AUTHOR COMMENTARIES - 2009

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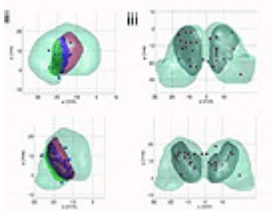

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Tim Behrens

Featured Scientist Interview

Magnetic resonance imaging (MRI) has played a major role in the investigation of brain structure, function development, and pathologies. MRI experiments on the human brain can be divided into two categories: structural experiments, which rely on the biophysical properties of brain tissue, and functional experiments, which are sensitive to temporarily changing neuron activity. The interrogation and analysis of MRI data is exceptionally challenging in terms of the software required to produce three-dimensional images from the raw data.

An analysis of the field of Neuroscience and Behavior in Essential Science Indicators℠ *from Thomson Reuters over the past decade has highlighted the publication record of Dr. Tim Behrens. His record in the database includes 1,500 total citations for 35 papers published in this field alone from January 1, 1999 to June 30, 2009.*

Dr. Behrens is a Research Lecturer at the University of Oxford, working for the Centre for Functional MRI of the Brain at the John Radcliffe Hospital. In this interview,* ScienceWatch.com *European correspondent Dr. Simon Mitton examines the key contributions to computational neuroscience made by Dr. Behrens and his colleagues.

SW: Your Masters degree is in engineering, so how did you come to be working in neuroscience?

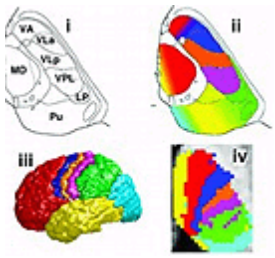
At Oxford I studied information engineering and machine learning for my MEng degree. I was interested in doctoral research, but could not settle on an area. Then I became attracted to brain imaging by an ebullient person, Professor Sir Michael Brady, who is a leading figure in the disciplines of artificial intelligence, medical image analysis, and robotics. After I had made a literature review it struck me that diffusion imaging was an exciting potential tool for mapping the connections in the brain.

I adopted an information engineering approach to see if we could make it work. The question I posed was this: can diffusion MRI measurements be used to infer something about the connections between different regions of the brain? A number of groups were working on it at the time, so it was an emerging field.

SW: How do you like to describe your present research interests?

I have two main research interests. The first is in understanding anatomical brain connectivity, which you can picture as the paths of the wires that connect different regions of the brain. My second interest is to understand learning and decision-making in the human and

macaque brains from a computational perspective.



Using probabilistic diffusion tractography (Behrens et al. MRM 2003) we were able to segment the human thalamus on the basis of its connectivity to the cortex (Behrens et al. Nat Neurosci 2003).

View other probabilistic diffusion tractography figures with descriptions at the Web site of the University of Oxford's FMRIB Centre, Department of Clinical Neurology.

SW: Your most-cited papers are on the application of diffusion imaging for structural and functional mapping. What are the principles underlying this technique?

The human brain is made up of neurons, and they send signals to other neurons via their axons. Axons act like the wiring in a phone network. Obviously it is of great importance to understand how different parts of the brain are interconnected because you cannot understand what a region of the brain does until you know what information it has access to, and what influence it might have on other brain regions. The challenge, of course, has always been to develop imaging techniques that can safely be used on a live subject.

About 20 years ago, researchers at the National Institutes of Health made a breakthrough with developing diffusion MRI to image brain structure in stroke patients. Diffusion MRI exploits the fact that the neural axons are insulated with an outer sheaf of myelin, which is fat. Water finds it difficult to penetrate myelin, so if you can imagine trying to measure diffusion in an axon, you would find that water molecules diffuse preferentially along an axon rather than across it. So you can tell the direction of an axon by looking at the direction of local diffusion.

SW: How have you contributed to the development of diffusion MRI?

I have designed techniques that will trace diffusion paths, in vivo, to let us measure the connections between brain regions. I joined the field through the technical aspects of making diffusion MRI work. My top two papers (Behrens TEJ, *et al*., "Non-invasive mapping of connections between human thalamus and cortex using diffusion imaging," *Nat. Neurosci*. 6: 750-7, 2003; Smith SM *et al*., "Advances in functional and structural MR image analysis and implementation as FSL," *NeuroImage* 23: S208-19, 2004) show some of the very first results from this field, demonstrating that you can map out the connections between different brain regions.

As an engineer trying to improve the technology of brain imaging, I have needed to work alongside enthusiastic neuroscientists who can tell me whether my measurements and the pathways they represented look reasonable. That's how I came to collaborate with Heidi Johansen-Berg, who became interested in the technique I was developing. We did a lot of work on mapping the anatomy of the human brain by comparison to what is known in monkeys, with me providing the computational expertise and Heidi the anatomical expertise ("Changes in connectivity profiles define functionally distinct regions in human medial frontal cortex," *Proc. Natl. Acad. Sci. USA* 101: 13335-40, 2004; "Functional-anatomical validation and individual variation of diffusion tractography-based segmentation of the human thalamus," *Cereb. Cortex* 16: 1418-30, 2005).

Ever since then I have been working on the boundary of methods development and neuroscience. Almost everything I do involves methods that I have had to develop in some way. But over the last 10 years I have become a neuroscientist as well as an engineer.

When I began, the field needed moving out of the realm of simply looking at big white matter bundles, which are easy to measure, into the more subtle question of asking which grey-matter regions are connected to each other. This is important, because it is the grey-matter regions that contain the cell bodies where computations are performed. To move beyond that I developed algorithms that made much better use of the raw data, so it became possible to ask a whole host of new questions.

