

27 The Future of Functional MRI

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Abstract

This chapter involves detailed speculation on how fMRI technology, methodology, interpretation, and applications will advance in the next five (2016), ten (2021), and twenty (2031) years. We chose these time frames since five years is close enough to speculate with some degree of accuracy, and twenty years is approximately double the age that fMRI is now. Ten years was chosen as a reasonable intermediate point. For each of the four highly overlapping and complementary areas mentioned above, a brief summary of the current state of development is given so that perspective can be applied to speculation on how the future will play out. The intent of this chapter is of course to be as accurate as possible, but also to reveal important trends as well as potentially rich avenues of future research. In addition, the goal is to inspire the user to embrace the idea that fMRI development is not even close to showing any sign of plateauing in any way. If anything, with the onset of spontaneous fluctuation or functional connectivity research, fMRI decoding, completely novel contrast mechanism, growing multi-modal integration, real time fMRI, high field and high resolution development, and burgeoning clinical applications, the rate of advancement is clearly accelerating in almost all areas, forcing us to reframe the nature of our questions on brain function and organization so that we make optimal use of tools that are and will be available.

27.1 Introduction

We all would like to know what's going to happen next. A measure of how well we understand a system is that of how accurately we can predict what it will do at some point later in time. The field of functional MRI (fMRI), considered as a system, is diverse and complex so this prediction task is extremely difficult. Breakthroughs, such as the discovery of blood oxygenation level dependent (BOLD) contrast itself by Ogawa et al (Ogawa, Lee et al. 1990), are impossible to predict with any accuracy at all. In fact, after Thulborn made his first observation of the influence of blood oxygenation on blood T2 in 1982 (Thulborn, Waterton et al. 1982), the time was ripe for BOLD to come along. While Ogawa's discovery was an insightful leap by any measure, why it took eight years, following Thulborn's results, and not one year or twenty years is an interesting question in itself. This type of question touches upon the high level of variability that defines an advancing field. The emergence of more stable scanners, the growing use of echo planar imaging (EPI), the diminishing focus by the community on the "low hanging fruit" in basic MRI development, and openness to the potential of a completely different kind of contrast - rather than a rigid scientific agenda - is what may have led to the discovery of BOLD. On the other hand, it may have been one person plowing along on his path. It's almost impossible to speculate.

A goal in this chapter is to try to predict the future of fMRI. Again, we emphasize that this is extremely difficult since we barely understand all that influenced the advancements, or lack thereof, in the past. The act of taking on the task of prognostication is also risky, as our views will, in five, ten, or twenty years, may appear more myopic than prescient. The future is fun to

think about, and can certainly stimulate how we approach the present – adding depth and perspective.

With any future prediction, accuracy is directly related to how well we size up the present as well as how well we can model its temporal behavior. For this reason, when talking about the future of functional MRI (fMRI), it's useful to briefly discuss what the current state of fMRI is and how it has been evolving so far. Therefore a short discussion of the current state of each topic will precede the future speculation. We will then, where reasonable, speculate as to the direction these specific trends are going, where they will be in five (2016), ten (2021), and twenty years (2031). The last time point is about double the age that fMRI is now.

To start, it's useful to look back to a review article that summarized the state of the field of functional magnetic resonance imaging in 1990 (Moonen, Van Zijl et al. 1990). The article is edifying not only for what is reported but also for what is *not* reported. Only one year before the discovery that focal brain activation-induced hemodynamic changes can be measured with MRI, there is absolutely no mention of this technique at all. From conversations with people in the field, only a few were thinking of ways to do this. Those who did imagine it was possible did not yet have positive human results. We speculate that researchers such as Seiji Ogawa, Ken Kwong, Bob Turner, and others had a good idea (Ogawa and Lee 1990; Ogawa, Lee et al. 1990; Ogawa, Lee et al. 1990; Turner, LeBihan et al. 1991), and during this time, Jack Belliveau was working on his new contrast agent-based method that would usher in MRI of brain activation, (which quickly settled in to be called fMRI - although Bob Turner was floating the acronym MRFN – magnetic resonance functional neuroimaging...or just “more fun”), winning him the ISMRM young investigator award and the cover of *Science* (Belliveau, Kennedy et al. 1991), but

would become obsolete almost the very month it was published. It was invasive, and cumbersome relative to endogenous contrast fMRI, but it worked, and inspired us all! This illustrates not only how incredibly unpredictable the future is when it comes to new scientific or clinical methods, but also what an explosive revolution in brain imaging fMRI - using blood oxygenation dependent (BOLD) contrast (Ogawa, Lee et al. 1990) - ushered in.

In the Moonen et al. review article, mention is made of the latest advances in angiography, baseline blood volume and perfusion imaging with gadolinium contrast, diffusion contrast, magnetization transfer contrast, and metabolic or chemical shift imaging. Twenty years later, these methods are all still around. Angiography, gadolinium-based perfusion imaging, and diffusion imaging have been incorporated into regular clinical use. Magnetization transfer has experienced a recent resurgence in utility, and chemical shift imaging is still, after over 20 years, the next big potential clinical tool. What has changed over this time? Five things: 1. Imaging and processing technology has steadily become more sophisticated and powerful. 2. The images themselves, resultantly, have improved in terms of signal to noise ratio (SNR), resolution, and speed of acquisition. 3. Implementing these methods has become more streamlined and routine. 4. The data contained in these images is much more interpretable. We understand them better. 5. There are many more people working on developing and applying these methods. The applications of these methods are much wider.

In terms of how they evolved, some have plateaued, some have had multiple resurgences, while most have steadily become better. These five main points are what we can expect of future fMRI technology, methodology, interpretation, and applications. What's most predictable is that there will be steady growth in the sophistication of the methods and quality

and interpretability of the images. Harder to predict are the specific applications. So far, while fMRI has revolutionized much of brain imaging research for normal and clinical populations, it has been less than successful in terms of making inroads to daily clinical use. This limitation is certain to change, but how this change will occur is hard to predict. Impossible to predict are revolutions – as fMRI itself was.

In this chapter, we speculate on the future of fMRI technology, methodology, fMRI signal interpretation, and applications. The progression of each of these areas are highly intertwined and overlapping, yet these divisions are useful for trying to organize our descriptions of the progress and the future. Technology consists of the components involved with scanning: the magnet, gradient coils, RF coils, shim coils, receivers, computers for reconstruction, as well as subject interface devices. Methodology consists of everything from paradigm design to time series processing, image processing, normalization, data pooling, and display. Interpretation is mostly related to the scope, fidelity, and accuracy of neuronal information that can be derived from the hemodynamic response. Lastly, the applications all feed off of the advances in the previous three areas. These will be discussed last.

Again, our speculations will likely vary wildly in accuracy. Nevertheless, the act of trying to speculate insightfully, rather than simply guessing, we hope is edifying, enjoyable, and perhaps even inspiring. We very much look forward to reading this chapter again in 20 years!

27.2 Technology

MRI Technology - the magnets, gradient coils, RF coils, shim coils, subject interface devices, and any other hardware engineered to allow for higher spatial resolution, temporal resolution, robustness, and perhaps higher fidelity and novel information - continues to improve steadily as long as tangible benefits are achieved. It appears as if the demands imposed by clinical utility as well as by high field strength continue to drive many technological improvements. In this section, we do our best speculation on the future of MRI technology.

27.2.1 High Field Strength

Since MRI was first used for human clinical scanning in about 1984, the highest magnetic field strength used for human scanning has increased at a rate that is well approximated with a straight line. Figure 1 shows the approximate year when each field strength was first used to scan a human. According to this linear projection, in 2011, we will have a human 11.7 T scanner in operation. In 2016, we will have a human scanner at about 13 T, in 2021 we will have a human scanner at about 15 T, and at 2031, we will have reached a 19 T human scanner. The 2011 prediction is likely to come true either at the National Institutes of Health, where an 11.7 T human scanner is currently being installed, or perhaps elsewhere as there are several other institutes planning 11.7 T or higher field human systems.

The primary factors that influence magnetic field strength are bore size, the electric current through wires that are wound around the bore, and the number of windings possible. The

larger the bore, the lower the field is at a given current and number of windings. While “standard” superconducting materials (niobium-titanium: NbTi), and magnet design has allowed for higher field strength for human-sized bore magnets, it appears that to go beyond 11.7T, much more costly materials (such as niobium-tin Nb₃Sn) need to be used. While technologic and economic factors come into play, neither may turn out to be prohibitive for at least one or two groups in the world.

The benefits of increasing field strength are many. These include linear or super-linear increase in signal to noise ratio, linear to super-linear increase in BOLD contrast to noise ratio, increase in T₁ allowing for more effective arterial spin labeling methods for perfusion imaging, increased NMR phase contrast for imaging very subtle anatomic susceptibility differences in tissue (Duyn, Van Gelderen et al. 2007). High resolution magnitude and phase related susceptibility contrast at high field is rapidly emerging as a clinically useful source of contrast, and may be the entry pass for 7T and higher field strength scanners into the clinical arena.

The gains in signal to noise ratio can be directly traded for higher spatial resolution for both anatomic imaging and functional imaging, or can be traded for shorter scan duration. Both are desirable for clinical use. Ultra-high (> 4T) field strengths allow for routine sub-millimeter anatomic and functional imaging on individuals in a single session. Functional imaging of orientation columns (<0.5mm) (Yacoub, Harel et al. 2008) as well as resting state functional connectivity between cortical layers have been demonstrated using 7 T scanners (Polimeni, Fischl et al. 2010). With layer or cortex specific activation, we might be rapidly approaching a biologic spatial limit in fMRI rather than an image resolution or signal to noise - limited resolution. The motive to go to even higher field strengths would still be to image

hemodynamic effects at higher resolution than the hemodynamic control itself - as with optical imaging. Another motive would be to perform ultra-high resolution imaging on an individual level or in significantly more brief scanning sessions (Murphy, Bodurka et al. 2007). Lastly, we are still contrast to noise limited with regard to robustly and accurately measuring resting state fluctuations. The gains at ultra-high fields would be substantial (Hale, Brookes et al. 2010; Kalthoff, Seehafer et al. 2011).

