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Review

fMRI at 20: Has it changed the world?

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A R T I C L E I N F O

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A B S T R A C T

The prevalence of fMRI in cognitive neuroscience research is clear, but the overall impact of the associated research in the broader scope of our scientific community, and of society, is less obvious. The first reports of fMRI garnered huge interest in many areas, giving rise to a wide range of applications and technical developments over the past 20 years. Using five primary areas, i.e. scientific impact, clinical practice, cognitive neuroscience, mental illness, and society–this essay examines the question: Has fMRI changed the world?

Contents

Introduction

Functional MRI brings physics and technology face-to-face with psychology, neuroscience, and medicine. This juxtaposition, whereby each domain has driven developments in the other, has been a source of excitement throughout the past two decades. When individuals

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with exceptional expertise in one area work together with their counterparts in different domains, important developments are realized in all areas. Indeed, this Special Issue is filled with papers that are testimony to this process, bringing together the perspectives from many of those who were key pioneers, across all of these domains, in the development and application of this tool, discussing early developments and historical antecedents through to highlights of today's applications in basic neuroscience and medicine. To our community, the developments of 20 years ago were seminal—for some of us, they are the very foundation of our academic careers. Functional MRI has changed us and what we do. But as important as these developments were to the readers of this issue, another question can be asked: were these developments important beyond our small community? Has functional magnetic resonance imaging had an impact on the broader ways we practice medicine, do science, or live our lives? For better or worse, has fMRI changed the world?

This essay is based largely on a lecture given by the first author in May of 2011. We begin by describing his personal perspectives on the events of 20 years ago. The remainder of the essay examines the impact of fMRI on the broader stage of science, medicine, and society. As with any description arising from a singular point of view, there are inherent limitations—like a back projection reconstruction, the real image only forms from the sum of many perspectives. In the case of the present essay, this applies both to the history, and the selection of topics in the subsequent discussion.

Earliest days

The 10th anniversary meeting of the Society for Magnetic Resonance in Medicine (SMRM[1]) in 1991 featured two seminal presentations. The first was by Jack Belliveau, the winner of the society's Young Investigator Award that year, and the second was by Tom Brady, in a plenary lecture entitled, “Future Prospects for MR Imaging”.

Belliveau used dynamic susceptibility contrast MRI (DSC) to map changes in cerebral blood volume as a function of neural activation in response to a simple visual stimulus. The subtraction images he presented (Belliveau et al., 1991b), shown in Fig. 1a, represent the first unequivocal images of human brain activity changes seen using MR, and led to the iconic image featured on the cover of *Science*, shown in Fig. 1b.

Dynamic susceptibility contrast has long since been supplanted by BOLD-based imaging for most cognitive experiments (although it is still widely used for clinical imaging of perfusion and blood volume in the evaluation of stroke, brain tumors, and other cerebral pathologies). Nonetheless, it is worth noting that the discussion section of that poster's abstract (Belliveau et al., 1991a) included the observation that the potential presence of stable intravascular tracers, “offers the potential to perform continuous serial imaging of cortical function with subsecond temporal resolution… The ability to perform complete 2-D images in times as short as 50 ms implies that the hemodynamic response time of neuronal activation… will ultimately limit the temporal resolution of this technique” (Belliveau et al., 1991a). Jack Belliveau's work and enthusiasm brought brain mapping to our group in a way that inspired the entire laboratory, and Jack's prediction, above, did not have to wait long to be seen as prophetic.

These two ideas, dynamic imaging and endogenous contrast, were brought together in Ken Kwong's experiments of May 9, 1991 with human subjects. Ken's work was presented by Tom Brady in his keynote address at the same 1991 SMRM meeting. This was the first public presentation of Ken's work on dynamic BOLD and flow contrast functional mapping in humans using MRI. There were two endogenous contrast mechanisms used: arterial spin labeled flow contrast (Detre et al., 1992), and the intrinsic intravascular susceptibility contrast agent deoxyhemoglobin (Ogawa et al., 1990; Thulborn et al., 1982). Brady's presentation included a video of Ken's data, showing dynamic imaging of cerebral activation (Fig. 2). It was certainly not Hollywood quality, but many people in the audience appreciated its potential immediately; and for some, it changed the course of their careers.

It is inspiring to look at Ken Kwong's lab book from the day he first succeeded in this work. Two pages from this lab book, dated May 9, 1991, are shown in Fig. 3. On the left is a sketch of a “block design” for his experiment. Although the block design paradigm for fMRI seems obvious now, 20 years ago all functional brain imaging studies were done with single time-point injections, repeated many minutes apart, with analysis tools designed to identify the differences between sets of independent images. Ken's block design represented a new paradigm for activation studies, requiring different timing and analysis techniques, and remains the most commonly used functional paradigm more than 20 years later. The two sections on the right hand page show the contrast mechanisms involved. Ken first described an imaging sequence for BOLD contrast using gradient echo (GE) during the block design; then, immediately below, the T1-weighted inversion recovery (IR) imaging sequence to achieve contrast based on cerebral blood flow (CBF). Superimposed on these two pages is a visual activation subtraction map from the BOLD contrast experiments performed that day, and later published (Kwong et al., 1992).

