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Functional magnetic resonance imaging of tinnitus

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Introduction and outline of the Thesis

1.1 Outline of this thesis

Aims and scope

Tinnitus is a phenomena which, according to Wikipedia¹, can be described as:

Tinnitus (pronounced /tɪˈnaɪtəs/ or /ˈtɪnɪtəs/ from the Latin word *tin-nītus* meaning “ringing”) is the perception of sound within the human ear in the absence of corresponding external sound [...]

This definition implies that tinnitus is some kind of phantom sound in the sense that it cannot be objectified by others. Furthermore, it appears that the perception of this sound takes place in the human ear. In this thesis, it is argued that this definition is not entirely correct and fails to describe that the central auditory system is presumably playing a major role in generating tinnitus.

According to another definition ([U.S. National Library of Medicine, 2009](#)), tinnitus may be described as

A nonspecific symptom of hearing disorder characterized by the sensation of buzzing, ringing, clicking, pulsations, and other noises in the ear. Objective tinnitus refers to noises generated from within the ear or adjacent structures that can be heard by other individuals. The term subjective tinnitus is used when the sound is audible only to the affected individual.

This definition makes a distinction between objective and subjective tinnitus. Yet, the distinction between objective and subjective tinnitus ([Møller, 2003](#); [Lockwood *et al.*, 2002](#)) is debatable ([Jastreboff, 1990](#)) in a sense that it is based on whether a sound can be detected or objectified by an external observer, rather than on the possible underlying mechanisms. In addition, it describes tinnitus as noises in the ear while often patients report it outside the ears (i.e. centrally in the head or lateralized outside the head).

Our definition of tinnitus is therefore different and describes it as:

Tinnitus is an auditory sensation without the presence of an external acoustic stimulus.

Important is our definition is that tinnitus is by definition a percept. Whether it is generated in the peripheral auditory system (‘in the ear’), the central auditory system or a combination of both is not essential in the definition. Also the distinction between objective or subjective is not made explicit. Tinnitus is similar to auditory hallucinations. Yet, these are two distinct phenomena which, respectively constitute meaningless sounds (e.g. buzzing, clicking or high-frequency tones) or meaningful sounds (e.g. music or voices) ([Silbersweig and Stern, 1998](#); [Griffiths, 2000](#); [Møller, 2007](#)).

¹Wikipedia – <http://en.wikipedia.org/wiki/Tinnitus>; as of October 8, 2009

Although the exact mechanism of generation of tinnitus in humans is not known, a number of hypotheses based on data from animal models have led to the idea that tinnitus is a disorder of the central auditory system. This disorder may be triggered by a peripheral cause (e.g. hearing loss), which in turn may lead to (plastic) changes in the central auditory system. Nevertheless, none of the proposed mechanisms has unequivocally been proven in humans. This thesis discusses the application of functional magnetic resonance imaging (fMRI) to study the central auditory system and tinnitus in humans and provides evidence that supports existing hypotheses.

fMRI is used as the main research method in the study of tinnitus since it offers the possibility to study the human brain in a non-invasive manner and is recognized as a tool to investigate the functions of the brain, especially for localizing functional changes. The main objective of this research project was to gain insight into functional changes in the auditory system and non-auditory areas, that may relate to the generation and perception of tinnitus.

This objective was pursued by means of a methodological approach, by designing studies comparing the neural responses in subjects without tinnitus to those in subjects with tinnitus. Therefore, the aims of the research project were:

- i. to explore experimental designs tailored to study tinnitus in an fMRI environment.
- ii. to study relevant groups of subjects with tinnitus, and to compare the functions of the brain in these groups with those in closely matched groups of subjects without tinnitus to gain more insight in changes that may underlie tinnitus.

For these purposes, a number of studies were designed and performed of which the main results obtained are presented in this thesis.

