



# Functional Neuroimaging

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## Chapter 1: Introduction

Good morning. I'm Joy Hirsch, and I'm the director of the Functional Magnetic Resonance Imaging Program here at Columbia. And it's my pleasure this morning to tell you a little bit about new directions in functional MRI, and I'm going to particularly focus on clinical applications. There's some very exciting things going on in functional MRI for clinical purposes, and I enjoy presenting that to you today.

But before I get to that point I'm going to quickly go through a rapid background of the ideas of functional specificity, how they've emerged, and the role that they play today, and some of the basics of MRI; and then we'll get to some very specific applications having to do with mapping for neurosurgical planning, mapping for seizure localization, mapping for diagnosis of psychiatric disorders, and so on.

## Chapter 2: Functional Specificity

Starting at the very, very beginning, the most fundamental idea of functional neuroimaging in general is to understand this very complicated relationship between the structure of the brain and the brain's function. The idea of functional specificity has been with us for a very long time, and emerged around 1840 with Broca,



as you all know, who made the important connection between injury to the left inferior frontal gyrus and aphasia; and Wernicke, who around the same time made a similar link between injury to the superior temporal gyrus and a particular type of aphasia where speech is produced perfectly well but simply doesn't make any sense. In the middle of these two seminal events that really launched our understanding of functional specificity of the brain was the very famous story of Phineas Gage; John Harlow was his physician, and following a very unfortunate accident where a tamping rod was propelled through the frontal lobe of Phineas Gage, he emerged as a very different personality. Previous to the accident he had been a very moral, upstanding citizen, trustworthy in all respects. When he emerged from the sequelae of this accident, he was a completely changed personality, completely considered amoral by the standards of the time, and was killed three years later in a bar brawl. Harlow tried to present his findings in the clinical case, proposing that not only did language and sensory motor functions have specific locations where they were managed in the brain, but so did morality. And the editors of the time decided in their infinite wisdom that that result should not be published without interpretation, because we all know that morality is a purview of God, certainly not the purview of the brain. But even that attitude has markedly evolved today. And so I sort of present that to you as a contrast of the attitudes that we have today.

Mechanisms associated with functional specificity really depend upon neural activity being intimately coupled with blood flow. All of our neuroimaging techniques depend on that critical idea. Its origins or understanding came from clinical observations with Angelo Mosso, and then the theoretical models around that coupling were developed originally by Roy and Sherrington. Around the same time, Brodmann also made his seminal discoveries of the various cytoarchitectural areas of the brain, and showing that the multiple different regions of the brain were distinctive and associated with different functions of the brain.

The idea of functional specificity was taking another quantum leap with Penfield, who did his very, very precise intraoperative cortical stimulations—techniques that are used today actually—to map in the OR. His contributions really contributed a very, very fine structure to sensory and motor areas showing that dif-



ferent body parts were organized in a precise manner along the sensory motor strips. He did similar studies for the visual system, the auditory system, the olfactory system, memory systems, association areas, and so on. He received the Nobel Prize for those major advances in understanding functional specificity of the brain.

### **Chapter 3: Developments in Brain Imaging**

Around the same time, quite unrelated, it would seem that engineers and physicists were making the seminal observations that would lead to our current ability to image function in the brain. The first, most notable perhaps, is Rabi—get a little Columbia crown because magnetic resonance was discovered at Columbia around 1936. Pauling, at the same time, made a seemingly quite unrelated discovery that the magnetic state of hemoglobin changed with oxygen content, which is a very, very important principle that allows functional imaging today.

The development of imaging machines continued through the 1970s; most notably the first MRIs were built by Lauterbur and Manfield, supported very substantially by the work of Damadian who showed that biological tissues that are different have different relaxation rates, which is a fundamental idea for structural and functional imaging. And then based on the major engineering and physical advances, the first machine that was actually developed for clinical purposes from this set of discoveries was the PET [positron emission tomography] machine, and here you see it. Probably you got some of that history in the previous talk.

