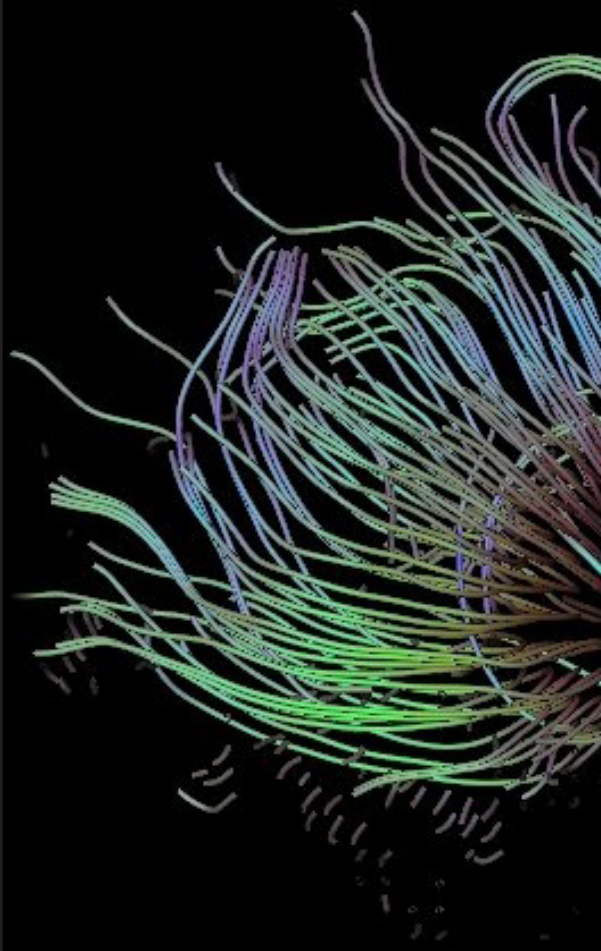

# Mapping the Mind

By Natalie Twitchell

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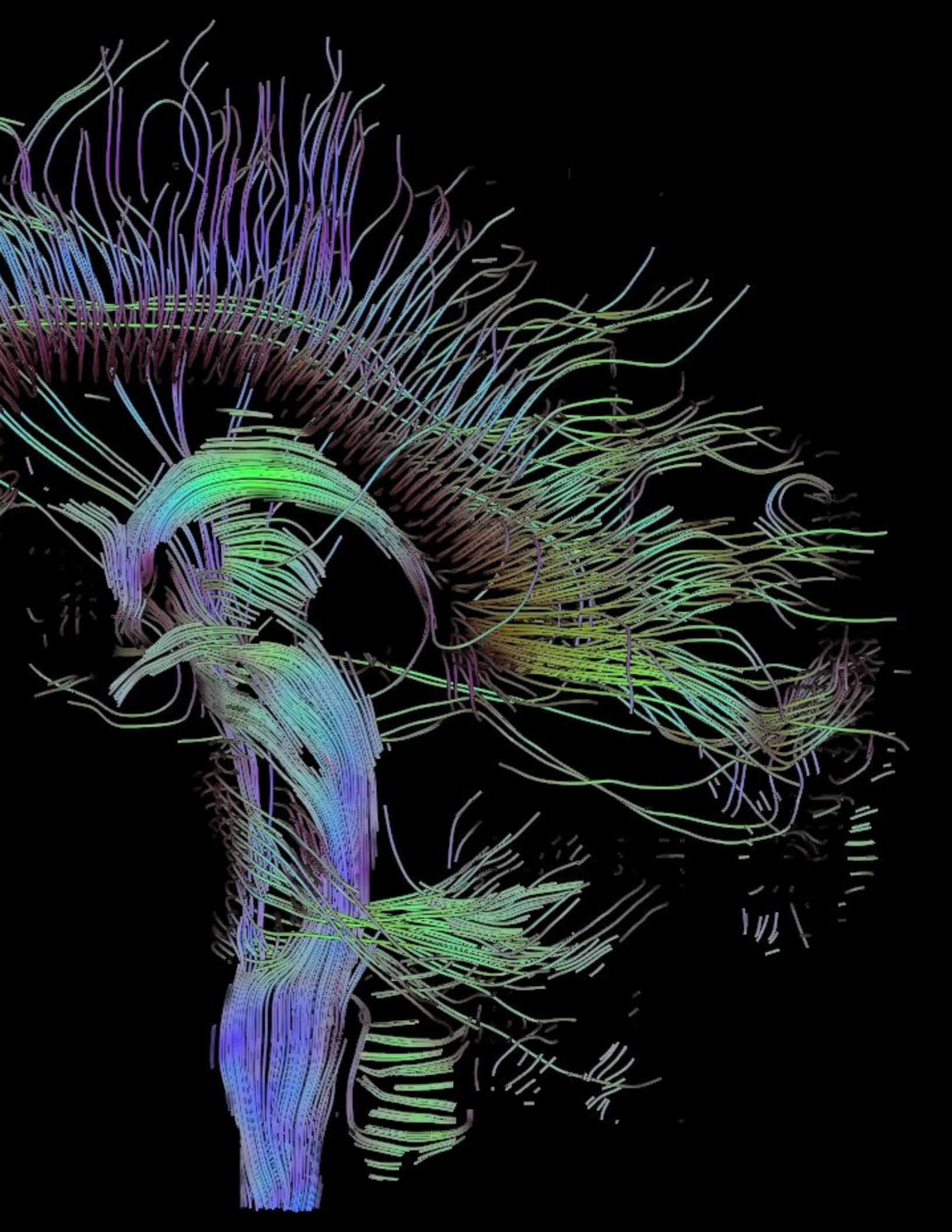


