OPINION

Diffusion imaging of human connectome doesn't hold water

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23 DECEMBER 2014

Monkey see: Diffusion imaging charts some brain connections that don’t exist in monkeys and misses others that do.

Over the past five years, researchers have made a big **push to map** white matter, the tracts of nerve fibers that connect different regions of the brain. Building an accurate atlas of these tracts could help researchers understand autism, which is thought to **involve abnormal long-range connections** in the brain.

Efforts to map this so-called ‘connectome’ rely mainly on **diffusion imaging**, a noninvasive method that uses a magnetic resonance imaging (MRI) scanner to measure the direction and flow of water in the brain. Researchers then use sophisticated computer algorithms to translate these data into colorful depictions of the brain’s wiring.

Scientists **quibble over the details** of the best way to build that wiring diagram. But there is widespread faith that these white matter maps are becoming more accurate with advances in scanner resolution and computing power.

A study published 18 November in the *Proceedings of the National Academy of Sciences* calls that faith into question, pointing out that diffusion imaging can **provide only an indirect view** of white matter. As such, it’s unlikely to ever trace the brain’s anatomy with perfect accuracy.

In the study, researchers scanned the preserved brain of an adult male rhesus macaque using diffusion MRI. The scan was so detailed that collecting comparable images from a living human brain would require a person to lie still in a scanner for thousands of hours, the researchers say.

They applied four different methods of tractography — the computer analysis that translates diffusion imaging data into a model of fiber pathways in the brain — to map the connections between two areas of the cerebral cortex and the rest of the brain.

Finally, they compared these results with an existing atlas of macaque white matter, which was created by injecting neurons with a radioactive dye that traces the paths of individual neurons across long distances. This tracer method is the most reliable way to study the structure of white matter, but it can't be used in living people.

Inconsistent results:

The study spotlighted some major shortcomings of diffusion imaging. In some cases, the technique identifies false connections; in others, it cannot untangle pathways that the tracer method maps clearly. The balance between these false-positive and false-negative results depends on the specific parameters and assumptions of the tractography model used. No single method — not even the most sophisticated one — consistently yields the best results.

The publication **sparked some snarky commentary** by neuroscientists on Twitter. "What a surprise! DTI doesn't match tracer injections! Really," wrote **Partha Mitra**, professor of neuroscience at Cold Spring Harbor Laboratory in New York. (DTI stands for diffusion tensor imaging, which is one type of diffusion imaging but is sometimes used as shorthand for the approach as a whole — particularly in 140-character quips.)

"The surprise is it took so long to actually directly do the comparison on the same brains! Taking pretty pics on faith," responded **Kevin Mitchell**, a neurogeneticist at Trinity College in Dublin, Ireland.

Although many researchers who use diffusion imaging are **sober and cautious about what this method shows**, it's easy to get caught up in the colorful images and forget that the 'wiring diagram' is still a metaphor.

Still, this doesn't mean that the whole effort to map the human connectome is a wash. "On more positive note, those kinds of comparisons should help derive DTI algorithms that give more accurate picture," Mitchell added.

The new study suggests a few strategies for improving the method's use. For example, rather than arguing over the best method of tractography, scientists should use a combination of approaches to map different areas of the brain, the researchers say.

They also recommend comparing pathways identified through diffusion imaging with those mapped by the dye method in nonhuman primates. Although brain anatomy varies across species, we have enough in common in the noggin with our nearest relatives to make this an important strategy for grounding the diffusion imaging data.

This seems like a reasonable course to chart. While diffusion imaging isn’t a perfect compass, it’s still the best tool we have for mapping white matter pathways in humans.