BRAIN: innovative neurotechnologies for imaging and therapeutics

George M. Church, PhD

Abstract

Conceived with the aim of meeting the needs of the neurobiology and clinical communities, the Brain Research through Advancing Innovative Technologies (BRAIN) Initiative builds on the lessons learned from major projects in genetics, such as the Human Genome Project. It concentrates on the use of new imaging technologies in conjunction with genomics to inform therapeutic decisions.

Keywords: *BRAIN Initiative; imaging; Genome Project; genomics*

Author affiliations: Department of Genetics, Harvard Medical School, Boston, Massachusetts, USA

Address for correspondence: Department of Genetics, Harvard Medical School, Boston MA 02115, USA
(e-mail: gmc@harvard.edu)

The BRAIN Initiative

At the September 2011 meeting on "Opportunities at the Interface of Neuroscience and Nanoscience," at the Kavli Royal Society International Centre, UK, six of the attendees proposed an idea. Within days this became a white paper at the US Office of Science and Technology Policy, and then gained momentum among government granting agencies and private foundations, such that by April 2013 its creation was announced by the US president, complete with acronym: "Brain Research through Advancing Innovative Neurotechnologies" (BRAIN). For many proponents and critics alike, this acronym was a very positive nuance. It indicated that this project would not be a crank-turning, dollar-burning, unstoppable juggernaut locked into 2013 technologies, but rather a dynamic, cost-saving project, responsive to the real needs of the basic neurobiology and clinical communities. The goal of that project is aligned with the theme of this journal issue—creative imaging technologies employed to guide therapies.

Lessons from the Genome Project(s)

Due to the scarcity of examples of either type of project caricatured above (production or technology), we scrutinize the few that exist for analogies and insights to enhance the best and avoid the worst.

Lesson one: aggressively encourage technology development from the start. There was not a single Genome Project, but three fundamentally different strategies and phases—a technology-assessment phase initiated by the Department of Energy (1984-1990), the NIH-driven production phase (Human Genome Project, HGP, 1990-2004), and the NIH Advanced Sequencing Technology Development (ASTD, 2004-2013) phase. The BRAIN project will hopefully focus on the ASTD precedent, which (with annual funds only 6% of the HGP) helped drop the cost of sequencing by a million-fold in 6 years. It achieved this via advanced imaging and highly multiplexed biochemistry, not mere parallelism via conventional lab robotics.

Lesson two: Consider practical applications from the start. It could be said that brain technologies seem less mature than genomics at the corresponding project start points. In reality, no commercial or clinical applications of genomics existed in 1984. In contrast, at the start of the BRAIN project, millions of patients already benefit from cochlear, cardiac, retinal, and deep-brain electrode implant therapies as well as EEG and imaging technologies.

Lesson three: The goal need not be "simple." While it may seem that the HGP was digital and one-dimensional, the deliverable was not raw data of three billion letters (A, C, G, T). Instead our goal was an "annotated" genome, including the locations of regulatory elements and descriptions of the impact of mutations and epigenomics on developmental biology, disease, and aging. From this perspective, the BRAIN project is not harder than the genome project—indeed, it is an unfinished subset.

Lesson four: Lack of prior "understanding" should not impede innovation. Vaccines were amazing well before we understood the immune system. Did we know "THE genetic code" before HGP? That code only applied to 1% of the genome (the part encoding proteins) and, even there, did not reveal function.

The role of innovative imaging technologies

We can leverage exponentially advancing technologies (optical, electronic, imaging, nanotechnology, and synthetic biology) to radically improve the accuracy, cost,

and comprehensiveness of neurotechnologies capable of measurement and alteration of brain development and functioning in animal models and clinical settings. Especially valuable would be applying and integrating a variety of such methods in a single ("Rosetta") brain sample. This would include an initial behavioral phase including MRI, ultrasound, and electrical/optical stimulation/recording, followed by a serial section phase exploiting fluorescent in situ sequencing (FISSEQ) to assess RNA transcriptomes, barcoded connectomes, and time series data (ranging from developmental lineage to biochemical changes in cell membranes and nuclei). The physical limits and work-arounds for a variety of imaging modalities and means of transducing the data on potential neurons in a brain to an external device have been recently reviewed.[1]