At the time it was unknown whether BOLD, via gradient echo images, would yield SNR comparable to CBF-based imaging. Thus, on one day–May 9, 1991, Ken documented the conceptual paradigm for block-design fMRI and performed experiments using the two dominant modes of endogenous contrast that we use today: gradient echo BOLD imaging, and arterial spin labeling flow imaging. Not a bad day's work.

Has fMRI changed the world?

Beyond these and other early observations documented in this Special Issue, much has happened in our field. How can we think about the impact of this work? We will consider whether fMRI has changed the world by looking at its impact on each of the following domains: scientific impact, clinical practice, cognitive neuroscience, mental illness and society more broadly.

Scientific impact

One way to assess the impact of fMRI on scientific research is to use the tools associated with citation counts. We ask how fMRI compares with other high-profile scientific discoveries of the last few years. Table 1 illustrates one such comparison, based on the number of PubMed citations for eight high impact key words—words reflecting several recent Nobel prizes in medicine and physiology. On one hand, fMRI has not been cited nearly as many times as knockout mice, HIV or MRI more generally. On the other hand, fMRI has more citations than such important discoveries as telomerase and the human papilloma virus (HPV), and is comparable to RNA interference (RNAi) and in vitro fertilization. Functional MRI has clearly achieved an impact comparable to other very important biomedical discoveries and inventions.

Clinical practice

Perusing the 400 abstracts that were part of the Organization for Human Brain Mapping's first meeting in Paris (Mazoyer et al., 1995) reveals the vast range of medical topics for which fMRI was proposed very early on. Such topics included presurgical planning in

[1] The Society for Magnetic Resonance in Medicine and the Society of Magnetic Resonance merged in 1994 to form one organization: The International Society for Magnetic Resonance in Medicine (ISMRM). One of their annual meeting events is the “Lauterbur Lecture”, named for Paul Lauterbur, who shared the 2003 Nobel Prize in Medicine with Peter Mansfield in recognition of their contributions to the development of magnetic resonance imaging. The first author delivered that named lecture in 2011, and it became the basis for the present essay.

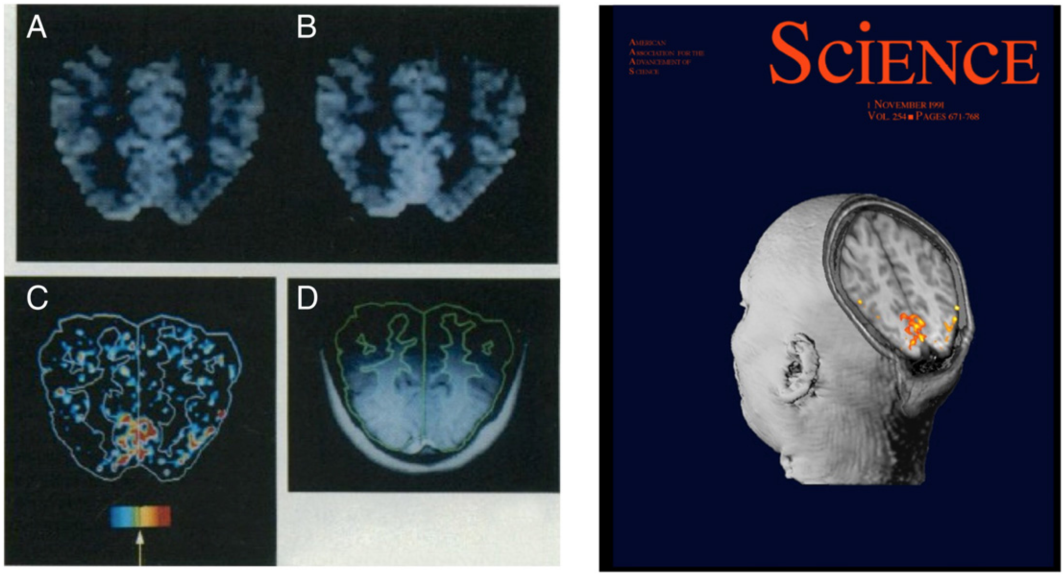

Fig. 1. On the left, the subtraction images associated with the first CBV changes, as measured with MRI, associated with neural activity. On the right, the cover of the issue of *Science* in which the figure appeared. A and B are CBV maps obtained when photic stimulation was OFF or ON, respectively; C is the pseudo-colored subtraction image between "A" and "B" with warmer colors indicating more activity in the ON condition; D is "C" superimposed on a structural MR image of the anatomy.
From Belliveau et al. (1991b); reprinted with permission from AAAS.

conjunction with resection of the brain to treat tumors or epilepsy, treatment outcome evaluation after stroke, and diagnosis of psychiatric disorders, to name just a few. Have these early hopes been realized, after 20 years?

Presurgical planning

In some medical institutions fMRI is routinely used for presurgical planning of invasive neurosurgery procedures. The American Medical Association (AMA)'s issuing of 3 CPT codes (Current Procedural Terminology) for fMRI in January 1, 2007 made these procedures eligible for routine billing and reimbursement. This was an important change from the preceding years, when the use of fMRI was limited to that of an investigational tool to supplement the surgeon's information, and hospitals could not formally bill for the procedure. One recent and thorough review (Pillai, 2010) profiles many examples of studies that reported both medical and practical benefits of fMRI for presurgical planning, including reduced surgery time and less need for Wada tests in a substantial percentage of cases. Pillai also mentioned that fMRI led to the creation of a new organization, The American Society of Functional Neuroradiology (ASFNR), established in 2004, and suggested that the ASFNR would help spearhead definitive studies of fMRI's clinical effectiveness.

