REPORT OF

THE INTERNATIONAL ADVISORY COMMITTEE ON BRAIN RESEARCH IN ISRAEL

SUBMITTED NOVEMBER 2011

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1 EXECUTIVE SUMMARY

The National Forum for R&D infrastructures (TELEM) established the International Advisory committee on Brain Research in August 2010. The charge to the Advisory Committee as offered by Dr. Jacob Ziv, Chair of TELEM, was as follows.

1. Evaluate the scientific level of existing Israeli brain research its research centers, groups and infrastructure, and to compare them with those in leading brain research centers worldwide.
2. Examine the needs of Israeli neuroscience-based R&D and the potential benefits that could accrue from strengthening existing centers and/or establishing new focal activities in this area.
3. Examine ways to increase the contributions of Israel to cutting edge in brain research and it's potential contributions to the medical sciences and related industry, potential contributions to the economic and society welfare and to additional aspects of national strength as well as possible R&D synergism between the above.
4. Evaluate the need for further supporting neuroscience-based interdisciplinary research in the natural sciences, exact sciences and humanities.
5. Examine the existing Israeli industry in the applied Brain research area, for its own R & D activities, its scale and its current and future global positioning.
6. Propose a modus operandi for national neuroscience centers (including virtual ones), and estimate their required number, cost, infrastructure, cross-collaboration, manpower, based on a broad evaluation of brain research in Israel and on the potential use of the infrastructure of the research centers for the promotion and advancement of R&D in the Israeli industry.
7. Suggest an appropriate Request-for-Proposals (RFP) that could be used to advance such an initiative, including milestones, criteria and indicators (and their relative weights).

The Committee met three times: twice in Israel and once in New York City. In addition, individual members of the committee met in Israel and in the US to prepare and complement the committee meetings and they interacted frequently by phone and email. Members of the Committee conducted interviews with scientists and science administrators in Israel. Academic institutions, hospitals, and industry leaders in relevant companies were polled regarding existing facilities and perceived needs. Databases were consulted to obtain information about neuroscience in Israel, and about companies that are developing therapies and/or devices to enhance the function of the disordered or the normally functioning brain. Data are presented in *Appendices 2.1 through 2.7* and are summarized below.

We found that Israel has great strengths in all areas of neuroscience ranging from molecules to mind. The strengths are evident in universities, academic institutes, hospitals within large medical centers and in many companies throughout the country. Because of its traditions and current activities, Israel can become a world leader in fundamental and translational neuroscience with great impact on brain disorders and normal brain function.

We recommend the creation in Israel of multidisciplinary RESEARCH CLUSTERS made up of members from basic and clinical sciences and from industry that will stimulate new research, enhance existing projects, create new jobs, and industry, and lead to new sources of funds.

By sharing information, this strategy will lead to research results, of marked societal and economic significance.

As a first step, the following Clusters should be considered.

- Neurodegeneration
- Stroke and Other Ischemic Disorders
- Traumatic Brain and Spinal Cord Injury
- Disorders of Mood and Motivation
- Cognitive Disorders
- Development Disorders
- Disorders of Neuron Excitation and Conduction
- Disorders of Sensation and Movement
- Rehabilitation and Regenerative Medicine
- Brain Inspired Computation and Technology (BICT)

We also recommend the creation of Infrastructure Centers that will house certain facilities that are crucial for the success of the RESEARCH CLUSTERS but that are in short supply or lacking altogether in Israel. Infrastructure support is needed in the areas of brain imaging, brain stimulation, brain inspired technologies, genome sciences and animal models of human diseases. Centers should be housed in academic and medical centers, but they should all be available to qualified members of industry.

We recommend investments in basic research directly relevant to neuropsychiatric disorders and transitional research to move more efficiently into meaningful health outcomes.

A supplementary recommendation that amplifies recommendations in the main document in regard to Brain Inspired Computation and Technology was submitted by three members of the Committee. This recommendation and an associated budget are included at the end of the Report.

We finally recommend that priority investments be made (a) in basic research concerning mechanisms of neurological disorders and (b) in transitional research to translate the findings in basic research more quickly and efficiently into meaningful health outcomes, whether those are physical, mental, or social outcomes.

2 INTRODUCTION

2.1 Neuroscience

Neuroscience is our best hope, perhaps our only hope for understanding how the human brain gives rise to normal and disordered thoughts and behaviors. The need to relate brain function to behavior is perhaps the most important challenge facing all modern societies. Neuroscience is now in a remarkable period of growth driven by advances in genetics, imaging, molecular genetics cognitive science, and computational science. Working at the frontier of this field, Israeli scientists are likely to produce great societal and economic benefits.

In an ongoing revolution in medicine, psychiatric disorders including anxiety, depression, schizophrenia and autism, once considered "mental" disorders, are now considered as brain disorders along with the traditional neurological disorders such as Alzheimer's disease, Parkinson' disease, epilepsy and stroke. We are dealing with one organ, the brain, and insights in one area of study have great import for the others. A major emphasis in this report is, therefore on brain disorders.

We have focused on brain disorders but we want to emphasize that this is a two way street. Studies of the disordered brain will inevitably lead to a deeper understanding of normal brain function and how such functions might be enhanced. This can be achieved by sophisticated biotechnologies and by interfacing with smart artificial devices and systems.

Our recommendations capitalize on strengths now evident in the Israeli neuroscience community, and they point to new developments that will maximize the likelihood of leadership in the future. We believe that a greater understanding of the human brain will help Israel face the pressures imposed by the modern world.

2.2 Brain disorders

Brain disorders take an enormous toll on patients, their families and the economy. The prevalence of brain disorders is startling and rising. For example, in the US and Europe, Alzheimer's disease now affects 50% of the population over age 85. About one in one hundred children will fall somewhere on the Autism Spectrum, and an equal number will suffer from schizophrenia. About 1% also suffers from epilepsy. Nearly 50% of the population will suffer a disabling major depression. Disorders of impulse control including drug and alcohol abuse take a great toll. Brain trauma and suicide are major causes of death among young people. More than 50% of those returning from combat suffer from post-traumatic stress disorders (PTSD).

In addition to the high prevalence, one must consider the staggering toll taken by brain disorders in terms of disability. The World Health Organization reports that four brain disorders (five if "accidents" involving brain and spinal cord injury are counted) are among the top ten in Europe and North America in terms of Disability Adjusted

Life Years (DALYs). Depression is predicted head then list by 2030. Autism and other pervasive developmental disorders are lifelong disabilities that challenge entire families as well as the probands, but they are not even included in WHO DALY surveys.

2.3 The needs

The need for truly novel, more effective therapies is urgent. Despite the burden to society, few new medicines have been developed in the past 25 years. Large pharmaceutical companies are no longer willing to take the financial risk of advanced, Phase III clinical research. The "valley of death" that has blocked the transition from promising translational research to compelling results in human subjects has proved difficult to bridge. Many Big Pharma companies including Pfizer, Lilly, Merck, Astra Zenica, and Glaxo–Smith-Klein have reduced or closed their neuroscience programs.

2.4 Opportunities

Perhaps the major reason for retrenchment is the lack of relevant biomarkers that might lead to the elusive "proofs of concept" needed for further investment. This is true for biomarkers at the level of molecules and cells, and also for biomarkers at the level of neural networks and behavior. Rather than retrench or give up altogether, now is the time to invest in research on new, more effective, safe neuroactive drugs. Although large pharmaceutical companies have closed their own programs, they have increased investment in academic labs and small start-up companies. This situation provides opportunities for the innovative Israeli science community.

Powerful tools are now available for exploring target based and phenotype (clinical) based biomarkers for novel treatments. It may be that multiple targets and multiple interventions must be assayed simultaneously. The need for biomarkers is evident in all branches of medicine, but the need is most acute in dealing with neuropsychiatric disorders. Better animal models of complex brain disorders would greatly facilitate target validation and the relevance of phenotypic markers. Hypotheses are needed for development of assays based on synaptic function and the behavior of key neural circuits.

Ultimately, candidate therapies require clinical validation. Treatments must be assayed in human subjects. Imaging is the best route to determine appropriate dose regimens and the efficacy of brain stimulation. These resources are described below.

Now is also the time to invest in innovative devices that can be used to stimulate the brain or that can be driven by electrical signals led from the brain. Combined with parallel developments in engineering, material sciences, nanotechnology, and mathematics, new information about the function of complex neural circuits can be used to ameliorate sensory, motor, and cognitive deficits, and, in some cases, to augment normal human capabilities. We have arrived at a new, exciting, frontier of research in brain stimulation and other devices inspired by the function of the brain itself. Brain inspired computing and technology is an area of great expertise in Israel. It is an area that has great implications for brain disorders and also for the industry.

We believe that the entrepreneurial spirit in Israel along with the depth of expertise in all aspects of neuroscience, and the tradition of multi-disciplinary research, which have already yielded remarkable achievements in areas such as computer sciences and avionics, place the Israeli neuroscience and technology community in the forefront of efforts to capitalize on remarkable opportunities now on the horizon.

This report calls for close collaboration between academia, industry, government agencies and private philanthropy to in order to develop new medical treatments and new devices to treat brain disorders, and, perhaps to enhance normal function. One of the great failings in industry is the lack of sharing of information regarding failures as well as successes. This involves matters of policy and also lack of appropriate technology. In the "precompetitive" stage, there is a great benefit in sharing genetic information, imaging results and data on toxicology and results from brain stimulation and recordings.

We recommend the creation of multidisciplinary RESEARCH CLUSTERS made up of members from basic and clinical sciences and from industry, which will stimulate new research, enhance existing projects, share information about research results, create new jobs for young new members from Israel and from abroad at the academia and industry, and lead to new sources of funds.

We have identified infrastructure needs that are essential for the entire program. Thus, we also recommend the creation of Infrastructure Centers that will house certain facilities that are crucial for the success of the RESEARCH CLUSTERS but that are in short supply or lacking altogether in Israel. Infrastructure support is needed in the areas of brain imaging, genomics, gene expression and animal models of human brain disorders, brain Machine Interface. Centers should be housed in academic and medical centers, but they should all be available to qualified members of industry. There is also a need to train and/or recruit new scientists interested in basic neuroscience and in translational/clinical research.

3 RESEARCH CLUSTERS

We envision RESEARCH CLUSTERS made up of individuals from academia and industry that would work together to define key issues, solve problems at basic and practical levels and develop new products in their areas of interest.

The Clusters described below are not entirely independent of one another. Concepts, mechanisms, technologies and therapeutic approaches may be shared. Thus individual investigators or companies might participate in more than on Cluster.

What follows are initial descriptions of RESEARCH CLUSTERS. Final definitions will certainly evolve as specific proposals are considered. They should be considered as dynamic groups. Over time, individual groups may be disbanded and new ones formed.

The overarching goal of the RESEARCH CLUSTERS and the Infrastructure clusters that will support them is to improve the quality of life of all who suffer from brain disorders and to enhance the well-being and security of those who live in Israeli.

3.1 Neurodegeneration

Alzheimer's disease, Parkinson's disease, and fronto-temporal dementia are prime examples of neurodegenerative disorders. Nerve cell death by a well characterized metabolic pathway called "apoptosis" operates in these conditions.

It is now clear that degenerative processes begin long before the disorder is clinically evident. Some studies suggest at least a 15-year latent period in Alzheimer's disease. It is essential, therefore, to develop early biomarkers and behavioral for diagnosis and therapy. It is possible that many of the treatments now deemed ineffective would have more profound effects if administered before neuronal loss was advanced. Preservation of function even by five years would have great impact on patients and their families.

