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Review

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Functional Imaging of the Auditory System: The Use of Positron Emission Tomography

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Key Words

Auditory cortex • Functional localization • Hallucinosis • Hallucinations • Hemispheric asymmetry • Melody, human • Music • Persistent vegetative state • Positron emission tomography • Presurgical mapping • Rhythm • Spatial localization • Speech • Temporal processing • Tinnitus

Abstract

Modern brain imaging methods now afford unprecedented opportunities for the in vivo study of central auditory system function. Positron emission tomography (PET) has been used as a functional imaging technique for more than 15 years to study the distribution of cerebral haemodynamic changes associated with auditory stimulation, in subjects with normal and abnormal auditory function. Many of these studies concern processes related to, but not identical with, audition, such as speech perception, melodic processing and directed attention. Additionally, PET has been used to explore auditory perception in clinical populations such as cochlear implantees, neurosurgical candidates and people with tinnitus and auditory hallucinations. The spatial resolution of PET does not appear sufficient to address ques-

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tions of a fine anatomical grain, e.g. exploring functional specialization within the primary and secondary auditory cortex. Nevertheless, PET has considerable potential as a tool in basic research on, and clinical assessment of, many auditory phenomena. Although functional magnetic resonance imaging can now be used for many studies for which formerly only PET was suitable, PET still possesses unique advantages. For example, it permits acquisition of data from inferior frontal and anterior temporal areas, can be used with subjects with cochlear and other implants (such as pacemakers) and can be used to map neurochemical pathways and receptors.

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Introduction

In just two decades, functional imaging methods (including positron emission tomography, PET) have made an enormous impact on the way we assess human perception and cognition in vivo. Detailed anatomical images, acquired by computerized tomography and magnetic resonance imaging (MRI), can be combined with functional information from PET, functional MRI (fMRI), quantitative electro-encephalography and magneto-encephalogra-

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Fig. 1. A schematic diagram of a PET detector ring. The ring consists of radiation detectors that are electronically connected in pairs (e.g. 'A'). Whenever a positron annihilation event occurs in the brain, two gamma rays (photons) with trajectories 180° apart are emitted and are registered by the two detectors of a pair (depicted with white lines). The annihilation event is presumed to have occurred along the coincidence line between the two detectors. Focal concentrations of tracer are reflected in focal regions of photon emission, which can be observed by reconstructing images using the principles of computed tomography.



phy to produce a cohesive picture of brain function in the normal human brain and in a variety of clinical states.

These tools have been used primarily to examine vision, speech and language, memory and more 'central' cognitive functions such as attention and working memory. Although relatively few studies of auditory processing have been conducted to date, these have been plentiful enough to draw some conclusions regarding both basic auditory neuroscience and applied research. Areas of basic research that have received some attention include functional organization within the auditory system (particularly the cortex), attentional modulation of auditory activation and substrates of auditory localization and melodic processing. Clinical research, which is perhaps where PET holds the most future potential, includes exploration of the neural concomitants of functional recovery after cochlear implantation, brain bases of auditory hallucinations, mapping of function in neurosurgical candidates and prognostic diagnosis of persistent vegetative state (PVS).

Although fMRI has developed very rapidly and has overtaken PET as the imaging modality of choice for many experimental questions, PET retains considerable advantages. It is more appropriate than fMRI for assessing function in the inferior frontal and anterior temporal lobes (because of susceptibility artefact in fMRI), for use with subjects with cochlear and other implants (such as pacemakers) and for assessing subjects who are claustrophobic, have conditions which require medical equipment or which preclude lying very still for a long period of time, or who require considerable contact with the experimenter. Finally, PET is a quiet imaging technique. fMRI produces considerable background noise (up to 130 dB), which must be counteracted in some way in auditory studies.

Methods

PET is the general name for a large set of techniques used to image metabolism in body tissues, including the brain. This review will concentrate on the subset of techniques relevant to imaging cerebral function, particularly 'fast' blood flow imaging techniques. The validity of these methods is based on the observation that changes in regional neuronal activity, in humans and other animals, are accompanied by robust changes in local blood flow. This relationship was documented more than 100 years ago [James, 1890], although the physiological coupling between neuronal activity and blood flow change is still not well understood [Fujita et al., 1997; Mintun et al., 2001; Ohta et al., 1996].

How It Works

PET is sensitive to the local tissue concentration of biologically important compounds that have been labelled with positron-emitting isotopes of oxygen, fluorine, nitrogen, carbon and other elements. These isotopes are incorporated into glucose, water, brain amines or drug compounds that are then introduced into the body. It is possible to monitor the distribution of these compounds in the brain without disturbing their biological properties and physiological behaviour, with a temporal resolution ranging from several seconds to several minutes and an effective spatial resolution of about 6 mm [Malison et al., 1995].

Positrons are positively charged electrons that are emitted from the nucleus of unstable radio-isotopes, such as oxygen-15. The emitted positron combines with an ordinary electron of a nearby atom in an annihilation reaction, turning the mass of the two particles into two gamma rays (photons) that are emitted at 180° from each other. These photons easily escape from the human body and can be recorded by a ring of radiation detectors: the PET scanner (fig. 1). Opposing detectors within the PET scanner's ring are electronically coupled to form a coincidence circuit. When coincident photons are detected, positron annihilation must have occurred somewhere along the coincidence line (the straight line connecting the two detectors). The intersection of many successively detected coincidence lines pinpoints areas of relative concentration of the radioactive substance. Most cognitive activation studies use oxygen-15-labelled water as a tracer since ¹⁵O has a short half-life (2 min), water is a ubiquitous component of biological tissue (including blood), and it crosses the blood-brain barrier easily. Although inhalation of oxygen-15-labelled CO₂ was a common delivery method in the late 1980s, current PET activation studies employ the water bolus technique. H₂¹⁵O is injected into the bloodstream of the volunteer or patient, usually in the arm, and diffuses rapidly throughout the blood supply. Increases in regional neuronal activity are reflected in regional blood flow increases that in turn increase the local concentration of oxygen-15: these local concentration changes are detected by the PET camera. Most PET studies that use the water method acquire 8-16 scans, each approximately 1 min long, with a 7- to 10-min interscan interval (long enough for the tracer to decay substantially). Three to 6 different experimental conditions (e.g. the presentation of stimuli with different acoustic characteristics) are usually tested within a single subject, with approximately 10 subjects in a study.

Physiological Basis of the Signal

An underlying assumption of the PET H₂¹⁵O bolus technique is that water passes the blood-brain barrier very easily, leaving the vascular system and perfusing the brain parenchyma almost instantaneously. In other words, local activation, from the moment of measuring, is assumed to arise from neuronal tissue and not (to any important degree) from the vasculature. This assumption incorporates a number of simplifications: for example, it does not take bloodbrain barrier filtrational and diffusional permeability or capillary surface areas into account in determining water uptake [Ohta et al., 1996]. Furthermore, there is no place in such a simple model of the relationship between neuronal activity and blood flow for any intermediate, vasomotor-response-producing, agent that is spatially distributed (e.g. nitric oxide, dopamine or acetylcholine; see Hoge and Pike [2001] or Krimer et al. [1998]) and might therefore reduce the spatial resolution of the blood flow response. In fact, limited diffusion of water across the blood-brain barrier has frequently been reported [Raichle et al., 1983; Ohta et al., 1996], and detectable concentrations of oxygen-15 have been located in the vascular bed at significant distances from the perfusion signal [Fujita et al., 1997]. In sum, although the cerebral blood flow signal is local, it is difficult to say, precisely, how local it is and to what extent relatively large-

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calibre vessels at a distance from the active tissue can display concomitant blood flow increases that are detectable by the PET camera.

Experimental Design

Neuroimaging experiments are designed to quantify relative changes in brain activity (indexed by regional cerebral blood flow, rCBF) consequent upon changes in stimulus characteristics or task demands. The two most commonly used approaches are subtractive designs and correlational (or parametric) designs. The basic assumption behind the idea of cognitive subtraction is the following: if two conditions, A and B, are identical except that A requires a particular cognitive function f while B does not, then one can identify those cortical regions that are involved in f by subtracting the pattern of rCBF observed during B from that during A. This approach is essentially an extension of Donders' method for the interpretation of reaction time measures. In this method, response time for executing a simple task (responding to any light) is measured, and then the task is made more complex (respond only to a particular colour of light), and a new response time is measured. The difference between the two times is taken as the time necessary to deal with the complication (reprinted in Donders [1969]). In general, the conditions, A and B, will differ in one of two ways. The stimuli presented during the two conditions may be identical, but the participants may be required to perform different tasks [Zatorre et al., 1992]. Or the participants may be presented with different kinds of stimuli in each condition, but the task that they are required to perform may be identical [Scott et al., 2000]. An elaboration of the idea of cognitive subtraction is the hierarchical subtractive design. In studies of this type, conditions are successively 'built up' of cognitive or perceptual components which are assumed to be additive. For example, in a study of speech perception, a condition involving listening to words could be compared to listening to signal-correlated noise bursts, which, in turn, could be compared to rest. In most functional PET studies, scans are specific to one condition, and so comparisons between conditions are expressed as comparisons between scans.

Correlational/parametric designs are based on the assumption that the magnitude of the focal CBF response (rCBF increase) is proportional to processing 'load' – the more cognitive resources engaged by a task, the greater the response. (This assumption has been shown to be invalid in some cases, e.g. for very high or low values of 'load'.) Such designs are used to examine the relationship between a stimulus parameter (such as word presentation rate) or a behavioural response (such as reaction time) and rCBF. This approach is elegant because it avoids many of the complexities of interpretation intrinsic to subtractive designs (including uncertainty about the assumption of additivity of cognitive processes, also called pure insertion; see also Friston et al. [1996] and Sidtis et al. [1999]).