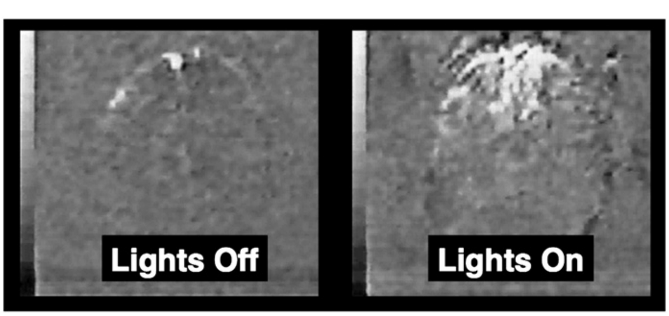

Fig. 2. MR images from the data of Ken Kwong, as presented by Tom Brady at the 1991 ISMRM meeting. On the left, one frame of the movie taken when the photic stimulation was off; on the right, one frame of the movie taken when the photic stimulation was on.

And yet, despite the very positive signs for using fMRI in presurgical planning, it has not yet been widely adopted. Why is there still resistance to fMRI in this context? Perhaps the biggest reason is that there are still no well-controlled studies that conclusively demonstrate its efficacy. In a review of presurgical planning for tumor resection, Stefan Sunaert stated, "Unfortunately, randomized trials or outcome studies that definitively show benefits to the final outcome of the patient when applying fMRI presurgically have not been performed" (Sunaert, 2006). Hence, while an increasing number of neurosurgeons use fMRI presurgically, it has not yet become a routinely used procedure.

There may be another reason fMRI has not been widely adopted in hospital settings. Processing and interpreting the findings from an fMRI study, even in the context of the relatively simple motor and language paradigms typically used in presurgical planning, can often be daunting in the clinical setting. Except for a relatively small number of teaching institutions, most hospitals today receive few requests for fMRI. Such low frequency of use does not typically supply either the practice or the funding to develop the necessary in-house expertise with the tool. Hence, while fMRI has certainly entered the world of clinical practice in the context of presurgical planning, and its use is growing, its current impact on clinical practice worldwide must be considered modest.

Treatment evaluation and clinical assessment

Outside the operating room, one of the challenges in justifying the use of fMRI in clinical practice is determining a fair comparison with other methods. For instance, one can use fMRI to obtain quantitative retinotopic maps of the visual system, but a short neurological testing session, in which the neurologist wiggles his or her fingers at various locations in the subject's visual field, is sufficient in most clinical settings to determine the presence and localization of scotomas. What information of actionable clinical impact is gained by administering an expensive, tricky-to-analyze, time-consuming, and possibly uncomfortable fMRI study? With treatment options for most neurological conditions limited, this can be a difficult question to answer even for advocates of functional imaging technology.

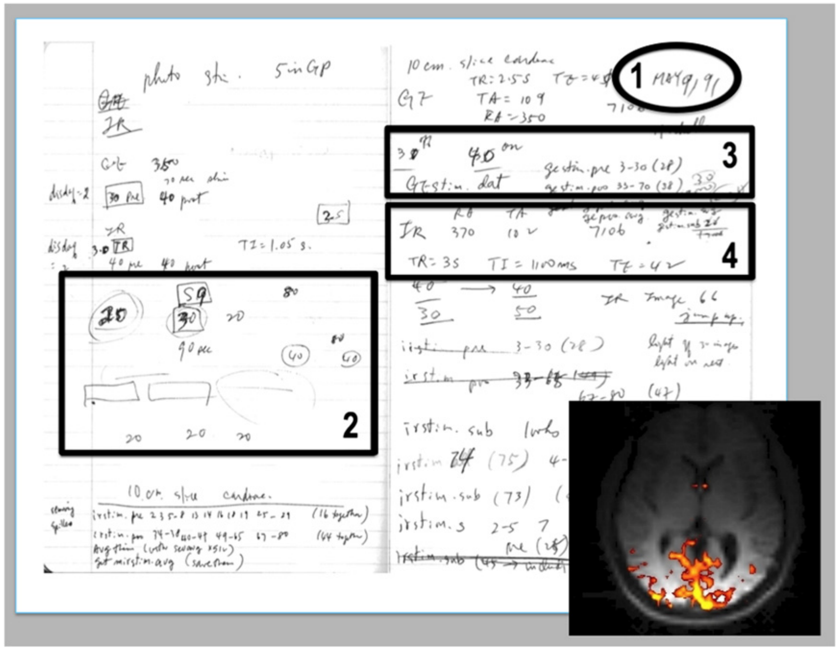

Fig. 3. Pages from Dr. Kenneth Kwong's laboratory notebook, on May 9, 1991, showing the first human fMRI study using a block design, and using both BOLD-based and flow-based contrast mechanisms. (1) The date; (2) sketch of block design using 20 and 30 second blocks; (3) BOLD (T2*-contrast) and (4) inversion recovery (IR) flow (T1-contrast). The superimposed color image on the lower right is a visual activation subtraction map from the BOLD contrast experiments performed that day.