Neuroimaging actually started on PET machines. The first seminal study was done by Peterson, Fox, Posner, and Raichle at Wash U, and they simply had individuals in the camera generating verbs. And so they injected the heavy water, actually, to look at the emission of gamma rays, and they were able to identify increased blood flow to Wernicke's area and Broca's area during that process. This was their published version of the proof of principle, that one could image function in a normal human brain. At the same time MR had actually



reached the clinical service level, and in 1981 the first clinical scanner, 1.5 tesla, was installed by Sadat Hillel here in the Neurological Institute—so we get another Columbia crown, just a little advertisement. This was this scanner, and it sat in the scanner bay in Neurological Institute until just recently actually.

Functional imaging, which is the topic of my lecture today, brought it all together in about 1990, where the principle of blood flow into working brain, variation in brain tissue, and the change in magnetic properties of blood with increased oxygenation resulted in quite an accidental finding that led to functional imaging as we know it today. The observation was made by Seiji Ogawa at Bell Labs in 1990, which simply was he was imaging rats in the scanner and he made an accidental observation that the contrast of the MR signal in the occipital lobe of his rats when the lights were on was higher than when the lights were off. He reasoned from that observation that he was looking at the change in magnetic susceptibility that was due to the increased blood flow to the local active area. That hypothesis was tested later by Belliveau in humans at Harvard where he did a similar experiment where he alternated a flashing checkerboard—a very salient visual stimulus—with a rest period, observing activity in the human brain. This was an endogenous signal, it's not a very high resolution, and this really was the beginnings of functional magnetic resonance imaging, which enables us now to noninvasively, with high resolution techniques, observe function of the brain. So this really was the emergence from structural imaging of the brain to functional imaging of the brain.

The visual specificities that we knew existed could be readily replicated with functional imaging, and vision scientists and neuroscientists began applying this technique to repeat things that we knew so well. The first is retinotopic mapping, and you all know that the center of the visual field is represented in the posterior tip of the occipital lobe, and that as the visual field extends to the periphery, as you can see here with this expanding annulus, the activity associated with that stimulus is actually adjusted along the margins of the occipital lobe in a retinotopically organized manner. If one flashes a light on and off you can confirm with functional imaging that the responses to that light simply hug the calcarine sulcus. Again, another beautiful example of functional specificity, and of course the



lesion studies also, in this case a patient with homonymous quadrantanopia of the superior left hemisphere. You can see the field corresponding to the absence of activity in the right hemisphere of the occipital lobe. I want you to notice that I have switched from the normal radiologic convention which I use in almost all of my images to a neurological convention just for one slide, so left is left and right is right; and the reason for that is that this slide used to drive me nuts because of the dissonance between—you know how we all understand the projection fibers of the visual system, when you go from the visual field to the eye, then they cross, then they go over to the opposite side—this slide drove me nuts when that slide was reversed. And so for this one, this is physiologically correct.

Functional imaging is done in a very, very straightforward way. We have somebody in the scanner, in this case the task that is being done is a simple object naming task. And I want to illustrate for you how easy it is to map a human language system of the brain. So we put somebody in the scanner, this person is looking up through a slanted mirror on the head coil—in this case this suggests a back projection screen, although can present visual stimuli using goggles over the patient's eyes, or in a variety of different ways. The patient's task is during the imaging series to look alternately at the flashing checkerboard, which is the rest period, and these funny little pictures, and silently to himself name the picture. That's the task, simply look at the picture and name it. A task that simple will yield a map of the language system, the system map of that person, the individual person. You can see from the midsagittal view the location of the axial slice that I'm showing. The colored blobs indicate the activity that's associated with that task, and notice that we have rediscovered of course what Wernicke and Broca and Penfield and everybody told us before: that we've got over here on the left Broca's area; and you'll see Wernicke's area loud and clear there, and all of the visual system activity in the back of the brain; and the top the medial frontal gyrus, which is the motoric aspect of speech. On an individual patient in a very, very convenient manner—by convenient manner I mean each of these runs takes about 2 minutes and 24 seconds; I usually run it twice, so in 5 minutes asking somebody to do this naming task, we can do a complete map of the language system.