Image Processing and Analysis

The analysis of imaging data is a multistage process (fig. 2). Generally scans need to be corrected for movement of the subject's head over the scanning session (realignment). Scans are then often spatially normalized: this refers to the process by which the brain volumes are deformed in shape to match a template brain volume (usually an average of many representative individual brain volumes). This is done to facilitate comparison across different subjects, who will have brains of different shapes and sizes. The data are then smoothed. This improves the signal-to-noise ratio, ensures that the data conform to the assumptions of the statistical model used and also com-



Fig. 2. Image processing and analysis is conducted over several stages. (The analysis package known as Statistical Parametric Mapping, SPM [http://www.fil.ion.ucl.ac.uk/spm], is used to illustrate the procedure, but similar steps are followed in all functional PET analyses.) First, the individual scans are corrected for subject movement over the scanning session (realignment). Then the scans are usually transformed into a standardized stereotaxic anatomical space, to facilitate comparison and averaging across subjects (spatial transformation/normalization). The data must then be spatially blurred in order to conform to the assumptions of the statistical model

pensates for individual differences in structural and functional anatomy. A statistical model is then applied to the data, and local areas of statistically significant signal change show up on activation maps.

Limitations

One must be aware of the limitations of functional imaging techniques in order to interpret imaging findings appropriately. In the functional PET domain, these limitations include poor temporal (smoothing). The design matrix depicts the experimental factors (test conditions, e.g. sound or silence) that are used to model predicted activation, and this model is tested in each voxel over the image. Significant activation is identified when a significant amount of variability in CBF over scans can be explained by an experimental factor (a column in the design matrix). The degree to which each condition explains the observed CBF is indexed by parameter estimates. Activation foci can be displayed graphically as a statistical parametric map.

resolution (temporal integration times usually >20 s) and poor spatial resolution (the effective spatial resolution of PET is dependent upon a number of factors including type of task, but is generally in the order of several millimetres or more). Studies of function within the ascending auditory pathway up to the thalamus suffer from a lack of sensitivity and power: for example, brainstem activation is only rarely observed, because auditory nuclei are too small to be adequately resolved in most PET studies (for an exception, see Lockwood et al. [1999b]). There are strict guidelines regarding the administration of ionizing radiation, which in most countries limit the annual dose given to general members of the public to 5–10 millisieverts (mSv; 5 mSv in the UK). Four to 5 mSv is a common dose to be administered over 12 scans in a typical activation PET study: this can be compared to natural background radiation, which in the UK ranges from 2.5 to 7.8 mSv per annum (in areas with quite high natural concentrations of radon). Regulations in most places stipulate that PET cannot be used as a research tool with children or, in the UK at least, with women of child-bearing age. Concerns about the radiation dose thus limit the extent to which tests can be repeated within subjects. For example, longitudinal studies, such as those examining functional reorganization in cochlear implant patients, can only be undertaken in a very limited fashion. Finally, empirical data underline the difficulty of relating activation foci to underlying anatomy, as shall be discussed in a later section.

Advantages

Although fMRI is overtaking PET as the imaging modality of choice, PET has advantages. Unlike fMRI, PET is a quiet imaging technique and can easily incorporate high-fidelity sound delivery, making it a valuable tool in auditory research. PET is the only imaging technique compatible with the metallic and magnetic components contained in many cochlear and brainstem implants. PET has been used with a variety of patient groups: for example, to delineate the neural systems involved in the disturbing condition of tinnitus, to assess systems of preserved function in patients with disorders of consciousness such as coma and PVS and to assess language dominance and localization in patients prior to brain surgery. Most fMRI protocols do not permit as close a contact with the patient as PET (in which the patient is scanned for at most 2 min at a time, preceded and followed by contact with the investigator or radiographer), and most existing MR systems are not head-only and are more likely than PET machines to provoke claustrophobic reactions. PET images do not suffer from geometric distortion and signal loss in anterior temporal and inferior frontal regions, a current (although potentially soluble) problem with fMRI data. PET can be used to derive absolute measurements of rCBF, although this requires a rather more invasive procedure than does the more commonly used technique of measuring relative changes in rCBF. Absolute quantitation of rCBF is helpful for establishing the validity of assumptions made in brain imaging research (such as that of a linear relationship between cognitive processing load and brain activation), and absolute quantification of the BOLD (blood-oxygenation-level-dependent) signal is still under development. Finally, PET is not restricted to oxygen as a tracer: other radio-isotopes can be incorporated into an array of ligands that bind specifically to brain receptors of various types (for example, see Busatto and Pilowsky [1995] and Reith et al. [1994]). Thus, PET is a tool with considerable potential for mapping and studying neuroreceptors and neurochemically specific processes in vivo.

Functional Organization within the Auditory Cortex

PET studies of auditory function can be divided into those that explore the representation, within the auditory cortex, of tonotopicity and other stimulus parameters

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such as loudness, band width, amplitude or frequency modulation rate, and studies that seek to characterize neural circuitry on a wider scale, such as those of auditory spatial localization, processing of music or speech and attentional modulation. These two types of studies shall be dealt with separately, because the success of PET as a tool for exploring them has been rather different in the two cases.

Anatomical Considerations

Functional organization within the auditory cortex is still not well understood, particularly in humans. Microelectrode recordings can only be undertaken in rare circumstances (such as during neurosurgery), post-mortem histological material is difficult to obtain and in vivo tracer studies are currently not possible. Neuroimaging techniques, including PET, have been brought to bear on the question of functional parcellation within auditory regions in humans. However, it is unclear whether these results accord convincingly with anatomical and electrophysiological data from humans or other species.

Functional differentiation is likely to respect anatomical parcellation according to histological and neurochemical criteria. Since the seminal paper by Pandya and Sanides [1973], primate (including human) auditory areas have been conceptually organized in terms of a 'core' of primary-like cortices, receiving a large input from the thalamus, projecting to a surrounding 'belt' composed of several different cortical areas. These belt areas connect with lateral 'parabelt' fields, and these parabelt fields connect with more distant cortex. Each of these regions core, belt and parabelt - possesses a distinctive histological composition, thalamocortical and corticocortical connections, and unique electrophysiological characteristics [Kaas and Hackett, 1998; Kaas et al., 1999; Rauschecker et al., 1995; Rauschecker, 1998; Recanzone et al., 2000]. For example, the core in the macaque monkey displays multiple tonotopic (cochleotopic) gradients and is highly responsive to pure tones. Belt areas, while still exhibiting some tonotopic organization, are more responsive to complex stimuli than to pure tones [Kaas et al., 1999; Rauschecker et al., 1995; Rauschecker, 1998; Recanzone et al., 2000]. Parabelt areas, together with the more distant regions with which they are connected, appear to subserve integrative functions required for such abilities as auditory memory and the perception of auditory location. Thus, systematic sensitivity and responsivity differences appear to exist between neurons in core, belt and parabelt areas.

The few studies of anatomical organization that have been carried out on human tissue have identified discrete



Fig. 3. The auditory cortices are found on the superior temporal plane, on the lower bank of the Sylvian fissure. The first transverse HG, containing the PAC, follows a posteromedial to anterolateral course upon the superior temporal plane. It is bounded medially by the circular sulcus and insula (I), posteriorly by Heschl's sulcus and the planum temporale (PT) and anteriorly by the transverse temporal sulcus and planum polare (PP).

auditory subregions similar to those observed in other animals [Galaburda and Sanides, 1980; Hackett et al., 2001; Morosan et al., 2001; Nakahara et al., 2000; Rademacher et al., 1996, 2001; Rivier and Clarke, 1997], consistent with separate core, belt and parabelt regions. This scheme, therefore, provides a framework within which functional responses can begin to be interpreted.

In humans, the primary auditory cortex (PAC) is found in the medial portion of the first transverse temporal gyrus of Heschl (HG), located on the superior temporal plane on the inferior bank of the Sylvian fissure in both hemispheres (fig. 3, 4). Importantly, if multiple transverse temporal gyri are present, the PAC is generally found on the anteriormost gyrus [Rademacher et al., 1993, 2001; Morosan et al., 2001]. A number of micro-electrode [Celesia, 1976; Liegeois-Chauvel et al., 1991], cyto-architectonic [Galaburda and Sanides, 1980; Morosan et al., 2001; von Economo and Horn, 1930; Rademacher et al., 1993, 2001] and chemo-architectonic [Clarke and Rivier, 1998; Hackett et al., 2001; Nakahara et al., 2000; Rivier and Clarke, 1997] studies support the localization to HG. The central core area is surrounded by secondary auditory cortices [Galaburda and Sanides, 1980; Rademacher et al., 1996; von Economo and Horn, 1930; Rivier and Clarke, 1997; Clarke and Rivier, 1998]. Importantly, the anteriormost HG is easily observed on structural MR scans and can therefore serve as an effective landmark for core auditory areas.

Researchers debate several morphological characteristics of HGs, such as the relative volumes of HG and PAC in the two hemispheres [Rademacher et al., 2001; Penhune et al., 1996], and the frequency of multiple transverse gyri in the two hemispheres [Leonard et al., 1998; Penhune et al., 1996]. Researchers agree, however, on two things: one, that there is a very large degree of inter- and intrasubject variability in the morphology and extent of the transverse gyri and PAC [Leonard et al., 1998; Rademacher, 2001], and, two, that HG and PAC are asymmetrically located in the two hemispheres [Penhune et al., 1996; Rademacher et al., 2001].

Penhune and colleagues [Penhune et al., 1996] used 3dimensional visualization software to measure the volumes of grey and white matter in the region of HG on high-resolution magnetic resonance (MR) images of 40 hemispheres (20 left, 20 right) from neurologically normal individuals, transformed into stereotaxic space. They found that HG was shifted 5–8 mm anteromedially in the right hemisphere, compared to the left, enough so that the right PAC may be incorrectly identified when its location is extrapolated either from the left-hemisphere location or from the atlas of Talairach and Tournoux [1988], still one of the most commonly used atlases for the localization of neuroimaging foci [Penhune et al., 1996].

Rademacher and colleagues corroborated and extended this work, by mapping the cyto-architectonic borders of the PAC in 27 brains. In 10 of these, MR images were available so that each histologically defined volume of the PAC could be digitized and registered with its corresponding MR volume. The images could then be normalized into Talairach space [Talairach and Tournoux, 1988] using a coordinate transformation. Rademacher and colleagues found that the average location of the right PAC was shifted anteriorly by 7–11 mm, compared to the left PAC and to the coordinates given in Talairach and Tournoux [1988], a relatively large asymmetry that needs to be taken into account by neuroimaging researchers when localizing activation foci.

