To arrive at the edge of the world's knowledge, seek out the most complex and sophisticated minds, put them in a room together, and have them ask each other the questions they are asking themselves.

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Annual Question:

WHAT DO YOU CONSIDER THE MOST INTERESTING RECENT [SCIENTIFIC] NEWS? WHAT MAKES IT IMPORTANT?

Simon Baron-Cohen

One morning, 3 years ago, my talented PhD student Dwaipayan Adhya (known affectionately in the lab as Deep) came into my office. He looked at me straight in the eye, and said he'd like to grow autistic and typical neurons (nerve cells) in a dish, from the earliest moment of development, to observe how the autistic neuron differs from the typical neuron, day by day. I dropped everything and listened.

Sounds like science fiction? You might imagine that to grow a brain cell in a dish the scientist would first have to pluck a neuron from a human embryo, keep it alive in a lab petri dish, and then watch it under the microscope, measuring how it grows day by day. If that's what you're imagining, you're wrong. There is no way to get a neuron from a human embryo in any ethically acceptable way, for obvious reasons.

So what method was Deep planning to use, if there are no ways to study the development of the embryonic human brain in a prospective (*forward*) direction?

Deep told me about Shinya Yamanaka in Kyoto, who won the Nobel Prize in 2012 (along with Cambridge scientist John Gurdon) for his work on induced pluripotent stem cells or iPSC. In the lab, we call this magic. Here's how it works.

Pluck a hair from the head of an adult, then take the follicle from that hair, and using the Yamanaka method, *reverse* the cell, *backwards* from the adult hair follicle, back into the state of a stem cell; that is, back to being an undifferentiated cell, before it specialized into becoming a hair follicle. This is not an embryonic stem cell – it is an "induced pluripotent" stem cell. Induced, because the scientist has forced the adult hair follicle (though you could use any cell in the body), by genetic reprogramming, to go back into the state of a stem cell. And pluripotent, meaning it can now be genetically programmed to become *any* kind of cell in the body that the scientist chooses: an eye cell, a heart cell, or a neuron. If the latter, this is referred to as "neuralizing" the iPSC.

Now you can see why we call this magic. I said to Deep, let's do it! It seems entirely ethical, as most adults would be happy enough to donate a single hair from their head, and no animal is "sacrificed" in this kind of science, and it enables scientists to study the development of *human* neurons in the lab.

The importance of Yamanaka's scientific breakthrough is that if you want to study development from the first moment of life, iPSC bypasses the need for an embryo. In addition, previously, if you wanted to understand the autistic brain, scientists would rely on post-mortem studies, where someone with autism has tragically died, and where their next of kin donate their relative's brain to scientific research.

Brain donations are invaluable, but from a scientific perspective, post-mortem brain tissue has many limitations. For example, you may end up with a set of brains that are donated from individuals of different ages, each of whom died from different causes. Interpretation of results thus becomes difficult. A further complication is that you may know very little about the person before they died (e.g., what their IQ or personality was like) and it is too late to gather such information. Post-mortem studies are still informative, but come with a handful of caveats.

Alternatively, if you want to study the autistic brain, you can use an animal model, where for example you create a "knock out" mouse—a mouse genetically engineered to lack a particular gene that you as a scientist suspect may play a role in autism—and observe the behavior of the knock-out mouse compared to a typical (or wild-type) mouse. If the knock

out mouse shows "autistic" behavior, for example being less sociable, you conclude this gene may be causing one or other of the symptoms of human autism. You can see the limitations of such animal studies immediately: how do you know that sociability in a mouse is the same thing as sociability in a human? The interpretation of results from such animal experiments is as littered with caveats as are the post-mortem studies.

Now we can see the power of adding iPSC to the scientist's tool kit for getting answers to questions. If you want to observe the living human brain, you can study the brain from the person you are interested in, and you can gather as much information about that person as you want: IQ, personality, precise diagnosis, or anything else you want. You can even look at the effects of different drugs or molecules on the neuron, without having to do these arguably unethical drug studies on an animal.

iPSC is not without its own limitations. An iPSC may not be exactly identical to an embryonic stem cell, so the neuralized iPSC may not be exactly the same as a naturally growing neuron. All tools in the scientist's tool kit have their limitations, but this one—to my mind—is more ethical, and a more directly relevant method to autism, than is animal research. Many labs (like ours) are testing if you get the same results from both iPSC *and* post-mortem studies, since this strengthens the conclusions that can be drawn.

Deep's exciting results will be published in 2016. The combination of a break-through scientific method, in the hands of a talented young PhD student, might be just the cocktail to be a game-changer in our understanding of the causes of autism.

Date:
[Sat. Dec. 26. 2015]

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