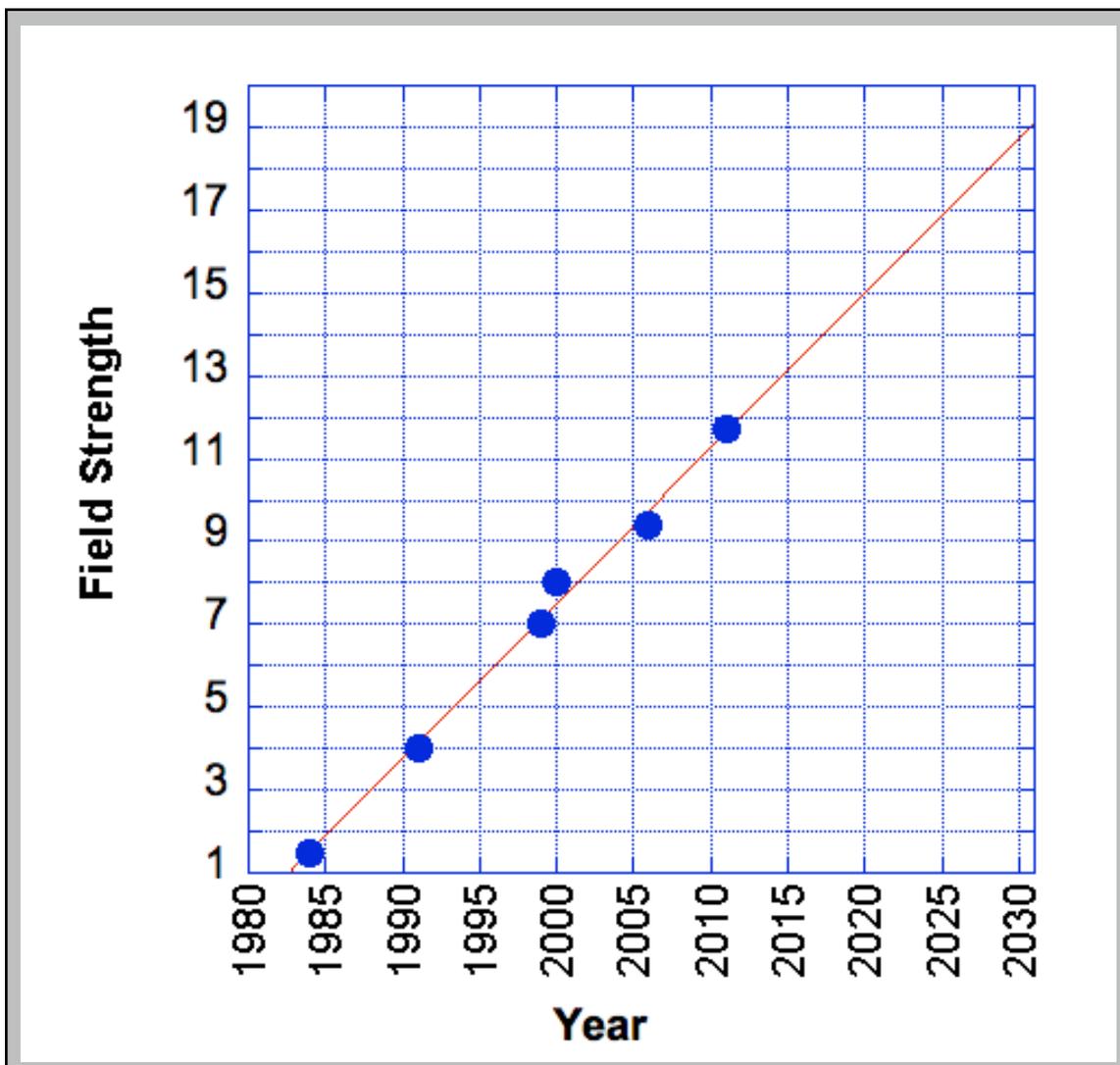


Figure 1: A plot of the year corresponding to the highest field strength first used to scan a human. As of March 2011, the last data point is proposed.

Higher field strengths are accompanied by additional tradeoffs and major obstacles. Magnetic field inhomogeneities induced by susceptibility gradients increase linearly as field strength increases, but the effects on image quality are nonlinear. When the susceptibility related field gradient across a voxel approaches that of the applied imaging gradients, the signal from that voxel can fall off the edge of the acquired k-space and vanish. This effect is seen as signal voids at 7T and even 3T, but will expand rapidly at higher field. A host of tools can be used to mitigate this effect, including spin echoes, shorter TEs, thinner slices, etc, but all come at a cost in contrast to noise ratio that reduce the advantage of higher fields. To combat these tradeoffs, methods that currently exist but have not yet become mainstream, such as multidimensional RF pulses, and local high order active and passive shim hardware will likely become necessary. RF excitation homogeneity is also much harder to maintain with higher field strength, but this problem will likely be essentially solved by parallel transmit technology. RF power deposition, which nominally scales with B_0^2 , will be a limiting factor, and will require monitoring methods with ever increasing sophistication to control and detect the development of local hot spots. Subjective physiologic effects of high field also become more apparent. At 7T the reported occurrence rate of transient or long term (over a day in duration) vertigo, nausea, phosphenes (which are brief spots of light brought on by eye movement), and/or a metallic taste in the mouth have increased. While these symptoms are not known to be health-threatening, they are uncomfortable and unsettling and may ultimately require some limits on who can volunteer and how frequently.

Regardless of these limits, from our first glimpses at ultra high field results, the motivation for imaging at fields at or above 7T will grow. Even in these early stages of ultra high field imaging, results such as orientation column function and ultra high resolution anatomic imaging, are only

possible at 7T. Likewise, it is also likely that a select set of questions might only be addressable at 11.7 T or higher as well. For the general fMRI users and most clinicians, 3T will remain the workhorse field strength for at least five to ten more years, with 7T settling in as the standard about fifteen years from now.

The following predictions assume an optimistic outlook on our ability to solve ever growing challenges in B_0 field homogeneity, RF power deposition and homogeneity, as well as superconducting material. Regarding the highest field used on humans, we would predict that in five years, about five 11.7T human scanners will exist in the world, yet the highest field strength will still be 11.7T. In ten years, there will likely be a human scanner with a field strength within the vicinity of 15 T and over ten operating 11.7T scanners. In twenty years, we will have a human scanner in the vicinity of 20T. This prediction is very similar to the linear prediction of Figure 1.

27.2.2 Low Field Strength

On the other extreme, low field strengths ($<\mu\text{T}$) NMR and MRI results have shown some progress as well. While SNR for these techniques is of course extremely low, it can be increased by a method known as prepolarization in which spins are polarized to a mT field range, yet precess at the lower field (Kraus Jr, Espy et al. 2007; Kraus Jr, Volegov et al. 2008). This method shows promise in the context of creating MR images without the need of a scanner (great for field work!). For functional MRI, BOLD contrast would be undetectable, but another source of contrast, the phase shift or signal dephasing around dendrites created by magnetic fields associated with the electric current conduction through the nerves themselves, is independent

of field strength and might be selectively detectable at low field strengths. One intriguing hypothesis is that if one collects images at Larmor frequencies that overlap with specific neuronal firing frequencies (5 to 500 Hz), then neuronal firing might work to alter relaxation rate properties of the spins experiencing these similar frequencies. Maps of baseline brain activity at specific frequencies might therefore be able to be created by simple observation in the variation in the intrinsic relaxation characteristics of cortical tissue, depending on the Larmor frequency used for imaging. Only a small handful of groups are working on ultra-low field imaging, so progress is likely to be slow unless preliminary results showing brain activity are demonstrated.

Regarding the future, there is a large potential for low field imaging because of the possibility of generating unique contrast mechanisms, and relatively low cost. The prospects for fMRI at ultra low fields are significantly less certain since there is no clear evidence that neuronal currents are detectable at 3T, much less at SNR's over 10 times lower. we would conservatively predict a gradual increase in the number of groups performing low field research and a market for ultra-low field scanners being established in ten years. In twenty years, we would guess that there will be about 500 ultra-low field scanners in the world. As for neuronal current imaging, this topic is covered more extensively in section 27.4.1.

27.2.3 Gradient Coils

For many years, gradient performance was limited by the hardware itself, but as gradient power increased, gradient systems began to run up against the more fundamental limit of peripheral nerve stimulation (PNS). At present, the maximum gradient slew rate that can be used without PNS is approximately 200mT/m/ms. This level of gradient performance requires

nearly one Megawatt of peak gradient power, tremendous engineering efforts to contain vibration and acoustic noise, and significant cost, but has resulted in large advances in imaging spatial and temporal resolution in dynamic imaging methods such as fMRI. While pinned against the PNS limit, there is still some room to improve usable duty cycles to nearly 100% with improved cooling and electronics, and this will happen in the 5 year time frame. Pushing through the PNS barrier requires a different approach, the most obvious of which is the use of insertable gradient coils, which can achieve higher gradient amplitudes and slew rates, at lower power and lower risk for PNS, simply by virtue of smaller size. PNS depends on field slew rate and not gradient slew rate, and coils with fields of smaller size produce lower peak fields at a given gradient strength. For head gradient coils, an increase in both gradient amplitude and slew rate by a factor of two or more is achievable using current technology, and increasing commercialization of this technology will occur over the next 5 years. In the 10 year time frame, the development of coordinated systems of non-linear gradients and RF coil arrays specifically designed for reduction of PNS (Hennig, Welz et al. 2008) will push the speed envelope by another factor of 3 or more. In the 20 year time frame, the combination of these methods with RF transmit gradients may provide the basis for further breakthroughs in imaging speed.

27.2.4 Shim Coils

Even at 3T, the field inhomogeneities induced by biological susceptibility gradients are of much higher spatial order than can be corrected using whole body sized shim coils. As we push to higher fields, localized shim solutions will be necessary in order to significantly control field inhomogeneity at its source. Both active and passive shim technologies have been demonstrated at the local level, either at the RF coil level, or applied even closer to the head,

and can reduce high order inhomogeneities. These technologies will be developed over the next 5 years. They can in principle be extended to large arrays of electrically or mechanically controlled shim units - or simple custom-made molds for each head. These molds may contain layers of materials having different susceptibilities (Lee, Goodwill et al. 2010). In 10 years we will be able to largely repair any inhomogeneity that Maxwell's equations allow to be fixed using sources outside the head. In 20 years these arrays of shims will be automatically adjusted in real time using feedback from field mapping pulse sequences. Inhomogeneities caused by sources deeper in the head (ie some sinuses, dental work, localized iron, etc.) will continue to be difficult to manage. Under special circumstances, internal shims in the mouth or nasal cavities can be effective, but will require extremely motivated subjects.

