SUBIC: Stockholm University Brain Imaging Center

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Abstract

This contribution presents an outline of SUBIC (Stockholm University Brain Imaging Center, working name). SUBIC is conceived as an interdisciplinary infrastructure that will promote Stockholm University's participation in international cutting-edge research focused on the function and the morphologic evolution of the brain.

Introduction

SUBIC is conceived as a brain imaging infrastructure to be hosted by Stockholm University for advanced research in the Humanities, Social Sciences, Evolutionary Zoology and Law. The new infrastructure will supplement the range of resources for scientific research already available at Karolinska Institute's current brain imaging infrastructures by offering low noise (quiet) brain imaging technologies specifically tailored to the special needs of behavioral, psychological and developmental studies involving spoken language and other acoustic stimuli as well as advanced technology to study the morphological and functional evolution of the brain in non-human species. This combination of functional brain research in humans with the zoological perspective on the morphological and functional evolution of the brain in other species will integrate Stockholm University's multidisciplinary expertise and create a brain research center of both national and international relevance.

The geographic proximity and complementarity of the brain imaging resources that will be available both at Karolinska Institute and at Stockholm University will trigger important scientific synergies and place SU's at the cutting-edge when it comes to sophisticated brain imaging facilities dedicated to a wide range of psychological, social and developmental scientific research. In addition, from a scientific and a logistic perspective, Stockholm University is in a unique position to make productive use of such an advanced infrastructure with its in-house scientific expertise as well as to provide excellent integrated laboratory space for that infrastructure. Needless to say adequate scientific expertise and specialized technical competence are necessary conditions to insure a high-quality output from brain imaging studies but there is a critical mass of researchers within Stockholm University's four faculties – Humanities, Social Sciences, Natural Sciences and Law – who are already engaged in scientific research that uses brain imaging techniques. Indeed, many of these researchers are today collecting their brain imaging data at the Karolinska Institute or abroad. Also the necessary detailed knowledge of magnetic and electric fields, as well as of the cryotechniques involved in MRI and MEG devices for brain imaging, is available from among researchers from the University's Department of Physics. The same goes for the needs of advanced computational competence, which is available with Stockholm University at the Departments of Mathematics and the Department of Statistics, for instance. In parallel with the availability of expertise to carry out the methodological and computational tasks required by the advanced brain imaging technology per se, a significant contribution will come from Stockholm University's Faculties of Humanities, Social Sciences, Natural Sciences and Law in terms of non-clinical research areas, addressing central basic research questions concerning the fundamental nature of both non-human and human cognition, learning, information processing and interactions with other individuals. We argue that it is via this basic research that Stockholm University's contribution will be most significant because it will provide high-quality reference information on the fundamental functions and features underlying – i.e., essential knowledge on human and non-human behavior underlying a wide range of scientific research.

In addition to the scientific expertise and breadth of potential research questions per se, the laboratory space available at Stockholm University is an optimal location for a well-planned brain imaging center, with easy access for handicapped, parents with small children, a number of non-model animal species as well as for the delivery and storage of lab supplies. Stockholm University has made available a 360 m2 laboratory space on a single ground level plan that meets all the requirements of volume dimensions and energy supply imposed by the brain imaging infrastructure.

The infrastructure will be available for national and international academic researchers from all the disciplines. Specialized technical staff (1.5 fulltime) will maintain the infrastructure and assist researchers with technical issues and experiment design. The infrastructure may also be available, with lower priority, for non-academic research.

A multidisciplinary board will manage the infrastructure and be ultimately responsible for planning and assessing study proposals as well as allocating technical and other staff resources to conduct the studies.