Anticholinesterase drugs, neurotrophic factors, anti-amyloid antibodies, and drugs that affect the metabolism of beta amyloid and tau protein are among the current candidates. To date, these targets and others involved in apoptosis have failed as a therapeutic target. It is, therefore, important to explore new targets and therapeutic strategies in neurodegeneration and particularly in AD. Opportunities exist for intervention at different points in the same pathways new targets have emerged in recent studies of learning and memory that should be advanced as candidate therapeutic targets for Alzheimer's dementia.

Novel biomarkers must be discovered that will enable detection of the disease process before it is clinically evident. Ratios of amyloid peptides in the CSF and blood, structural and functional Magnetic Resonance Imaging (MRI) and Positron Emission

Tomography (PET) scans with agents that bind to beta amyloid are currently under investigation.

Precise studies of all aspects of memory are essential to distinguish Minimal Cognitive Impairment, which is a precursor to Alzheimer's dementia from Benign Senescence Forgetfulness which is not.

3.2 Stroke and Other ischemic Disorders

Stroke is the third leading cause of death and leading cause of disability in developed countries. Nearly 800,000 Americans and 15,000 Israelis have stroke each year. The acute event triggered by interruption of blood supply to part of the brain is the direct cause for sudden death of nerve cells. Following the acute insult, a slower, apoptotic process ensues that greatly extends the acute damage. Indeed, clot-busting is one of the strategies in treatment of ischemic stroke. tPA (tissue plasminogen activator) changed the treatment of ischemic stroke when introduced in 1996 but it is associated with damaging side effects including intracerebral hemorrhage in a significant percentage of the cases. In addition, due to severe limitations on the time window for its use, it is efficient within 3 to 4.5 hours after onset and suites from 2 to 5% of stroke victims in the US (<1% in Israel). No new agents have been introduced in the past 15 years.

Both the acute and later phases are in need of new therapeutic intervention. Developments of clot-busting treatments in Israel are on early stage and yet to be proven competitive. On the contrary, Israeli industry is a world leader in exploring of two alternative approaches, i.e., neuroprotection and opening of collateral blood vessels. The opportunity for Israeli basic research and industry is in development of neuroprotective medicine and in design of devices facilitating blood recirculation.

Since the slower process takes hours or even a day to mature, it holds a promise that treatments in a much larger window than the 4-5 hours allowed today for tPA can be developed which will shift the course of the disease. Of note, the therapeutic strategies in stroke are quite synergistic and development of a combined treatment (e.g., neuroprotection + recirculation) could be an important task for stroke cluster.

In addition, opportunities exist for improvement of existing therapies. For example, devices built on the nano scale may enhance the clot-busting efficacy of tPA and other agents by allowing them to be introduced into the microvasculature of the brain, directly affecting the clot region without endangering other areas.

Beyond hemorrhagic and occlusive stroke, vascular dementia, migraine, transient ischemic attacks and altered function of the blood-brain barrier might be included in this Cluster.

3.3 Traumatic Brain and Spinal Cord Injury

Acute brain and spinal cord injury and peripheral nerve damage are major causes of disability and death among individuals under the age of 25. In addition, seemingly minor injuries that include loss of consciousness (concussions), when repeated, lead to long-term degenerative changes and dementia.

Nerve, spinal cord and brain injuries are common following accidents that occur in civilian life. They are, of course, much more common in times of strife and outright war.

It is noted here that it is not sufficient to simply promote regeneration of nerve cells. Proper connections must be re-established once the regrowing nerve cell extensions (axons) arrive near their targets. Restoration of coordinated movement requires reconstruction of functional neural circuits. This, in turn, requires directed growth of axons and corrects choice of synaptic partners.

In fact drug development for stroke and for brain/spinal cord trauma requires similar expertise and may be considered as almost the same area of interest. Therefore, they may be in one mega-cluster or in two separate but friendly clusters.

Neuropathic pain, a common incapacitating consequence of traumatic nerve injury caused by injury or limb amputation (commonly performed to treat late complications of diabetes) is often misdiagnosed and poorly treated.

3.4 Disorders of Mood and Motivation

Depression, anxiety disorders, post-traumatic stress, and addiction are among the most common, debilitating of all brain disorders. They are among the leaders on the WHO DALYs (Disability Adjusted Life Years) list. No novel, truly useful, safe medications have been introduced in the past 20 years.

Promising studies have appeared in which deep brain stimulation was used to treat refractory, "malignant" depression. New electrodes, protocols, and targets within the cerebral hemispheres are under investigation. 'Non-invasive' transcranial stimulation methods are also researched.

Evidence is accumulating that profound depression and persistent anxiety are associated with the loss of nerve cells in key parts of the brain. Precursor, "stem" cells renew aging populations under normal circumstances. They fall behind under conditions of chronic stress such as prolonged depression and anxiety. This pathway offers new opportunities and Israel has great expertise in this area.

Substance abuse and other forms of addiction are now recognized as profound, often refractory brain disorders. It is not sufficient to blame the individual and tell them to just "stop" their injurious pattern of behavior. It is a problem in every developed nation, particularly among the youngsters.

New, alternative medicines and new devices are currently understudied in a search for effective, long-lasting treatments.

3.5 Cognitive Disorders

Schizophrenia, autism and ADHD are prime examples. They are prevalent disorders, each one affecting about 1% of the population. Modern genetic studies have identified previously unsuspected risk factors. For example, more than 100 genes may impart risk of autism. We are not dealing with Mendelian, single gene disorders. New computational approaches are needed to determine if the abundance of genes converge on certain metabolic or functional pathways, and if any of the targets are "druggable". The extreme heterogeneity is considered a barrier by some, but, in fact, it is an opportunity as new targets have emerged in the many different pathways. Chemists, molecular biologists and engineers are needed to develop novel compounds and methods for delivering them to specific targets in the brain.

Genes encode proteins and useful medications and devices might be developed with this information. But the gap between genes and behavior must be explored. This can be accomplished by non-invasive imaging of identified genotypes. Such stratification of populations may identify subsets that are more susceptible to certain therapeutic approaches.

3.6 Development disorders

This cluster would include autism, ADHD, intellectual disability of various degrees, specific language impairment, dyslexia, and learning disabilities. It is estimated that 5% of all live births in the US will require sustained care as they survive into adulthood. This problem is urgent.

Studies in this area as well as those described below might lead to medicines and devices that enhance sensation, perception and learning.

3.7 Disorders of neuron excitation and conduction

Epilepsy, in all its forms (focal, generalized, partial, complete), is common worldwide, affecting about 1% of the population. Epilepsy is also a co-morbid condition in a variety of states ranging from autism to brain trauma. Treatment of the seizures may affect the course of the other condition.

Seizures can be controlled in about 75 % of the cases. That is not good enough. Moreover, many of the "effective therapies are limited by significant side effects such as sedation. New agents, perhaps delivered directly within the brain by "nano-perfusion" would solve this problem. In addition, surgical approaches including micro-ablation of the seizure focus are under investigation. Deep brain stimulation and stimulation of the Vagus nerve are currently under investigation in attempts to minimize or eliminate seizures. Both approaches must be optimized.

Multiple Sclerosis (MS) is associated with a breakdown of the myelin sheath that surrounds nerve fibers. It is now possible to alter the relapsing/remitting nature of MS with agents that affect the immune response. This will call on the strong immunology community in Israel. TEVA has been a leader in this field.

3.8 *Disorders of Sensation and Movement, Rehabilitation and Enhancement*

Stem cells, prosthetic devices, and Brain Inspired Devices are all relevant here.
Loss of hearing is high on the WHO list of DALYs. Deficits in hearing, vision, olfaction and other senses offer opportunities for repair with devices and also with stem cell implantation. More than 100,000 cochlear implants are already in place and devices implanted in the optic nerve or visual cortex offer the promise of partial restoration of vision

The remarkable potential of Brain Machine Interface and of artificial cognitive systems in augmenting the capabilities of individuals is highly promising. Electrical signals led from multielectrode arrays implanted in the subject's motor cortex have been used to drive external, sophisticated robotic devices. Particularly promising are non-invasive approaches. Hence arm movements and even complex hand movements involved in reaching for and grasping an object have been initiated by robotic arms driven by the mere thoughts of a paralyzed subject. They can potentially be applied to remote operating of machinery by healthy individuals as well. Such systems are likely to occupy a significant place in the economy in areas that have broad impact on everyday life. Their development necessitates close collaboration between neuroscientists, computational scientists and engineers.

Israel has proven capabilities in similar multidisciplinary collaborations, which provide an outstanding advantage. To date they have proven successfully mainly in the defense sector, but intriguing spin-offs in high-tech industries world-wide are beginning to emerge.

3.9 *Brain-Inspired Computing and Technology (BICT)*

The brain-Inspired Computations and Technology (BICT) Research Cluster is envisaged to include research on:

1. Computational neuroscience and theory.
2. Brain machine interface.
3. Artificial computing systems: Brain-Inspired Computer Architecture
4. Computational Intelligence: Machine Learning, Computer Vision, Natural Language Processing, and Robotics.

This cluster will develop novel brain-inspired capabilities and technologies of marked personal, societal and economic value. Some of its research will interface with the research conducted in disease-oriented research clusters.

BICT has great potential for a major impact on the Israeli high-tech industry. The connections between computational and theoretical neuroscience and applications of computational and artificial intelligence are vast and impressive. One indicator of these connections is the large number of graduate students who studied computational neuroscience in Israel and are now leaders of industrial research institutes and of major US companies in Israel (See Demographics, below). Moreover, brain inspired models of visual, auditory, somatosensory and olfactory capabilities are developed and researched at major research centers in Israel. Some of these efforts have fueled startup companies in computer vision, speech and natural language processing.

Understanding the behavior of large network models inspire and enhance industries in distributed computing and communication networks. Models of perception and action are directly linked with the growing Israeli robotics industry, the booming applied research of autonomous airplanes and vehicles. Furthermore, research of human perception and cognition is directly affecting companies who deal with human-machine interaction, e-learning and training. All of the above have direct and positive interaction with the large and highly successful defense related industry in Israel.

An outstanding example of academy driven BICT Company is small company called MobileEye. A very significant number of its R&D personnel being graduates of the computational neuroscience programs. The company is revolutionizing the car industry all over the world with its vision based accident avoiding alarm system.

On top of that, BICT require and inspire new computer architectures, and together with the new algorithms that emerge from machine learning, computer vision and NLP, give birth to the emerging area now called computational intelligence, which, as noted below, Intel has correctly identified as one of Israel's academy great promises.

4 INFRASTRUCTURE CENTERS

All infrastructure needs cannot be listed as part of this report. However, we feel that the resources outlined above will provide useful synergies and stimulate interest in the following areas several of which are already partially underway funded by I-CORE, TELEM, Bi-National (i.e., see *Appendix 4.19*) or MAGNET grants.

INFRASTRUCTURE NEEDED FOR TARGET DERIVED (GENES AND PATHWAYS) AND CLINICALLY DERIVED (IMAGING) BIOMARKERS, See *Appendixes Infrastructure: 3.1-3.14 and Position papers: 4.1-4.19.*

Centers of excellence can be identified in several academic institutions (see recent creation of Brain Research Centers at a number of Universities; Israel Science Foundation-supported projects at particular universities or with inter-university collaboration; and I-CORE on advances in brain and cognitive science), but there is a need for expansion and for renewal.