A special journal issue (Levin et al., 2006) was devoted to this and related questions. One contributor to that issue (Hodics et al., 2006) concluded that fMRI is an effective tool to document changes in neural activity associated with stroke recovery, even after the so-called "plateau" period. On the other hand, they also pointed out that there are many uncontrolled variables across the collection of studies they reviewed. Definitive conclusions on the true merits of fMRI for these purposes must be based on future work.

Psychiatric diagnosis

Steven Hyman, former Director of the National Institute of Mental Health (NIMH) wrote an elegant essay examining the subtle problem that a diagnostic system such as the one embodied by the Diagnostic and Statistical Manual of Mental Disorders, the DSM4, can impose on scientific research (Hyman, 2010). These concerns and others were important contributors to the motivation to create the next generation of diagnostic manuals, the DSM5 (scheduled for final release in May, 2013). Surprisingly, despite the widespread adoption of fMRI as a tool for research investigation into mental illnesses, the DSM5 includes virtually no role for fMRI and other functional imaging techniques. This likely reflects a widespread belief in the psychiatric community that functional imaging tools like fMRI have not yet had an impact on day-to-day practice of psychiatric medicine. Although we return to this theme later in the essay (when discussing issues in mental illness beyond diagnosis) it is worth noting here that this perception is *not* controversial, especially as it applies to the major psychiatric disorders, i.e., schizophrenia, depression, and bipolar disorder. Leaders in the development of the DSM5 agree that fMRI does not presently play a role in routine diagnosis.

Table 1
Number of peer-reviewed publications, cited in PubMed, associated with various important scientific findings of the past 20 years.

Discovery	Number of Pub Med citations	Number in a recent year: 2010
fMRI	21,382	>3000
Telomerase	10,524	>900
Human papilloma virus HPV	9363	~900
RNAi	25,611	>4500
In vitro fertilization	23,915	~1000
Knockout mice	82,035	>9000
HIV	66,550	~3400
MRI	267,935	>22,000

Overall impact on medical practice

Functional MRI is certainly playing some role in medical practice, but currently that role is a modest one. The number of patients who undergo fMRI for medical (in contrast to research) purposes remains small. The total number of physicians, even the percentage of neurosurgeons, who request fMRI-based examination of their patients is similarly small. Hence, while the potential for continued growth remains, it cannot yet be said that fMRI has changed the world of clinical practice in a dramatic way.

Cognitive neuroscience

Of course, when we think about functional imaging, we don't just think about pre-surgical planning and its clinical applications, we think about its ability to give us information and insights into the broader realms of human brain function. So what is the impact of fMRI in the domain of cognitive neuroscience? Here the data for fMRI's impact is more compelling—indeed, many of those 20,000 fMRI-related publications in Table 1 are directly or indirectly related to cognitive neuroscience. One way to illustrate this impact is seen in Fig. 4. It shows the distribution of research tools used in articles published in one of the premier journals in the field, *The Journal of Cognitive Neuroscience*. Starting at zero in 1990, fMRI has grown to become by far the most frequently used technology in the journal, representing 52% of the journal's articles in 2010. The impact of this is felt at all levels. For example, a quick survey of the top 11 psychology/neuroscience departments in the United States (as ranked by *US News and World Report*) reveals that a remarkable 10 of them have their own full or part time research magnets!

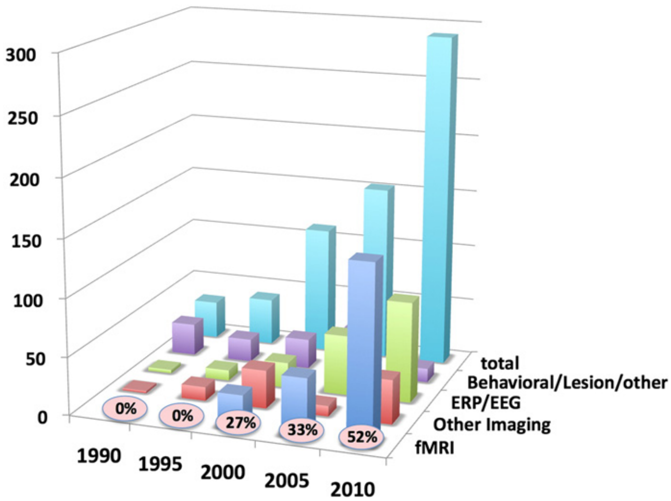

Fig. 4. Distribution of technologies used in papers published in the *Journal of Cognitive Neuroscience* between 1990 and 2010.

In terms of quantity, then, it is clear that fMRI has had an enormous impact on cognitive neuroscience. How does one assess quality? This is not just an abstract question. At least one prominent cognitive psychologist (Coltheart, 2006) has argued that functional neuroimaging has not contributed at all to the understanding of "mind" in cognitive psychology. His provocative target essay in a special issue of the journal *Cortex* elicited a lively discussion and many interesting examples from other investigators who believe that functional neuroimaging *has* taught us fundamental and new things about how the brain works. While there may be no absolute way to assess the "quality" question, there can be no doubt that the broadest segment of the Psychology and Cognitive Neuroscience communities have adopted fMRI as the fundamental tool in their investigations into the links between brain and behavior.