Scientific aims

The main scientific aim to be achieved by this infrastructure is the study is to integrate the cognitive, social and evolutionary perspectives in the study of brain function. To achieve this, SUBIC will be a physical laboratory facility within which Stockholm University's multidisciplinary expertise will meet, discuss and run experimental studies addressing fundamental research issues regarding the functional evolution of the brain and brain function within central aspects of human behavior. Interdisciplinary scientific exchange within SUBIC will be promoted by requiring that scientists from all fields involved in SUBIC participate into regular high-level weekly interdisciplinary seminars for the discussion of ongoing brain imaging research experiments or fundamental scientific issues. Through the participation in the seminars and the availability of laboratory facilities, a culture of interdisciplinary scientific exchange is expected to emerge and attract scientists from other national and international institutions. Another intimately related scientific aim is to contribute to the Human Brain Project with a high-quality scientific data describing brain function associated with a broad range of human behaviors.

Several lines of research within the social sciences and humanities have already integrated in their methodologies the benefits of the available brain imaging technology but more systematic work must be done. The study of learning, development of concepts, memory and how it is affected by stress, by sleep or altered with age (Ebner, Maura, Macdonald, Westberg, & Fischer, 2013; Fischer et al., 2010; Kuhl et al., 1997; Kuhl, Williams, Lacerda, Stevens, & Lindblom, 1992; MacDonald, Nyberg, Sandblom, Fischer, & Backman, 2008; Marklund, Schwarz, & Lacerda, 2014; Norrelgen, Lacerda, & Forssberg, 1999; Werheid et al., 2010), are just a few examples of basic research where the new brain imaging technology already plays a central role. For instance, fMRI techniques are currently being applied to sleep research within the large on-going collaborative project involving KI and SU, "Sleepy Brain", addressing issues like brain connectivity during different phases of sleep, consolidation processes of pre-sleep learning, effects of sleep reduction and REM-sleep disturbance on emotional regulation. Indeed, virtually all aspects of the human behavior are linked to brain activity and brain imaging technology is nowadays a well-established and very successful methodology in different areas of Experimental psychology. However, there still are important areas of research that are not yet well acquainted with the opportunities offered by this methodology to address brain function in relation to central aspects of typical and atypical human behavior. Linguistics offers a good example of a scientific area within which the availability of SUBIC's new brain imaging technology is likely to trigger a paradigm shift. Let us look closer at its example.

Traditionally, linguistics has been focused on structural descriptions of languages. It has been concerned mainly with syntax and morphology but essentially lacking a biological link to language as used by interacting individuals. Noam Chomsky's revolutionary work introducing the concepts of generative grammar provided powerful descriptions of how a finite set of elements could capture an individual's syntactic competence. Nevertheless it offered an essentially static idealized description, which was limited in both developmental perspective and a serious pursuit of its biological bases. Indeed, in so far as the latter were considered at all, they were seen as secondary issues. As a result most of the contributions to the study of the biological foundations of language and spoken communication have come from empirical cognitive psychology and other disciplines rather than from core linguistic research.

The social relevance of a discipline is linked to its practical use. There are numerous applications – specifically in the educational and clinical domains - that rely on solid knowledge of how use of spoken language works and how mastery of both one's native and a second language is acquired. These practically based research needs provide strong motivation for shifting the focus - from structural descriptions of languages – to language use and language learning. It is in this sense we see the advent of brain imaging and a neuroscience perspective that are likely to promote a paradigm shift: From abstract structural descriptions to behaviorally based functional accounts.

In this context Experimental phonetics can be said to have been the only field of linguistics attempting to contribute with independently motivated and biologically anchored explanations, but it is fair to say that despite such developments by and large phonetics remains trapped by the structuralist paradigm and descriptive work is still its dominant theme. To be sure, good descriptive data is a necessary basis for further scientific work but the most significant advances are to be expected from meta-analyses and testable hypotheses emerging from those data. However, deeper insights on the processes underlying language communication and the linguistic interaction between individuals are only possible through experimental work that reveals how linguistic capabilities emerge during early development and how they are modulated by the social processes in which the individual is involved throughout life. Experimental phonetics has contributed significantly during the last decades with answers to some of these questions. In the new intellectual framework it will continue to grow in depth and breath.