*C. elegans* shown at high magnification (12)

In 1986, at the birth of the information age, the Royal Society devoted a massive three-hundred forty pages of an issue of one of their academic journals to the work Sydney Brenner and his colleagues had done on a relatively unknown microscopic roundworm. This animal, *Caenorhabditis elegans*, would go on to become one of the most significant model organisms in the biological sciences, particularly in neuroscience. However, the full significance of Brenner's study remained unrealized until computers became powerful enough for a new branch of neuroscience, called connectomics, to emerge. Connectomics seeks to diagram the means of communication between brain cells—also called neurons—with the end goal of understanding the precise route through which a sensation becomes a thought, a thought becomes a memory, a memory becomes a rationale, and a rationale becomes an action. The field has grown from these humble origins to profoundly influence our understanding of neural anatomy, hardware design, and even consciousness itself.

Brenner's paper, simply and ambitiously titled *The structure of the nervous system of the nematode Caenorhabditis elegans*, was the culmination of over a decade of study. The paper delivered exactly what its title promised: a full diagram of every one of the *C. elegans*' three-hundred two neurons and how they connect with each other. Although *C. elegans* has a much simpler nervous system compared to other animals,this was a herculean task given the nearly eight thousand unique connections among these cells. A map of neural connections such as this is called a connectome.

Although *C. elegans* is very different from a human being, the systems that drive *C. elegans* motion and neural activity are very similar to a human's. Therefore scientists can glean insight about humans from understanding this worm. For this reason, *C. elegans* is commonly used a model organism—a simpler animal that can be studied to learn the basics of human biology. However, more complicated behavior such as cognition requires a more complicated model—a challenge many teams in the thriving field of connectomics are taking on. Work is being done to diagram the fruit fly brain, as well as parts of the mouse brain. The most ambitious and large scale initiatives, such as the European Union's Human Brain Project and the American National Institute of Health's Human Connectome Project, are working towards whole-brain modeling, which is the ability to describe an entire human brain in terms of individual cells.

## From Neuron to Nuance:

### Finding Ourselves within the Brain

The search for the mind—what gives us personality and identity beyond biology—has intrigued philosophers and other thinkers long before neuroscience as a field existed. It has eluded humanity's best efforts to characterize it, and many think that it will continue to elude thinkers even after our knowledge of neuroscience is much more complete than it is now. What is known, however, is that complex processes such as movement and behavior can arise from the electrochemical signals, called action potentials, that neurons send to each other.

The moment a sensory stimulus—such as a smell, texture, or ray of light—touches your body, the first action potential in a sequence is triggered. This stimulus causes the neuron to physically change in a way that alters the concentration of chemicals—called ions—inside the neuron. This triggers a change called an action potential, in which the neuron sends an electrical signal down its length. Once the signal has

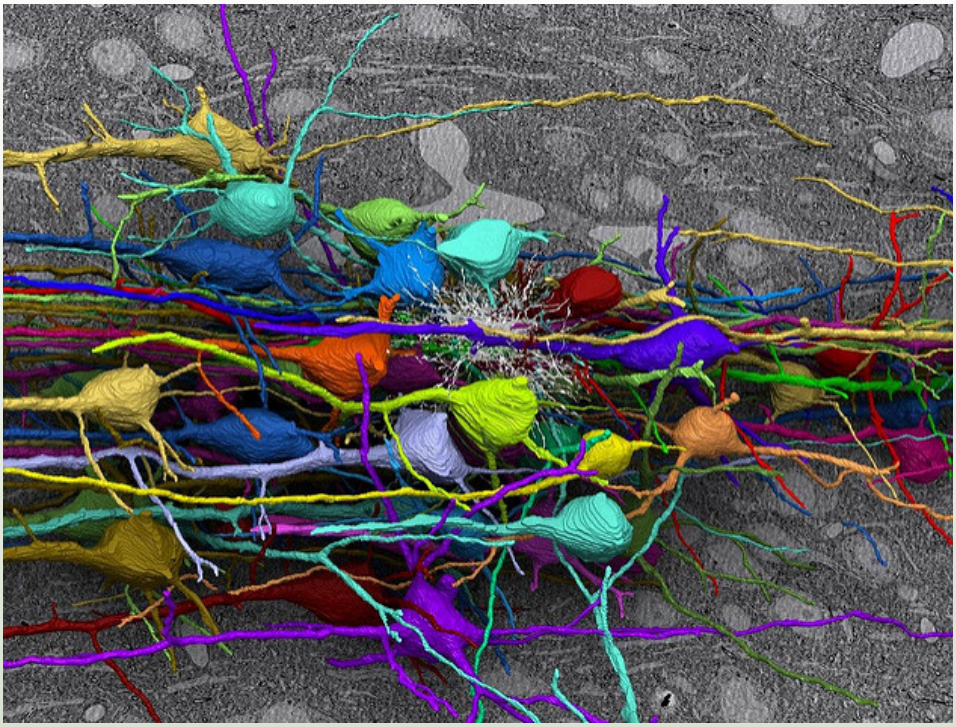
reached the end of the neuron, it is converted into a chemical, called a neurotransmitter, that triggers an action potential in the next neuron. This signal ricochets from one cell cluster to another throughout the brain, causing different functional regions to be activated, translating a biological response to stimuli into a response made up of higher order functions such as actions and emotions.