- Clinically relevant laboratory research is strong in Israel, but the type of translational research that can lead through applied projects (e.g. creation and systematic evaluation of animal models) to "proof of concept" results, are needed for development of effective, marketable therapeutics.
- Multidisciplinary research can achieve remarkable results with a minimum of red tape in Israel. Recent examples include Israel National Nanotechnology Initiative (INNI) and technology advances in the Department of Defense related Institute.
- The entrepreneurial spirit in Israel is evident in the many start-ups, the number of patents, and the number of patent applications that have emerged in recent years.
- Great advantages for clinical research and in searching for genetic risk factors in Israel as stable, relatively homogeneous populations with a rich variety of genetic backgrounds (ethnic diversity). Tradition of excellent clinical neurosurgical, neurological, and psychiatric research, high quality publications. Example of Parkinson's Disease consortium). Sensitive to the need for biomarkers (gait in PD). Example of Sourasky Hospital.
    - 2,000 MRIs/year
    - 60% use = research
    - Phase 1 unit at Sourasky
    - 14.6 M NIS neuro with 50M NIS total research budget. Research lags not supported by VATAT. Donors "adopt" physicians couldn't contribute to research
    - Trained docs with considerable clinical research expertise
    - Delivery of health care (socialized) favors clinical research?
    - Stroke consortium with Hadassah and Ramban and Sourasky

- Relatively few hospitals increase the potential for collaboration in clinical trials (of necessity)

Our review, as summarized in *Appendix 3.2* indicates that new standardized equipment and resources are needed for the success of the RESEARCH CLUSTERS described above. Infrastructure is needed at all levels of investigation ranging from cells to human subjects. Our focus across the spectrum from basic science to clinical research is the path most likely to capitalize on strengths in Israel and efforts now underway. It is also the most likely path to attract funds from industry, and private investment as well as philanthropy.

In each instance the new equipment and new facilities require trained scientists, clinicians, and technicians to operate them to innovate in enhancing the design of the equipment and in novel uses of the resources. The facilities described below, in the hands of skilled Israeli biologists, physicists, chemists, nanotechnologists, engineers, and computer scientists will help ensure the success of the RESEARCH CLUSTERS as they develop medical and device-based therapeutics.

New administrative structures are needed to facilitate interactions among all interested parties.

4.1 Imaging

Imaging systems measure neuronal activity using methodologies and devices such as fMRI, MEG, PET, EEG, optical imaging and multielectrode arrays. In short is includes all approaches to understanding the functional anatomy of the human brain

We recommend the purchase of three MRI scanners, of at least 3T field strength and preferably one 7T system, that will be situated in existing research centers. The machines should be dedicated entirely for research so they can be used for non-human primates as well as for human subjects. Ideally, one scanner would be placed at a facility in the North of Israel, one in the Center, and one in the South. The same machines can be used for structural and for functional studies.

The scanners should be interconnected so that data gathered at one site can be interfaced with data gathered from the others. Further, interconnectivity might open the way to performing simultaneous multi-participant experiments that offer advantages in some types of research (see below). In time, other magnets within and outside of Israel can be brought into this network.

4.1.1 Magnetic Resonance Imaging (MRI)

Structural MRI can provide important best surrogate biomarkers for human brain disorders.

Factors that have limited the usefulness of MRI studies are the variability between brains, the variability between machines, and the small number of subjects in each study. It is important, therefore, to standardize measurements among imaging centers in Israel.

The ADNI project (Alzheimer's Disease Neuroimaging Initiative) in the US, addressed these issues, might provide a useful model for Israel. Funded for five years at $60M, with $40M from the NIH and $20M from the pharmaceutical industry and private foundations, this longitudinal study was designed to trace the course of minimal cognitive impairment as it evolved into full-scale dementia. About 800 individuals will be imaged under standard conditions and the data will be made available to all qualified investigators. This "precompetitive" project will provide important information for those interested Alzheimer's disease and in other brain disorders. New grants have been written and new funds from industry have been invested based on the initial findings.

The thought driving this project is that early diagnosis via imaging biomarkers might facilitate therapeutic intervention at an earlier stage – perhaps before neuronal loss is far advanced.

The Human Connectome Project initiated in the US at four major universities will evaluate 1,200 "control" subjects and it will, eventually involve many other imaging centers. Israel should play a major role in this effort. New coil designs and higher field strength magnets have dramatically improved spatial resolution by improving signal to noise ratio. New approaches to Diffusion Tensor Imaging and Fractional Anisotropy allow the charting of long axon tracts in unprecedented detail

In addition, capability for MR-spectroscopy (MRS) is extremely important to define normal brain composition, to record human and animal biochemistry in vivo and its perturbation by pharmacological and pathological events. MRS has practical utility in discovery and monitoring of neuronal and axonal markers, measures of energy status, membrane constituents, and osmolytes, as well as some xenobiotics, such as alcohol. This requires specific computational analysis, and more important exports in analyzing the results. Although these methods are currently most frequently encountered in human studies, as well as with transgenic and knockout mouse models, MRS adds a new dimension to anatomic and histopathologic descriptions.

They raise the possibility of a complete map of connections in the human brain at a on the sub-millimeter (mesoscopic) scale. This knowledge will allow investigators to stratify populations based on brain connectivity, and the ability to deal with heterogeneity in brain connections will enable more accurate evaluation of new therapies for brain disorders.

4.1.2 Functional Magnetic Resonance Imaging (fMRI)

4.1.3 Magnetoencephalography (MEG)

Event related neural signatures, captured when subjects are directed to perform a specific task, have proven useful in studies of memory, attention, movement and sensory perception. They are also critical in understanding cognitive pathologies, since functional disconnection between brain regions can occur even in the face of apparently normal structural connections.

In a remarkable recent development, information has begun to emerge in studies of non-event related activity when the brain is presumably at rest. Synchronies between different regions of the brain have defined "default" networks. Different patterns of activity within the resting brain default networks may provide biomarkers for a variety of cognitive and mood disorders. Patterns of activity in this situation have emerged that distinguish the cognitive, and emotional differences between neurotypical individuals as well as those afflicted with defined disorders.

Such findings offer opportunities for local brain stimulation and/or drug delivery (see below). This field is in its infancy.

Activity sensed by fMRI currently is Blood Oxygen Level Dependent (BOLD) and, thus, the spatial (several millimeters) and temporal (several seconds) resolution depends on blood flow. New probes, perhaps more directly related to neuronal activity are needed to improve spatial and temporal resolution. This type of research calls for the type of interdisciplinary cooperation that is strength in Israel.

Although investigators were identified in Israel which are leaders in MRI and MEG imaging, they often have to carry out experiments at odd hours or at sites located in other countries. At the time of writing, Israel has only one fMRI center devoted solely to research (3T scanner at the Weizmann Institute), and only one MEG (at Bar-Ilan University). In other locations fMRI is performed on clinical MRI scanners. Moreover, standardized infrastructure for coordinating MRI research across institutions hardly exists in Israel.

4.1.4 Electroencephalography (EEG)

EEG offers the advantages lower cost, ease of use and flexibility for long term (overnight) studies. Numerous laboratories in Israel use this relatively cheap and accessible tool. Recently, Israel has led in solving the technical difficulties in combining EEG and fMRI measurements in the same site and at the same time. For example, the National Institute for Psychobiology in Israel funded a project at the Tel Aviv Ichilov Hospital for developing this capability as a National Core Facility.

4.1.5 Positron Emission Tomography (PET) and Receptor Biology

PET in humans and animals will facilitate drug discovery by demonstrating the location within the brain of drug binding sites. It is also an essential tool for estimating receptor occupancy. A cyclotron must be located on site for generation of labile isotopes which may decay in a matter of minutes.

4.2 Genetics, Gene Expression, and Drug Discovery

4.2.1 Genomics

A Center should be established for high throughput DNA sequencing dedicated to studies of gene expression and for evaluation of genes that enhance the risk of brain disorders. These efforts are essential to identify biomarkers that are known to be involved in disease pathogenesis. Target derived biomarkers is a key avenue for drug discovery.

This Center should be located at an academic medical center but it should serve the needs of industry as well as academia in regard to analysis of brain disorders. Such a center must have the capacity to sequence hundreds, perhaps thousands exomes and/or genomes. Computational power must be adequate store many terabytes of data and to rapidly perform the computations required for the accurate reassembly of billions of nucleotide bases.

With increasing speed of DNA sequencing machine the advent of barcodes to "multiplex" sequence reads, and the accuracy afforded by new protocols, coupled with declining costs, the era of individualized medicine is rapidly approaching. Several Medical Centers in the US are drawing blood from all patients for whole exome or whole genome sequencing. It is estimated that sequencing of one individual's genome will be measured in the hundreds of dollars – a far cry from the billion dollars for the first genome!

In addition to individual DNA base pair variants (Single Nucleotide Polymorphisms - SNPs); it is now possible to identify small insertions and deletions (Indels) and larger Copy Number Variants (CNVs) by DNA sequencing. Such variants have been recognized since 2007 as the major source of genetic variation between individuals.

In the future, therapies will certainly be designed informed by individual genotypes. Most importantly, clinical trial design must include stratification based on genomic profiles. Many useful therapies have failed Phase III trials and have been discarded due to poor trail design that did not reach statistical threshold in heterogeneous populations. At this point, Israeli diverse population might offer an advantage for population studies in a relatively small number of subjects.

Other efforts are underway in Israel for "next generation" DNA sequencing, but none are dedicated to neuroscience. Judging from Genomics Centers in the US (Boston, New York, St. Louis, Texas) and in Europe, the need for increased capacity in Israel is clear. A request has been submitted to TELEM for a "Post Genomic Center" (see *Appendix 3.12*). However, neither this request nor the I-CORE center for "Gene Regulation in Complex Human Disease" (diabetes, inflammatory bowel disease, cancer, viruses), can handle the needs anticipated in the area of neuroscience and brain disorders. The sequencing centers should collaborate, sharing reagents, rapidly evolving technologies, and expertise to the benefit of all.

Several commercial opportunities arise from this effort. Laboratories, usually in the private sector, must be established to confirm results from high throughput sequencing in a manner that meets CLIA approved, high standards for human subjects. This might be performed by targeted DNA sequencing, by Comparative Genome Hybridization or by the Polymerase Chain Reaction – all of which can be performed by private labs. Genetic counselors must be recruited who can guide patients in difficult choices that must be made. Informed clinicians, knowledgeable enough to tailor therapies to genetic profiles, must be trained.

In some cases, the sequencing may be outsourced to CLIA compliant companies. Israel should be in the forefront of this effort. The ethnic diversity so evident among the peoples of Israel and the stability of the population are great advantages in searching for genetic risk factors.

Resources are needed to establish patient registries, blood collection, DNA preparation and storage. Interoperable databases are needed for data entry, cleaning and analyses. (See above). Most importantly, genetic councilors must be trained to transmit this formation to families and advise them of consequences for their families and opportunities for research.

Identification of genetic risk factors in the nervous system, coupled with new analytic tools to predict gene and protein networks, will point to signaling pathways and new 'druggable" targets. Such targets must be evaluated in animal models and in cell based assays. We recommend, therefore that mouse transgenic facilities and stem cells facilities be incorporated into the Genomics Center. This will take a combined effort of academia and industry.

4.2.2 Gene Expression

Once genetic risk factors are identified, one must determine environmental factors and genetic modifiers that govern gene expression. This will require the production and critical examination of appropriate animal (mouse) models, and the production of stem cells bearing the genetic variant in question. These are areas in which Israel has expertise but which needs to be expanded and enhanced to meet the needs of brain science.

