in SCA3/MJD. NBRC International symposium, 2003.

P. Dikshit, A. Goswami and **N. R. Jana**. Curcumin promotes mutant huntingtin aggregation and mutant huntingtin-dependent cell death. NBRC International symposium, 2003.

A. Goswami, P. Dikshit, D. Narender and **N. R. Jana**. Increase in mutant huntingtin aggregation and mutant huntingtin-dependent cell death by unfolded protein response and alteration of cellular redox state. NBRC International symposium, 2003.

Mechanisms of curcumin-induced neuronal cell death and differentiation

Principal Investigator: Dr. Nihar Ranjan Jana

Research Fellows: Anand Goswami
Priyanka Dikshit

Technical Assistant: D. Narender

Curcumin, a polyphenolic phytochemical, is the primary component of the spice turmeric (*Curcuma longa*). It has been demonstrated to have anti-inflammatory, antioxidant and anti-proliferative activities. The pharmacological safety of curcumin is well documented by the fact that people in certain countries including India have consumed curcumin as a dietary spice for centuries in amount in excess of 100mg/day without any side effect. Ample evidence exists to support its use in cancer prevention for its anti-proliferative and anti-carcinogenic properties. Curcumin, *in vivo*, suppresses carcinogenesis of the skin, stomach, colon, breast and liver in mice and it has been shown to inhibit the growth of a wide variety of tumor cells *in vitro*. Although, its precise mode of action remains elusive, studies have shown that chemo-preventive action of curcumin might be due to its ability to induce apoptosis. The pathway through which curcumin induces apoptosis and whether mitochondria play any role in curcumin-induced apoptosis is not fully understood.

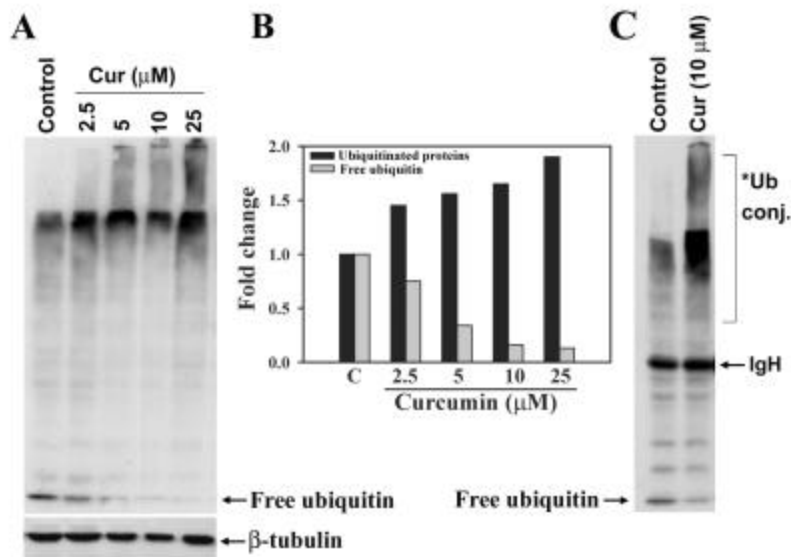
The major objectives of this project are (1) to identify mechanism of the neuronal cell death caused by curcumin and (2) whether and how curcumin promotes neuronal cell differentiation.

Investigations are on the cell death mechanisms induced by curcumin using neuro2a (mouse neuroblastoma) cell line. Last year, we have shown that the curcumin induces cell death in the mouse neuro2A cell line in a dose- and time-dependent manner and dividing neuro2a cells are more sensitive to curcumin compared to the differentiated neuro2a cells. In an attempt to identify the cell death mechanism, we found that curcumin-induced apoptosis is mediated through the impairment of ubiquitin-proteasome system. Exposure of curcumin to mouse neuro2a cells causes dose- and time- dependent decrease in proteasome activity and increase in ubiquitinated proteins. Curcumin exposure also decreases the turnover of destabilized enhanced green fluorescence protein, a model substrate for proteasome. To further confirm curcumin-induced proteasomal malfunction, we investigated the half-life of two well-known substrates of proteasome, p53 and I κ B- α . As expected, curcumin exposure increased the half-life of both cellular p53 and I κ B- α proteins. Presently the studies are on the consequences of extended half-life of both p53 and I κ B- α in the curcumin treated cells.

The relationship between the proteasomal inhibition and cell death caused by curcumin, was studied to establish the possible role of curcumin on mitochondrial dysfunction and activation of caspase-9. Proteasome inhibition has been shown to induce dual apoptotic signaling pathways (caspase-8 and caspase-9), consisting of early release

of mitochondrial cytochrome c into the cytosol and caspase-9 activation; followed by independent activation of Fas/caspase-8 pathway. Cytochrome c binds to Apaf-1 and forms the apoptosome complex that activates caspase-9, and in turn cleaves and activates downstream executioner caspases. We observed that addition of curcumin to the neuro2a cells induces rapid decrease in mitochondrial membrane potential and release of cytochrome c into cytosol followed by activation of caspase-9 and caspase-3.

Exposure of low dose of curcumin to neuro2a cells induces neurite outgrowth. Now the study is to link the possible role of MAP kinase pathways in the curcumin-induced neurite outgrowth.



Curcumin exposure results in increased accumulation of ubiquitinated proteins.

Fig: **A)** Neuro 2a cells were treated with curcumin and the cell lysate were made and processed for immunoblotting using anti-ubiquitin. **B)** Quantitation of the free ubiquitin and ubiquitinated protein levels from the blot represented in (A). **C)** Cells were transiently transfected with ubiquitin plasmid. Twenty four hours later, cells were exposed to curcumin for 8 hrs and then the cells were processed for co-immunoprecipitation by using HA antibody. Blot was detected with ubiquitin antibody. Cur, Curcumin; IgH, Immunoglobulin heavy chain

Publication:

N. R. Jana, P. Dikshit, A. Goswami and N. Nukina. Inhibition of proteasomal function by curcumin induces apoptosis through mitochondrial pathway. **Journal of Biological Chemistry**, 279, 11690-11695, 2004.

Regulation of Neurogenesis in the Cerebellum

Principal Investigator: Shyamala Mani

Research Fellow: Rashmi Mishra (JRF)

The goal of this project is to understand pattern formation in the central nervous system and how the positional information provided by patterning molecules are involved in the regulation of neurogenesis at the level of single cells.

Towards furthering our understanding we have been using the patterning of cerebellar folia as a model system. The cerebellum is important for motor coordination and this depends on the precise synaptic wiring of the different types of cells in the cerebellum. The most abundant cell type in the cerebellum is the glutamatergic granule cell and these cells control the output of the Purkinje cells and thus regulate cerebellar output.

Granule cells play a crucial role in cerebellar output mutations in which there is a loss of granule neurons and this results in severe ataxia. Granule cells are generated in the external germinal layer (EGL) where they undergo extensive proliferation during the first two postnatal weeks. Eventually the granule cell precursors exit the cell cycle, extend axons that synapse with the dendrites of the Purkinje cells in the molecular layer and migrate past the Purkinje cells to form the inner granule cell layer (IGL). Several extrinsic cues such as Sonic hedgehog (Shh), basic fibroblast growth factor (bFGF) and brain-derived growth factor (BDNF) control each of these events in granule cell neurogenesis.

Growth Associated Protein 43 (GAP-43) is a nervous system specific actin binding protein that is required for cell-adhesion mediated signaling. All GAP-43 knockout mice have abnormal cerebellar foliation pattern. They also have smaller cerebella and reduced size of EGL. We are investigating the role of GAP-43 in coordinating cell cycle responses, as this will provide important information about how regulation of neurogenesis is involved in cerebellar patterning.

We investigated whether the reduction in EGL layer is due to reduced cell proliferation. Postnatal day (P) 4 is the first time point at which there is proliferation and generation of EGL cells. P4 pups from heterozygote crosses were genotyped and cerebella were dissected and cerebellar cultures were prepared. Shh or bFGF was then added to the cultures from knock out or wild type animals. Proliferation rates were assessed 12hr, 24hr and 48 hr after the addition of factors and was done by adding BrdU to the cell cultures 12 hours prior to fixing.

Interestingly, results showed that there was a two-fold increase in BrdU labeled cells in the knock out cultures as compared to the wild type cultures. However, when bFGF was added to the medium the effect on cell proliferation and fold induction of BrdU labeling was greater in the wild type animals than in the knock out animals. This is

particularly significant as it had been previously shown that GAP-43 is required for transducing FGF mediated signals at the growth cone of growing axons. The fold induction in the wild type animals as compared to the knock out animals was also higher in response to Shh.

Taking together the fact that the size of the EGL is reduced in the knockout but the number of S-phase cells is increased in the knock out cerebellar cultures we are currently testing the two hypotheses. One hypothesis is that the length of the cell cycle is altered in the knockout animals. This could lead to more number of cells being labeled which have longer cycling times. This hypothesis has support from previous experiments that were done in which the GAP-43 allele was disrupted in P19 embryonal carcinoma cells. In these experiments disruption of cell cycle kinetics was observed. Another hypothesis that we are testing is to see whether cells in the EGL knock out animals are undergoing apoptosis at a higher rate than in the wild type animals.

Collaborator: Karina Meiri, Tufts University, USA

Funding: Fogarty International Research Collaboration Award (FIRCA) NIH, USA

Presentation:

R. Mishra, E. Donohoe, K.F. Meiri and **S. Mani**. Role of GAP-43 in differentiation of cerebellar granule cells. **Society for Neuroscience**, New Orleans, November 2003.

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

Principal Investigator: Shyamala Mani

Research Fellow: Manoj Kumar (JRF)

Technical Assistant: Bandita Bagchi

Intrinsic factors that control the commitment to neuronal lineage and that play a role in neuronal differentiation and cell type specification are largely controlled by transcription factors that contain the basic helix- loop- helix (bHLH) motif. Proneural bHLH factors are involved in the commitment of a multipotent neuroepithelial progenitor cell to the neuronal lineage. These include the neurogenins and Mash. Terminal neuronal differentiation further involves a second class of bHLH factors known as neuronal differentiation factors. These include NeuroD, NDRF and Nex. The pattern of expression of neural differentiation genes in vivo is overlapping but not identical. Some of these genes are expressed in specific subsets of neurons and suggests an additional important function of these factors, that they may be involved in specifying neuronal cell type. Expression of neuronal differentiation factors results in cell cycle arrest and differentiation of neurons in culture.

The goal is to elucidate the function of proneural and neural differentiation bHLH genes using ES cells as a model system for studying neuronal differentiation.

In order to express bHLH genes in ES cells we have been looking at different promoters that are available and the expression pattern of these promoters during ES cell differentiation. One of the promoters that we characterized is the immediate early promoter of the human cytomegalovirus ($P_{CMV\ IE}$) that has commonly been used to drive transgene expression in several mammalian cell lines. For this purpose stable embryonic stem (ES) cell lines that express enhanced green fluorescent protein (EGFP) under the control of $P_{CMV\ IE}$ were created. The activity of $P_{CMV\ IE}$ was then studied during ES cell differentiation. ES cells were differentiated by aggregation of the ES cells in the presence of retinoic acid (RA) followed by dissociation of cells and plating onto an adhesive substrate. It was seen that the activity of $P_{CMV\ IE}$ was highest in undifferentiated cells and in aggregates. Addition of RA to the aggregates leads to the maintenance of expression from $P_{CMV\ IE}$ and results in an increase in the number of cells that remain in the cell cycle.

Interestingly we found that the activity of $P_{CMV\ IE}$ was correlated with cells of specific lineages rather than only being correlated with cycling cells. While nestin positive neuro-epithelial precursor cells did not show EGFP expression, fibroblast like cells expressed EGFP at high levels.

Taking advantage of the correlation between down-regulation of $P_{CMV\ IE}$ and differentiation of cells into nestin positive precursors the molecular changes that accompanied this transition were probed. Two well characterized regions of the CMV promoter, a 19 base pair repeat which contains a consensus CRE binding site and a

21base pair sequence that modulate the activity of the CMV promoter were chosen. Nuclear extract from undifferentiated ES cells and cells that have been differentiated with RA were made. Electrophoretic mobility shift assay showed that proteins that were present in the nuclear extract from undifferentiated cells bound to the CRE sequence and the 21 base pair sequence. These proteins were not present in cells that had been differentiated. This result is significant since it implies that these proteins that are absent may play an important role in the conversion of ES cells into cells of the neuroectodermal lineage. Further these results also highlight the fact that exogenous promoters that drive transgene expression during ES cell differentiation may not be expressed in all cells at all times even when the cells have been stably transfected and clonally selected.

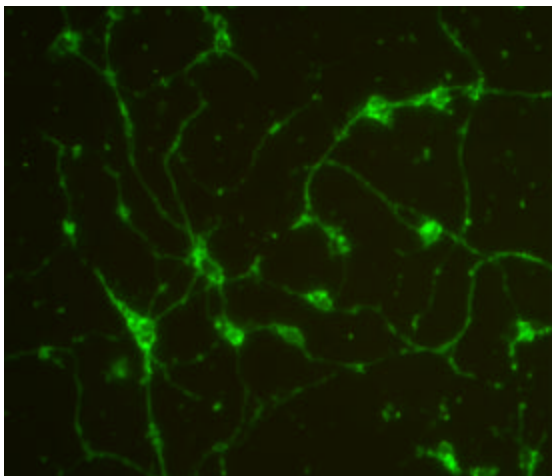
Publications

Bandita Bagchi, Manoj Kumar and **S. Mani**: The CMV immediate early promoter is regulated by cell-cell interaction and retinoic acid during differentiation of embryonic stem cells. Stem Cells (submitted)

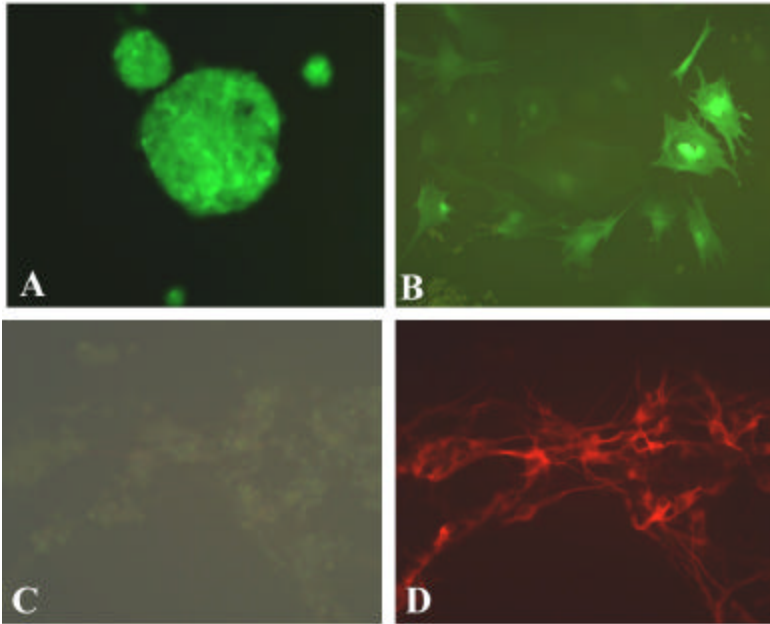
Presentations:

New neurons for old: Functional significance of adult neurogenesis. TRENDYS series of scientific talks, CDFD, Hyderabad, November 2003.

Funding: Department of Biotechnology as extramural support.



P6 cerebellar cultures from wild type mice showing expression of GAP-43.



ES cells: Figure shows $P_{CMV IE}$ is active in undifferentiated cells (A) and in differentiated fibroblast like cells (B) but it is not active in neurons (C). Neurons have been stained with neuron specific TUJ1 antibody (D).

Cytochromes P450 Dependent Metabolism of Drugs in Brain

Principal Investigator: V. Ravindranath

Research Fellows: Harish Pai
Reddy Peera

Technical Assistant: V.K. Prasanna

The variable pharmacological response to psychoactive drugs typically seen in population groups is often not accountable by considering dissimilarities in hepatic metabolism. Metabolism in brain specific nuclei may play a role in the pharmacological modulation of drugs acting on the CNS and help explain some of the diverse response to these drugs seen in typical patient population. Our working hypothesis is that brain cytochromes P450, the major drug metabolizing enzyme, play an important role in the pharmacological modulation of drugs acting on the CNS and it is therefore important to understand major cytochrome P450 (P450) mediated biotransformation and characterize the enzymes mediating such reactions in the human brain. While many isoforms of P450 are expressed in brain, is there anything unique about their presence there? The long-term objective of the proposed project is to understand the role of in situ cerebral drug metabolism in the pharmacological action of psychoactive drugs.

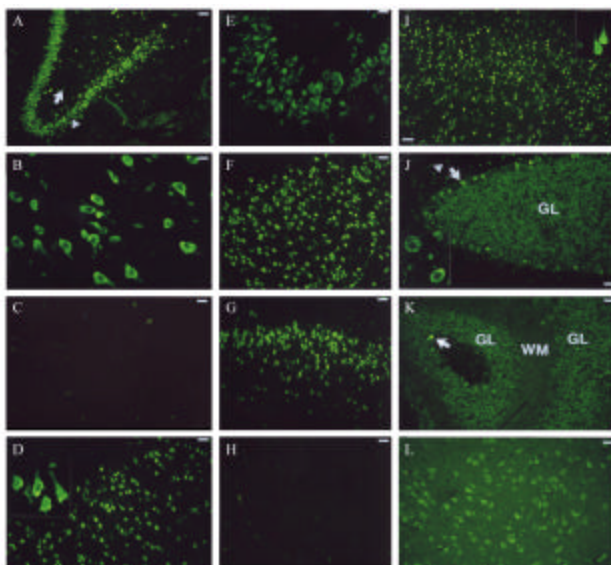
Cytochrome P4502D6 is an important P450 enzyme since it metabolizes a number of psychoactive drugs. We have identified a unique splice variant of cytochrome P4502D7 in human brain that metabolizes codeine exclusively to morphine. A frame-shift mutation 138delT generates an open reading frame in the pseudogene, cytochrome P4502D7 (CYP2D7) and an alternate spliced functional transcript of CYP2D7 containing partial inclusion of intron 6 was identified in human brain but not in liver or kidney from the same individual. mRNA of the brain variant CYP2D7 was detected in 6 out of 12 human autopsy brains. In liver, the major organ involved in drug metabolism, a minor metabolic pathway mediated by CYP2D6 metabolizes codeine (pro-drug) to morphine (active drug) while nor-codeine, is the major metabolite. In contrast, when expressed in Neuro2a cells, brain variant CYP2D7 metabolized codeine to morphine with greater efficiency compared to the corresponding activity in cells expressing CYP2D6.

In order to determine if the brain variant CYP2D7 protein was expressed in human brain, we generated an antiserum to the 19 amino acid peptide representing 57 bp of intron 6 present in the brain variant CYP2D7. The peptide used to generate the antiserum did not share homology with any known P450 enzyme and the antiserum did not cross-react with P4502D6. Expression of brain variant CYP2D7 protein as assessed by immunoblotting was seen in 6 of the 12 brain samples that were positive for the presence of brain variant CYP2D7 mRNA by RT-PCR indicating the concordance between the RT-PCR and immunoblot results.

Since the brain variant CYP2D7 was present only in about 50% of the human brains examined, we developed a genotyping assay to detect the 138delT relative to ATG. Genomic DNA was isolated from the 12 human brain samples that were used for RT-PCR and immunoblot experiments. This DNA was used as template for PCR amplification of the region spanning 45-551 bp (506 bp) relative to the ATG start codon of the genomic sequence of CYP2D7. The 138delT (CCTGC) was found only in those samples in which the mRNA and protein of the brain variant CYP2D7 was detected, others had complete sequence similarity with the pseudogene CYP2D7 (CCTTGC). Incidence of CYP2D7 genetic polymorphism was examined in a small sample set. DNA isolated from blood samples of 8 volunteers was used as template and the region spanning 45-551 bp (506 bp) relative to the ATG start codon of the genomic sequence of CYP2D7 was amplified using PCR. The 138delT (CCTGC) was found only in 4 out of 8 samples analyzed. The others had complete sequence similarity with the pseudogene CYP2D7 (CCTTGC).