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Fig. 4. A This coronal series of images displays the PAC in a single post-mortem specimen, defined by staining tissue for cell bodies and then using cyto-architectonic criteria (data from Morosan et al. [2001]). Note that the PAC is found on HG, and both PAC and HG are displaced anteriorly in the right hemisphere relative to the left: both of these features are commonly observed [Leonard et al., 1998; Penhune et al., 1996; Rademacher et al., 1993, 2001; Morosan et al., 2001]. B Axial slices through a high-resolution anatomical MR scan from a neurologically normal young adult (the SPM99 canonical brain; http://www.fil.ion.ucl.ac.uk/spm). HG is delineated in white. The 'core' area of the PAC is found on, or overlapping, the medial portion of HG [Rademacher et al., 2001] and is surrounded by a belt of secondary auditory cortex [Kaas and Hackett, 1998; Rivier and Clarke, 1997]. Fortunately, HG is relatively easy to identify on anatomical scans making it a useful gross morphological landmark for the auditory cortex (but see Rademacher et al. [2001]).



Thus, previous work in humans and other animals makes two predictions regarding the results of PET studies of functional organization in the auditory cortex. The first is that functional activations should respect the anatomical asymmetry in the auditory core areas described above. Second, the core, belt and parabelt areas should be functionally distinguishable in humans using PET, as they have proved to be in other animals using other methods.

Do PET Activations Respect the Established Hemispheric Asymmetry in the Location of the Primary Auditory Cortex? A Meta-Analysis

An important premise of functional imaging is that activation will follow anatomy: anatomically homologous areas in the two hemispheres, which are presumably simi-

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lar in function (such as the PAC) should show similar activation patterns. Given that auditory stimuli generally yield strong, bilateral auditory cortical activations, this assumption can be tested directly, by examining whether the right-left asymmetry evident in the anatomy of the PAC is also evident in functional data. Under conditions in which the PAC is assumed to be activated (in comparing sound conditions to silent baseline conditions, for example), one would expect to observe peak activation more anteriorly in the right auditory region than in the left, if activation does respect the anatomical asymmetry. We tested this hypothesis by comparing, across a range of published PET studies of audition, activation foci in the right and left auditory region to the centroids (centres of mass) of the auditory cortex in the two hemispheres, using

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Study	Activation condition	Baseline condition	Classi- fication	Left				Right			
				x	у	Z	Z score	x	у	Z	Z score
Belin et al. [1998]	harmonic complexes incorporating formant transitions	silence	complex tones	-58	-16	0	5.05	50	-22	4	4.83
Gandour et al. [2000]	lowpass-filtered pairs of Thai monosyl- lables; same/different pitch judgement	silence	complex tones	-51	-17	2	4.30 ¹	55	-26	2	5.00 ¹
Thivard et al. [2000]	harmonic complexes incorporating formant transitions	silence	complex tones	-38	-26	8	7.18	62	-32	14	7.77
Mirz et al. [1999a, b]	classical music	silence	music	-48	-18	4	65.00 ²	54	-9	0	53.00 ²
Zatorre et al. [1996]	familiar songs, pitch change judgement on read words	read word pairs; compare length	music	-55	-18	5	10.18	59	-18	3	9.38
Griffiths and Green [1999]	coherent noise and rotating noise	silence	noise	-44	-32	18	5.69	44	-28	10	6.54
Holcomb et al. [1998]	pure tones in noise; alternating keypress	silence, eyes open	noise	-34	-38	12	4.92	58	-34	12	4.32
Weeks et al. [1999]	noise bursts	silence	noise	-48	-38	8	4.29	42	-40	4	4.33
Zatorre et al. [1992]	noise bursts	silence	noise	-46	-30	13	3.05	55	-30	8	3.14
Engelien et al. [1995]	environmental sounds	silence, eyes closed	other	-48	-22	8	_3	52	-26	12	_3
Fiez et al. [1995]	pure-tone triplets, vowels, CV syllables and CVC words	visual fixation	other	-50	-18	11	7.70 ¹	50	-26	11	5.301
Kojima et al. [1997]	click sequences approximating sentences	silence	other	-48	-20	8	2.78	40	-22	-4	4.92
Mirz et al. [2000a, b]	pure tones and 'engine room' sound	silence	other	-40	-33	12	9.201	42	-23	9	9.801
Laureys et al. [2000] ⁴	click stimuli (rate 5.1 Hz) to one ear, white noise to other	silence	other	-40	-28	12	_5	40	-30	12	_5
Frith and Friston [1996] ⁶	listening to tones presented at 0, 103, 0, 50, 70, and 90 wpm		pure tones	-38	-34	12	6.18	48	-30	12	6.83
Griffiths et al. [1999]	pure-tone sequences: same/different judgement on pitch and duration	silence	pure tones	-70	-28	4	4.66	66	-30	6	5.93
Zatorre et al. [1999]	random series of 3 pure tones; keypress to lowest tone	silence	pure tones	-36	-37	11	5.23	58	-33	11	5.88
Bookheimer et al. [2000]	subjects saying 'bah noh dee pie kay' repeatedly	visual fixation	speech	-52	-16	12	4.78	48	-12	4	4.57
Ganguli et al. [1997]	hearing and recalling spoken word lists	visual fixation	speech	-58	-20	4	4.89	56	-24	0	6.30
Grasby et al. [1993]	hearing and recalling spoken word lists	silence ⁷	speech	-52	-30	8	2.91	50	-28	4	3.26
Müller et al. [1997]	sentences	silence	speech	-53	-26	4	6.20	55	-22	-2	6.30
Mummery et al. [1999]6	two-syllable nouns and signal-correlated noise at rates of 1, 5, 15, 30, 75 wpm		speech	-48	-34	8	8.00	44	-24	4	8.30
Paus et al. [1993]	hear 'ay', say 'bee'; hear 'el', say 'em'	silence	speech	-56	-18	5	5.60	62	-23	2	5.30
Petersen et al. [1989]	nouns at 60 wpm	visual fixation	speech	-46	-30	14	2.46	42	-36	12	2.76
Silbersweig et al. [1993]	sustained keypress during sentences	silence	speech	-52	-22	0	8.67	48	-20	0	10.47
Silbersweig et al. [1994]	sustained keypress during sentences	silence	speech	-51	-22	4	13.311	51	-22	1	14.201
Warburton et al. [1999]	verb generation to spoken nouns	silence	speech	-56	-48	18	6.70	54	-44	10	6.50
Wise et al. [1991]	non-words with English phonological structure	silence	speech	-50	-24	12	3.65 ²	50	-22	12	3.902

Table 1. Details of studies included in the analysis, including conditions, stimulus classification, stereotaxic coordinates [Talairach and Tournoux, 1988] and indices of rCBF change from baseline

CV = Consonant-vowel; CVC = consonant-vowel-consonant; wpm = words per minute. 5

1 T statistics, not Z scores. 2

No quantitative data. 6

rCBF magnitude values. No quantitative data, but signal change greater in right than in left. Data collapsed over left- and right-ear stimulus presentations. 4

Correlational studies. Resting data from a different set of subjects. 7

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either the probability-weighted centroids of HG [Penhune et al., 1996] or the probability-weighted centroids of the PAC itself [Rademacher et al., 2001]. In addition, in order to determine whether there was any consistent difference in magnitude of activation between the two hemispheres across different stimulus types, we compared left and right peak signal change magnitudes. We used non-parametric methods since signal change values were indexed in a variety of ways (magnitude of rCBF change, Z or t statistics).

We combed the literature for published studies, with data in stereotaxic space ('Talairach' or 'Talairach-like' space [Talairach and Tournoux, 1988]), in which auditory conditions were either compared to a silent baseline or the stimulus level or rate was parametrically varied to reveal a correlated activity in the auditory cortex. Studies were included if stimulus presentation was diotic or if data were collapsed across the ear of presentation. We found 28 PET studies of auditory function that met these criteria (table 1) and selected a single contrast from each study. Wherever possible, we selected a contrast involving nonlinguistic auditory conditions. When more than one contrast fit this criterion (or none did) we selected the contrast with the largest bilateral Z value. Within a contrast, when more than one significant peak within the left or right auditory area was listed, we chose the peak that was closest to the centroid of the PAC in that hemisphere (as calculated by Rademacher et al. [2001]).

Of the 28 studies, contrasts from 11 of them involved speech sounds. Stimuli ranged from self-generated consonant-vowel syllables [Bookheimer et al., 2000; Paus et al., 1993] to externally produced sentences [Silbersweig et al., 1993, 1994]. Contrasts involved pure tones in another 3 studies, musical stimuli in 2, bursts of noise in 4 and harmonic complexes in 3. The remaining 5 studies presented stimuli that were not classifiable as any of the above (for example, click trains with the same temporal structure as sentences [Kojima et al., 1997] and environmental sounds [Engelien et al., 1995]). Although all standardized spaces are quite similar, homologous locations can vary among 'Talairach' and 'Talairach-like' spaces by a few millimetres. The location of activation foci (in stereotaxic space) will therefore depend somewhat on the way in which the data were anatomically standardized. The anatomical template that was used will affect the final shape and size of the transformed image, as will the transformation algorithm (a landmark-based algorithm will result in a different template match than an algorithm employing minimum norm estimation; an algorithm incorporating non-linear warping will match differently than one that

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uses strictly linear transformations). Although methodological details in the studies were sometimes scanty, it appears that the image processing and analysis package Statistical Parametric Mapping (SPM; www.fil.ion.ucl. ac.uk/spm) was used to analyze the data in 18 studies; an analysis package developed at the Montreal Neurological Institute (DOT) was used in another 5, and the remaining 5 studies used other methods. Most versions of SPM use an anatomical template different to that of DOT. SPM also employs a minimum norm, smoothly non-linear anatomical standardization algorithm, whereas that used by DOT is landmark based and strictly linear. However, the stereotaxic spaces that both techniques operate in are otherwise quite similar. Analysis methods are described in the papers listed in table 1. Although the localization provided by non-SPM non-DOT methods is less certain, in all cases images were transformed into a 'Talairachlike' space, which must approximate the space used in the DOT and SPM analyses.