27.2.5 RF Coils

Over the past two decades, the primary push in RF coil design has been toward ever increasing numbers of coil elements, initially for SNR, and later for SNR and parallel acceleration. With approximately 100 channels available in some research labs now, basic SNR is approaching theoretical limits, with significant additional gains expected only in the most superficial regions of the cortex. Arrays that are distributed nearly isotropically allow for uniform parallel acceleration in all directions. For very high levels of parallel imaging acceleration, more is still better, and the limits are not yet clear.

On the transmit side, the development of transmit arrays for B1 shimming at higher fields and for tailored excitation profiles is currently moving rapidly. In 5 years, transmit arrays will have begun to penetrate the commercial scanner market, making 7+T scanners clinically plausible, and in 10 years, the problem of transmit uniformity at high fields will be largely solved.

Yet to be explored is the concept that excitation and data collection may not need to be compartmentalized in time as much as it is now, and the availability of many independently programmable and spatially distinct channels on both the excite and receive sides of the measurement open the possibility of the MR pulse sequence becoming a more complex spatio-temporal modulation of the spins.

27.2.6 Pulse sequences

For BOLD fMRI, the primary goals for pulse sequence design are sensitivity to the BOLD effect, maximization of the BOLD contrast to noise ratio, spatial and temporal resolution, and in many cases coverage of most or all of the brain. This has led to the current state of the art, which can provide roughly 2mm isotropic whole brain coverage every second. To achieve this performance, a host of tools are combined: EPI or spiral type trajectories in 2D or 3D, parallel acceleration in two dimensions with large coil arrays, partial Fourier acquisition, simultaneous multislice excitation and readout, and time multiplexing of echoes. Over the next 5 years, the improved hybridization of these technologies, along with advances in RF coil and scanner hardware, will make sub-second, sub-2mm whole brain imaging a standard push button fMRI tool. When this becomes robust, there will be almost no reason not to use it for most of BOLD fMRI. With good coil arrays, imaging at this resolution will still be physiological noise dominated, which means that lower spatial resolution would not help detection, and lower temporal resolution would reduce statistical power. Pushing to still higher spatial resolution involves moving into a more thermal noise dominated regime, and detection power is reduced. In this direction, specific motivation for higher resolution is required, such as questions

involving cortical layers or columns. While sub-millimeter resolution is available now in limited regions of the brain, or at low temporal resolution, the path to sub-millimeter, sub-second whole brain imaging is less clear. In the 10-20 year time frame, cutting edge MRI will employ pulse sequence and hardware design that is more tightly integrated. For example, unconventional pulse sequences using nonlinear gradients (Hennig, Welz et al. 2008), may provide single shot whole brain coverage with sub-millimeter resolution at the cortical surface, with lower resolution deeper in the brain.

27.3 Methodology

Methodology involves all the ways in which the investigator makes use of technology, what is known about the hemodynamic response, what is known about neuronal activity to extract spatial and temporal brain function information from individuals and groups. This includes brain activation paradigm designs, processing methods, data pooling methods, and data comparison. Advances in methodology are catalyzed by advances in technology and signal interpretation. For example the higher resolution at which we can scan (technology), the more sophisticated methods we need to assess and compare individuals. The more we understand the information in resting state fluctuations (interpretation), the more we can optimize processing methods to extract meaningful information about brain organization. Below we discuss a few of the major areas of methodological advances, and attempt to assess future trends.

27.3.1 Paradigm design

Functional MRI paradigm design - how an investigator plays out a sequence of tasks or stimuli to activate the brain with specified or precisely measured magnitudes and timings - has been an area of steady growth since the inception of fMRI. In 1991, block design paradigms, modeled

after those used in lower temporal resolution techniques such as Positron Emission Tomography (PET), were the standard. In 1992, event-related designs using visual stimuli were demonstrated (Blamire, Ogawa et al. 1992), and their use explosively increased in 1996 after two groups showed their utility for cognitive paradigms (Buckner, Bandettini et al. 1996; McCarthy, Luby et al. 1997). Rapid event related designs, allowing for hemodynamic overlap, gained popularity as well (Dale and Buckner 1997). In the mean time, continuous stimulation paradigms were being optimized for retinotopic mapping (Engel, Glover et al. 1997). A few other types of paradigm designs, such as orthogonal design (Courtney, Ungerleider et al. 1997) or random design (Clark, Maisog et al. 1998) - in which multiple on-off sequences of specific tasks were presented, all having hemodynamic responses which were more or less orthogonal to each other - were developed.

A slow change in paradigm designs emerged as simultaneous behavioral measurement methods in the scanner became more sophisticated. Researchers could then have the subject perform a task in a more “free-form” fashion and simply measure all the relevant parameters in an accurate and continuous manner (Grafton, Schmitt et al. 2008). An example of this would involve the use of a virtual reality driving environment, and having subjects navigate (Spiers and Maguire 2007; Spiers and Maguire 2007; Calhoun, Kiehl et al. 2008). Each measure relevant to the stimulus or to the driver’s actions would then then be used as a regressor for the time series, thus allowing the experimenter to observe an entire range of parametrically varied measures with which to compare brain activity. Another very clever example is with movie viewing (Hasson, Nir et al. 2004), and subsequent comparisons of the time-series fluctuations across subjects who viewed the movies played out in precisely the same sequence, to derive the functional maps. This we refer to as free behavior design.

Sometime during this free behavior design development period, resting state fMRI exploded on the scene. Here, a subject simply lies quietly in the scanner with eyes open and fixated or eyes closed, and the correlation between the time series of one voxel or region of interest or in a systematic manner every voxel, is calculated against the entire brain. Maps of which voxels show the highest temporal correlation are created. Like event-related fMRI (introduced in 1992), resting state fMRI was introduced early - in 1995 (Biswal, Yetkin et al. 1995) - but required several years of incubation in relative obscurity before it caught on in the fMRI community. Section 27.3.2 is entirely devoted to resting state.

A more recent development in paradigm design is the fMRI adaptation paradigm (Grill-Spector and Malach 2001), in which stimuli of varying similarity (it's the similarity which is being tested) are repeated in rapid succession. Neurons that show similar responses between stimuli quickly habituate and decrease in their responsivity, while those that do not remain active for each successive stimuli. In this manner, very fine delineations between neuronal populations can be made.

A useful example of what might be considered a false start in paradigm design is mental chronometry. Given that the spread in delays in the hemodynamic response is at least four seconds, it is impossible, without a further task timing modulation (Menon, Luknowsky et al. 1998; Bellgowan, Saad et al. 2003), to separate out with an accuracy of less than 1 second, the temporal sequences of cascaded brain activity. Researchers have achieved, with the use of a single, yet extended, task timing (Formisano, Linden et al. 2002), mental chronometry of well separated (> 3 sec) events. Nevertheless, only by modulating the task timing such that one part of the brain activation cascade is activated at a different time, can one start to derive the

relative brain activation timing. A necessity, and goal, for those wishing to use fMRI for mental chronometry of sequential activations separated by less than 1 seconds with a single task timing is to create a whole-brain calibration map of only the hemodynamic related delays, such that subsequent timing maps could be normalized to these.

The future of paradigm design lies in how accurately we can interpret subtle BOLD signal dynamics, how much SNR we have to work with, and how much we can use BOLD contrast information in conjunction with other modalities that give us more or complementary information of underlying neuronal activity or higher spatial and/or temporal resolution. Progress has been made as more researchers investigate how to modulate brain function more subtly and measure behavior more precisely. Entire review articles are devoted to problems and issues of understanding how the brain is organized and issues with designing paradigms (Friston, Price et al. 1996; Price and Friston 1997) that can tease out basic brain networks or, more ambitiously, principles of brain function, by ever more fine delineations of responses to specific tasks or stimuli. While we may not anytime soon solve these issues, researchers will continue, likely at a more rapid rate to find more clever ways to differentially activate the brain.

The trend is that researchers will continue towards more natural stimuli and behavioral environments but will accompany these with a much more comprehensive array of simultaneous behavioral measurements. Extremely useful information for all paradigms can be derived from skin conductance, eye position, respiration depth and rate, heart rate, button press force and timing, electrical measures with EEG, and much more. Stimuli suites will be much more immersive. In five years, we will have many more paradigms that use natural responses with simultaneous measures. In ten years, we will start to see the emergence of

algorithms that design, carry out, and adapt these natural paradigms on subjects towards specific questions. More and more paradigms will be “bottom up” in that rather than giving a specific set of tasks or stimuli and determining regions of activity, the paradigm design algorithm might give many different, perhaps random stimuli or tasks and then determine the brain response for each, and then adjust the stimuli accordingly to allow the brain to further inform the investigator how it processes or groups or categorizes the processing of these stimuli or tasks. In twenty years, humans might be completely removed from the entire design and optimization process paradigm design, data processing, as well as removed from the brain organization inference process.

27.3.2 Resting state fMRI

Resting state fMRI, otherwise known as functional connectivity fMRI (fcfMRI) or fMRI of spontaneous fluctuations, first reported in the breakthrough paper of Biswal et al (Biswal, Yetkin et al. 1995) has explosively emerged on the fMRI scene in the last 5 years as an alternative to activation-based fMRI. It turns out that probing the spontaneous oscillations of the brain when it’s not necessarily performing an overt task or receiving an obvious stimulus is quite informative! It is clear that even though the term resting state has and will be used, these fluctuations are the created as a result of the brain being continuously and spontaneously active.

Central questions related to interpreting spontaneous fluctuations that will be addressed in the next twenty years are as follows: What aspect of neuronal activity do they reflect? What is the biologic significance or purpose of them? What neuronal mechanism causes them and what, neuronally, does a change in the resting state fluctuations indicate? To what degree do they

reflect conscious vs. unconscious processes? With regard to more practical issues, the questions that will be asked include: How can we best measure and map these in individuals and in groups? What are the specific temporal properties of these networks? How do they change from moment to moment? How many resting state networks are there? Is the number of resting state networks spatial and temporal scale dependent? What is the best way to remove all other non-neuronally related fluctuations in the fMRI time series?