The recent development and availability of brain imaging technology have created important new challenges and research options for humanities, in particular regarding the study of natural language, and the neurobiological organization and pragmatic aspects of its interactive use and acquisition.

In summary, the proposed brain imaging infrastructure will allow researchers from the humanities, social sciences and natural sciences to integrate a unique evolutionary perspective on functionally induced changes in brain morphology with cutting-edge studies of brain function under advanced cognitive tasks and how brain function is modulated by factors like stress, sleep, age or life experience. More specifically the following interdisciplinary lines of study have been discussed and can initiated once the brain imaging infrastructure is available:

- *Memory processes as a function of age, stress, sleep and multisensory information*
- *Implicit learning as a function of age, background or additional information and sensory modality (primarily visual and audio as well as a combination of the two)*
- *Early language learning, the multisensory bases of the emergence of linguistic concepts early in life, the emergence of syntactic structures and morphological generalization*
- *The emergence of concepts and linguistic processing in sign- and oral language*
- *Representation of faces and voices and their social significance*
- *Decision making and risk assessment in economic decisions and game situations*
- *Memory processes and witnesses' judgments*
- *Face and voice recall in everyday life and in forensic contexts*
- *Implicit learning in game situations and cultural transfer*
- *Cultural changes and priming influences in representation and ranking tasks*
- *Non-human species' evolutionary morphologic brain changes associated with changes in brain function*

Some of these studies are already being conducted using available infrastructures but the SUBIC infrastructure will allow for much wider and more integrated interdisciplinary research gains.

Significance

The brain is involved in all sensory representation and information integration as well as in human cognitive and motor activities. The functional study of the brain is one of the most challenging scientific goals and obviously demands a broad range of coordinated interdisciplinary efforts. The functional study of the human brain also extends the scope of traditional clinical research directly associated with the physiological consequences of conditions like aphasias, epilepsy or brain injuries, by providing integrated models of how multisensory information is processed by the brain and underlies the formation of central concepts and behaviors. The range of competences necessary to address such broad functional aspects is, of course, extremely vast and cannot be strictly predicted or dictated in advance. The coordination of the partial knowledge provided by each of the involved disciplines and their current methodologies requires a culture of systematic scientific research capable of generating well-grounded and testable explanatory models as well contributing with high-quality and well documented data for future research efforts and re-analyses. The functional study of the human brain raises this challenge because it attempts to account for how the human brain handles the individual representations of sensory information throughout life, as well as how those representations impact on the individual's behaviors, cognitive representations and also are modulated through the individual's social interaction and relation to her ecologic settings. The academic environment provided by Universities – with the combination of, on the one hand knowledge from disciplines within the Social sciences, the Humanities and Law, and on the other hand the methodological and physical knowledge from disciplines within the Natural sciences – is clearly the necessary and probably the optimal context to start addressing the full scale of issues raised by the functional study of the brain without losing the important individual and social perspectives.

The growth of neuroscience during the past few decades has been characterized as explosive. Despite numerous significant insights in many subareas of the field, neuroscientists from different specialties have expressed concern that recent developments have come with a snag: Radical progress in developing new treatments for brain disease is an obvious possibility but reaching those goals will require a long-term effort. It will not happen in the immediate future. In their report to the European Commission, the applicants of The Human Brain Project point out:

> "*We find that the major obstacle that hinders our understanding of the brain is the fragmentation of brain research and the data it produces*. …. *Today we urgently need to integrate this data – to show how the parts fit together in a single multi-level system*."

The Human Brain Project (awarded €1bn by the EU) involves a large group of scientists with backgrounds primarily in neurobiology and computational science the goal of the project being to develop new treatments for brain disease and new brain-like computing technologies.

We here maintain that the "integration of brain data" that the above quote refers to should go beyond the clinical areas by including contributions from the Humanities, the Social Sciences and Natural Sciences that throw light on how normal non-human and human behaviors work. To explain diseases scientifically, to diagnose them and treat them, fundamental knowledge of the underlying normal behavior is a prerequisite. That is the international and intellectual context in which the SUBIC initiative is presented. Stockholm University combines this type of fruitful academic environment with the geographic proximity to the more clinically oriented research driven by scientists at the Karolinska Institute.