A significantly large proportion of the studies (19/27; no magnitude information given in Laureys et al. [2000]) demonstrated greater activation in the right hemisphere compared to the left ($\chi^2 = 4.48$, p < 0.05). Even among the 11 speech studies, which might be reasonably expected to produce greater activation in the left, 8 produced greater activation in the right. This finding of generally greater activation in the right compared to the left is surprising and hard to reconcile with conventional neuroimaging assumptions.

The activation peaks from the 28 studies are plotted in figure 5, along with the centroids of the PAC [Rademacher et al., 2001] and HG [Penhune et al., 1996]. Displacements of the activation foci from the centroids of the PAC [Rademacher et al., 2001] and HG [Penhune et al., 1996] are plotted in figure 6. The mean total (Euclidean) displacement from either set of centroids was greater in the right hemisphere than in the left, with PAC: t(27) =3.27, p < 0.005; HG: t(27) = 2.50; p < 0.05. When total displacement was broken down into its three orthogonal components, it became apparent that the significant difference was owing almost entirely to a significant difference in the anterior-posterior dimension: mean activation was significantly more posterior to the centre of PAC/HG in the right hemisphere compared to the left, with PAC: t(27) = 7.90, p < 0.001; HG: t(27) = 3.78; p < 0.01. In the other two dimensions (medial-lateral, superior-inferior), the magnitudes of displacement did not differ between hemispheres, i.e. all t(27) < 0.83; p > 0.05. Thus, activation does not respect the anatomical asymmetry of the PAC but is instead focussed more posteriorly in the right

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Fig. 5. Results of the 28-study meta-analysis of auditory activations relative to HG in the two hemispheres, displayed on a series of axial sections through a multisubject average brain in stereotaxic space. The centroids of HG [Penhune et al., 1996] and PAC [Rademacher et al., 2001] are shown at +7 and +8 mm. Foci from studies were classified according to stimulus type (coded by colour; 6 classifications) and analysis method (coded by shape; 3 classifications). Neither

stimulus type nor analysis method leads to obvious clustering. Instead, foci for most studies are located around the centroids in the superior-inferior (z) and medial-lateral (x) dimensions (located within a few millimetres superiorly or inferiorly, medially or laterally) but, in the anterior-posterior (y) dimension, foci are generally posterior to the centroids, almost never anterior to them.

hemisphere than in the left, falling in secondary auditory areas. These results pertain to the centre of the observed activation: they do not speak to the boundaries or extent of the activated region. Thus, they do not necessarily imply that the PAC is not activated in these studies: in fact, the boundaries of the PAC and HG in the probabilistic maps of Rademacher [2001] and Penhune [1996] encompass a relatively large volume (a volume considerably larger, of course, than for any one individual), and activation in the majority of the studies reviewed overlapped to some extent with the probabilistic volumes. The results do indicate, however, that the PAC is activated at a lower intensity than that of the posterior secondary auditory cortex, particularly in the right hemisphere.

There did not seem to be any effect of stimulus type on the asymmetry in activation location. When each stimulus type was considered separately, the trend for a greater posterior displacement in the right hemisphere compared to the left was observed for speech (6.8 mm more posterior to the centroid of the right PAC than to the centroid of the left PAC, on average), musical stimuli (4 mm), noise (7 mm), pure tones (5 mm) and harmonic complexes (15 mm). (None of these hemispheric asymmetries in displacement reached significance, but the sample sizes are

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Fig. 6. Results of the 28-study meta-analysis of auditory activations relative to HG in the two hemispheres. All data are reported in stereotaxic 'Talairach' [Talairach and Tournoux, 1988] coordinates. **A** Displacements of activation foci in right and left auditory areas compared to the centroids of PAC given in Rademacher et al. [2001]. Activations are significantly lateral to the centroid in both hemispheres and significantly inferior in the right only. Although they are also significantly posterior to the centroid in both hemispheres, they are more posterior in the right than in the left. **B** Essentially identical results are obtained if activation foci are compared to the probabili-

ty-weighted centroid of HG, derived from the data of Penhune et al. [1996]. Although foci are no longer significantly lateral to the centroid, they are significantly posterior to the centroids in both hemispheres, more so in the right than in the left. Foci are also significantly inferior to the centroid in the right hemisphere only. The asterisk indicates significant differences (p < 0.05) between hemispheres in the magnitude of displacement. **C** Orientation of the three axes in standardized coordinate space. The x-axis defines the medial-to-lateral direction, y defines the anterior-posterior direction and z the inferior-superior direction.

small.) This observation, i.e. that the asymmetry in peak location does not depend on stimulus characteristics, contradicts assumptions regarding functional specialization. For example, it seems reasonable to have predicted that the observed left-right asymmetry would be either negated or reversed for speech sounds, since (by conventional accounts of functional organization for speech perception) speech sounds are likely to activate posterior (planum temporale) areas in the left hemisphere. In contrast, the right hemisphere peaks in speech studies cluster more posteriorly in the right than they do in the left, as do peaks for other sound types.

What can explain the persistent left-right asymmetry in peak location and the observed lack of sensitivity to stimulus effects? The most likely explanations involve vascular artefact and partial volume effects resulting from spatial smoothing. First, if a significant portion of labelled water is not extracted in the capillary bed (which seems likely [Ohta et al., 1996]), then a prominent vascular component in the PET signal may be obscuring more local signal changes with their origin in brain tissue. Large vessels course over and adjacent to HG and follow different courses in the two hemispheres [Hochberg and Le May, 1975; Szikla et al., 1997]. Vascular asymmetries are not yet well characterized, but the Sylvian fissure follows different trajectories in the two hemispheres [Westbury et al., 1999], and at least part of the vasculature in this region respects the asymmetry [Hochberg and Le May, 1975; Ratcliff et al., 1980]. It is also worth mentioning that the superficial Sylvian vein and the veins of Labbé and Trolard often meet at the Sylvian fissure in the region of HG, and this anastomosis, a place in which venous blood containing labelled oxygen can accumulate, may well be asymmetrically located relative to HG in the two hemispheres.

All sound conditions would be expected to result in an increased perfusion in auditory regions and thus produce the same, or similar, activation in large vessels in this region, relative to rest. Only by comparing different sound conditions to each other might one subtract this large vascular component and thereby stand a better chance of distinguishing the locations of auditory foci. In line with this possibility, the two correlational studies included in the review [Frith and Friston, 1996; Mummery et al., 1999] both demonstrated activation locations that respected anatomical asymmetries: more anterior in the right than the left hemisphere.

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Second, the spatial resolution of PET as implemented may be insufficient. A smoothing kernel with a Gaussian shape and a full-width at half-maximum distance of 14 mm (typical in such studies) would reduce the resolution, making it impossible to resolve two peaks less than 14 mm apart (in fact, the effective resolving power, given the intrinsic smoothness of the data, would be more like 18-20 mm). Such smoothing would cause a small peak in the PAC (reflecting the component of the labelled water extracted by the tissue) to merge with peaks within 1.5 cm of it (which could reflect the unextracted fraction of labelled water, transmitted by vessels). If large-calibre vessels course posteriorly to HG, the resultant activation peak would be posterior to HG. If the physiological characteristics of primary auditory tissue are such that this area consistently demonstrates a lower level of activation compared to posterior areas (or if the tissue component of the signal is smaller than the vascular component), then smoothing that integrates over these areas would cause activations to be observed behind HG. This does not help to explain the consistent hemispheric asymmetry, however: over many studies, spatial smoothing would influence the certainty with which a peak voxel can be located but should not influence the mean location itself. It is therefore most likely that this phenomenon interacts with another, such as the vascular hypothesis offered above, to produce the observed pattern of results.

Implications for the Exploration of Auditory Functional Organization using PET

The results of this review indicate that peak location and its signal change magnitude are not useful indices of functional activation in PET studies, at least not when a silent rest condition is used as a baseline. If a conventional whole-brain analysis were contemplated, we would advocate using a correlational or factorial design when exploring auditory functional localization using PET.

Analysis methods that do not rely on the location and magnitude of activation at the peak voxel as dependent measures may also be helpful in determining whether a structure of interest, such as HG, is significantly activated by a particular stimulus condition. One possibility is a measure of the areal extent of an activated cluster of voxels: do boundaries of an activation cluster encompass a structure of interest? Such an analysis is almost impossible to implement within a conventional whole-brain voxel-based analysis, because spatial smoothing confounds magnitude of activation and extent: more intense focal signal changes are 'smeared out' over a larger area than smaller ones. A more direct way to measure activation in a structure of interest is to average over signal within the anatomically defined structure, within subjects. Such an approach can be used with unsmoothed data: averaging over the volume of the structure of interest is smoothing, in an anatomically informed way [Johnsrude et al., 2000, 2001]. Unfortunately, it is currently not possible to divide much of the auditory cortex into subregions using anatomical criteria. Even the most basic parcellation into core, belt and parabelt is not certain. Although the core is quite well characterized [Hackett et al., 2001; Rivier and Clarke, 1997; Rademacher et al., 1993, 2001] and can be approximately identified using MR structural criteria, its subdivisions are not confirmed (but see Morosan et al. [2001]) and the borders of belt and parabelt regions are only beginning to be established [Rivier and Clarke, 1997].

Despite these problems, some indications of the functional organization of the auditory cortex can be gleaned from published PET studies; we review these below. We then go on to review studies of integrative functions such as speech and musical perception, attentional modulation and perception of auditory space and movement, which are dependent upon distributed neural systems and consequently do not suffer as much from limited spatial resolution, as the studies of auditory cortical organization do.

