"Our species is the only creative species, and it has only one creative instrument, the individual mind..."
-John Steinbeck, *East of Eden* (1953)

A proposal to advance our understanding of

The Human Brain in Health and Disease

at the Center for Brain and Cognition, University of California, San Diego

Respectfully submitted to Jeff Epstein
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WHY NEUROSCIENCE?

The progress of science typically moves through two stages: the experimental and the theoretical. Sometimes these progress simultaneously, but experimental observations usually precede theory. This is especially true of biological sciences, but was equally true of even “hard” sciences like physics and chemistry. Long before the emergence of modern theoretical physics, Michael Faraday performed a ten minute landmark experiment. Simply by moving a bar magnet in a coil of wire, he generated a current and induced what today we call electromagnetic induction. This endeavor linked two whole areas of physics: electricity and magnetism. We had to wait for Maxwell to use Faraday’s experimental results to develop quantitative electromagnetic theory, known today as Maxwell’s equations. This was a key turning point in the birth of modern physics. Many areas of science have experienced this evolution from observation to experiment to theory, and neuroscience is no exception. At the moment, while many areas of neuroscience are well understood, we don’t have a firm grasp of how the brain works as a whole. We at the Center for Brain and Cognition (CBC) consider this the most exciting time to work in an area of science. Many clinical and experimental observations have yet to be “explained” by a solid underlying theory. In fact, many of these observations have been relegated by some to the realm of psychology or even regarded as unexplainable oddities, outside the scope of neuroscience inquiry. But we at the CBC believe that such observations can provide valuable new opportunities for understanding the human brain.

Many examples of major Faraday-style breakthroughs have emerged in neuroscience in the last two decades—many of them originating in observations of human behavior. Perhaps the single most famous patient to neuroscience, named H.M., suffered from severe amnesia caused by brain damage he sustained during experimental surgery for seizures. The knowledge that researchers gained from studying H.M. led to our current understanding of the principles of memory organization in the brain. Researchers eventually homed in on a brain area called the hippocampus to identify the cellular mechanisms of memory. The following lines of research provide recent examples of developments that have been carried out by CBC researchers and their peers and colleagues, and provide a glimpse of the kinds of discoveries that are revolutionizing our understanding of the brain.

- Neuroscience held for decades the dogmatic view that our brain circuitry is hard-wired early in life and is not capable of plasticity. But often we have to rethink even the most basic ideas in order to move forward. In the last decade, it has become apparent that even basic connections in the brain can be altered well into adulthood. Much of this work has been pioneered at the CBC and at half a dozen other research centers in the country. This astonishing plasticity provides a

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powerful platform for advancing both theoretical and practical approaches to understanding brain function. Evidence suggests that the brain is more dynamic and malleable than we ever imagined.

- A new class of neurons has been discovered called "mirror neurons" (MNS or mirror neuron system). These cells allow our brains to rapidly create running virtual reality (VR) simulations from observations of others in order to predict their behavior. CBC scientists have used a combination of behavioral measures and brain imaging to demonstrate that these neurons may be deficient in autism. The lack of these cells so critical for recognition of social cues might explain the social withdrawal observed in patients with autism spectrum disorders.
- Equally important from a non-clinical angle is the potential role of the MNS in constructing a "theory of other minds" allowing you to view people as intentional beings- an ability that is vital for social interactions (Oberman & Ramachandran 2007; Ramachandran & Oberman 2006, 2007). The MNS allows one to experimentally approach such problems that have been mainly studied by social psychologists in the past.
- Mirror neurons also represent a valuable clinical approach for treating those who have had a limb amputated. This is illustrated by the following observation made by CBC scientists: when an amputee simply watches someone else stroking his own intact arm, the amputee feels the stimulus at his no-longer-existent arm. This "hyper-empathy" effect occurs because actual sensory information and specialized veto signals are not provided from the missing arm. This concept has been used to develop therapies for chronic pain in amputees; simply watching someone else massage her / his own arm causes a reduction in the patient's phantom pain. This is not a vague "psychological" effect - it is directly predicted by the discovery of the MNS.
- Cells in the hippocampus have been shown to fire when an animal walks to a specific part of its cage; these are called hippocampal "place cells." These neurons were discovered by O'Keefe and Dostrovsky nearly 40 years ago. We now understand that the brain uses them to create dynamic maps based on our experiences. Remarkably, while a rat sleeps, you can monitor its dreams by recording from place cells in the hippocampus and reconstruct where the rat has been wandering earlier in the day. We believe there is more to learn from further study of these neurons.
- Another strange phenomenon under investigation by CBC researchers is called synesthesia. In this sensory mix-up, an otherwise normal person sees a certain color every time he hears a particular sound note or sees a particular number. Scientists have discovered its neural basis, which has yielded a new appreciation of the neural interconnectivity between neighboring brain areas. This quirky phenomenon can provide key insights into the neural and genetic basis of creativity, a topic traditionally considered unapproachable by science.