In five years, we will likely have all the major spontaneous activity networks mapped out at the highest spatial resolution that we can scan - which will be about 1 mm cubed at 7T. At 3 mm cubic resolution we find about 40 networks, at 2 mm cubic resolution we will likely find 80 networks, at 1 mm cubic resolution, we will likely find about 150 networks. These results will force us to redefine exactly what we mean by “network.” Is the correlation between one voxel cluster in one area of visual cortex to another small cluster considered a network? It probably is. In five years we will also be much more aggressively pursuing understanding the temporal properties of these networks. Already there is growing evidence that these networks change and perhaps interact from moment to moment (Chang and Glover 2010), so averaging over five minutes to create a single data set of these networks might turn out to be a relatively crude thing to do.

In five years, resting state fMRI and correspondingly, resting state connectivity mapping will provide clear clinical potential. Even though we will not yet fully understand exactly the neuronal correlates of resting state fMRI, we will have revealed many differences in these networks in many clinical populations. So far, clear differences in resting state networks have been shown with populations that include Alzheimer’s disease, autism, and bipolar disorder.

The next step is to be able to take the resting state networks derived from an individual and then determine if they, in fact, can be diagnosed with a specific disorder. One interesting result in this direction has been published so far (Calhoun, Maciejewski et al. 2008). Research will rapidly continue towards individual assessment and clinical diagnosis with resting state fMRI.

In ten years, resting state fMRI will be widely used clinically. By this time we will have a very clear idea not only of the neuronal correlates of resting state fMRI, but of the significance, function, and relevance of resting state neuronal activity. We will have also developed robust methods that will enable clean removal of all non-neuronal fluctuations from the resting state time series MRI signal.

In twenty years, we will be routinely mapping all resting state networks for individual assessment, treatment monitoring, and biofeedback. The information that we will be obtaining and using on a routine basis may be able to indicate a wide array of neurological and psychological disorders as well as to assess a wide range of normal cognitive states and a wide range of abilities. Most evidence so far seems to point to the fact that there is a vast amount of untapped information in the resting state signal. In twenty years this signal will likely be well understood and efficiently extracted - perhaps in real time.

Furthermore, in twenty years, resting state fMRI will not be a distinct field. The well mapped spatial-temporal networks will provide a much more compact basis set upon which to project raw MR data than simple piles of pixels or Fourier components in time, and will lead to a new concept of the scanner collecting 'information' on the working brain in a manner that is at the same time more direct and more abstract. With the networks forming a compact domain, the scanner will be used to collect raw data that is spatially and temporally random, and used to

derive the network coefficients using compressed sensing or similar technology. The artificial concept that it is necessary to form human viewable images as an intermediate step, only to feed the images back into computer based detection schemes will no longer be necessary.

27.3.3 Real time fMRI

Real time fMRI was first developed in about 1996, but has not yet caught on as a widely accepted tool for neuroscience research since most paradigms are designed to carry out their brain activation sequences independent of any imaging data that is fed back. Also, most processing is performed offline. Real time fMRI can be a useful tool in a limited capacity however, as a method to monitor image quality as well as to determine if subjects have moved more extensively than that which would be correctible by typical motion correction methods. In the clinical realm, it will be absolutely essential to have real time monitoring of brain activation and data quality, as it would be a huge waste of resources and possibly negligent to not know if data were usable or not until after the patient had left the scanner.

Two interesting studies using fMRI were that of de Charms et al (DeCharms, Maeda et al. 2005) and that of Weiskopf et al (Weiskopf, Veit et al. 2003). In the study by de Charms et al, real time fMRI was used as a biofeedback tool, allowing subjects to see their activity - specifically in the anterior cingulate cortex - directly in slightly (5 to 10 sec) delayed real-time. Subjects were chronic pain sufferers. They were instructed to figure out a mental strategy for reducing the signal in this area. Once they did this, they also found that this learned strategy translated into reduced pain perception. The study by Weiskopf et al involved having subjects learn to move a “pong” paddle by modulating activity in regions associated with mental imagery or cognitive activity. More activity caused the pong paddle to move up, and less activity caused it to move

down. The subject saw the paddle movement in real time so could then have the appropriate feedback to work out a strategy to move it. Taking this further, real time has the potential as a device for enhancing communication with patients who are in a locked-in state (Laureys, Owen et al. 2004) or simply cannot talk.

Overall, real time fMRI is potentially quite useful for for following: minimizing motion via feedback to the subject (Yang, Ross et al. 2005) or via notifying the user of motion that is too extensive, therapy to the subject in the manner that de Charms has developed, open ended or branching experiments that proceed in directions that are determined by the location or amount of brain activation from previous tasks or stimuli, for communication with the subject or patient, and for human-machine interfacing. While the signal is delayed, it may be superior to other biofeedback methods since the signal is specific as it is based on chosen cortical areas, high signal to noise as useful information can be seen from a single activation (Richter, Ugurbil et al. 1997), and containing information that is not just from the autonomic nervous system (i.e. skin conductance).

The simple use of just signal magnitude is just the beginning of what can be fed into a computer , the investigator, or back to the subject. Multivariate analysis will allow for quite subtle changes to be assessed. One can imagine using real time feedback for interventions such as emotional therapy. One could be scanned while in a certain mental “state” that is excited, motivated, happy, or whatever, and then find ways of regularly achieving that state by trying to match their activation template to the optimal state template.

Additionally, there is no reason to limit the feedback to visual. It might be more useful to give auditory or tactile feedback from processed brain activation data.

While real time fMRI is becoming more sophisticated with regard to the amount and type of rapid, on-the-fly post processing that can be carried out while still remaining “real time,” the technique will probably not grow in usage until fMRI is used clinically on a regular basis. In the next five years, real time will still be gradually increasing in use as fMRI enters more into clinical use. In ten years, real time fMRI will start to become a standard tool for the researcher as processing speed will be able to be able to completely keep up with even the most rapid data producing scanning procedure. Being able to “tune” an experiment, task, or stimuli to a subject (as is performed routinely with electrophysiologic studies) will be a more standard practice in fMRI. In twenty years, many types of analyses procedures will be able to be performed in parallel in real time, allowing immediate comparisons. Real time fMRI will likely accompany standard lie detection tests, psychiatric assessments, or even job interviews. Machine learning algorithms will rapidly use and calibrate the brain responses and then effectively “read the mind” of subjects in the scanner as they rest or as they receive stimuli, perform task, or respond to questions stimuli. Section 27.3.6 on Decoding discusses this avenue. Such ability to obtain so much information from a subject’s mind will have, well before twenty years from now, opened up many ethical debates on when or how real time fMRI accompanied by brain decoding should or should not be used.

27.3.4 Multi-modal integration

Functional MRI has been used in conjunction with transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), electroencephalography (EEG), deep brain stimulation, optical imaging, positron emission tomography (PET), NMR spectroscopy (namely GABA spectroscopy), measures of eye position and pupil dilation, skin conductance, heart rate, breathing depth and rate, externally measured motion parameters, finger movement, tongue

movement, movement of other body parts, and muscle tension. This complementary information helps to inform processing methods, allowing for a more precise extraction and interpretation of fMRI signal changes as well as more efficient removal of artifactual signal changes.

The simultaneous use of EEG with fMRI has aided progress in epilepsy research by helping to identify temporal signatures of transient seizure related brain activity that can then be used as regressors for localization with fMRI. The simultaneous use of EEG and fMRI also holds potential for uncovering the mechanisms of resting state fMRI where one cannot repeat the sequence of spontaneous activity precisely with separate sessions. While activation studies can benefit greatly from multi-modal measures and methods to modulate brain activity, resting state fMRI studies have the most to gain since the signal is the least constrained and the least understood. Any method that would help separate spontaneous neuronal activity from artifact, or allow even more efficient extraction of ever more subtle activity, is highly valuable and worth the engineering development effort. One could argue that no experiment, no matter how well controlled, is perfectly repeatable, therefore there is always a preference for complementary measures to be obtained simultaneously. Combined PET and MRI scanners have recently been developed. Quantitative metabolic and/or neurotransmitter activity offered by PET is a very useful complement to fMRI and high resolution anatomical scans.

What does the future hold for multi-modal integration? Certainly, the benefits are clear, so we predict steady progress in engineering advances that will allow for an array of complementary brain and behavioral measurements to be carried out in the relatively hostile environment of a small bore and high magnetic field. In five years, we will have commercially available combined

simultaneous multi-modal suites. Within five years, almost all functional connectivity fMRI research will also employ at least one other simultaneous measure, and more likely will utilize at least three simultaneous measures. In ten years, with improvement in time of setup and ease of use, simultaneous measures and brain modulation methods will be standard for almost all experiments. In twenty years, performing just an MRI or fMRI experiment without any other simultaneous measures or methods for brain modulation will seem quaint...and not very useful. By this time, simultaneous measures will be completely integrated into the entire scanning process and processing stream.

27.3.4.1 Transcranial Magnetic Stimulation (TMS) and Transcranial Direct Current Stimulation (tDCS)

It should also be noted that performing fMRI simultaneously with brain modulation methods (tDCS or TMS) will become much more commonplace as these have potential to probe nodes of networks, allowing the inference of causality or at least necessity. If a transiently lesioned (as with TMS) or stimulated (as with tDCS) area changes subject performance, then inferences about the necessity or causality associated with the region or node on the network can be made.

The future, as a brain activity modulation method, of tDCS is showing promise, as a few somewhat sensational results have emerged showing increased efficiency to make observations or to perform math when the direct current is applied. The precise mechanism by which this works - likely involving lowering of the neuronal firing threshold - requires more research to be fully clarified. Precisely where these currents (being applied on the scalp) go in the brain also needs to be investigated. Perhaps in five to ten years, we will have a massive commercial market for tDCS "thinking caps" that will help us focus better, behave more creatively, or make

better decisions. While this is not necessarily part of the future of fMRI, it is certain that fMRI will help in understanding the mechanism of action.

The future of TMS lies in more precise placement of the magnetic field pulses. A major limitation in fMRI is that of inferring causality or necessity to specific nodes in brain activity networks. An area might be active but non-essential for a task. Selectively stimulating or transiently lesioning an area or a node will substantially increase our understanding of human brain networked activity. In five years, it appears that both tDCS and TMS techniques will improve in sophistication and accuracy. It appears that tDCS because of its ease of use, low cost, portability, and somewhat dramatic behavioral effects, will far surpass TMS in popularity between five and ten years from now.