The example of cortical plasticity

Ask 10 cognitive scientists in what domain fMRI has made the biggest contribution to our understanding of human brain function, and you'll get at least a dozen answers. The list includes concepts associated with memory (increasingly understood as a tool for predicting future events), reward circuitry (and its implications for understanding everything from overeating to economics), and the discovery and functional definition of the default mode network—each of these important advances in cognitive neuroscience can be written about extensively as being fundamentally altered through fMRI. We will limit ourselves to just one topic because it has great importance across many domains: the increasingly recognized plasticity of the human brain, both in the context of normal development and in response to injury. Within the broad domain of plasticity, we will focus on one particularly surprising phenomenon: the role of visual cortex in language processing in the absence of vision.

Recent research has demonstrated that two parts of the cortex that are as far removed from one another as might be thought possible, i.e., the language processing areas of the frontal lobes and the vision processing areas of the occipital cortex, can be remapped and rewired following various insults to the system. For example, Bedny et al. (2011) showed that the occipital cortex is active when congenitally blind subjects performed language comprehension tasks. The activity seen in the visual cortex was similar to that seen in typical language processing areas of the brain. The question of whether this visual cortical activity actually played a role in language processing was more directly addressed in an experiment by Amedi et al. (2003), which employed tasks requiring the use of verbal memory, verb generation, and Braille reading. Notably, the verbal memory task did not have *any* direct sensory stimulation during the critical period of the experiment. Moreover, the degree that individual subjects within that group showed visual cortex activation was strongly correlated with their performance on the verbal memory task, indicating that the visual cortex activation was not just ancillary. Perhaps the most conclusive demonstration that this phenomenon plays a *functional* role is the follow-up study by Amedi et al. (2004), in which transcranial magnetic stimulation (TMS) was used to disrupt activity in the visual cortex of both blind and sighted subjects. Only in the blind subjects did this TMS stimulation interfere with performance on a language task. This phenomenon is not seen just in congenitally blind people. A striking analog can be seen in normally sighted humans, using tactile processing. Mirabet et al. (2008) deprived subjects of all external visual stimulation for 5 days. After that period, they were tested on Braille character discrimination. The vision-deprived group performed better than controls, and this improvement in ability disappeared with TMS disruption of the occipital lobe.

Functional MRI has played a significant role in understanding brain plasticity after trauma when examined in many other contexts as well (Lomber and Eggermont, 2006). Today we understand that the brain is much more adaptable than we believed it to be 20 years ago—able to dynamically alter its functional neuroanatomy in the face of changing demands. This new understanding further motivates existing efforts to harness the brain's plasticity to improve recovery of function in settings like traumatic brain injury, stroke, and neurodegenerative diseases. And plasticity is a critical theme in *normal* development as well—a topic whose impact we discuss later.

Overall impact on cognitive neuroscience research and beyond

Has fMRI changed the world of cognitive neuroscience? The unequivocal answer is "yes". But it is not just the traditional domain of cognitive neuroscience that has felt the impact of fMRI.

Not only has the number of articles published risen over time, the number of *different* journals that include fMRI-based research reports has also increased. That number has gone from a small handful of journals in 1993 to more than 200 journals today (Illes et al., 2003). Even more impressive, and perhaps a better indicator of fMRI's broader impact, is the creation of *new* journals. The implication is that wholly new disciplines are being developed, driven by fMRI-based research.

One important example is in the domain of *social* neuroscience. At least two new journals, *Social Neuroscience* and *Social Cognitive and Affective Neuroscience*, focus on the brain-based underpinnings of social psychology and interpersonal interactions. As an informal indication of the central role played by fMRI, 5 of the 6 articles in the premiere issue of *Social Neuroscience* used fMRI as the primary research tool.

The notion of the "social brain" is a concept that has developed recently, and it has been suggested that social competition was the primary evolutionary force driving the explosive growth of the hominid brain (e.g., Bailey and Geary, 2009). With substantial portions of brain devoted to social cognition, it is not surprising that disorders are being increasingly attributed to abnormalities in those brain networks. Insel and Fernald (2004) discussed the circuitry of the social brain and noted that key developmental disorders such as autism and schizophrenia are characterized by abnormal social cognition and corresponding deficits in social behavior. This leads naturally to a more general consideration of the impact functional neuroimaging has had in the area of mental illness.

Mental illness

Tom Insel, Director of the National Institute of Mental Health, when asked in an informal conversation: "What has been the impact of fMRI?" replied, "Despite 4000 papers, not a single finding has changed routine clinical care in psychiatry." Pausing briefly, he then followed by saying that this will change in the next few years, and the change will revolve around a new definition of psychiatric diseases as *disorders of brain circuitry*—that this evolving understanding will change our definition of mental illnesses and our understanding of their causes, treatments, and preventions. In a review published more than 10 years ago, Frith and Dolan (1998), said "It is becoming increasingly evident that a lesion model is inappropriate and that a more relevant characterization will be found in terms of disorders of functional interconnections between brain regions."