We will use a holistic approach that encompasses all aspects of variation in brain morphology and behavior in a suite of organisms, ranging from Drosophila fruit flies to humans, to investigate multiple aspects of brain evolution, brain function, and clinical aspects of the brain. The expertise in Stockholm University in the disciplines of Psychology, Linguistics, Culture evolution, Game theory, Brain evolution, Neuro economy, Decision processes and the methodological development of brain imaging makes Stockholm University the perfect host for this national center of Brain Imaging. Together with other leading experts both from Swedish and International universities, the Stockholm University Brain Imaging Centre will offer a state of the art hub for future endeavors into the remaining key-questions in Science focusing on brain evolution, integrated brain function throughout life, brain development and aging. And all this will be achieved in a center that emphasizes the importance of the welfare of the subjects through animal/infant/child/adult friendly technology.

Finally, the proposed infrastructure will allow to unleash the power of basic scientific research by addressing strong long-term fundamental issues intimately linked to the very human nature and to the urgent need of deeper insights on human cognition and how human brain function evolved in relation to other species.

Survey of the field

Brain imaging facilities have become a common tool in most medical faculties, both in Sweden and other industrialized countries. An increasing number of non-medical Universities in Europe, the USA and Japan have also been investing in brain imaging facilities, which are typically used in research conducted within Psychology, with more recent expansions towards neuro-economics and studies of decision-making.

EEG

For more than one century ago, the fundamental Physics knowledge generated by basic research in electronics and electromagnetism reached a level of understanding of central electronic phenomena that made it possible to start building devices capable of amplifying electrical signals. Among the extremely wide range of applications for the new amplifying devices, the development of sensitive and low-noise amplifiers opened for the first Electroencephalographic (EEG) studies of the living brain, both in animals and in human subjects. Many of the initial studies of EEG activity in the human brain were understandably triggered by clinical needs, like the study of cortical processes associated with aphasia, epilepsy and other neurological diseases, but the technology was quickly adopted to the study of non-clinical basic research questions, in particular within Psychology and Linguistics. EEG measurements provide cortical activity data with high temporal resolution, which makes them suitable to register Event Related Potentials (ERP), but the measurements spatial resolution is poor. In addition, the registered electrical signals are affected by the skull's thickness, which may difficult the direct comparison and interpretation of amplitude measurements obtained from different electrodes.