27.3.4.2 Optogenetics and Transcranial Pulsed Ultrasound

Regarding brain modulation, two novel techniques, so far used only in animal models, have emerged. These are known as optogenetics (Miller 2006; Deisseroth 2011) and transcranial pulsed ultrasound (Tufail, Matyushov et al. 2010). With regard to optogenetics, the method of the year for 2011, according to Nature Methods, mice are genetically modified such that light at specific frequencies can cause an increase in neuronal activity in selected neurons - either inhibitory or excitatory. This method therefore allows delivery of extremely precise, relatively non-invasive stimulation or inhibition to probe neuronal circuitry in animals. This method shows potentially more promise than the current standard of using electrode delivered electrical stimulation. With such (relatively) easy and precise control of neuron type, location, and timing, networks can be probed at a new level of depth and precision, potentially uncovering a wealth of information on brain organization and development. Transcranial pulsed ultrasound is a bit

more of a blunt instrument, but the idea that sound itself, delivered through the skull, can stimulate neuronal activity, is thought provoking - opening up questions of precisely what the mechanism of action is (neuronal shaking?), and what the precision is. There are rumors of such devices being designed for humans to be used in the same way as tDCS. It is important of course to determine any short or long term effects of this type of brain stimulation before human use. Nevertheless, these two methods are perhaps only the beginning of an onslaught of alternative ways to modulated brain function - striving for noninvasivity, spatial and temporal precision, as well as specificity to specific types of neurons.

The future is extremely exciting for these nascent techniques since they are both extremely new and appear to have room to grow from a methods and applications perspective. Only a handful of groups are using them, yet, in these groups, the results are dramatic. we think optogenetics has more potential than transcranial pulsed ultrasound, but both should be in use by perhaps a hundred groups in about five years. In ten years, we can imagine an entire array of embedded light stimulators in these genetically modified mice (or perhaps non-human primates by then), allowing detailed and highly efficient probing of networks through computer algorithm aided efforts to create simulated actions, perceptions, or emotions by carefully sequenced excitation/inhibition timing.

27.3.4.3 γ -Aminobutyric acid (GABA) Spectroscopy

While spectroscopy of the inhibitory neurotransmitter, γ -Aminobutyric acid (GABA) has been used for years, recent work involving the relationship between GABA concentrations, MEG contrast, and BOLD contrast has shed some light mechanisms underlying BOLD and has launched a revival of aspects of spectroscopy in general. In work by Muthukumaraswamy et al.

(Muthukumaraswamy and Singh 2008; Muthukumaraswamy, Edden et al. 2009) GABA concentrations, MEG signal, and BOLD signal were measured in the visual cortex. The results of this study show that across individuals, gamma oscillation frequency is positively correlated with resting GABA concentration in the visual cortex, BOLD magnitude is inversely correlated with resting GABA, and gamma oscillation frequency is strongly inversely correlated with the magnitude of the BOLD response. These results clearly demonstrate that neuroimaging measures are highly dependent on the excitation/inhibition balance in an individual's cortex and have implications for the interpretation of functional imaging results, particularly when making between-group comparisons in clinical research.

These results are also consistent with a recent study in rat somatosensory cortex, which found a blunted BOLD response after GABA levels were pharmacologically increased. In humans, a study combining GABA MRS and fMRI demonstrated that the negative BOLD response in the anterior cingulate region of the default mode network increased with increasing GABA across participants. All of these recent data suggest that individuals with relatively high GABA concentrations in an area will exhibit relatively small positive BOLD responses and relatively large negative BOLD responses.

Other studies provide results which are less explainable but are interesting in that they suggest that BOLD contrast is not necessarily measuring the same aspects of neuronal activity as MEG contrast (Muthukumaraswamy and Singh 2008). Muthukumaraswamy and Singh compared fMRI and MEG Gamma frequency (40 to 60 Hz) responses to a visual stimulus which was varied in spatial frequency and temporal frequency. While the spatial overlap between brain activation measured with the two modalities was substantial, the parametric dependence of

the signal's dependence curves were generated for both spatial frequencies. With MEG, high spatial frequency showed much higher power across temporal frequency than low spatial frequency.

Recently Stagg et al, using tDCS, GABA measurement, and behavioral assessment, found that tDSC reduced the amount of the neuronal inhibitor GABA, which then led to an increased efficiency in learning new motor skills (Stagg, O'Shea et al. 2009; Stagg, Lang et al. 2010; Stagg, O'Shea et al. 2010). This type of research, combining brain modulation, direct neurotransmitter measurement (or any other type of neuronal activity measurement) and behavioral assessment is precisely where the future of neuroimaging is going to be: multi-modal investigation that has impact on basic mechanisms of action and immediate potential for therapy, treatment, or generally, the understanding of the healthy and diseased brain.

27.3.5 Individual assessment

Functional MRI has been high successful with regard to group comparison studies. Anatomic and functional differences between a wide range of groups with psychiatric, neurologic, physiologic, developmental, or other types of disorders have been characterized with high levels of certainty. While group studies are essential for the furthering of our understanding of normal brain organization and structure as well as deviations associated with disorders, they are almost useless for immediate clinical use and for many types of neuroimaging studies that rely on assessment of individual variations and subsequent correlation of signal changes and patterns with these individual differences. For a clinical diagnosis or assessment of treatment or for providing any other supporting information in the clinical setting, robust, reliable data must be able to be obtained on an individual basis. As an example, anatomic MRI is an extremely

effective clinical tool for identifying anatomic problems (i.e. tumors, lesions, etc.). No subject averaging or group inferences are required. The radiologist can just look at the image and see the tumor. This type of single person assessment, while a distant goal and while not quite achieved in the same manner as anatomic MRI, is achievable in fMRI with the proper classification algorithms and with enough functional contrast to noise and repeatability.

Functional MRI, since the early days in 1991 has been able to show brain activation results on individuals obtained from a single scanning session, or even a single scanning run...or even a single activation! Why then can it not be used in for clinical purposes? While results are robustly and repeatably obtained on individual subjects, subtle differences in activation magnitude, location, and pattern are simply too small and variable - using current scanning and processing methods - between populations to allow for placement of an individual in one population or another. This shortcoming will certainly change as more sophisticated classification methods are developed. There is a huge potential for automated machine learning algorithms towards this end. One other potentially significant obstacle for using fMRI in this manner is that other physiologic factors that can have a large influence BOLD contrast - such as blood pressure, hematocrit, etc. - may need to be identified and accounted for to eliminate any systematic bias for an individual. While the goal of individual diagnosis might be a bit too high for most disorders in the immediate future, using fMRI to aid in treatment decisions may be more realistically achievable.

Performing brain activation studies on individuals and regressing the results against a wide array of subject specific variables appears to be a very promising and relatively unexplored avenue in basic neuroscience research. One other important practical point to consider is that

spatial normalization algorithms usually require spatial smoothing with 5 mm smoothing kernels, thus obviating most of the benefits of scanning at higher fMRI resolution. Spatial normalization of populations of subjects simply cannot be performed - at least over the entire brain - at resolutions less than 3 mm³. This problem in itself is forcing researchers to rethink how they perform multi-subject studies at ultra-high field and ultra-high resolution.

In five years, neuroscience research will be well populated with the study and comparison of individual subjects. Many already are published, and have been for years. Here is one useful example of the type of study that will be most common in the relatively near future: combining fMRI, behavior, and individual difference assessment (Duncan and Boynton 2003). While group averaging and spatial normalization will certainly not disappear, the popularity of this approach will rapidly diminish as other more effective ways of comparing and pooling high resolution individual data emerge. We may still perform spatial averaging, but it will perhaps be region or structure focused. In ten years, we think that the use of any 3D spatial coordinate system will be in decline. Replacing this will be a coordinate system that identifies function relative to specific networks. In general, a 3D or surface-based system for thinking of brain organization will be replaced by a functional region and network - based system. In twenty years, the significance of raw activation data will be measured relative to a highly multivariate matrix of previous findings and relative network locations. Anyone trying to work with graph theoretical network displays will likely agree that, as a whole, this complex data will not lend itself to the sizing up of useful information by visual inspection, but will be assessed and collapsed in any chosen or most useful dimension by classification algorithms.

27.3.6 Beyond Mapping: Multivariate Analysis and Decoding

The approach of analyzing fMR data in a multivariate pattern-wise manner rather than mapping individual voxels or blobs has, in the past few years, seen a tremendous surge of interest due to the dramatic results produced (Haxby, Gobbini et al. 2001; Cox and Savoy 2003; Kamitani and Tong 2005; Kay, Naselaris et al. 2008; Kriegeskorte, Mur et al. 2008). This class of techniques is generally known as multivariate analysis, pattern recognition, or information mapping. It has been used very effectively in the process of performing fMRI decoding. Decoding in fMRI is the set of procedures- including multivariate analysis - that aim to identify a perceptual representation, activation, or cognitive state on the basis of fMRI signals. When a perceptual representation can be decoded from the activity pattern, the brain region studied contains information about the stimulus. It's important to note that one can perform decoding without the use of multivariate analysis, and, likewise, one can perform multivariate analysis without using it for decoding (Kriegeskorte and Bandettini 2007; Mur, Bandettini et al. 2009). Nevertheless, multivariate methods have proven to be extremely helpful for fMRI decoding.

Multivariate techniques in neuroimaging were introduced over a decade ago (Worsley, Poline et al. 1997), but the current interest in the information-based approach is based on the hypothesis that brain activation patterns reveal information carried by a neuronal population code at the scale of imaging voxels or smaller. This idea motivates multivariate analysis in single subjects without smoothing of the data. Information undetected by activation-based mapping can often be detected using multivariate mapping. If the information resides in the fine-scale pattern of the activity, the spatial average may be similar between conditions, so no effect may be found by conventional methods. Or, additionally, the fine scale pattern of activity might look like "salt and pepper" noisy artifact, when, in fact it is true activation. An effective way to determine if this noisy scattered signal, which to the eye looks like nothing special, is true

activation is by using a decoding approach, as was first performed in fMRI by Haxby et al (Haxby, Gobbini et al. 2001).