Now in basic science, of course, we are not interested just in the imaging of individual patients, as we are in clinical service, we're interested in what is conserved and generalizable across a population of patients. And so we have an additional tool that we use that allows us to essentially merge the brains together of a lot of different subjects that participate in experiments. If we didn't know the language system of the brain and wanted to understand it, we would do experiments; we'd run many, many subjects, as we did here in this case, and put all those brains on a standard coordinate stereotopic system, and look at what is generalizable across all of the subjects. You can see here I've taken the brain away just for convenience, but this is the two partitions, dorsal and ventral, of Broca's area, Wernicke's area, and medial frontal gyrus. This suggests a kind of formalism that actually extends the hypothesis of functional specificity from specific areas of the brain mediating complex functions, to specific functions of the brain that represent constellations of areas that work together in a coordinated manner to drive complex functions. Just for reference, we see here each of these areas has, of course, its conventional anatomical names: superior temporal gyrus, inferior frontal gyrus, medial frontal gyrus, and so on, with the popular name, Wernicke's area, Broca's area, and so on. Now we can also add an additional nomenclature, and that is the X, Y, and Z addresses of each of those areas. We could begin to think of these systems in terms of identifiable units, if you will, that have a group of coordinates.

#### **Chapter 4: Principles of Functional MRI**

I just want to review for a couple of minutes—and I know that most of you are probably very familiar with these ideas, but just to put us all on the same page—what the basic principles of functional MRI are, and how they relate to the basic principles of conventional MRI imaging in general. The next four slides are going to relate to these basic principles of where the signal comes from, and then I'll go on to the clinical applications.

This slide illustrates here the general time series of the task. Remember the slide showing the individual looking at the pictures. There is a time period of rest where just the crosshair is shown, a period of activity where the pictures are



shown and the patient is instructed to name the object, and then that goes away and there's another period of rest, and so on. These alternate for a couple of cycles. The origin of the blood oxygen level dependent signal, which is what BOLD stands for, comes from two factors, physiology and physics. The physiology is based on the coupling between neural activity and increased blood flow, and the fact that that increased blood, that new blood, that's flowing to the neurally active area is highly oxygenated. The physiological result is a pool of blood in which there is a reduction in the proportion of deoxyhemoglobin. On the physics side of the ledger, we all know that deoxyhemoglobin is paramagnetic, and anything that's paramagnetic distorts the signal, causing a signal loss. What's happening is that this increase in signal here is due to a reduction of paramagnetic effects of deoxyhemoglobin. Essentially we say less distortion of the magnetic field results in a local MR signal increase. This increase is about a 5% signal, so it's not a large signal but it's a very detectable signal using good signal enhancement techniques. So that's the basis of the BOLD signal.

Let me just remind you of some of the basic physics that lead to the conventional MR signal, and you could see how this fits on top of that. You all know that a conventional scanner simply aligns many of the protons, a very large proportion of the protons, along a standard cardinal axis. That a radio frequency pulse is applied to those protons, and as such the protons then start to precess. As they precess, they're sort of knocked over at an angle, and as they start to wobble or precess, they actually emit a signal that is the MR signal. We add to that a nice little feature by putting a gradient on the magnetic field, so the magnetic field varies from 1.5 tesla and change plus, to 1.5 tesla and change minus, a small minus, and that gradient actually provides the basis for identifying where each of the MR signals originates from. You all know that as the protons return to their aligned state they emit a signal, and that signal is proportional to the field strength that they're in, and that identifies actually the location of each voxel of volume element in the field. So that's how we know how to reconstruct these beautiful images of the brain. There's a very sophisticated bookkeeping system that identifies where each voxel is from, and from that we can put together these beautiful images. Functional imaging adds really the fourth dimension (I'm showing this slide again) which is really the change of variation in the local magnetic



field properties; but it evaluates that over time, and so time is the additional factor that allows functional imaging, in addition to change in magnetic susceptibility.

## **Chapter 5: Brain Mapping for Surgical Planning**

Now I want to switch gears a little bit, and give you some examples of current ways in which functional magnetic resonance imaging actually is impacting standard of care in various clinical and medical specialties. The first I want to talk about is brain mapping for neurosurgical planning, and then I'm going to take the same ideas and discuss some recent developments using functional imaging to assess levels of awareness in disorders of consciousness, identification, localization of seizures, anxiety disorders—something sort of fun, just lying, because it's gotten so much press I'd like to show you a little bit about that—and alternate and atypical neurocircuitry generally from genetic or congenital conditions; and then if we have time a case study for neurosurgical planning.