Although the distance between cells, called the synapse, is microscopic, it perhaps represents the widest gulf between known and unknown in connectomics. This is partially on account of the sheer number of synapses—the human brain has billions of neurons, forming trillions of synaptic connections[1].

However, whereas the number and placement of neurons remains mostly fixed throughout an organism's lifetime, the synapses they form onto each other vary tremendously. Each day, unused synapses decay and previously unconnected neurons reach out to one another as the brain learns and adapts. This means the connectome changes as the organism interacts with its environment. In addition, the brain is similar to every other part of the body in that it has general similarities but granular differences. For example, the vast majority of human beings have eyes that work in a very specific way, but the precise combination shape, color, and capability of that your eyes have is extraordinarily rare. This tremendous amount of variability means that scientists working in connectomics must contend validate their results by working with more than one organism in each study. As a result, each connectomics study contends with terabytes of data (orders of magnitude higher than what a cell phone can hold) to even map a portion of the human brain. The challenges inherent to a dataset this large mean that, in order to find techniques to analyze their data, these neuroscientists work at the frontier of data science and hardware engineering, advancing one field in pursuit of the other.

The convergence of the insights derived from connectomics and the bleeding edge of engineering points to a possibly unsettling location of the mind—within the mechanics of the brain itself. The advent of neuromorphic hardware—hardware based on the mathematical and physical structures of the brain, has provided proof of concept that the remarkable speed and organization of the brain is not mystical, but mathematical. By applying algorithms and theories originally developed by computer scientists to studies of brain function, scientists have made discoveries about the functionality of the brain that push us closer to understanding human thought and how it is constrained the same physical and mathematical laws as other systems that convey information.

In light of these dramatic implications, it is crucial to remember that connectomics is in its infancy. Even the most sophisticated models cannot claim to have described essential human behavior—such as thought, motivation, and identity—in their entirety. Even so, connectomics has provided tools to both doctors and research scientists that allow them to address complex questions in ways that would have been impossible before the advent of the silicon chip.

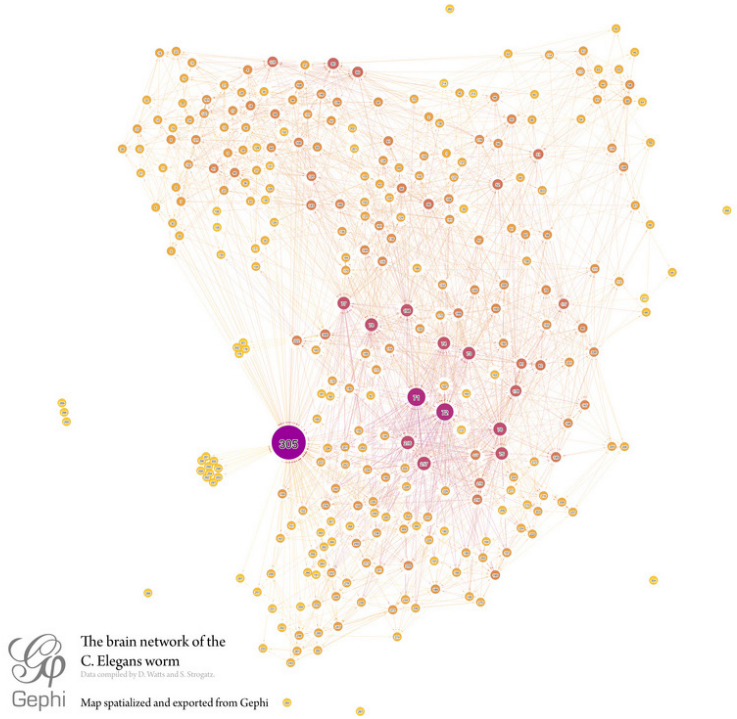


*Neurons, each artificially colored in a different hue, send out projetions that meet, forming synapses[13].*

## A New Page in the Connectome

In order to trust bold claims and results from connectomics, it is important to make sure that the models used accurately reflect what they are meant to. To this end, a group of scientists led by Gang Yan tested the ability of Brenner's original *C. elegans* connectome to make predictions about how the worm moves that transfer from *in silico* (on the computer) to *in vivo* (in a living organism).

In order to do this, they had




*A visualization of the connections in the C. elegans connectome. Each neuron is a numbered dot, and each line is a synapse[14].*

The results of these calculus equations are called Linear Controllability Predictions. Linear Controllability Predictions made based on the *C. elegans* connectome identified specific neurons that, if damaged, would prevent the movement from occurring. Remarkably, these predictions held in a real *C. elegans*, validating both the *C. elegans* connectome and the use of computer science principles to describe how information is transmitted in the brain[1].

Even so, the *C. elegans* nervous system is not fully mapped. The type of signaling pathway—synaptic connectivity—that Brenner mapped is only one of the many kinds of signaling that the brain uses constantly. In order to develop a richer picture, another group of scientists have studied the signaling networks of peptides (tiny signaling protein-like molecules) and monoamines (the celebrities of neurotransmitter molecules, such as dopamine, norepinephrine, and serotonin).