Outline

This thesis consists of a number of chapters:

Chapter 1 *Introduction*

Chapter 1

This first chapter is meant as a general introduction to the auditory system. A short overview is given, describing the most important parts of the auditory system, ranging from the peripheral auditory system to the auditory cortex. In addition, an introduction to tinnitus is given. The final section of this chapter describes functional magnetic resonance imaging techniques and explains the indirect blood oxygen level dependent (BOLD) effect—a measure of neural activity.

Chapter 2 *Neural activity underlying tinnitus generation: Results from PET and fMRI*

Chapter 2

Presents a systematic and comprehensive review of the functional imaging literature on tinnitus. An overview of experimental designs and neuroimaging methods that were previously used to study neural correlates of tinnitus is given. The main points of emphasis are that tinnitus is associated with central auditory activity and that also non-auditory regions of the brain are implicated in the sensation of habitual tinnitus, especially frontal cortex,

limbic regions and the cerebellum.

Chapter 3 **Chapter 3** *Functional imaging of unilateral tinnitus using fMRI*

Presents a study on sound evoked responses in the central auditory system. The major aim of this study is to determine tinnitus-related neural activity in the central auditory system. We investigate sound-evoked responses in subjects with unilateral tinnitus and compare those to subjects without tinnitus.

Chapter 4 **Chapter 4** *Unilateral tinnitus: changes in lateralization and connectivity measured with fMRI*

This chapter is an extension of chapter 3 and specifically investigates the lateralization of sound-evoked responses. Furthermore, it describes connectivity patterns between nuclei of the auditory pathway and the vermis of the cerebellum. The central idea is that activity in different parts of the brain that covary suggest that the neural processes underlying this activity may be interacting. This chapter describes normal sound-evoked responses, the lateralization of these responses, and the connectivity patterns between nuclei of the auditory pathway. Additionally, differences in neural activity between subjects with unilateral tinnitus and controls are described.

Chapter 5 **Chapter 5** *Neural correlates of human somatosensory interaction in tinnitus*

Is a chapter that investigates neural correlates of somatic tinnitus. In this form of tinnitus, somatic maneuvers elicit tinnitus or modulate the psychoacoustic attributes of tinnitus. Neural responses that underly these perceptual changes of the tinnitus are studied by using a maneuver that causes a change in the loudness of tinnitus: jaw protrusion. In addition, somatosensory and auditory integration are studied, which may form the neural basis for this perceptual change.

Chapter 6 **Chapter 6** *A diffusion tensor imaging study on the auditory system and tinnitus*

Explores the use of diffusion tensor imaging (DTI) to investigate the anatomical connectivity patterns between auditory and non-auditory areas in the brain. This chapter focusses on the structural integrity of white matter axons and compares several measures of connectivity between the auditory system and the limbic system in controls and subjects with tinnitus.

Chapter 7 **Chapter 7** *General discussion, conclusions and future perspectives*

Discusses and integrates the main outcomes of this thesis and their implications on further research.

1.2 From sound to neural signals

This introductory chapter is meant as a general introduction into the field of hearing research. It provides a brief overview of some topics in hearing research and the application of functional neuroimaging methods to this field. These first sections explain how sound can be described and how sound is translated into a neural signal—the basis for perception.

This section describes the auditory pathway and briefly explains the functions of the nuclei that are part of the auditory pathway (section 1.2). Furthermore, a short introduction on tinnitus is given, describing some basic aspects of tinnitus (section 1.3). The last section describes basic principles of functional magnetic resonance imaging (fMRI), the coupling between neural activity and fMRI signal intensity, and describes the main data processing steps (section 1.4).

Sound

In most cases, sound reaches us as fluctuations of atmospheric pressure (measured in Pa) over time. The characteristics of our hearing organ are such that we are only sensitive to a certain range of fluctuations. If the frequency of the fluctuations is between 20 Hz and 20 kHz, humans perceive it as sound.

