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Megascience Efforts and the Brain

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Several recent megascale neuroscience efforts in the U.S. and Europe are concerned with developing infrastructure for tools, modeling, or neuroinformatics. It may seem surprising that they are not instead focused directly on gaining fundamental new insights into brain function.

During the last few decades, neuroscience has seen a phenomenal development on two levels (Figure 1). First, there has been a focus on the cell biology of the nerve cell and its synapses, particularly with regard to the genetic and molecular level and the many signaling pathways underlying neuronal function. This development has led to a revolution in our understanding of the nerve cell. It has also allowed for genetic manipulations in order to investigate, for instance, the effect of a deletion or overexpression of a given gene and the effect that it may have on the behavioral level. In this case, we are dealing with a correlation, since very rarely do we have sufficient knowledge of the intervening steps. On the other extreme level, we have human brain imaging, which has informed us of where in the brain different processes (e.g., sensory, motor, or emotional) take place and how they have been modified in different disease states. The resolution in this case is instead at the level of thousands of neurons. The challenge of modern neuroscience is to bridge between these two levels and be able to account for the neural bases of action, perception, and the many aspects of behavior in terms of cellular, synaptic, and microcircuit building blocks. We need, in fact, to appreciate all intervening steps between genes/molecules/cells/synapses to networks/systems and specific aspects of behavior to understand how a gene modification in reality can affect behavior.

The neuroscience reported in more than 100,000 articles each year has, however, (mostly) had a fact-finding character. This has provided a great number of facts but much less in terms of new insights reached into the fundamental mechanisms of the brain, whether on the cellular or systems level. A number of exciting new tools have been developed, but formidable breakthroughs have been scarce. One major limitation is the fragmentation into many different subfields and the difficulty to obtain an overview of the different areas of neuroscience extending from genetics to psychiatry. Such a broad overview is at the same time often required for synthesis.

It is somewhat distressing that the new very large neural research programs in neuroscience are directed primarily toward infrastructure development, rather than a concerted effort toward a solution of major questions regarding brain function, such as the neural bases of emotions and related anxiety, the neural bases of behavior and related movement disorders, or memory storage and retrieval, and so forth. The list could be made very long.

The first, and so far largest, effort is the European Human Brain Project planned to be financed over 10 years, which was followed by the Obama BRAIN initiative, which will, at least in the beginning, focus on developing new tools for neuroscience. It has in turn been followed by a Japanese brain project concerned with developing the primate marmoset model, which would allow for transgenic interventions. Subsequently, China and Australia have indicated that they will initiate their own brain projects. Another major effort that provides important information is that of the Allen Brain Institute, which explicitly aims at providing a platform for displaying the expression of different molecules in different parts of the nervous system in a way that is easily accessible for the entire community. It has also been extended to include a systematic exploration of connectivity, also with utilization of electrophysiological methods. These different major efforts are important and will channel new resources to neuroscience, and novel infrastructure developments are in any case useful for neuroscience. They provide new tools that can be used to ask important questions, but to my mind, the focus should be on the questions being addressed. One would thus rather like to have tools developed to be able to address specific questions.

The Human Genome Project

The strategy of these different projects is to some degree similar to that of the human genome project, which was a concerted effort that led to the resolution of the human genome, the mouse, the zebra fish, and many other genomes. This achievement was very important, but in itself mainly of a descriptive character. The net result is, however, platforms with genetic information from which other researchers can formulate specific questions of analytical character. This information has become invaluable, and bioinformatics plays a key role in current cell biology.

Bioinformatics and Neuroinformatics

One major important challenge is the difficulty to bridge or get access to available data in all steps between the cellular and behavioral level. The reason is that a great number of fields deal with the brain, each with a particular approach and set of techniques. The difficulty is to go between these different areas. Take, for instance, linguistics and geriatrics versus structural biology or genetic processing. All fields are important, but each with its own methods and terminology, and each potentially important for human brain function. To facilitate the process of rapidly moving between different levels