Recently, Barry Bentley and his lab have attempted to understand how monoamine and peptide signaling connects the same neurons described in the traditional connectome. They described the synaptic connections as 'wired' connections between two neurons, because information travels directly between one to another. Much like a computer chip, groups of cells that are highly interconnected are physically close to each other. They found that monoamine and peptide networks break all of these rules. Unlike in man-made networks, critical groups of one type monoamine—or peptide—signaling cells are not located in the same physical space as these 'hubs' of other types of cells. In addition, the monoamine and peptide emitting cells communicated not with just one neuron at a time, but with a wide range of neurons, allowing their signaling molecules to float through the fluid of the brain over relatively long distances. For this reason, these connections are deemed 'wireless.' A shocking ninety-six percent of monoamine connections—connections which may be implicated in anxiety, addiction, and memory in humans—are not described by the classic connectome[2].

By combining the wired and wireless connectomes, scientists are able to understand C. elegans better than ever before. Even so, our map of the nematode mind is still incomplete. The authors of the study worked with an incomplete definition of what guarantees that a cell will send or receive a certain neurotransmitter, simply because all of the anatomical and biological factors at play are not known. But even a perfect C. elegans connectome would not be able to fully describe and predict what happens in the brain of a human being. For that, it is necessary to look at the nervous system of a more complex organism, an initiative only possible since the advent of high throughput computing systems.

The current front-runner for the second full connectome is the *Drosophila melanogaster*—better known as the fruit fly. When not bringing home ribbons at science fairs or colonizing trash cans, the fruit fly provides valuable data to biological scientists. Because the fruit fly has a short genetic sequence and an even shorter time between generations, abnormal changes in the DNA (called mutations) are easy to study. Some genetic information that causes human illness or underlies necessary biological functions were first discovered in a fruit fly that did not appear or behave normally. The fruit fly's brain, although not as complex as a human being's, possesses 20,809 neurons and 1,044,020 synapses and can learn, emote, and choose. Clearly, these are too many to map by hand as Brenner and his colleagues did. A research group led by Yu-Chi Huang turned to Artificial Intelligence to develop a platform that they are calling

"Flysim" that simulates the entire brain of the fly *in silico*. This project is analogous to Brenner's original C.elegans connectome modeling, only wired connections and not taking into account external stimuli. Although the project has only just begun, it has yielded impressive results. The Flysim team developed an algorithm that combed through a database of pictures of fruit fly neurons in order to reconstruct a three-dimensional model of how they connect in space[3].

Flysim is capable of not only predicting how a pair of neurons will connect and subsequently exchange electrical signals, but synthesizing these million connections into a model of the brain at rest. This task is extremely complex due to the large amount of processing power and amount of information that must be managed. Early simulations have indicated that brain modeled by Flysim would have electrical patterns similar to those seen in actual brains, validating the accuracy of these connections. This is important because conditions such as epilepsy are connected to misregulation in neural electrical patterns[3]. With science this promising so early on, it seems that the fruit fly will continue as a model organism into the information age.

## Beyond the Neuron

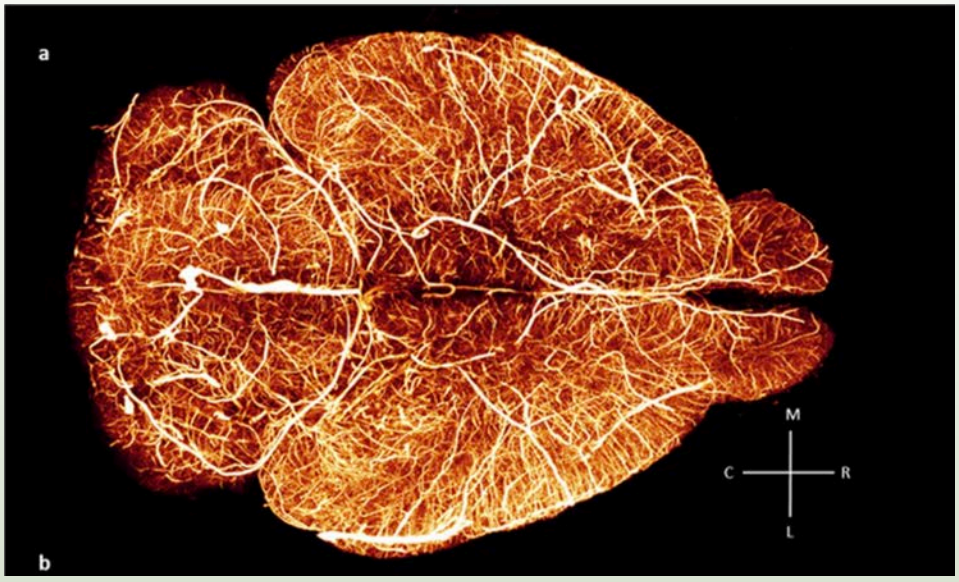
For all their strengths, these models only look at one type of cell in the brain: the neuron. Neurons do not communicate solely among themselves; they act in concert with glial cells - multifunctional nervous system cells that aid in brain function - and other bodily systems such as the immune system, vasculature, and the digestive system. In order for connectomics to understand how the brain works and why it fails, it is not enough to take into account the neuron alone.