Physically, a (constant) sound can be described in the temporal domain and in the frequency domain. In the temporal domain, a sound is characterized by a function of the air pressure over time (t) and can be described by a single sinusoidal if it is a pure tone, or as a summation of sinusoidal functions if it is a complex sound. In the frequency domain, sounds can be described by their frequency content, and correspond to a repeating period T in the time domain for a pure tone or a complex of repeating periods, each with its own amplitude, for a complex sound.

The primary characteristic of a sound is its sound pressure level (SPL). Sound pressure level is a logarithmic measure of the root-mean-square sound pressure of a sound (p_{rms}) relative to a reference value (p_{ref}). It is measured in decibels (dB) above a standard reference level.

$$SPL = 20 \cdot_{10} \log \left(\frac{p_{rms}}{p_{ref}} \right) \quad (1.1)$$

The commonly used reference sound pressure in air is $p_{ref} = 20 \mu Pa$ (rms), which is usually considered the threshold of human hearing at a frequency of 1000 Hz (Yost, 2000). An intensity level is thus defined as the level compared to a reference level. An 20 dB increase in intensity corresponds to a 10-fold increase of pressure and a 60 dB increase in intensity corresponds to a 1000-fold increase of pressure.

Both the sound pressure level and the frequency are represented in the central auditory system. First, the sound pressure waves need to be transformed to electrical signals by the peripheral auditory system which is covered in the following section.

The peripheral auditory system

The peripheral hearing organ can be divided in three distinctive components that each serve different functions (see figure 1.1). These partitions correspond to the external, mid-

dle and inner ears. Sound is transmitted from the external environment to the inner ear through two conductive components of the peripheral auditory system.

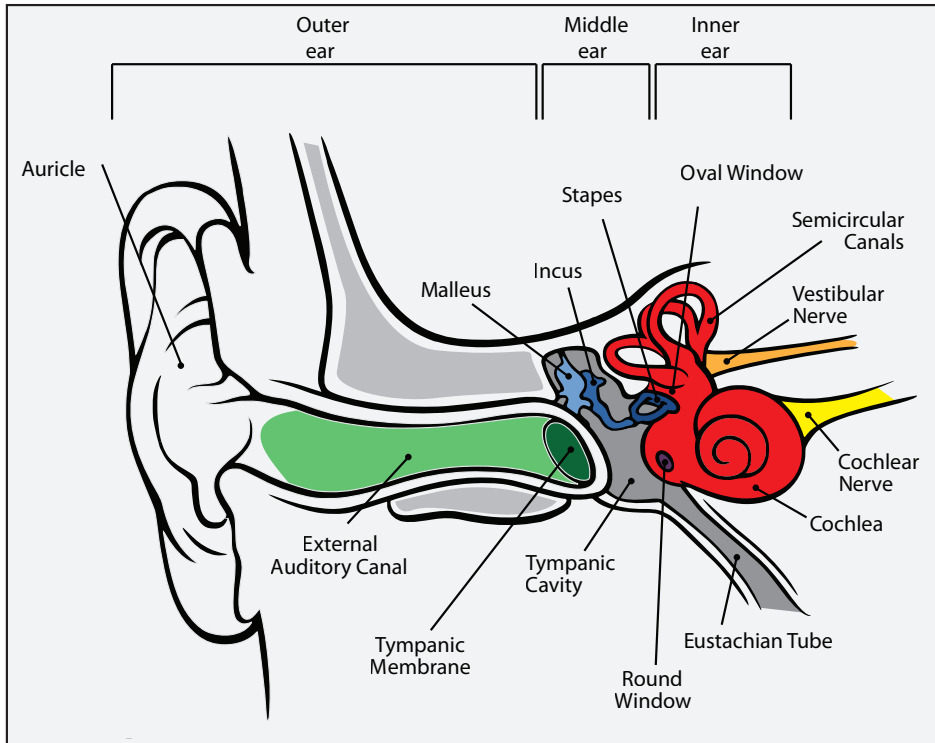


Figure 1.1 The peripheral auditory organ consists of three parts: the outer, middle and inner ears. From the outer ear, sound vibration reaches the tympanic membrane, which in turn moves the ossicles (malleus, incus and stapes) and causes fluid in the cochlea to vibrate. This in turn, causes vibration of the basilar membrane following deflection of hair cells triggering neural firing. (Adapted from: [Chittka and Brockmann \(2005\)](#))