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WHY OUR LABORATARY IS DIFFERENT

The mission of the Center for Brain and Cognition is to bring together top experts - faculty, students and researchers - who share an interest in neural mechanisms underlying human perception, cognition and emotions, and the application of knowledge about cognitive mechanisms to real-world human problems. The center was founded by Drs. George Mandler, David Rumelhart and J. McClelland, whose weekly seminars were legendary and became the basis for the current "neural network revolution." CBC activities now include a well-attended research talk series, a neuro-imaging data analysis facility used by researchers examining MEG and fMRI data, and internationally visible research activities. The CBC focuses on behavioral neurology and cognitive neuroscience, neural plasticity and rehabilitation from stroke, visual cognition and basic visual processes, the relationship of cognition and emotion, and language processing. The CBC at UC San Diego is small by choice, and the intent is to keep it so. While the center facilitates highly productive collaborative programs, its philosophy – born of lessons from history – is that novel innovations and important discoveries can and often do emerge from the interaction of a small group of scholars and their students. Molecular biology is a multimillion-dollar global enterprise today, but it began with two or three researchers unraveling the structure of DNA while working in a shed. This group included the late Francis Crick, a professor at the CBC, Adjunct Professor at UC San Diego, and Professor and President of The Salk Institute. The discoveries of this small team marked the dawn of modern biology. Even the structure of the atom was unraveled by a handful of people at the Cavendish laboratory in Cambridge, based on a "shoestring and sealing wax" approach. In this age of high technology, there is a tendency to think that simple methods can't possibly yield such revolutionary breakthroughs. But the CBC faculty disagrees. Without denying the role of large teams, we believe that individual creativity and innovation continues – and should continue – to play an important role in the decades to come.

The CBC's approach is unique in two respects. First, we encourage cross-disciplinary interactions between brilliant, world-class researchers in different campuses throughout San Diego and La Jolla. Without such sharing of abilities and resources, no fundamental understanding of brain function, whether normal or abnormal, can be achieved.

Second, the CBC focuses on developing interventions that are inexpensive, non-invasive and often simple enough that the patient can have the procedure performed by a caregiver at home. For example, the "mirror feedback" therapy introduced by V.S. Ramachandran

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and co-workers in the early 1990s for phantom pain and stroke rehabilitation has now been confirmed in several controlled clinical trials as extremely effective. This therapy is starting to be used widely in rehab centers throughout the world. Without drugs or surgery, it relieves excruciating pain completely in a sub-set of patients, and there is a substantial – though not complete – reduction of pain in many others. Notably, the center is committed to developing procedures that are non-invasive, simple, and inexpensive, so they may be useful not just in the U.S. but also in developing countries.

INNOVATION: FUTURE RESEARCH OPPORTUNITIES

The CBC's main objective is to understand the functions of the normal brain. The CBC has pioneered a number of new approaches. For example, the sensory phenomenon of synesthesia (discussed above), was long thought to be rare and was considered either to be a fabrication or nothing more than a curiosity. Now we know that about 5% of the normal population experiences synesthesia. The CBC not only established its neural basis through a combination of perceptual experiments and brain imaging, but also pointed out its broader relevance to the evolution of creativity in humans, a topic considered unapproachable by most neuroscientists. After this was published by Dr. Ramachandran's group in the late 1990s, it spawned a host of new studies in the field by other groups. What was once a curiosity has become a thriving field of research with far-reaching implications for our understanding of the brain.

