SPECIAL TUTORIAL

Principles of Functional Magnetic Resonance Imaging: Application to Auditory Neuroscience

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Abstract

Functional imaging based on magnetic resonance methods is a new research frontier for exploring a wide range of central nervous system (CNS) functions, including information processing in sensory, motor, cognitive, and linguistic systems. Being able to localize and study human brain function in vivo, in relatively high resolution and in a noninvasive manner, makes this a technique of unparalleled importance. In order to appreciate and fully understand this area of investigation, a tutorial covering basic aspects of this methodology is presented. We introduce functional magnetic resonance imaging (fMRI) by providing an overview of the studies of different sensory systems in response to modality-specific stimuli, followed by an outline of other areas that have potential clinical relevance to the medical, cognitive, and communicative sciences. The discussion then focuses on the basic principles of magnetic resonance methods including magnetic resonance imaging, MR spectroscopy, fMRI, and the potential role that MR technology may play in understanding a wide range of auditory functions within the CNS, including tinnitus-related activity. Because the content of the material found herein might be unfamiliar to some, we provide a broad range of background and review articles to serve as a technical resource.

Key Words: Auditory system, functional magnetic resonance imaging, hearing, magnetic resonance spectroscopy, perception, phantom perception, tinnitus

Abbreviations: AL = anterior lateral, BOLD = blood oxygen level dependent, Cho = choline, CL = caudal lateral, CNS = central nervous system, CR = creatine, EEG = electroencephalography, EPI = echo planar imaging, ER = event related, ETS = echo-time shifting, fMRI = functional magnetic resonance imaging, FOV = field of view, G = Gauss, GET = gaze-evoked tinnitus, GRE = gradient-recalled echo, MEG = magnetoencephalography, ml = myo-inositol, ML = medial lateral, MRI = magnetic resonance imaging, MRS = magnetic resonance spectroscopy, NAA = N-acetylaspartate, NMR = nuclear magnetic resonance, PET = positron emission tomography, PRESTO = principles of echo shifting with a train of observations, RF = radio frequency, ROI = regions of interest, SE = spin echo, STEAM = short-TE stimulated echo acquisition mode, T = Tesla, TE = echo time, TR = repetition time

Within the last decade, major strides have been made in understanding various forms of information processing in vivo in the human brain. Advancements in this area have been due in large part to the rapid growth of functional magnetic resonance imaging (fMRI), which evaluates spatially sensitive hemodynamic changes in the central nervous system (CNS) in response to physiologic activations (for general reviews see Shulman et al, 1993; Cohen and Bookheimer, 1994; Ellerman et al, 1994; LeBihan and Karni, 1995; Cohen, 1996; Moseley et al, 1996; Bandettini and Wong, 1997; Kim and Ugurbil, 1997; Forster et al, 1998; Ogawa et al, 1998; Turner et al, 1998; Howseman and Bowtell, 1999). The
temporal and spatial coupling between hemodynamic events (blood flow and metabolism) and synaptic activation links these two processes together and sets the stage for a discussion of functional imaging methods. Figure 1 provides a schematic diagram that compares fMRI with other experimental procedures used to study brain function in the context of their spatiotemporal properties and the degree of invasiveness of the procedures. The benefits of using fMRI in the study of human neurofunction are grounded on the facts that it is noninvasive, does not require exposure to ionizing radiation or radiopharmaceuticals, has good temporal and spatial resolution, is well suited for single-subject repeated-measurement designs, and the results can be superimposed on the individual's own brain structure (MRI) without the need for image transformation or warping (Moonen et al, 1990; Cohen and Bookheimer, 1994; Toga and Mazziotta, 1996; Frackowiak et al, 1997). In the domain of information processing, studies using fMRI have successfully investigated visual (Blamire et al, 1992; Menon et al, 1993; Serano et al, 1995; Fransson et al, 1998), auditory (Melcher et al, 1999a), vestibular (Bucher et al, 1998; Lobel et al, 1998), olfactory (Koizuka et al, 1994; Levy et al, 1997; Sobel et al, 2000), gustatory (Faurion et al, 1998), motor (van Gelderen et al, 1995; Rao et al, 1996; Mattay and Weinberger, 1999), and cognitive/linguistic systems (Binder, 1997, 1999; Bullmore et al, 1996). Moreover, as basic science studies continue to explore new areas, clinical-research applications are also being realized. Most prominent in this area is the role that functional imaging may play in planning neurosurgical procedures (Holodny et al, 1999; Lee, 1999), particularly as image-guided technology is being applied with greater frequency in the operating room (Grimson et al, 1999). In this context, fMRI has the potential to replace more invasive procedures (i.e., the Wada test) for establishing the language-dominant hemisphere, in helping to determine whether language is bilaterally represented and/or whether language dominance is atypical (Binder et al, 1995a, b; Cuenod et al, 1995; Desmond et al, 1995; Shaywitz et al, 1995; Benson et al, 1996, 1999; Binder, 1997; Gaillard et al, 1997; Baciu et al, 1999; Frost et al, 1999; Lee et al, 1999; Springer et al, 1999). Evidence is also accumulating that suggests that good concordance exists between fMRI maps of language function and those obtained by more direct cortical stimulation methods in individuals with CNS lesions (Schlosser et al, 1999). When used alone or in combination with magnetic resonance spectroscopy (MRS), magnetoencephalography (MEG), and/or electroencephalography (EEG), fMRI can also provide spatially localizing information about seizure foci in epilepsy (Jackson et al, 1994; Morris et al, 1994; Detre et al, 1995; Warrach et al, 1996). If surgery becomes nec-
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necessary for seizure control, and/or in cases when operable CNS lesions (tumors, arteriovenous malformations, etc.) are in or adjacent to sensory, motor, and/or language areas of the brain, then delineating diseased from normal tissue takes on additional significance for reducing morbidity and improving quality of life after surgery (Fried et al, 1995; Latchaw et al, 1995; Atlas et al, 1996; Bookheimer, 1996; Maldjian et al, 1996; Righini et al, 1996; Achten et al, 1999).

Other clinical areas where fMRI can play an important role include the study of neurodegenerative disease (Moseley et al, 1996), headache (Cao et al, 1999b), in evaluating brain activation patterns in individuals with implanted sensory devices (cochlear implants) (Eddington et al, 1999; Melcher et al, 1999a; Truy, 1999), or from electrical stimulation in the ear canal (Hofman et al, 1999); the study of the neurobiology of various learning disabilities, such as dyslexia (Richardson et al, 1997; Eden and Zeffiro, 1998; Shaywitz et al, 1998; Richards et al, 1999), where standard imaging procedures have not been conclusive in identifying abnormalities (Beaton, 1997); and the study of plasticity and procedural learning in normals and in instances of CNS reorganization secondary to physical injury, surgery, or as a result of intrinsic neurologic insult such as stroke (Karni et al, 1995; Krings et al, 1997; Graveline et al, 1998; Rossini et al, 1998; Toni et al, 1998; Cao et al, 1999; Thulborn et al, 1999).

Thus, in a relatively short period of time, fMRI research has provided insight into sensory, motor, and cognitive/linguistic processing systems and is evolving in a variety of areas that have potential clinical value. This paper reviews the underlying physics and pertinent technical considerations necessary for understanding research in this area and focuses on the imaging of auditory-related activity using MRI, fMRI, and MRS. Whereas the majority of studies to date have focused on auditory system activation secondary to the use of external stimuli (tones, music, speech, etc.), this is not the only application for this technology. A challenging but less straightforward area of investigation concerns the use of functional imaging methods in the study of phantom perceptions like tinnitus and/or other perceptual experiences that occur in the absence of overt (external) sensory stimulation (hallucinations [auditory and visual], pain, synesthesias, mental imagery, etc.) (Cacace, 1999). To date, the exciting area of fMRI research has had an impact on theoretical, experimental, and clinical issues and is poised to play an important role in auditory neuroscience research.

MAGNETIC RESONANCE

Background and Historical Perspective

In the mid 1940s, two independent research groups, one at Harvard (Purcell et al, 1946) and the other at Stanford University (Bloch et al, 1946) demonstrated that nuclear magnetic resonance transitions between two different spin states of an atom could be experimentally measured. This hallmark discovery earned Purcell and Bloch Nobel prizes in chemistry and set the stage for future developments in MRS and MRI. Prior to 1983, the scientific designation of the Bloch/Purcell discovery was termed "nuclear magnetic resonance" (NMR). However, the commercial manufacturing of whole-body NMR imaging systems in the early 1980s brought about the removal of the letter "N" for marketing reasons. The less accurate but more common uses of MRI and MRS were subsequently codified in late 1983 by the American Journal of Roentgenology.

The initial application of MR was in the field of chemistry, where MRS was used to study the underlying structure of composite materials and biologic tissues in vitro. However, it would take another 30 years of refinements in various scientific disciplines to reach the current state of MR where in vivo spatial imaging applications are possible. Critical in this evolution were notable advancements in the areas of superconducting materials, affordable computers, and mathematics. The mathematical component led to the development of the projection reconstruction method of image formation (Lauterbur, 1973). Image reconstruction based on the two-dimensional (2D) Fourier transformation method, which forms the basis for current techniques, was developed thereafter (Kumar et al, 1975). Of course, many other individuals made unique and fundamental contributions to MR development. A more complete biography of these individuals and their contributions can be found elsewhere (Mattson and Simon, 1996). Thus, with this brief historical overview as a background, we now consider basic principles of MR, since a working knowledge of this area is necessary to fully appreciate the current state of the art, where physiologic as well as exquisite neuroanatomic
information of the living human body and brain can be attained with available technology.