The function of the outer ear is two-fold. First, sound is deflected inwards by the auricle and is focussed towards the tympanic membrane. Due to the structure of the auricle and ear canal, the sound intensity is amplified, especially in the range near 3 kHz ([Yost, 2000](#)) where the sensitivity of human hearing is best. Second, the sound is filtered due to the morphological structure of the auricle and thereby provides cues for vertical sound localization ([Van Wanrooij and Van Opstal, 2004](#)).

The middle ear provides at least two methods to bridge the mismatch in impedance between the atmospheric air (a low impedance medium) and the fluid in the inner ear (a high impedance medium). The first method is based on the difference in area between the tympanic membrane and the (much smaller) oval window, causing an amplification of the pressure on the tympanic membrane. The second method relates to the mechanic lever

action of the three connected ossicles amplifying the pressure even more. A reduction of the amplification may also occur due to an acoustic reflex. When presented with a high-intensity sound, the stapedius muscle and the tensor tympani muscle cause the ossicles to contract ([Hüttenbrink, 1988](#)). This acoustic reflex decreases the transmission of vibrational energy to the cochlea.

The sound pressure wave that has reached the tympanic membrane now enters the cochlea via the oval window and enters the fluid-filled compartments of the coiled cochlea. These compartments are separated by membranes of which the basilar membrane is crucial in sound detection. The mechanical properties of this basilar membrane are such that it is narrow and stiff at the basal end of the cochlea and wide and flexible at the apical end. This arrangement causes a gradual change in resonance frequency along the length of the membrane, decreasing in frequency towards the apex. Sounds of different frequencies thus have a different place of resonance along the basilar membrane, which is referred to as a tonotopic organization. The cochlea acts as a mechanical frequency analyzer, mapping the frequency content of the sound spatially onto the length of the basilar membrane, resulting in a frequency decomposition of the sound signal.

The organ of Corti is situated on top of the basilar membrane (figure [1.2](#)) and consists of hair cells which are coupled to the tectorial membrane. Two types of hair cells exist that each have a distinctive organization and function. The inner hair cells (IHCs) form a single row of hair cells that protrude from the basilar membrane. In addition to the IHCs there are three rows of outer hair cells (OHCs) that are innervated by (efferent) central auditory system neurons. Sound causes mechanical vibration in the cochlea at a site of resonance. This movement causes deflection of the tectorial membrane relative to the basilar membrane and causes deflection of the stereocilia of the hair cells. This evokes neural discharges in some of the afferent fibers of the cochlear nerve. The OHCs display somatic electromotility, i.e. the mobility of the hair cells, which in turn influences the motion of the basilar membrane ([Zheng *et al.*, 2000](#); [Dallos, 2008](#)). The OHCs thus function as an active acoustic amplifier with the ability of sharpening the frequency selectivity. One effect of this active amplification is the occurrence of spontaneous otoacoustic emissions that are presumed to relate to an instability of the feedback amplification system ([Probst *et al.*, 1991](#)).

The peripheral hearing organ can be affected in many ways which may lead to several types of hearing loss: conductive hearing loss, sensorineural hearing loss or a combination of these two. Conductive hearing loss results from disfunction of parts of the outer ear, the middle ear or a combination of these two, which can be characterized by a reduced signal transmission to the sensory hair cells.