MRI

A more recent technology for brain imaging, introduced in the early 1990-ies, is Magnetic Resonance Imaging (MRI). As in other cases, the technique itself emerged from a combination of basic research in neurophysiology and in Physics, like Electromagnetism, Atomic Physics and the physics of extremely low temperature electrical conduction (superconductors). The MRI technique is suitable for both structural, functional (fMRI) and diffusion (connectivity) brain imaging, which serve different purposes. Like with the EEG, most of the initial MRI studies were concerned with structural assessments of the clinical brain, but the range of applications has progressively expanded towards more general basic research questions that obviously feed back into the need to understand the clinically relevant cases. The technique explores different aspects of the magnetic resonance properties of hydrogen nuclei, depending on if the goal is to obtain structural or functional measurements. For instance, in the case of fMRI the oxygenation-dependent magnetic properties of the haemoglobin are the key to the investigation of brain regions involved in different tasks. As the neuronal activity level in a brain region increases when a subject is requested to perform a certain task, the neurons' heightened activity level demands more oxygen and richly oxygenated haemoglobin floods into the region. However, after a few seconds the more active neurons have all the oxygen supply they needed but the oxygenated blood continues to flow for a short while. This causes a temporary excess of highly oxygenated blood in the region, which can be measured because of the differences in the magnetic behavior of oxygenated haemoglobin (diamagnetic) and deoxygenated haemoglobin (paramagnetic). Obviously, functional MRI (fMRI) is an extremely important technique for both basic and clinical research because it generates high spatial-resolution data of the whole brain from which it is possible to identify regions of heightened neuronal activity associated with different experimental tasks. However, because fMRI actually measures the excess of oxygenated blood resources overflooding the active brain region, the temporal resolution of fMRI is typically in the range of a couple of seconds – which is much poorer than millisecond resolution available from EEG measurements – but fMRI's high spatial resolution is an excellent feature for investigation of a range of psychological phenomena where it is important to identify the brain structures involved in specific tasks. Furthermore, the same equipment can be used to obtain detailed structural brain data, which is very important for the study of long-term structural changes in the brain (like aging, specializations like in high level music performance, structural differences associated with the development of sign or oral language skills, long-term effects of environmental conditions, etc.) or to provide individual anatomical descriptions of a subject's brain – descriptions that provide valuable information for the interpretation of EEG, MEG and NIRS data as well as for the design of TMS experiments. The use of MRI scanners, both in functional and structural studies, is well established in many fields of psychology involving the representation of all types of sensory stimuli (although still less with regard to auditory stimuli) and in the last decades there has been an increasing demand for the use of fMRI technology in the study of sociological, economical, cognitive and decision-making processes. The two major drawbacks of the technique until quite recently have been its poor temporal resolution and the disturbing levels of intermittent noise generated during the scanning sequences. This has not been a problem for the methodologies used in the above mentioned research fields but the limited temporal resolution makes the technique inadequate for the study of rapidly time-varying phenomena, like the cortical processing of speech stimuli or cognitive responses associated with speech stimuli. Also the noise levels in the scanner pose serious difficulties to studies requiring the presentation of speech or good quality audio signals. Indeed, even though earplugs and specially designed headphones do improve much of the disturbance caused by the scanner's noise, the control of the presentation levels or of the spectral details of the stimuli actually delivered to the subjects is far from satisfactory in most of the traditional fMRI cameras. Fortunately, a new generation of much less noisy scanners has appeared recently which will facilitate basic research involving representations of auditory stimuli as well as minimizing the disturbance and tension that the MRI scanner noise can cause in young children.

Evolutionary Zoology is yet another research area where MRI scanning is an important tool for the structural study of the evolution of the brain across species. Scanners for this purpose have to meet species-specific needs of spatial resolution and volumes of operation. For instance, for morphological brain scanning of animals, like dogs, wolves or foxes, smaller versions of 3 T equipment provide good enough brain images, but small rodents, small fish or insects require much stronger magnetic fields (9.4 T) to obtain brain images with enough spatial resolution though within scanning volumes as small as 1000 cm^3.

NIRS

The near-infrared spectrophotometry (NIRS) is a technique that uses differences in the way oxygenated and deoxygenated haemoglobin reflects infrared light. Its working principle is similar to that of MRI in that it measures the amount of re-emergent light when illuminating cortical blood vessels with a near-infrared light source. The amount of reflected light varies with the oxygen level in the haemoglobin and can therefore be used to estimate the amount of oxygenated blood being requested to a cortical region. The technique has a better temporal resolution than fMRI and better spatial resolution than EEG. It can measure fast variations in the blood oxygenation level achieving a temporal resolution of about 200 ms as well as the slow varying oxygenation levels caused, as in fMRI, by the local excess of oxygenated blood flooding to the active brain region. Although a temporal resolution of 200 ms still is poor for the study of events linked to specific speech or auditory features, NIRS offers a good compromise of temporal and spatial resolution. In addition, the NIRS equipment is portable and its use is not constrained by the common requirements of electromagnetic shielding because it operates in the infrared range of the electromagnetic spectrum.