**Magnetic Resonance: Basic Principles**

From basic physics, it is well known that the nuclei of certain atoms, such as hydrogen and phosphorus, possess a spin and thus rotate about their own axis. Fundamental to this concept is the knowledge that a magnetic dipole moment is associated with this nuclear spin. In the presence of an external magnetic field ($B_o$), such as in the case of an individual placed within an MRI scanner, the hydrogen atoms from water molecules or other metabolites tend to become directionally polarized and align in the direction of the external magnetic field. This is analogous to the behavior of a compass needle in the earth's magnetic field, where magnetic moments may become aligned with the north or south poles of the magnet in either parallel or antiparallel directions. Since a lower amount of energy is associated with the parallel orientation, the number of magnetic moments in this direction slightly exceeds that of the antiparallel direction, resulting in a small net magnetization ($M$). This small net magnetization ($M$) is the source of the MR signal. The alignment of $M$ with $B_o$, however, is never complete, leaving room for $M$ to move around or precess about the external magnetic field $B_o$ like a gyroscope (Fig. 2), with a precession frequency that is dependent on the nucleus and strength of the magnet. The precession or Larmor frequency ($\omega$) is represented by the equation:

$$\omega = \gamma B_o$$  (Equation 1)

where $\gamma$, the gyromagnetic ratio, refers to the nucleus specific constant of proportionality. The gyromagnetic ratio for the hydrogen atom is $\gamma = 42.57$ kHz/Gauss (kHz/G). For many magnets in the clinical setting, $B_o = 1.5$ Tesla (T) ($1.5 \times 10^4$G), although even higher field strengths are desired for functional imaging applications (Kim et al, 1996). As a point of reference and for comparison with other magnetic phenomena, the average magnetic field strength at the surface of the earth is approximately 0.00005 T (0.5 G).

The near alignment of the magnetization with the external field (i.e., the longitudinal state), however, is not conducive to MR signal measurements. This results from the fact that when the magnetization is in the longitudinal direction, the area intercepted by the precessional motion is so narrow that the change of motion cannot be measured by the detection device (a receiver coil) used by the MR instrumentation. Thus, the detection of the MR signal requires that the magnetization be tilted or nutated away from the longitudinal axis. This is accomplished by the use of circularly polarized radio frequency (RF) pulses (henceforth referred to as $B_1$). RF pulses are applied orthogonal (per-

![Figure 2](image-url)  
**Figure 2**   
*Top,* An atom with nonzero nuclear spin is shown to precess (like a gyroscope) about an externally applied magnetic field ($B_o$). *Bottom,* The projection of the precession motion to a horizontal plane is represented as a rotating vector. The position of the vector at any point in time can be represented in terms of its phase (360° of total cyclic motion).

![Figure 3](image-url)  
**Figure 3**   
*A,* The motion of the tip of the magnetic moment in the presence of magnetic fields $B_x$ and $B_z$ as observed by a viewer at a distance. *B,* The motion of the same magnetic moment as observed by a viewer precessing about $B_z$ with the same precession frequency as that of the magnetic moment. In this rotating frame of reference, only the precession about $B_z$ is observed at a distance.
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Functional Magnetic Resonance Imaging

The essence of MRI is the spatial localization of the MR signal. This is achieved using the field dependence of the MR phenomenon, whereby...
In the presence of magnetic field gradients, the strength of the external magnetic field experienced by a spin depends on its location as illustrated for gradients in A, the x-direction; B, the y-direction; and C, the z-direction. Note that irrespective of the direction of the magnetic field gradient, the magnetic field is in the direction of the externally applied field $B_0$.

The signal is spatially localized to individual volume elements (voxels) within the field of view (FOV) or area of interest. Let us now consider how this might occur. If we assume that each voxel is associated with a slightly different precession frequency, and if as many signal values as there are voxels could be recorded (although the recorded signals would be from the entire volume and not from individual voxels), then it would be possible to determine the signal associated with each voxel. The precession frequency of each voxel is altered through the application of magnetic field gradients (i.e., spatial variations of an external magnetic field). As depicted in Figure 5, the net magnetic field is different at each voxel depending on the direction of the gradient. The signal is recorded following a delay (echo time $T_E$) subsequent to the application of the RF pulse in the presence of a gradient applied along one of the directions, commonly referred to as the readout or frequency-encoding direction. In the direction perpendicular to the readout, the so-called phase encoding direction, a unique frequency is assigned to voxels by applying a gradient, this time prior to recording the signal. The time elapsed between two consecutive RF pulses is known as the repetition time (TR). One can think of voxel localization as analogous to the organization of an organ or piano keyboard, where each key is associated with a unique frequency (a musical note). Likewise, a different precessional frequency is associated with each voxel.

In summary, the spatial localization of the MR signal is accomplished by using pulse sequences, which prescribe the currents to be applied for the $B_1$ field, the slice selection, readout, and phase encoding gradients (Fig. 6). When a gradient is present, the precession frequency of the spins is different at each voxel and thus spatial localization becomes possible. The number of applied gradients equals the number of voxels in one of the directions of the imaging plane, known as the phase encoding direction. For each phase encoding gradient, the signal is then recorded multiple times in the presence of a perpendicularly applied gradient in the readout direction.

With conventional MRI techniques, when the magnetization is tilted into the transverse plane prior to each phase encoding, the acquisition time is directly proportional to the number of phase encodings. In fMRI applications, where temporal resolution (i.e., the necessity for rapid and repeated sampling of the hemodynamic response of the brain) is an important consideration, the choice of the pulse sequence becomes crucial.

As we will emphasize in subsequent sections, whether one is detecting hydrogen atoms from water molecules (MRI) or biochemical compounds in the body (MRS), spatial localization is achieved through magnetic field gradients. The difference between the two applications is in the timing of the applied gradients. MRI uses gradients during the readout or acquisition portion of the pulse sequence to enable spatial localization, whereas in MRS, no gradients are applied during acquisition to preserve frequency information (i.e., chemical-shift resolution).

Different MRI Techniques

MRI techniques, alternatively referred to as pulse sequences, are distinguished primarily by their transverse magnetization refocusing
approach (i.e., restoration of phase coherence by application of magnetic gradients or RF pulses), their k-space coverage design, and echo-shifting properties. In any discussion of MRI, however, it is important to consider the concept of k-space. K-space is a mathematical construct used to characterize the spatial properties of an image in two dimensions. It is derived by regrouping the variables in the mathematical formula for the Fourier transformation (Bradley et al, 1999) and where the x-y coordinates are expressed in units of phase. The underlying premise of Fourier analysis is that any complex signal can be broken down into their respective component frequencies (sine waves). In MRI, since sine waves are used to characterize an object in the x-y plane, the axes have units of spatial frequency (cycles per millimeter) rather than units of temporal frequency (cycles per second). In the domain of spatial frequency representation, low spatial frequencies describe the bulk of the image, whereas high spatial frequencies fill in the details. Figure 7 depicts a rectangular grid in k-space, which is a prerequisite for 2D Fourier transformation (Bracewell, 1986). The signal recorded at each k-space point has information pertaining to the entire image. The center of k-space gives information about the average gray scale level of the image. Points that are off from the center by one provide information about very large structures that can be modeled by one sinusoid across the image. Similarly, k-space points that are off from the center by two are for structures that can be modeled by two periods of the sinusoid across the image. To be accurate, no structure can be modeled by just one sinusoid; thus, a weighted combination of many sinusoids is required. In terms of the imaging pulse sequence, with each application of the phase encoding gradient, the position in k-space moves up by one line. At a particular k_y location, the signal along k_x is recorded in the presence of the readout gradient. The distance traversed in k-space is, in fact, angular distance, which is equivalent to the phase that the spin acquires while precessing about B_0. Thus, depending on the phase accumulated, it is possible to have trajectories in k-space that do not conform to a rectangular grid, as is the case for spiral imaging.

In such cases, the acquisition points are regridded onto rectangular coordinates (Jackson et al, 1991) to benefit from the convenience of the Fourier transform.

In this section, to orient the reader to pulse sequence terminology and protocols, examples of some common imaging techniques based on rectangular k-space trajectories are briefly discussed and compared with respect to functional imaging applications. They include spin echo (SE), gradient-recalled echo (GRE), echo planar imaging (EPI), and principles of echo-shifting using a train of observations (PRESTO). For auditory studies, an additional technical variant to enhance signal recovery during subcortical processing has been used, so-called cardiac gating. Initially applied in the mid-1960s by investigators in nuclear medicine to study images of the beating (moving) heart in vivo (Pickens, 1988), the use of cardiac gating to the field of functional imaging has expanded research opportunities for auditory investigations (Guimaraes et al, 1998). Thus, as we proceed through the next sections, it should become evident that the MR physicists and engineers have been very creative in developing the pulse sequences and the analysis techniques necessary to enhance various applications, taking into consideration the limitations imposed by available hardware and complexities involved in studying the human brain in vivo.

\footnote{Note that in k-space, although one of the axes is referred to as phase encoding and the other as frequency encoding, both axes represent units of phase (e.g., as spins move around at a certain speed [angular frequency], they traverse a certain angular distance [phase]).}
SPIN ECHO

GRADIENT ECHO (No 180°)

Figure 8 The GRE and SE pulse sequences can be differentiated based on their method of refocusing. The SE pulse sequence employs a 180° pulse for refocusing, whereas the GRE pulse sequence employs gradients to reverse the movement of the spins in order to bring them into phase with each other.

CONVENTIONAL TECHNIQUES

Spin Echo and Gradient-Recalled Echo

In conventional techniques, a single line of k-space is acquired for each application of the RF pulse. Thus, during each TR, one readout line is recorded. At times coincident to TE, there is complete refocusing along the readout and all recorded points fall along the ky axis of Figure 7. The beginning and end of a k-space line correspond in turn to negative and positive accruals of phase, respectively. Movement in the kx direction (i.e., recording of successive horizontal lines) is accomplished through the application of phase encoding gradients with gradient magnitudes augmented for successive TRs.