In order to determine if the metabolism of codeine to morphine takes place at the site of action of the morphine, namely the neurons in periaqueductal gray that contain μ opiate receptors, we performed immunohistochemistry using antisera to brain variant CYP2D7 and μ -opiate receptor on serial sections of periaqueductal gray from human brain. Brain variant CYP2D7 and μ -opiate receptor co-localized in the neurons of periaqueductal gray. Histiospecific isoforms of P450 generated by alternate splicing, which mediate selective metabolism of pro-drugs within tissues, particularly the brain, to generate active drugs may play an important role in drug action and provide newer insights into the genetics of metabolism.

CYP1A1, another P450 enzyme plays an important role in the bioactivation of polycyclic aromatic hydrocarbons to the ultimate carcinogen. It also participates in drug metabolism. We have recently identified a splice variant of CYP1A1 in brain.



Localization of CYP1A1 mRNA in human brain by fluorescence in situ hybridization.

Presence of CYP1A1 mRNA in granule cells of dentate gyrus (A), pyramidal neurons of CA3 (B, F), CA2 (G) and CA1 (D, E) is depicted. Corresponding control sections are shown in (C, H). Differential fluorescence was seen in neuronal cells delineating the laminar architecture of the cortex. (I). Purkinje cells and the granule cell layer (GL) were labeled in cerebellum (J, K). Sparse staining was observed in the reticular neurons of the midbrain region (L).

A region of the cDNA of human P4501A1 (Genbank Accession no. K03191) representing exons 3-7 (967-1339 bases) was amplified by RT-PCR using the cDNA synthesized from total RNA of 15 human brain cortex obtained at autopsy was conducted on samples obtained from Brain Bank, NIMHANS. In all 15 samples were examined, a 301 bp fragment was amplified instead of the anticipated 394 bp product, showing the existence of a splice variant for cytochrome P4501A1 in the human brain, which had deletion of exon 6. Thus a unique brain CYP1A form is present in human brain. Further characterization of this gene product is being carried out.

Collaborator[s](#): Prof. H. W. Strobel, Univ. of Texas Medical School, Houston, USA
Prof. M.R. Boyd, Univ. of South Alabama, Mobile, USA

Funding: NIH-RO1

Ph.D. Thesis (Submitted): Harish Pai

Publications:

Pai,H.V., Kommaddi,R.P., Chinta,S.J., Mori,T., Boyd, M.R. and **V. Ravindranath**: A frame shift mutation and alternate splicing generates a functional isoform of the pseudogene, cytochrome P4502D7 in human brain that demethylates codeine to morphine. **J. Biol. Chem.**279: 27383-9, 2004.

Pai,H.V. and **V. Ravindranath**: Dexamethasone induces total P450 levels but not P4503A in brain. **Neurochemistry International**. (Submitted).

S.J.Chinta, H.V. Pai and **V.Ravindranath**: Presence of splice variant forms of cytochrome P4502D1 in rat brain but not in liver. **Molecular Brain Research** (Submitted).

S. J. Chinta, R. P. Kommaddi, H. V. Pai, C. M. Turman, H. W. Strobel and **V. Ravindranath**: Constitutive expression and localization of CYP1A1 in rat and human brain: Presence of a splice variant form in human brain. **J. Neurochem** (Submitted).

Presentations:

V. Ravindranath: “Understanding analgesic action of codeine: a unique human brain specific cytochrome p4502d metabolizes codeine predominantly to morphine” – Invited Talk Presented at The Symposium Of Advances In Cellular And Molecular Pharmacology in December, 2003.

Harish V. Pai, Reddy P. Kommaddi and **V. Ravindranath:** “A functionally active splice variant of cytochrome P4502D7 pseudogene metabolizes codeine principally to morphine” -Presented at The International Symposium Held at NBRC in December, 2003

Reddy P. Kommaddi, Shankar J. Chinta, Prasanna VK and **V. Ravindranath:** Constitutive expression and localisation Of CYP1A1 in human brain: Identification of a unique brain splice variant” –Presented at The International Symposium held at NBRC in December, 2003

V. Ravindranath: “Drug metabolism in brain by unique isoforms of cytochroms P450 generated by alternate splicing” – Invited Talk Presented at The National Symposium On Cellular And Molecular Biophysics, NIMHANS At Bangalore in January, 2004.

Harish V. Pai, Reddy P. Kommaddi and **V. Ravindranath:** “Understanding analgesic action of codeine: a unique human brain specific cytochrome CYP2D metabolizes codeine exclusively to morphine” – Presented at The Indo-US Workshop On Research & Development in Genomics held in September, 2003 At Bangalore.

H.V.Pai, SJ Chinta, K.P. Reddy and **V. Ravindranath:** Codeine addiction: a unique human brain specific cytochrome p450 metabolizes codeine exclusively to morphine. Presented at the Annual Meeting of Society of Neuroscience, USA – November 2003.

Mitochondrial Dysfunction and Protein Thiol Homeostasis In Neurodegenerative Diseases.

Principal Investigator: Prof. Vijayalakshmi Ravindranath

Research fellows: Rajappa S.Kenchappa
Smitha Karunakaran,
Niranjan Kashyap

Human ingestion of “chickling peas” from the plant *Lathyrus sativus* containing an excitatory amino acid, L- β -N-oxalyl amino-L-alanine (L-BOAA) leads to a neurodegenerative disorder, neurolathyrism. This is a type of motor neuron disease characterized by spastic paraparesis that targets betz cells in motor cortex (MC) and the anterior horn cells in the lumbosacral cord (LSC).

Our laboratory has shown that L-BOAA toxicity in mice is associated with mitochondrial dysfunction seen as loss of complex I activity in MC and LSC. While MC recovers after an initial insult, sustained injury is seen in LSC. We, therefore profiled global gene expression changes by microarray analyses in mice CNS regions during recovery from L-BOAA toxicity. Mouse cDNA arrays were hybridised with RNA from MC and LSC of control and L-BOAA treated mice. Data was analysed using Array vision and Spot-fire software.

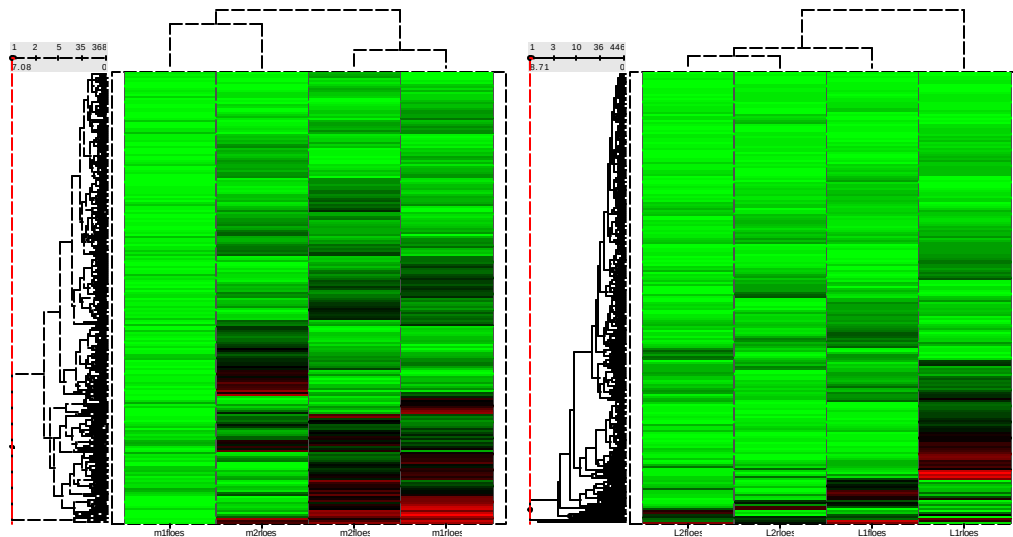


Fig: Hierarchical clustering of genes up-regulated in motor cortex and lumbosacral cord of male mice treated with L-BOAA.

In concurrence with our earlier results glutaredoxin, a thiol disulfide oxidoreductase was upregulated in both MC and LSC. Glutaredoxin is required for maintenance of complex I function. However, the up-regulation of NADH dehydrogenase (Complex I) was seen only in MC and not in LSC in agreement with the activity of complex I seen earlier. Upregulation of genes related to energy metabolism, antioxidant

enzymes, MAP kinases and ubiquitin proteasomal pathways was seen in MC indicating their potential role in the recovery. In contrast in LSC, genes related to MAP kinases and anti-oxidant were unchanged, instead programmed cell death gene(s) were upregulated.

These studies demonstrate the differential responses of CNS regions to a common excitotoxic insult and help identify factors responsible for differential vulnerability of CNS regions often seen in neurodegenerative diseases.

Molecular Mechanism of Estrogen Mediated Neuroprotection

Principal Investigator: V. Ravindranath

Research Fellows: Rajappa
Latha

Project Assistant: Jeet Singh Khushdil

Epidemiological studies have shown that the incidence of neurodegenerative disorders in general is lower in women as compared to men. Although it is well documented that estrogen offers neuroprotection, the molecular mechanisms involved in the neuroprotective effects of estrogen are not well understood. In humans, the incidence of neurodegeneration is more common in men, while women are less prone to the disease although consumption of the chickling pea is not significantly different. This gender difference in the neurotoxic response to L-BOAA is reflected in the mouse model of L-BOAA toxicity. The animal model of L-BOAA toxicity not only mimics the gender difference but also the site specificity of L-BOAA action wherein only motor cortex and lumbosacral cord are affected. We, therefore, examined the molecular mechanisms underlying the neuroprotection against excitotoxicity seen in female mice using this model.

L-BOAA mediates neurotoxicity through the AMPA subtype of glutamate receptor in the motor cortex and lumbosacral cord of male mice and causes loss of the anti-oxidant, glutathione and increase in protein-glutathione mixed disulfides that results in inhibition of mitochondrial complex I, a major component of the mitochondrial electron transport chain. The inhibition of mitochondrial complex I activity by L-BOAA occurs through glutathionylation of critical thiol groups in subunits of complex I. Glutaredoxin (also known as thioltransferase; Grx1), a thiol-disulfide oxidoreductase, specifically and efficiently reduces glutathionylated proteins to protein thiols thus regenerating the enzyme activity. Grx1 is required for maintenance of complex I function in normal conditions and its up-regulation is critical for recovery of complex I function following L-BOAA administration. β -N-Oxalyl-amino-L-alanine triggers glutathione loss and inhibition of complex I activity in motor cortex and lumbosacral cord of male mice but has no such effect on female mice.

Pretreatment of female mice with ICI 182,780, an estrogen receptor antagonist sensitizes them to β -N-oxalyl-amino-L-alanine toxicity indicating potential role of estrogen receptor. Increased AP1 transcription, upregulation of the mRNA of glutaredoxin and γ -glutamyl cysteine synthetase were seen only in male mouse CNS but not in females. Constitutive expression of glutaredoxin is significantly higher in female mice brain regions as compared to males and treatment with estrogen receptor antagonist ICI 182,780 down-regulates glutaredoxin. Higher constitutive expression of glutaredoxin could potentially contribute to neuroprotection seen in female mouse following exposure to excitotoxins.

Collaborators: Prof. A.J. Rao, IISc, Bangalore.

Ph.D. Thesis (Submitted) – R. Kenchappa

Publications:

Kenchappa, R.S., Diwakar, L., Annepu, J and **V. Ravindranath:** Estrogen and Neuroprotection: Higher constitutive expression of glutaredoxin in female mice offers protection against MPTP mediated neurodegeneration. **FASEB J.** 18 1102-1104 (2004).

Kenchappa, R.S., Diwakar, L., Annepu, J and **V. Ravindranath:** Estrogen receptor antagonist down regulates glutaredoxin and renders female mice susceptible to excitatory amino acid mediated complex I inhibition in the CNS. **J. Neurochem.** (submitted).

Presentations:

V. Ravindranath: Protein thiols, mitochondrial dysfunction and neurodegeneration” – Invited talk presented at the meeting of FAOBMB in December, 2003.

L. Diwakar, S. Karunakaran, R. Kenchappa and **V. Ravindranath:** “Estrogen mediated protection against excitotoxicity: higher constitutive expression of glutaredoxin in female mice offers protection against excitatory amino acid mediated mitochondrial dysfunction” – presented at the International Symposium held at NBRC in December, 2003

R.S. Kenchappa, N. Kasyapa, L. Diwakar, V.K. Prasanna and **V. Ravindranath:** Microarray based gene expression profiles of motor neurons during recovery from excitotoxic insult – Presented at the International Symposium held at NBRC on December, 2003

S. Sampath and **V. Ravindranath:** Polymorphism studies of glutaredoxin (grx1), a thiol disulphide oxidoreductase involved in maintenance of mitochondrial complex I – Presented at the Indo-US workshop on Research & Development in Genomics held on September, 2003 at Bangalore.

L. Diwakar, S. Karunakaran and **V. Ravindranath:** “Molecular mechanisms underlying the neuroprotective effect of estrogen thiol” –Presented at the Indo-US workshop on Research & Development in Genomics held on September, 2003 at Bangalore.

R. S. Kenchappa, N. Kasyapa, Latha Diwakar and **V. Ravindranath:** “Microarray based gene expression profiles of motor neurons during recovery from excitotoxic insult” – presented at the Indo-US workshop on Research & Development in Genomics held on September, 2003 at Bangalore.

R.S.Kenchappa, N. Kasyapa, L. Diwakar and **V. Ravindranath**: Global gene expression analysis using microarray to study differential vulnerability of CNS regions to excitotoxicity” –Presented at Asia Pacific Society for Neuroscience meeting at Hong Kong on February, 2004.

Evaluation Of The Molecular Basis Of The Pharmacological Action Of Traditional Medicinal Preparations Used In The Treatment Of Mental Illnesses Including Dementia

Principal Investigator: V. Ravindranath

Research Fellows: Sajla Singh

Project Assistant: Sandhya Singh

Brain related disorders contribute up to one-third of the total diseases in both developed and developing countries. Among the brain related disorders, which comprise of both neurological and psychiatric illnesses, those of serious concern are the age-related disorders such as senile dementia, Alzheimer's disease and Parkinson's disease etc. These disorders are progressive and irreversible, and currently no cure is available since the etiopathogenesis of these disorders is poorly understood.

Of particular concern, with reference to our country is the fact that with increasing longevity, the demographic profile of the country is rapidly changing and a significant proportion of our population would consist of aged individuals.

Senile dementia including Alzheimer's disease is extremely distressing since it results in severe cognitive dysfunction including memory loss for which no treatment is currently available. Traditional systems of medicine such as Ayurveda offer a knowledge base that can be utilized for development for therapeutic intervention strategies for treatment of these disorders.

In this project we propose to examine the neuropharmacological effects of six plants, which are used in traditional system of medicine for improving higher mental function. The plants to be examined are *Withania somnifera*, *Centella asiatica*, *Acorus calamus*, *Bacopa monnieri*, *Celastrus paniculatus*, *Nardostachys jatamansi*. Recent advances in molecular biology and neuroscience offer us the tools such as cell lines expressing human neurotransmitter receptors and transporters, DNA microarray technology, transgenic animal models, rationally-defined, validated methods for testing higher cognitive functions such as memory which can be used suitably for assessing the therapeutic potential of the plants used in ancient systems of medicine.

In vitro receptor binding assays were carried out using membrane preparations from human autopsy brain samples. The plant extracts from *Acorus calamus* and *Withania somnifera* were able to displace the binding of the radioligand to the muscarinic receptors indicating their substantial affinity for the receptor. Among the 4 plant extracts tested *Withania somnifera* had the maximum receptor binding activity to muscarinic receptor, followed by *Acorus calamus*. Comparatively *C. asiatica* and *B. monnieri* showed lower activities. We have just acquired the Presenilin 1/ APP transgenic mice, which are used as animal models for Alzheimer's disease and the plant extracts will be

tested in the transgenic mice to determine their efficacy in preventing the behavioural and pathological hallmarks of Alzheimer's disease.

Collaborator: Arya Vaidya Sala, Kerala

Funding: Department of Biotechnology

General Talks:

V. Ravindranath. “Newer Therapies and Cures for Brain Disorders Through Brain Research” – Invited talk presented at the ALNC Oration, Chennai on June, 2003.

V. Ravindranath. “Brain Disorders : Recent Advances And Challenges Ahead” – Invited talk presented at the Indian National Science Academy on August, 2003

V. Ravindranath. “Neuroinformatics: Linking Molecules To Behaviour” – Invited talk presented at the Ministry of Communications and Information Technology on November, 2003.

V. Ravindranath. “Towards Understanding The Pathogenesis Of Neuro-Degenerative Disorders” – Invited talk presented at the Indian Science Congress on January, 2004.

V. Ravindranath. “The Brain And Mind” – Invited talk presented at the India International Centre on January, 2004.

V. Ravindranath. “Women In Science: Strategies For Overcoming Barriers” – Invited talk presented at National Institute of Science, Technology and Development Studies (NISTADS) on March, 2004.

Understanding the Role of Transcription Factors in the Differentiation of Photoreceptors and Related Retinopathies.

Principal Investigator: Prabodha Swain

Research Fellow: Sandeep Kumar

Project Assistant Dharmesh Patel

Photoreceptors are specialized neurons in retina necessary for phototransduction. In mammalian retina there are two distinct populations of photoreceptors known as rods and cones. Each of these photoreceptor cells has distinct cellular architecture and function in terms of sensitivity to light. Characteristically rods are sensitive to dim-light vision, whereas cones are necessary for colour or bright light vision. Retinal cells like any other cells in the body are regulated by specific transcription factors. Few photoreceptor specific factors such as Neural retina leucine zipper (NRL) and Photoreceptor specific nuclear receptor (PNR) have been suggested to have key regulatory role in photoreceptor differentiation and normal functioning in adult retina. It is known that (a) mutation of both NRL and PNR genes are associated with retinal degeneration, (b) phenotypes observed in human and knock-out mouse are very similar and (c) expression of the genes in mammalian retina is confined to photoreceptors.

Although it has been hypothesized that both the factors are involved in photoreceptor (rod) differentiation pathway, the hierarchical regulation and interaction with other retinal proteins are yet to be identified. Identification of such factors is important to understand their role in the disease phenotype.

Transcription is a stringent regulatory process controlled by more than hundreds of proteins. Few of these proteins are termed as general transcription factor and others are specific activators/repressors that impart cell specific regulation in the mammalian system. NRL is a positive regulator of rhodopsin expression. Close proximity of NRL-response element and TATA box in the rhodopsin proximal promoter sequence prompted us to analyse if NRL binds directly to the TATA-box binding protein (TBP). Analysis of the immuno-precipitated protein complex with anti-TBP and anti-NRL suggested that NRL and TBP form a part of the retinal protein complex that can be co-precipitated with both the antibodies. To understand if the interaction between NRL and TBP is direct, a GST pull down assay was performed. Radiolabeled TBP was pulled down specifically by GST-NRL suggesting a direct interaction between both NRL and TBP. The exact domain responsible for the interaction is being ascertained.

In our analysis of the other proteins that can interact specifically with NRL, we identified CREB-1 and Pax6, which are co-immunoprecipitated in the retinal protein complex. CREB-1 is expressed in retina and has role in the differentiation of ganglion cells. It also contains carboxyl terminal leucine zipper motif, which potentially interacts with leucine zipper of NRL to form heterodimer. Similar co-immunoprecipitation assays were performed to find out interaction of NRL and PAX6, a

homeodomain protein. NRL is reported to interact with PAX6 in the differentiation of lens genes. However we are yet to confirm the direct interaction of PAX6 and CREB-1 with NRL. Identification of target genes regulated by the combination of NRL and CREB-1 is important to understand its role in differentiation of photoreceptors.