An important example of this "circuit-based" understanding of mental disorders, and how to treat them, is the work of Helen Mayberg. She has been leading the efforts to do targeted electrode-based modulation of deep brain structures in cases of medically refractory depression—patients whose depression is resistant to medical treatments such as antidepressants. In a review (Mayberg, 2009), she noted how, in the last 20 years, we have gone from a view of psychiatric disorders as being primarily psychological and neurochemical in nature, to one that includes greater emphasis on the modulation of brain circuits—echoing the points made by Tom Insel, Raymond Dolan, and Chris Frith. "Facilitating this evolving paradigm has been the growing contribution of functional neuroimaging, which provides a versatile platform to characterize brain circuit dysfunction underlying specific syndromes as well as changes associated with their successful treatment" (Mayberg, 2009). Indeed, it was functional imaging studies—both her own PET studies and subsequent fMRI studies—that identified Brodmann Area 25 as a potential target for this modulation, and the successful treatment of depression by the intervention at a level of a specific brain circuit identified by neuroimaging. Whether through direct electrical stimulation or cognitive activation, network-based interventions have the potential to fundamentally change how we treat mental disorders.

fMRI's impact on attitudes toward mental illness

Functional MRI has had impact beyond the treatment and understanding of any one syndrome. In speculating about the future, after a long and distinguished medical career, British psychiatrist Robert Kendell suggested that psychiatry would ultimately become "less different" from other areas of medicine, and that this would come about as physiological measurements like fMRI yield better routine information about patients' brains. He wrote, "As functional magnetic resonance imaging becomes a routine diagnostic tool, and changes in cerebral blood flow in response to mental tasks come to be measured in much the same way as electrocardiogram responses to exercise are monitored by cardiologists at present, psychiatry will come to seem less different, both to patients and to other doctors" (Kendell, 2000). In 2000 this was a speculative prediction; but only 10 years later, there is quantitative data to indicate that this prediction is becoming a reality.

In a recent study (Illes et al., 2009) Judy Illes examined the impact of the very existence of functional brain imaging reports on the attitudes of both patients and physicians with regard to important issues in the public's perception of mental illness. Her study found overwhelming positive change in peoples' attitudes about major depressive illness, in the sense that functional imaging findings made it easier for them to detach depression from its stigmatizing associations to mental illness. She also showed that the imaging data had significant impact on patients' willingness and ability to cooperate with their physicians' advice, by taking their medicines and trying new treatments.

Mental health parity

There is an even more impressive example of how imaging data has changed the dynamic of how our society thinks about mental illness. It comes from the world of health insurance and the issue of so-called "mental health parity": the idea that insurance reimbursement for mental illness should be handled in a manner that parallels that of other health care needs. It may be surprising to some readers from outside the United States, but it is only relatively recently that US federal health care policy has mandated that mental illnesses be treated in the same way as all other illnesses (and it still isn't for many of our citizens, whose health insurance comes from private or state sources). It took almost 20 years of effort to achieve this parity. The legislative battle began in 1992 with the first Federal bill to address this issue, but full parity at the Federal level was not achieved for 16 years, until 2008. How did this change finally come about? What was the impetus that led lawmakers to change their minds?

Ultimately, it was the change in public perceptions about mental illness. The parity issue was championed by then US Senator Peter Domenici of New Mexico (along with Senators Ted Kennedy, Paul Wellstone and others). The key strategy was focusing on *biologically based mental illness*. On various occasions, including congressional testimony presented in 2000, Senator Domenici talked about the brain as the organ of the mind, and just like other organs of our body, is subject to illness. He noted, "Medical science is in an era where we can accurately diagnose mental illnesses and treat those afflicted so they can be productive. I would ask, then, why with this evidence would we not cover these individuals and treat their illnesses like any other disease?" (Domenici, 2000). And what was this evidence? It was congressional testimony by scientists like Steve Hyman, then Director of the NIMH, not only saying "…Diseases like manic-depressive illness represent serious, but reversible abnormalities in the function of specific brain circuits" (Hyman, 2000), but, perhaps most importantly, *showing images of brain function change* when depression was treated (Fig. 5).

From Senator Domenici's perspective, the goal was to display what his staffers referred to as the "broken arm" picture—something so compelling, like x-rays of a child showing a broken arm and the same arm x-rayed after healing—that the need for treatment was obvious, and the effectiveness of treatment was shown in a way that was convincing to each Senator, and the broader public they represented. Congressional and NIMH staffers agree that the images, beyond the words, carried great weight in the political discourse that ultimately led to the first mental health parity act in the United States, in 2008.

So, has functional MRI (and other functional imaging data) changed the world of mental illness? Yes. Although its contributions to treatment are just emerging, the fact that we are more universally treating mental illness today, on a routine basis, owes a large debt to the power of our images to demonstrate, not just to our scientific peers but to the public at large, that mental illnesses are brain diseases amenable to treatment. This may be one of the most important consequences of the work our community has taken on over the last 20 years.