The SE and GRE techniques constitute different examples of conventional methods. In SE imaging, nuclear spins that are dephased in the transverse plane are refocused by a 180° pulse (Hahn, 1950), which flips the spins about the axis along which it is applied, as depicted in Figure 8. Identical timing between 90° to 180° and 180° to TE periods ensures that the spins travel the same angular distance during these two periods, enabling complete refocusing. In GRE, a single k-space line is acquired per RF pulse and no 180° pulses are applied. Consequently, both the TR and the overall acquisition times are considerably shorter due to the partial nutation or tilt into the transverse plane and rapid refocusing (Frahm et al, 1986). Initially, spins precess in the reverse direction in GRE under the influence of a negative gradient and are subsequently refocused during the readout period (see Fig. 8). This is in contrast to SE, in which spins maintain the same precession direction. Although GRE refocuses only the effects of externally applied gradients, SE can also refocus the effects of static field inhomogeneities, which act similarly to low-amplitude positive gradients. As a result, with SE, \( T2^* = T2 \), since \( T2^* \) inhomogeneity effects are compensated for, whereas in GRE, \( T2^* \) has contributions from both \( T2 \) and \( T2^* \) (Equation 2). In fMRI applications, temporal resolution considerations make the conventional implementation of the SE pulse sequence unfavorable. However, variants of SE, alternately referred to as rapid acquisition with relaxation enhancement (RARE) (Hennig et al, 1986) or fast spin echo, which phase encode multiple echoes per RF pulse, have been used in fMRI (Constable et al, 1994). The SE pulse sequence can also be used in fMRI when incorporated into faster imaging techniques such as EPI.

ECHO PLANAR IMAGING

In single-shot EPI, the entire k-space is acquired after a single application of the RF pulse (Mansfield, 1977), considerably curtailing image acquisition time. To complete the acquisition prior to signal decay, fewer phase encodings and readout points are recorded at a higher sampling rate. Consequently, spatial resolution is worse (2–4 mm in EPI vs ~1 mm for conventional imaging), and the images are noisier due to the increased bandwidth resulting from higher sampling rates. Nevertheless, despite the artifacts caused by \( T2^* \) decay (Farzaneh et al, 1990), the depiction of the brain is of sufficient quality to make EPI one of the more coveted sequences, primarily due to the increased temporal resolution (Bandettini et al, 1992; Blamire et al, 1992; Kwong et al, 1992b; Turner et al, 1993; Menon et al, 1995). Whereas a single GRE slice can be acquired in 3 to 4 sec, multiple EPI acquisitions can be completed in 1 sec. Different variations of EPI include the SE-EPI and the GRE-EPI, named after the method of preparation analogous to their conventional counterparts. Nonetheless, data acquisition is accomplished in a single shot. Multishot versions of EPI also exist whereby the image is acquired during the course of several RF pulses (McKinnon, 1993). The gain in spatial resolution provided with these sequences, however, is at the expense of a reduction in temporal resolution.

PRINCIPLES OF ECHO SHIFTING WITH A TRAIN OF OBSERVATIONS

Functional MRI has also been carried out in conjunction with three-dimensional (3D)
pulse sequences such as PRESTO, which improves the temporal resolution of the conventional GRE sequences while maintaining T2* sensitivity, specifically by introducing the echo-time shifting (ETS) concept (Moonen et al., 1992). With PRESTO, multiple k-space lines are acquired within a single repetition period (van Gelderen et al., 1995), and TE is extended using the principle of ETS. Thus, PRESTO can be viewed as a type of multishot EPI method (Moonen and van Gelderen, 1997). With ETS, the refocusing of the magnetization nutated into the transverse plane is deferred to a subsequent repetition cycle leading to TE > TR. In the great majority of sequences where TE < TR, extension of TE to maximize T2* sensitivity inevitably leads to an extension of TR as well, causing an increase in the overall acquisition time and loss of temporal resolution. With ETS, T2* sensitivity is obtained without a sacrifice in acquisition time. Volumetric acquisitions are rarely possible in conjunction with MRI due to lengthy acquisition times, yet they provide a special benefit in terms of minimizing arterial inflow effects (Duyn et al., 1994a). The PRESTO technique refocuses all residual gradients within each repetition cycle and regulates the timing of echoes through additional gradients to enable the use of volumetric acquisitions in conjunction with fMRI.

Magnetic Resonance Spectroscopy

Whereas in MRI, imaging hydrogen atoms from water molecules is of primary interest, MRS aims to detect metabolites in the millimolar range such as N-acetylaspartate (NAA), choline (Cho), creatine (Cr), myo-inositol (mI) and lactate, which can only be observed after water suppression. Being able to quantify metabolic information from MR technology is analogous to performing a noninvasive in vivo biopsy of body or brain tissue. The term neurospectroscopy, in particular, is synonymous with proton (1H) MRS and relates to the diagnosis made from MRS in evaluating the human brain. In this context, Danielsen and Ross (1999) consider two main aims for the clinical application of neurospectroscopy:

1. Clinically diagnostic in vivo biochemistry in patients (i.e., the ability to make relevant biochemical measurements directly, thereby influencing medical management either by diagnosis or by exclusion);
2. Defining new features in the pathophysiology of disease that will lead to:
   a. New therapies based on MRS results,
   b. Disease progression or therapeutic response monitoring by use of MRS,
   c. Refining disease prognosis by noninvasive MRS metabolic measurements in patients.

In the normal human brain, the 1H MR spectrum can be understood by the concept that each metabolite has a unique signature, and when added to other major metabolites, the combination results in a complex spectrum of overlapping peaks. Interpretation of MR spectra involves determining the presence of each cerebral metabolite and noting whether specific peaks are elevated, reduced, or unchanged in relation to a reference, usually Cr. In the evaluation of individuals within a clinical context, NAA is considered a marker of neuronal metabolic activity, Cho is considered a marker of overall cellular density, Cr is considered a marker of cellular energetics, and mI is considered a marker of glial cell compartments. In MRI,

![Figure 9 Magnetic resonance spectroscopy in white matter of the centrum semiovale showing metabolites (e.g., N-acetylaspartate [NAA], choline [Cho], creatine [Cr], glutamate/glutamine [Glu/Gln], myo-inositol [mI]). In this example, the short-TE stimulated echo acquisition mode (STEAM) pulse sequence was used.](image-url)
Table 1

<table>
<thead>
<tr>
<th>Metabolite (Normal Cerebral Concentration)</th>
<th>Increased</th>
<th>Decreased</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactate (Lac) (-1 mmol/L; not visible)</td>
<td>(Often) Hypoxia, anoxia, near drowning, stroke, hypoventilation, Canavan’s, Alexander’s, Hydrocephalus</td>
<td>(Unknown)</td>
</tr>
<tr>
<td>N-acetylaspartate (NAA) (5, 10, or 15 mmol/L)</td>
<td>(Rarely) Canavan’s</td>
<td>(Often) Developmental delay, infancy, hypoxia, anoxia, ischemia, intracranial hemorrhage, herpes II encephalitis, near drowning, hydrocephalus, Alexander’s, epilepsy, neoplasm, multiple sclerosis, stroke, diabetes mellitus, closed head trauma</td>
</tr>
<tr>
<td>Glutamate (Glu) and/or Glutamine (Gln) (Glu = ? 10 mmol/L; Gln = ? 5 mmol/L)</td>
<td>Chronic hepatic encephalopathy (HE), acute HE, hypoxia, near drowning</td>
<td>(Unknown) Possible Alzheimer’s disease</td>
</tr>
<tr>
<td>myo-Inositol (ml) (5 mmol/L)</td>
<td>Neonate, Alzheimer’s disease, diabetes mellitus, recovered hypoxia, hyperosmolar states</td>
<td>Chronic HE, stroke, tumor</td>
</tr>
<tr>
<td>Total creatine (Cr) (8 mmol/L)</td>
<td>Trauma, hyperosmolar increasing with age</td>
<td>Hypoxia, stroke, tumor, infant</td>
</tr>
<tr>
<td>Glucose (Glc) (-1 mmol/L)</td>
<td>Diabetes mellitus, parenteral feeding HE</td>
<td>Not detectable</td>
</tr>
<tr>
<td>Choline (Cho) (1.5 mmol/L)</td>
<td>Trauma, diabetes, white vs gray, neonates, after liver transplant, tumor chronic hypoxia, hyperosmolar, elderly normal (?Alzheimer’s disease)</td>
<td>Asymptomatic liver disease, HE, stroke, nonspecific dementias</td>
</tr>
<tr>
<td>Acetocacetate, acetone, ethanol, aromatic aminoacids, xenobiotics (propanediol, mannitol)</td>
<td>Detectable in specific settings</td>
<td>None</td>
</tr>
</tbody>
</table>

From Danielsen and Ross (1999).

whereas signal intensities are displayed in the form of an image, in MRS, signal intensities are more commonly expressed as a function of frequency (a spectrum) (Cousins, 1995).

An MRS spectrum represents a series of peaks along the x-axis labeled in parts per million (ppm) or Hertz (Hz) to refer to the precession frequency. For a proton $^1$H spectrum acquired at 1.5 T (63.5 MHz), 1 ppm corresponds to 63.5 MHz. The ppm scale provides an easy comparison of data obtained at different field strengths since, irrespective of the strength of the magnetic field, a substance with a resonance at a chemical shift of 2.0 ppm still resonates at 2.0 ppm at 0.5, 1.5, or 4.0 T. A typical $^1$H spectrum is displayed in Figure 9, obtained from white matter of the brain. Spectroscopic information can also be displayed in the form of an image, with each image representing a different metabolite. In this context, the post-processing involves integrating the area under the relevant resonance peak for each voxel to derive metabolite-specific information. In this format, different colors are used to represent the spatial distribution of a particular metabolite over regions of interest (ROI). When many spectra are simultaneously obtained, rendering such information into an image format is a succinct method of presentation.