In a separate strategy Glutathione-S transferase-NRL affinity chromatography was used to identify retinal proteins interacting with NRL. After washing non-specifically bound proteins with non-ionic detergents, GST-NRL bound proteins were analysed by SDS-Chromatography and visualized by silver staining. Two protein bands of molecular weight range 30-45 kD were differentially bound to GST-NRL but absent in GST bound fraction. However, it was confirmed that 45 kD protein is different from TBP, and does not interact with the specific anti-TBP antibody in the immunoblot analysis. Further characterization is in progress.

NRL is a phosphoprotein. More than seven phospho-isoforms of NRL are present in most mammalian retina. Several NRL-mutations identified in the affected population are potential phosphorylation sites in the protein. In-vitro transactivation assay using mutated NRL showed severe alteration of the rhodopsin transcription. To identify the possible kinase(s) and signalling pathways involved in the phosphorylation of NRL, we fractionated bovine retinal proteins using different chromatographic techniques. More than one fractions were tested positive for NRL specific kinases. Interestingly two of these fractions contain NRL and one of the widely expressing mitogen activated protein kinase (MAPK). We are using subsequent chromatography and phosphorylation assays to determine the identity the kinase responsible for NRL-phosphorylation. It will help us to define the molecular role of NRL in rod-differentiation.

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

Principal Investigator: Prabodha Swain

Project Assistant: Dharmesh Patel

Technical Assistant: Sanjay Kumar

Neural cell differentiation is regulated by both intrinsic and extrinsic factors. These factors induce programmed differentiation to generate distinct neural cell types in retina as well as other part of brain. Besides transcription factors different cell cycle molecules also have a major role in the successive steps of differentiation and fate determination of retinal cells. Differentiation of retinal neurons is stage specific. Cell lineage and birth date analysis in rodents suggest ganglion cells are generated early in the embryonic stages; followed by the amacrine, cone and horizontal cells during mid gestation and rod, bipolar and glia are generated at late embryonic stages. Identification of stage specific factor(s) can potentially serve as markers for one or more retinal cell progenitors. Identification of any such marker of photoreceptor progenitors will be an important tool to characterize and purify such cells from the mixed population of mitotic retinal cells. These cells can be induced by specific extrinsic factors (like FGF, SHH, taurine and retinoic acid) to produce post-mitotic photoreceptors. These progenitors with limited mitotic activity then can be used as potential replacements for photoreceptors in damaged retinae.

Some of the recent findings suggest that iris cells can produce retina specific factors when induced with specific retinal genes. Since iris and retina originate from the same inner layer of the optic cup in embryonic retina, it promises to be an interesting model to study the specific pathways that can be triggered by the introduction of retina specific factors.

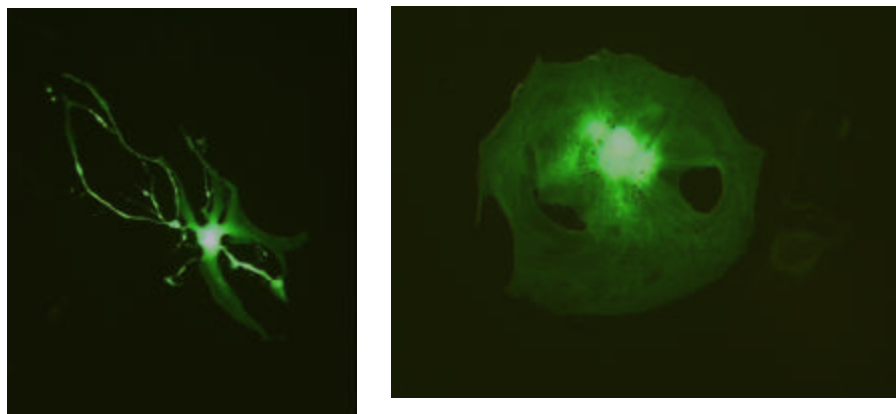


Fig: Adult Bovine Iris cells grown in vitro and transfected with EGFP constructs

We have been successful in culturing primary iris cells from cadaver bovine eyes. In spite of 6-7 hrs post mortem delays we have been growing these cells regularly in DMEM containing 10% fetal bovine serum. After 2 days DMEM was substituted with DMEM-Neurobasal (1:1) containing 5% serum and 1X B27 growth factor. Though B27 is necessary for primary neuronal culture, in case of bovine iris simple supplementation of foetal bovine serum is adequate to promote in the cell growth. Cells were cultured successfully for 4 months and standardized to perform transfection using lipofectamine methods. To ascertain the identity of the cells we checked the expression of PAX6 and Six3 expression in the cells. Both the proteins are known to express in iris cells. In addition to these specific markers, primary iris cells also tested positive for the expression of Tuj-1 and GFAP by immunohistochemistry staining.

Publication:

*Wang QL, Chen S, Esumi N, **Swain PK**, Haines HS, Peng G, Melia BM, McIntosh I, Heckenlively JR, Jacobson SG, Stone EM, Swaroop A, Zack DJ. (2004) QRX, a Novel Homeobox Gene, Modulates Photoreceptor Gene Expression. **Hum Mol Genet.** 13 (10):1025-40

*Pittler SJ, Zhang Y, Chen S, Mears AJ, Zack DJ, Ren Z, **Swain PK**, Yao S, Swaroop A, White JB (2004) Functional analysis of the rod photoreceptor cGMP phosphodiesterase alpha -subunit gene promoter: Nrl and Crx are required for full transcriptional activity. **Journal Biol Chem.** 279(19):19800-7

* work done elsewhere

Presentation:

Invited to speak on the Microarray Technology and its Application at Defence Institute Physics and Allied Sciences, Delhi on 28th November 2003.

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Molecular Approaches to Understanding Virus Induced Neurodegeneration

Principal Investigator: Dr. Pankaj Seth

Understanding cellular and molecular events of virus-cell interactions during the course of infection is essential for defining a disease and developing potential therapies. A wide range of neurological complications is associated with acquired immune deficiency syndrome (AIDS), including the late-stage syndrome of human immunodeficiency virus (HIV-) associated dementia that involves severe cognitive impairment, motor disturbances, and behavioural changes. HIV-1 invades the central nervous system (CNS) and productively infects brain macrophages and microglial cells. A subpopulation of infected astrocytes is also routinely detected in brain autopsies from HIV patients in adult as well as pediatric cases.

The world wide incidence of HIV- associated dementia has been reported to be more than 30% of AIDS population. The genetic variation of HIV-1 has lead to the classification of viral strains into phylogenetically distinct groups and subtypes which continue to complicate the development of effective vaccines and treatments to limit the AIDS pandemic and also the neurological complications arising in AIDS patients.

Of the various subtypes of HIV-1 (subtype A-J), subtype C is implicated for more than 50% of the HIV infections globally and is linked to rapidly growing epidemics in sub-Saharan Africa, China and most importantly for us in India. It is believed that around 90% of HIV-1 infections in India are due to the subtype C, making it essential to understand the biological properties of this strain and its role in neurological complication arising in patients infected with this subtype.

As many of the first HIV-1 genomes to be studied at both the molecular and phenotypic levels were subtype B variants from United States and Europe, much of our understanding of biology and pathogenesis of HIV-1 comes from analysis of subtype B viruses. It remains unclear whether the subtypes that are defined purely on the basis of sequence similarity, also define groups with any biological and immunological differences.

Despite major advances in last two decades of HIV-1 research, determining the mechanisms by which HIV-1 infection in the CNS causes neurological complications remains a challenging task, moreover limited information on details as to how HIV-1C affects brain functioning, calls for immediate research studies to understand HIV-1C induced neuropathogenesis, especially with Indian perspective.

As per our current understanding, the incidence of HIV associated dementia is reported to be unusually low (around 2%) in our country, and only two studies have been done so far. The low incidence of HIV associated dementia has often been debated to be due to prevalence of other opportunistic infections, like TB, cryptococcus, toxoplasma in HIV patients, over all under-diagnosis, shorter life expectancy, and certain other issues associated with an economically developing nation like ours

The low incidence of HIV associated dementia in India may also be attributed to the fact that a different subtype of HIV-1, subtype C is prevalent, rather than subtype B as seen in the Western world, where incidence is higher (around 30%), however data to support such assumptions are unfortunately lacking. We are therefore interested in examining the biological differences with these two strains subtype B and C, to better understand the molecular and biochemical pathways for neuropathogenesis following infection with HIV-1, specifically in terms of inflammatory markers and neuronal apoptosis.

We would be using novel cell culture systems derived from human fetal brain cells to investigate certain viral-cell interactions. We are currently establishing such cell culture systems to use as tool to investigate virus - induced neuropathogenesis. These studies would provide insight into the various neuropathogenesis mechanisms of the two different subtypes, B and C, which affect the majority of AIDS population around the globe. Such studies may also have great clinical significance in designing therapeutic regimens for managing neurological complications in people living with AIDS.

Publications:

P. Seth, F. Diaz and E.O. Major. JC virus induces a non-apoptotic cell death of human CNS progenitor cell derived astrocytes. **J of Virology** (In Press). *

D.M.P. Lawrence, L.C. Durham, L. Schwartz, **P. Seth**, D. Maric and E.O. Major. HIV-1 infection of human brain derived progenitor cells. **J of Virology** (In Press). *

* Work done elsewhere

Presentations:

P. Seth and E.O. Major. Cell culture model for studying virus induced neurodegeneration. Invited talk at United States Army Center for Health Promotion and Preventive Medicine, Aberdeen Proving Ground, Edgewood, USA, Jan 2004.

P. Seth, F. Diaz, Jean Hou and Diane Lawrence and E.O. Major. Molecular Mechanisms to Understanding Virus Induced Neurodegeneration. Invited Speaker at International Symposium on Molecular Toxicology and Environmental Health, Lucknow, India, Nov 5-8, 2003.

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

Principle Investigator: Soumya Iyengar

Research Fellow: Nazia Khurshid

Technical Assistant : OP Sharma
Arvind Singh Pundir

The areas surrounding primary auditory cortex in adult humans have recently been subdivided into a number of non-primary auditory cortical areas which appear to function in perceiving speech-related sounds. Some of these areas are also involved in sound identification and localization. Although it is known that hearing begins as early as the 26th foetal week, few studies have focused on whether the non-primary auditory areas are present early in development or whether they emerge during the late foetal and early postnatal period in response to auditory input from the environment.

This study focuses on the ontogeny of the auditory cortex during early development in humans using postmortem tissue. For the first part of this project, serial coronal sections of post mortem brain tissue from the late foetal and neonatal stages, young childhood (1-12 years) and adulthood will be stained for Nissl, cytochrome oxidase and acetylcholine esterase to study the cytoarchitecture of the developing auditory cortex. We will then reconstruct the overall volumes of different auditory cortical areas using an image analyser and quantify relative changes in these areas.

Another aspect -which we will try to examine is whether cortical areas responsible for identifying sounds mature prior to those which are important for localizing them or vice-versa. Earlier studies have shown that different subdivisions of the auditory cortex in adult humans, which are important for sound localization and identification differentially, express the calcium binding proteins calbindin, calretinin and parvalbumin. We will stain serial sections of post mortem developing brains using immunohistochemical markers for these calcium binding proteins to study their patterns of expression and for comparing with the pattern seen in adult humans. For this project, we are processing foetal, neonatal and adult tissue for histochemistry (for cytochrome oxidase and acetylcholine esterase) and are in the process of standardizing immunohistochemistry for the expression of calcium binding proteins. We have also standardized the Golgi technique (Golgi-Kopsch and Golgi Cox), which will later be used to study cytoarchitectural details of neurons in the auditory cortex.

Collaborators: Dr. T. Asha (Guntur Medical College),
Dr. S. Shankar (NIMHANS),
Dr. PC Dikshit (MAMC)

To Study the Expression of Schizophrenia Susceptibility Genes in Post Mortem Foetal Human Brains at Different Stages.

Principle Investigator: Soumya Iyengar

A growing list of genes have recently linked to an increased risk for inheriting schizophrenia. Some of the most promising amongst these candidate genes are neuregulin 1 (NRG1), which alters the expression of NMDA receptors and regulates glial cells and myelination, dysbindin (DTNBP1) which is found in postsynaptic brain densities and catechol-O-methyl transferase (COMT) which encodes an enzyme important for the breakdown of the neurotransmitter dopamine. Interestingly, the expression patterns of these genes have been found to be abnormal in post mortem brain tissue from the dorsolateral prefrontal cortex of adult patients of schizophrenia compared to controls. The abnormalities in the expression patterns of the schizophrenia susceptibility genes may be present very early during development, especially since schizophrenia has been classified as a neurodevelopmental disorder.

Our goal is to study the expression of these genes during early development in the prefrontal cortex from postmortem brains of fetuses using in situ hybridisation. So far, we have started standardizing the protocol for in situ hybridisation using a probe for GAP-43. The GAP-43 gene is expressed abundantly during foetal development and will be used as a positive control before using probes for the schizophrenia susceptibility genes.

Collaborators: Dr. V. Ravindranath (NBRC)
Dr. J. Kleinman (NIMH)

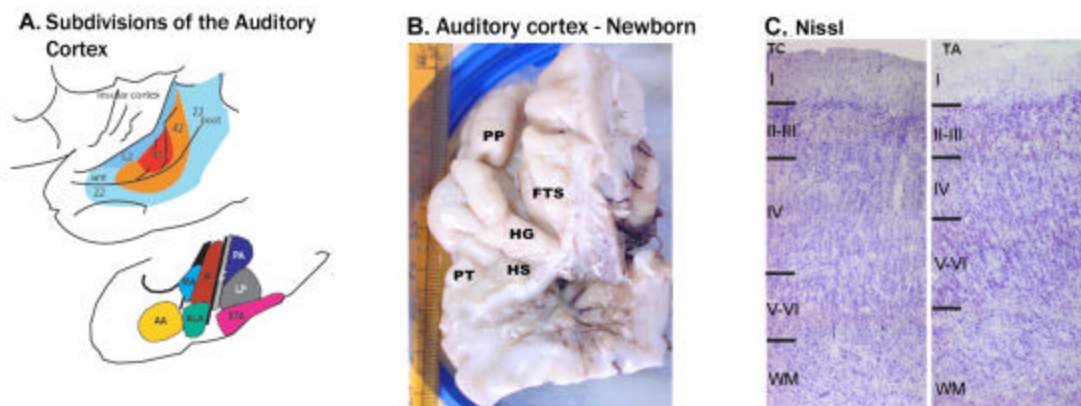


Fig: (A.) Schematic showing different subdivisions of the adult human auditory cortex. Area 41 or AI corresponds to the primary auditory cortex whereas area 42 corresponds to the belt region and areas 22 and 52 correspond to the outermost 'parabelt' region. Belt and parabelt are non-primary auditory cortices which include the smaller areas AA, ALA, LA, STA, PA and MA. These areas respond maximally to speech and environmental sounds. **(B.)** The overall organization of the auditory cortex at birth is similar to that at adulthood and all parts such as HG (Heschl's gyrus), HS (Heschl's sulcus), PP (Planum polare) and PT (Planum temporale) can be easily delineated. **(C.)** The cytoarchitecture of the auditory cortex in a newborn as seen with Nissl staining is also similar to that in adults. The primary auditory cortical area (TC) has a

prominent granular layer (LIV) which is much smaller in TA (a non-primary auditory region). Neurons in both areas are arranged in columns and area TA has prominent pyramidal cells in LIII and LV.

Brain Reorganization following Spinal Cord Injuries

Principal Investigator: Neeraj Jain

Research Fellow: Shashank Tandon

Project Assistant: K B Ramakrishnan

The somatosensory system processes tactile inputs from various types of touch receptors in the skin. The inputs are processed in a number of different regions in the lower brain stem, thalamus and cortex. Besides enabling tactile perception the somatosensory inputs also provide feedback to the motor system for control of movements such as during palpation and grasp. Our research program aims to understand how the primate sensorimotor system processes sensory information to enable tactile perception and motor control, and how do peripheral and central nervous system injuries in adults during early development and affect the functional organization of the system.

One of our goals is to determine the extent to which lesions of the dorsal columns of the spinal cord affect organization of different somatosensory areas of the brain viz. 3a, 1, 2, S2 and PV and the motor areas. Using multiunit mapping and intracortical microstimulation techniques we are determining the extent and nature of these reorganizations. We are also determining how behavioural recoveries and certain permanent deficits in the use of the hand deafferented as a result of the unilateral dorsal column lesions relate to the reorganization of different sensorimotor areas of the brain. We will also determine if and to what extent (1) synaptic changes (such as changes) in the levels of various excitatory and inhibitory neurotransmitters and neurotransmitter receptors, and (2) growth and sprouting related changes underlie brain plasticity.

We have done unilateral lesion of the dorsal columns in monkeys at cervical level and the behaviour of the animal is being documented for recovery in posture, locomotion, placing, holding large objects and feeding. The animal can use its deafferented hand for most of the normal activities except to pick up small food items. Although the animal can use the hand for picking up large objects it does so clumsily and the object tends to slip from the grip. The motor cortex and somatosensory areas other than area 3b will be mapped in this animal.

Another goal is to determine how injury early in development affects organization of sensorimotor areas. We will determine if the animals with lesions early in development show a more 'normal-like' organization of the sensorimotor areas mentioned above because the system is still immature and capable of compensating for the partial lack of inputs. Experiments were done at Vanderbilt University during a visit as an ongoing collaboration, to determine changes in the sensorimotor cortex following unilateral lesions of the dorsal columns of the spinal cord in a newborn monkeys. Monkeys were mapped that had sustained lesions of the dorsal columns within a week after birth. The data show that the somatosensory cortical area 3b does not reorganize in the same manner as it does in adult animals following lesions of the spinal cord. There was very limited

expansion of the face representation in the deafferented area 3b. However, at most of the recording sites in the hand region of area 3b, neurons responded weakly to peripheral stimulation, required stimulation of deep receptors, often had large receptive fields and the somatotopy was abnormal. In the primary motor cortex or area 4 the region with representation of the digits was considerably smaller in proportion as compared to normal animals while representation of the shoulder and upper trunk was expanded. Although dorsal column lesions cut only part of the ascending somatosensory pathways and leave all the motor pathways intact, the motor cortex get extensively reorganized. Experiments are being initiated to fully characterize effects of dorsal column injuries on motor cortex.

Funding: International Senior Research Fellowship from the Wellcome Trust, UK.

Publications:

Mike Remple, **Neeraj Jain**, Pamela S Diener and Jon H Kaas. Bilateral effects of spinal overhemisections on the development of the somatosensory system in rats. **J. Comparative Neurology**. 475: 604-619, 2004*.

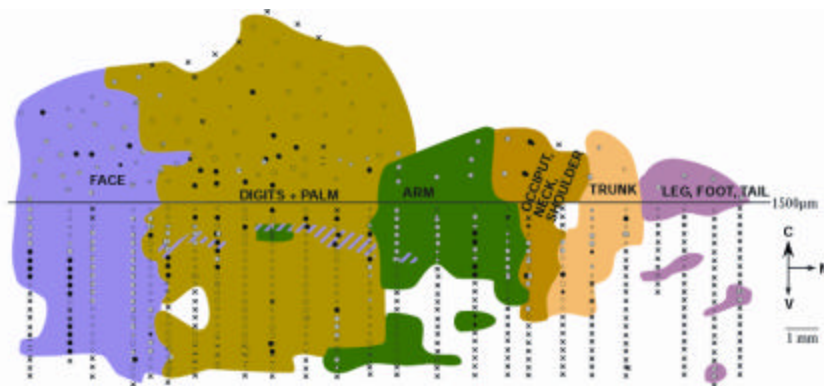
Neeraj Jain, Pamela S Diener, J.-O Coq and Jon H Kaas. Patterned activity via dorsal quadrant inputs is necessary for the formation of organized somatosensory maps. **J. of Neuroscience** 23:10321-10330, 2003*.

* Work done elsewhere

Presentations

Brain reorganization following spinal cord injuries- maps, neurons and behaviour: Centre for Cellular and Molecular Biology, Hyderabad. March 23, 2004.

Effects of Spinal cord injuries on the brain - plastic maps on static modules: Department of Molecular Reproduction, Development and Genetics, Indian Institute of Science, Bangalore. March 24, 2004.