Moving into functional imaging as it applies to neurosurgical planning, and we consider the problem that neurosurgeons have if a tumor has to be resected, and has to be resected in what our surgeons refer to as “high rent districts”; that is, areas that may be involved in critical functions such as language, sensory motor, and so on; it's very, very useful in protecting against morbidity to know exactly on an individual patient level where those functions might be located; and especially in the case of a space-occupying lesion these functions are often mislocated because they're simply pushed out of their expected positions because of the tumor. And so on an individual patient we can map these functions. This is sort of a funny little slide that shows a survey we did of 125 cases where we asked the surgeons about what the most feared morbidity was for those patients, and you can see language and sensory motor were by far the winners. We adapted a standard battery to map those functions in all cases of neurosurgical planning. The standard battery has four separate conditions. This battery takes about 20 minutes to implement, and we can map sensory motor functions using finger-thumb tapping and passive touching of the hand; and the hand of course varies depending on the hemisphere of interest for the surgery. We map the lan-



guage areas, both an active form, using the picture-naming that I showed you, and a passive form, just listening to words. And of course the freebie sensory systems that we get in doing that is the high level visual system, auditory, primary, and secondary. Then I use flashing checkerboards simultaneously with the sensory motor conditions to capture the low level visual systems. And so it's pretty much a total brain map, except what's omitted here are memory functions, and we have other maps special to do that. In a normal person the map would look something like this, where sensory and motor areas are mapped quite precisely with those tasks, language from the visual task; this is Broca's area, this is Wernicke's area, they're repeated really usually in the active and passive conditions, and then of course the visual system activities.

Now the reason I like to kind of start with these examples in this part of the talk is because I think that at least some of you may be asking how in the world do we know we get it right? You know, these pretty blobs can be created in lots of different algorithms, we all know that. When we go from images to computations there are a lot of assumptions that are made; so how do we know that we have it right, and how do we know that a surgeon could make decisions based on this? One of the differences in doing basic science and doing clinical applications is that in basic science we have the advantages of samples and groups and our error bars look at differences across individuals, and we mush it all together, and we can make inferences to a population from that. That's very, very different than doing mapping of this kind where the individual patient matters. We have the disadvantage of a small sample size, that is,  $N$  is only 1, and we're working in a zone of zero tolerance for error—that is, you've got one patient and you simply can't be wrong. And so setting the standards for that level of confidence is not an easy matter, and it's one that we and others that have done this type of work take extremely seriously. Validation techniques to confirm that our methods are working is extraordinarily important.

So early on, and we continue to do this on a regular basis, we confirm the functional maps, this is a sensory motor map here, using the conventional methods of somatosensory potentials. You all know what that is, a pulse is given to the median or the Alner nerve, and then we can read the electrical output on a strip



of electrodes at the side of the craniotomy. Similarly we use direct cortical stimulation, like the Penfield methods, to confirm that the functional map is concordant with these conventional results.

Of course there's surgical outcome as a method of after-the-fact confirming that you've done the right thing. This was a case of an 11-year-old child with a ganglioglioma located right at the central sulcus. In the conventional world at the time this was not considered operable, but with the additional information that this space-occupying lesion had just displaced the function motor and sensory regions, medially and posteriorly, this tumor could be resected safely. And indeed it was, and six months later we have a normal system again.

Similarly in the language system, this is the case of a very aggressive GBM [glioblastoma multiforme], but this patient gave us an opportunity to map the activity associated with Broca's area and confirming the location of Wernicke's area, displaced posteriorly by this lesion. In that case the intraoperative cortical stimulation of Broca's area, as indicated by the map, resulted in speech arrest, which is the cardinal hallmark of Broca's area; and similarly this area was confirmed as Wernicke's area, doing the same type of stimulation with the result of the paraphasic speech areas that are typical of Wernicke's aphasia. Similarly, postsurgery for language, we don't need to spend a lot more time on this.

I want to sort of extend this a little bit, that the mapping of sensory and motor functions is not just restricted to awake and behaving adults, but can be extended to infants and children as well by just adapting the techniques ever so slightly, so that in the case of a sedated patient all of the stimulations are completely passive. Notice with this little baby, these goggles—these are the Grass goggles that are used to just flash checkerboards through closed eyelids. One can observe a very active response in the occipital lobe of the visual cortex, if that is working. These big earphones illustrate the presentation of auditory stimuli. And for babies, what we do is we record the mother or the father or a salient adult speaking to the child, and just the narratives played to the child during the functional imaging sequence are sufficient to activate language areas in very young children actually; in this case a pre-verbal child, confirming happily in this case



that the Broca's area was developing on the right side of the brain, far away from this aggressive PNET [primitive neuroectodermal tumor] here, which was resected with very wide margins. The child is still alive and well today without a return of that tumor, which is very nice.