For this reason, Antonino Paolo Di Giovanna's lab became interested in connectomics and whole brain modeling have turned their attention to understanding the vasculature of the brain down to the level of capillaries, the tiniest blood vessels, where the interchange of oxygen, nutrients, and waste takes place. Capillaries nourish brain cells and are a potential entry point for viruses, medications, and illicit drugs. In order to build this model, the group had to utilize AI to make predictions about how the vessels traced from disjointed two-dimensional sections of dead cross sections of neural tissue on slides would connect into a whole brain[4].

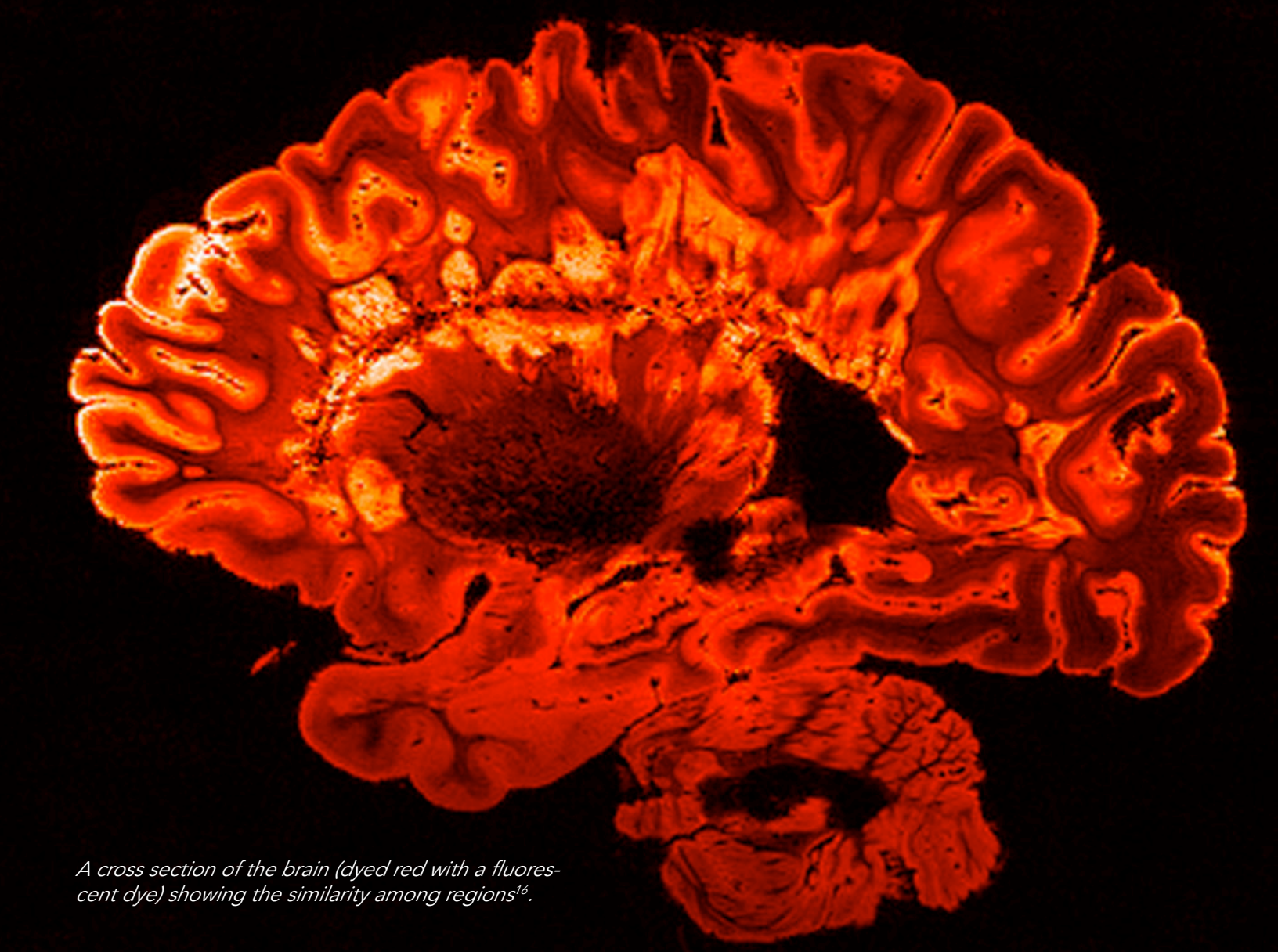
Another recent study by Estibaliz González de San Román and labmates expanded on connectomics by looking at the molecular makeup of the primary visual cortex, an area of the brain that is crucial to our ability to see, that has already been mapped in the traditional ways. This area was of particular interest because the biological mechanism behind image processing remains a mystery and it has a distinct pattern of subareas. San Román's group used a technique called multimodal mass spectrometry, which combines multiple different methods of identifying specific particles and cell types using chemistry. This tool allowed the researchers to identify certain proteins, fats, and metal atoms that were present in specific subareas but not others. Since proteins, fats, and metal atoms are used by cells for signaling and manipulating their environment, this information is a valuable step towards whole brain imaging and may provide insight as to how this mysterious region of the brain processes visual information[5].

## Reshaping the Brain

Even the connectome alone has been a boon to neuroscientists who study the anatomy and regional connectivity of the brain. It is well known that certain regions of the brain have a high degree of control over certain functions, and anatomists have worked to map circuits of multiple regions that work in concert to regulate particular tasks, such as monitoring balance, responding to a drug, or recognizing the face of your baby. Still, brain anatomy remains a morass of unsolved questions. Even well characterized regions can be involved in multiple circuits,




*Di Giovanna et. al's model of vasculature of the mouse brain[15].*



*A cross section of the brain (dyed red with a fluorescent dye) showing the similarity among regions[16].*

and can be divided into distinct sublayers, such as in the primary visual cortex. These regions are made of neurons that look similar and communicate through a similar set of neurotransmitters, but can have vastly different functions based on what other regions their region is connected to.