Reorganization of area 3b (primary somatosensory area) following unilateral transection of the dorsal columns at the age of 5 days. The animal was mapped when it was about 4 years old. There is limited expansion of the face representation into the hand region. Following similar lesions in adult animals there is more extensive expansion of the face representation.

Saccadic Eye Movements as a Model to study the Control of Action.

Principal Investigator: Aditya Murthy

Research Fellow: Supriya Ray

Our visual sensitivity is not uniform but rapidly declines centrifugally from the centre of gaze as a result of which objects in the periphery cannot be identified clearly. To counter this problem our brain has evolved a mechanism whereby the visual scene is explored in discrete steps, each of them corresponding to an eye movement called a saccade, followed by a fixation. By carefully observing the pattern of fixations a number of behavioral studies have shown that saccades are not random but direct gaze to objects of interest. Therefore, before each gaze shift, perceptual processing must identify potential targets for the eye movement and motor processing must prepare and execute the motor command.

The role of cognition also provides an added level of complexity since behavior is not strictly dictated by perceptual processes: internal goals are important. The challenge therefore is to understand the representations of the image that guides orienting responses and the computations that subserve and link visual and cognitive processing, and eye movement programming.

The long-term goals of the proposed project are to understand how vision and cognition guide action. This goal is being approached through investigations of visually guided saccades in novel paradigms designed to probe the oculomotor control in normal human subjects.

Control of actions during errors. The capacity to detect and correct errors is necessary for goal directed behavior and is thought to reflect cognitive control. The aim of these experiments is to provide insights into the nature of such control during error correction.

To probe the nature of such control in relation to eye movements, human volunteers performed a double-step task under different instructions: to FOLLOW the appearance of successive targets; or to cancel the initial saccade and REDIRECT gaze to the final target location. Saccade sequences occurred in the FOLLOW and REDIRECT conditions where they represented correct and corrective behaviour, respectively.

We have previously reported that corrective responses were faster than correct responses, and concurrent preparation of saccades was facilitated during error correction, providing behavioral evidence of a cognitive system that is engaged during error correction. In the last year we have extended the analyses using a countermanding task. Subjects were instructed to withhold a partially prepared response when a 'STOP' signal (auditory or visual) appeared. As observed for the REDIRECT task the timing of corrective responses suggested that they were being prepared in parallel with the erroneous response. These results although counterintuitive suggest that our brains

possess the capacity to predict the consequences of actions. We are currently in the process of developing a behavioral paradigm to test this idea more directly.

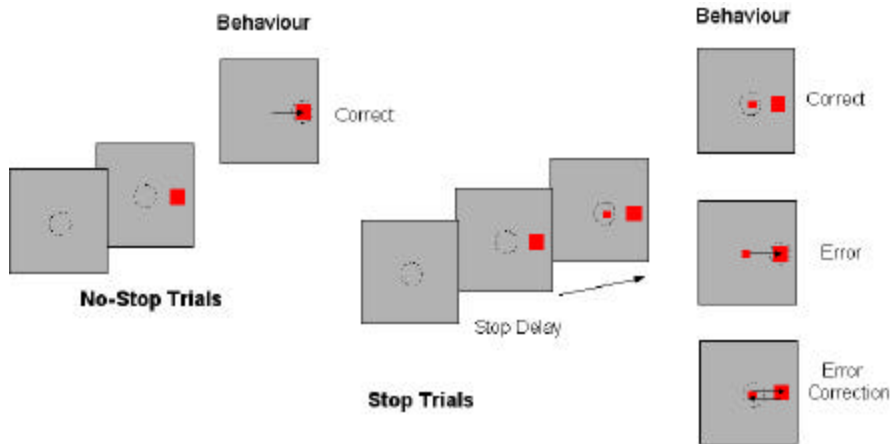


Figure 1. Schematic of the countermanding task used to probe inhibitory control and error correction

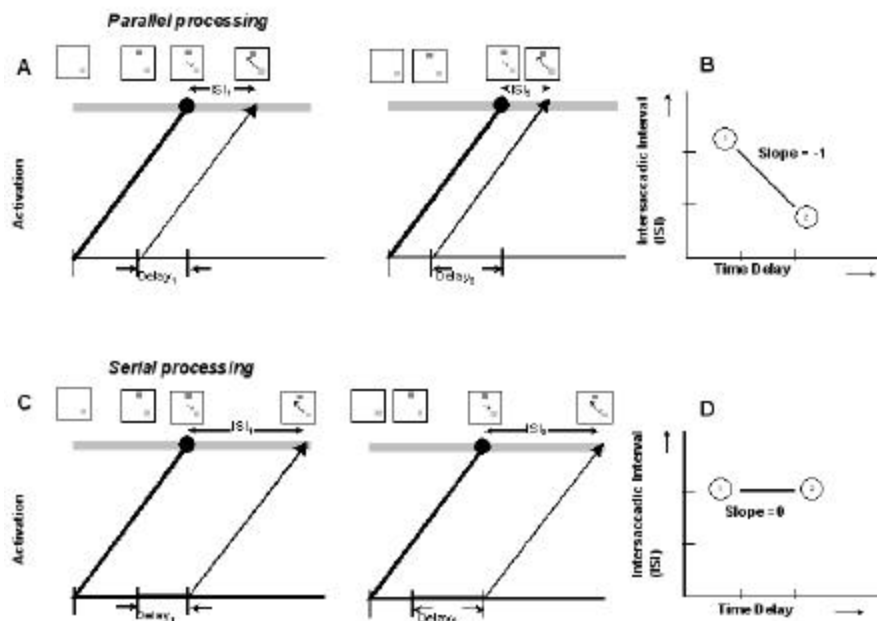


Figure 2. Theoretical framework to understand whether the preparation of the corrective response (blue) occurs after (serial) or during (parallel) the programming of the erroneous (red) response. Panels on the right are behavioral signatures of parallel (top) and serial (bottom) modes of

corrective saccade preparation. Parallel preparation is implied if the intersaccadic interval (ISI) varies inversely with time delay. Serial preparation is implied if the intersaccadic interval (ISI) is independent of time delay.

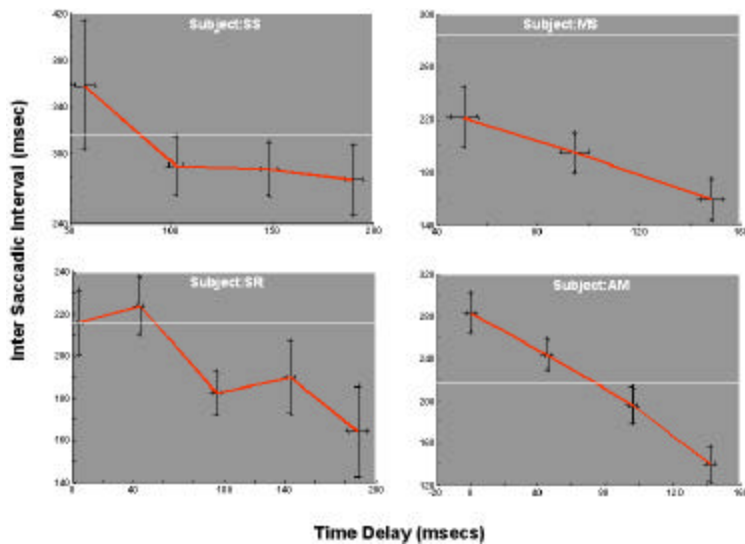


Figure 3. Data from four subjects suggesting parallel preparation of corrective saccades.

Funding: This work is supported by a grant from DST

Publication:

S. Ray, J.D. Schall and **A. Murthy**: Parallel programming of double step saccade sequences: modulation by cognitive control. **Vision Research** 44: 2707-2718 (2004).

A Murthy, S. Ray, Shorter-Jacobi, S.M. Thompson, K.G. and J. D. Schall. Predictive error correction by frontal eye field. (submitted to **Nat. Neuroscience**)

Presentation:

A. Murthy: Computational Vision. Lecture for Computational Neuroscience workshop at IIT Kanpur (2003).

A. Murthy: Neural Control of Action. Conference on Building the Brain held at NBRC, Manesar, India (2003).

Brain Mechanisms of Action Control In Humans

Principal Investigator: Aditya Murthy

Research Fellows: Supriya Ray (NBRC)
Dr. Faiz (AIIMS)

Project Assistant: Snehal Chokarinde

Understanding the neural basis of voluntary control is a central problem in cognitive neuroscience. Goal directed movements involve participation of a number of different brain areas. Some of these areas such as the basal ganglia, the anterior cingulate, the prefrontal cortex and the parietal cortex while not being obviously motor or sensory in nature still make important contributions. However, the nature of their role in motor control remains uncertain since lesions in these areas do not appear to affect the execution of specific movements such as those observed in primary motor cortex for example.

In order to test specific hypotheses about the function of associative brain areas in relation to the voluntary control of action we use the saccadic eye movement system as a model system. In oculomotor tasks, decisions about where to direct gaze requires an interaction between visual and motor systems and therefore provides an opportunity to study the role of networks mediating their interactions. Understanding how the brain controls action is necessary to understand the causes underlying various psychopathologies and motor abnormalities where there is a failure of control. These series of experiments are being carried out in collaboration with **Dr. Sarat Chandra (Dept. of Neurosurgery, A.I.I.M.S.)** and **Dr. Madhuri Behari (Dept. of Neurology, A.I.I.M.S.)**, where a facility to measure eye movements in real time under computer control has been set up.

Brain mechanisms of inhibitory control. A hallmark of the voluntary control of action is the ability to inhibit a planned movement when confronted with situations that render current goals inappropriate. This ability to inhibit inappropriate actions is of considerable interest because it involves an internal act of control by which overt movement is stopped/redirected. Inhibitory control can be probed in a version of the cancel task (see Fig 1) in which successful performance requires inhibiting a preprogrammed eye movement. Using this task we have recorded the behavior of patients with focal lesions frontal eye fields, the basal ganglia (Parkinson's patients), the prefrontal cortex and cerebellum. Using a simple theoretical construct called a race model we estimate the time it takes to inhibit a response (eye movement). The aim of this line of work is to understand how and where inhibitory control is implemented in the brain.

Brain mechanisms of error correction. In the cancel task when inhibitory control is successfully implemented, it results in the cancellation of the preprogrammed eye movement. However, as the delay between the appearance of the target and the stop signal increases, subjects increasingly fail to inhibit their responses leading to errors.

When subjects make such errors they frequently make quick corrective movements (see Figure 1). Such behavior implies that the brain has the capacity to evaluate the consequences of actions and provide a means to correct erroneous behavior. Thus the response to errors can provide novel insights into the basis of supervisory control of actions. The aim of this line of work is to provide some insights into the neural basis of supervisory control. For this project we are recording data from patients with lesions in the frontal eye fields, the basal ganglia (Parkinsons' disease), the prefrontal cortex and cerebellum.

Co-PI: Dr. Behari (Dept. of Neurology, AIIMS)
Dr. Sarat Chandra (Dept. of Neurosurgery, AIIMS)

Funding: A grant from DST provides support for the project

Neuronal Processing in Normal and Impaired Brains.

Principal Investigator: V. Rema

Post Doctoral Fellow: Renuka Ramachandra

Research Fellows: Zia Ud Din

Deleterious influences on the brain due to injury, exposure to toxins, nutritional or sensory deprivations etc could cause neurological deficits in people of all ages. These adverse conditions could potentially alter neurotransmission and produce significant, long lasting behavioural and cognitive deficits. The degree of recovery of neurological functions, in most instances would depend on the type, severity and extent of deficits. Interventions using combination of pharmacological and rehabilitative therapy given at the right time could have positive outcome.

Designing optimal intervention requires in depth knowledge of the response of the brain to the adverse influence: what neural mechanisms are affected and what are the ongoing changes that occur during recovery? Observations from our earlier studies have shown that the mechanisms regulating the activity of neurons and the ability of the brain to learn and adapt to novel experiences are affected in animals with brain injury, prenatal alcohol exposure, sensory deprivation and ageing. These results suggest that activity-dependent synaptic mechanisms regulating excitation and inhibition might be most vulnerable to any type of insult to the brain. We are using neurophysiological and molecular techniques to identify the basic mechanisms of excitatory and inhibitory neurotransmission that are affected in impaired brains.

Our research is also directed at determining the behavioural consequences of such negative influences on the brain and whether a combination of social (complex/enriched environment) and pharmacological interventions and use of stem cells at the site of brain injury will accelerate functional recovery.

Current experiments in our laboratory are directed at addressing the following questions:

- 1) What are the changes in the molecules involved in excitatory and inhibitory neurotransmission after focal injuries to the somatosensory cortex (SI)?**
- 2) What is the effectiveness of social and pharmacological interventions to enhance and accelerate functional recovery? Can embryonic stem cells reduce functional deficits?**

At various recovery time points after SI lesions using immunohistochemical and DNA microarray techniques we are examining ongoing changes in the molecules involved in: (a) excitatory neurotransmission (b) inhibitory neurotransmission and (c) neuromodulation. Changes in the levels of plasticity-related molecules following unilateral aspiration lesions were assessed using immunohistochemical analysis at 1, 3

and 7 days post lesion. Levels of expression of excitatory amino acid receptors of both NMDA (NR1, NR2A, NR2B) and AMPA (GluR1, GluR2/3, GluR 4) subtypes were examined. We observed reduction in the expression of these molecules not only at penumbra of lesion but also in the homotopic contralateral hemisphere. Reduction in cholinergic cell bodies in the contralateral hemisphere was detected using VAcHT antibody. The inhibitory amino acid receptors GABA A(α 1) and GABA A(α 3) show reduced expression at the penumbra of the lesion but not in the contralateral hemisphere. These results give an insight about the molecules involved in the deficits seen in electrophysiological properties of neurons suggesting that cortical lesions have negative effect on both excitatory and inhibitory pathways.

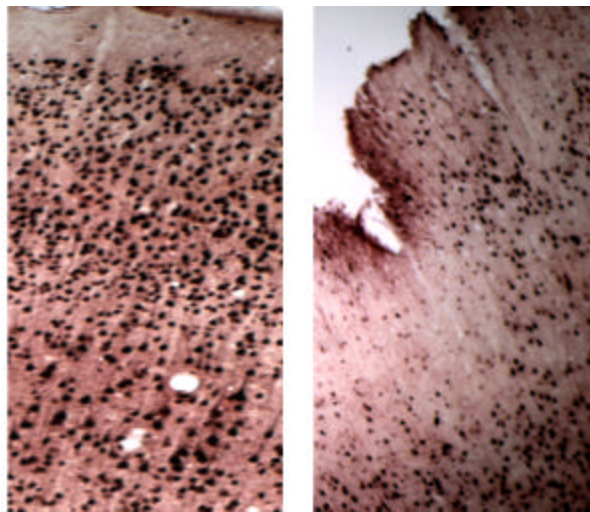


Fig: Excitatory neurotransmitter receptor GluR1 gets reduced around the cortical lesion site (on the right) which could be one of the causes for low activity in brain after an injury.

Our earlier experimental results show that there is partial recovery of neuronal responses in lesioned rats exposed to an enriched environment. Hence we think interventions that increase the levels of excitation in the brain might be most beneficial. We will determine whether increased social interaction in an enriched environment with a larger group of animals in combination with intraperitoneal administration of the neuroprotective drug cytidine-5'-diphosphate (CDP)-choline will further enhance functional recovery.

Though it is known that CDP-choline enhances memory related functions, the effectiveness of the drug on the neuronal morphology is unknown. Therefore before its use *in vivo* in animals with cortical injury we tested different concentration of CDP-choline on the neuronal and glial morphology. We saw an increase in the survival of neurons with increasing concentrations of CDP-choline. Further analysis of the changes in cellular morphology is underway.

Our initial experiments introducing embryonic stem cells into cortical lesions have been promising. Partially differentiated neuronal stem cell were applied into the lesion and we were able to detect incorporation and survival of these stem cells for 21 days at the site of the lesion and also migration of these cells into thalamus ipsilateral to the lesion site. Electrophysiological recordings will be done to determine if these stem cells show differentiation into neurons or glia and whether they have made functional connection with the surrounding neurons.

Collaborator: Dr Shyamala Mani (on the Stem Cell work)

Funding: Wellcome Trust International Senior Research Fellowship and NBRC Core Funds

Publications:

* **Rema V.**, & Ebner, F.F. Lesions of mature barrel field cortex interferes with sensory processing and plasticity in connected areas of the contralateral hemisphere. **Journal of Neuroscience** 23:10378-10387 (2003).

* **Rema V.**, Armstrong-James, M, & Ebner, F.F. Short exposure to an enriched environment accelerates plasticity in the barrel field (whisker) cortex of adult rats. **Neuroscience** (under revision)

* Work done elsewhere

Presentations:

Renuka. R, Zia Ud Din & **Rema V.** Molecular Changes in the brain following unilateral lesion of somatosensory cortex. NBRC International Conference –Building the Brain. Dec 2003.

“Effect of cortical injury on synaptic plasticity.” Invited Talk- International Senior Fellows Meeting 24th – 26th March 2004.

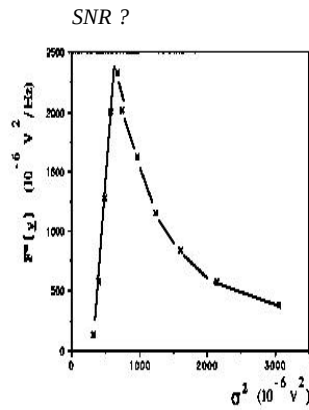
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Application of Stochastic Resonance and Stability Analysis for Brain Imaging and Therapy

Principal Investigator: Prasun K Roy.

A recent advancement in biophysics is the incisive phenomenon of the Stochastic Resonance Effect (SRE), whereby optimized perturbation or random-wave fluctuation is used to impressively enhance the behaviour or sensitivity of a system to an input parameter or signal. SRE occurs because the positive peak of the weak signal, under specific conditions, adds up with positive peaks of the noise, resulting in a considerable stronger signal or signal:noise ration (SNR) [fig 1].

SR has been used to enhance optical, electron-paramagnetic-resonance, microscopic and Raman images or spectra. Here we aim to apply the SRE paradigm for increasing the efficiency of neuroimaging, in MRI, fMRI and CT [fig 2]. We have devised a method to administer random-wave perturbation to obtain a multiple gain of the signal, at post-processing stage. Noise power is optimised for peak enhancement. We adapt the classical SR technique to increase signal: noise ratio. We undertook to use SR to enhance and differentiate MRI brain images of post-radiotherapy tumour recurrence vis-a-vis radiotherapy-induced necrosis which are often an ordeal to distinguish radiologically.



Noise →

Fig 1: SR. Peak in Signal:noise ratio

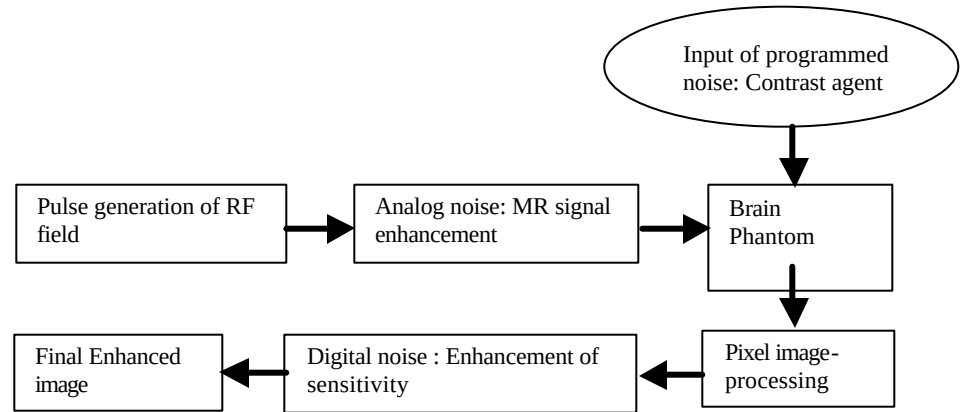


Fig 2: A route for Stochastic Resonance Imaging

Perturbation design: We have first investigated the mechanics of administering perturbation to the MRI/fMRI process. We probed the possibility of giving noise via the paramagnetic contrast medium, such as gadolinium, copper, iron (deoxyhemoglobin) etc. We have administered noise to the MR resonating process itself, by varying the amount of the paramagnetic contrast agent. The experiment has been done in a 1.5 Tesla Siemens Magnetom MRI scanner at INMAS, New Delhi. The image of the phantom (radiological

model) was obtained by the scout sequence. Spin echo sequence was used to measure T_1 - T_2 periods at TR = 300 ms and 2000 ms respectively, using dynamic analysis option. Localizer sequence was given, and then long external radiofrequency pulse of width 200 ms administered, with TR = 500 ms. A sum of 128 acquisitions were taken and frequency was adjusted (receiver gain = 64). The spectra and post-processed image was taken, and the amplitude observed. Amplitude was measured for the agent, the variation being given to the kinetic noise level, in terms of milimolar activity (mM) (fig 3a).