Examples of conductive hearing loss include excessive ear wax blocking the auditory canal, perforation of the tympanic membrane and stiffening of the ossicle chain (sclerosis). Sensorineural hearing loss results from damage or dysfunction in the inner ear or the central auditory system. Loss or dysfunction of inner or outer hair cells cause sensorineural hearing loss. Noise trauma, ototoxic drugs and various diseases may cause sensorineural hearing loss.

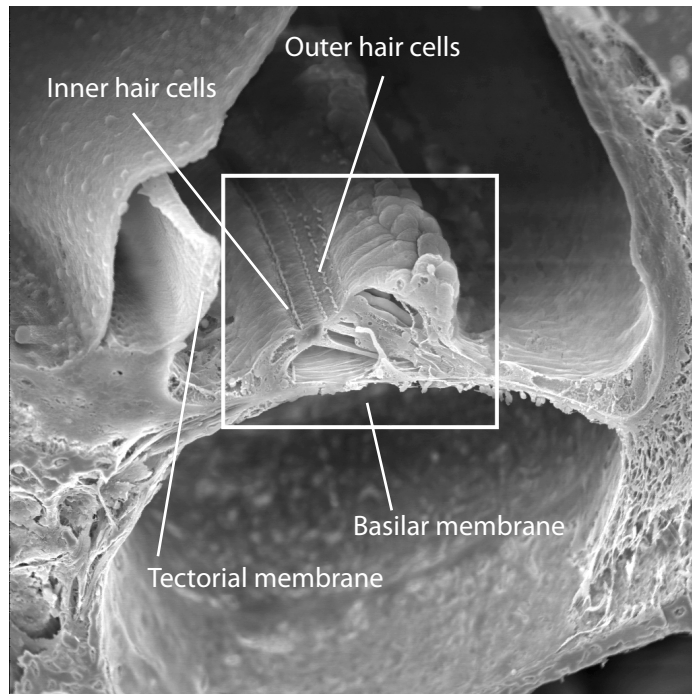


Figure 1.2 A cross section of the cochlea showing an electron microscopic picture of the organ of corti as indicated by the white box (Adapted from B. Kachar, NIDCD, NIH). In the boxed part, the two types of hair cells are visible. On the left side, a single-row of inner hair cells is visible while more to the right three rows of hair cells can be observed. The tectorial membrane is separated from the outer hair cell bundles due to the preparation techniques that were used.

In summary, the outer ear (1) receives sound (via pressure waves traveling through the air) and conducts it to the eardrum. It thereby translates air vibration in mechanical vibration. The middle ear performs (2) impedance matching between vibration in air and vibration in fluids and is capable of attenuation of loud sounds by the acoustical reflex. Finally, the inner ear functions (3) as a frequency analyzer and converts mechanical (fluid) vibration into electrochemical signals. The next section describes the path of the signals—the auditory pathway.

The auditory pathway

The organ of Corti, with its outer and inner hair cells is responsible for the conversion of mechanical vibration to electrical neural signals. Afferent fibers, sensory nerves carrying information from the periphery to the brainstem, constitute the auditory nerve (nVIII) and carry the information from the inner ear to the cochlear nucleus.

As a result of the tonotopic mapping of the cochlea, each nerve fiber is most sensitive to a particular frequency, its characteristic frequency. Information regarding the frequency of the stimulus is not only determined by the place along the basilar membrane that shows maximal resonance (i.e., place theory), but is also coded by the discharge rate (i.e., the temporal theory of frequency coding). Note that at frequencies above approximately 5000 Hz the phase-locking of the firing pattern to the stimulus is not possible anymore, since the discharge of auditory nerve fibers is limited to a minimum period of approximately 0.2 msec (called the refractory period).

Sound intensity is also preserved in the firing rate in auditory nerve fibers. It is assumed to be encoded by an change in the discharge rate of a single nerve fiber. In order to encode the 140 dB dynamic range of humans, information from multiple nerve fibers is used, combining information from low-, medium-, and high threshold fibers—each with an individual dynamic range of less than 35 dB (Ehret and Romand, 1997; Yost, 2000).