Currently, decoding has been hyped in the media with claims of “brain reading” and “lie detection.” Nevertheless, this method is not all flash. It has tremendous potential to pose and answer extremely subtle questions about how the brain is organized that are not addressable using standard mapping techniques. Recently, researchers have further pushed the limits of decoding mental content from brain activity. In past decoding studies, the experiments have been divided between a training set in which the spatial pattern of brain activity was associated with an object (or object category), orientation, or position and an experiment set in which the same stimuli used in the training set were used. The training set and test set was the same or highly similar stimuli. Recent studies have extended fMRI decoding to allow the accurate identification of brain activation associated completely novel stimuli or tasks (Kay, Naselaris et al. 2008; Mitchell, Shinkareva et al. 2008).

A significant advancement that appears to be happening with fMRI decoding is that of using a large training set focused on more elemental aspects of a brain state (i.e. from visual stimulus or word set) to predict the brain activation pattern associated with novel stimuli or brain states. Not only do these studies pave the way for extensive applications of fMRI for “brain reading” but also lend a unique insight into how the brain processes information by being able to identify the “most informative” voxels and regions. In addition, principles of how the brain is organized can be derived by assessing how well various elemental stimuli or tasks can predict activity associated with more complicated stimuli or tasks.

As fMRI continues to increase in spatial resolution, multi-voxel pattern assessment will become more predominant as low frequency activation blobs give way to very fine grained, and sometimes hard to visually interpret - brain activation patterns. The most efficient way of assessing these tortuous, speckled patterns will not be by forcing a center of mass on them, but rather by comparing these patterns against other “calibration” patterns of activation. Multivariate methods are increasing in popularity since they are not only complementary to standard techniques, but are more sensitive in fine grained spatial information that would otherwise be lost. Several key questions remain to be answered regarding these approaches. One question is exactly what spatial scale of activity is revealed by this method? Is the activity on a sub-voxel level or on a multi-voxel scale? The likely answer is that this method can be sensitive to activity across several spatial scales - from subvoxel to multivoxel. Regardless of what spatial scale the method observes, it can extract neuronal activation information with a robustness, accuracy, and sensitivity that was previously not possible with univariate methods.

An important point to make is that decoding can be performed using simple univariate approaches. As a trivial example, increased activation in the motor cortex tells us that the subject is moving his fingers. The simple act of decoding can, on a very basic level, be proof that fMRI works, and at its most useful, can tell us, from moment to moment not only what a person is thinking but what they might be doing in the next five minutes or five hours, how they might vote in the next election, what soft drink they prefer, how they make decisions at all, or possibly, what the probability is that they will commit a crime in the next 10 years. The general area of using fMRI-derived brain activity to predict short and long term behavior or potential for behavior will certainly show rapid growth since, so far, it has been surprisingly successful. Recently a dramatic study predicted future video game learning ability by observation of

activity in the dorsal striatum (Vo, Walther et al. 2011). There have been several other studies which have come out showing how fMRI can predict success in short and long term memory, and short term future decision making among other behaviors (Haynes and Rees 2006; Bles and Haynes 2008; Bode and Haynes 2009; Anders, Haynes et al. 2010).

In the next five years, many more results will emerge, further demonstrating not only the effectiveness of multivariate assessment and fMRI decoding but expanding well into attempts to probe fundamentals of brain organization by how well activation associated with vast learning sets or sensory input, motor output, or cognition can predict associated behavior in individuals and across individuals. In addition, we will better understand the sources and limits of these techniques (Op De Beeck, Haushofer et al. 2008). During these five years, multivariate methods in general will further usher in a strong trend away from simple mapping of blobs of activity to probing highly complex and interacting fine grained patterns of activity. How “real” an activation is will be determined by multivariate algorithms that take into account information content and repeatability, rather than how subjectively clean the activation maps look.

In ten years, a new construct for describing brain activation patterns and pooling brain activity data will be required. This requirement, and this activation data, will be complemented by the very large number of resting state networks that will have been revealed at high resolution and high field. Rather than collapsing data into a location or magnitude, it will be necessary to create shape and texture descriptions as well as network - based descriptions of activity. Given the many networks and many scales of activity in the brain, these descriptions, as mentioned previously in this chapter, may not lend themselves as much to visual presentation. The brain

activity maps may be so complicated as to no longer be meaningful to the human eye. In this case, in ten years, algorithms will come into play to collapse and compare the data much more effectively than a human eyeing and comparing coordinate systems can. In twenty years, to make an analogy, brain maps of today will resemble 16th century exploration maps of the new world, having much “terra incognita,” oversimplified areas, and distorted detail. Maps of twenty years from now will be like current highly layered Google maps - highly reference-able and searchable and revealing much information and interaction across layers of information, as well as spatial and temporal scales. Instead of pasting our brain activation maps onto high resolution anatomical maps, we will paste them, so to speak, onto a vast reference database of activation, behavioral, anatomic, and genetic information, thus able to mine their functional relevance almost immediately. We will have a highly developed “Google Maps” of the human brain. It’s important to note that this will not happen by coercing groups to submit their data to a database in a specific way when submitting papers, but, rather, by perhaps one or two highly motivated groups that will take it on themselves to create this database, that will then become highly attractive to use and contribute to. This model is something like that of the Allen Brain <http://www.brain-map.org/>. In fact, it might be a future manifestation of the Allen Brain project.

Regarding decoding, it’s clear that in five years, this research will increase as demonstrations of its utility continue. In ten years, it will likely be used extensively with real time fMRI in the context of psychiatric and neurologic assessment. Decoding will be a highly utilized tool for understanding on a finer spatial and temporal scale, neural correlates of a wide range of behavior. Regarding non-clinical uses, it will likely be introduced as evidence in trials involving the need to determine if a person is being deceptive or more likely, if they recognized a crime

scene or knew an individual, as these types of signatures will likely be robustly extractable. With this level of processing sophistication, implementation of brain-machine interfaces will be relatively straightforward in ten years. One problem, not for decoding, but for brain-machine interfaces that will remain is the 6 to 10 second hemodynamic delay. In twenty years it is possible that we will have discovered other, more rapid sources of contrast, such as neuronal current imaging or DTI, but the SNR will still likely be too low to use easily in this manner. One solution, likely to emerge in the next five years, as discussed above, will be the simultaneous use of EEG and fMRI for robust decoding and brain-machine interface development. Lastly, in twenty years, it is likely that we will be able to apply machine learning algorithms in the manner described by Mitchell et al (Mitchell, Shinkareva et al. 2008) and Kay et al (Kay, Naselaris et al. 2008) across subjects in order to create extremely accurate and subtle “prediction maps” for each individual for a large range of tasks and stimuli. Inferences drawn from these maps will help in clinical diagnosis, pre-surgical mapping, clinical assessment, therapy, biofeedback, in court, and in marketing of products.

27.3.7 Databases

The future of fMRI and brain mapping depends in large part on how effectively we can ultimately organize, integrate, filter, and access our collective results from all experiments around the world. One strategy is to develop databases, or databases of databases: meta-databases. This is a huge problem since data are rapidly becoming highly multidimensional as well as highly variable across center, modality, experimenter, subject, and even day or time of day. We will need to develop an efficient way to be able to handle and use these variables.

On the other hand, an alternative stance to massive databases is also legitimate: That is, if we don't embrace databases, much of science will continue with researchers collecting all of their own data or teaming up with a limited number of groups, to advance science one important step at a time. This approach is much more manageable and nimble - especially in light of the fact that the data collection process itself as well as the type of data stored is and will be for years to come, in a state of rapid evolution.

That said, there is an important place for the development of databases. Ambitious projects so far including the Allen Brain <http://www.brain-map.org/>, the Alzheimer's Disease Neuroimaging Project (ADNI) <http://www.adni-info.org/>, and Brain Map <http://www.brainmap.org/>. Several project have attempted, and are attempting, to store raw data with the idea that this is yet another dimension worth exploring and using for tool development. These raw databases, it seems might require fewer datasets to be useful, and conversely, will likely have diminishing use with size above about 1000. In fact, depending on the question, the optimal database size will vary considerably.

In the future, highly ambitious individual groups will inevitably develop massive databases with a clear, elegant and flexible standard of reporting. Early in brain mapping, Talairach coordinates were reported. This approach has been effective for over 20 years for relatively low spatial resolutions. As brain activity descriptors become more complicated with better tools, brain mapping databases will have to adapt. As described above, new and better neuroimaging tools will allow brain activity to be mapped at a spatial resolution on the order of microns and temporal resolution of milliseconds. Other dimensions of information include changes over time, interactions (as nodes on a network), causality, magnitude, refractory period, and many

more. How would this information be stored, pooled, and cross referenced? How would nuances of experimental design be accounted for?

In five years, we can imagine the emergence of fMRI based databases that are more networked-focused rather than location-focused. Of course we will also have the growth of the resting state fMRI raw data database. The rationale for saving the raw data is that we have not yet found the best way to process this data. Access to the raw data is an effective way to allow the techniques to be developed and compared. In the next 10 years, we will see the emergence of complementary databases of anatomy, susceptibility contrast images, DTI, EEG, MEG, optical imaging, TMS, and tDCS databases. Ultimately, perhaps in twenty years, we might have the emergence of a meta-database, bringing all of these together. As the most useful equipment availability falls off in pace to the number of groups performing research, pure database research may become a growing discipline or at least a significant component to anyone's laboratory.

27.3.8 The Experiment

The fMRI experiment itself has undergone some development over the years. Today we use 3T and 7T scanners rather than 1.5T, 2mm resolution EPI, RF coil arrays rather than single quad coils, and have more sophisticated subject interface devices that setup quickly and efficiently. We perform both more standardized yet also sophisticated analysis, and ask questions that are built upon the huge body of basic and applied research that currently exists for fMRI and other human and animal brain imaging and assessment methods.