One of the really exciting accomplishments of this last year is that functional imaging for neurosurgical planning has been approved with three CPT [current procedural terminology] codes. The editorial board for the AMIA [American Medical Informatics Association] for CPT codes approved them in November. They are going through all of the bookkeeping that they have to go through to decide what the reimbursement will be. But they are expected to be usable in January 2007. So the first code—well there are three codes here, one code for neurology and two for radiology, and they really vary in the extensiveness; it's just simple motor, sensory, language functions that can be done by standard procedures on scanners, when they're upgraded to do this, will have one code. A more complicated case of selecting a variety of tasks for evaluation, mostly for neurosurgical planning, has a different code. Similarly for the neurologist who is administering more complex behavior tasks. So these three codes will be available for reimbursement. Now patients that come for this mapping either pay for this themselves or they are entered on some kind of a research protocol that provides this. I'm not going to go over the vignettes just because I don't have time. But all of the vignettes, if any of you have been involved in the development of CPT codes, just simply describe the types of clinical cases for which they would apply. If any of you are interested specifically in that, talk to me about it afterwards. This is just to illustrate that this is a technique that I think that, just based by the number of cases, requisitions that we get every year, you can expect this to enter the mainstream of clinical care at a very rapid rate.

## **Chapter 6: Assessment of Consciousness with fMRI**

I want to switch gears and talk to you about another application of functional MRI, answering a very important clinical question having to do with the assessment of awareness and consciousness, or perhaps a probability of emergence of patients that are in an altered state of consciousness. And the importance of this



question I think is illustrated again by the most unfortunate events of last year, of Terry Schiavo when her clinical status was very much a political controversy; and then the more recent events of the Sago mine accident where Randall McCloy, who now I understand is emerging and talking; we still don't know quite what his status is, but the question for a long time as he was in an altered state of consciousness—would he emerge and what would his function be? The truth of the matter is the standard of care is we simply don't know because we have very little information about how to make these predictions and how to make these assessments. And so functional imaging we think can make some contribution to that question, and I'm going to show you how in just a moment.

Just to remind you, a minimally conscious state is a state that's metaphorically illustrated here by this lifeline that just sort of crosses, barely crosses, the threshold here between the underwater part of consciousness and the above threshold consciousness, if you will—where a patient on an inconsistent basis, perhaps unreliably but occasionally, demonstrates a volitional response to a command. So while most of the time the patient is unresponsive, occasionally will respond if you say something like "Reach for this glass of water" or "Tell me what your name is" and once in a while a response will emerge. This is an official category now in neurology that was actually made official a couple of years ago, and there are approximately 300,000 people in the United States today with the diagnosis of minimally conscious.

If the coma state is somebody who does not have awake cycles you can imagine his lifeline way down here. And the persistent vegetative state is somebody who remains unaware but does have wake and sleep cycles. The minimally conscious state is the highest state of functioning in the disorders of consciousness, [in] at least those three. In the case of minimally conscious patients we ask the question, "What levels of awareness might we expect from them?" If we could image their brains using passive stimulation, as we have with our sedated children, in mapping. We do the usual language system maps, and here is a group map showing if somebody is just listening to a narrative; this is the Wernicke's area, some of Broca's area, this is a group of ten people, I guess. This is a healthy volunteer that's listening to a narrative. It turns out this is the same nar-



rative that the minimally conscious patient was listening to, and you see exactly what we expect of a normally conscious individual—Wernicke’s area, Broca’s area—on this one salient slice.

Minimally conscious patient. This was a policeman who was in a car accident here in New York, had been minimally conscious for approximately five years, listening to a narrative of his sister saying to him, “Remember when you were the best man at my wedding? Do you remember when we were kids?” and so on. And you see the incredible activity [in] Wernicke’s area, visual system activity as if he was remembering perhaps. Other slices show more active areas and Broca’s area. There is no way, based on these maps of this patient and others—we’ve done approximately 20 patients now—to distinguish from these functional studies the minimally conscious patient from the normal patient in some cases. Sometimes these patients have emerged and some have not.