SW: Can you give me an example?

My quantitative work has included, for example, calculating the probability that two regions of the brain are connected. In this way it became possible to trace the pathway from grey matter to grey matter. That's all covered in the 2003 *Nature Neuroscience* paper on the non-invasive mapping of thalamic connections. That's the first paper that showed how to trace from grey matter to grey matter, with quantitative mapping. The paper covers the techniques we developed, but it also demonstrates that the architecture of the thalamus in the human brain is similar to that of the macaque

monkey.

"The challenge, of course, has always been to develop imaging techniques that can safely be used on a live subject."

SW: The citations to your papers indicate worldwide interest in your techniques. How did that arise?

The key technical papers are the three published in the journal *NeuroImage*: the 2004 Smith SM, *et al*. paper, as well as Behrens TEJ, *et al*., "Probabilistic diffusion tractography with multiple fibre orientations: What can we gain?" (34: 144-55, 2007); and Smith SM, *et al*., "Tract-based spatial statistics: Voxelwise analysis of multi-subject diffusion data," (31: 1487-1505, 2006). These are technical accounts of new techniques for imaging different regions of the brain.

The 2004 paper with Steve Smith describes a whole set of tools that are used worldwide. I should emphasize that these papers are from the large functional imaging group in Oxford headed by Steve Smith, which consists of nearly 20 scientists, most of whom work on tools, only one of which is the method I have described. We have produced a software library that is freely used by 5,000 labs worldwide to analyze brain data. One of the tools is the diffusion imaging I have been describing. Other tools look at functional imaging, structural imaging; they basically let you interrogate and understand your brain imaging data.

SW: Can you give me examples of the clinical applications?

The software from our imaging group is used to map out connections in different parts of the brain. The clinical applications include looking at how connections might change in different diseases. A number of citations are by clinical researchers who, having found activations in the thalamus, then want to know to which cortical region it connects. We have gone on to develop new techniques for understanding the influence that anatomical connectivity patterns have on functional specialization in grey matter. This is taken up in the 2004 *PNAS* paper, which presents the information in atlas format. So if a patient has a lesion in the thalamus it is possible to conclude which region of the cortex will be affected.

As another example, there's a new type of treatment for motor disorders that involves implanting a stimulator into particular sub-cortical nuclei, but it is very hard to identify where the nuclei are located in an individual brain. Our technique lets you take a big sub-cortical structure and locate within it the target, for example, the motor nucleus in the case of motor disorder. This may enable a neurosurgeon to position the deep brain stimulator correctly.

SW: Your second interest, learning and decision-making research, has focused on understanding the computational algorithms that are employed in human learning, and how they affect human behavior. What aspects of learning interest you?

"If you need one, try this: "The software from our imaging group is used to map out connections in different parts of the brain."

I work with Matthew Rushworth. We are trying to understand decision-making from a more formal perspective than most researchers. I build models of how people learn, and I use those models to predict what choices they will make when presented with a decision, and also to predict activity in parts of the brain. This is a new and exciting idea in neuroscience because we combine computational neuroscience with recordings of brain activity.

I try to understand the algorithms the brain uses for learning. For example, you can show that certain computational parameters are necessary for particular patterns of behavior. You can then solve an inverse problem: by witnessing a pattern of behavior you have evidence that the parameter is coded somewhere in the brain. We look for brain activity that predicts or correlates with how that hidden internal parameter in the computational model is changing.

Together with Dr. Rushworth, I have concentrated on how the brain combines recent information with our historical experiences. We show in our 2007 *Nature Neuroscience* paper, "'Learning the value of information in an uncertain world" (Behrens TEJ, *et al*., 10:1214-21), that a key computational parameter for performing this task optimally is coded in the Anterior Cingulate Cortex (ACC) in the course of learning. Our 2006 *Nature Neuroscience* paper, "Optimal decision making and the anterior cingulate cortex" (Kennerley SW, *et al*., 9:940-7) shows that removal of this ACC region causes a specific deficit in this aspect of learning.

SW: In conclusion Dr. Behrens, could you tell me what you are working on right now?

Recently we have been toying with the idea that we might be able to use formal computational models of behavior to model social interactions between individuals, and so we can find parallels between

parameters that are rather similar in two different domains: one where you are learning about your own behavior, and the other where you are learning about someone else's behavior.

In the ACC, one location codes for learning about rewards, and an adjacent location codes for the same computational parameter when learning about someone else's behavior. Based on which area has more activity we can predict whether somebody is going to be more influenced by their own interactions with the environment or more influenced by advice from other people. We are using mathematical formalism to model social behavior in terms of brain mechanisms.

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Tim Behrens's current most-cited paper in *Essential Science Indicators*, with 241 cites:

Behrens TEJ, *et al*., "Non-invasive mapping of connections between human thalamus and cortex using diffusion imaging," *Nat. Neurosci.* 6(7): 750-7, July 2003.. Source: *Essential Science Indicators* from Thomson Reuters.

KEYWORDS: MAGNETIC RESONANCE IMAGING, MRI, BRAIN STRUCTURE, BRAIN FUNCTION, BRAIN DEVELOPMENT, BRAIN PATHOLOGY, ANATOMICAL BRAIN CONNECTIVITY, LEARNING, DECISION-MAKING, HUMAN, MACAQUE, DIFFUSION IMAGING, AXON, BRAIN IMAGING TECHNOLOGY, ANTERIOR CINGULATE CORTEX, COMPUTATIONAL MODELS.

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