It is essential to determine the levels of gene expression (levels of messenger RNA and protein in small regions of the brain at various stages of development. This will be important for diagnosis and monitoring therapies.

Multi-photon, high resolution, light microscopes are needed to assay the number and distribution of rare molecules at synapses throughout the brain. Many bioassays will depend on this approach. It is now possible to modify the function of cells and circuits in genetically engineered neurons with light of different wavelengths. Such "optogenetic" approaches will provide new targets for analyses of circuits and for assay of drug action.

4.2.3 Transgenic Mouse Facilities

Mice are the models of choice for studies of genetic risk factors identified in human neuropsychiatric disorders. There is currently only one core facility in Israel

(Weitzman Institute) for creation of transgenic, and conditional knock out, knock down, and/or knock in mice that is equipped with facilities for imaging and sophisticated behavioral analyses. A new national facility open to the entire scientific (academic and industrial) community is needed.

Gene targeting will require improved viral vectors for introducing genes to specific nuclei within the brain at designated times during development and in adult animals (see *Appendix 4.3 & 4.4*). Precise methods for evaluation of gene expression include multiphoton microscopy, biochemistry, imaging, high resolution (RefSeq) evaluation of gene expression, and electrophysiology equipment for in vitro and in vivo recording. Most importantly, automatic and precise methods for evaluating the behaviors of genetically altered mice are essential. This will involve observation over prolonged periods of time – often in the context of social behaviors. Automated data collection and machine learning paradigms are now in the forefront of such analyses.

The same mouse facility might serve as a breeding and distribution center for all of Israel, including the industry. At present, only the Weizmann Institute has a Center of this type in Israel (*Appendix 3.4*). This center is used 80% of time by local researchers and the remaining 20% with collaboration with investigators from other institutes, mainly abroad. It is not adequate to handle the required volume. We don't plan to build a new mouse facility; however, we recommend financing the adjustments needed for making part of existing facility as a service center that must serve also the industry. Behavioral monitoring and video tracking systems should be part of the center.

Other animal models should be explored as appropriate. Currently, human genetic risk factors make use of flies (Drosophila), worms (C. elegans), and Zebra fish (D. rario). We believe that studies of invertebrate animals will identify relevant biomarkers for drug development in the coming years.

4.2.4 Stem Cell Facility

Resources are needed for the creation and distribution of pluripotent stem cell lines established from human embryos (blastocysts) and from adult tissues via induced pluripotent stem cells. Such cells have become integral to high throughput drug screens, for analysis of mechanisms related to particular brain disorders. TELEM's RFP is underway for the establishment of Stem Cell service centers (*Appendix 3.11*), and therefore, the proposed budget in this report does not include this cost.

Implantation of stem cells to repair neuronal loss due to a degenerative process in different regions of the spinal cord or brain is now under way at a few centers around the world. Israeli scientists have been in the forefront of this effort.

iPS cells offer three advantages. First, as they are derived from the individual who may need them, the possibility of immune rejection is minimized. Second, since they are derived from an individual with a particular brain disorder, the pathophysiology is likely to be manifest in these cells when grown under appropriate conditions. Thus, they can be used to study disease mechanisms as well as to monitor the efficacy of drug action. Third, ethical issues dealing with human blastocysts and egg donors are minimized.

4.3 Brain Machine Interface

4.3.1 Brain stimulation

There is a large and growing market for effective targeted brain stimulation devices. Efforts are underway at several institutions and companies in Israel to treat brain disorders by "invasive" and "non-invasive" stimulation of cranial nerves such as the Vagus or the Sphenopalatine Ganglion, and also by stimulating peripheral nerves in the limbs.

Applications of stimulation include control of neuropathic pain that follows nerve injury or occurs as a late complication of diabetes, migraine headache, epilepsy, and neurological disorders that are accompanied by significant inflammation. Devices implanted in the eye, optic nerve and visual cortex that correct visual defects and that may even enhance vision are in early stages of development. Cochlear implants to improve hearing are commercially available. Notably, in a novel application, ganglia stimulation can target cerebral blood flow and hence ameliorate damage caused by stroke.

Transcranial Magnetic Stimulation (TMS) is currently under investigation in studies of selective attention and memory as well as in neuropsychiatric disorders such as autism, depression and ADHD.

More "invasive" approaches that involve stimulation though electrodes implanted in the brain have already shown great success and more applications with improved techniques are under investigation. Deep Brain Stimulation in drug-resistant Parkinson's disease is perhaps the most successful in this area. More than 100,000 stimulating electrodes have been implanted in the US alone. Successes have been reported in drug resistant depression, in obsessive-compulsive disorder, and in minimally conscious states following brain trauma.

Deep brain stimulation is now expanding beyond movement disorders (PD and dystonia) into new frontiers including depression, obsessive – compulsive disorder, addiction, and epilepsy. Therefore, Brain Inspired Devices/ robotics require novel engineering approaches. Improved multielectrode arrays are needed suitable for implantation in the human brain to monitor activity and activate circuits implicated in these neuropsychiatric disorders.

Direct recording from nerve cells in the exposed human brain, during surgeries performed for other reasons, is an emerging frontier. This approach builds on data gathered by MEG, EEG and fMRI. It will yield more precise data that can be used to drive robotic devices and to model human cognitive systems. Because of the nature of the methodology, this system should be placed in a top neurosurgery unit in a medical center, but should ensure proper ongoing interaction with a major academic center and with industry.

As noted above, the road between the laboratory and the clinic is a two way street. We must learn how each stimulation paradigm "works" to better design electrodes, electrode placement and stimulation protocols. New computational approaches are needed to analyze signals from neural ensembles recorded with multielectrode arrays. Efforts in this area will provide data for theorists interested in modeling various aspects of human cognition.

4.3.2 Robotics

Several examples are now evident in which electrical signals have been led from the brain to drive external devices such as robotic arms, hands and legs. The potential here and the need in Israel for correcting deficits that follow brain or spinal cord or peripheral nerve injury are obvious.

4.3.3 Brain-Inspired devices

The main goal here is to provide the vast computational facilities require for brain simulation and modeling, and to enable the development of new brain inspired (neuro-morphic and other) computer architectures and hardware. An excellent example to the synergy between novel and heterogeneous computer architecture was recently provided by Intel's investment in the computational intelligence institute in Israel.

Developing new hardware and computer architectures for BICT is certainly too expensive to be done in more than one cluster in Israel.

4.3.4 Nanotechnology

Approaches are needed for the design of nano-scale, selective, stable recording and electrical stimulation of neurons in selected targets. Nano- scale approaches are also need to improve local drug delivery, perhaps minimizing side effects. Nanotechnology is needed to design and implement tools for local delivery (on the micron scale) of drugs, genes and cells, precise placement of diagnostic probes, and focal recording and stimulation. See TELEM program in Nanotechnology, and also in *Appendixes 4.12-4.14*.

A center for neurophysiology should be established that includes equipment for hi-throughput electrophysiology to screen for targets and chemical compounds that act on them. Multi-array patch clamping, of isolated cells and brain slices.

4.3.5 Technical Development and Technical Support

We recommend on establishing a centralized facility for construction and maintenance of devices that will enable or enhance brain research and that are not available commercially. (See MCKINSEY report for president PERES, *Appendix 4.20 & 4.21*). This will be subsidized at first but expect it to become self-supporting in a few years.

Israel has strong groups in each of the areas outlined above, yet new approaches and improved devices, including electrodes and drug delivery systems are needed. This will take fundamental research in close collaboration with companies interested in immediate, practical applications.

4.4 Other needs to be incorporated into infrastructure centers

4.4.1 Brain bank

For collection and processing of brain tissue obtained at surgery or autopsy (See TELEM effort on tissue banking, *Appendix 3.9*, and also in *Appendixes 3.10 & 4.15*).

4.4.2 Bioinformatics and computation

New computational approaches and new ways of thinking about neural circuits are needed in most of the Research and Infrastructure Centers described above. Theory, computation, and bioinformatics (including clinical trial design and database management) should be incorporated into one or more of the Center applications and their relevance made clear in each case. The same is true of research at the level of neural theory.

Bioinformatics tools are needed to create databases that are powerful enough to monitor vast amounts of clinical data from large population's patients and controls. Data entry, data cleaning and sophisticated statistical analyses are often limiting in complex clinical studies. The databases should be "interoperable" to capture data from relevant centers within and outside of Israel.

4.4.3 Recruitment and Training of Clinician - Scientists

The Israeli neuroscience community is strong, but as is the case world-wide, there is a need for renewal. Young investigators, with novel ideas, must be enlisted in both academia and industry as part of this effort. First we must bring talent in different disciplines and different aspects of the same discipline together. And then we must show that the system works!

A focused effort is needed to support the recruitment in universities of top young investigators who currently stay abroad over the intended postdoctoral training, and in medical centers of top MDs who cannot exploit their expertise in Israel.

Buy back of clinical time essential for training of clinical investigators and research.
Special programs for training physicians and PhDs across the spectrum of translational/clinical research are needed.

5 DEMOGRAPHICS OF NEUROSCIENCE IN ISRAEL

5.1 Academia

There are approximately 1,600 members in the "Israeli Society for Neuroscience"(ISFN), 30% of whom participated in the last annual meeting. The members include about 600 PhD/MD/DSc, including postdcos, with students and technical staff comprising the remaining members (see *Appendix 2.1*).

The committee request information from eleven research institutes about principle investigators (PIs) and description of their main interest in research. Based on the provided information, 286 PIs were assigned to the clusters, as described above. The raw data is found in *Appendix 2.2*. The summary of the findings are presented in *Figures 1a and 1b.*

Figure 1a – Investigators classified by Clusters and Figure 1b: Number of investigators in each cluster in each institute