Figure 1.3 illustrates schematically the principal ascending auditory pathway. The auditory nerve terminates in one of the divisions of the (ipsilateral) cochlear nucleus, the anterior ventral cochlear nucleus (AVCN), the posterior ventral cochlear nucleus (PVCN) and the dorsal cochlear nucleus (DCN). The frequency spectrum of the sound stimulus is preserved in the cochlear nucleus. The lower frequency axons innervate the lateral-ventral portions of the dorsal cochlear nucleus and the ventrolateral portions of the anteroventral cochlear nucleus. In contrast, the axons from the higher frequency organ of Corti hair cells project to the dorsal portion of the anteroventral cochlear nucleus and the dorsal-medial portions of the dorsal cochlear nucleus.

The (AV)CN projects information bilaterally to the next nucleus in the auditory pathway: the superior olivary complex (SOC). Binaural processing takes place at this level – especially sound localization in the horizontal plane—by means of interaural time differences, processed by the medial superior olive (MSO) and interaural level differences, processed by the lateral superior olive (LSO).

The SOC, in turn, projects to the inferior colliculus (IC) via the lateral lemniscus (LL). The majority of the ascending fibers from LL project to IC. Parts of the ascending auditory pathways converge here. IC acts as an integrative (relay) station and is involved in the integration and relay of multimodal sensory perception, mainly startle reflex and vestibulo-ocular reflexes. Not only is there an indirect path from the CN via the SOC and LL but there are also direct connections from the CN and SOC. So, the CN and SOC both project to the IC.

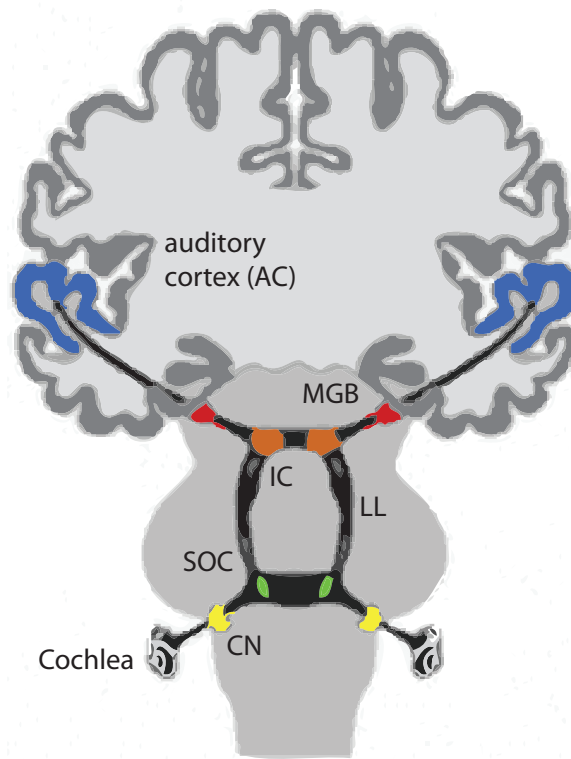


Figure 1.3 Schematic outline of the ascending auditory pathway. Fibers project from the inner hear cells in the cochlea to the cochlear nucleus (CN). From this point on the system is a bin-aural system. This auditory pathway projects to both, bilateral superior olivary complex (SOC) nuclei where horizontal sound localization takes place. Signals are transmitted via the lateral lemniscus (LL) to the inferior colliculus (IC). The IC not only receives information from this binaural pathway but also receives information from the contralateral and ipsilateral CN. The IC is the major auditory processing center of the midbrain and receives multimodal information. From the IC, signals are projected to the bilateral medial geniculate nuclei of the thalamus (MGB). From this point, signals are projected to the auditory cortex (AC) in the temporal lobes. (Adapted with kind permission from: C.Liberman and J.Melcher; Eaton-Peabody Laboratory, Massachusetts Eye and Ear Infirmary, Boston.)