Another area of rapid progress in the last three decades has been in ***clinically relevant applied neurology***. There is a great deal of optimism in the field, yet there are no cures for even the most common disorders, including those related to stroke. Standard rehabilitation techniques that are currently in vogue are only marginally effective. The same holds for chronic pain, whether of central origin (such as following a stroke) or caused by damage to body or limb. Almost 70 percent of amputees, for example, suffer from severe phantom limb pain that can last for years and become so intense that patients become profoundly depressed, even suicidal. The currently available treatment options, whether based on drugs or surgery (including deep brain stimulation), are often

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ineffective or only partially effective in relieving chronic pain of any kind, despite the fact that pain research has searched intensively for breakthroughs for five decades.

We believe the main reason for the limited efficacy of many of these techniques is the lack of a "big picture" understanding of how chronic pain actually emerges in the nervous system. What are the pain circuits and exactly how do they interact with other sense modalities? Only through such deeper understanding can we design more specifically targeted therapies for chronic pain. This holds true for other devastating disorders of the nervous system as well. To a neuroscientist, understanding pain and paralysis represent intellectual challenges; to a patient, dealing with pain can take over his or her whole life. The number of potential patients helped could be staggering, given that 10 percent of us will experience disability from stroke, and another estimated ten percent of the population suffers from disabling chronic pain.

Over the last decade, the CBC has become world-renowned for breakthrough work pioneering highly effective new treatments for stroke rehabilitation and for many types of chronic pain, including phantom limb pain.

The CBC's stroke rehabilitation procedure leads to an almost complete recovery of arm or leg function in a small sub-set of patients, and a doubling or even tripling of hand function (such as grip strength and finger and thumb movements) in about half the patients; this is compared to several months of more standard intensive rehab which produces recovery in only 5 to 10 percent of participants. One of the CBC's goals will be to explore the reason for the differences: Why do some patients recover substantially whereas others don't? This will provide clues toward improving the procedures' effectiveness. These innovative new procedures have already had tremendous impact on rehabilitation neurology and are likely to revolutionize the field.

The mirror visual feedback technique has now been confirmed in placebo-controlled trials by other groups. Stroke rehabilitation, phantom pain, and stroke–related paralysis therapies have also held up to scrutiny. However, even though a majority of patients show improvement, a substantial minority do not. Dr. Ramachandran intends to use brain-imaging techniques (FMR and MEG) to explore the exact mechanism by which the visual feedback acts on the brain. This will be conducted concurrently with controlled clinical trials. A similar evaluation will be carried out on patients with stroke-related pain to determine the cause of variability in responsiveness to caloric vestibular stimulation, combining clinical trials with brain imaging. All references to technical literature will be provided upon request.

UCSD is also the home of one of the most advanced state-of-the art virtual reality research centers in the world (CAL-IT2). Within this virtual environment you can create

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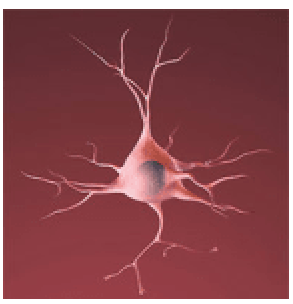
a virtual room with virtual furniture that you can “sit” on or even look under. Intriguingly, Dr. Ramachandran has found that you can create virtual twins in such environments – leading to uncanny out-of-body experiences. Dr. Ramachandran (in collaboration with CAL –IT2) intends to use this technology not only to explore how the normal human brain constructs body image but also to develop new therapies for bodily disturbances such as anorexia and fibromyalgia for which there are presently no cures.

CBC RESEARCH CHARTS A NEW PATH

As noted above CBC has two agendas; basic research on brain function and applied clinical research. The emphasis is on the former, for without a deep-seated understanding of theory, no clinical applications are possible. And theoretical and experimental approaches must – in their turn – be informed by evolutionary thinking.

BASIC RESEARCH

A few examples include recent work on the mirror neuron system and on synesthesia (discussed above) – such as the emergence of empathy, theory of mind, and proto-language (through gestures) - and as a source of new therapies.
Another focus is the evolutionary origins of self-awareness explored, for example, by studying our sense of being anchored in a body (“embodiment”), which can be studied using mirrors, virtual reality, and under ketamine (which creates out of body experiences).