We have taken this a little bit farther, and of course we’re very interested in using functional MRI, one to assess the potential for emergence, and one to understand a little bit more about levels of awareness in these conditions. One of the differences that we have seen in many of these patients is that when we compare (the black line here are the normals) and when we compare the response of a patient—this is just representing two patients here that are quite different from each other, the patient to—this is just volume of brain activity, a patient responding to the forward speech, looking very much like the normal. This is a very usual result. Once in a while we have a patient who is very different in all respects, and we assume that that patient has a much reduced level of awareness. So in the case where the forward speech is approximately the same for the normal and the MCS patient, we have looked at the responsiveness to the reverse speech.

Now if we compare responses to speech going forward and speech going backwards, we should have some internal control of how much the brain is responding to the content of the language. If you listen to speech played backwards you know perfectly well that it’s speech, you can probably even identify the speaker, but you do not know what is being said, it sounds like a foreign language that



you don't know. So when we compare the brain images to forward speech and backward speech we have a way of assessing the neurophysiology that's associated with the understanding of the language. In many of these minimally conscious patients when we do that, [we] see a marked difference from the normal. In this case we see an example of the normal listening to backward speech, and notice it's about the same as forward speech, note the exact areas are different, but the brain resources devoted to this task are about equal. It is as if the normal brain works really hard to understand it, because you know it's speech, you even know who the speaker is, and you're just trying to figure it out, so there's a lot of resources devoted to it.

In the case of the minimally conscious patient, oftentimes we see much less in terms of resources devoted to these ambiguous stimuli, and so it's led us to investigate in a more systematic way, what we call top-down models of consciousness, where it seems that the stimulus has to make sense, and there's a gateway almost to disambiguating these complex and difficult stimuli. This is ongoing research that goes beyond what I want to talk about in this lecture, but the point that I want to leave you with is that there are ways using functional magnetic resonance imaging to provide a voice to patients who are nonresponsive, and that voice may give us some information about their level of awareness and their, perhaps, potential for emergence. That statement is very much under active investigation by us and others, and hopefully in another year or a couple of years when I give this lecture I'll be able to provide more information on that.

## **Chapter 7: Brain Mapping of Seizures with EEG**

Third item. Mapping for identification of location of seizuregenic brain. This is kind of cool, and we have just developed techniques to use the EEG, electroencephalography, in the scanner while we're doing mapping. This is a major, major engineering feat. And so I'm sort of bragging a little bit today, we've just done this, and it's just a real accomplishment for us and I just want to share with you some of the potential for clinical applications here. This is a seizure actually going on now, and this timeline showing the result from the electrodes. The red



is the seizuregenic brain and the blue is the contralateral side of the brain. In a few moments you will see that this settles down and goes back to the normal quiet lines. This was done simultaneously in the scanner with the mapping which happened just slightly before this. The patient went in with the electrodes. I was able to do the mapping of the language areas and then conveniently, almost like on schedule, she had this seizure. This doesn't really happen in your life. Now look, see the seizure's over, pretty much over, still a little bit of movement. But the first thing that we were doing of course is mapping, just straightforward mapping, language areas on a patient that had intractable seizures secondary to a stroke that had affected the left inferior frontal gyrus, as you can see here, actually extending superiorally. And so she was right-handed, and the question is, is she left side dominant for language? In thinking about a surgical therapeutic for her to relieve her of the seizures—where was the language? Well, we see that much of the language activity is observed over here on the right, particularly in the frontal areas and Broca's area. I'm still quite concerned that here on the left Wernicke's area, although there's considerable activity here, that this still might be representing the essential language areas. But anyway, this is the map of her language areas, and at the same time we got a map of the seizure going on.