MEG

Magnetoencephalography (MEG) is another very important brain imaging technology. MEG was first implemented in 1968 by David Cohen, a physicist from the University of Illinois (now at the Harvard Medical School in Boston), but it was only during the last few decades that its use became more widespread. In contrast to the thousands of fMRI equipment available at hospitals and many universities around the world, the number of MEG cameras in the world is still less than one hundred with nearly 50% of the cameras located in Japan and the USA. MEG measures the very weak magnetic fields generated by the brain's neuronal activity, i.e. fields of about 10 fT (10×10^{-15} Tesla) to be measured against the one billion times stronger earth's 25-65 μT (25×10^{-6} to 65×10^{-6} Tesla) magnetic field. MEG is a silent and passive technique that combines the temporal resolution of EEG with a good spatial resolution. Therefore, although MEG's spatial resolution is not as good as fMRI's, the technique's excellent temporal resolution and silent environment, makes it an optimal compromise for the study of cortical activity associated with rapidly varying stimuli, like speech stimuli or animated visual sequences. Another important feature is that the measured magnetic fields are not affected by the skull's thickness allowing, for instance, for more reliable measurements of infants' brain activity because MEG data are not affected by differences in fontanel's development. In addition, the combination of simultaneous MEG and EEG data provide a very reliable and unambiguous source localization results while keeping the high temporal resolution. MEG measurements are typically complemented with the individual subject's structural MRI data, which significantly increases the precision of the source localization estimates and strengthens the interpretation of the MEG and EEG data.

TMS

Transcranial magnetic stimulation (TMS) is a non-invasive technique to induce momentary electrical disturbances in the brain function by using a rapidly varying magnetic field. It is silent and allows localized stimulation of target cortical regions that polarizes or depolarizes the neurons in the targeted region, which momentarily impairs their normal function. Brain function is restored immediately as soon as the stimulation ends and there are no reported long-term effects from TMS use in scientific research. TMS is an important technical resource to test hypotheses about the localization of different brain functions. For instance, TMS is currently been used in speech research to investigate the role of Broca's area in the perception of speech contrasts or to study how blockage of motor cortex areas involved in certain speech articulation movements influences the perception of speech sounds that are produced by those articulatory movements.

LSF microscopy

Light-sheet fluorescent microscopy (LSF) is a technique to obtain high-resolution images from biological structures by systematically illuminating successive thin layers of tissue. This technique is highly beneficial for certain questions particularly in very small animals because it offers higher resolution than even a 9.4T MRI while being very fast, allowing collection of high resolution images for large sample sizes. This will be particularly important for large scale analyses of brain morphology in small vertebrates and insects. Suggested use would target for instance comparative analyses of fine-scale aspects of brain morphology across multiple species of small vertebrates and insects, and artificial selection experiments on various aspects of brain morphology.

Societal impact

Basic research in the Humanities and Social sciences that contributes with fundamental knowledge about the function of the human brain. Research that produces good quality data and answers to fundamental questions. Understanding of the human brain.

Spin-off effects due to the interdisciplinary character of the research and the available critical mass at Stockholm University.

Basic research on the similarities and differences in brain morphology and function between dogs, wolfs and humans. Basic research on invertebrate and vertebrate brain morphology evolution through the tree of life. In particular, zoological studies in the center will start with large-scale analyses of the evolution of brain morphology and behavior in dog breeds and wolves, rodents, insects and fishes.

Attracting to Stockholm international research on brain function

Like in the advent of digital computers in the early 1970-ies, brain imaging resources are still a very expensive and specialized technology with most infrastructures allocated to hospitals. The investment on brain imaging infrastructures at non-medical universities will trigger a natural increase in the knowledge of the functional brain and stimulate the development of methodologies that will integrate brain imaging in a broad range of academic research. The availability of the resources and the increasing volume of their use are expected to offer new research avenues to academic areas that study the complex relationship between individuals and their interaction with others, but that traditionally do not explore empirical methods. For instance, the possibility of studying changes in brain activity in connection with the complex human experiences, like films, literature or music, may help proposing specific accounts of the human behavior in terms of explanatory models that strengthen the traditional theories within the humanities.

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