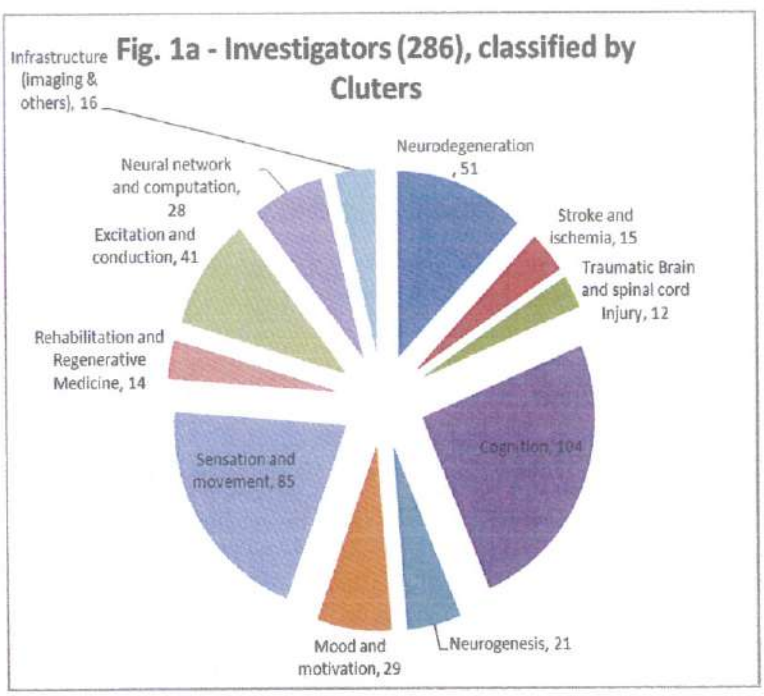
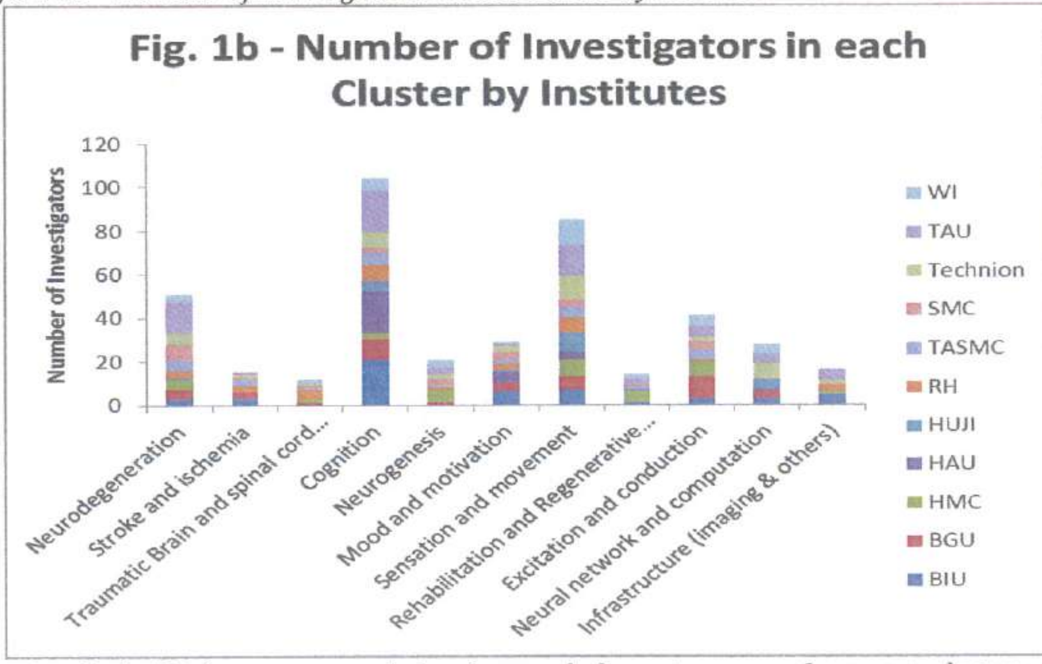


Figure 1b – Number of investigators in each cluster by institute



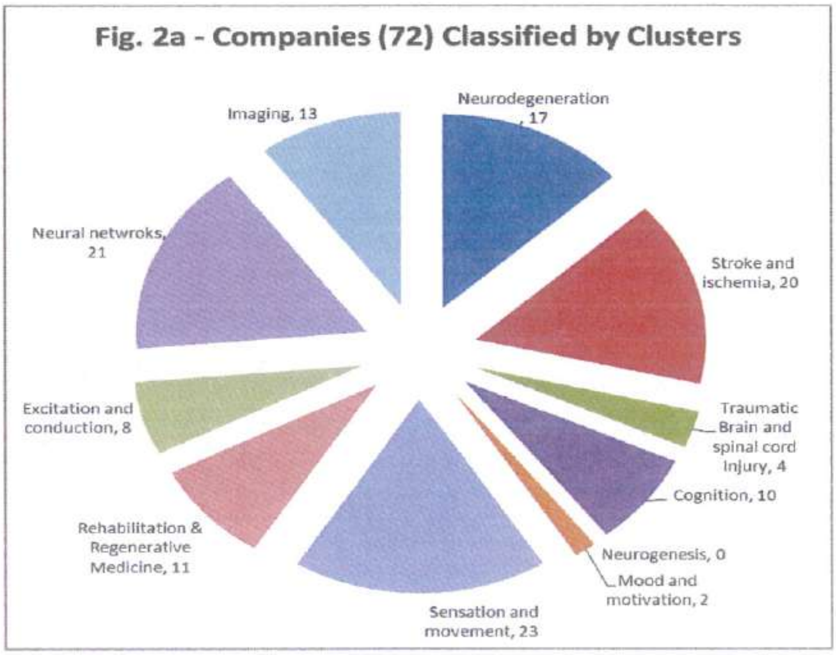
* *note:* Each PI (or company below) may belong to more than one cluster, and therefore, total number in all clusters is higher than the absolute number of investigators or companies included in the survey.

This data clearly shows that more than 1/3 (36%) of the scientists work in the area of cognition, sensation or movement. Each institute focuses on multiple areas.

5.2 Industry

A total of 72 companies in Healthcare were included in the analysis. A summary of their main research focii can be found in *Appendix 2.3* and their classification by cluster is presented below in *Figure 2*.

Figure 2a: Number of companies in Health Oriented Clusters



One additional cluster, the development of imaging devices ("Imaging"), was included in the classification of companies. We clearly show that "sensation and movement" is strong both in academia and industry. However, there isn't a direct correlation between the research focus of academia and the density of companies in those clusters. The largest academic focus is on cognition, while the majority of companies focus on neurogeneration, stroke, sensation and movement, and computational neuroscience.

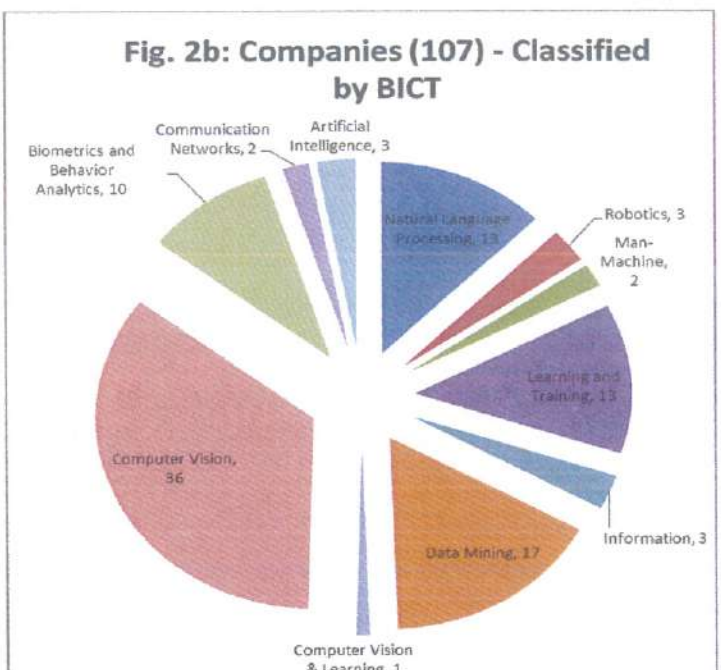
In addition to companies in healthcare, major Industrial-Research in the area of Brain-Inspired Computing and Technology are based in Israel. These include:

- IBM Research Labs. Machine Learning, Natural Language Processing, Natural Language and Speech, Computational Biology and Verification algorithms. Led by graduates of machine learning and computational neuroscience programs. Work in close collaboration with CS and Academic Brain Research Centers.
- GM Labs, Israel. Sensing-Acting systems, human-machine interfaces, Natural Language Processing, Computer Vision, robotics and autonomous vehicles. Led by graduates of CS and ICNC PhD programs.
- Microsoft Research Israel. Human-Machine Interfaces, Computer Graphics, Natural Language Processing, Machine Learning.
- Google Labs, Israel. Machine Learning, Data Mining, Computer Vision and Video analysis, Natural Language processing.
- Intel Israel: New Institute for Computational Intelligence (announced last week). From Intel's announcement: In order to effectively design and create the intelligent computing systems of the future, research is needed to advance the state - of - the-

art in the areas of machine learning and heterogeneous computing. For example, advanced machine learning algorithms can process the wealth of sensory data available in the environment today to enable intelligent computing systems that deliver a high level of perception and knowledge to the human. This will require power-efficient, high -performance computation using processors with multiple, heterogeneous processing elements. Heterogeneous (brain-inspired) computing adds a new level of complexity to the already challenging problem of parallel computing. Intel expects this research institute to drive disruptive advances in machine learning and heterogeneous computing. It is noteworthy that Intel is planning to invest over $15M in this institute in Israel, in the next 5 years.

We therefore analyzed this specific relevant industry in Israel. As shown in *figure 2b*, 107 are included in the list (some were also included in the HealthCare analysis), and these were subgrouped based on their focus and areas of interest.

Figure 2b: Israeli Companies in Brain-Inspired Computing and Technology

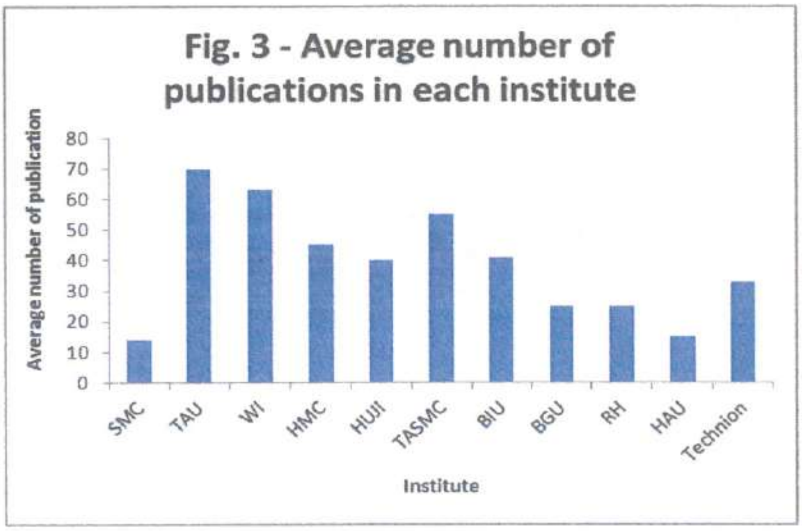


This diagram clearly shows the magnitude of the effort in this area within Israel.

5.3 Strength in Neuroscience research in Israel

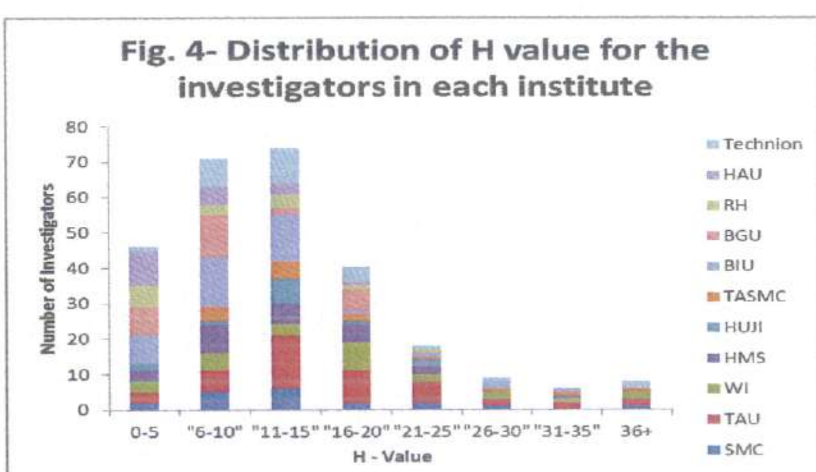
For each investigator we also looked at the number of publications, citations, and the H-value, as measures to quantify an individual's scientific research output (as published by Hirsch JE in PNAS, 2005 102:16569-72). Raw data is found in *Appendix 2.4*. The average number of publications for the 10 past years per PI in each institute is shown in *Figure 3*.