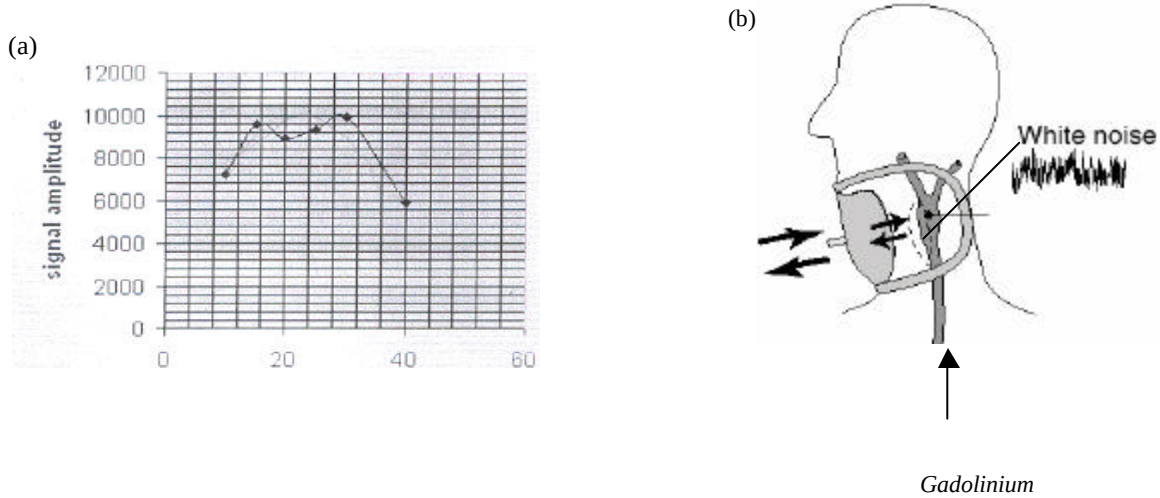


Fig. 3. (a) Stochastic Resonance enhancement of MRI signal using gadolinium contrast agent: Peak signal (y-axis) as kinetic perturbation intensity of gadolinium varies (x-axis). (b) Pneumatic neck chamber (thick arrows) to give stochastic perturbation to gadolinium contrast agent input.

Contrast agent enhancement: We discern that SR peak occurs at kinetic noise intensity induced by 24 mM of the paramagnetic agent; there is amplitude decrease on higher or lower noise intensity (i.e. paramagnetic agent concentration). This is characteristic of stochastic resonance (fig 1). At a certain level (optimal level), the noisy collision events of the paramagnetic contrast agent in water dominate the proton relaxation dynamics. This has a signature in the MR signal showing a peaking in the signal at an optimal level of the intensity of kinetic events from the paramagnetic agent (fig. 3a). We have also devised a method to administer random-wave perturbation to obtain a multiple gain of the signal of the gadolinium contrast agent. We adapt the classical SR technique to increase signal to noise ratio. Furthermore, we have also undertaken to use SR to enhance and differentiate MRI brain images in clinical conditions which are usually very difficult to distinguish radiologically. Since time-repetition of SR response improves performance, we are sampling the image in high speed computer at 50 Hz frame rate, giving perturbation in each frame record and displaying the time-averaged enhanced image.

Collaborators: Dr S. Khushu, Institute of Nuclear Medicine & Allied Sciences, Delhi.

Presentations:

P. Roy: Stochastic Activation as a new approach for biomedical intervention. Presentation at Center for Computational Neurodynamics, University of Memphis, June, 2003.

P. Roy: Use of non-equilibrium dynamics in brain research: Application of perturbation analysis, University of Delhi, December 2003.

P. Roy: New enhancement technology for medical informatics: Russian-Indian joint program on Biotechnology, Indian Institute of Information Technology, Allahabad, February 2004.

Non-Equilibrium Information Theory and Spatiotemporal Processing in Neurones: A Neurocomputational Approach

Principal Investigator: Prasun K. Roy.

Probably the most fundamental challenge in neuroscience is understanding the neural code, how the neural system encodes and communicates information. On the other hand, the basic code in bioscience has been known for over half a century, namely the genetic code comprising a template of different aminoacids. In contrast, the template of neural information transmission is the same, the spikes are all alike. Herein lies the fundamental feature of neuroscience.

It is now known that the same spike can transmit different types of information depending on inter-spike arrangement and its statistical distribution. We study this mechanism using communication theory and multiplexing operation where multiple entities of information can flow through the same medium (neuron) using the same symbol (spike), under real-life biological condition of environmental and biophysical noise. Using nonlinear dynamic approach, we focus on the constructive role of fluctuations or noise (stochastic transition and resonance) in information transmission at various neurobiological levels, from single neurons, to ensembles, to the full neurocognitive system. Our approach extends realistically the classical Shannon-Nyquist communication model, ‘the stochastic binary channel with noise’ [fig.1].

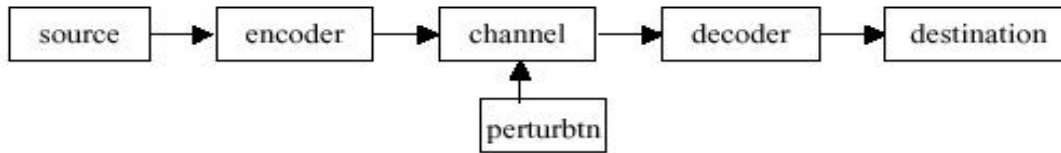


Fig. 1: Extending the stochastic binary channel model of information transmission with intrinsic noise(perturbation)

Multiplexing in neural coding: We have observed that information transmission occurs via two modes, namely the equilibrium mode (first-order mode) vis-a-vis the non-equilibrium mode (second-order mode) [fig. 2a]. We found that at an optimal level of fluctuations, there is a transition point, the “iso-dissipation point”, where first and second order modes equalizes. For such balanced or equimodal information transmission situation, there is an optimal level of system fluctuation, thus indicating a process of stochastic activation and resonance. As our work show, there are multiple modes (multiplexing) of information transmission through the channel, under more intensive or demanding conditions requiring high throughput of information or activation. Conventional communication models cannot analyze information transmission during conditions such as high intensity adaptation, plasticity, habituation, or in clinical conditions as epilepsy, migraine or tinnitus. The formalism presented here endeavours to open a path in this direction.

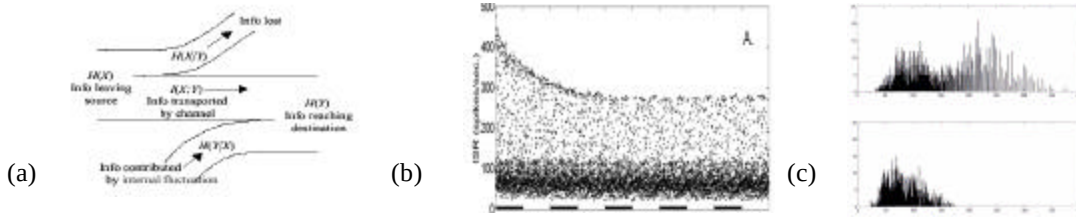


Fig. 2. (a): Extra information channel facilitated by stochastic activation or fluctuation (b) Multiplexed information transmission in neuron using two-channel (c) The relative intensity of the two channels.

From axonal to cortical information transmission: We have mathematically derived the fluctuation-dissipation formulation for information communication. We find that the high-intensity (non-equilibrium) and low-intensity (equilibrium) regimes of information transmission are characterized respectively by intrinsic and extrinsic information dissipation functions (fast-mode Y_1 function and slow-mode Y_2 function). We have applied the above theoretical formalism and have investigated some experimental data on two prototype information transmission channels studied in neuroscience, a micro-level and a meso-level and high-level level information systems, which are motivated by our initial studies on simple neural systems (fig 2b,c). These prototype systems are the axonal communication system and the cortical ensemble system. From experimental data, we have found that in both the systems [fig. 3], there are definitive quantitative correlates that characterize the first-order (extrinsic) and second order (intrinsic) information transmission modes, namely:

- In axonal information processing, the first and second order modes are respectively characterized by Na^+ -activated K^+ current and Ca^{++} -activated K^+ current,
- In the cortical neural ensemble system, the modes are parametrized electroencephalographically by the entropy dissipation of the driving hyperactivated zone and the driven hypoactivated zone respectively.

Practical applications are being explored, such as finding the concordance of the electrical source and sink of epileptogenic focus which would help in more efficient understanding and therapeutic planning of the disorder.

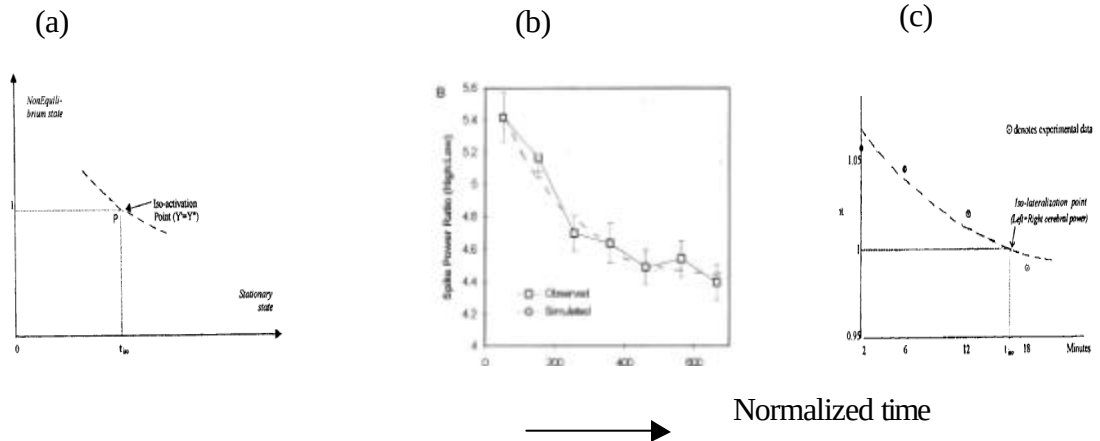


Fig. 3. (a). Mathematically derived curve predicting the iso-dissipation state as an information transmission

system approaches stationarity; at the iso-dissipation point, the linear and nonlinear components of information transmission equalizes. Confirmatory findings illustrating the iso-point is shown for experimental data: (b) from information transmission in neuron, (c) from information transmission in neural ensembles (activation zone) in cortex.

Collaboration: Prof. John Miller, Montana State University, Bozeman.

Publications:

P. Roy: Cognitive Processing: An Analysis using Stochastic Activation. **J. Institution of Electronics and Telecommunication Engineers**, 49(2), 183-195, 2003.

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P. Roy: Battu, B, Analyzing neuronal processing using non-equilibrium thermodynamics: Implications for Neuroengineering, In: N Singh (Ed), **Theoretical Neurobiology**, National Brain Research Centre, Gurgaon, 2003.

Presentations:

P. Roy: A Quantitative Approach to Second-Order Information Processing Systems: Non-equilibrium Information Theory with Experimental Neuronal Evidence, Computational Biology Colloquium, Montana State University, Bozeman, August 2003.

P. Roy: Stochastic Activation And Enhancement: Experimental application to Neuronal Information Processing and targeted signal transmission, Fifth Asian Neurobiology & NeuroInformatics Workshop, Korean Advanced Institute of Science and Technology, Daejeon, November 2003.

Computational Analysis of Speech in Normal and Autistic Children

Principal Investigator: Nandini Chatterjee Singh

Communication is accomplished via language in the form of sounds, gestures, signs, or marks. Speech is the spoken form of language and is an expression of ideas by the voice; sounds, expressive of thought, articulated by the vocal organs

Auditory processing is the ability of the brain to process incoming auditory signals. The brain identifies sounds by analyzing their distinguishing physical characteristics frequency, intensity, and temporal features. These are the features that we perceive as pitch, loudness, and duration. We know that the most basic unit of any language is the phoneme, the smallest unit of sound that differentiates meaning. It has been postulated that auditory processing plays a crucial role in the development of phonological systems.

There are many children who have no trouble detecting the presence of sound, but who have other types of auditory difficulties (e.g., difficulty learning new vocabulary words or languages) that can affect their ability to develop normal language skills, succeed academically, or communicate effectively. In the past, speech development has been well studied using behavioural methods for decades, yet this major childhood accomplishment is not well studied using acoustic analysis.

From a signal processing approach, human speech signals have a time varying frequency structure and thus require joint representations of time and frequency. In the current scenario, scientists “visualize” sound in terms of temporal and modulations of amplitude envelopes. In this framework sounds are characterized by broadband spectra with energy at many different frequencies and elaborate spectral and temporal structure. We use the modulation spectrum, which presents a representation where any sound can be broken into series of temporal and spectral modulations to study human speech particularly in children.

The primary objective behind this study is to gain insight into the nature of both speech development and disorders that disrupt speech in pediatric populations. Clinically, speech is one of the earliest markers for development or acquired pediatric neurological disorders. We believe that children with speech impairments may have a basic problem in perceiving speech sounds, which leads to difficulties acquiring speech early in development. Since the modulation spectrum is a representation of sounds in terms of temporal and spectral modulations, one would expect that a modulation spectrum of the speech sounds of children with speech impairments would reflect the modulations missing in their speech versus the speech of normal children.

Development of speech in normal children

In the same line of thought we have investigated the variability patterns of acoustic properties of speech as a function of normal development. We measured and

compared the joint spectral and temporal features by estimating modulation spectra of short English sentences as produced by 35 children aged 3 to 7 years. These modulation spectra were obtained by setting up the modulation spectra of the sound stimulus in its spectrographic representation (Figure 1). Various parameters were determined to quantitatively study the changes in these features and results revealed significant differences that might be related to learning that occur during development (Figure 2). The examination of such characteristics in children provides us with information on how these parameters of speech are acquired and mastered as a function of development and we can better understand their relation to the underlying anatomical and neuromuscular development.

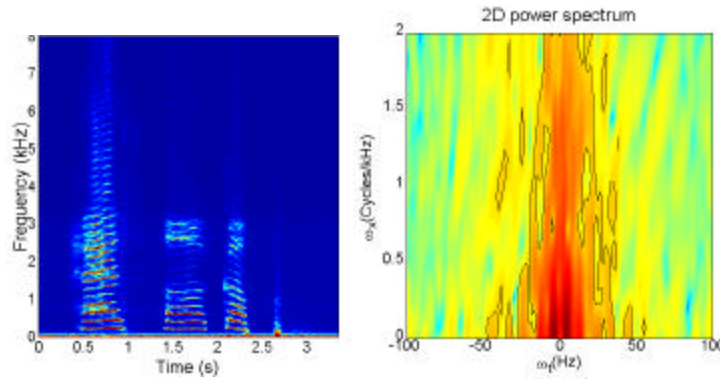


Figure (1) Spectrogram and modulation spectra of a four year boy saying “Has a Cup”

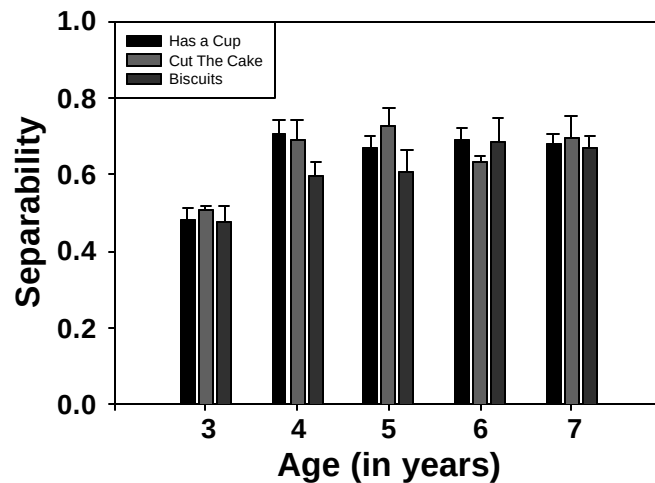


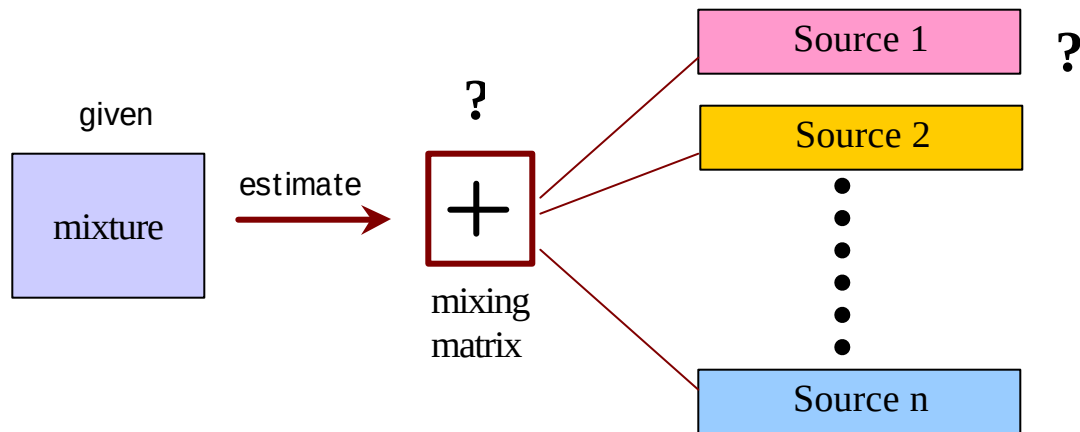
Figure (2) Variation in separability of modulation spectra with age.

These results are currently being tabulated and quantifiers have been set up to study various features of speech. This work will potentially provide insight into the speech generation mechanisms in normal children. We are also studying the speech of children who are autistic and will compare their speech with that of normal children

Recovery of Components from Mixed Signals Using ICA

Principal Investigator: Dr. Nandini Chatterjee Singh

Independent Component Analysis (ICA) is a statistical and computational technique for revealing hidden factors that underlie sets of random variables, measurements or signals. It is a linear transformation method of representing multivariate data, in which the desired representation is one that minimizes the statistical dependence of the components of representation. Such a representation seems to capture the essential structure of data in many application fields typical examples being simultaneous speech signals, brain waves recorded by multiple sensors, etc.



We investigated the applicability and efficiency of ICA as a model in blind source separation. Recently, blind source separation by ICA has received attention because of its potential signal processing applications such as speech enhancement systems, telecommunications and medical signal processing. Blind signal separation consists of recovering unobserved signals or sources from several observed mixtures. The adjective ‘blind’ stresses the fact that (i) the source signals are not observed and (ii) no information is available about the mixture.

We have been investigating the applicability and efficiency of ICA as a model in blind source separation by mixing various periodic signals of known frequencies and amplitudes, randomly and applying ICA to recover them. It was seen that signals having frequencies within close interval of each other ($f, f+\epsilon$), were not recovered successfully whereas those having different frequencies showed good retrieval. The possible reason for this difference is the extent of statistical independence of mixing signals. To quantify this independence we have been trying to set up new quantifiers to calculate the statistical independence of the mixtures and act as indicators for the successful application of ICA.

PUBLICATIONS

PUBLICATIONS

U. Nagaoka, K. Kim, **N. R. Jana**, H. Doi, K. Mitsui, F. Oyama and N. Nukina: Increased expression of p62 in expanded polyglutamine-expressing cells and its association with polyglutamine inclusions. **Journal of Neurochemistry**, 2004. (In Press) *.