Magnetic resonance spectroscopy is becoming an important adjunct to standard MRI in large part because diseased and pathologic
states have identifiable neurobiochemistries (see Table 1 for differential diagnostic uses). As a result, MRS is becoming routinely used for the clinical evaluation of primary CNS lesions, the evaluation of neurometabolic disorders, mitochondrial disorders (such as mitochondrial encephalomyopathic, lactic acidosis, and stroke-like episodes; MELAS), the localization/lateralization of epileptic foci, acquired immunodeficiency syndrome (AIDS) related brain disorders, Alzheimer's disease evaluation, brain injury from hypoxia, near-drowning episodes, evaluation of postsurgical and postradiation tumor beds, etc. (Cousins, 1996; Frahm and Hanefeld, 1997; Danielsen and Ross, 1999; Wilichowski et al, 1999).

Apart from its clinical value in assessing organic brain disorders, and given the robustness of these measures over time (Brooks et al, 1999; Hoshino et al, 1999), MRS has potential to play a role in understanding the neurochemical correlates of human development. Some important aspects of this area include providing a better understanding of individual differences in cognition and intelligence in normal brains (Hashimoto et al, 1995; Jung et al, 1999a, b) and in providing basic insights into the neurobiology of various learning disabilities such as dyslexia (Richardson et al, 1997; Rae et al, 1998; Richards et al, 1999). Moreover, studies characterizing neurobiochemical properties of cortical auditory structures of normal individuals and in individuals with sudden idiopathic hearing loss (Richards et al, 1997; Syka et al, 1998) have also been initiated.

FUNCTIONAL MAGNETIC RESONANCE IMAGING

A historical review of functional imaging (Raichle, 1998) reveals that changes in circulation related to mental activity were reported over 100 years ago in the late 19th century. Available techniques used for functional brain imaging are based on the elementary principle that neuronal activity requires energy and that increased energy demands, as reflected by local increases in blood flow and metabolism, can be visualized (see Magistretti and Pellerin [1999] for an overview of cerebral energy metabolism). However, it has been only with the advent of positron emission tomography (PET) in the 1970s that in vivo functional imaging experiments on humans have become possible (Phelps et al, 1981; Raichle et al, 1983). PET measurements reveal that changes in blood flow and glucose metabolism far exceed that of oxygen metabolism during brain activation (Fox and Raichle, 1986; Fox et al, 1988), leading to increased arteriovenous oxygenation levels. The increased oxygenation levels also form the basis of the blood oxygen level dependent (BOLD) contrast, commonly employed in fMRI studies. The BOLD effect was initially demonstrated in the laboratory setting on rats (Ogawa et al, 1990) and was subsequently applied to in vivo functional activation studies of the human brain (Kwong et al, 1992a; Ogawa et al, 1992). Other techniques based on external contrast agents (e.g., gadolinium diethylene-trimine-pentaacetic acid) have also been used in sensory activation studies to map the visual cortex by measuring changes in regional cerebral blood volume (Beliveau et al, 1991). However, in BOLD imaging, it is the paramagnetic deoxyhemoglobin of blood that serves as an intrinsic or endogenous contrast agent. Here, blood acts like an external T2 altering relaxation agent with the degree of paramagnetism determined by the oxygenation state imposed by the activation (Thulborn et al, 1982). In human investigations, fMRI studies based on BOLD contrast are preferred over those based on the use of exogenous contrast agents because the former are noninvasive and are not limited by temporal considerations. The rapid passage of the external contrast agent through the brain restricts the number of repetitive on/off stimulus cycles in a blocked-stimulus paradigm or the number of individual stimulus presentations in an event-related fMRI study. Note that blood flow can also serve as a T1 modulation mechanism due to the exchange of H2O across the blood-brain barrier during the traversal of blood through the capillaries (Detre et al, 1992; Williams et al, 1992):

\[
\frac{1}{T1'} = \frac{1}{T1} + \frac{\mu}{\lambda}
\]  
(Equation 3)

where \(\mu\) refers to flow, \(\lambda\) to the blood-brain partition coefficient, and \(T1'\) to the modulated longitudinal relaxation due to flow. However, note that for EPI sequences, T1 effects cannot play a substantial role, as the TRs are on the order of one second or more, leading to considerable longitudinal recovery of magnetization. In discussions pertaining to fMRI, BOLD effects refer to the prolongation of T2* due to flow-based oxygenation level increases, as opposed to flow effects, which cover the contribution of incoming fresh spins and T1 changes.
Blocked-Stimulus Presentation and Postprocessing

The goal of functional imaging is to localize within the brain activated regions that respond to a stimulus by developing techniques that are sensitive to external manifestations of neuronal changes. Briefly, fMRI studies begin with a localizing sequence, which is used to prescribe the slice or slices of interest in imaging applications and the ROI in spectroscopic applications. To date, by far the most common technique used for fMRI studies is based on the blocked-stimulus paradigm. With this technique, functional acquisitions are conducted in the presence of an intermittent external stimulus, where blocks of stimuli that represent activation or on states are alternately interleaved with rest or off states, where no stimulus is presented. For example, a motor paradigm can consist of alternating cycles of a finger opposition-tapping task with rest conditions. Finger tapping can be replaced by an illuminated reversing checkerboard pattern for a visual paradigm; by tones, speech, or music presentation for auditory paradigms; or by the presentation of special words or sentence structures for language or working-memory paradigms. Additional complexities can be imposed by adding various attentional demands or memory loads to underlying experiments, making the technique well suited for studying modality-specific and supramodal processes. Alternatively, stimuli may be generated internally, as in the case of tinnitus or other phantom perceptual events. Irrespective of the nature of stimulation, it is required that data be sorted with respect to the presentation paradigm and analyzed in order to isolate the activation response. Upon completion of the stimulus presentation and acquisition process, the functional data are registered to compensate for in-plane head motion and statistical tests are conducted to determine whether the data collected during the activation states are significantly different from those collected during the rest states. Although the type of statistical testing has been a topic of debate, various parametric and non-parametric techniques such as the t-test, z-score, correlation analyses, and Kolmogorov-Smirnov tests have all been applied (Bandettini et al, 1993; Cohen and Bookheimer, 1994; Friston et al, 1995a; Xiong et al, 1996; Kuppusamy et al, 1997; Rabe-Hesketh et al, 1997; Lange, 1999). For example, when the t-test is used in the blocked-stimulus paradigm, the average of the signal intensities recorded during the rest or off state is subtracted from the average signal intensity during the activation or on state and divided by the pooled variance, which is a measure of the extent of signal fluctuations. Results of statistical testing are then thresholded, color coded, coregistered, and subsequently superimposed onto the anatomic reference images to allow for interpretation and display. Figure 10 shows several fMRI activation patterns in striate cortex based on a blocked-stimulus paradigm. The purpose of this graph is to illustrate the effects of magnetic field strength on the detection of the BOLD fMRI response.

Functional activation can be further assessed by plotting the signal intensities over time (pixel values from consecutive images at a given activated voxel) to visualize the pattern of the time series during the on and off sequences. In cases where brain activation may not necessarily follow precise on-off patterns, more sophisticated techniques such as principal component analysis (Friston et al, 1995b), fuzzy clustering algorithms (Baumgartner et al, 1997), and independent component analysis may be more appropriate (Makeig et al, 1997).

Event-related fMRI

The alternative to the blocked-stimulus paradigm is the recent development of event-related fMRI (ER-fMRI), which can detect activation without the need for repetitive on-off cycles, thus allowing for more transient aspects of the hemodynamic response to be studied (Rosen et al, 1998; Buckner, 1998; Buckner and Braver, 1999). ER-fMRI refers to the detection of cortical activation from single or selectively averaged trials of a particular task (Buckner et al, 1996; Dale and Buckner, 1997) and has already been applied with success within the auditory modality (Hickok et al, 1997; Robson et al, 1998; Belin et al, 1999). There are several aspects of ER-fMRI that make it advantageous and in some instances preferable to the use of the blocked-stimulus paradigm, particularly in applications studying various cognitive processes. These advantages include the ability to randomize trial presentations, the flexibility of which allows for post hoc sorting of the stimulus response based on response time, type, or accuracy (Buckner and Braver, 1999), and the opportunity for testing the differences in the onset time of neural activity evoked by different trial types (D’Esposito et al, 1999). Other areas that are also being explored include the use of perfusion-based ER-fMRI (Liu and Gao, 1999).
where perfusion provides a more direct assessment of the BOLD hemodynamic response. ER-/fMRI approaches testing in a similar manner to that used with sensory or motor evoked potentials based on EEG or MEG, where single-trial presentation and signal averaging is used to improve signal-to-noise ratio. Thus, ER-/fMRI has additional value such that combined fMRI, EEG, or MEG studies can be compared under similar experimental conditions (Rosen et al., 1998; Buckner and Braver, 1999; Gevins et al., 1999; McCarthy, 1999).