Robert Langner and his colleagues used a relatively recent tool called meta-analytics to search for circuits that may be involved in our ability to self-regulate. Meta-analytic studies use large databases of previous studies and use statistics to seek patterns in the results. In his study, the authors looked at studies that postulated networks that might regulate two separate but interconnected systems involved in self-regulation called cognitive action regulation (CAR) and cognitive emotional regulation (CER). They selected studies that had rigorous methods for detecting activation of a brain region and used the field standard coordinate system to describe their measurements of the brain.

Meta-analytics harnesses the power of using measurements from more than one brain. Human beings are incredibly complex—mental and neurological illnesses, genetics, and even life experiences can alter the physiological structure of the brain. By including dozens of studies, each with multiple patients, means that any single study with nonrepresentative volunteers or mistakes in methodology will not entirely skew the results.

Once the dataset was assembled, the group used an algorithm to evaluate their predictions. They identified functional associations and postulated networks. Their finding, that CAR and CER moved through some of the same areas, but are distinct, comes at a time when the field's opinion is divided as to the relationship between the two mechanisms. Although not conclusive, this study represents a solid attempt to use whole-brain modeling to resolve a crucial neuroscience question in a relatively unbiased way[6].

Jianghai Ruan's anatomy lab has also used whole brain modeling to confirm brain structures that were dentified visually over a century

ago. Their first step was to perform coactivation studies, which look at which areas of the brain send and receive signals at the same time. Next, they algorithmically identified the boundaries of two areas that are important to neuroscientists—the supplementary and pre-supplementary motor areas, which, as the names suggest, are involved in preparing the body to move. Algorithms, although influenced by the limitations and biases of their programmers, are ruthlessly consistent, and able to identify patterns that their creators may not have been able to see on their own. Therefore, they can provide insight into trends in physiological data, as in this study, where the algorithm, looked for trends in physiological markers and functional boundaries to confirm the boundary between these two brain regions, which is important to neuroscientists who study motion[7].