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N. R. Jana and N. Nukina: Assessment of impaired proteasomal function in a cellular model of polyglutamine diseases. In **Methods in Molecular Biology: Trineucleotide repeat protocols** (Y. Kohwi ed), Humana Press, vol. 277, pp 271-276, 2004.

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N. R. Jana, P. Dikshit, A. Goswami and N. Nukina: Inhibition of proteasomal function by curcumin induces apoptosis through mitochondrial pathway. **Journal of Biological Chemistry**, 279, 11690-11695, 2004.

B. Bagchi, M. Kumar and **S. Mani**: The CMV immediate early promoter is regulated by cell-cell interaction and retinoic acid during differentiation of embryonic stem cells. **Stem Cells** (submitted)

H.V. Pai, R.P. Kommaddi, S.J. Chinta, T. Mori, M.R. Boyd and **V. Ravindranath**: A frame shift mutation and alternate splicing generates a functional isoform of the pseudogene, cytochrome P4502D7 in human brain that demethylates codeine to morphine. **J. Biol. Chem.** 279: 27383-27389, 2004.

H.V. Pai and **V. Ravindranath**: Dexamethasone induces total P450 levels but not P4503A in brain. **Neurochemistry International**. (Submitted).

S.J. Chinta, H.V. Pai and **V. Ravindranath**: Presence of splice variant forms of cytochrome P4502D1 in rat brain but not in liver. **Molecular Brain Research** (Submitted).

S. J. Chinta, R. P. Kommaddi, H. V. Pai, C. M. Turman, H. W. Strobel and **V. Ravindranath**: Constitutive expression and localization of CYP1A1 in rat and human brain: Presence of a splice variant form in human brain. **J. Neurochem** (Submitted).

R.S. Kenchappa, L. Diwakar, J. Annepu and **V. Ravindranath**: Estrogen and Neuroprotection: Higher constitutive expression of glutaredoxin in female mice offers protection against MPTP mediated neurodegeneration. *FASEB J.* 18 1102-1104, 2004.

R.S. Kenchappa, L. Diwakar, J. Annepu and **V. Ravindranath**: Estrogen receptor antagonist down regulates glutaredoxin and renders female mice susceptible to excitatory amino acid mediated complex I inhibition in the CNS. *J. Neurochem.*: (submitted).

Q.L. Wang, S. Chen, N. Esumi, **P.K. Swain**, H.S. Haines, G. Peng, B.M. Melia, I. McIntosh, J.R. Heckenlively, S.G. Jacobson, E.M. Stone, A. Swaroop, D.J. Zack.: QRX, a Novel Homeobox Gene, Modulates Photoreceptor Gene Expression. **Hum Mol Genet.** 13 (10): 1025-1040, 2004 *.

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M. Remple, **N. Jain**, Pamela S. Diener and J.H Kaas. Bilateral effects of spinal overhemisections on the development of the somatosensory system in rats. **J. Comparative Neurology**. 475:604-619, 2004*.

N. Jain, S. Pamela, Diener, J.O. Coq and J. H Kaas.: Patterned activity via dorsal quadrant inputs is necessary for the formation of organized somatosensory maps. **Journal of Neuroscience**. 23:10321-10330, 2003*.

S. Ray, J.D. Schall and **A. Murthy**: Parallel programming of double step saccade sequences: modulation by cognitive control. **Vision Research** 44: 2707-2718, 2004.

A. Murthy, S. Ray, S.M. Shorter-Jacobi, K.G. Thompson, and J. D. Schall: Predictive error correction by frontal eye field. (submitted to **Nat. Neuroscience**)

R. Velayudhan, & F.F. Ebner: Lesions of mature barrel field cortex interferes with sensory processing and plasticity in connected areas of the contralateral hemisphere. **Journal of Neuroscience** 23:10378-10387, 2003 *.

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P. Roy: Cognitive Processing: An Analysis using Stochastic Activation. **J. Institution of Electronics and Telecommunication Engineers**, 49(2), 183-195, 2003.

P. Roy: Experimental Evidence for a critical phase transition in neural systems: Stochastic systems analysis. In: M Kalit (Ed), Recent Advances in Systems Science, **Allied Publishers**, 2004 (Accepted).

P. Roy, B. Battu: Analyzing neuronal processing using non-equilibrium thermodynamics – Implications for Neuroengineering, In: N. Singh (Ed), **Theoretical Neurobiology**, National Brain Research Centre, Gurgaon, 2003

P. Seth, F. Diaz and E.O. Major: JC virus induces a non-apoptotic cell death of human CNS progenitor cell derived astrocytes. **J. of Virology** (In Press). *

D.M.P. Lawrence, L.C. Durham, L. Schwartz, **P. Seth**, D. Maric and E.O. Major: HIV-1 infection of human brain derived progenitor cells. **J. of Virology** (In Press). *

* Work done elsewhere

Distinctions, Honors and Awards

Distinctions, Honors and Awards

V. Ravindranath: National Representative for the Toxicology Commission of International Union of Pure and Applied Chemistry (IUPAC).

V. Ravindranath: Member, Working Group on Neuroinformatics of Global Science Forum.

V. Ravindranath: Member, Editorial Board, Indian Journal of Biochemistry and Biophysics.

V. Ravindranath: Member, Governing Council of International Brain Research Organization (IBRO).

V. Ravindranath: Member, Council of Federation of Asian and Oceanian Neuroscience Societies.

V. Ravindranath: Secretary, Federation of Asian and Oceanian Neuroscience Societies.

V. Ravindranath: Member, Council, National Academy of Sciences, India.

V. Ravindranath: Member, “Medical Sciences Research Committee” of CSIR for the period 2004 – 2007.

V. Ravindranath: Member, “Programme Advisory Committee” on Health Sciences under Department of Science and Technology.

V. Ravindranath: Member, “Task Force on Medical Biotechnology, Immunodiagnostics and Vaccines” of the Department of Biotechnology.

V. Ravindranath: Chairman, Building Committee, Institute of Life Sciences, Bhubaneswar.

V. Ravindranath: Member, Research Advisory Committee, EMR, CSIR

V. Ravindranath: Member, Editorial Board of the International Journal, “Neurotoxicity Research”, USA.

V. Ravindranath: Member, Editorial Board, Anti-oxidants and Redox Signaling.

V. Ravindranath: Member, Editorial Board, Indian Journal of Biochemistry and Biophysics.

V. Ravindranath: Member, Editorial Board, Current Science.

P.K. Roy: Travel fellowship award from DST for participating at the 5th Asian Neurobiology and NeuroInformatics Workshop, at KAIST, Daejeon, Korea.

P.K. Roy: External Member of Dissertation Examination Committee, Indian Institute of Information Technology, Allahabad.

P.K. Roy: Reviewer, IEEE Transactions on Nuclear Science, Institute of Electrical and Electronics Engineers, New York.

Presentations

PRESENTATIONS BY NBRC SCIENTISTS

U. Nagaoka, K. Kim, **N. R. Jana**, H. Doi, K. Mitsui, F. Oyama and N. Nukina: Identification of p62 as an increased protein in expanded polyglutamine expressing cells. Society for Neuroscience meeting, 2003.

A. Goswami, P. Dikshit and **N. R. Jana**: Alteration of cellular redox state and unfolded protein response promotes mutant huntingtin aggregation and mutant huntingtin-dependent cell death. Indo-US workshop on genomics. Bangalore, 2003.

N. R. Jana, P. Dikshit, A. Goswami and D. Narender: Possible involvement of CHIP in the misfolding-dependent ubiquitination of polyglutamine-expanded ataxin-3, the defective gene product in SCA3/MJD. NBRC International symposium, 2003.

P. Dikshit, A. Goswami and **N. R. Jana**: Curcumin promotes mutant huntingtin aggregation and mutant huntingtin-dependent cell death. NBRC International symposium, 2003.

A. Goswami, P. Dikshit, D. Narender and **N. R. Jana**: Increase in mutant huntingtin aggregation and mutant huntingtin-dependent cell death by unfolded protein response and alteration of cellular redox state. NBRC International symposium, 2003.

R. Mishra, E. Donohoe, K.F. Meiri and **S. Mani**: Role of GAP-43 in differentiation of cerebellar granule cells. Society for Neuroscience, New Orleans, November 2003.

S. Mani: New neurons for old: Functional significance of adult neurogenesis. TRENDYS series of scientific talks, CDFD, Hyderabad, November 2003.

V. Ravindranath: "Understanding analgesic action of codeine: a unique human brain specific cytochrome p450d metabolizes codeine predominantly to morphine" – Invited Talk Presented At The Symposium Of Advances In Cellular And Molecular Pharmacology On December, 2003

H. V. Pai, R. P. Kommaddi and **V. Ravindranath**: "A functionally active splice variant of cytochrome P450D7 pseudogene metabolizes codeine principally to morphine" – Abstract Presented At The International Symposium Held At NBRC On December, 2003

R.P. Kommaddi , S. J. Chinta, V.K. Prasanna and **V. Ravindranath**: Constitutive expression and localisation Of CYP1A1 in human brain: Identification of a unique brain splice variant" –Abstract Presented At The International Symposium held At NBRC in December, 2003

V. Ravindranath: “Drug metabolism in brain by unique isoforms of cytochroms P450 generated by alternate splicing” – Invited Talk Presented At The National Symposium On Cellular And Molecular Biophysics, NIMHANS At Bangalore On January, 2004.

H.V. Pai, R. P. Kommaddi and **V. Ravindranath:** “Understanding analgesic action of codeine: a unique human brain specific cytochrome CYP2D metabolizes codeine exclusively to morphine” – Presented At The Indo-US Workshop On Research & Development In Genomics Held On September, 2003 At Bangalore.

H.V. Pai, S.J. Chinta, R. P. Kommaddi and **V. Ravindranath:** Codeine addiction: a unique human brain specific cytochrome p450 metabolizes codeine exclusively to morphine. Presented At The Annual Meeting Of Society Of Neuroscience, USA – November 2003.

V. Ravindranath: Protein thiols, mitochondrial dysfunction and neurodegeneration” – Invited talk presented at the meeting of FAOBMB in December 2003.

L. Diwakar, S. Karunakaran, R. Kenchappa and **V. Ravindranath:** “Estrogen mediated protection against excitotoxicity : higher constitutive expression of glutaredoxin in female mice offers protection against excitatory amino acid mediated mitochondrial dysfunction” –Abstract presented at the International Symposium held at NBRC in December, 2003

R.S. Kenchappa, N. Kasyapa, L. Diwakar, V.K. Prasanna and **V. Ravindranath:** Microarray based gene expression profiles of motor neurons during recovery from excitotoxic insult – Presented at the International Symposium held at NBRC on December, 2003

S. Sampath and **V. Ravindranath:** Polymorphism studies of glutaredoxin (grx1), a thiol disulphide oxidoreductase involved in maintenance of mitochondrial complex I – Presented at the Indo-US workshop on Research & Development in Genomics held on September, 2003 at Bangalore.

L. Diwakar, S. Karunakaran and **V. Ravindranath:** “Molecular mechanisms underlying the neuroprotective effect of estrogen thiol” –Presented at the Indo-US workshop on Research & Development in Genomics held on September, 2003 at Bangalore.

R.S. Kenchappa, N. Kasyapa, L. Diwakar and **V. Ravindranath:** “Microarray based gene expression profiles of motor neurons during recovery from excitotoxic insult” – Abstract presented at the Indo-US workshop on Research & Development in Genomics held on September, 2003 at Bangalore.

R.S. Kenchappa, N. Kasyapa, L. Diwakar and **V. Ravindranath:** Global gene expression analysis using microarray to study differential vulnerability of CNS regions to excitotoxicity” –Presented at Asia Pacific Society for Neuroscience meeting at Hong Kong on February, 2004.

P. Swain: Invited to speak on the Microarray Tecnology and its Application at Defence Institute Physics and Allied Sciences, Delhi on 28th November 2003.

N. Jain: Department of Molecular Reproduction, Development and Genetics, Indian Institute of Science, Bangalore. March 24, 2004.

N. Jain: Centre for Cellular and Molecular Biology, Hyderabad. March 23, 2004.

A. Murthy. Computational Vision. Lecture for Computational Neuroscience workshop, given at IIT Kanpur, 2003.

A. Murthy. Neural control of Action. Conference on Building the Brain held at NBRC, Manesar, India, 2003.

R. Ramachandra, Zia Ud Din & R. Velayudhan: Molecular Changes in the brain following unilateral lesion of somatosensory cortex. NBRC International Conference – Building the Brain. Dec 2003

R. Velayudhan. “Effect of cortical injury on synaptic plasticity.” Invited Talk-International Senior Fellows Meeting 24th – 26th March 2004

R. Velayudhan. “Cortical plasticity in response to novel experiences and injury”. Invited Talk – Centre for Cellular and Molecular Biology 23rd March 2000

P. Roy. Stochastic Activation as a new approach for biomedical intervention. Presentation at Center for Computational Neurodynamics, University of Memphis, June, 2003.

P. Roy. Use of non-equilibrium dynamics in brain research: Application of Perturbation analysis, University of Delhi, December 2003.

P. Roy. New enhancement technology for Medical Informatics, Russian-Indian joint program on Biotechnology, Indian Institute of Information Technology, Allahabad, February 2004.

P. Roy. A Quantitative Approach to Second-Order Information Processing Systems: Non-equilibrium Information Theory with Experimental Neuronal Evidence, Computational Biology Colloquium, Montana State University, August 2003.

P. Roy. Stochastic Activation And Enhancement: Experimental application to Neuronal Information Processing and targeted signal transmission, Fifth Asian Neurobiology & NeuroInformatics Workshop, Korean Advanced Institute of Science and Technology, Daejeon, November 2003.

P. Seth and E.O. Major: Cell culture model for studying virus induced neurodegeneration. Invited talk at United States Army Center for Health Promotion and Preventive Medicine, Aberdeen Proving Ground, Edgewood, USA, Jan 2004.

P. Seth, F. Diaz, J. Hou and D. Lawrence and E.O. Major: Molecular Mechanisms to Understanding Virus Induced Neurodegeneration. Invited Speaker at International Symposium on Molecular Toxicology and Environmental Health, Lucknow, India, Nov 5-8, 2003

INVITED PRESENTATIONS BY SCIENTISTS VISITING NBRC

Dr. A. Basole: "Mapping multiple features in the population response of visual cortex." **July 8, 2003.**

Dr. Tariq Allana: University of California, Davis. "Ca²⁺ Channel: Synaptic Vesicle organization at the Crayfish Neuromuscular Junction." **July 21, 2003**

Dr. Shanti Raman: "AUTISM." **July 24, 2003.**

Dr. Shobini Rao: "Cognitive Neuroscience." **July 24, 2003.**

Dr. Amal Bera: Department of Physiology and Biophysics, Albert Einstein College of Medicine, New York, USA. "Determination of the role of GABA receptor M2-M3 loop in channel structure and function." **September 19, 2003.**

Dr. Ashutosh Tiwari: University of Massachusetts Medical Centre. "Mutant SOD1 instability: A cause of ALS?" **November 21, 2003.**

Prof. Yoshikuni Mizuno: Juntendo University, Tokoyo, Japan. **December 3, 2003.**

Dr. Mriganka Sur: MIT. **Dec 12, 2003.**

Dr. Bedu Chakrabarthi: University of Pennsylvania. **January 7, 2004.**

Dr. Christof Koch: California Institute of Technology. **January 16, 2004.**

Dr. Thiagarajan Sambandam: Department of Neurology, University of Alabama. "Post Translational Modification and Inflammation in Neurodegenerative diseases." **February 3, 2004.**

Prof. Micaela Morelli: University of Cagliari, Department of Toxicology, Italy. "From L-Dopa to novel dopaminergic and non-dopaminergic therapy in Parkinson's disease." **February 6 2004.**

Dr. Anita Talwar: Dr. B.R. Ambedkar Centre for Biomedical Research, University of Delhi. “Ambulatory Physiological Monitoring in Animal Models: Implications on Antiepileptic Drug Research.” **February 10, 2004.**

Prof. Nancy Rothwell: Division of Neuroscience, University of Manchester. “New Mechanisms of Brain damage: role of inflammation and cytokines.” **February 17, 2004.**

Dr. Karina Meiri: Department of Anatomy and Cell Biology, Tufts University. **February 24, 2004.**

Prof. Klaus Obermayer: Department of Electrical Engineering and Computer Science, Department Head of the Neural Information Processing (NI) group, Technical University of Berlin, Germany. “Models of Adaptation in the Primary Visual Cortex.” **February 26, 2004.**

Dr. Bindu: NIMHANS. “Role of Subiculum on cognitive processing of spatial information.” **March 17, 2004.**

LIST OF RESEARCH PROJECTS FUNDED BY EXTERNAL AGENCIES

Dr. Nihar Ranjan Jana

Molecular Mechanism of the Pathogenesis of the CAG Repeats in Neurodegenerative Diseases (DBT)

Molecular Mechanism of the pathogenesis of polyglutamine diseases (Riken Brain Research Centre, Japan)

Please list the DBT and RIKEn grants separately with different titles.

Dr. Shyamala Mani

Development Neurobiology & Regulation of Neurogenesis in the Cerebellum (FIRCA, NIH, USA).

To investigate the Mechanisms by which Neural Stem Cells Differentiate into Distinct Neuronal Subtypes (DBT)

Prof. Vijayalakshmi Ravindranath

Psychoactive Drug Metabolism by Brain Cytochrome P-450 (National Institute of Health- RO1).

Mitochondrial Dysfunction and Protein Thiol Homeostasis in Neurodegenerative Diseases (US-India fund for Cultural, Educational and Scientific Co-operation).

Genomic micro-array R&D programmes on infectious diseases and neurological disorders (DBT).

Evaluation of the Molecular basis of the Pharmacological action of Traditional Medicinal Preparations used in the Treatment of Mental Illnesses including Dementia (DBT).

Dr. Neeraj Jain

Brain Reorganization following Spinal Cord injuries (Wellcome Trust, UK).

Dr. Aditya Murthy

Dynamic Control of Saccade Target Selection (TWAS).

Control of visually guided eye movement in humans (DST).

Dr. Rema Velayudhan

Injury induced Changes in Neurophysiological, Molecular and Behavioural Functions following Focal Lesions to the Brain (Wellcome Trust, UK).

Abbreviation

DBT: Department of Biotechnology, Government of India .

DST: Department of Science & Technology, Government of India.

FIRCA: Fogarty International Research Collaboration Award, NIH, USA

TWAS: Third World Academy of Science, Italy.

Academic Courses

(A Picture of a Ph.D classroom with students)

Academic Courses

Ph.D Neuroscience

Based on the recommendations of the University Grants Commission (UGC), NBRC was accorded the status of Deemed University by the Ministry of Human Resource Development in the year 2002. One of its mandates is to develop trained human resources with capability to carry out inter-disciplinary research and create a vibrant neuroscience community in India. NBRC recruits students every year from diverse backgrounds for its Ph.D. programme including M.Sc. from any branch related to neurosciences, M.B.B.S., B.E. or B. Tech., as understanding brain function requires fusion of knowledge from multiple disciplines. The admission to the neuroscience Ph.D programme is through a widely publicized advertisement on the website and in national dailies and a rigorous admission process to ensure that only serious and deserving candidates are selected. The goal is to train Ph.D. students with an understanding of different aspects of neuroscience integrating information across traditional disciplinary boundaries. The Ph.D. programme at NBRC has two components –course work including lab rotation, and research work.

NBRC faculty members teach most of the courses. Wherever required, faculty from other institutions with expertise in specific areas are invited to give lectures as part of the course work. The course work is spread over two semesters covering major disciplines of Neuroscience, such as Neuroanatomy, Neurophysiology, Neurochemistry, Molecular Neurobiology, Development & Regeneration, Neurogenetics, systems & Cognitive Neuroscience, Systems & Clinical Neuroscience and Computational Neuroscience. Assignments and seminars constitute an integral part of the course work. Students are required to participate in the Journal club where recent important new findings pertaining to neuroscience research are presented and discussed to keep them abreast with the continuously advancing field of neuroscience. The rotation of students at the lab is for a minimum of two stints of three months each.