While efforts have changed, they have also stayed the same. We still, as in the early days of scanning, bring our setup over to the scanner (now with laptops rather than with computer

racks on wheels) with our small contingent of people running the scanner and various equipment. We typically recruit our own volunteers and wait for them to show up. We instruct them on the paradigm and emphatically tell them to hold still. Once in, we pack their heads in all kinds of motion nullifying stuff. Along with the functional scan, we perform a series of anatomical scans, and perhaps now, an additional resting scan - if it is not the main part of the study itself. Once finished, we thank the subject, download the data, and go back to our computers to see what we did. This ritual has been carried out hundreds of thousands of times more or less in the same way since 1991. We remember carting everything - including our own gradient coil - through the hospital tunnels at 9:30 PM, when the scanner freed up, and saving the data on 20 Megabyte reel to reel tapes or rather large cassette tapes which we transported back to the once computer in the lab - a Techtronics workstation. This we called the "sneaker net." We then performed recon at 3 AM since we never wanted to wait until the next day to see what we did. Sometimes, if the results indicated that we made a mistake, we would go back at 4 AM to try the experiment again.

So, is this ritual the best way to do the science? For much low level or basic development where the experiment is always changing, and that don't involve over 15 subjects all receiving the same paradigm on mostly standard protocols, we would say yes. Is it the most optimal for huge experiments that collect data from hundreds of subjects or patients using the identical protocol and analysis stream? To this we would tentatively say no. we can imagine, in the next five to ten years, centralized scanning centers set up to handle researchers needs. These scanners can be located thousands of miles away. As more groups, working with less money, desire to do fMRI research on scanners that are unfortunately more dormant at many centers because of a lack of grant money to pay for scan time the model of one or two scanners per center is starting

to show some stress. It seems that a potentially efficient and profitable option would be to start up scanning centers, where experts receive orders which specify subject parameters, subject interface, pulse sequences, paradigm details, and basic processing. They make a request and then perhaps send in the paradigm details. The employees at the scanning center then about collecting the data. Once finished, they send the data to the user to analyze further as they wish. This could certainly be applicable to low field strength scanners and would be even more applicable to extremely high field strength, very expensive scanners. For much of the basic fMRI scanning in the world, the procedure is straightforward enough to not need much if any physical oversight by an investigator. In twenty years, we can imagine these centers thriving, driving the costs of fMRI research down, and allowing more people to embrace fMRI research, thus likely advancing the field.

27.4 Interpretation

The utility of fMRI is not only a function of implementation ease or sensitivity, but is also a function of the fidelity with which the measured hemodynamic signal represents underlying neuronal activity. Over the years, the utility of fMRI has grown as users have become more confident that the signal changes quite accurately reflect underlying neuronal activity at relatively high spatial and temporal resolution. Much work has been devoted to understanding the “hemodynamic transfer function” and how it varies in shape, timing, or magnitude with task, brain location, time, subject, physiologic manipulation, and pulse sequence. Currently, while it’s understood that many hemodynamic factors - including the dreaded “draining veins” - have a significant impact on the magnitude, temporal, and spatial certainty of hemodynamically-inferred neuronal activity, the upper functional spatial resolution is about 0.5 mm (Yacoub, Harel et al. 2008), and the upper functional temporal resolution is generally about

1 second (Kim, Richter et al. 1997; Bandettini 1999). With modulation of task timing, the detectable difference in the hemodynamic timing between regions can be as low as 50 ms (Menon, Luknowsky et al. 1998), but with a single task, the certainty that one area is activated before another, is only on the order of a second.

An alternate approach towards probing inhibitory networks, and towards characterizing extremely rapid communication between nodes using fMRI has been pioneered by Ogawa et al (Ogawa, Lee et al. 2000). This involves sequential activation of an inhibitory source and then the target of the inhibitory source. At a specific timing (<100ms typically), the inhibitory activation suppresses the fMRI response in the target area. While this approach has not seem much progress recently, we believe it has much potential to probe human brain circuitry and causality between nodes of networks.

While the hemodynamic response is extremely well behaved within any given voxel or ROI, the differences in space of the hemodynamic response are considerable and very difficult to characterize or calibrate. With regard to magnitude, it's well accepted that the largest signal changes for any given task are likely to come from the voxels that have the highest blood volume within them - the big veins. In some situations, this can alter the activation hotspot or center of mass location by as much as 1 cm.

Efforts at calibration, while having been in place for over a decade, using either global signal alterations induced by CO₂ or by vein identification, have produced limited success and distribution. The primary reasons for their limited success is that the pulse sequences used (simultaneous flow and BOLD types) are non-standard and non-clinical - therefore not widely available on clinical scanners, physiologic manipulations are cumbersome, the implementation

typically reduces overall signal (and contrast) to noise by at least a factor of two, and, importantly, the results are not significantly helpful for most applications.

Aside from the hemodynamic transfer function and efforts at calibration, much work has been carried out with animal models and concordant electrophysiologic data in an attempt to understand precisely what aspect of neuronal activity the hemodynamic response is sensitive to (Laufs 2010). Open questions that remain are related to whether BOLD is most sensitive to local field potentials or spiking, inhibition or excitation, and what precisely causes negative BOLD signal changes (Logothetis 2008)?

At the time of the writing of this chapter, resting state fluctuations in fMRI are experiencing an explosive growth in use. Groups are finding new processing methods to extract resting state fluctuations, new ways (tasks, physiologic manipulations, pulse sequences) that resting fluctuations can be modulated, and new differences in fluctuations across populations. A handful of groups are working at understanding precisely what the neuronal correlates of resting state fluctuations are, what are the temporal characteristics of these fluctuations, why the frequencies are so low, how do these change over time, how many correlated networks exist, and what MEG, EEG or electrophysiologic frequencies best predict these correlations? As most tools are already in place to address these questions, it's almost certain that they will be mostly answered in the next ten years. Also in ten years, it will mostly be resting state fMRI research and some high resolution activation studies that will push most fMRI researchers to 7T. This may seem optimistic, but I believe that 7T will be a solid workhorse in at least one hundred centers for clinical use. In twenty years, the delineation between resting state or spontaneous activation-related fluctuations and task or stimuli related fMRI will be eliminated.

Most paradigms will involve careful modulation and measurement of both task-related and spontaneous changes in fMRI time series. In twenty years, the optimal pulse sequences and processing methods will have been developed for resting state experiments. The careful classification of resting state networks and changes over time will significantly aid in patient diagnosis, brain decoding, and therapy or intervention. In fact, our guess is that the clinical utility of resting state fluctuations will far surpass the “resting state.” Rather these will be considered steady state, spontaneous, or endogenous fluctuations.

Regarding the future of fMRI interpretation, in five years, it appears that from the rate of progress that is being made, we will have some very clear answers as to specifically which aspects of neuronal activity influence hemodynamic contrast. In ten years, we will have robust and relatively easy to implement methods for calibrating the fMRI response for all to use. In twenty years, optimal pulse sequences, calibration, and accurate interpretation will be fully integrated into all scanning and analysis procedures. Inhibitory and excitatory activity will be able to be discerned as well.

27.4.1 Alternative fMRI Contrast Mechanisms

Because BOLD contrast is based on blood oxygenation changes that are dependent on the precise interplay of flow increase and metabolic rate increase, the temporal and spatial accuracy as well as the interpretability of the signal is fundamentally limited. Many researchers are busy trying to develop an MRI-based functional contrast that may somehow be a more direct, sensitive, quantitative measure of neuronal activity. Indeed, many other functional contrasts have been put forward as possible. These include the non-invasive measures of activation induced changes in perfusion itself (Detre, Leigh et al. 1992), blood volume (Lu, Golay

et al. 2003), diffusion (Le Bihan, Urayama et al. 2006), CMRO₂ (Davis, Kwong et al. 1998; Hoge, Atkinson et al. 1999), temperature (Yablonskiy, Ackerman et al. 2000), and presumably magnetic field changes in the vicinity of active neurons (Bandettini, Petridou et al. 2005; Petridou, Plenz et al. 2006). These results have always been met with extreme interest by the imaging community but none have proven superior to BOLD - because the techniques are more technically challenging or, more often, the effect size produced using the specific contrast sensitivity is considerably less than BOLD contrast. Perfusion imaging has come the closest to BOLD in terms of utility and functional contrast. While it generally has less brain coverage, lower temporal resolution, and lower functional contrast to noise than BOLD, it does have the advantages of higher specificity, baseline information, and less baseline drift. The latter advantage is significant when probing very slow brain activation timing (Aguirre, Detre et al. 2002).

Each of these functional contrasts has the potential to providing unique information not only about brain activity location, timing, and magnitude but also about cerebral physiology. This information is not only useful for brain mapping but may be useful for understanding more deeply, neurovascular coupling and variations of this with disease. What's exciting about fMRI is that the potential impact of the field is not limited to mapping brain function, but rather to understanding many more aspects of brain physiology at a depth not previously achieved with more invasive methods. An exciting direction that we feel has significant potential in fMRI is the simultaneous collection of multiple contrasts and even the simultaneous collection of data across multiple modalities. The simultaneous collection of this information allows detailed temporal behavior of the signal changes and the noise to be carefully studied in a temporally and spatially registered manner.

In five years, we might find that multi-echo EPI-based fMRI will emerge as highly useful in the context of image acquisition for resting state fMRI or for standard activation-based fMRI because of its ability to separate BOLD-related from non-BOLD related fluctuations based on direct T2* measurement. With regard to alternative functional contrasts in five to ten years, two other alternative contrast maps will be available non-invasively with fMRI - baseline oxidative metabolism and baseline blood oxygenation. We will be able to obtain the necessary information to quantify these parameters on a voxel-wise basis, thus proving very useful clinically. Also in ten years, we will have a high enough intrinsic signal to noise and efficient enough pulse sequences to quantitatively image perfusion almost as well if not better than BOLD for most purposes. The simultaneous collection of flow and BOLD information towards the time series measurement of CMRO₂ changes will finally show an increase in use as these more experimental or non-standard sequences start to become standard on clinical scanners. In twenty years, we might have just high enough signal to noise, and sophisticated enough paradigm designs and processing methods to extract direct neuronal current information using fMRI.

27.4.2 Anatomic Changes with Learning

Findings such as the famous result by Maguire showing that London taxi drivers have larger hippocampi than an average person (Maguire, Gadian et al. 2000), strongly suggests that brain tissue grows with increased rate of use. Time constants of the change, permanence of the change, mechanisms of action, or even what actually changes, are not at all clear. Nevertheless, the findings continue to come in (Kelly and Garavan 2005; Draganski and May 2008). While these changes are extremely subtle and may not be localized to the area that's most active or even to any specific brain tissue type, the findings have not only been repeated, but are now

being demonstrated in far better controlled animal models (Lerch, Yiu et al. 2011). What are the possible mechanisms? These changes could reflect new neuronal connections being made, more tissue iron, cell swelling, or an increase in vascular density, among many other things. This is also an area that is certain to show rapid growth in the future as we develop more reproducible learning paradigms, methods to robustly detect these changes, and a better understanding of the mechanism and timing of the changes.