NEURAL PLASTICITY

Until 20 years ago, the most commonly prevalent view of brain function was that it consists of a large number of hard-wired “modules” (specialized regions or circuits), each of which has permanently fixed connections and functions independently of others. It was

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held that this "fixity" of connections was the reason why there is so little recovery of function after brain damage, and why neurological disorders are so notoriously difficult to treat.

Due to the work of a small handful of researchers in the fields of neurology and neurobiology, there has been a radical shift away from this view of the brain. (These researchers include most notably V.S. Ramachandran working at UC San Diego, Michael Merzenich at UC San Francisco, and Jon Kaas at Vanderbilt). There are specialized brain regions, of course, but far from being autonomous they are highly modifiable and are in a constant state of dynamic equilibrium with each other and with the environment in which they are immersed. According to this view, many (but not all) neurological disorders occur not from permanent irreversible damage to modules but from shifts in equilibrium away from optimal function. If so, one can devise treatments that are relatively simple but highly effective procedures for shifting the equilibrium back to normal - as if by pressing a "reset" button. This is a radical new concept in neurology pioneered by the CBC, and one that we must pursue, given the financial opportunity.

FUNDING OPPORTUNITIES

The work of Dr. Ramachandran's group at CBC has been recognized as worthy of support from the top funding institutions in the country. Historically, this work has garnered funding from the National Institutes of Health (NIH), with additional support from the Mind Science Foundation; the McDonnell Foundation and Pew Charitable Trusts; the U.S. Office of Naval Research; the Kavli Institute for Brain and Mind (of which Dr. Ramachandran is a board member), and generous contributions from private donors.

The NIH funding level has in recent years been cut back severely, to an estimated two to three percent. ***Only three percent of all proposals submitted receive NIH funding.*** This is a major setback for the advancement of scientific knowledge, and innovative new research in particular, as NIH funding now typically goes toward refining pre-existing treatments rather than to innovative new approaches. In addition to stunting innovation, there is a secondary effect: many brilliant young thinkers are choosing to pursue careers elsewhere. Where there is no funding for start-up academic research, there is no start-up research.

To advance new ideas, we must rely increasingly on the vision and generosity of philanthropic institutions and private individuals who share a curiosity, wonder and desire to expand our knowledge of the functions of the brain, including neurological disorders and treatments. CBC's faculty believes that the following initiatives will have the greatest impact, and therefore have highest funding need:

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- ***Intensive Mirror Neuron System Research and Clinical Trials*** that have been initiated by Dr. Ramachandran, our top priority at the CBC.
    - Two post-doctorates: *$60,000 per year*
    - Research assistants and lab personnel: *$80,000 per year*
    - Three graduate students: *$30,000 per year*
    - Researcher travel: *$15,000 per year*
    - Scientific journal publication costs: *$6,000 per year*
    - Subject payments and travel: *$25,000 per year*
    - Neuroimaging costs: *$80,000 per year*
    - Equipment: *$200,000*
    - Miscellaneous lab supplies: *$15,000 per year*

    Immediate need $511,000; five year need $1,755,000

- ***Annual Symposia*** – To seed, germinate, and share ideas, the CBC would like to host an interdisciplinary, international, two-day symposium each year. The symposium would alternate yearly between applied clinical research and basic research. Each symposium could be named for the main sponsor, and donors will be invited guests. *Immediate need $20,000; five year need $100,000*

- ***Visiting Scholars Program*** to bring outside professionals to UC San Diego's CBC for up to two weeks. The program would expose our students to new sources of ideas and areas of research. This program would be named for its major donor. *Immediate need $60,000; five year need $300,000*

- ***Innovation Grants*** to initiate new directions of research, which, if successful, can lead to federal funding. The CBC would like to award four grants of $500,000 each for two years, renewable for an additional two years after that period. These awards may be named for the donor. *Long-term need $2,000,000*

Our long-term goal is to attract funds up to $5 million; this will establish an endowment, the payout from which would cover the programs outlined in the list above, in addition to annual operating costs, enabling the center to become self-sufficient in perpetuity. The seed money the center has received so far is a promising start in this direction, but clearly not enough.

Your contribution toward this goal would make a big difference and be greatly appreciated.

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