Currently 19 students are enrolled for Ph.D programme.

DISTRIBUTED INFORMATION CENTRE

(A Picture of DIC staff with computers)

DISTRIBUTED INFORMATION CENTRE

The Distributed Information Centre (DIC) plays a key role in providing computing facilities and support to NBRC.

The Infrastructure

To keep up with the advances in the field and the growing needs of NBRC, DIC has set up a state of art high speed computing facilities in the form of a SUN Enterprise 420R server with four processors, connected to fast T300 storage arrays that run the web server on a Solaris 8 operating system. The T300 storage array is used as a repository for neural data and high-resolution graphics. The IBM server, which provides file service, runs the Windows 2000 Server operating system and acts as the Primary Domain controller. All the users are connected to this server through the local area network. DIC comprises of balanced personnel to deliver greater output. There are 5 computer operators assisting in solving technical problems in addition to helping the scientists and three system managers handling the servers. All the technical associates and non-technical members of NBRC have been provided with powerful PCs running Windows 2000 Professional/XP. All the servers and PCs are hooked on to the network to access and share resources.

DIC Activities

Virtual Private Network – BioGrid, India

DIC of NBRC manages the private network called Virtual Private Network (VPN) on behalf of Department of Bio-Technology (DBT). This is aimed at integrating scientific research among Indian research institutes, and connects 11 DBT locations through which scientific information and data is shared. This year IIT, Delhi has been hooked up in to DBT BioGrid as the 12th Location. The VPN uses 4Mbps-shared bandwidth for internet and 1 Mbps internet bandwidth among any two locations, which can be utilized by various professionals viz, scientists and students belonging to the 12 locations connected across India. The objective of the VPN is to enhance research facility in India among these 12 locations. In due course the VPN facility will be extended to several other research institutes.

At the Centre, DIC has expanded its internal network by adding several computers, servers to keep in mind the needs of increased strength of students and research fellows. FTP server has been established to transfer bulk data from NBRC to another location or vice versa. DNS server has been set up in house in view of the increased IT demands of NBRC. The NBRC official web site was redesigned at DIC and the web address is www.nbrc.ac.in. NBRC has been able to integrate all of its administrative tasks seamlessly to become paperless and digital, wherever possible. This has been primarily possible because of the efforts of DIC. Various application forms are now available online and information queries can also be posted online.

DIC staff also assist to carry out post data analysis of Micro Array and DNA sequencer by using various scientific software like Spot fire, Array vision, Image Quant, Phred phrap, Consed, Sequence Analyzer,

New Initiatives at DIC

DIC is working towards developing specialized manpower; particularly for the micro-array analysis and sequencer analysis to further enhance our capabilities. At DIC, we are striving to develop new computational techniques for faster and efficient data management and analysis that are obtained from our rigorous research programmes. We believe that these efforts would be beneficial to the neuroscience community at both national and international levels.

NBRC is making efforts to set up a Video conferencing facility at the institute to provide lectures to various university students across the country in the field of Neuro science & Neuro informatics.



Library

(Picture with students Referring to Journals)

Digital Library

The NBRC library is fast becoming one of the leading digital libraries in the country. It is acquiring documents, books, e-books and e-journals along with CD ROMs in different areas of research field enriching the collection at its circulation desk. All bibliographic details of books, journals and information databases are accessible through the campus-wide network that facilitates easy access to journals and reduces the manpower requirement to a large extent. The library subscribes to over 560 scientific national and international journals, most of them on-line. It has established contacts with over 15 national and international organizations for exchange of the papers / articles and has established inter-library loan arrangement.

The library of the Institute aims to be a leading digital library in the fields of scientific research areas such as- Neuroscience, Theoretical Neuroscience, System Neuroscience, Molecular and Cellular Neuroscience, Biochemistry, Genetics, Molecular Biology, Immunology & Microbiology, Pharmacology, Toxicology, Psychology, etc. It also aims to provide excellent services to researchers / scientists of NBRC and its Network Centres in related areas.



NBRC library caters adequately to the institute's research and teaching activities. It is also open to other academic users for reference. The NBRC Library has developed a Digital website for NBRC Library including important informatics links.

The links are as follows:

1. Journals List services (JLS)

It provides the list of all journals subscribed by “National Brain Research Centre”. Users can request for articles from the above list of NBRC subscribed Journals and NBRC staff would download the articles as PDF files and send the same to them by e-mail.

2. Free links to Electronic Atlases

This link provides access to 10 free atlases, such as Human Atlases, Mouse Atlases, Monkey Atlases, Tissue Atlases, Structures, Images/ Pictures of Brains and Animations.

3. Free links to Electronic Journals

This link provides access to 109 free electronic journals of different subject areas of Life sciences, Medical Science, Neuroscience, Physics, Mathematics, Psychology and other science areas.

4. Free links to Electronic Books

This link accesses various subject areas i.e. Mathematics, Chemistry, Biology, Genetics, Developmental Biology, Biochemistry, Physics, Computer, Medicine, Physiology, Molecular Biology, Ecology, English and General Subjects.

5. Free links to Electronic Encyclopedia

The Electronic Encyclopedia link is available for broad information about Human Brain and Science Subjects.

6. Free links to “How Stuff Works”

This link will access information in the area of science, electronics, and general topics that mostly answer all questions related to our daily life and all this by a mere click of the mouse.

The Library has developed an Electronic Digital Delivery Services (EDDS), which provides requested articles to all networked centers in India. NBRC library is receiving a very good response from EDDS Services.

The EDDS Provides selected full text articles as required by Scientists / Researchers / Doctors and Research Students of all over India. This electronic mode provides free of cost references, papers, full text articles, copies of reprints of relevant literature to all users. They can also send their requirements of article through ONLINE Submission or through email to library@nbrc.ac.in. An online request form is available on the NBRC Library website.

Who can use the EDDS Services?

The EDDS system is available for all Scientists, Researchers, Doctors and Students all over the country. Requests however are not entertained on phone or letter formats, as there are sometimes difficulties due to incomplete information regarding the request. NBRC has designed an online request form for the same, which is available on the NBRC website. NBRC Library reserves the right to limit the processing of requests during busy times to three requests per requester per day. Usually, as many requests as possible are accommodated and the documents are sent promptly.

Submission & Pickup of Requests

Use of the online request form to submit orders are strongly encouraged. Requests may also be submitted through email to library@nbrc.ac.in in the standard format with full details. Requested articles ordered via these services are attended to within 2-3 working days. An email address must be entered in the appropriate box on the online form. Library delivers only those articles that are available at NBRC Library and is unable to provide those articles, which are not available in the Library.

Cost of Services

The library services are totally free of cost.

NBRC Library has a proposal of an Institutional Depository Scheme i.e. NBRC library will link all NBRC publications with full text for world-wide users through E-print or D-space free software. This service will enable the NBRC community to archive their pre-prints, post-prints and other scholarly publications. NBRC expects this service to facilitate the Institute researchers in self-archiving of their scholarly publications, provide easy access to these publications world-wide and improve impact of their research. While access is provided freely worldwide submission of documents to this archive is limited to the NBRC research community.

NBRC will also link the full text with individual scientist published paper under publications section, which will be updated on a monthly basis or whenever a new publication appears.

The NBRC library has received average 450 requests per year for articles from our networked centers. These articles are downloaded and sent to the requestors in PDF format using e-resources.

NATIONAL FACILITIES

(Pictures of DNA micro array and Sequencing facility)

NATIONAL FACILITIES

DNA MICRO ARRAY FACILITY

Genomic micro-array R&D programs on infectious diseases and neurological disorders.

Progress Report

At National Brain Research Centre we have set-up a core micro-array program specially to cater to the needs of the neuroscience research community in India. This facility is available to scientists who are interested in using this technique to ask neuroscience related questions through the institute and collaborating research centers within and outside our network.



The micro-array facility was commissioned in September 2002 at the NBRC interim facility at Gurgaon. The facility is currently in use by NBRC research laboratories and several other investigators from different parts of the country for their research projects.

The procurement of equipments and recruitment of staff was completed within the specified time frame to run the facility. The major equipment purchased in the facility includes a Typhoon 9210, which is a versatile micro-array scanner, and an automated hybridization station.. The Icyler is used for real time quantitative PCR applications, which is essential to validate the microarray data. To expedite the standardization of labeling procedures and scanning operations preprinted micro-array slides were purchased from Micro-array Centre, Toronto, Canada through a material transfer agreement (MTA). Four NBRC scientists have been enrolled in the agreement to obtain

slides at regular intervals depending on the experimental demands. Initial standardization was performed with the low-density human slides containing 1.7K ESTs. Subsequent experimental conditions were also optimized to use both human 19K (19000 human ESTs) and mouse 15k ESTs (15000 mouse ESTs) pre-arrayed glass slides of Micro-array Center. We have been using post-labeling strategies to incorporate cy-fluorescent dyes into the cDNA. Total RNA isolated from different research samples (human or mouse tissue, cell lines) have been used as the starting material. Both the labeling and hybridization conditions have been optimized to give excellent quality of arrays for scanning.

We are encouraged with the response to our invitation to various investigators and their research teams for using the micro-array technology and its applications as a national facility.

DNA SEQUENCING FACILITY

The National Brain Research Centre has established a centralized DNA sequencing facility to strengthen the infrastructure for use by cellular and molecular neurobiologists at NBRC as well as by several investigators in the neuroscience community in the country. Currently, NBRC has MegaBACE™ 1000 DNA Analysis system, a high-throughput, fluorescence based DNA sequencing system utilizing capillary electrophoresis with up to 96 capillaries operating in parallel. The fully automatic system performs sample injection, gel matrix replacement, DNA separation, detection and data analysis. This system has the ability to sequence 96 samples in just two hours and perform up to 9 runs per day. Average read length with dye primer chemistry is 550bp. This system can also be used for genotyping and SNP analysis.



EXTRA MURAL ACTIVITIES

EXTRA MURAL ACTIVITIES

Network Activities

NBRC has been working towards better interaction, resource sharing and capacity building among the neuroscience community of the country to promote multidisciplinary research. To facilitate this NBRC has established a network with existing neuroscience centers in India to prevent redundant duplication of work and facilities that already exist. The number of networked centres and interaction between them has been steadily increasing over a period of time. It has worked out to be a successful model that has enabled sharing of expertise and available infrastructure in a mutually beneficial way. This network helps to bring together researchers from varying backgrounds to pursue common research objectives that may be beyond the capacity of an individual investigator, group or institution. Major achievements in neuroscience are achieved through a multidisciplinary approach; this brings together scientists from various disciplines into the main stream of neuroscience and brain research activity. It has successfully fulfilled the objective of establishing network centres with NBRC.

We currently have the following institutions and universities as member of our network activities that collectively assist in promoting neuroscience research across the country.

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 Cellular & Molecular Biology (CCMB), Hyderabad
5. Central Drug Research Institute (CDRI), Lucknow
6. Centre for DNA Fingerprinting and Diagnostic, Hyderabad
7. Central Food and Technological Research Institute (CFTRI), Mysore
8. Cochin University of Science and Technology, Cochin
9. Department of Biotechnology
10. Delhi University, South Campus, Delhi
11. Dr. A. L. Neurosurgical Centre, Chennai
12. Indo American Hospital Brain and Spine Center, Kerala
13. Institute of Cybernetics, Systems and Information Technology, Kolkata
14. International Centre for Genetic Engineering and Biotechnology (ICGEB), New Delhi
15. Institute of Genomics and Integrative Biology (IGIB), Delhi
16. Institute of Human Behaviours & Allied Sciences (IHBAS), Delhi
17. Indian Institute of Information Technology (IIIT), Allahabad
18. Indian Institute of Technology (IIT), Mumbai
19. Indian Institute of Technology (IIT), Delhi
20. Indian Institute of Technology (IIT), Kanpur
21. Indian Institute of Science (IIS), Bangalore
22. Indian Institute of Chemical Biology (IICB), Kolkata
23. Institute of Nuclear Medicine and Allied Sciences (INMAS), New Delhi

24. Industrial Toxicology Research Centre (ITRC), Lucknow
25. Indian Statistical Institute, Kolkatta
26. International School of Photomics, Cochin
27. Jawaharlal Nehru University (JNU), New Delhi
28. Jawaharlal Nehru Centre for Advance Scientific Research (JNCASR), Bangalore
29. Jiwaji University, Gwalior
30. M.S. University of Baroda (Dept. of Microbiology and Biotechnology Centre),
Baroda
31. National Centre for Biological Sciences (NCBS), Bangalore
32. National Informatics Centre (Medical Informatics and Telemedicine Division),
(NIC) New Delhi
33. National Institute of Mental Health & Neuroscience (NIMHANS), Bangalore
34. Nizams Institute for Medical Sciences (NIMS), Hyderabad
35. National Neuroscience Centre (NNC), Kolkata
36. Sanjay Gandhi Post-Graduate Institute of Medical Sciences (SGPGIMS),
Lucknow
37. School of Information Technology, West bengal University
38. Shree Chitra Tirunal Institute for Medical Sciences and Technology,
Thiruvanthapuram
39. Sri Venkadeswara Institute of Medical Sciences, Tirupati
40. Tata Institute of Fundamental Research (TIFR), Mumbai
41. University College of Medical Sciences (UCMS), Delhi
42. University of Hyderabad, Hyderabad
43. University of Calcutta, Kolkata
44. Vidyasagar Institute of Mental Health and Neuroscience (VIMHANS), New Delhi

Network Meeting, Dec 17, 2003

The third meeting of the NBRC network centres was held on December 17th, 2003 at the Heritage Village Resort, Manesar following an international symposium organized on the occasion of Inauguration and Dedication to the Nation of the NBRC campus by the President of India. Representatives from all our network centres were also invited to attend the symposium and the inauguration. Over twenty centres were represented at the meeting.

Prof. Vijayalakshmi Ravindranath, Director, NBRC welcomed the representatives of the networked centers and highlighted various network activities. Director recounted the recommendation of the first network meeting regarding setting up of a digital library network so the Journal articles can be shared between network centres. This activity has received a tremendous response. NBRC library currently subscribes to many print journals and online periodicals. NBRC library received requests for over 400 articles from the network centres during March,'02-April, '03 as compared to 246 requests during the same period in the previous year. Most of the requests were met within a day. NBRC has also set up centralized facilities for microarray and DNA sequencing, both of which are fully functional and are being used on a regular basis. NBRC organized two microarray training workshops for representatives from network centres. NBRC has also

sponsored training programmes in computational neurosciences at network centres every year. The Director invited proposals for workshops on basic neuroscience techniques that could potentially be funded by NBRC. NBRC has sponsored members from network centres to attend international collaborative workshops in Korea, Japan, China and other countries. The centre is in the process of setting up a database of all the neuroscientists in the country, which will have information about the research activities, and technical expertise of the investigators. Prof. Ravindranath urged the members present to send the information by e-mail to NBRC so that it can be collated in the database.

It was stressed that in order for the network to grow and make an impact on the status of neuroscience research in the country it should be a two way street and that the centers should also take an interest in fostering cooperation. As an example the Director requested that when the network centers hold national/international meetings they inform the other centers so that the entire neuroscience community benefits.

Prof P N Tandon, President NBRC Society, highlighted the objectives and philosophy of NBRC which include not duplicating research being carried out anywhere else and strive to have close interaction, collaboration and resource sharing with neuroscientists working in various institutes in India. Prof Ravindranath invited members' comments on ongoing network activities, suggestions for their enhancement and improvement, and suggestion for new activities.

All the representatives appreciated the journal article delivery service offered by NBRC. Many, including Dr Shashi Wadhwa of AIIMS, Dr Shubha Tole of TIFR, Dr Basabi Bhowmick of IIT-D offered to share articles from their libraries Dr Bapi Raju of Central University Hyderabad proposed setting up a central repository of PDF files that may be of interest to many neuroscientists across the country.

Dr Vidita Vaidya of TIFR suggested that regional nodal cities could be set up to manage network activities in order to achieve a more equitable distribution of the work load. She offered services of her institute as one of the nodal centres for the western region. Subsequently, Dr Prakash Babu of the Central University Hyderabad offered that perhaps his institute could act as one of the nodal centres. Prof. Ravindranath promised to explore this idea further. Dr. Vaidya also suggested that there could be links to the websites of all the network centres at the NBRC web site. She also suggested that there could be single site to advertise positions open in neuroscience throughout India. Many members appreciated NBRC sponsoring various workshops and offered suggestion regarding this activity. Dr C S Paulose of Cochin University particularly appreciated sponsorship of workshop in techniques on neuroscience in 2000. Prof Shashi Wahdhwa, AIIMS, suggested that there could be workshops that focus intensively on a single technique used on neuroscience research rather than many techniques, a suggestion that was echoed by Dr Patro of the Neuroscience Centre, Jiwaji University, Gwalior.

Prof Ravindranath said she would look into the feasibility of the suggestions and how it can be implemented. She thanked the members for attending the network meeting, appreciated their participation and enthusiastic support of the NBRC network activities

and for their suggestions to improve this unique, perhaps first of its kind activity in the country.

TRAINING

Summer Training and Short –Term Programmes

Students from various academic institutions are encouraged to apply for project work as part of their post-graduation training and for summer training programmes at NBRC. Student applications for the training programme that are received through their parent institutions are screened and the candidates are selected based on the availability of space in the various laboratories at the centre. The students are assigned to a NBRC scientist for guidance and are exposed to the ongoing research activities of the institute and they get hands-on-experience of various tools used for deciphering neuroscience questions. Most of the students benefit from this program and return for future interactions with the centre.

We consider this as motivation of a young mind towards basic neuroscience research and as their “First step” to be a neuroscientist in the future.

INTERNATIONAL COLLABORATION

(Picture from Building the Brain with some Foreign Delegates)

INTERNATIONAL COLLABORATIONS

International collaborations help in promoting scientific excellence as well as in building the little known neuroscience community that exists in our country through exchange programs. NBRC has made sincere efforts to identify, establish and nurture such collaborations with intent of mutual benefit to the scientists of the collaborating institutions and has been successful in establishing research collaborations with various prestigious neuroscience institutions around the globe, as listed below.

Indo-US

Under the umbrella of collaborative efforts to carry out world-class neuroscience research at NBRC, the centre signed a MOU with National Institute of Mental Health (NIMH), one of the institutes of National Institutes of Health (NIH), Bethesda, USA. Since then, we have made significant progress with exchanging ideas and expertise between the scientists from the two countries.

Indo-Russian

Indo-Russian collaboration is another front where NBRC is trying to establish research agreements and collaborations so that scientists from both the countries can jointly work on some common issues dealing with CNS disorders.

Indo-Japan

Currently, Dr. Nihar R. Jana's laboratory is working on a collaborative research project dealing with pathogenesis of the CAG repeats neurodegenerative diseases, with the Dr. Nobuyuki Nukina of the RIKEN Brain Science Institute, Japan.

MEETINGS AND WORKSHOPS

MEETINGS AND WORKSHOPS

Micro array Training Programme

As on ongoing effort to train and improve the overall skills of manpower resource, a Microarray training programme was held at NBRC in collaboration with Amersham Inc between June 18-20, 2003. During the three-day training programme lectures by experts as well as hands-on-training were provided on the important aspect of data analysis. Trainees attended the programme from institutions around the country as well as from our Centre.

Computational Neuroscience Workshop at IIT Kanpur

Since 2001, NBRC has been sponsoring a workshop on computational neuroscience.

The workshop is held with the following objectives -

- To create interest and awareness amongst students from different technical backgrounds in Neuroscience.
- To emphasize the nature of computations performed by the brain and implementation of such computations.
- To develop tools in algorithms to analyse the huge amount of data obtained from neural experiments.

This workshop is organized every year at different institutes/universities, this year it was held at IIT, Kanpur from 7th-18th July 2003. An overwhelming response was received from students from various Institutes and Universities throughout India and about 75 students participated in the workshop.

