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THE NEUROCENE

Neuroscience of Disease

Defending against cerebellar disease

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Abstract

A hedge fund billionaire's children are suffering from cerebellar disease. He invited a group of neuroscientists to plan a search for therapies. What resulted is the outline of an implantable neural emulator that might electronically replace the damaged part of the brain.

cerebellum; disease; Purkinje cells

RETHINKING A SCIENTIFIC MEETING

In all of my career, a scientific meeting only meant one thing: a series of talks. So when I was invited to this meeting in New Mexico, I assumed that this would be a similar story. But here I was, listening to the opening remarks and still having no idea of what we would be doing during the 3 days that we were together. All I had were cutesy titles for scheduled events like "Call to Action," "Incubation Walk," and "Research Karaoke." Honestly, it sounded like a kinder garden.

Actually, it began like a kinder garden. We were given a large piece of paper and a felt pen and asked not to write about ourselves, but the random person who was sitting in front of us. We sketched their face, and then interviewed them and wrote what we learned in sections titled "fun facts," "expertise," and "superpowers." I learned that among us was a plane crash survivor, a builder of violins, and a person who had met the Queen of England. Among the superpowers, lots of people proclaimed to be good organizers, many could see the big picture, and even a few viewed themselves as good listeners.

Slowly, I saw that behind this flaky-sounding schedule was a novel idea: In a regular meeting, when the talks are over, you bump into a colleague, and you start talking. What I take away from those short conversations is often more than what I learn from the long series of talks. Here, the radical idea was to jettison all the talks and focus only on the short, one-on-one (or small group) conversations.

Each conversation was with a scientist who often had a very different area of expertise. There would be a behavioral neuroscientist talking to a virologist or an imaging expert talking to a neurophysiologist. We might not share the same toolbox, but we had the same goal: at the end of the conversation, we would write a proposition, not in the form of a for- mal paper, but as a sentence on a Post-it note and place it on the "questions" wall (Fig. 1).

The last time I felt this uninhibited, and this excited, was when I was a sophomore in college, talking to a friend about how I was going to figure out the brain after having just watched a television documentary titled "The Brain." My naivety, both when I was a sophomore, and also at this meeting, was overlooked because my friend implicitly granted me a Heisenberg Compensator, figuratively letting me beam people from one place to another, as in the show Star Trek,

Figure 1. The “questions wall”: setting intermediate goals that would be good to achieve to battle cerebellar disease.

without concern for the difficult physics problems. The resulting creativity was cultivated by the safe space of conversations, magnified by the need for cooperation—exactly the elements that are suppressed in traditional scientific meetings.

A CEREBELLAR NEURO-EMULATOR

How do you organize a group of scientists to creatively produce a defense plan? On *day 1*, in our conversations, we imagined an intermediate goal that should be achieved first. This produced over 400 ideas, written as Post-it notes that covered an entire wall. Questions like: "How might we develop a nonhuman primate model of cerebellar disease?," "How might we study both the motor and cognitive deficits in cerebellar disease?," and "How might we stimulate the deep cerebellar nucleus to produce the correct output?".

On *day 2*, we selected from this massive number of questions and through conversation, reduced them to 50 "wouldn't it be great (WIBG) if we could do this by doing that" statements. Statements like: "WIBG if we corrected for the genetic disorder via gene therapy," "WIBG if we intervened early in the at-risk children via behavioral training," and "WIBG if we built a central care center like Roosevelt's Warm Springs but for ataxia."

On *day 3*, we distilled these ideas into 15 detailed statements, described as "idea stewarding." One of the key ideas that emerged was engineering a neuro-emulator for the cerebellum, which when implanted, would effectively bypass the diseased and dying parts with an artificial neural network (ANN): the ANN would listen to the inputs that the cerebellum received and then produce the correct outputs that the rest of the brain needed to control behavior. This idea is theoretically feasible because a critical feature of the cerebellar cortex anatomy is that the input-output function is measurable: the inputs arrive via spikes in the mossy fibers and climbing fibers, and the outputs are conveyed via spikes in the Purkinje cells. Thus, if the Purkinje cells are dying, perhaps an implanted circuit, called a neuro-emulator, can replace the computations that are performed by the malfunctioning circuitry.

Although we do not know exactly what these computations are, in animals we can record from the inputs to (mossy and climbing fibers) and the outputs (Purkinje cells) from the cerebellar cortex, at least in small regions, and then in principle build an ANN that emulates the computations. The technology to perform the recordings is available today in both rodents and nonhuman primates. We can repeat the approach in various areas of the cerebellum, from the midline regions that control movements to the lateral regions that influence emotions and cognition. Perhaps we will find that there is a consistent computational function shared among the various regions of the cerebellum, thus allowing us to train a cerebellar neuro-emulator.

A key feature of this device would be its adaptability. After all, the cerebellum's input-output patterns are not static, but modifiable through learning. This plasticity is at the core of the ability to learn new skills, like playing tennis, or a piano sonata. Cerebellar learning relies on the climbing fiber inputs, providing a teaching signal that modifies the Purkinje cell output. By measuring the climbing fiber inputs, and then implementing a learning algorithm that resembles the one in the cerebellar cortex, the ANN may provide a close approximation of the function lost in the diseased tissue.

The closest parallel to this approach is the cochlear implant, which replaces the inputs from millions of neurons in the auditory nerve with stimulation via a few channels. The success of this approach suggests that bypassing a damaged part of the nervous system through an emulation of the missing signals, however primitive that approximation may be, encourages the remaining healthy brain to learn the new language of the emulator, restoring some of the lost functions.

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AUTHOR CONTRIBUTIONS

R.S. prepared figures, drafted manuscript, edited and revised manuscript, and approved final version of manuscript.