Describe a Framework for Replacing Damaged Cortical Tissue and Fostering Circuit Integration to Restore Neurological Function

TASK GROUP DESCRIPTION

Background

With worldwide demographics increasingly shifting toward an aging population, neurological diseases are increasingly common. Stroke, for example, is now the third largest medical cause of death in the Western world, and among those who survive its ravages, nearly two-thirds become disabled. Furthermore, the effects of these disorders are particularly debilitating, due to their profound impact on sensation, cognition, and other tasks that are often central to the afflicted person’s identity. To rise to this challenge an original therapeutic framework is needed to restore critical functions associated with damaged areas of the brain, either through the introduction of new tissue or other material into those areas or via the facilitated adoption of the original functions by new brain areas.

A promising target for such treatments is the cerebral cortex. In addition to vitally underpinning much of perception, movement, and executive function, the cortex has the additional benefit of retaining significant plasticity for change throughout the lifespan. Furthermore, some evidence suggests that the cerebral cortex may perform a general computation that can be generalized across modalities; thus, a generalized circuit that recapitulates this fundamental computation might serve as a useful replacement for multiple possible areas of cerebral cortex. It is possible that cortical prostheses that even partially restore cognitive function lost due to brain trauma or dementia could reduce the disabilities in patients. It would be beneficial if exogenously assembled elements could be made to function as cerebral cortex does, or if the remaining nondamaged portion of brain could respond to new inputs and perform useful functions that replace damaged portions. The ultimate goal of implantable neuronal networks will require insights from the developmental neurobiology of the cerebral cortex, as well as advances in a range of technologies necessary for creating brain networks, promoting neuronal connections, engineering stem cells to match host tissues, devising biodegradable materials as scaffolds for implantable networks, and delivering molecules to brain tissues.

Initial Challenges to Consider

- What kinds of disease conditions could be alleviated by a cerebral cortex prosthesis? Would different diseases require different approaches?
- How does the cerebral cortex function? What computation does it perform? Does the cerebral cortex perform a general computation or transformation of information that can be generalized across modalities, and can this be taken advantage of?
- What do you feel is the most promising general substrate for a cortical prosthetic?
  - tissue transplanted from analogous regions in the same or a different brain;
  - tissue grown externally and then implanted;

    - tissue already existing in the brain that could be coaxed to co-opt the function of interest; or
    - a nonbiological circuit substrate engineered to adopt the requisite function.
- Distinguish these potential avenues based on currently available technologies, cost of procedures, likelihood of success, and ethical considerations.
- A persistent problem with introducing new material into the brain is that the material is rejected by immune or neuroprotective responses. How might these responses be placated to facilitate the adoption of the new material by host brain?
- A further problem is that the substitute neural tissue may need to reasonably match the host tissue in order to function effectively. For example, the prosthesis may need to be primed to be responsive to specific activity levels, and its response properties and activity levels must in turn roughly correspond to those expected by their downstream projections. What functional properties are most critical for general functional integration, and how might these properties be imbued into the substitute neural tissue?
- Finally, the prosthetic must be structurally connected to and integrated with surrounding circuits. What treatments might facilitate this connectivity? Candidate treatments could operate on either the macroscopic level by promoting axonal outgrowth from one region to another, or on a more refined scale by fostering the development of individual local neuronal connections.

Initial References

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TASK GROUP SUMMARY

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- James Fallon, Professor, Anatomy and Neurobiology, University of California, Irvine
- William Foster, Assistant Professor, Physics, The University of Houston
- William Heetderks, Director, Extramural Science Program, National Institute of Biomedical Imaging and Bioengineering, National Institutes of Health
- Pedro Irazoqui, Assistant Professor, Weldon School of Biomedical Engineering, Purdue University
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Summary

Complicated problems often require new ways of thinking. And replacing cortical tissue, connecting it, and convincing it to work is about as complicated as they come. So, when neurosurgeons, neurobiologists, physicians, engineers, and a philosopher got together at the National Academies Keck *Futures Initiative* Conference in November, they began by brainstorming ways to think about the problem. "We all have different perspectives and will probably define the problem a bit differently," said Randolph Nudo, director of the Landon Center of Aging and professor of molecular and integrative physiology at the University of Kansas Medical Center. "I'd like to get a feeling for what people think our challenge is."

The Problem Defined

Ideas began to flow. Then came the questions. What types of tissue should be included? What kind brain damage should be considered? Who would the patients be?

Should the solution be based on tissue growth or an implanted chip? Should growth or connectivity be the main concern? The conversation continued this way until David Mooney, professor in the Division of Engineering and Applied Sciences at Harvard University, suggested the group take a step back. “Right now we are talking about a number of things,” he said. “The scope will fall from the definition of the problem.”

Mooney’s advice led the group to the drawing board, literally. James Fallon, professor of anatomy and neurobiology at the University of California, Irvine, grabbed a marker and began sketching arrows on the board in the front of the room to represent the feedback systems in the brain.

“Do we care about information that goes to the brain stem or spinal cord?” Fallon asked.

“Forget about it,” replied Ted Berger, director of the Center for Neural Engineering at the University of Southern California.

“Do we need anything else?” Fallon asked.

“Just stop there; that is enough,” Berger replied.

The diagram looked a little overwhelming but the exercise was instructive. And since Fallon accidentally used a Sharpie marker on the white board, the group could refer back to the diagram throughout the day. After a bit more discussion, a problem statement emerged. Such is the process of science.