Figure 3: Average number of publication in each institute for years 2001-2011



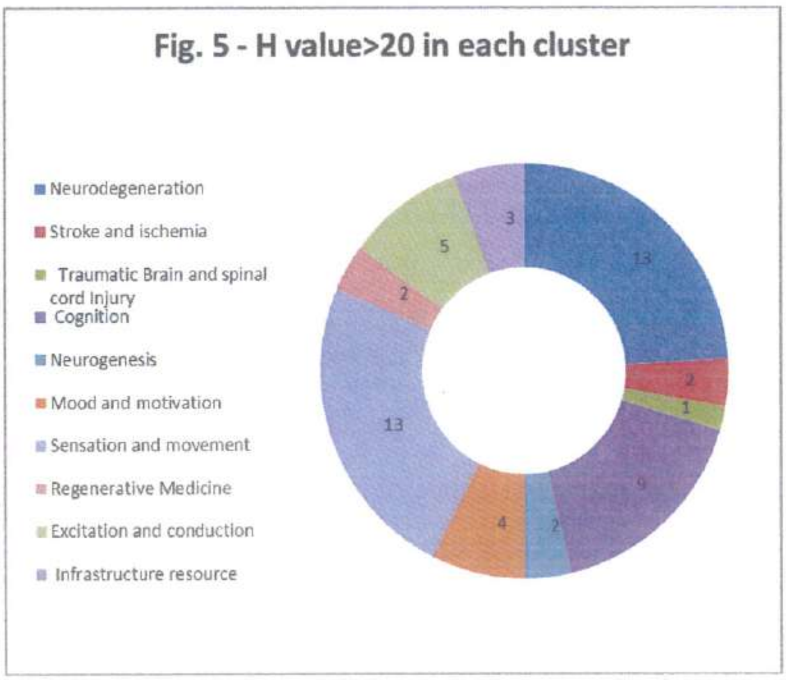
We then looked at the distribution of *H* value, as a measure for the scientific output of a researcher through citations. The distribution in the H-value for the scientific neuroscience community in Israel is shown in *Figure 4.* While H values are only one measure of scientific productivity and should never be used in isolation to judge a person's, a university's or a country's productivity, we use it here as a first approximation to indicate the distribution of highly qualified scientists in particular fields. Obviously, future selection of clusters, cluster sites, and membership in clusters will need more detailed scrutiny of individual scientific impact.

Figure 4: Distribution of H value for the investigators



According to this method of analysis, an H-value of 20+ is considered a high score, and represents a significant research contribution in the given subject. Neurodegeneration and sensation and movement were the two clusters with the highest number of investigators with H-values greater than 20(*figure 5*).

Figure 5: Number of investigators with Value>20, by cluster



5.4 Clinical studies

For the analysis of clinical studies conducted in Israel, we used the data base published by the NIH: http://clinicaltrials.gov/ct2. We first compared the number of clinical studies conducted in Israel and in the US for several indications in each cluster. The raw data is found in *Appendix 2.5.* Table 1 below shows the total number of studies conducted in Israel and in the US for the same indications, sub-grouped by clusters. Note that Israel has about 1/50th the US population, (something like one average state), and perhaps, proportionately, a somewhat larger scientific community. Nevertheless, the number of Israeli studies in Table 1 are far greater than 1/50th the US studies.

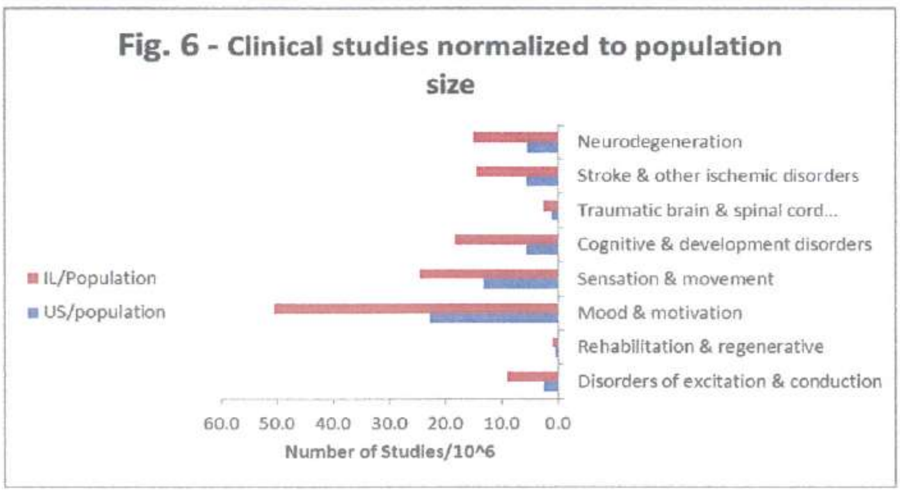
Table 1: Clinical Studies in Israel and the US for A Given Group of Indications, Grouped By Cluster

	Total	US	IL
Disorders of excitation & conduction	1455	764	66
Rehabilitation & regenerative	360	134	7
Mood & motivation	12103	7086	372
Sensation & movement	7689	4109	181
Cognitive & development disorders	3133	1771	134

Traumatic brain & spinal cord disorders	768	339	18
Stroke & other ischemic disorders	3422	1759	107
Neurodegeneration	2513	1706	111

The above results were then normalized to a population size of 10^6, and compared to the US values (*figure 6*). We used the base population numbers of 7.35 million in Israel and 310.20 in the US.

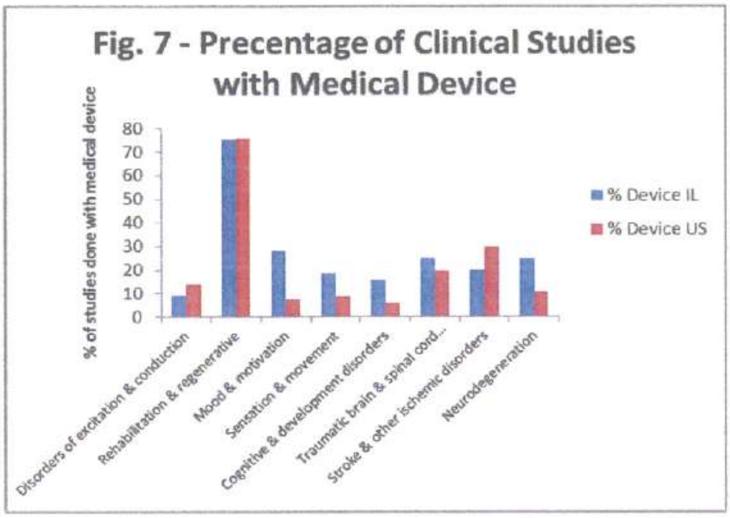
Figure 6: Number of Clinical Studies by Cluster, Normalized to Population Size in IL and US



Although the absolute number of studies is higher in the US, when normalized to population size, a significantly higher relative number of studies are conducted in Israel. Interestingly, among all clusters, studies related to mood & motivation is figure prominently.

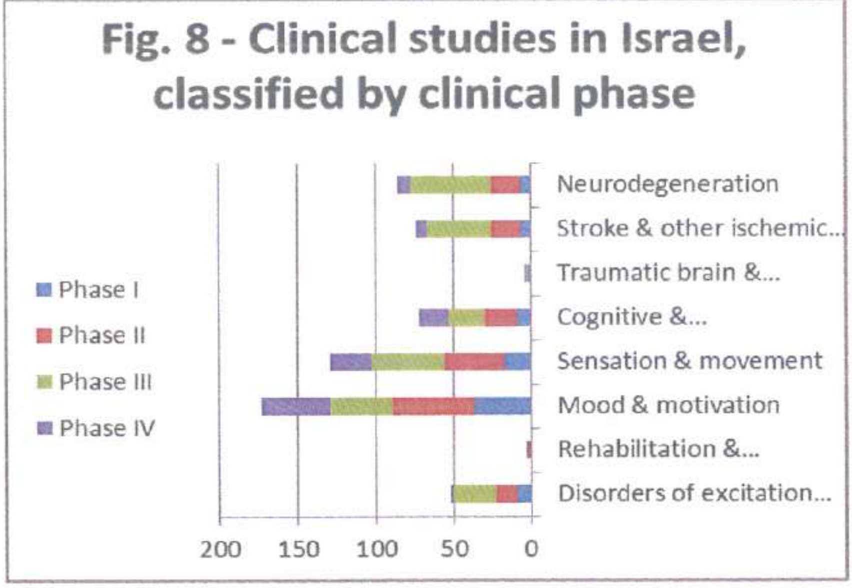
An analysis of the above results, based on type of intervention in both locations, as shown in *Figure 7* below, indicated a slightly higher proportion (%) of studies on medical devices in Israel relative to the US. This result is not surprising, and is supported by the number of Israeli companies developing medical devices (see *Appendix 2*).

Figure 7: Comparison of the Percentage of Clinical Studies on Medical Devices in Israel and in the US, By Cluster



Israeli clinical studies were then broken down by clinical phase. This breakdown, also by cluster, is presented in *Figure 8* below.

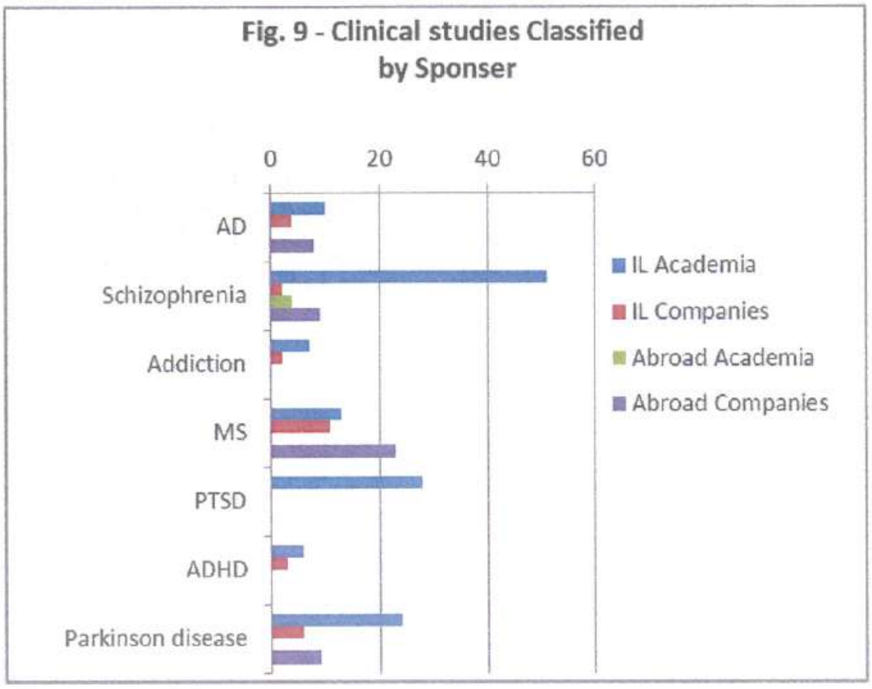
Figure 8: Clinical Phase Breakdown of Israeli Clinical Studies in Neuroscience, By Cluster



The above results emphasize Israel's capabilities to conduct clinical studies in both early and advanced stages.

Finally, we analyzed study sponsors in specific indications (*Figure 9*), and found that the majority of studies are sponsored by Israeli academic groups, such as medical centers and universities.

Figure 9: Israeli Clinical Study Sponsors by Indication



There are two likely reasons behind the high sponsorship level of academic groups and the low sponsorship level of industry: (1) Immaturity of the research field; (2) Collaboration of companies with investigators at the medical institutions, which applies as the study sponsor.