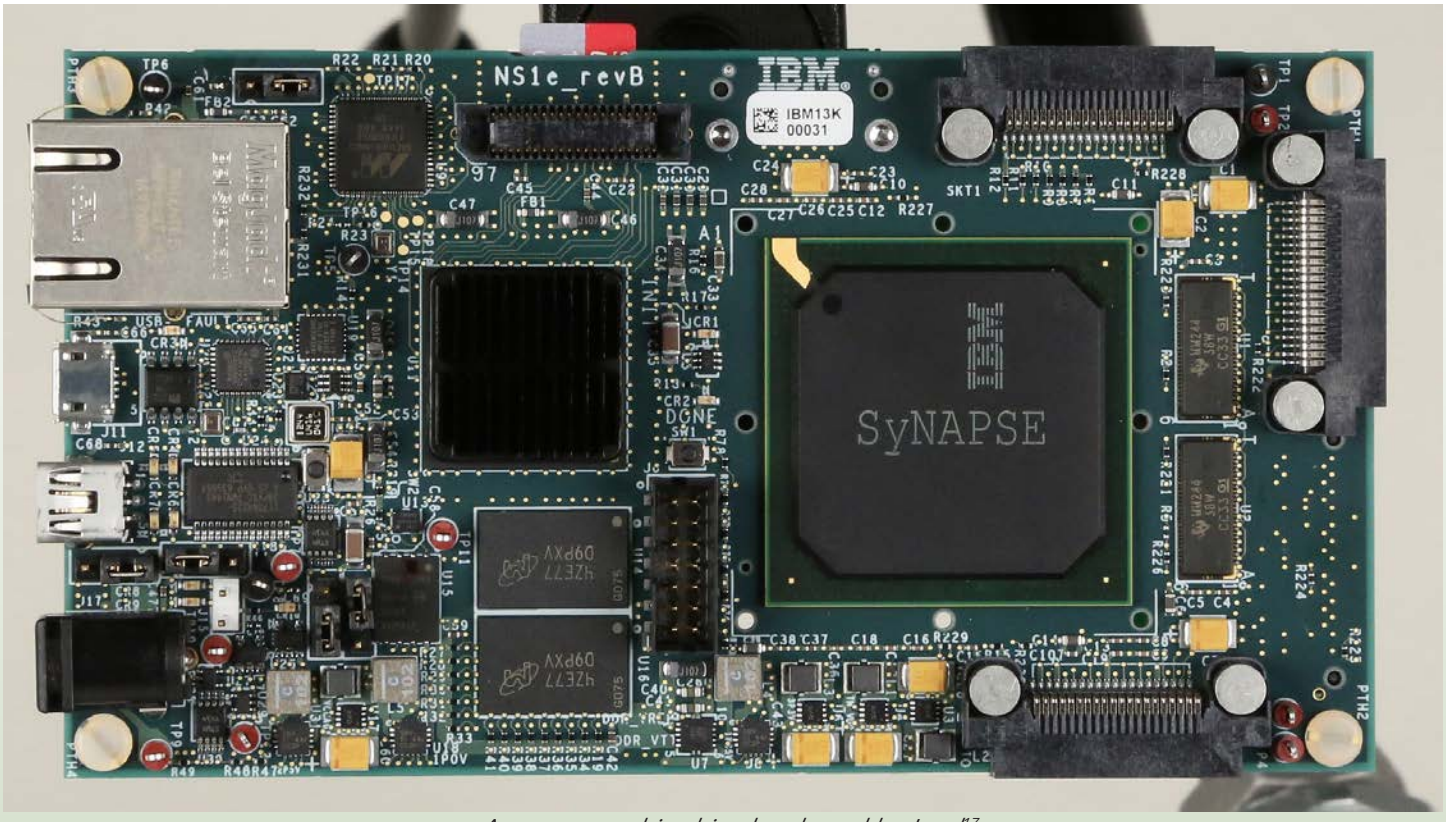
## In Silico

Modeling the brain at this level of precision and raises the question of whether complex systems such as the brain can be replicated by mankind. Hardware engineers, inspired by the efficiency of the human brain, have taken results from neuroscience and applied it to their work.

A team of theoretical computer scientists, led by Guillaume Bellec, who are working to make computer processing more efficient was inspired by contrast between complexity of our thoughts and the small space between our ears. Specialized projects such as connectomics require computers much more powerful than the standard laptop, and therefore much more technologically elaborate, will be required, *small*. energy efficient chips will make these projects not only accessible, but in some cases possible.

In order to tackle this problem, the engineers developed an algorithm called DEEP R. DEEP R takes inspiration from the brain's ability to make and delete connections in response to new information. This process, which is called learning when it happens in the brain, was adapted for DEEP R. Instead of just making new connections between pieces of information, and therefore generating more data, like traditional algorithms, DEEP R deletes connections that no longer hold information in order to keep the memory usage of the algorithm low, and therefore the efficiency high. Surprisingly, this leads to the algorithm outperforming its traditional counterparts[8].

Other groups have taken further inspiration from neurobiology. Computer chips have been made that attempt to—and are very close to—direct analogs to neural circuitry both in hardware and software. As our need for computation for grows,




*A neuromorphic chip developed by Intel*[17].

the sophistication, capacity, and efficiency of these chips, called neuromorphic hardware, will rise to meet it. However, it is important to remember that these chips are not able to think. They are extremely task-specific, and only adaptable to a degree[9].

## Defining the Mind

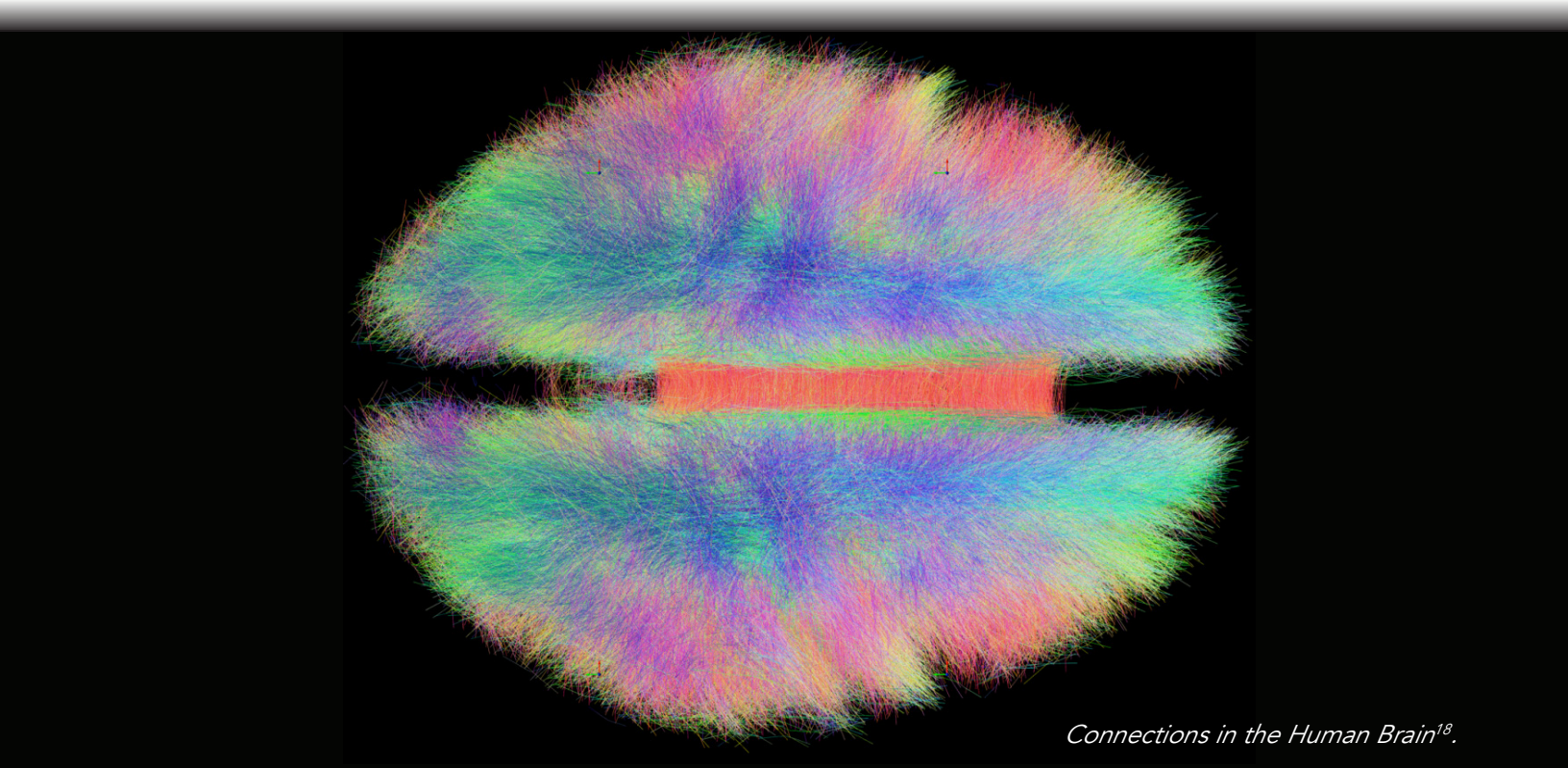
Although the project of the human connectome is not finished, it is already bolstering our ability to treat patients.