Dennis Barbour, assistant professor of biomedical engineering at Washington University in St. Louis, wrote a possible statement on the board. “This is a problem statement,” Barbour said. “Should this be our problem statement?” With a few word changes a specific but flexible definition of the problem took shape.

The group decided to focus on damage to the cerebral cortex, the outer surface of the brain responsible for reasoning, mood, and perception. Members also decided to limit the solution to severe and permanent damage. For this reason the solution would be most useful in situations where conventional treatment failed. A simple solution that could work for a number of types of damage would also be ideal. Fallon's arrows provided some first clues. And at the end of the first day the group had something to work with.

The Model

When the group reconvened, Barbour decided to take advantage of PowerPoint. Everyone could see the screen and he could easily pull up needed information. "This is a lot easier than messing around with the white board," Barbour said. Berger joked back, "Particularly because we can't erase it anymore." All kidding aside, the group had defined the problem, but what next? Pedro Irazoqui, assistant professor of biomedical engineering at Purdue University, said the next step was hiring graduate students. The group thought long and hard and decided that instead they needed to get back to work.

Vision could provide a good model to help solve the group's problem because damage to the visual cortex is localized and easy to test. In addition, the circuitry underlying the visual function in primates has been studied extensively, which could help successfully model some of this circuitry. The information passes for the most part in one direction. The group focused on central scotomas—blind spots sometimes caused by stroke. Berger had worked with a similar pathway in the hippocampus. "If you have to reproduce every connection in every single cell, you might as well go home," Berger said. "You have to approximate the problem with some smaller inputs and sample the outputs you simulate.” He said the smallest details of what happens where are not necessarily important. Instead, the group needed to understand and recreate the signal. This, of course, would be no small task.

Berger encouraged the group to think of information traveling from point A to B to C. At each stage the information is processed in some way. If B is eliminated, researchers can measure the signals leaving A and entering C, and then they can develop a chip that replicates B’s function. “It just does an input-output mapping,” Berger said. “And if you don’t like the model, you change what is inside there and you get a different one.” By breaking the problem down into steps and by avoiding too many details, the group could move forward. Solutions began to emerge, a bit piecemeal, but by the final day they came together.

The Solutions

After agreeing that there was no perfect solution, the group decided to outline possible solutions. Bill Heetderks, director of the Extramural Science program at the National Institute of Biomedical Imaging and Bioengineering, supported this move. “It seems to me if you are buying stock where you don’t know the result, you should diversify,” he said. “The notion that we can put forth one solution is not realistic for what we know.” Instead, the group began with two assumptions. All of the solutions involve artificial electronic circuits and all require cortical plasticity. The group stuck with the visual cortex as a model.

The first solution the group called the “electronic prosthesis.” In this solution an artificial computational system on a microchip would replace the damaged tissue. Wires would connect the chip to inputs and outputs and the chip would serve the function of the damaged cortex. Electrodes would supply the signals. The second solution, called the “hybrid electronic neural prosthesis,” would be similar except neurons instead of electrodes would interact with the chip.

But both these options present a number of challenges. “There is a significant problem with the interface,” Nudo said. “We are talking about systems where we have cultured neurons growing on a substrate . . . but the neurons don’t like the prosthetic environment.” If a workable interface could be developed in the first case, the number and density of the electrodes would also need to be considered. And if the system worked, scientists would still need to model the inputs and outputs and have the computational power to make the process possible. In the case of the hybrid system, scientists would also have to learn to direct neuronal growth.

A third option would involve growing new cortical tissue and using the microchip to teach this tissue to serve the required function. The group called it a “de novo engineered neural circuitry prosthesis.” And a fourth alternative would be to co-opt less important tissue in the brain and use a chip to train this region to serve the missing tissue’s function. The third and fourth, called the “in situ cortical isograft prosthesis,” would capitalize on circuitry that already exists. And both would mean the device could eventually be removed. “The brain could remodel over time,” said William Foster, assistant professor of physics at the University of Houston.

But these solutions also present challenges. Both would still require a workable interface. And scientists would have to know how to train synaptic connections and train neurons to differentiate and to grow in the right places and in the right directions.

Furthermore, in the case of the third solution, cortical tissue would have to be grown. Berger said this is a challenge, though material scientists are developing some scaffolding. “One of the problems is neurons can attach and grow nicely, but they grow in both directions,” Berger said.

The Next Step

The group came to no consensus on the best first approach to test, and group members still had general concerns. Would unconsidered solutions be easier or safer? And is a general solution even possible? More research needed to be done in neurobiology, bio- and nanomaterials, tissue engineering, computer engineering, and computational physiological modeling to answer these questions. Still the group worked until the last minute, cross-examining their ideas and assumptions. “Is it OK to make bionic people?” asked Irazoqui. “What public policy changes would have to be made with cognitive enhancing abilities available?” continued Berger. After eight hours of discussion and a healthy amount of hand waving, the group had defined approaches and challenges associated with each.

In the United States 700,000 people have strokes each year and 1.7 million suffer from traumatic brain injury. A proportion of these lose important brain function, including function associated with sight, control of extremities, and language capacity. The group members certainly weren’t ready to begin accepting volunteers for clinical trials, but they were able to integrate old ideas and develop new ones. And the product of their work proves that 15 interdisciplinary professionals committed to a problem can make progress.