Society

Of course, every new technology also brings dangers. In 2002 *The Economist* featured a cover story about the ethics of brain science, in which they said, "Genetics may yet threaten privacy, kill autonomy, make society homogeneous and gut the concept of human nature. But neuroscience could do all of these things first" (Economist, 2002). And what was the focus of this dubious distinction? Functional

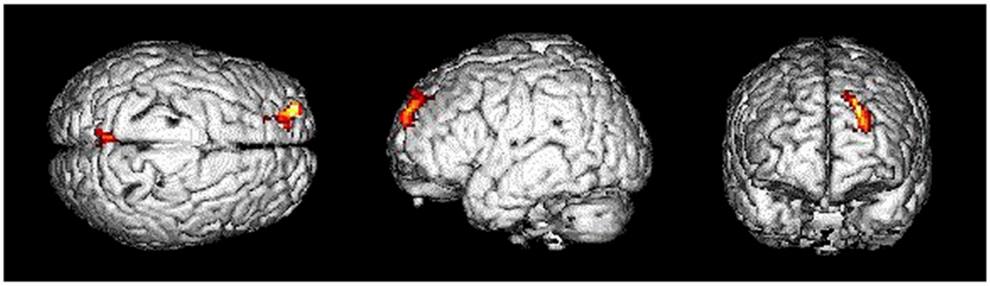

Fig. 5. This image, documenting changes in the brain consequent to treatment for depression, was shown in 2000 by then NIMH Director Steve Hyman during his congressional testimony on mental health parity. His testimony included the powerful challenge: "Try to explain to the family member of a person with schizophrenia why Parkinson's disease - a chronic and not yet curable disease that affects dopamine systems in the brain - might be fully covered by insurance while schizophrenia - another chronic and not yet curable disease that affects dopamine systems in the brain - is not. Think of how you might explain to the parent of an autistic child why chronic genetic diseases that cause childhood seizures might be fully covered but why a highly genetic brain disease such as autism is not" (Hyman, 2000).

MRI, of course, and the concern that fMRI would allow the creation of better lie detectors and enable examination of one's underlying (formerly private) motivations. But the most uncomfortable issue raised, near the end of the article, was that this tool might permit measurement of things that go to the heart of "human nature".

How reasonable are the above fears? Adina Roskies argues that these fears *do* have some basis in reality (Roskies, 2007). She compares and contrasts ethical issues consequent to advances in genetics with ethical issues associated with advances in brain imaging. Her conclusion is that, in addition to significant areas of overlap, there are areas where functional neuroimaging presents unique ethical dilemmas. These include issues of consciousness, moral cognition, and the relationships between decision-making and free will—collectively, what *The Economist* referred to as the heart of "human nature".

Human nature: consciousness, moral cognition, and free will

In each of these domains, fMRI-based studies have become widely accepted probes of human behavior. The issue of *consciousness* has long been a challenge for psychology and philosophy; and now neuroscience has entered the discussions. One area where this discussion has been especially active—and where this question has become a medical as well as ethical issue—involves people in vegetative and minimally conscious states. Owen et al. (2006) reports a case where, "These [fMRI] results confirm that, despite fulfilling the clinical criteria for a diagnosis of vegetative state, this patient retained the ability to understand spoken commands and to respond to them through her brain activity, rather than through speech or movement. Moreover, her decision to cooperate with the authors by imagining particular tasks when asked to do so represents a clear act of intention, which confirmed beyond any doubt that she was consciously aware of herself and her surroundings." Similarly, in terms of the underlying circuitry, Schiff et al. (2004) showed that fMRI revealed intact underlying neural circuitry and connectivity in a minimally conscious patient.

The brain circuitry underlying *moral cognition* has been extensively explored in a series of behavioral and fMRI studies by the philosopher-turned-neuroscientist, Joshua Greene (e.g., Greene et al., 2004). In the imaging studies, subjects were asked to decide whether a person (the "actor") had made a morally acceptable decision when they took action while facing a complicated ethical dilemma. By far the most well-known pair of such dilemmas is the "Trolley Problem" and the "Footbridge Problem", highlighting a tension in Western philosophy going back to Kant and Mills over whether actions have their own inherent morality independent of consequences, or whether consequences themselves define the moral balance. In each case the actor faces a situation in which a trolley car is about to inadvertently run over and kill 5 workmen. In the Trolley Problem, the actor throws a switch that changes the course of the trolley car, knowing that the new course will cause the trolley to run over one workman on a different track. In the Footbridge Problem, the actor pushes a large person off a footbridge to his death in front of the trolley, causing the trolley to stop and thus prevent it from running over 5 workmen on the track (the actor could not jump off the bridge to the same effect because he was too small). Thus, in both situations, an action is taken that saves the lives of 5 innocent people, but at the expense of one innocent bystander. In one case the action involves throwing a switch from a distance away—an "impersonal act"; whereas in the other situation the action requires physically pushing another person to their death—a very "personal act".

Interestingly, though the consequences are identical in terms of lives saved and lost, the final judgments of subjects confronting these two situations, and the brain processes activated in reaching that final judgment, are different. Greene et al. (2004) wrote, "The present fMRI data support a theory of moral judgment according to which both 'cognitive' and emotional processes play crucial and sometimes mutually competitive roles… We speculate that the controversy surrounding utilitarian moral philosophy reflects an underlying tension between competing subsystems in the brain."