PET Studies of Functional Organization within the Auditory Cortex

Tonotopy

Cochleotopic organization is a hallmark of primary auditory areas, and evidence for a tonotopic organization within the auditory region in humans has been sought using PET. Lauter et al. [1985] demonstrated that activation to a 500-Hz tone was anterior and lateral to activation in response to a 4-kHz tone, in each of 5 volunteers. Tones were presented to the right ear, and this frequencyspecific pattern, aligned to the long axis of HG, was only observed in the left (contralateral) hemisphere. This is an early example of the measurement of rCBF as an index of function and is preliminary, with results for only two frequencies. In a recent group study, Lockwood et al. [1999b] also presented 500-Hz and 4-kHz sinewave tones to the right ear of 12 subjects. In general, the 4-kHz tone always activated a greater number of pixels than the 500-Hz tone in auditory system loci in the left hemisphere (including but not restricted to the cortex). In addition, they observed a site lateral to the left HG that was activated by both tones and another, more medial and on HG, that was

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more responsive to the 4-kHz tone. They also observed a site near the left medial geniculate body that was more responsive to 4-kHz tones than to 500-Hz tones. Similar to Lauter et al. [1985], they found no evidence for tonotopicity in the ipsilateral temporal lobe. These two studies are not very substantial given the clear prediction, originating in anatomical and electrophysiological work, in humans and other animals, of multiple tonotopic gradients within the primary auditory 'core'. The dearth of published studies, despite almost two decades of work, suggests that many studies may have been undertaken that have yielded null results. If this is the case, it again underlines the unsuitability of PET for the exploration of functional organization in the auditory cortex.

Effect of Side and Intensity of Stimulation

Unit recording studies in animals indicate that both intensity of stimulation and ear of presentation can have marked effects on patterns of evoked responses. An early PET study, measuring regional cerebral glucose metabolism (using 2-fluoro-deoxyglucose as a tracer), recorded a 7% increase in contralateral metabolism over ipsilateral temporal cortical metabolism, after subjects had listened to a monaurally presented factual story [Greenberg et al., 1981]. Lauter et al. [1985] observed greater contralateral than ipsilateral activation, regardless of stimulus frequency, in their pure-tone study. A similar observation was made by Laureys et al. [2000], who noted that activation evoked by click stimuli extended from HG to the lateral surface of the superior temporal gyrus and to the temporoparietal junction only in the hemisphere contralateral to stimulation: activation evoked on the ipsilateral side was confined to HG. Perhaps surprisingly, speech stimuli also appear to activate primarily contralateral tissue: Hirano et al. [1997] observed more activation in the right temporal cortex when speech was presented to the left ear and vice versa. They did not quantify this asymmetry, however, nor did they test for an effect of the ear of presentation on the magnitude of this asymmetry. From the figures in their paper, it appears that the asymmetry may have been less pronounced when speech sounds were presented to the left ear compared to the right.

Lockwood et al. [1999b] report a study in which 500-Hz and 4-kHz sinewave tones (500 ms on, 500 ms off, continuous stimulation) were presented to the right ear at four different intensities (30, 50, 70 and 90 dB HL). They did not observe any asymmetry in the magnitude of cortical activation but did find activation in the left pontine tegmentum (containing the cochlear nuclei and superior olivary nuclear complex), extending rostrally to the level

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of the medial geniculate body. At this level, auditory structures would be predicted to exhibit bilateral activation. Thus, the reported unilateral activation would be puzzling except that it is unusual to observe brainstem activation using water bolus PET in the first place.

In general, the number of activated pixels in auditory system loci (including but not restricted to the cortex) increased with increasing stimulus intensity. A significant correlation of activation with intensity was observed at sites around HG in the left hemisphere: for the low tone, the correlated site was centred on a voxel placed laterally in the brain, whereas for the high tone both lateral and medial correlated sites were observed. Furthermore, Lockwood and colleagues observed that, in the ipsilateral hemisphere, the z coordinate (indexing the inferior-superior dimension; see fig. 6) of the observed activation focus in the auditory cortex increased systematically with stimulus intensity, providing some evidence for an 'amplitopic' organization in the hemisphere ipsilateral to stimulation.

Temporal Processing

'Temporal processing' is the overarching term for a (probable) set of cognitive operations that recruit partially overlapping neural circuits and work on different time scales but have in common the processing of the temporal structure of sound.

At the millisecond scale, this describes processes by which periodic (sinusoidal) sounds come to have a pitch, and by which speech sounds, with quickly changing information encoding phoneme identity, are perceived. At a more coarse temporal scale, it can be used to describe stages of rhythmic and melodic and prosodic perception, which rely on the accurate perception of signal changes occurring over several hundred milliseconds [Griffiths, in press]. Much of the processing of information in the millisecond range occurs in brainstem structures and is therefore largely inaccessible to the PET camera. PET has been used successfully by Griffiths et al. [1998a] to examine the cortical correlates of pitch perception based on temporal cues, by employing an elegant set of stimuli called iterated rippled noise. These are noise stimuli in which the longterm energy spectrum is held constant but the temporal microstructure is altered in order to vary the temporal regularity and thus the impression of pitch. The researchers found that temporal regularity (and pitch strength) correlated with CBF change in the probable non-PAC bilaterally (lateral, anterior and inferior to the centroids of the PAC [Rademacher et al., 2001] in both hemispheres).

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Other PET studies have explored the processing of auditory information of a fine temporal grain (such as temporal ordering of tones or frequency glide discrimination), but few of these have demonstrated systematic correlates within auditory cortices [Belin et al., 1998; Fiez et al., 1995; Johnsrude et al., 1997; Pedersen et al., 2000]. Belin et al. [1998] scanned people while listening to complex speech-like stimuli, composed of a fundamental and four formants. The frequency of peak energy in each formant changed by 25% over the initial and final 40 ms of the stimulus, whereas the central 200-ms portion was steady state. Passive listening to such stimuli was contrasted with passive listening to stimuli that were identical in all respects except that the duration of the formant transitions (and total duration) were increased to 200 ms (600 ms). The stimuli were designed to be unidentifiable as speech, and subjects did not identify them as speech sounds. Auditory cortices in both hemispheres were strongly activated in both listening conditions relative to a silent baseline. Whereas activation in left auditory regions was equivalent in extent and magnitude in the two conditions, a cluster of voxels centred just posterior and medial to the PAC in the right hemisphere was observed to be less active for rapid transitions than for slow ones. This result is consistent with the hypothesis that the left-hemisphere specialization for language may be based, in part, on a preferential responsiveness within the left auditory cortices (possibly including primary areas) to information of a fine temporal grain, such as is contained in some speech sounds. Thivard et al. [2000] compared activation evoked by stimuli very like the 'slow transition' stimuli of Belin et al. [1998] to that evoked by stimuli that had a similar composition and 'formant-like' structure, but without any spectral-energy change. They observed bilateral activation just caudolateral to HG, in an area that is possibly within the human belt region, an area that, in monkeys, is known to contain neurones sensitive to the direction and rate of frequency modulation [Rauschecker, 1998].

PET Studies of Auditory Integrative Function

Speech Perception

Speech comprehension must comprise multiple processing stages as sounds are mapped onto stored linguistic representations and then combined to derive a representation of the meaning of an utterance. Do auditory cortical regions merely process the acoustics of speech, leaving determination of the linguistic identity and significance of speech sounds to higher-order, associative areas (in and around the temporal lobe of the dominant hemisphere), or is some linguistic processing also accomplished in auditory regions? Several PET studies have demonstrated that the superior temporal gyrus, anterior to the PAC in both hemispheres, is activated by speech sounds compared to rest, noise bursts or tonal stimuli [Démonet et al., 1992; Zatorre et al., 1992; Mummery et al., 1999; Scott et al., 2000; Wise et al., 1991; Giraud and Price, 2001]. The results of many such studies are not clearly interpretable with respect to the question above, since the acoustic complexity of speech sounds is difficult to match in control conditions (but see Zatorre et al. [1992], Mummery et al. [1999] and Scott et al. [2000]).

Mummery et al. [1999] performed a correlational PET study in which they presented spoken words or signal-correlated noise [Schroeder, 1968] at six different rates. (Signal-correlated noise is made by multiplying the amplitude of a speech stimulus by white noise.) They found that HG in both hemispheres, and the superior temporal gyrus lateral to it, showed correlation of activity with rate of presentation, regardless of the type of stimulus. In contrast, a more anterior and inferior part of the superior temporal gyrus (STG) extending to the superior temporal sulcus (STS) and a posterior site within the STS demonstrated activity that correlated uniquely with word presentation rate. This latter peak was observed in the left (dominant) hemisphere only. Evidence supporting a functional dissociation of the right and left STG activations observed by Mummery et al. [1999] comes from PET studies by Giraud and Price [2001] and Scott et al. [2000]. Giraud and Price contrasted words, syllables and environmental sounds with noise bursts and observed activation bilaterally in the mid STG. When words and syllables were contrasted with noise and environmental sounds, activation was observed anterior and posterior to the PAC on the STG in the left hemisphere only. In the study of Scott et al. [2000], normal subjects were scanned while listening to intelligible noise-vocoded sentences [noise-vocoding is a process that largely removes spectral information but that preserves temporal cues; Shannon et al., 1995], normal sentences or (unintelligible) control stimuli created by spectrally inverting stimuli from the two intelligible conditions [Blesser, 1972]. (The inversion involves spectrally rotating a speech signal about a particular frequency axis.) Importantly, rotated normal speech, although unintelligible, contains some phonetic information (e.g. unvoiced fricatives), but rotated noise-vocoded speech does not. The researchers observed activation along the left STG extending laterally and anteriorly from HG in response to any stimulus type containing phonetic information. A

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similar response pattern was seen in a site in the posterior STS, near that observed by Mummery et al. [1999]. In contrast, a left STG/STS area, anterior and inferior to the first location, was activated solely by intelligible speech. These results are consistent with the fMRI literature and also with what would be predicted based on what is known from other primates regarding anatomical connectivity and levels of processing in the auditory region: that a stream of hierarchically organized cortical processing levels extends laterally and anteriorly from the PAC within the temporal lobe [Kaas and Hackett, 1998, 2000; Rauschecker and Tian, 2000; Tian et al., 2001].