Understanding how and why the brain physically changes with learning and experience will result not only in our understanding of brain physiology and principles of organization and change with use, but might introduce an entire field of cortical phrenology - a strange but potentially rich twist on an old and of course outdated hypothesis. In fact, in the next five years, we foresee a rapid growth in these kinds of studies in conjunction with concordant fMRI studies. Given the continued success in this area, in ten years, we will see an even more rapid expansion of this avenue, tracking changes that occur not only over months and weeks, but perhaps over days and even hours. It might turn out to be a way for assessing therapy progress, or in a non-clinical context, a way to assess how a brain has been shaped by years of experience or to assess what potential a brain might have. In twenty years, tracking, modulating, or enhancing brain changes might be a field in itself, and extremely high resolution MRI at high field will likely be the tool of choice. By then issues of image registration, warping, RF inhomogeneity, and dropout will be almost eliminated by hardware and processing advances. A recurring theme for all these techniques as they advance beyond our most ambitious expectations is that the more powerful the technique, the more complex ethical issues it introduces. Neuro-ethics will no-doubt have entire subfields devoted just to neuroimaging.

27.5 Applications

Assuming that the predicted progress in fMRI technology, methodology, and interpretation, continues, the applications of fMRI will continue to grow in number and sophistication. Cognitive and basic neuroscience will continue to benefit from fMRI-derived information and clinical applications of fMRI will finally find a foothold in individual assessment. These clinical applications will include pre-surgical mapping, mapping of function *during* surgery, mapping of function during neurological or psychological assessment, diagnosis assistance, diagnosis and treatment assessment of disorders such as schizophrenia, bipolar disorder, addiction, depression, antisocial disorders, anxiety, borderline personality disorder, and chronic pain. As mentioned, the use of real time feedback of the fMRI signal also has potential to be a powerful tool for chronic pain perception alleviation as well as behavior and emotion modification. It can and may very well become, among other things, a therapeutic tool.

The current use of fMRI outside of neuroscience research has been sparse. It has been taken up by some marketing companies in an attempt to gauge brain function associated with product preference. In addition, several companies have emerged claiming that it can be used as a tool that is more effective than a polygraph for lie detection or perhaps as an aid in questioning criminals or potential terrorists when determining if they have seen other individuals, locations, or scenes before. It is likely that the neuronal signature of person or place recognition is detectable by fMRI, and, importantly, not able to be hidden. Attempts have been made to introduce fMRI lie detection evidence in court, but so far it has been successfully removed from these cases. It is clear that while someday it is likely that it will be used regularly, right now, it is far too premature for this kind of specific use. The accuracy and subtlety of inference requires

far more stability than is possible in the most motivated and experienced volunteer, much less an uncooperative or perhaps overly enthusiastic (depending on the side of the court case) volunteer. After twenty years since its inception, over-interpretation of fMRI data remains perhaps the most prevalent problem in the field. This problem will likely remain even after another twenty.

While fMRI is probably not ready to be used in the above mentioned non-clinical ways yet, it is certain that technology, methodology, and signal interpretation will improve such that in ten to twenty years its use will be commonplace in marketing, crime suspect questioning, and in the court of law. What needs to happen for it to be used in this way is that we need to have a clear signature of brain activity associated with any of the above mentioned goals - a clear and specific signature for a desired product and not just an attention signature, a clear and specific signature for recognition, and not just a general modulation of the amygdala, etc, and a clear and specific signature for deception, and not just enhanced activity of frontal lobes generally associated with confabulation. So far, the activity that is associated with these types of detections are not specific enough to render the findings conclusive. Also, as these subjects might be uncooperative, any movement typically is correctable only to a limited degree, and many false positives are produced, invalidating any test. These problems are all able to be overcome, but it will take time and patience.

Other uses of fMRI include any application where one wants to assess whether or not a person has the potential to perform a task well, make good decisions, learn new tasks effectively, respond well to stress, or become a natural charismatic leader. If more information can be gleaned from an fMRI scan than can be obtained from a battery of behavioral tests, then these

applications of fMRI will grow rapidly. In addition, these same tests might, importantly, be able to assess future problems in personality or performance, and hence be extremely useful for job screening in civilian and in military scenarios. Of course, as this application becomes closer to being manifest, ethical issues, again, will have to be carefully cleared. It may very well turn out that in the next twenty years clearing ethical hurdles to many of these applications will be more challenging than clearing the technological hurdles.

Aside from use in industry, fMRI may become so easy to use and cheap that fMRI and MRI scanning may be yet another device that is used in spas, health clubs, shopping malls, or amusement parks. People could walk in, pay a couple hundred dollars or less, and get an MRI and fMRI of their brain. For a bit more, they could have their brain rendered in 3D or, better yet, get a 3D life-sized printout of their brains. For a bit more, they could be compared against the mean in a vast array of measures that have implications on behavior, happiness, or potential. This kind of commercial use of fMRI will likely come about after ten years and start to thrive by twenty years.

27.5.2 Our Understanding of the Brain

The brain is organized on many different spatial and temporal scales. The hemodynamic response offers a noisy glimpse at a specific temporal and spatial scale. While the hemodynamics are a significant limiting factor in fMRI, we have not yet fully characterized the relationship between all aspects of this hemodynamic response and the neuronal activity that underlies it. Optimistically, once we characterize fully this transfer function, we might be able to infer neuronal information on a much finer temporal, spatial, and magnitude scale as our hemodynamic measurement. This full characterization will probably take place in the next ten

years with the aid of a wide array of complementary measures in humans and in animal models. The potential of fMRI for helping to understand networks, causality, and organization across several spatial and temporal scales is far from being fully realized. A huge effort in brain modeling is underway, and substantial progress is being made with regard to network propagation and inferring causality in brain networks (Friston, Harrison et al. 2003). Even at twenty years old, fMRI is a nascent technology. We are still very much in the heady early days and have much to look forward to with regard to how our imaginations will drive development and applications.

27.5.3 The Unexpected

As mentioned at the start of this chapter, if all the variables are not fully accounted for in a system, it is nearly impossible to project how it will play out beyond a certain time frame. We would love to channel the character Hari Seldon of Isaac Azimov's Foundation Trilogy and create a science of fMRI "psychohistory" to see and periodically influence the 1000 year future of fMRI. Unfortunately, we don't have the information and can't anticipate the unknowns. On the good side, we may have huge breakthroughs: For instance, neuronal current imaging may be revealed to show a huge effect with the right method, thus increasing the temporal resolution and accuracy by an order of magnitude over hemodynamic effects. On the negative side, we might find that RF power or high fields cause early dementia, thus fatally hampering progress in this direction. Assuming these extremes don't happen, we believe the future is still extremely exciting and overall quite optimistic for fMRI overall, and as outlandish as some of these predictions might seem, our prediction on the predictions is that they will likely fall on the conservative side or simply be very different from what will actually happen in twenty years.

27.5.4 Looking Further Out

We are going to go way out on a limb and try to project far into the future...let's say in 50 to 100 years. We would like to end this chapter with some truly wild, fun, long term speculation that won't matter a bit to most of us since we won't be here to enjoy it! This is just complete guessing on what the implications of some specific improvements will be. First, if robots and/or computers have not taken over the world and even if they have, and if we have not run out of natural resources, in 50 to 100 years, we should have room temperature superconductors. From our understanding on how the science of superconductivity is advancing, this development is not at all a certainty. We just think it's a high probability given that we will have had 100 years of making attempts at just the right material composition. We should also have stunningly high bandwidth wireless communication. We should have all kinds of biologic prosthetics to enhance the quality, fidelity, or selectivity of our experience of the world. One example of what might come about is that we will have retinal projections, or direct visual / auditory/sensory cortex input of our choice of a huge array of different types of information - among them, fMRI scans. With room temperature superconductors - and let's say the wire is a microfilament mesh, wireless transmission, we might be able to walk around - each with a wearable or implanted MRI/EEG/MEG scanner - literally "seeing" our own or others' thoughts and emotions, allowing better communication or perhaps just for fun. One troublesome thought is that the more direct measures will be so much more efficient than the sluggish messy hemodynamics that fMRI might very well have died out after say, 50 to 75 years from now. That sad thought aside, brain machine interfaces will be the norm. Genetic modification will likely have fought through many ethical battles to surface in some limited controlled manner. Suffice it to say that our genetically modified/computer modified/brain scanner and

stimulator- modified personal experience of reality will be wildly...hugely...different than what we experience now. Hopefully we'll be happier as well! MRI and fMRI might still be around, but they will be at least highly portable if not wearable or implanted, and will be just one source of a vast amount of ready information that we will have at our fingertips. Sounds like fun!

27.5.5 Conclusion

In this chapter, we have attempted to paint a picture of the future of fMRI based on an assessment of how it has evolved and where it is now. We have speculated on the primary areas of fMRI related technology, methodology, interpretation, and applications. For each of these areas, we attempted to look five, ten, and twenty years into the future. Of course it's too easy to say that technology will be more sophisticated and that everything will get faster, higher resolution, more powerful, useful, and more information rich...and cheaper. We made every effort not to fall into this mistake. Our sincere attempt here was to try to point to specifics in these four areas and then speculate on why and how they will improve and what the implications might be. Many of these predictions might be way off, and a few might turn out correct. Nevertheless, a primary goal of this chapter was not only to make bold and interesting predictions, but rather, to generate new perspectives, new ideas, new information, and new directions to the expert and layperson on what seems important, what to anticipate, and perhaps what to work towards. Perhaps the most important goal was to inspire the readers, and ourselves, to think about doing more than dotting the i's and crossing the t's, but to dare to think more creatively, wider, and deeper in hope that completely new engineering, physics, and computer science projects as well as neuroscience experiments and clinical investigations can be tried in fMRI today.

27.6 Acknowledgements

This work was supported by the Division of Intramural Programs at the National Institute of Mental Health. PAB would also like to thank his wife for proofreading the document while on maternity leave.

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