Magnetic resonance imaging

The NIH Human Connectome Project (HCP, 2009-2014) is ongoing at Washington University, University of Minnesota, Harvard University, Massachusetts General Hospital, and UCLA. HCP is largely focused on imaging methods, which include structural magnetic resonance imaging (MRI), diffusion tensor imaging (DTI), high-angular-resolution diffusion imaging (HARDI), functional MRI (fMRI), and diffusion spectrum imaging (DSI). To connect imaging to behavior, the HCP includes the NIH Toolbox for Assessment of Neurological and Behavioral function. The highest practical field gradients, so far, 300 mT/m (with slewing at 200 T/m/s), has resulted in temporal and spatial resolutions of 0.62 msec and 1.5 mm respectively. (One mm^3 contains roughly 50 000 neurons). Some of the above limits are set by unwanted peripheral nervous system and retinal stimulation.[2] Proton MRI is limited to 100 ms temporal resolution by water T1 relaxation time, and limited to spatial resolutions of 40 μm by the self-diffusion of water. T1 premapping could allow T2 contrast on a 10-msec timescale.[1]

Extracellular electrical recording

Since the maximum recording distance is about 100 μm to 200 μm measured from electrode to neuron, at current noise levels, 100 000 minimum in theory and 10 million electrodes in practice would be required to enable sorting of noisy, temporally overlapping spikes using current algorithms. Current arrays are in the hundreds of electrodes, and keeping total volume of the multielectrode below 1% of the brain volume is challenging. Alternatively, wireless data transmission or implanted recording are options. Wireless data transmission at optical and infrared (IR) frequencies are needed to obtain adequate single-channel data rates. Radio-frequency (RF) transmission of whole-brain data would draw excessive power due to bandwidth constraints. Multiplexing RF wavelengths is likely inadequate, but optical/IR or ultrasound allow frequency and spatial multiplexing. Implanted electrical recording would require a 1000-fold increase in the power efficiency of electronics relative to current devices to scale to whole-brain simultaneous recordings.

Optical imaging

Light scattering imposes significant limits on optical techniques, but strategies exist which could negate the effects of scattering, such as implantable optics, infrared fluorescence or bioluminescence, and online inversion of the scattering matrix. In larval zebrafish, a calcium indicator (GCaMP5G) in vivo captured, at 0.8 Hz, 80% of all of the 100 000 neurons of the whole brain at single-cell resolution[3] but scaling this to thicker, less transparent brains is quite challenging. Whole-brain multi-photon excitation could overheat the brain, except in very short experiments, unless ultrabright inorganic indicators or similar strategies can be developed.[4] For beam scanning microscopies, optical phase modulators, in principle, could reposition beams at 1-GHz switching rates with fluorescence lifetimes in the 0.1–1.0 ns range constrain and enable design of ultrafast scanning.

Ultrasound

Ultrasound is attenuated by brain tissue at the 100-MHz frequencies needed for single-cell resolution ultrasound imaging such that it is hard to detect even in theory. Nevertheless, ultrasound may be a viable medium for spatially multiplexed data transmission from embedded devices.[3]

Molecular recording devices

These fall within reasonable physical limits, but their development represents major challenges in synthetic biology.

Innovative therapeutic and preventative neurotechnologies

A subset of the above imaging methods have variations capable of patterned neuronal stimulation, notably electrical and optical methods. This may enable repair or accommodation of disorders acquired during a lifetime of trauma and environmental and immune factors. Some psychiatric and neurodegenerative diseases can be prevented at even earlier stages, via their inherited, (auto)immune and microbial/viral origins. Genomics is finally overcoming decades of false-positives in such diseases including autism, schizophrenia, obsessive-compulsive disorder, bipolar disorder, etc. The reasons for the improved discovery are larger cohorts and better genotyping via next-generation sequencing, for example for de novo mutations in family trios including point mutations and so-called structural variants. Imaging and molecular methods increasingly help classify and stratify causes to enable preventative strategies ranging from preconception carrier screening, lifestyle, immunogen/allergen management, and small molecule/protein/gene therapies to direct management of patterns of neuronal activity. ❑

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