Perception of Melody and Rhythm

PET has been used to explore the neural bases of music processing in a relatively large number of studies [Griffiths et al., 1998a, 1999; Platel et al., 1997; Zatorre et al., 1992, 1994, 1996, 1998, 1999; Halpern and Zatorre, 1999; Blood et al., 1999; Perry et al., 1999; Sergent et al., 1992; Sergent, 1993]. As one might expect, given the highly complex, artistic and subjective nature of musical experience, most of these studies concern integrative cognitive functions that rely upon a large network of areas, extratemporal as well as temporal. For example, Blood et al. [1999] examined rCBF changes related to affective responses to music. Volunteers listened to 6 versions of a novel musical passage in which dissonance was varied systematically, and activation correlated with dissonance in several distinct paralimbic and neocortical regions that had been previously associated with pleasant/unpleasant emotional states. We will restrict our attention in what follows to studies that reveal something about the function of the temporal auditory cortex.

In addition to demonstrating areas in which activation correlated with increasing temporal regularity (see 'Temporal processing' above), Griffiths et al. [1998a] were able to pinpoint areas in which temporal regularity (and hence the strength of the pitch percept) provoked a stronger increase in rCBF when there was some pitch excursion between stimuli than when pitch variation was much more limited (although pitch range was held constant). In the former case, increasing pitch strength would result in the emergence of a melody; in the latter, it did not. Areas associated with melodic perception were found bilaterally on the STG, both anterior and posterior to HG. These findings have recently been replicated using fMRI [Griffiths et al., 2001].

Robert Zatorre and his colleagues have conducted an extensive series of PET studies investigating brain systems involved in musical processing, including melodic

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perception, memory and imagery, rhythmic perception and production, and singing [Zatorre et al., 1992, 1994, 1996, 1998; Halpern and Zatorre, 1999; Penhune et al., 1996; Blood et al., 1999; Perry et al., 1999]. These studies were based, in part, on the observation of deficits on many tasks of musical perception and memory in patients with excisions from the right, but not left, anterior temporal lobe. Excisions generally included some belt, parabelt and higher-order auditory regions. In one of the earliest studies, Zatorre et al. [1994] played subjects unfamiliar 8-note tonal melodies and had them either listen passively, compare the pitches of the first two notes of the melody or compare the first note with the last. Passive listening (compared to noise bursts) revealed a network of activation involving the right fusiform gyrus and the right STG, near the posterior activation observed by Griffiths et al. [1998a]. In contrast, the pitch memory tasks (compared to passive listening) both activated a wider network of areas, including frontal regions, cingulate and cerebellum, and these were not restricted to the right hemisphere. None of the conditions appeared to elicit activation in HG (compared to control conditions), a finding consistent with the idea that primary and proximate belt areas are involved in acoustic processing at a low level, and do not subserve cognitive capacities such as memory for particular tones or perception of tonal sequence.

Perception of Auditory Spatial Location and Movement

The perception of location and movement in auditory space requires sensitivity to a number of acoustic cues, such as relative phase and amplitude at the two ears, and changes in these over time. Work in animals indicates that information from the two ears first converges in the superior olivary complex in the brainstem [Irvine, 1991], and so binaural positional information is potentially available at all higher levels. Work in animals also demonstrates that primary auditory cortical lesions interfere with the detection of dynamic phase differences between the two ears, information which may be important for sound position identification and tracking [Altman and Kalmykova, 1986]. In the macaque monkey, there appear to be at least two broad streams of information flow: the anterior belt and parabelt areas project anteriorly, along the temporal lobe and into the ventrolateral frontal cortex, whereas the posterior belt area projects posteriorly and dorsally and may be part of a processing stream including the parietal cortex and dorsolateral frontal cortex [Hackett et al., 1999; Romanski et al., 1999]. These ventral and dorsal streams are strongly reminiscent of the

tut Pasteur - CeRIS .99.10.101 - 2/17/2023 6:01:36 PN 'what' and 'where' pathways evident in the visual system [Romanski et al., 1999; Kaas and Hackett, 1999; Ungerleider and Mishkin, 1982].

The results of PET studies of auditory spatial localization are in line with the hypothesis that a dorsal processing stream, including parietal and dorsolateral frontal areas, is involved in the perception of spatial position of auditory objects [Weeks et al., 1999, 2000; Bushara et al., 1999; Griffiths et al., 1998b; Griffiths and Green, 1999; Rauschecker and Tian, 2000]. Bushara et al. [1999] used PET to compare auditory and visual spatial localization. They created a virtual auditory space by synthesizing band-passed noise bursts and convolving these with headrelated transfer functions, separately for each ear. Subjects were scanned while identifying azimuthal positions for these sounds, and activation was compared to that evoked by passive stimulation. Analogous tasks were employed in the visual domain. Although the precise locations activated by visual and auditory stimuli were distinguishable (activations were modality specific), the general activation pattern observed was similar for both modalities, namely bilateral activation in the superior and inferior parietal lobules and middle frontal gyrus, right medial frontal cortex and left lateral cerebellum [Bushara et al., 1999]. Weeks et al. [1999] found that the right inferior parietal lobule was significantly more activated when subjects performed a stimulus localization task very similar to that used by Bushara et al. [1999], relative to when subjects performed a task requiring stimulus frequency discrimination. Griffiths et al. [1998b] presented stimuli incorporating a linear change in both phase and amplitude difference between the ears: this results in the perception of a moving sound (if the resultant direction of movement is the same for both amplitude and phase cues) or a stationary one (if the cues 'point' in different directions and are balanced to cancel). Comparison of activation in these two conditions reviewed a peak in the right dorsomedial parietal cortex. A peak in a similar location, along with other peaks in parietal regions bilaterally, was observed in a replicative fMRI study [Griffiths et al., 1998b]. In a conceptually similar study, Griffiths and Green [1999] recorded from within the ear canals of subjects while they were listening to amplitude-modulated broad-band noise emanating from 4 speakers placed around the head. The amplitude modulation was either in phase at all 4 speakers (stationary percept) or 90° out of phase at successive speakers (producing a rotating percept). The ear canal recordings were then played back to subjects in the PET scanner. The rotating stimuli (compared to stationary stimuli) evoked activation in right

parietal and bilateral premotor (frontal) regions, again consistent with parietal and frontal regions, particularly in the right, being recruited during the localization and tracking of auditory objects in space.

Modulation of Primary and Secondary Cortices by Attention

Attentional modulation presumably performs an important 'gating' function for perceptual information, as manifested in our awareness, at any point, of only a select few of the sensations potentially available [Rees and Frith, 1998]. An extensive body of evoked response potential literature supports the view that the processing of auditory sensory information can be influenced by attention at a relatively early stage [Woldorff et al., 1993], and the influence of attentional factors in modulating activation in primary and adjacent auditory cortical regions has been quite intensively studied in recent years using both fMRI and PET. Most such studies have compared attention to auditory stimulation either to passive listening [Tzourio et al., 1997] or to attention to the visual modality [Alho et al., 1999; Frith and Friston, 1996; Kawashima et al., 1999]. In some studies, researchers have asked subjects to attend selectively to a particular stimulus parameter, such as ear of entry [Alho et al., 1999; O'Leary et al., 1996; Tzourio et al., 1997; Zatorre et al., 1999] or stimulus frequency [Zatorre et al., 1999], usually in the context of a target detection task.

A number of researchers have demonstrated increases in rCBF in auditory cortical areas contralateral to the attended ear [Alho et al., 1999; O'Leary et al., 1996; Tzourio et al., 1997]. In at least one of these studies [Alho et al., 1999], the peak of the attention-contingent effect was located on HG, probably within the PAC (coordinates within 11 mm of the centroids of the PAC as reported by Rademacher [2001]).

Auditory Areas and Functional Integration

Most functions examined by cognitive neuroscientists have their physical basis in the coordinated activity of large-scale networks. Several PET studies have demonstrated activation in auditory cortical areas as a result of stimulation in other sensory modalities or as a result of associative learning. Such studies inform about the functional architecture of the brain and the role of auditory regions in a variety of cognitive systems. For example, Paus et al. [1996] measured changes in rCBF while subjects whispered syllables ('ba lu') at different rates. Lowintensity white noise was used throughout to mask any auditory input resulting from whispering. They found a

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significant correlation between rCBF and whisper rate in normal subjects in two regions in the left temporal lobe, just medial and posterior to HG, in what are probably auditory belt areas [Galaburda and Sanides, 1980]. They interpret these activations as reflecting excitatory input from other brain regions, such as motor speech areas, and speculate that disturbances of this feedback mechanism may be related to auditory hallucinations, discussed in greater detail in a subsequent section.

Associative learning can also produce modulation of activity in auditory cortical regions. Molchan et al. [1994] studied eyeblink conditioning by scanning during sessions in which presentations of an 80-dB 1-kHz tone (diotically presented) and an airpuff to the right eye were (a) unpaired, (b) paired or (c) the tone was presented on its own. The total number of tones was held constant across conditions. A significant increase in rCBF in auditory regions was noted in the paired (associative learning) sessions relative to both the unpaired and tone-alone sessions, and this was more extensive in the left, contralateral to the airpuff. Molchan et al. [1994] locate these activations in the PAC, and the coordinates do fall within the probability volumes of Rademacher [2001] in both hemispheres, albeit within a relatively low probability zone. Alteration of activity in auditory cortical regions as a function of learning was also observed by Morris et al. [1998]. They used a discriminatory classical conditioning procedure, in which one pure tone (either 8 kHz or 200 Hz; presented diotically at \sim 70 dB) signalled the occurrence of diotic 100-dB noise bursts, and another did not. After conditioning, they observed significant deactivation in the auditory cortex in both hemispheres and in the medial geniculate body in the left, to the tone (either 8 kHz or 200 Hz) signalling noise, relative to the tone that signalled absence of noise (during scanning, the tones were presented without noise). The cortical activations fall well within the probabilistic volumes of the PAC [Rademacher, 2001], indicating that the primary sensory cortex itself was modulated by learning.