So where is this seizuregenic brain that's causing these electrodes to indicate the presence of electrical activity. This is not the patient, these are guys in my lab—this is actually currently a medical student here at Columbia—and this is just an illustration of putting electrodes on before they go in the scanner, so these are just conventional EEG electrodes that go in the scanner with the patient being mapped. These are cuts from the seizure map. I just picked five electrodes that were active. These are, as I said, the opposite side of the brain, and the two red ones are the ones that are giving us the story, although there were many electrodes that happened. Early time, nothing's going on, seizure captured here, and then the seizure was quiet. From that information I knew exactly when the seizure occurred, because I had it on the EEG, and so then I could write a computer algorithm that would identify the location of activity at that time. Knowing the time allowed us to identify exactly where it was occurring. One this slide you see just a few slices going from ventral to dorsal, and the next slide I take it all the way to the top of the brain. So here, slice by slice, and these



are time intervals every 10 minutes; note, seizure starts here, time 0; and then continues, time 2; extends, time 3; all the way through the brain, time 4; it's extending, crossing the hemisphere, time 5; and as we go up through the brain you see the same thing. This is either a little bit of stealing of blood, or a little bit of movement that I can't align out of this. But you see the top of the brain, the extension, the growth of this activity associated with the seizure.

In time, we've taken 9 slices here and you could watch the seizure progress. The beginning of the movie here, now watch it's starting here on the left, starting and growing, expanding. The duration of this seizure was approximately one minute. It's kind of cool, huh? We'll develop this more. This was our first observation, the first time we were able to do this, and it was about three weeks ago. And since this time this patient has been implanted with electrodes to actually do these types of measurements by the conventional way, and then surgery will be evaluated. This is very much in real time, but I just wanted to share this with you. In another year we'll have this developed a lot better, but I think there's real promise here for interesting future directions.

From an individual voxel point of view, this is an example of the BOLD [blood oxygenation level dependent] signal. This is a five minute time frame here, that the BOLD signal is doing nothing, this is just normal variation, and then it reaches the point in this time period where the BOLD signal is rising and becoming very, very variable, and then back to normal. This of course is the BOLD signature of the seizure occurring. At the same time this is the EEG, the TP7 electrode that is just about over exactly the location, the X-Y coordinate, of that voxel. And you see the electrode. Note, this is kind of puzzling to us, that the electrical activity seems to be starting post the BOLD activity. It could be that the source of this is sufficiently internal—it's taking it that long to get to the surface electrode. That seems a little bit too long to me for that to be happening, so there may be some interesting physiology there, so stay tuned.

## Chapter 8: Neurocircuitry of Fear Circuits

I want to just leave you with some fun things that are going on with functional



imaging. The neurocircuitry that's associated with fear circuits, for example, are readily available and can be used in assessing anxiety states, and so on. I wanted to just give you an idea of what we do to scare the wham out of our subjects. It's not quite that bad. The point is that we can look at neurocircuitry associated with unconscious stimulation, such as fear. And in the case of this, we use actually fearful faces, and fearful faces can be presented either explicitly, as they are here, or they can be presented in a backwardly masked format so that the fearful face is not perceived but is effective. We know that it's effective because of the increase in reaction time to respond to some nonrelated task. In doing studies like this we've been able to identify partitions in the amygdala, which is the primary component of fear circuitry, that respond to the unconscious presentation of the fearful face; and the conscious, so we're able to partition the amygdala with respect to the neurocircuitry associated with these fearful stimuli, and show that the area of response to the backwardly masked or the nonperceived or unconscious stimulation actually corresponds to individuals' trait anxiety level. We can show differences in individuals' trait with respect to how modulated activity in the amygdala is in response to these fearful faces. We think that this is a very fundamental entry level to the anxiety and fear system, and we're of course looking at this in a very active way, in clinical states with general anxiety disorder, phobia, and other types of anxiety-related conditions. Don't ever tell a lie—brain can detect it. That's the bottom line.

Neurocircuitry associated; I think this is a very important clinical application, I think that in the future, functional imaging will be used quite readily to diagnose conditions such as dyslexia. You all know that the Shaywitz's study showing that a normal person processing words uses most of the posterior aspect of the brain, but a dyslexic tends to rely on the more frontal parts of the brain. This is just a little replication that one of my students and I did doing exactly the same thing. Dyslexic subjects, 20 of them actually here, use the frontal part of the brain to process words, where the normals use the back part of the brain. Simple task could be used in diagnostic purposes for dyslexia and other congenital disorders such as, hopefully, autism and other conditions.

I'll finish on time. Any of you guys want to stick around for more I'll be happy to talk with you. Thank you.