Interestingly, we found that approximately 5% of all the total studies in neuroscience are conducted in Israel, while only ~3% in the area of cancer (data not shown). Most of the studies are sponsored by an Israeli entity. An explanation for this finding was given by Dr. Michal Roll, director of R&D at the TASMC, as follows: "The results are not surprising. There are many first line therapies in cancer that their effects are known, and studies with new drugs usually are conducted in patients that are not responding to anything. Therefore, the competition for patients is very high, and many of the studies are not done here in Israel. (see *Appendix 4.18*)

5.5 Patents

Patents were also examined as a parameter for demonstrating activity and strength in neuroscience research. The numbers of registered **patents** and patent **applications** were derived from the data base published in the "United-States Patents and Trademarks Office" (web site: http://patft.uspto.gov/), and are found in *Appendix 2.7* to this report.

The number of patents since 1976 and patent applications since 2001 in Israel for several indications, by cluster, are shown in *Table 2* below:

Table 2: Patents in Israel by clusters

Indication	Patents	Applications
Neurodegeneration (Alzheimer, ALS, Parkinson, Huntington)	90	98
Stroke and ischemia (Stroke, Vascular dementia, Migraine)	49	55
Cognition (Schizophrenia, Autism)	16	22
Mood and motivation (Depression, PTSD, Anxiety)	45	67
Sensation and movement (Pain)	213	459
Excitation and conduction (MS, Epilepsy)	45	70

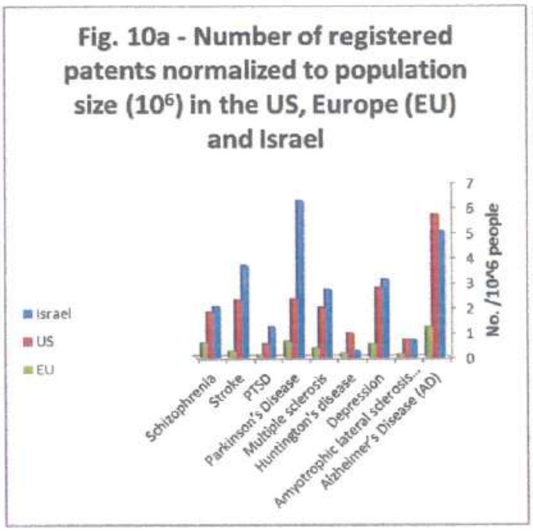
The results in Table 2 clearly demonstrate that "sensation and movement" has the highest number of existing patents and patent applications. Additionally, this is the only cluster for which the number of applications is double the number of existing patents. This finding indicates the research trend towards that cluster, and most likely reflects on the number of translational researches in the field, as suggested by *Figure 2a and 2b*.

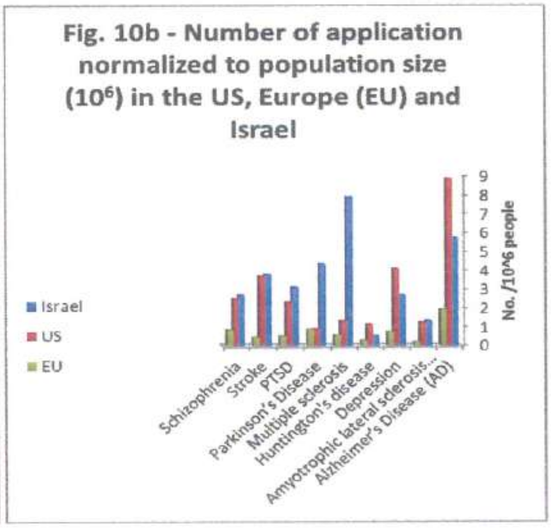
We then broke the clusters down to specific indications, and compared the number of existing patents and patent applications by indication in Israel, the US, and the EU (*Table 3)*. This analysis was also normalized to population size (*Figures 10a and 10b*).

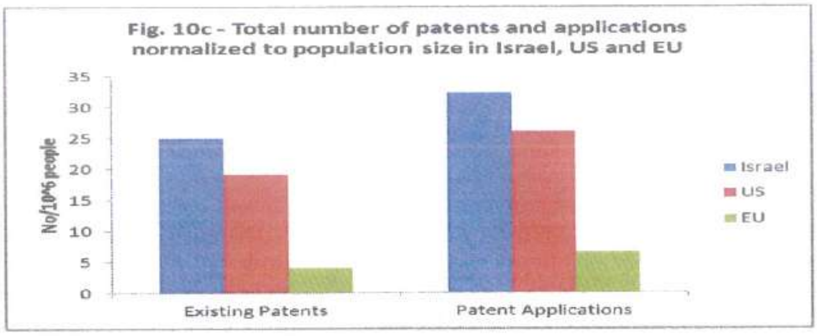
Table 3: Total Number of Patents in Israel, US and Europe, by Indication

	Patents			Applications		
Indication	**IL**	**US**	**EU**	**IL**	**US**	**EU**
Alzheimer's Disease (AD)	37	1770	605	42	2735	980
Amyotrophic lateral sclerosis (ALS)	5	216	65	10	386	106
Depression	23	866	263	20	1266	385
Huntington's disease	2	303	80	4	358	140
Multiple sclerosis	20	620	182	58	418	290
Parkinson's Disease	46	723	322	32	281	442
PTSD	9	167	50	23	727	255
Stroke	27	708	126	28	1144	231
Schizophrenia	15	562	292	20	776	435
Total	184	5935	1985	237	8091	3264

Figure 10: Comparison in the number of patents (10a) and applications (10b) for specific indication and a summary (10c) normalized to population size (10^6) in the US, Europe (EU) and Israel.







All of the above data supports the conclusion that Israel's neuroscience community is strong overall, and particularly in the areas outlined above. This strength is also evident in the major academic centers and hospitals throughout the country.

6 GOVERNANCE

Each Research Cluster and each Infrastructure Center should include members from academia, industry and relevant government agencies. Each one should be co-chaired by individuals from academia and industry. To ensure diversity of views, Clusters should consist of 10 – 20 members who will be responsible for planning and overseeing research projects. Clear milestones should be established and progress judged by the Board of Directors (see below) on a regular basis.

Each Cluster and each Infrastructure Center should hold regular (at least bi-monthly) group meetings to plan new activities and to evaluate progress. The TELEM group should sponsor an annual Colloquium open to a wider audience.

All Clusters and Centers should report to a **Board of Directors** that will meet at least once each year. A subcommittee of the Board of Directors, including members nominated by TELEM, will be responsible for assigning funds to each cluster based on their accomplishments and future plans.

An International Board of Scientific Advisors drawn from academia and industry should be formed to evaluate ongoing science and new ventures proposed by the Clusters and Centers. They will meet as necessary and they will report to the Board of Directors.

Before approving a Research Cluster, prospective partners should reach agreement in principle regarding intellectual property. Much of the research will likely be "precompetitive" so issues regarding IP may be clarified as the research progresses.

As part of the working plan of the cluster, a mechanism of data sharing between the parties and the other clusters must be established.

General considerations related to the infrastructure centers:

- The Centers will operate on the basis of service center, and will not have any intellectual property rights regarding the results of the research performed by the Clusters. The hosting institute will not have any priority in doing research in the center.
- **Infrastructure Center Executive Committees** at each site will approve the projects and prioritize requests. Top priority should be given to subjects described in this report. Priority is for any other research; the use for clinical procedures is at the last priority, and only if there is an unused time for research.
- *Subcommittees should be considered for*:
    - *Standardization of procedures (SOPs)* to facilitate information sharing.
    - *Ethical and Regulatory issues*: for the use of these devices for human uses out of hospitals. Note that in Israel this is allowed by law only if a

hospital is part of the research or gives its authorization - Helsinki agreements
    - Clinical designs for the experiments, including physicians, geneticist, etc.
    - Data management
- Service fees should be set to cover operating expenses. All income from fees should be reinvested to upgrade equipment and improve services.

7 REQUEST FOR PROPOSALS - SELECTION CRITERIA

7.1 *Criteria for the RFP*

The following issues should be addressed in evaluating RFPs for each cluster.

- *The potential societal and economic value.*
- *The need for therapeutics* in the area of interest. This should include medical treatments and devices, a description of what exists now including advantages and risks.
- *The competitive potential world-wide.*
- *Relevant basic research* essential to reach the stated goals of the cluster.
- *Translational research,* including the development of appropriate animal models that will bring basic discoveries to the proof of concept stage.
- *A data sharing plan* must be spelled out in detail. This includes issues relevant to Intellectual Property as the projects evolve
- *Participants* Including discussion of individuals from academia, industry and government agencies that might participate in each cluster and plan for attracting talented scientists and business persons back to Israel.
- *Availability of validated biomarkers and endpoints* that will maximize success at each stage (preclinical and clinical). This should include target - derived markers as well as empirical observations.
- *Infrastructure needs* essential to move the projects forward at each stage. A few of the most obvious needs at various levels of analyses were listed above. Each item on the list must be documented in detail. The list will certainly grow as the papers are written.
- *International collaborations* with industry, philanthropy and venture capital firms.
- *Manufacture and marketing* plans for successful therapeutics should be formulated, preferably within Israel or in close collaboration with international firms. Plans should be formulated for worldwide distribution of successful products.
- *Metrics* to measure progress and success in regard to stated goals.

7.2 *Infrastructure Centers*

- *Relevance and need for goals described by the RESEARCH CLUSTERS*
- *Expertise in the use and maintenance the equipment and informatics.*
- *User communities* must be specified.
- *Experience* with the requested equipment.
- *Technical staff* must be described in detail
- *Plans for self – sufficiency* after five years of support.

7.3 *Measures of success*

- Number of new patents
- Number of new Phase 1 trials

- Number of publications
- Number of meaningful industry/academia collaborations, such as published articles resulting from cooperation between the universities and the industry
- Number of new world-class leading scientists recruited as faculty members
- Number of junior scientists / post-docs/ Ph.D. students/ M.Sc. students

7.4 Challenges

- Issues involved in the sharing of ideas, data, and intellectual property are formidable and must be addressed as we explore industry – academia - government collaborations.
- Positions provided at universities to sustain the TELEM effort.
- Governance (jealousies)
- Hospital have no money for salary support (to buy time) even though the have money for research.
- Administrative hang ups, bureaucracy slows things down.
- The need for funds is clear. Sources within Israel and from Europe are meager, far below what is required for front rank research, by any measure. Our recommendations must include pathways to new funds – beyond the usual granting agencies.
- The situation with regard to postdoctoral fellows in Israel has become acute. Many talented fellows leave Israel and few return.

8 BUDGET

We present the whole budget needed for the project but the way to share between TELEM, the institutes, privet donors and the industry is up to TELEM capabilities and desires. Nevertheless, the model that INNI was financed (1/3 TELEM, 1/3 Universities and 1/3 Donations) seems reasonable for our project.
The budget was built in a modular way and implementation step by step could be considered. For example starting with 4 RESEARCH CLUSTERS at the first year and only in the third year considers having more clusters.
We estimated the costs according to the present prices, but prices of equipment in this field tend to go down thanks to technological developments. One must look at our detail budget as a way to set the framework and the board of directors should revised the budget when the call for proposal is been published according to the future prices and capabilities.
The budget is not including the construction of buildings. We believe that the hosting institute of each center should provide the building .Only room adjustments (electricity, faraday cage etc.) should be part of the TELEM budget.