Studies of Auditory Function in Clinical Populations

Tinnitus

Tinnitus can be defined as a sound, such as buzzing or ringing, in one or both ears, that is not caused by external stimulation. Tinnitus can be associated with a wide range of disorders, and its pathophysiological origin remains largely unknown. A peripheral disorder, very often a hear-

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ing loss [Pilgramm et al., 1999] associated or not with spontaneous acoustic emissions [Penner, 1990; Powers et al., 1995; Chéry-Croze et al., 2000], is often related to the symptom. The actual generator of tinnitus, i.e. aberrant neuronal activity, is however thought to be central in most cases [Bauer et al., 2000], and central factors including attentional and emotional aspects are also likely to contribute to the chronic persistence of tinnitus [Hazell and Jastreboff, 1990]. Several studies have used neuroimaging, including PET, to explore the neural substrate of tinnitus. Many of these studies have found tinnitus to be associated with increased activation in auditory regions. Arnold et al. [1996] observed increased asymmetry in the temporal transverse gyri in tinnitus patients with higher levels of spontaneous activity on the left side, irrespective of tinnitus laterality. Lockwood et al. [1998] showed that tinnitus provoked by jaw movements gave rise to activation in the PAC and secondary auditory cortex that correlated with subjective loudness of the abnormal perception [Lockwood et al., 1999a]. These results are consistent with the notion that tinnitus is correlated with activity in largescale neuronal circuits that include regions located outside the PAC and secondary auditory cortex, particularly in attentional and limbic systems.

In a recent paper [Giraud et al., 1999], we present results from a PET study on 4 people suffering from a form of tinnitus that is evoked by eye movements performed in the horizontal plane. We scanned them while moving their eyes horizontally and contrasted activation with that from conditions in which subjects also performed eye movements but did not perceive tinnitus. We consistently observed bilateral activation of middle temporal and temporoparietal regions when they experienced tinnitus [Giraud et al., 1999] compared to when they did not. Similar results were found by Mirz et al. [1999a, b, 2000a] when comparing a condition in which tinnitus was perceived with a condition in which tinnitus was suppressed, by either noise masking or lidocaine suppression. They observed activity in middle frontal and middle temporal regions, and in limbic areas, possibly owing to the aversive nature of the tinnitus percept. Other studies in control subjects suggest that those regions implicated in tinnitus are also implicated in the processing of other, aversive, auditory stimuli [Mirz et al., 2000b; Morris et al., 1998].

The long integration time of PET, usually considered a disadvantage of this technique, is not a problem for studying tinnitus, since it is usually a permanent sensation that can be modulated by external noises over time periods compatible with PET constraints. Due to loud noise background levels, fMRI probably remains less well adapted as tinnitus often worsens after exposure to intense noise.

Cochlear Implants

Cochlear implantation is a unique therapeutic means of restoring a sensory modality. This technique allows very young children suffering from congenital or prelingual sensorineural deafness to develop normal language and postlingually deaf adults to recover speech comprehension. Cochlear implants also offer an interesting approach to neural plasticity associated with sensory reafferentation, deafness and speech comprehension recovery. Many conventional cochlear implant devices are not compatible with fMRI, so PET has often been used to investigate neural activations associated with electrical hearing [Herzog et al., 1991; Naito et al., 1995, 2000; Nishimura et al., 2000; Okazawa et al., 1996; Truy et al., 1995; Wong et al., 1999].

Giraud and colleagues used PET in a series of experiments exploring brain activation in response to auditory stimuli in: (a) naive implant patients who had recently been implanted and therefore had poor comprehension, (b) patients who had incompletely recovered comprehension and (c) in fully rehabilitated patients [Giraud et al., 2001a, b]. We observed virtually no speech-related activation in the auditory/language regions of the left hemisphere just after implantation, which is consistent with the inability of most patients to distinguish between speech and noise, and meaningful and meaningless sounds, respectively, in the days following the first implant set-up. After 1 year of practice, the superior temporal regions became activated, mostly on the right side, irrespective of the side of implantation. This regained responsiveness coincided with recovery of speech comprehension. Finally, fully rehabilitated patients showed activation patterns close to normal in classical speech regions of the left hemisphere.

However, when comparing directly brain activations in fully rehabilitated implant patients and controls with equivalent comprehension performance, speech-related patterns were not exactly the same [Giraud et al., 2000]. Using auditory stimuli with or without phonological structure and with or without meaning, we could distinguish regions recruited by patients and controls under identical task conditions from regions showing a different functional specialization between the two groups. The left and right superior temporal cortices and the left insula were activated in both patients and controls when they repeated words and syllables and named environmental sounds compared to when they produced a fixed verbal response to noises. In contrast, Wernicke's area responded specifically to speech sounds in controls (words and syllables) but showed no functional specialization in patients.

By comparing groups of subjects matched with respect to performance during scanning and by using a design that disentangled different steps in auditory word processing, we could demonstrate that implantation is associated with an alteration of the functional specialization of the posterior superior temporal region. These findings suggest that implant patients are able to process a large range of complex sounds in a region that normally responds selectively to speech [Giraud et al., 2001a].

We also observed new regions that were recruited by patients only: the left dorsal occipital cortex showed systematic activation by words, syllables and environmental sounds versus noise baselines. Using a cross-sectional analysis that involved 18 patients at different times after implantation, we found that the response in the visual cortex increased as a function of time elapsed since implantation. Its functional specialization also evolved, progressively acquiring selectivity to those sounds that are likely to convey a meaning, in particular speech sounds. Behaviourally, we not only observed an increase in speech comprehension after implantation but also an increase in lip-reading performance alone. Blood flow in the visual cortex correlated with lip-reading performance and we observed that subjects with the highest lip-reading performance were also those who had the highest activity level in the visual cortex. These results altogether suggest that, by restoring hearing, cochlear implants restore crossmodal interaction and promote a mutual reinforcement of hearing by vision and vision by hearing [Giraud et al., 2001b].

Using PET, we were able to study plasticity related to implantation as focal alterations of the functional specialization of speech areas and as modifications at the level of large-scale neural circuits, revealing a particular form of cross-modal interaction (see review by Giraud et al. [2001c]).

Auditory Hallucinations and Hallucinosis

PET has been used to explore the neural substrates of a variety of auditory hallucinatory phenomena. Hallucinations are formed, organized percepts arising in the absence of external stimuli, and can occur either as a symptom of psychotic illness (such as schizophrenia), as a result of structural brain lesions or epilepsy or as a concomitant of peripheral hearing loss [Berrios, 1990; David, 1999;

Griffiths, 2000]. The content of the hallucinatory experience depends to some degree on aetiology. Psychotic hallucinations almost always involve 'voices' and comprehensible speech [Nayani and David, 1996], whereas hallucinosis related to brain lesions, epilepsy and hearing loss is more variable, often involving music [Griffiths, 2000]. (Tinnitus is considered separately since it lacks the organized structure and content of hallucinations, although activation in brain areas specialized for auditory processing is observed in both phenomena.)

Theories of auditory-verbal hallucinations often emphasize the similarities between these and inner speech, and postulate a breakdown in the mechanism by which self-generated speech is identified as such [Friston and Frith, 1995; McGuire et al., 1995, 1996a, b; Paus et al., 1996]. A number of PET studies have been conducted which are consistent with this. For example, the study by Paus et al. [1996] revealed systematic modulation of auditory cortical areas as a function of speaking rate. The authors interpret this activation as evidence for a feedback mechanism and speculate that its dysfunction may be related to auditory hallucinations (see also Friston and Frith [1995]). Further evidence for this idea was supplied by McGuire et al. [1995], who studied schizophrenic patients with PET and found that they failed to activate certain left temporal areas, compared to normal control volunteers, when generating internal speech.

Griffiths [2000] and Griffiths et al. [1997] used PET to study musical hallucinosis in acquired deafness. Griffiths views such phenomena as indicative of intact central mechanisms for the perception of musical patterns. Assuming that the PAC is necessary (but not sufficient) for the perception of the acoustic components of music, while the surrounding belt, parabelt and associative cortex integrate this information into a musical percept, musical hallucinations ought to involve these higher-order, integrative areas. Six subjects with moderate or severe bilateral deafness and a history of musical hallucinosis were each scanned 12 times. At the end of each scan, they were asked to rate the severity of their hallucinatory symptoms during the scan and to detail the content of any hallucinatory experiences. An analysis in the 4 subjects who showed a relatively normal brain structure and some variability in symptom severity across scans revealed significant correlations between activation and symptom severity in a network of areas, including the planum temporale extending onto the lateral surface of the posterior STG bilaterally, posterior middle and inferior temporal gyri (particularly in the right), right basal ganglia and frontal operculum, and left dorsolateral frontal cortex. This pat-

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tern is similar to what is observed in normal volunteers when actually listening to music, except for the lack of activation in primary areas [Griffiths et al., 1999]. PET studies of musical imagery in normal volunteers with intact hearing have revealed a pattern of activation similar to that observed in Griffiths' patients [Zatorre et al., 1996; Halpern and Zatorre, 1999], including a lack of activation in HG. Studies of auditory-verbal imagery [McGuire et al., 1995, 1996b; Silbersweig and Stern, 1998] also fail to demonstrate activation of HG. Taken together, the data from these studies suggest that at least some auditory hallucinations may arise from spontaneous activity in a network subserving musical imagery, a network that, with the exception of the PAC, is similar to that underlying musical perception.

The absence of PAC activity in hallucinations is not absolute, however. An event-related fMRI study in paranoid schizophrenic patients revealed an increase in BOLD signal in HG during auditory verbal hallucinations [Dierks et al., 1999]. The researchers suggest that, in fact, HG activation during psychotic hallucinations might help to explain why such phenomena are perceived as real (attributed to external sources).