of organization, the development of neuroinformatic databases is very important (Bjaalie and Grillner, 2007). A "google" brain would markedly facilitate the ability to go between organizational levels and facilitate the interaction between the many fields of neuroscience. Bioinformatics considers mainly the gene, proteome, and biochemical levels and has within a short time become an indispensable tool at the cellular and molecular level. Neuroinformatics interfacing with bioinformatics needs to develop more complex databases extending from the bioinformatics level to that of behavior, cognition, and the many diseases of the brain. Neuroinformatics databases will be a critical factor in the development of simulation models, and the data would preferentially be stored in a format so that it can be entered directly into the simulation engines. The infrastructure for neuroinformatics has now, in a number of years, been in focus for the NIH, NIF, and the International Neuroinformatics Coordinating Facility (INCF) in Stockholm and is also an explicit goal for the Human Brain Project (HBP). The latter is financed from the "Future Emerging Technology" section of the European Commission and it has in a sense a similar character as the human genome project, but it is much broader and includes not only brain research but nearly 50% is concerned with brain-inspired technologies (neurorobotics, high-performance computing, and brain-inspired neuromorphic engineering).

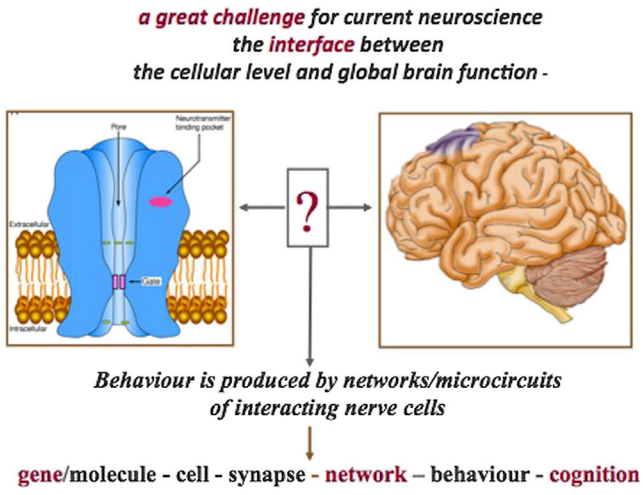

Figure 1. The Interface between the Cellular Level and Global Brain Function Is the Major Challenge for Current Neuroscience
The two extreme levels of neuroscience that have evolved rapidly, cellular (left) and brain imaging (right). The challenge is to bridge these levels in order to be able to explain behavior in terms of cells and synapses. It emphasizes the fact that in order to have a solid underpinning of the circuits underlying a specific function, one needs to be able to bridge from gene through the different steps indicated below in the figure to, for instance, a cognitive or behavioral function.

Bottom-Up Modeling Approaches at the Microcircuits and Systems Level

A major effort of the HBP is the very extensive and sophisticated modeling tools that are developed for simulation of microcircuits at different levels from cortex and subcortical structures, based on detailed biological information including neurons, glia, and biochemical signaling pathways underlying synaptic plasticity. The core in HBP is a development of a very competitive infrastructure for simulations, based on rigorous experimentation on the cellular, synaptic, and microcircuit level. A model does obviously not become better than the biological data on which it is based. In each dynamic system, like the different circuits of the brain, many factors covary and interact. Moreover, it is virtually impossible to dissect the role of different factors without simulation. This part of the human brain project is dedicated to bottom-up analyses that are required if we are to understand the brain, based on the experimental data on cells, transmitters, receptor subtypes, and the like. This approach is critical to move ahead, but it is primarily at the level of the microcircuits in the cortex, amygdala, basal ganglia, thalamus, and the many brainstem-spinal cord networks underlying motor behavior (Grillner et al., 2005). At this level, marked progress can be made in a time frame of not so many years and with the help of software developed, for instance, within the Human Brain Project. The next level is the integration of these circuits into more complex systems, like the selection of action, networks for storage and retrieval of information, circuits for spatial navigation depending on stored information—a property that small invertebrate brains can handle as well as primates, including man. These more complex functions will undoubtedly require more time and effort. The HBP software development required for these simulations should be an infrastructure accessible for the neuroscience community at large.

Although I have so far discussed modeling in general terms regarding basic neuroscience, the need for bottom-up approaches applies also to the many detrimental diseases of the brain. Biochemical signaling pathways interact in a very complex pattern and again detailed modeling is critical and will most likely play an important role in elucidating the mechanisms underlying the many degenerative diseases, like Alzheimer's disease and multiple sclerosis. It has to be recalled, however, that in each case the experimental data that goes into the models will determine the validity of the model and its usefulness. At another level are the psychiatric diseases, depression, schizophrenia, and so forth. A specific problem here is that it may be questioned how much of specific human diseases (particularly psychiatry) is captured by the different experimental rodent models.