In retrospect, it is understandable why the commonly used blocked-stimulus paradigm has come under criticism, particularly by those studying cognition (Rosen et al., 1998; D'Esposito et al., 1999). Consider, for example, that with such an approach, predicting the shape and/or time course of the fMRI response a priori can be difficult, particularly when studying isolated cognitive processes. Indeed, in these instances, if the activation response does not follow precise on-off sequences, then deterministic analysis methods that rely on such predictions may reach erroneous conclusions about underlying cognitive processes. In fact, these issues are not limited to cognitive paradigms, as nonstationary time series have also been discussed in the context of auditory-based sensory stimulation experiments (Gaschler-Markefski et al., 1997). Efforts to conceptualize these issues and optimize experimental fMRI studies are based on the recognition that different types of experiments may require different designs. Therefore, emphasis is placed on such important distinctions as stochastic (stationary or nonstationary) versus deterministic events (Friston et al., 1999). Another issue in this area concerns the linearity of the response. The BOLD response has been found to be approximately linear at the presentation rates commonly employed, justifying the selective averaging employed in ER-/fMRI (Rosen et al., 1998). Yet, it is difficult to analyze ER-/fMRI using statistical techniques that require exact knowledge of the response waveform because the peak response in ER-/fMRI is typically characterized by only a few points. Therefore, the analysis of variance method becomes particularly appropriate because assumptions about shape and time course of ER-/fMRI activation are not necessary (Clare et al., 1999). Clearly, as different experimental paradigms evolve to optimize fMRI activation, understanding the linkage between sensory stimulation, hemodynamic events, metabolism, and neuronal activity becomes crucial. With this in mind, we now focus on the underlying response of the
microvasculature to appreciate the strengths and limitations of these techniques.

**CAPILLARY CHARACTERIZATION**

The ultimate goal of any functional study is to identify the brain parenchymal contribution where neuronal activity resides. Thus, the capillaries and their surrounding gradients are of primary importance in fMRI. However, imaging of parenchyma as distinct from capillaries is not an attainable goal, given that the capillary diameter can be less than 5 μm (Fulton, 1955) and the MR pixel resolution is at best ~1 mm. Depending on the paradigm, the resolution can be even worse in fMRI by a factor of 3, due to temporal resolution trade-offs. Thus, the challenge is to restrict BOLD and flow-related effects to the capillary level. The so-called "brain versus vein" effects, referring to the capillary versus flow contribution, have been an ongoing concern within the fMRI community (Duyn et al, 1994b; Frahm et al, 1994). Arterial contributions are not a part of this discussion as they are an unlikely source of activation. Arteries are 95 percent oxygenated and do not allow exchange across the blood-brain barrier (Fulton, 1955); therefore, oxygenation level does not change with activation, making them immune to T2* and T1 effects, respectively. Neither are arterial inflow effects a consideration for long TR sequences, such as EPI, where there is total replenishment of flow within the slice. Arterial inflow effects become a concern with conventional GRE sequences depending on the TR, slice thickness, and magnitude of flow/velocity changes. Even gradient-recalled sequences become immune to arterial inflow effects when the nature of the analysis is 3D, as is the case for the PRESTO technique (van Gelderen et al, 1995).

The primary concern then becomes to differentiate the capillary contribution from those of larger veins. It has been shown that at the most commonly used field strength (1.5 T), the main contributors to activation are the larger veins. The microvasculature gains prominence only at the higher magnetic field strengths, that is, 4T (Menon et al, 1993). It is of interest to note that at higher field strengths, preceding the increase in signal enhancement, a short-lived signal decrease is observed (Ernst and Hennig, 1994; Menon et al, 1995). This initial dip, initially discovered by optical studies, is claimed to be more localized to the capillary activation sites (Malonek and Grinvald, 1996) and can also serve as a mechanism by which to differentiate capillaries from veins. However, at most clinical centers, higher magnetic field strengths are not available, making the choice of pulse sequence and the accompanying parameters important considerations (Kennan et al, 1994; Weisskoff et al, 1994). Another method of localizing capillary regions is by using the delay in the activation response. The response to activation is not instantaneous, and shorter delays are associated with the capillaries (4–8 sec) and longer delays with the larger veins (8–14 sec) (Lee et al, 1995). For example, one can sensitize GRE sequences to the microvasculature by lengthening the TE. The T2* weighting of GRE sequences is affected by the characteristic diffusion time (τr), which, in turn, is proportional to the square of the vessel radius. Vessels with τr < TE exhibit quadratic decay, whereas those with τr > TE exhibit linear decay (Yablonsky and Häacke, 1994). Thus, at short TEs, the capillary contribution decays more readily. By extending TE, a quadratic decay can be imposed on large vessels as well, making the relative capillary contribution more pronounced. In gradient-recalled acquisitions, ETS, as used in PRESTO, is one way of extending TE to increase contributions from the microvasculature.

**IMAGING AUDITORY PATHWAYS FROM COCHLEAR NUCLEUS TO CORTEX: USE OF EXOGENOUS STIMULI**

Studying auditory system activation using fMRI is an area that is in early stages of development. Melcher et al (1999a) have recently provided an overview of studies and discussion of pertinent issues that have arisen in studying this modality. Herein, our main intent is to illustrate by various examples the range of potential applications and methodology that may enhance signal recovery and help to formulate and test various hypotheses. Then, we will provide a contemporary update on imaging tinnitus-related activity with functional imaging methods.

**Analysis of Subcortical Processing**

Until recently, fMRI studies in the auditory modality have focused on activation patterns in auditory cortex and related areas. However, the work of Guimaraes et al (1998) demonstrated that major nuclei in subcortical auditory pathways can also be mapped with fMRI at a field strength of 1.5 T. The key to these initial studies was the application of cardiac gating, which
was used to synchronize fMRI data acquisition to a particular point on the cardiac cycle. Unique features of this technique were not limited to cardiac gating but also included fast EPI and a FOV, which was confined to a single slice of neuroanatomy. Combined, this approach serves to minimize brainstem motion secondary to vascular pulsation, reduces imager-related background acoustic noise, and, as a result, provides a means for acoustically driven activity in subcortical auditory nuclei to be reliably detected. Consequently, this important advancement now allows for all aspects of the auditory pathways to be investigated and sets the stage for studying a wide range of monaural and binaural subcortical auditory processes in both normal and pathologic populations, including tinnitus-related activity. Figure 11 compares the BOLD fMRI response to binaural acoustic stimulation with and without cardiac gating. From this example, it can be seen that the cardiac gating technique has its greatest influence in detecting activation patterns in subcortical (inferior colliculus) versus auditory cortical areas.

Analysis of Cortical Processing: Neuroanatomic Considerations

Before considering studies of auditory cortical activity, it is important to put these investigations within a contemporary neuroanatomic and physiologic frame of reference because as fMRI paradigms increase in complexity, data interpretation will be directly linked to our current knowledge base. The neuroanatomic organization of auditory cortical areas has been conceptualized within a framework consisting of primary core, belt, and parabelt areas. The core area on the superior temporal plane (including Heschl's gyrus) contains three cochleotopically organized fields that are highly responsive to pure-tone stimuli (Kaas et al, 1999). This core is surrounded by a belt of association areas, which, in turn, are surrounded by parabelt association areas, which extend to the lateral surface of the superior temporal gyrus. The anterior-lateral (AL), medial-lateral (ML), and caudal-lateral (CL) belt regions contain three mirror-image cochleotopic maps (Romanski et al, 1999b).
belt and parabelt zones also have regions that are distinct in terms of cytoarchitecture and connections (Hackett et al., 1999), and there is speculation and some support for the view that these auditory association areas may be specialized for processing more complex temporal and spatial stimulus features. Polysensory regions of the temporal, parietal, and frontal cortex also receive inputs from auditory cortex (Pandya, 1995). Based on combined electrophysiologic and neuroanatomic tracer studies, it has been shown that two major processing streams, one ventral and one dorsal, originating from the auditory cortex (AL and CL belt regions) project to different areas within the prefrontal cortex. The CL pathway targets the caudal dorsolateral prefrontal cortex, whereas the AL pathway targets rostral and ventral areas of prefrontal cortex (Kaas and Hackett, 1999; Romanski et al., 1999a, b) (Figure 12). Because it is well known that prefrontal cortex has been linked to various cognitive (memory), motor, and supramodal processes, and since this cortical area has been shown to have a distinct proclivity toward differentially processing auditory stimulus features, it has been suggested that aspects of central auditory system organization are functionally segregated in a manner similar to visual and somatosensory systems, that is, into "what" and "where" processing streams. This interpretation is compatible with the suggestion that the "what" processing stream has a functional specialization for object recognition (stimulus identity), and the where processing stream has a functional specialization for spatial aspects of stimuli (Kaas and Hackett, 1999; Khalaffa et al., 1999; Rauschecker, 1999). As might be expected, the projections from auditory cortex to the prefrontal cortex are more complex than described above, but the precise details of this organization must await further experimental study.
Whereas much of the combined physiologic and neuroanatomic information describing central auditory system organization has been derived from experiments in macaque and rhesus monkeys, there are obvious parallels in human studies, although the full extent of these associations has yet to be realized. Contemporary neuroanatomic staining methods and various imaging-related activation studies suggest that the human auditory cortex can be subdivided into at least eight different putative regions (Rivier and Clarke, 1997). Other proposed schemata can also be taken into consideration when attempts are made to delineate various cortical areas (Rademacher et al, 1993). Thus, with this information as a background, we now consider some examples of sensory information processing in human auditory cortical areas being elucidated by fMRI.

**Tonotopic Frequency Organization**

Having a spatially sensitive method to investigate the tonotopic organization of auditory cortex allows one to compare and contrast human data with single-unit mapping studies obtained from experimental animals. The fMRI work of Talavage et al (1996, 1997; also cited in Melcher et al, 1999a) provides direct evidence for multiple, tonotopically organized areas on the medial and lateral aspects of Heschl's gyrus in humans. Bilecen et al (1998) studied frequency representation in auditory cortex using binaurally presented low- (500-Hz) and high-frequency (4000-Hz) pure-tone stimuli. The low- and high-frequency tonal stimuli showed properties of different frequency organization in the ML, frontal-occipital, and crano-caudal orientations in both hemispheres. In the majority of individuals, the 4000-Hz tonal stimulus had a more frontal and medial orientation than the 500-Hz tone. Strainer et al (1997) evaluated normal-hearing subjects and found that pure tones activated medial and lateral aspects of the transverse temporal gyrus, whereas complex stimuli produced activation in association areas. Whereas microelectrode studies have been the gold standard for mapping tonotopic areas in experimental animals, they have rarely been performed on humans for obvious reasons. However, Howard et al (1996) reported such a study in an individual with normal hearing being monitored for medically intractable epilepsy. When recordings were made from a multicontact depth microprobe stereotaxically placed within the long axis of Heschl's gyrus on the right side, a tonotopic frequency representation was found with higher best frequencies localized at more posterior-medial recording sites and lower frequencies along more AL sites. Whereas this type of data is of particular importance in validating the concept of tonotopicity in humans, the inherent limitations of using just a single-depth probe study cannot address the issue of multiple tonotopic fields. Thus, the impressive work demonstrating multiple tonotopic fields in human studies by fMRI takes on additional importance when compared to recent work in monkeys (e.g., Kaas et al, 1999; Romanski et al, 1999b).