Presurgical Mapping

Surgery is an effective treatment for seizure disorders in many patients, but it is considered successful only if it leaves the patient free from debilitating neurological deficits, such as aphasia. Patients with lesions in or near putative speech zones - the inferior frontal cortex, the lateral temporal neocortex and around the temporoparietal junction of the dominant hemisphere - are a population that must be treated with particular care in this regard. Traditionally, procedures such as the intracarotid sodium amobarbital (Amytal) test and electrocortical stimulation mapping during surgery have been used to map crucial functions so that an 'eloquent' cortex can be avoided. These are highly invasive procedures, often frightening for the patient, and costly to perform. Functional imaging provides a potentially revolutionary alternative with many advantages over traditional procedures. Like the Amytal test, functional neuroimaging can be used to evaluate hemispheric dominance for language (in left-handed patients, for example, who have a moderate change of having atypical speech dominance). Unlike the Amytal test, imaging allows the mapping of functional organization within individuals. Previously this was only possible by stimulating with electrodes over the exposed cortex in awake patients: a challenging procedure (for both surgeons and patients).

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A large number of studies have evaluated functional blood flow neuroimaging techniques (originally PET; now, increasingly, fMRI) for their utility in mapping speech function preoperatively. (PET investigations include, for example, Bookheimer et al. [1997, 2000], Herholz et al. [1997], Klein et al. [1997] or Leblanc et al. [1992]; for reviews, see Gaillard et al. [1997] or Xiong et al. [1997].) Most such studies compare the results of imaging studies of language (PET or fMRI) with those of electrocortical mapping and Amytal. In general, lateralizing measures derived from functional imaging data are concordant with Amytal test results [Desmond et al., 1995; Binder et al., 1996; Hunter et al., 1999; Worthington et al., 1997; Benson et al., 1999; Leblanc et al., 1992], and the locations of activation foci coincide with areas that produce speech arrest and disruption under electrocortical stimulation [Bookheimer et al., 1997; Fitzgerald et al., 1997; Herholz et al., 1997; Klein et al., 1997; Yetkin et al., 1997; Bittar et al., 1999; Schlosser et al., 1999]. This work is still in its early stages, however. A number of issues make a straightforward comparison with other mapping methods difficult, if not impossible. For example, the size of an activation 'blob', and hence the size of the apparently activated cortical region, changes as a function of significance threshold: the actual extent of the tissue that contains the neural populations responsive to the experimental condition is difficult to determine. Second, imaging techniques reveal not only areas critical for the performance of a particular task, but also those in which activity is correlated with task performance. It is the critical areas that are of primary interest to the operating surgeon, of course, but these cannot be identified without converging evidence from other modalities (stimulation mapping, for example).

Although it has not been employed very often to date [Klein et al., 1997], functional imaging data can be combined with frameless stereotaxic navigation techniques, in order to provide intra-operative, interactive feedback to surgeons, allowing them to visualize the location of functional activation foci relative to tissue that they are preparing to resect. Although more work needs to be done before these techniques are clinically accepted alternatives to the traditional methods of determining language dominance, the initial findings are promising.

Assessment of Residual Function in Patients in a Vegetative State

The increasing sophistication of medical technology means that more severely brain-damaged patients can be kept alive than ever before. The ultimate level of recovery among such patients is variable: some remain in a coma, some recover awareness, and some recover some autonomic function without awareness, a condition known as PVS. Jennett and Plum [1972] described PVS as a state of 'wakefulness without awareness', and this description captures the essence of the disorder. Although this disorder has been formally defined, and there is an established set of diagnostic criteria [ANA Committee on Ethical Affairs, 1993], recent reports have raised concerns about the accuracy of diagnosis in some patients, and the extent to which, in a selection of cases, residual cognitive functions may remain undetected [Childs et al., 1993; Andrews et al., 1996; Laureys et al., 2000; Owen et al., in press; Schiff and Plum, 1999; Schiff et al., 1999]. The aetiology is highly variable, and PVS can result either from widespread cerebral damage or from more focal damage to diencephalic and/or cortical regions [Schiff and Plum, 1999]. A diagnosis of PVS is not normally considered until between 1 and 3 months post ictus at which point there must be no evidence of sustained, reproducible, purposeful or voluntary behaviour in response to any kind of external stimulus, in any modality, pleasant or noxious. There must also be no evidence of language comprehension or expression. There is generally sufficiently preserved hypothalamic and brainstem autonomic function to permit survival with medical care. In contrast to patients in coma, who present with eyes closed and lack any consistent sleep-wake cycles, patients with PVS demonstrate a cyclic (albeit often irregular) state of circadian sleeping and waking.

Behavioural assessment of residual cognitive function can be extremely difficult since damage to output systems will be confounded with perceptual or processing impairment. Motor responses can be inconsistent in many vegetative patients and undetectable in others. Examination of covert processing by functional neuroimaging holds great promise, therefore, in the assessment of preserved function in patients with a clinical diagnosis of vegetative state [Owen et al., in press; Schiff and Plum, 1999]. The PET activation method, which is more resistant to movement artefact and permits greater patient access and contact than fMRI, is particularly ideal. In addition, auditory stimulation (at least when brainstem auditory evoked responses are not absent bilaterally) may be preferable to visual stimulation, since spontaneous eve closure will not interfere. Furthermore, auditory stimulation appears to be more efficacious than visual stimulation at maintaining the vegetative patient in an awake state [Owen et al., in press].

Indices of residual cognitive function in PVS have been sought in several PET studies: a handful of these concern the assessment of auditory and speech functions [Owen et al., in press; Laureys et al., 2000]. The goals of such studies are twofold: to assess perceptual and processing systems, and to seek correlates of eventual clinical status (PVS, coma or some level of awareness). Laureys et al. [2000] used PET to explore resting metabolism and stimulus-contingent blood flow in the superior temporal region in 5 patients who had recently (3-38 days) fallen into a vegetative state. All patients showed preserved brainstem auditory evoked potentials bilaterally, and no signs of sleep during electro-encephalographic recording concurrent with PET scanning. Despite a resting metabolism that was on average 61% of normal values, significant activation in HG was observed bilaterally in response to monaural click stimuli. Activation in the patients differed from that in normal subjects in two important ways. First, the normal subjects showed activation in auditory association areas contralateral to the stimulated ear, whereas the patients did not. Second, an analysis of psychophysiological interactions [Büchel and Friston, 1997] revealed coordinated activity in normal subjects, but not in patients, within a network of areas including the parietal association cortex, the hippocampus and the anterior cingulate. For Laureys et al. [2000], these demonstrable functional disconnections illustrated the fragmentary nature of cognitive function in vegetative patients. Three of the patients subsequently recovered awareness, but no correlate of this eventual recovery was observed in the PET data. It is interesting to speculate whether predictors of recovery may have been found if the stimuli had been more amenable to higher-order processing (stimuli such as speech or music): a recent case report is suggestive [Owen et al., in press]. The patient was a 30-year-old female road traffic accident victim who showed no consistent signs of volitional activity 14 weeks after her accident. A speech perception task was employed, in which concrete nouns were presented diotically at 3-second intervals during 6 of 12 activation scans. During the remaining scans, signal-correlated noise bursts were presented at the same intervals. Subtraction of control from test stimuli (speech) revealed significant rCBF increases in HG bilaterally and more posteriorly in the left planum temporale. These findings correspond closely with PET results from a recent study of 6 healthy control subjects using identical stimuli [Mummery et al., 1999] and suggest that this patient was exhibiting some residual language comprehension at the time of scanning. Importantly, the patient had recovered

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significantly by 1 year after admission [Owen et al., in press].

The favourable prognostic value of reports of preserved metabolism in PVS is yet to be fully established, but the results of Owen et al. [in press] are promising. These studies involve multiple logistic and procedural problems, but the results have major clinical and scientific implications and provide a strong basis for the systematic study of possible residual cognitive function in patients diagnosed as being in a PVS.

Future Role

fMRI has largely overtaken PET as the imaging modality of choice for the investigation of a broad range of cognitive functions, including auditory processing. It is noninvasive, can provide an increasingly wide array of physiological information and has temporal and spatial resolution superior to that of PET. The future use of PET as a functional imaging tool will probably be confined to two domains. One, those activation studies for which fMRI, for whatever reason, is not suitable include studies of patients who must be scanned at the same time as nonmagnet-compatible equipment is being used, for example studies of auditory function in cochlear implant users or studies in which the cognitive capacities of gravely ill patients are evaluated. Two, the domain in which PET has the potential to continue to make a valuable contribution to basic neuroscience research is through the use of radioligands to explore the anatomy, physiology and function of cerebral neurochemical systems. PET is able to detect exceedingly small concentrations $(10^{-12} M)$ of radiotracer, and tracers can be specific to a neurochemical pathway and even a particular receptor subtype [Busatto and Pilowsky, 1995; Malison et al., 1995]. Furthermore, changes in neuroreceptor ligand binding related to pharmacological intervention [Carson et al., 1997] or cognitive condition [Koepp et al., 1998] can be measured and modelled statistically [Aston et al., 2000]. Auditory cortical subregions are neurochemically distinguishable [Rivier and Clarke, 1997; Goldsmith and Joyce, 1996]. For example, D₂ receptors are absent from the PAC but present in high concentrations in non-PAC areas [Goldsmith and Joyce, 1996]. It may therefore be possible to design tests with which to examine changes in receptor binding related to different stimulus parameters or listening conditions; this would yield a high degree of anatomical specificity.

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Conclusion

PET has been used to explore auditory functions in humans for more than a decade and has proven its utility. It has limitations: studies of brainstem function are not possible, only a relatively small amount of data can be collected on each subject, the spatial and temporal resolution are quite poor, and studies of functional organization within the auditory cortex have generally yielded disappointing results. Nonetheless, PET has been productively used to explore auditory integrative functions such as musical processing, attentional modulation and speech perception, functions that are instantiated in neural networks that extend beyond the auditory cortex. The use of PET for the exploration of function in normal individuals is being gradually superseded by fMRI, which is non-invasive and has superior temporal and spatial resolution. The future of PET to examine function probably lies within the clinical domain, as a research and assessment tool. To

date, PET has been successfully used to explore the neural mechanisms of tinnitus, musical hallucinations and functional recovery after cochlear implantation, to assess functional organization prior to brain surgery and as a prognostic indicator for patients in a PVS. Finally, the use of PET for the mapping of neurochemical pathways and receptors, in both health and disease, is an area in which PET will probably make the greatest contribution in the future.

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