A third broad area where fMRI has fused neuroscience and philosophy is decision making, and its implications for discussions of *free will*. In one striking experiment, Soon et al. (2008) used fMRI to study decision-making processes in the brain, and found that the brain reaches a final decision for action a full 10 seconds before decisions are consciously or overtly recognized. To quote from their abstract, "There has been a long controversy as to whether subjectively 'free' decisions are determined by brain activity ahead of time. We found that the outcome of a decision can be encoded in brain activity in prefrontal and parietal cortex up to 10 s before it enters awareness. This delay presumably reflects the operation of a network of high-level control areas that begin to prepare an upcoming decision long before it enters awareness." What does it mean for our understanding of free will if our decisions are made well before we are consciously aware of making them?

Decision-making, of course, is a key aspect of our lives, including (and perhaps especially) our economic lives. Daniel Kahneman (Kahneman and Tversky, 1979) won the Nobel Prize in economics, for his work exploring cognitive psychology of humans evaluating information and making decisions. Not surprisingly, then, fMRI has been vigorously applied in the study of economic decision-making. This has been true scientifically—as in the work of Knutson et al. (2007) on neural predictors of purchasing—as well as commercially, as indicated by the long list of companies that now offer their services to use fMRI to study your particular problem in marketing. A quick look on the web yielded at least 15 different sites offering such services.

Of course, it is not only marketing decisions that can be based on brain state. Haynes and Rees (2006) review a collection of research reports that discuss the use of pattern analysis to turn fMRI into a tool for so-called "Brain Reading" (e.g., Cox and Savoy, 2003). Haynes and Rees, as have many others, point out the various potential dangers associated with such power, if it really comes to exist. What would be the consequences of such tools for probing private attitudes, for detecting lies, for exposing private motivations? These are old social/ethical questions, but they are arising anew, in a technological world driven in important ways by fMRI. Today, there are at least two companies marketing their services for using fMRI in lie detection. Given this backdrop, it is hardly surprising that fMRI-based research is now showing up in the courts.

fMRI and the legal system

Owen Jones, Director of the MacArthur Foundation Law and Neuroscience Project, has made a list of six areas where brain imaging data is already having an impact on legal practice: third-party judging (i.e., juries deciding guilt and/or severity of penalty); neural lie detection; determination of mental states; memory; the adolescent brain; and brain-based appeals. Indeed, so widespread has the practice of using brain imaging data become in cases involving the death penalty that it is now considered “ineffective assistance of counsel” if an attorney *fails* to obtain such data for the defense or appeal-of-sentence of a client in a capital case (Jones et al., 2009). In other words, an attorney can be sued for *not* obtaining and using brain imaging data!

Many of the implications of fMRI data on the legal system are still emerging, but in one of the areas listed above, i.e., the adolescent brain, fMRI data have contributed to a true watershed. Two recent US Supreme Court decisions have held that minors cannot be given a death sentence; nor can they get life imprisonment without opportunity for parole outside of homicide cases (Graham v. Florida, 2010; Roper v. Simmons, 2005). One of the principal reasons the court gave for reaching these decisions concerns the question of “culpability”: can adolescents be held to be fully responsible for their actions. The Court said “no”, and one reason is that the adolescent brain has not yet fully developed. In the petitioner's brief for Graham, reference was made to both functional and structural MR studies (including Bjork et al., 2007; Eshel et al., 2007) that documented the growth and maturation of the adolescent brain well into, and beyond, the teen years. These data had a direct impact on the Supreme Court's majority opinion. Justice Kennedy wrote: “Although the precise neurobiological mechanisms are the subject of continuing research, it now cannot be contested that important aspects of brain maturation, particularly those involved in the brain's executive functions, remain incomplete even in late adolescence” and “…developments in psychology and brain science continue to show fundamental differences between juvenile and adult minds. For example, parts of the brain involved in behavior control continue to mature through late adolescence… This biological basis for differences in juvenile conduct provides further support for the conclusion that less culpability should attach to juvenile conduct than to similar conduct by adults” (Petitioner brief, Graham v. Florida, 2010).

The broader impact of such logic is just beginning to be felt. For example, studies like the one by Raizada et al. (2008) have now demonstrated the importance of socioeconomic status on brain development in young children. How will these data influence our society's thinking, and change the political dialog around public policy in areas of education, poverty and social services? It is clear that prominent questions of social policy will be increasingly influenced and informed by the results of functional neuroimaging data.

“Society” encompasses many aspects of the world, and we have touched on only a few. It is clear that fMRI has had a significant impact on some of those areas. Has fMRI changed society as a whole, at this point? Perhaps it is most accurate to say, “It is beginning to…”.

Table 2
Summary of the conclusions about the title question: “Has fMRI changed the world?”.

Has fMRI changed the world?	Current answer
Scientific impact in terms of citations	✓
Medical practice	Not quite yet
Cognitive neuroscience	Yes
Mental illness	Yes (with more to come)
Society	It's beginning to…

Closing remarks

The title of this essay is undeniably audacious. Each of the contributors to this Special Issue has their own views about the impact of functional MRI on their work, on their lives, and on the research community at large. Has fMRI changed the world? Table 2 summarizes the conclusions of the preceding discussion. Looking it over, the answer must be yes, and in ways that go beyond our laboratories. While there are always dangers, including potential abuses associated with mind-reading, lie detection, and neuromarketing, the most important advances and likely future applications are broadly for the good. In medicine, in patients' attitude, in increasing access to mental health care, and in giving us a more enlightened view of fundamental aspects of human nature, the influence of fMRI-based research really has changed our world.

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