8.1 RESEARCH CLUSTERS

Each Cluster – Budget for 10 clusters Planning and conducting experiments	\$1.6M/year/cluster	\$80M

8.2 Infrastructure Centers

8.2.1 Imaging – Three centers

MRI machines for human- two 3T, one 7T	\$15M
MRI machines for small animals -one 11.7T, one 9.4T	\$4.5M
Computers	\$2M
Data management	\$2M
MEG & EEG machines (three EEG, one MEG)	\$3M
PET-CT one for human and one for small animals	\$3M
Personnel (2 physicist, 1 computer scientists, 2 technicians)	\$2.2M
<u>Total imaging centers</u>	**<u>\$31.7M</u>**

8.2.2 Genetics, Gene Expression, and Drug discovery

High throughput DNA sequencing	
Second generation seq plus enrichment solution	$4M
Personnel – Informatics, data analysis, storage, and distribution (1 bioinformatics PHD, 2 technicians)	$1.45M
Validation (re-sequencing, PCR)	$1M
Computational biology (network analyses)	$1M
Registries	$1M
Gene Expression	
RefSeq/ in situ hybridization	$2M
Epigenetic modifications	$2M
Drug discovery	
Mouse Models	$5M
Multiphoton fluorescence microscopy X2	$1M
Total Genetic center	**$18.45M**

8.2.3 Brain Machine Interface

Equipment

Animal facility including a surgery for primates:	$3 M
1 Robotics and virtual reality systems (including R&D in neuro-prosthesis systems):	$2 M
1 Advanced human psychophysics and behavior monitoring system:	$1 M
1 ECoG system– electrophysiology lab for humans including clinical testing of BMI:	$0.35M
1 Invasive electrophysiology system for recording in human patient:	$1 M
2 Closed Loop Deep Brain Stimulation Systems for Parkinson and other diseases for animal models and humans	$1.1 M
Telemetry devices for wireless communication of brain signals:	$1 M
Lab for new electrodes design- Mechanical plus electronics, including high resolution single cell recording devices	$2.3 M
Total equipment:	$11.75 M

Operating Costs (per year)

Technical staff - (2for labs, 1 for animals, 1 for workshops): 4 x $70K *5=$1.4M	$1.4 M
2 physicist salaries:	$1.5M
Total operation cost:	$2.9 M

Total Brain Machine Interface center **$14.65 M**

8.3 Total budget for the project

RESEARCH CLUSTERS	**80M**
IMAGING	**31.7 M**
GENETICS, GENE EXPRESSION, AND DRUG DISCOVERY	**18.45 M**
BRAIN MACHINE INTERFACE	**14.65 M**
TOTAL	**144.8 M**

8.4 Financial FLOW model for 5 years budget

YEAR	1	2	3	4	5	**Total (M$)**
RESEARCH CLUSTERS	**16**	**16**	**16**	**16**	**16**	**80**
		Imaging				
Equipment	14.75	14.75				29.5
Personal	0.44	0.44	0.44	0.44	0.44	2.2
Total	13.69	13.69	0.44	0.44	0.44	31.7
	Genetics, Gene Expression, and Drug discovery					
Equipment	8.5	8.5				17
Personal	0.29	0.29	0.29	0.29	0.29	1.45
Total	8.79	8.79	0.29	0.29	0.29	18.45
		Brain Machine Interface				
Equipment	5.875	5.875				11.75
Personal	0.58	0.58	0.58	0.58	0.58	2.9
Total	6.305	6.305	0.58	0.58	0.58	14.35
Total project	43.785	43.785	16.31	16.31	16.31	144.8

Specific funds should be set aside to support postdoctoral fellowships in neuroscience both the salaries for the fellows and a research budget to support their studies that would be awarded to specific labs on a competitive basis.

9 SUPPLEMENTAL RECOMMENDATION

A. Rationale and recommendations

1. We fully recognize the cardinal importance of advancing state-of-the-art infrastructure in the neuroscience in Israel to permit cutting-edge research in basic- as well as disease-oriented brain research. We hence endorse the main report recommendations concerning the 'infrastructure clusters'.

2. We also endorse the call for research clusters as in the main report, nevertheless, we propose that TELEM considers issuing RFPs for research in the disease-oriented domains under the general umbrella of "disease-oriented research in the neurosciences" rather than per a specific type of disease. Competition among RFPs will unveil the specific disease-related areas of excellence worthy of support.

3. We think that Brain-Inspired Computation and Technology (BICT) is a rich, critically important and promising domain of R&D that should be considered independently of disease-oriented research, since its potential implications for individuals, societies, cultures and economies at large in the forthcoming decades cannot be overestimated and much exceed its potential contribution to disease-oriented research.

4. The Israeli R&D community offers unique advantages in BICT R&D, because of multiple converging factors: availability of strong research groups in a spectrum of disciplines ranging from mathematics and physics, engineering, computer sciences, brain and cognitive science, and computational neuroscience; organizational culture favoring multidisciplinary, out-of-the-box thinking and reduced red-tape; and proven achievements, both in the civilian and the defense sectors, in areas that can inform and advance BICT R&D, including visint, avionics, data mining, cryptography, artificial networks, advanced electronics and engineering.

5. We therefore recommend that BICT R&D in Israel should be supported with an emphasis and scope significantly larger than those reflected in the main report. We specifically recommend the RFPs for research clusters in BICT be issued in the topics listed in B.1 below, and that infrastructure clusters be supported on the basis of RFPs as detailed in B.2 below. We recommend total investment of up to $45M in BICT areas combined over a 5 years period.

B. BICT Budget Estimate (per 5 years)

B.1. BICT Research clusters: $20M

5. Computational and Theoretical Neuroscience: $5M
   Based on estimate of funding 10 projects per year (100K per project/year)
6. Brain machine interfaces: $2.5M
   5 projects per year (100K per project/year)
7. Artificial computing systems: Brain-Inspired Computer Architecture: $2.5M
   5 projects per year (100K per project/year)
8. Computational Intelligence: $10M
   10 moderate size projects ($100K/y)
   4 large projects ($250K/y)

B.2. BICT Infrastructure clusters: $25M

1. Platforms for data acquisition storage visualization and analysis: $5M
2. Platforms for the engineering of brain-machine interface systems: $5M
3. Platforms for large scale simulation systems: $5M
4. Platforms for hardware implementation of brain inspired computing architectures: $5M
5. Platforms for the assembly of computational intelligence and robotic systems: $5M

Signed:

Dr. Yadin Dudai

Dr. Yitzhak Ben-Israel, Major Gen. (Res.)

Dr. Shaul Hochstein

10 LIST OF APPENDIXES

The appendixes are part of this report, and can download in the following website: (http://www.magnet.org.il/brain.html):

1. General
   1.1. CV of the committee members
2. Demographics
   2.1. ISFN.demographics 2009-2010
   2.2. Investigators by clusters
   2.3. Companies by clusters
   2.4. Publications and citations
   2.5. Clinical studies
   2.6. Registered patents and Applications
3. Infrastructure
   3.1. questionnaire to infrastructure
   3.2. Analysis of surveys to infrastructure needs
   3.3. Michall Neeman-IBMIT
   3.4. Weizmann_ infrastructure
   3.5. Brain Imaging Super Center-Weizmann
   3.6. TAU.ImagingCenterPresentandFuture
   3.7. costs for operation MRI center_Yanic_TAU
   3.8. Live molecular imaging at Sheba
   3.9. biobanking.translation of TELEMs report
   3.10. needs for brain Bank – yakov
   3.11. stem.cells.translation of TELEMs report
   3.12. proposal to TELEM for infrastructure to genomics
   3.13. Infrastructure_of_the_genomic.proteomic_center_for_complex_diseases_TELEM_17.3.11
   3.14. research centers-translation from the Neeman's report
   3.15. Selected Research Areas in BICT
4. Position papers
   4.1. Abraham Zanger-neurostimulation center
   4.2. Doron Havatzelet-TELEM Brain research Initiative
   4.3. Ilana Gozes-center for Neurodegenerative Diseases
   4.4. Kobi Rosenblum-Center for Gene Manipulation in the Brain
   4.5. Moshe Bar-Excellence Center for Psychiatric Neuroscience
   4.6. Nati Ezov-Major & Basic Neuroscience R&D Related Equipment
   4.7. Nicola Maggio-Center for Neuroelectrophysiology

4.8. Rivka Savi-MRI research unit at Rambam
4.9. Talma Hendler-Basic&clinical research in neuroscience
4.10. MRI units in Israel
4.11. Moshe Abeles-Developing MEG for localizing epileptic foci
4.12. NeuroNano-BGU
4.13. NeuroNano-BIU
4.14. NeuroNano-TAU
4.15. sheba-biobanking of brain tissues
4.16. Avi Israeli - Epilepsy research in Israel
4.17. Avi Israeli - Physical medicine and rehabilitation
4.18. MIchall Roll-clinical studies in Israel
4.19. BIRD Neurotechnology White Paper October 30 2011
4.20. MCKINSEY.report1
4.21. MCKINSEY.report2

11 EFFORTS UNDERWAY OR UNDER CONSIDERATION

- **Stem cells** – Approved for budging by TELEM - 10M USD. The RFP is underway. The summary of the report submitted to TELEM was translated, and is attached to this report in *Appendix 3.11*
- **BioBanking** - Approved for budging by TELEM - 10M USD. The RFP is underway. The summary of the report submitted to TELEM was translated, and is attached to this report in *Appendix 3.9*
- **Nano Centers** in TAU, BGU, Technion, BIU, HUJI, WI. Three Position papers related to NANO for neuroscience are attached to this report in *Appendixes 4.12-4.14*
- **The Smoler Proteomics Center**, Technion. A description of their capabilities and available infrastructure are found in the translation of "Neeman's report in *Appendix 3.14*, pages 6-7.
- **I-CORE** for "Gene Regulation in Complex Human Disease"- awarded to an inter-institutional team led by Prof. Haim Cedar (HUJI).
- New application for "**Post Genomic center**" was submitted on March 2011 to TELEM, *Appendix 3.12*
- **Genomics at the National Institute for Biotechnology in the Negev** [BGU]. List of Infrastructure are found in the translation of "Neeman's report in *Appendix 3.14*, pages 31-32, including:
    - The DNA Microarrays and DNA Sequencing Laboratory
    - Proteomics Unit
    - Microscopy and FACS Unit
    - Bioinformatics Core Facility
- All institutes have genomic infrastructure, most of them 2nd facilities
- **I-CORE** for Advanced Approaches in Cognitive Science – awarded to an inter-institutional team led by Prof. Yadin Dudai (WIS).
- **MAGNET** – a program at the OCS for consortium usually led by the industry to develop enabling technologies in different areas and subjects. These days, a new MAGENT program is being established for neuro-stimulation and neuro-imaging. This program may be run through the IC-BRAIN new initiative, in collaboration with Canada.
- **President PERES initiative.** See report in *Appendixes 4.20 & 4.21*

12 Acknowledgements

We wish to thank all Israeli universities and research institutions–particularly the respective Vice Presidents for research and their representatives for their cooperation and support for the Committee's work. We appreciate the insights received from the leading Researchers who helped and provided us with positions papers and many more information. We would like to thank several Israeli industry leaders for their useful comments and feedback on the needs in the field of neuroscience. We wish to thank "The Israel Academy of Sciences and Humanities" for their logistical help. Finally, we wish to thank Mrs. Annaliese Sharkey, the Chair's private assistant for her organizational efforts and for the large amount of work and time that she devoted to this committee.