Top-Down Approach

A top-down analysis may also be required, regarding the different cognitive functions, particularly the most advanced functions that are uniquely human, like language, but also the cognitive functions that are shared with other mammals. These are studied mainly with neuropsychological methods combined with a variety of imaging approaches and other ways of recording cortical events. Time resolution is key and therefore fMRI is at a disadvantage. fMRI provides information of where a given change of activity takes place in the brain. Positron emission tomography (PET) has a similar problem but can be combined with analysis of different molecular targets and only magnetoencephalography (MEG) and electroencephalography (EEG) can provide

appropriate time resolution to allow representation of the dynamic interaction between different brain areas. In this case, the maximal resolution consists not of single but rather of thousands of neurons! The challenge is to reach some insights into how these processes are operating based on neuropsychology, location, and preferably timing and attempt to relate these functions to the underpinning of neural circuits at the systems level. In this case, theoretical implementations of the data and exploration through top-down approaches provide an important additional strategy, also contained within the Human Brain Project.

The long-term, overarching goal is of course to make the bottom-up and top-down approaches meet and thereby be able to account for complex functions based on knowledge extending all the way from the cellular to the cognitive level—but this will undoubtedly take quite some time. To obtain a real understanding rather than just a correlation between different events, one needs to cover each part of the chain extending from gene products to cells and synapses to microcircuits and systems involved to the integrated processes leading up to a given pattern of behavior or global brain function in terms of for instance decision making.

The Brain Is Modular: Advantages for the Analysis

It is no question that the big infrastructural development in terms of neuroinformatics databases and sophisticated modeling tools will facilitate a rapid development of integrated neuroscience. Hopefully, this will catalyze a number of new projects that will lead to fundamental new insights into the many fundamental questions still to be solved. It is my conviction that having the focus directly on understanding the very complex achievements of the human brain in terms of reasoning and other high-level cognitive functions will make for slow progress. The underlying modular building blocks of the nervous system (see Shepherd and Grillner, 2010) first need to be elucidated, if an understanding based on rigorous science should be reached, rather than merely superficial interpretations.

Although the nervous system contains an immense number of neurons and synapses, it is fortunately divided into a number of *functional modules*, each of which is related to a specific function of the nervous system. These modules should be possible to understand by utilizing the many techniques of current neuroscience. Take for instance the following:

- structures like the amygdala (with its different compartments), controlling emotional reactions through the many different downstream targets;
- the motor programs underlying the expression of emotions;
- the functional modules of the basal ganglia that control, e.g., the visuomotor microcircuits at the superior colliculus level;
- the many networks that control basic patterns of motor behavior at different levels of the neuraxis;
- the modular circuits that serve evaluation (reward, aversion, etc.), involving the dopamine system, lateral habenula, and their control from different inputs including striosomal, pallidal, and cortical circuits;
- microcircuits like cortical columns, striosomes, or cerebellar microzones, provided that the physiological inputs are included and preferably also the output targets;
- the hippocampal microcircuits underlying the formation of place cells, grid cells, and head direction cells and their integrated role in controlling spatial navigation and potential role in accounting for episodic memory.

These are just a few examples of modules that with dedicated efforts utilizing all available neurobiological methodology can be understood. The implicit requirement, however, is a definition of which cells take part in the underlying network, their cellular and synaptic properties, rules of plasticity, and how the different components are recruited during behavior. Given the complexity with numerous dynamically interacting processes, detailed modeling based on rigorous experimentation will be a crucial aspect of any analysis. This is the only way to test if available information can, or cannot, account for the function of a network or a given module. In this way, one can over a number of years build up a series of modules that are reasonably well understood through a combination of experiments, reasonable predictions, and modeling utilizing also the new infrastructure developed, for instance, within the Human Brain Project. In a next step, this can be extended to a combination of modules subserving progressively more complex functions. This process can be aided by top-down analyses, as discussed above.

Conclusion

There are many reasons to welcome the different infrastructural development driven by the Allen Brain Institute, the Human Brain Project, and the Obama initiative and it will facilitate new fundamental research. It most likely will still remain for individual scientists and their groups to formulate creative questions to make the brain reveal its many secrets. Consider, for instance, episodic memory. How are we able to store complex sequences and retain this information, sometimes over a lifespan and moreover retrieve this information with minimal delay, sometimes with decade-long intervals? With complex questions such as these, a coordinated effort from many research groups with different expertise will be needed.

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