A recent study of patients with disorders of consciousness in France illustrated the power of whole-brain mapping in the clinical setting. Even though science has not reached a formal definition of consciousness, specific patterns in brain waves are fairly—but not entirely—reliable markers that doctors can use to identify whether a patient is conscious. Doctors can detect these markers using a noninvasive brain scanning tool called the EEG. Making sense of these markers is as difficult; disorders of consciousness are complex, individual, and poorly understood. As a result not every marker is present in every patient, and there is not a simple test that can be done. The analysis is left to the judgement of a physician.

A group of scientists working with machine learning—a type of Artificial Intelligence—developed a machine learning based algorithm to help doctors identify whether or not a patient is conscious. The algorithm does this by first analyzing previous EEGs and whether or not they came from a conscious person or not, and then applying the patterns from that dataset to the new EEG. The algorithm identified several markers of consciousness that seemed to be more significant than the rest, which on its own is an important piece of information to scientists attempting to understand brainwaves. The most groundbreaking result, however, is that the algorithm was able to better identify the patients' states of consciousness than a trained physician[10].

As connectomics and brain modeling become more saturated in medicine, it will become more important to understand both the power and fragility of this software. Like all scientific innovations, these algorithms are built by human hands, and therefore flawed, slated for improvement, and fallible. It should give us pause that algorithms based on datasets that may be incomplete in ways we do not know how to look for are modeling medical advances. But this is not so different than more traditional science - no individual scientist or clinician has perfect judgement.

Perhaps there is one last lesson to be learned from Brenner's *C. elegans* connectome: that the work he and his colleagues did by painstakingly mapping neurons by hand, although imperfect, incomplete, and unable to be realized fully by the technology of his time, would take part in creating a better future.



*Connections in the Human Brain[18].*

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## Image citations


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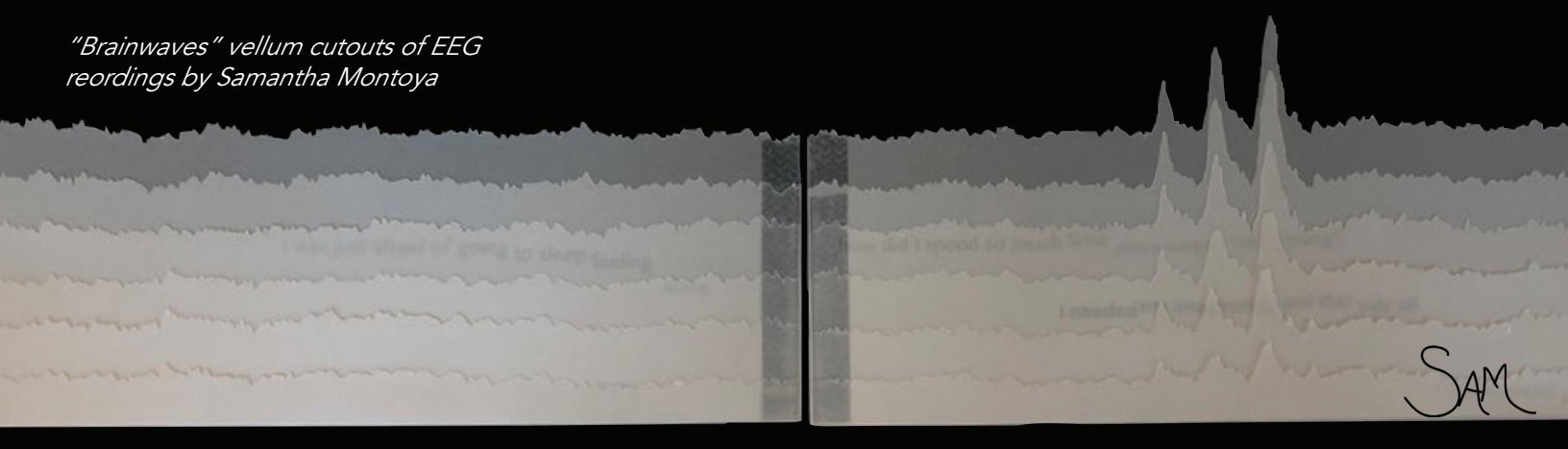
*"Brainwaves" vellum cutouts of EEG reordings by Samantha Montoya*



*Scotopic Apolipoprotein by Samantha Montoya*

Sam