**Intensity Coding**

Of fundamental importance to auditory signal processing is the area of intensity coding. In a parametric study using cardiac gating and the single-slice acquisition paradigm, Sigalovsky et al (1999) evaluated changes in stimulus intensity at the level of inferior colliculus. At this subcortical location, these authors showed a significant monotonic increase in fMRI activation with increases in stimulus level over a 40-dB range. In contrast, other experiments that have studied effects of stimulus intensity on auditory cortical areas have produced more variable results (Millen et al, 1995; Strainer et al, 1997; Mohr et al, 1999). For example, Millen et al used pulsed pure-tone stimuli at 1000 Hz and 4000 Hz and continuous speech presented at 20 and 50 dB SL to investigate auditory activation with fMRI. Whereas both pure tones and speech stimuli activated areas within the superior temporal gyrus, neither the intensity level nor the side of stimulus presentation produced significant alterations in the number of pixels activated. Mohr et al (1999) studied stimulus intensity of binaurally presented monosyllabic speech stimuli. Whereas intensity effects were reported and activation was localized to planum temporale, Heschl's gyrus, and superior temporal sulcus, large individual differences were observed. Jäncke et al (1998) used non-verbal pure-tone stimuli and various consonant-vowel-consonant speech tokens presented binaurally at three different levels (75, 85, or 95 dB SPL) to study auditory cortical activity. Although participants were not engaged in a discrimination task, they were required to detect a particular target stimulus as a means to maintain vigilance. Their analysis showed greater activation in the left versus right hemisphere in Brodman's area 22 for the verbal stimuli, particularly at higher stimulus levels (85 and
95 dB). However, similar activation with changes of intensity occurred in left and right hemispheres in Brodmann's areas 41/42 for both stimulus categories. Interestingly, significant activation was also found in the bifrontal regions for both verbal and nonverbal stimuli. The authors suggest that this activation pattern is consistent with the interpretation that a neural network consisting of processing streams from auditory cortex to frontal regions can be engaged during sensory processing tasks particularly when specific target stimuli are stored as internal representations and used in working memory. Indeed, based on evidence from other studies, data are accumulating, which emphasizes the role for both mesial temporal and frontal lobe structures in memory formation and retrieval (Buckner et al, 1999; Henson et al, 1999). This study demonstrates that as the experimental demands of a simple perceptual task are increased, the concept of hierarchical levels of processing can be demonstrated.

**Complex and Dynamic Stimuli**

Whereas it is well known that certain brainstem structures are directly involved in binaural processing, such as the localization of objects in space, we are also gaining insight into the role that cortical structures can play in spatial hearing, such as sound-motion perception. For example, auditory movement sensitivity was studied by Baumgart et al (1999) by comparing activation of the auditory cortex using stimuli with identical spectral-temporal patterns but differing in binaural timing, which induce the perception of moving versus stationary targets. Whereas both types of stimuli produced bilateral auditory cortex activation, the movement condition produced a stronger response in the right planum temporale region. In partial contrast, Griffiths et al (1996, 2000) suggested a mechanism of sound movement perception involving brain areas outside the classic auditory pathways by demonstrating involvement of the right parietal cortex, premotor cortex, and activation of prefrontal areas. By analogy, models of visual-motion processing are frequently based on specialized filters or feature detectors tuned to specific temporal patterns of receptor activation (Lu and Sperling, 1995). A similar organization may hold for auditory motion processing as well, although additional work is needed to convincingly validate this concept. Belin et al

![Figure 13](image-url) Functional MRI study showing a transaxial view of the auditory cortical areas in response to a binaurally presented auditory stimuli consisting of mixed musical and environmental sounds. The terms T1, T2, and T3 represent three cortical territories, oriented from rostro-lateral to caudomedial directions. Adapted from Gaschler-Markefski et al (1997).
(2000) investigated the role that the human voice might play in activating auditory cortical areas. They found that voice-selective regions exist bilaterally in the superior temporal sulcus. These authors also point out similar organizational features with the visual cortex, where face-selective regions have also been identified.

Because use of complex binaural stimuli may sequentially activate different areas of auditory cortex over time, the method used for the analysis of blocked fMRI data should be chosen carefully. Gaschler-Markefski et al (1997) demonstrate that both stationary and nonstationary time series can result from different tasks in a blocked-stimulus paradigm, as shown in Figure 13. Huckins et al (1998) used nonverbal tonal complexes and verbal stimuli presented monaurally to the right ear to study cortical auditory responses with fMRI. The unique feature of this investigation was the use of a small (5-in) surface receiver coil placed over the left temporal lobe. Use of a surface coil, in contrast to a much larger whole-head (birdcage) type receiver coil, was applied to maximize sensitivity and optimize signal-to-noise ratio during imaging. With this method, Huckins et al (1998) demonstrated highly localized responses in regions of the superior temporal lobe and good reproducibility within and between test sessions. However, no difference in activation patterns was observed between the two classes of stimuli. Whereas the novel use of a surface receiver coil has the benefit of providing increased sensitivity and signal-to-noise ratio, their design only provides information about one hemisphere and therefore limits information on laterality of function.

**EFFECTS OF ATTENTION**

Several studies have documented the influence that attention may have on several auditory tasks. Pugh et al (1996) found that when greater demands were placed on information processing by having individuals perform dichotic versus binaural pitch or speech token discrimination tasks, primary centers on the superior temporal plane and other areas in posterior parietal and inferior frontal systems were engaged. Jäncke et al (1999) studied the effects of attention on consonant vowel stimuli by having subjects listen passively (condition 1), actively attend to stimuli (condition 2), and detect a target syllable (condition 3). The authors evaluated the effects of attention, hemisphere, and primary versus secondary auditory cortex. They found a significant hemisphere and cortex effect but no interactions. The left hemisphere and primary auditory cortex showed the greatest effects, documenting greater activation in auditory cortex during active versus passive listening.

Seidman et al (1998) used an auditory continuous performance task made difficult by increasing working memory demands and interference. They found significantly poorer performance on working memory versus a simple vigilance task. In contrast to a vigilance task, working memory showed activation within a complex network including the lateral and medial prefrontal cortex, precentral cortex, mesial temporal lobe (insula and hippocampus), parietal-occipital cortex, cingulate, thalamus, and superior colliculus. Interestingly, performance and degree of activation was associated with IQ. Other work emphasizes that attention can act locally during auditory cognitive processing and that modulation of auditory and visual sensory cortex attentional demands can be modality dependent (Woodruff et al, 1996).

Larisch et al (1999) evaluated the effects of motivation on a dichotic listening task in a sample of five participants. Individuals included were those classified as success oriented, based on responses to a compendium of questions of motivational behavior (Schmalt's Questionaire). Two tasks were compared: a competition task (high motivation) for monetary compensation and a calibration task (neutral motivation). Whereas all participants showed significant bilateral activation in superior temporal gyrus during auditory stimulation and in the right anterior cingulate, in the high motivation condition, three of five participants showed activation in the cingulate and right prefrontal cortex. The authors attributed these activation patterns to nonperceptual motivational aspects of the experiment. Although the small sample limits the generalizability of results, the authors suggest that similar questionnaires be used when recruiting volunteers in fMRI experiments to help ensure homogeneity of results.

Yoshiura et al (1999) used fMRI to investigate brain activation patterns during auditory and visual oddball tasks by focusing on rare target stimulus detection and making comparison between target and nontarget stimuli. Whereas modality-specific activations were found (auditory tasks activated transverse temporal gyri and transverse temporal sulci bilaterally; visual tasks activated occipital lobes and the occipitotemporal junctions bilaterally), a broad
overlapping range of nonspecific activation patterns was also noted for each task. The authors interpret their results as demonstrating that target stimuli in an oddball task represent activity from a complex combination of multiple generators rather than from a single neural population. Opitz et al (1999) used surface-recorded event-related potentials and fMRI to study stimulus deviancy and target stimulus detection within an oddball paradigm to evaluate neuroanatomic constraints for dipole modeling. In instances of dipole modeling of surface-recorded EEG or MEG signals, assumptions or constraints regarding dipole number, orientation, and locations are necessary in order to find unique inverse solutions. Their results showed that when unattended deviants demonstrated a mismatch negativity by the event-related potential (100- to 160-msec range), fMRI activation was mapped to the superior-temporal gyrri bilaterally. When attended targets generated a mismatch negativity followed by $P_{200}$ response (280- to 320-msec range), fMRI activation was mapped bilaterally to superior-temporal gyrri and neostriatum. Their results show that inverse solutions for dipole modeling of mismatch negativity localization activity near Heschl's gyrus during stimulus deviancy processing, whereas the $P_{200}$ complex was localized to superior temporal gyrus during target detection. Clearly, further work is needed in this area to solidify many of the important unanswered questions that remain.