Faculty from IIT, Kanpur, Delhi and Mumbai, NBRC, University of Hyderabad, Dayal Bagh Engineering Institute, Agra delivered lectures on various subjects ranging from single cell models to neural networks, data mining to computational approaches to systems neuroscience.

Earlier workshops were organized at NCBS, Bangalore in 2001 and at IIT, Delhi in 2002.

Joint Workshop on Neurobiology and Neuroinformatics organized at Dajeon, Korea – November 2003.

The Fifth China-India-Japan-Korea Joint Workshop on Neurobiology and Neuroinformatics was organized on November 21-22, 2003 at the Jung Moon Soul Building, Korea Advanced Institute of Science Technology, Daejeon, Korea. This international workshop, which is now an annual feature, provides a platform for scientists

from four countries (China-India-Japan-Korea) an opportunity to interact and exchange ideas.

Scientists from India including NBRC and its network centers attended the workshop. The platform provided the scientists the opportunity to present their work and receive inputs from the community. They also got a chance to develop some collaborations and have initiated some discussions with scientists in Korea.

Dr. P.K Roy, Mr. P. Reddy and Dr. N C. Singh from NBRC and Prof. Rohit Manchanda from IIT, Mumbai presented work on neuroinformatics and neurobiology

The Workshop mainly focused on Neurobiology and Neuroinformatics, which covered broad areas in brain research. The participants included Neurobiologists, clinicians, Cognitive scientists, physicists, mathematicians, information scientists and scientists from various fields of engineering. It provided inputs for a wide spectrum of topics such as Neural Plasticity and Neurotransmitter, Biologically-Motivated Artificial Vision, Brain Disease, Biologically-Motivated Artificial Auditory System, Computational Neural Models, Brain-based Cognition and Inference System, Brain Signal Measurement and Analysis, Brain-based Human Behaviour.

“Building the Brain”: An International Symposium to commemorate dedication of NBRC to the Nation (December 15 - 17, 2003)

The permanent campus of the National Brain Research Centre was inaugurated and dedicated to the nation by the President of India, His Excellency, Dr. A P J Abdul Kalam on the 16th day of December 2004 at Manesar. Professor Murli Manohar Joshi, The Hon’ble Minister of Science and Technology, Human Resources Development and Ocean Development, The Hon’ble Governor of Haryana, Shri Babu Parmanand, The Hon’ble Chief Minister of Haryana Shri Om Parkash Chautala, The Hon’ble Minister of State for Science and Technology Shri B.S. Rawat, and Secretary of DBT, Dr. Manju Sharma also graced this memorable occasion.

To commemorate this historic event, an International Symposium ‘Building the Brain’ was organised from December 15th to 17th. The scientific programme began on the 15th of December by an introduction by the Director of NBRC, Prof. Vijaylakshmi Ravindranath followed by a lecture by the Chief Guest and Nobel Prize winner (Rockefeller University, USA) Dr. Torsten Wiesel titled “Do We Learn to See?” The Role of Nature and Nurture in Brain Development. The scientific sessions consisted of talks by distinguished Indian and foreign neuroscientists in diverse areas of Cellular and Molecular neuroscience, Systems neuroscience, Clinical Neuroscience, Theoretical and Computational Neuroscience and Neuroimaging. On each day, at the end of the lectures, scientists and students across the country working in these areas of Neuroscience presented posters and discussed their work with senior scientists and colleagues.

The first scientific session on 15th December, 2003, was on Systems Neuroscience and consisted of three talks. Prof. Tom Albright from the Salk Institute, USA presented a

talk on the “Influence of context on visual perception”. Using psychophysical experiments he demonstrated that neuronal responses are correlated with perception of visual scene properties and hence neuronal sensitivity should be assessed in variable contexts that differentially influence perceptual interpretation.

This was followed by a talk on “Goal-based Action Selection in the Medial Prefrontal Cortex” by Dr. Keiji Tanaka from RIKEN Brain Science Institute, Japan. His work showed how recent single-unit recording studies on behaving monkeys and functional imaging studies on human subjects have demonstrated that pre frontal cortex activity conveys information about anticipated rewards or goals.

Dr. Birendra N. Mallick from the School of Life Sciences, Jawaharlal Nehru University, New Delhi, talked on “How and What Do Neurons Share for the Generation of Rapid Eye Movement Sleep”. He discussed how single neuronal activities were recorded from the brainstem of freely moving cats and REM-ON and REM-OFF neurons were identified. Studies were also conducted to understand the neurochemicals responsible for inhibition of the REM-OFF neurons, which are responsible for the generation of REM sleep

The session after lunch was on computational neuroscience and began with a talk on “Molecular noise and synaptic selectivity” by Dr. Upinder S. Bhalla from NCBS, Bangalore. They investigated possible tuning mechanisms using experiments in conjunction with biochemically detailed simulations of several synaptic signaling pathways. Their simulations and experiments suggested stochastic resonance-like effect due to molecular noise may amplify tuning effects and give rise to macroscopic outputs. Second, it predicts a sparse, random pattern of expression of some forms of synaptic change. Third, it presents a specific instance where molecular noise may be harnessed to achieve graded system responses by combining individual all-or-none decisions of a population of cells.

“Variability and Coding in Primary Visual Cortex: Are Spikes Merely Estimators of a Firing Rate?” This was the title of the talk by Prof. Jonathan D. Victor from Cornell University, USA. They carried out quantitative statistical analyses and information-theoretic tools on the visual responses of single neurons and local clusters of neurons in the primary visual cortex of the macaque monkey. These analyses show that the pattern of neuronal activity, in time and across a local population, contributes both quantitatively and qualitatively to the representation of visual information. That is, a spike train are more than estimators of a firing rate, and that the detailed pattern of neural activity within individual spike trains and across a local population is important.

Dr. Nandini Chatterjee Singh, from National Brain Research Centre, Manesar, presented

“A new computational tool to study speech impairments in children”. Using the modulation spectrum which represents a 2-D Fourier decomposition of sound in terms of temporal and spectral modulations they presented a novel application of it to study speech impairments in children.

The first session on December 16th was on molecular studies in neuroscience. The first talk was titled “Gene and protein expression in human brain: The effects of susceptibility genes on the neurobiology of schizophrenia” and was presented by Dr. Joel Kleinman from (NIH/NIMH, USA). His talk focused on three genes (COMT, GRM3 and DTNBP1) associated with schizophrenia. He presented expression data for the genes and proteins in dorsolateral prefrontal cortex and related structures will be presented as well as their effects on other genes "downstream."

Dr. Vidita Vaidya from the Tata Institute of Fundamental Research, Mumbai, India presented a talk on “Thyroid Hormone regulation of Adult Hippocampal Neurogenesis”. They examined the effects of altered thyroid hormone status on adult hippocampal and her results indicate that the thyroid hormone status can regulate neurogenesis in the adult rat hippocampus

“BDNF-induced neuroprotection against neonatal excitotoxic brain lesions” was the title of the talk presented by Dr. Pierre Gressens from INSERM E 9935 & Service de genes, France His talk showed that the neuroprotective profile of BDNF against neonatal excitotoxicity and the involved molecular mechanisms are dependant upon the type of activated glutamate receptors, the lesion localization and the stage of development in a neonatal mouse model.

Dr. Nihar Jana from the National Brain Research Centre, Manesar, India presented a talk on the “Possible involvement of CHIP in the misfolding-dependent ubiquitination of polyglutamine-expanded ataxin-3, the defective gene product in SCA3/MJD” By using ataxin-3, the defective gene product of SCA3/MJD, they observed that the misfolding propensity and the cellular toxicity of a polyglutamine protein is directly proportional to the length of the glutamine repeats and inversely dependent on the size of the corresponding protein. Further, in search of the ubiquitin ligase specifically involved in the ubiquitination of the polyglutamine-expanded protein, CHIP (C-terminus of hsp70 interacting protein) was identified that interacts with the polyglutamine-expanded ataxin-3 or huntingtin and associates with their aggregates. Finally they also demonstrated that CHIP is responsible for the ubiquitination polyglutamine-expanded huntingtin or ataxin-3.

Dr. Preeti G. Joshi (Department of Biophysics, National Institute of Mental Health and Neurosciences, Bangalore) presented a talk on “Neuron-glia communication: Role of glutamate AND purinergic receptors” Her talk showed that the NMDA-induced signal in neurons is communicated to astrocytes via metabotropic glutamate receptors and purinergic P2Y receptors. Thus glutamate and purinergic receptors form a network for

two-way communication between neurons and astrocytes. Such mechanisms could play an important role in long range signaling and information processing in the brain.

Dr. John J. Mieyal from Case Western Reserve University, in Cleveland, Ohio, USA talked on “Reversible protein-S-Glutathionylation: an evolving mechanism of cellular regulation” His lecture focussed on the current status of the problem by examining particular examples of protein-S-glutathionylation that are pertinent to control of cellular processes. Mechanisms of formation and breakdown of protein-SSG intermediates were considered from the point of view of their thermodynamic and kinetic competence as regulatory events.

“Neuronal signaling through tyrosine phosphatases: one STEP at a time” was presented by Dr. Surojit Paul from Yale University, New Haven, USA. They are investigating the physiological function of STEP: a striatal enriched tyrosine phosphatase, expressed in the neurons of the basal ganglia and related structures to try understand the cellular mechanisms involved in normal signaling. Our findings demonstrate that STEP binds to and inactivates p44/p42 MAP kinase (ERK) through dephosphorylation of a regulatory tyrosine residue in ERK. Phosphorylation of a critical serine residue in STEP blocks STEP-ERK interaction and dephosphorylation allows STEP to bind to and inactivate ERK. Phosphorylation of this serine residue is mediated through dopamine/D1 receptor activation of the cAMP/PKA pathway. Dephosphorylation is mediated through glutamate/NMDA receptor activation of the Ca²⁺ dependent phosphatase, calcineurin. In this way, STEP acts as a switch to regulate the duration of ERK activation in response to extracellular stimulus.

On the third day of the conference which was December 17th Dr. Aditya Murthy from the National Brain Research Centre, Manesar, India presented a talk on the “Neural Control of Action”. His talk presented work to understand the contribution of task dependent error processing in relation to saccadic eye movement control. Analysis of saccadic reaction times indicated that when subjects made errors they frequently made quick corrective eye movements. An analysis of the data suggests that the programming of these error corrections may be predictive in nature, beginning prior to the subjects making the errors. Recording neural activity from the frontal cortex of awake behaving monkeys tested this hypothesis. Neural activity related to error correction could be observed prior to the occurrence of the error in some cells. These findings, although counterintuitive, are consistent with computational models of motor control that hypothesize the need for neural mechanisms that can predict the consequences of actions before they are executed.

Dr. Bapi Raju from the Dept of Computer and Information Sciences, University of Hyderabad, Hyderabad) presented a lecture on “fMRI Investigation of Aspects of Visuo-motor Sequence Learning”. His talk focussed on the 'representation' aspect of visuo-motor sequence learning using fMRI studies. Whereas previous experiments address the question of 'when' and 'where' activation is observed during visuo-motor sequence learning, their experimental design allowed them to additionally address 'what' type of sequence representation is being learned. These results form the first

comprehensive evidence for a model proposed based on computational considerations for sequence representations.

Dr. Shubha Tole from the Department of Biological Sciences, Tata Institute of Fundamental Research, Mumbai, India presented a talk on “LIM-HD genes in the developing forebrain” To explore the role of LIM-HD genes as well as the broader LIM gene family in dorsal telencephalic development, they examined the expression pattern of the members of this gene family and their co-factors in the developing mouse cerebral cortex. They found that several of these genes exhibit complex spatio-temporal patterns spanning different stages of cortical development, from embryonic to postnatal ages. Though most of the cortex is absent, the olfactory cortex appears to be spared in the *Lhx2* mutant, suggesting that it is specified by different mechanisms from those that operate in the neocortex.

“Prenatal sound overstimulation modulates inhibitory circuitry of the chick auditory nuclei” was presented by Dr. Shashi Wadhwa from the Department of Anatomy, All India Institute of Medical Sciences, New Delhi. The presentation explained the effect of prenatal auditory enrichment on development of SON neurons and their inhibitory GABAergic terminals in target auditory nuclei – NM and NL was studied following patterned species-specific sounds and music. It was evident that inhibitory neurons demonstrate plasticity during development and are susceptible to alterations in sensory experience during prenatal period. An enriched environment through excitatory inputs enhances the growth and maturity of inhibitory neurons.

Dr. R. Baughman from NINDS, Bethesda, USA presented “Strategies for Translational Research in Neuroscience”. He outlined the goal of the program to provide support for the development of disease-relevant cellular and animal models, for screening of candidate therapeutics, and for the testing of preclinical activity, toxicology and pharmacokinetics required for FDA applications. Details of the program and examples of projects were also described.

The scientific sessions ended with a panel discussion, which consisted of Dr. P.N. Tandon, Dr. Torsten Wiesel, Dr. Vijaylakshmi Ravindranath, Dr. Tom Albright, Dr. Tanaka, Dr. Jonathan Victor, Dr. V.S. Ramachandran, Dr. Joel Kleinman, Dr. Pierre Gressens, Dr. John Mieyal and Dr. R. Baughman. All panelists and participants appreciated the efforts made by NBRC to foster collaborations and organize more such meetings. This panel discussed the outcomes of the meetings and talked about integrated approaches to address the challenges faced by all neuroscientists. The panel also discussed how these efforts would help in understanding various neurological disorders that affect masses. It emphasized the need for studying neurological diseases at the experimental and clinical level and also the importance of basic neuroscience research in understanding the mechanisms underlying various disorders. This symposium also provided a unique opportunity for neuroscientists in the diverse areas of Cellular and Molecular Neuroscience, Systems Neuroscience, Theoretical and Computational Neuroscience, Clinical Neuroscience and Neuroimaging to interact and build up collaborations within India and also with scientists working outside the country.

The poster presentations provided an opportunity for budding Indian neuroscientists to discuss their research achievements with national and international peers. Awards were given to students for the best posters presented in the major areas of neuroscience.

National Science Day

Every year NBRC organizes special activities to celebrate the National Science Day. This year students of class 9th from the Amity International School, Gurgaon visited NBRC campus at Manesar along with the vice principal of the school and their biology teacher on February 27, 2004. The students were shown around the NBRC Manesar campus and laboratory to give them a first hand experience of a functional research laboratory. Students were addressed on various aspects of neuroscience and were made aware of the ongoing research interests of NBRC.

Dr. Neeraj Jain, Dr. Aditiya Murthy and Dr. Pankaj Seth gave them short interactive lectures on neuroscience topics which were thought provoking for them as they were excited to learn some facts about brain functions and we were inundated with interesting questions from the students.

SUPPORTING UNITS

SUPPORTING UNITS

Animal Facility/Primate facility

NBRC has a modern animal facility approved by Committee for the Purpose of Control and Supervision of Experiments on Animal (CPCSEA) for small animals and large animals. The salient features of the facility include central air conditioning with laminar airflow 12-15 times per hour, 100% fresh air changes, remote monitoring of the temperature and humidity facility to regulate day/light cycle in individual rooms, necropsy room with a laminar flow hood, deep freezer and a fire alarm system. There is a state of the art sterile surgery suite equipped with gas anesthesia machine, heart rate monitor, pulse Oximeter, surgical microscopes, surgical lights with intensity control, ultrasonic instrument cleaner and provision for sterilization of equipment using steam autoclaving or ethylene oxide. There is an outdoor play area for non-human primates, which has eight interconnectable large enclosures that provide flexible layout for optimizing enrichment and social interactions. The facility currently houses inbred and outbred stocks of mice, rats and rabbits and few non-human primates.



Digital Library

The NBRC library is rapidly building up to be one of the leading digital specific library in the country. It is speedily acquiring documents, books, e-books and e-journals along with CD ROMs in different areas of research field enriching the collection at its circulation desk. All bibliographic details of books, journals and information databases are accessible through the campus-wide network that facilitates easy access to journals

and reduces the manpower requirement to a large extent. The library has over 1000 scientific books, and it subscribes to over 560 scientific national and international journals. It has established contacts with over 15 national and international organizations for exchange of the papers / articles and has established inter-library loan arrangement.

The library of the Institute aims to be a leading digital library in the various fields of scientific research areas such as- Neuroscience, Theoretical Neuroscience, System Neuroscience, Molecular and Cellular Neuroscience, Biochemistry, Genetics, Molecular Biology, Immunology & Microbiology, Pharmacology, Toxicology, Psychology, etc. It also aims to provide excellent services to researchers / scientists of NBRC and its Network Centres in related areas. NBRC library efficiently caters to the institute's research and teaching activities.

NBRC Library has a proposal of Institutional Depository Scheme i.e. NBRC library will link all NBRC publications with full text for world-wide users through E-print or D-space free software. This service enables the NBRC community to archive their pre-prints, post-prints and other scholarly publications. NBRC expects this service to facilitate the Institute researchers in self-archiving of their scholarly publications, provide easy access to these publications world-wide and improve impact of their research. While it can be accessed by all, submission of documents to this archive is limited to the NBRC research community. NBRC will also link the full text with individual scientist published paper under publications section, which should be updated on a monthly basis or whenever a new publication appears.

PEOPLE

PEOPLE

SCIENTIFIC STAFF

SCIENTISTS

1. Prof. Vijayalakshmi Ravindranath
2. Dr. Neeraj Jain
3. Dr. Rema Velayudhan
4. Dr. P.K. Roy
5. Dr. Pankaj Seth
6. Dr. Aditya Murthy
7. Dr. Nandini C. Singh
8. Dr. Nihar Ranjan Jana
9. Dr. Prabodha K. Swain
10. Dr. Shyamala Mani
11. Dr. Soumya Iyengar

POST DOCTORAL FELLOWS AND PhD Students !!

1. Dr. Renuka Ramachandra
2. Dr. Sajla Singh
3. Mr. Reddy Peera K.
4. Mr. Supriya Ray
5. Mr. Rashmi Mishra
6. Mr. Anand Goswami
7. Ms. Latika
8. Mr. Manoj Kumar
9. Ms. Priyanka Dikshit
10. Ms. Smitha Karunakaran
11. Mr. Sandeep Kumar
12. Mr. Ziauddin
13. Mr. Amit Kumar Mishra
14. Mr. Shailesh Kumar Gupta
15. Mr. Shashank Tandon
16. Ms. Uzma Saeed
17. Ms. Manisha Chugh
18. Ms. Varsha Agarwal
19. Mr. Biswajoy Roy Choudri
20. Mr. S. Srirangan
21. Ms. Latha Diwakar

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2. Mr. Abhay Kumar Saini
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5. Ms. Snehal K. Chokhandre
6. Ms. Taruna Ladha
7. Mr. Dharmesh Kumar

8. Ms. Nazia Khurshid

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7. Mr. Manish Kumar Verma
8. Mr. Sanjay Kumar
9. Mr. Irshad Alam
10. Mr. Manish Kumar
11. Mr. P. Manish
12. Mr. Samresh Singh
13. Ms. Pooja Sethi
14. Mr. Jothi Basu V.
15. Mr. M.Pasupati

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2. Ms. Beena
3. Mr. S. Hariharakrishnan

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1. Dr. Shikha Yadav, Veterinarian
2. Dr. Metkari S.M., Technical Officer

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2. Mr. Amanulla K. Batcha
3. Mr. B. Satyananda Gupta
4. Mr. N. Ramachandran
5. Mr. K.V.N. Kasyapa
6. Mr. Deepak Jain
7. Mr. Jitendra Singh Bisht
8. Mr. Kedar Singh Bajetha
9. Mr. P.V.S. Shyam Kumar
10. Ms. Reema Saxena

VPN PROJECT

1. Ms. Manisha Bakshi

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Prof. Samir K. Brahmachari Director Institute of Genomics and Integrative Biology Mall Road, Near Jubilee Hall Delhi – 110 007	*Dr. B. Ramamurthy Neurosurgeon, Dr. A. Lakshmiopathi Neurosurgical Centre, Post-Graduate Institute of Neurological Surgery, Voluntary Health Service Hospital Chennai- 600113 * Deceased Dec 12, 2003

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