Advancements in speech reading research may also benefit from an improved understanding of the neural mechanisms involved in integrating auditory and visual stimuli. For example, when semantically congruent speech is presented simultaneously in the auditory and visual modalities versus conditions that present auditory or visual stimuli alone, responses were enhanced in modality-specific auditory and visual areas (Brodman's area 41, 42; visual area V5) (Calvert et al, 1999).

**PRE- AND POSTNATAL DEVELOPMENTAL ASPECTS**

Functional MRI investigations are not limited to investigations on adults, and considerable information about human CNS development might be derived by studying children of all ages. Probably, the most serious constraints in applying this methodology to infants and young children are issues related to cooperation and movement-related artifacts, which would, no doubt, negate interpretable data in many instances. However, like any complex area, where substantial challenges exist, successful implementation can also reap high rewards.

Hykin et al (1999) reported an intriguing study designed to evaluate the feasibility of mapping central auditory system function in utero using fMRI. Using auditory stimulation from a loudspeaker (recorded nursery rhyme) and presenting acoustic stimuli to the abdomen region of pregnant women, Hykin et al (1999) demonstrated that significant temporal lobe activation could be detected in the human fetus. The authors suggest that “...fetal /MRI has potential to become a powerful tool in investigating brain development.” Children of school age appear to be a viable population to investigate, and Ulualp et al (1998) have obtained useful data in response to acoustic stimuli in individuals as young as 6 years of age (range 6–10 years) in normal-hearing healthy children. Based on passively listening to a prerecorded sample of ongoing speech, Ulualp et al report bilateral activation in superior and transverse temporal gyri, planum temporale, frontal, parietal, and cingulate regions of the brain. In a recent review of central auditory processing disorders in school-aged children, Cacace and McFarland (1998) note the paucity of research in the area of cortical language organization and representation in children (Bates et al, 1992; Duchowny et al, 1996; Hertz-Pannier et al, 1997; Nobre and Plunkett, 1997). Clearly, the lack of normative developmental data on the neural representation of language and language development complicates full understanding of childhood language disorders. Indeed, efforts toward this end will be of considerable importance in helping to explain altered sensory information processing and other neurobehavioral limitations in children with various types of learning disabilities, such as dyslexia (Cacace et al, in press). Furthermore, in specific groups of children at risk for neurodevelopmental delay, such as those with epilepsy or other types of brain lesions, fMRI evaluation may potentially play a role in studying cognition, in monitoring disease progression, and in the context of language localization, particularly if surgery becomes necessary (Bookheimer et al, 1999; Booth et al, 1999).

To date, significant advances have been made that highlight the importance of fMRI as applied to a wide range of sensory processing...
Functional Magnetic Resonance Imaging/Cacace et al

The idea that using fMRI combined with various auditory psychoacoustic tasks will help understand the underlying basis of various auditory perceptual and cognitive/linguistic processes (Elliot, 1994) is beginning to materialize. However, the influence of imaging-related background noise on task performance, the ability to precisely control stimulus presentation, and numerous safety concerns (Savoy et al, 1999) are some of the technical issues that have not yet been fully resolved. Furthermore, because fMRI is sensitive to all types of brain activity, factors such as motivation, memory, motor skills, novelty of the environment, mental imagery, and word rehearsal need to be recognized and closely controlled. Attention to these concerns will help to reduce spurious results, eliminate alternative explanations, and minimize experimental confounds. Many of these important experimental design concerns have been addressed by others (see Aguirre and D’Esposito, 1999).

Below, we provide an overview of how functional imaging is beginning to play a role in the study of phantom perceptions like tinnitus. This is another area, which is in the early stages of development, where creative and novel experimental designs can have an impact.

**IMAGING TINNITUS-RELATED ACTIVITY: ENDOGENOUSLY GENERATED STIMULI**

Either implicitly or explicitly, most models and/or theories of tinnitus generation assume altered spontaneous firing rates or patterns of neuronal activity within the central auditory system (Eggermont and Komiya, 1999). These hypotheses are driving a concerted research effort to validate the tinnitus perception behaviorally and to localize and better understand the underlying neural substrate mediating such activity in the nervous system of experimental animals (e.g., Jastreboff et al, 1988; Chen and Jastreboff, 1995; Kaltenbach et al, 1996, 1999; Eggermont and Kenmochi, 1998; Bauer et al, 1999). Moreover, at the end of the 20th century, innovative research designs using fMRI and PET have been applied to the task of studying tinnitus-related neural activity. From a basic science and clinical standpoint, functional imaging investigations in humans are of considerable importance to tinnitus research since they have potential value in providing fundamental insight into the underlying physiology and pathophysiology of this complex clinical enigma. Because the area of functional imaging in studying tinnitus has not been limited to MRI, and since the literature at present is not voluminous, we will digress slightly here and discuss both PET and fMRI studies. These approaches, reviewed recently by Cacace (1999), include:

1. Evaluation of glucose metabolism in individuals with constant chronic tinnitus;
2. Evaluation of individuals that can modulate a constant background tinnitus by performing some type of overt behavior in another sensory, motor, or sensory motor modality, such as oral-facial maneuvers (jaw clinching) and change in eye position (eye gaze) from a neutral head-referenced condition;
3. Evaluation of individuals that can activate/trigger their tinnitus (turn it on and off) by performing an overt behavior in another sensory, motor, or sensory motor modality, that is, change in eye position from a neutral head-referenced condition or cutaneous stimulation of the hand or fingertip region;
4. Evaluation of stimulus-induced modification of lateralized tinnitus activity; and
5. Evaluation of pharmacologic-induced tinnitus-related activity.

The idea that tinnitus could potentially be imaged was initially proposed by Sasaki et al (1980) and Kauer et al (1982), based on an animal model of peripheral auditory deafferentation using autoradiography with a glucose tracer, [14C]2-deoxyglucose. Although innovative and novel, there were interpretive issues that limited the significance of this work (Meyerhoff et al, 1982). Similarly, with functional imaging applications in humans, the effects of hearing loss and the need to secure appropriate controls also remain as focal issues that can affect data interpretation. PET, which is based on tracer technology, is analogous to autoradiography (Lockwood et al, 1999b). However, what distinguishes it from autoradiography is that both endogenous and/or exogenously generated activities can be explored in the human brain in vivo. Along these lines, Arnold et al (1996) studied adult patients with chronic tinnitus and hearing loss using PET with [18F] deoxyglucose as a probe and compared them to controls without tinnitus or hearing loss. They assumed that if tinnitus was associated with synaptic hyperactivity, then the effects of such activity could be detected by increased glucose metabolism.
measureable by PET. In individuals with tinnitus but not in controls, asymmetric metabolic hyperactivity (predominantly localized to the left hemisphere) was detected in the region of Heschl's gyrus in the primary auditory cortex. Additional work along these lines has been carried out by Oestreicher et al (1999). They compared 25 tinnitus patients who were heterogeneous with respect to tinnitus and hearing loss to 20 controls who were audiometrically normal. The majority of tinnitus subjects (24 of 25, 96%) had significant sensorineural hearing loss. Of these, 15 of 25 (60%) had mild to severe sensorineural loss, 9 of 25 (36%) had profound unilateral deafness, and 1 had normal sensitivity. In this sample, 20 of 25 (80%) had described their tinnitus as a “high-pitched ringing,” which was localized to one ear, and the remaining 5 of 25 (20%) described their tinnitus as bilateral or localized “in the head.” Interestingly, and in contrast to Arnold et al (1996), Oestreicher et al (1999b) failed to show any significant activation patterns in primary cortical auditory areas. However, significant deactivations (i.e., reductions in blood flow) were observed in several nonauditory regions that included posterior parietal cortex, anterior insula, and posterior portion of the anterior cingulate cortex, which constitute portions of the limbic system. Whereas the interpretation of deactivations in PET studies is controversial (Mirz et al, 1999a), these authors suggest that their findings may represent a distributed neural processing network associated with the psychological component of the tinnitus perception.

In addition to studying glucose metabolism with PET, several other approaches have been proposed that would satisfy the conditions necessary for imaging tinnitus with fMRI or PET. That is, if the tinnitus percept could somehow be turned on and off, and/or if a constant background tinnitus could be consciously modulated (i.e., changed in loudness), then the conditions necessary for assessing a differential response, and thereby obtaining a difference image, would be satisfied (similar to the blocked-stimulus subtraction paradigm described previously using exogenous stimuli). It was initially suggested that individuals with gaze-evoked tinnitus could meet these criteria by internally generating on and off states during data acquisition (Cacace et al, 1994a). In its purest form, gaze-evoked tinnitus is absent in a particular setting (i.e., a central eye-gaze location) and present when a static change in eye gaze exceeds a certain spatial location and this eye position is maintained.
geniculate nuclei. To separate changes in CBF due to increases in tinnitus loudness, group subtractions were performed between PET results obtained during jaw clinching in controls and oral-facial movement in tinnitus patients. The subtraction procedure showed residual activation in the left thalamic region (left medial geniculate nuclei) in the tinnitus group. This was interpreted as indicating that the postsubtraction increase in neural activity was due to the increase in tinnitus loudness. In two patients where oral-facial movements decreased tinnitus loudness (e.g., where tinnitus was localized to the right ear in both individuals), a decrease in CBF was observed in the posterior and mid portion of the left middle temporal gyrus. Here the subtraction procedure showed a region of reduced CBF in the temporal lobe and hippocampus of the left hemisphere.

It has also been shown that cutaneous-evoked tinnitus, a previously unrecognized phenomenon, can also be imaged with MRI and the PRESTO method (Cacace et al, 1999a, b). In a single case, phantom auditory perceptions triggered by touching the fingertip region of the right hand produced localized activation in the temporal-parietal junction. This represented activation in auditory centers of the brain on the superior aspect of the temporal and inferior aspect of the parietal lobes. The finger opposition-tapping task also produced activity in the right (ipsilateral) caudate area, slight activation in the contralateral orbital frontal region, and prominent activation in the contralateral motor, premotor and pre-rolandic sulcus regions. A control finger opposition-tapping task with the other hand produced activation limited to the contralateral motor cortex, premotor cortex, and pre-rolandic sulcus regions. These data clearly dissociated cutaneous-evoked tinnitus-related activity from activation produced by the finger opposition-tapping task using the opposite hand. Recent evidence also suggests that somatosensory system interactions with auditory pathways can generate tinnitus perceptions in individuals without overt otologic disturbances (Levine, 1999). These observations, in conjunction with various other studies noted above, further expand the biologic basis of tinnitus generation. Although in early stages of development, modulation of tinnitus loudness by eye gaze, oral-facial movements, cutaneous stimulation, and cranio-cervical manipulation are some of the ways in which to demonstrate the potential for imaging phantom auditory perceptions in human subjects.

Other important paradigms have been reported in studying tinnitus-related activity in the CNS. For example, Mirz et al (1999b) used PET to study conditions of tinnitus suppression/inhibition using narrow-band acoustic masking, pharmacologic tinnitus reduction using intravenous lidocaine, and in combined conditions of acoustic masking plus lidocaine administration. In this study, tinnitus-related activity was localized to the right prefrontal (middle and superior) and right posterior (middle temporal and precuneous) gyri. Deactivations were observed in the left transverse temporal gyri. Recently, Melcher et al (1999b) demonstrated that tinnitus modified by lidocaine administration can also be detected with fMRI using methods described below.

A series of systematic experiments designed to study individuals with lateralized tinnitus based on an acoustic stimulation/masking paradigm and the single-slice fMRI method (Guimaraes et al, 1998) has been used by a group of auditory neuroscientists (Levine et al, 1998; Melcher et al, 1999b, 2000; Sigalovsky et al, 1999). In these experiments, both the method and selection of individual subjects are important considerations. To reiterate briefly, the single-slice fMRI method, which captures neuroanatomic segments of primary auditory cortex and inferior colliculi, uses a rapid EPI sequence with cardiac gating. In this context, imager-related background noise is reduced by studying a single slice of anatomy, and the cardiac gating method serves to minimize vascular-related movement of subcortical structures and subject-related head movement. The selection of individuals with normal hearing sensitivity and lateralized tinnitus also tends to reduce alternative explanations in comparison to using heterogeneous populations with both hearing loss and more complex tinnitus perceptions. In a group of adults with normal hearing sensitivity and tinnitus lateralized to one ear, they found that presentation of binaural noise induced activation in the inferior colliculi that was always more asymmetric in individuals with lateralized tinnitus than in controls. Interestingly, in comparison to normal controls, all individuals with unilateral tinnitus had abnormally low fMRI activations in response to binaural noise in the inferior colliculus contralateral to the tinnitus percept. Two models, the saturation model and the physiologic masking model, have been proposed to allow for systematic hypothesis testing. Both models tacitly assume elevated baseline neuronal activity from the continuous
background tinnitus, which is thought to be present at the level of the inferior colliculus.

Although advancements are being made, it should be recognized that the various methods described above are not without limitations. For example, whereas both PET and fMRI allow for tinnitus localization and assessment of potential connectivity patterns underlying the phantom perceptions, they do not delineate the temporal structure of the underlying neural activity that may be responsible for the tinnitus perception (i.e., single-unit spike trains, synchronized spontaneous activity, ensemble activity, etc.). Functional MRI studies of the auditory modality can also pose additional concerns due to imager-related background noise, as noted below.

**LIMITATIONS OF STUDIES IN THE AUDITORY MODALITY**

It should be recognized that fMRI studies in the auditory modality pose additional concerns because of inherent imager-related background noise, due in large part to system hardware-related switching gradients during data acquisition. For paradigms that require active discriminations, this background interference can be problematic. System-related noise is a complex issue because of level effects and sound/vibration transmission routes (air and bone conduction). As a result, passive attenuation devices (e.g., insert ear plugs, headphones, etc.) can only be partially successful at noise reduction (see Ravicz and Melcher [1998], Melcher et al [1999a], and Savoy et al [1999], for a more comprehensive discussion of these issues). Besides passive attenuation or even active noise cancellation/reduction devices (Goldman et al, 1989; McJury et al, 1997), other options include alterations in pulse sequences such as the presentation of the stimulus during quiet periods of the pulse sequence (Belin et al, 1999; Eden et al, 1999; Edmister et al, 1999; Talavage et al, 1999). With respect to the issue of scanner noise and in contrast to fMRI, PET may have certain advantages. For example, Salvi et al (1999) have reported that when hearing threshold testing is conducted in the PET scanner which insert earphones covered by earmuffs with employ active noise reduction, thresholds are comparable to those obtained from an audiometric test booth over a bandwidth from approximately 0.5 to 8.0 kHz. This indicates that auditory paradigms using low-level auditory stimuli are possible to study without noise interference under these conditions using PET.

**RELATIONS TO OTHER FORMS OF PHANTOM PERCEPTIONS**

In addition to tinnitus, studying other types of phantom perceptions may also be of value in order to gain insight into common properties of various forms of phantom events. Like gaze-evoked and cutaneous-evoked tinnitus, synesthesia is a condition where stimulation in one modality can evoke a conscious perceptual experience in another modality (cross-modal phantom perceptions). For example, in color-word synesthesia, words can serve to activate specific colors in the absence of visible-luminous stimuli. In a PET study of color-word synesthesia, Paulesu et al (1995) found that specific words but not tones evoked cross-modal synesthetic perceptions. Whereas words activated perisylvian language areas and nonprimary visual association areas (posterior inferior temporal cortex and the parietal-occipital junctions), it was also found that prefrontal cortex, the insula, and superior temporal gyrus were also activated. Thus, this study indicates that brain areas concerned with language and visual-feature integration may underlie these particular cross-modal synesthetic perceptions without requiring overt activation of primary visual cortex.

Capturing neural activity associated with the experience of other phantom experiences such as auditory and visual hallucinations (Sibeweig et al, 1995, 1996; Howard et al, 1997; Woodruff et al, 1997; Fytche et al, 1998; Szechtman et al, 1998; David, 1999; Lennox et al, 1999) represents another line of investigation using contemporary imaging modalities that may have parallels to understanding certain forms of tinnitus (also see Cacace et al [1999b] for a discussion). Consider, for example, an experiment designed to determine common brain areas involved in hearing, imaginal hearing, and hypnosis-induced auditory hallucinations in attempts to establish linkage between these different states. The premise is that auditory hallucinations share with imaginal hearing the property of being self-generated and with real hearing the experience of the stimulus as being an external one. In this study, Szechtman et al (1998) compared changes in regional blood flow using PET under conditions of hearing (auditory presentation of repetitions of a taped verbal sentence), imagining, hypnosis-induced auditory hallucinations, and a baseline nonactivated state. Data were obtained from university students who were divided into two groups: halluci-
cinators and nonhallucinators. In hallucinators, but not in nonhallucinators, it was found that a brain site in the right anterior cingulate region (Brodmann area 32) was activated by both real hearing and hallucinations but not by imaginal hearing. It was suggested that the right anterior cingulate region may be the site in the brain where an auditory event is tagged as being external. It is speculated that spontaneous auditory hallucinations could result from inappropriate activation of the cingulate cortex. This interpretation is consistent with other experiments implicating cingulate cortices in attentional/intentional processes and views that suggest that aberrant activity in these regions may result in inappropriate allocation of attentional resources or signal amplification in the modality of the hallucination (Vogt et al, 1992; Posner, 1994; Silbersweig and Stern, 1996).

Likewise, parallels between tinnitus and pain have also been suggested (Tonndorf, 1987; Möller, 1997, 1999). Like tinnitus, pain perception is complex and poorly understood, although functional imaging studies are beginning to yield new and important information on this topic as well (Berman, 1995; Davis et al, 1998a, b; Derbyshire et al, 1998; Disbrow et al, 1998; Oshiro et al, 1998; Porro et al, 1998; Cogbill et al, 1999; Ingvar, 1999, Treede et al, 1999). Based on neurophysiologically based models of tinnitus, affective emotional reactions to the tinnitus perception and limbic system linkage have been hypothesized. Functional MRI studies may also provide additional details about state and trait relationships and interactions with emotion (Davidson and Irwin, 1999).

CONCLUSIONS

Functional MRI is a research area that is providing insight into fundamental properties of human sensory, motor, and cognitive function in both normal and pathologic states. This tutorial provides a snapshot of this powerful method, which is rapidly evolving and improving over time. The appeal of this technique is based on its noninvasive nature, temporal and spatial resolution, suitability for studying humans, and potentially wide-range future availability. It is also gaining prominence as an experimental tool to study and quantify various phantom sensory events such as tinnitus. The application of fMRI to tinnitus research is particularly noteworthy since the lack of objective, noninvasive methods for studying this enigmatic phenomenon is one of many reasons that have limited advancements in this area. Although presently underused in the auditory modality, MRS is another powerful tool to further our understanding of a wide range of otopathologic conditions and potential treatments. One point, however, that cannot be emphasized enough is the fact that successful implementation of this technique requires constructive and close collaborations from a variety of scientific disciplines and individuals (MR physicists, engineers, organic and biochemists, statisticians, radiologists, sensory and cognitive scientists, etc.). Advancements in this area would not have occurred so rapidly without these important interactions.

Clearly, the future of fMRI looks extremely bright. This optimism is not understated because there is reason to believe that real-time functional imaging and analysis is on the horizon (Voyvodic, 1999; Yoo et al, 1999). Furthermore, if this particular application materializes, then clinical uses will no doubt expand. Although experimental in nature, and many issues remain to be fully resolved, this fascinating but complex area of fMRI opens up a whole new research frontier for auditory neuroscience to explore in the 21st century.

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