The IC comprises three major nuclei: the central nucleus (ICC), the external nucleus (ICX) and the pericentral nucleus. It provides the first level where horizontal and vertical sound localization are integrated and is also responsive to specific amplitude modulation frequencies, which might be responsible for detection of the pitch of a (complex) auditory signal. In addition, the IC is a multimodal nucleus, receiving input from the somatosensory system, via the spinal trigeminal system and the dorsal column nuclei (Zhou and Shore, 2006; Dehmel *et al.*, 2008), and it may play a role in somatosensory modulation of perceptual characteristics of tinnitus.

From the IC, connections pass to the bilateral medial geniculate body (MGB) of the thalamus. The thalamus is the major relay station for information to the cortex for almost all sensory systems, including the somatosensory system, the visual system (through the lateral geniculate body) and the auditory system. The MGB, in turn, projects to the auditory cortex (AC), which is located in the temporal lobe.

The auditory cortex

The primary destination of an auditory signal is –after several successive processing stages in the brainstem, midbrain and thalamus– a cortical area that corresponds to the auditory cortex. The auditory cortex is distributed over the upper part of the temporal lobe. Figure 1.4 shows the superior temporal surface with some distinct areas. It shows the transverse gyrus extending in the posteromedial to anterolateral direction which is called Heschl's gyrus (HG). The exact morphological features of the HG may vary between individuals and may also form a double or forked gyrus (Leonard *et al.*, 1998). Anterior to the HG is the transverse temporal gyrus that separates it from the planum polare (PP). The PP extends to the anterior tip of the temporal lobe, the temporal pole. Posterior to the HG is the planum temporal (PT), a triangular area that includes Wernicke's area, one of the most important functional areas for language. Note that this Wernicke's area is traditionally mostly functionally lateralized towards the left hemisphere.

The auditory cortex can be divided in several areas on the basis of the cell types, the cytoarchitecture. This division is based on the connectivity, neuro-chemical characteristics and cell morphology and composition of cell layers in the cortex, and follows the scheme according to Brodmann (1909). The auditory cortex can be divided in area 41 (BA 41, see figure 1.4B), which roughly coincides with the primary auditory cortex. Adjacent to this area is area 42 (BA 42), which is also known as the secondary auditory cortex. Surrounding these areas is area 22 (BA 22), the auditory association cortex. Although the architectonic location of the PAC does not always register with the morphological features of the cortex, mainly due to differences between subjects, it is approximately located in the medial two-thirds of the HG (Rademacher *et al.*, 2001); see figure 1.4A. Since there is no fixed nomenclature, the PAC may to a large degree also correspond to A1, and may largely overlap with three sub-areas: Te1.0, Te1.1 and Te1.2 (Morosan *et al.*, 2001).

Although there is evidence of a tonotopic mapping in the auditory cortex in non-human mammals (Ehret and Romand, 1997), the evidence for such a mapping in humans is sparse, and varies between several studies (Formisano *et al.*, 2003; Talavage *et al.*, 2004).

Relatively little is known about the functional differences between areas in the PAC regarding the processing of sound. The same holds for the surrounding (secondary) areas, often referred to as belt and parabelt areas.

Primary auditory areas presumably perform the processing of basic sound features like frequency and intensity level analysis (Hall *et al.*, 2001) while non-primary areas may play a role in spectrotemporally more complex sounds (Hall *et al.*, 2003; Langers *et al.*, 2003). It has been suggested that the cortical processing results in the re-encoding of incoming auditory signals into separate (parallel) streams. One of these streams seems involved in the identification of the (auditory) object—the 'what' pathway—while the other stream is engaged in the localization of the auditory object—the 'where' pathway (Alain *et al.*, 2001).

So, although much work has been done to characterize central auditory system processing stages, even the basic features of the representation of sound in the auditory brain (i.e. the auditory pathway from the periphery to the auditory cortex) remain to a large extent unknown.

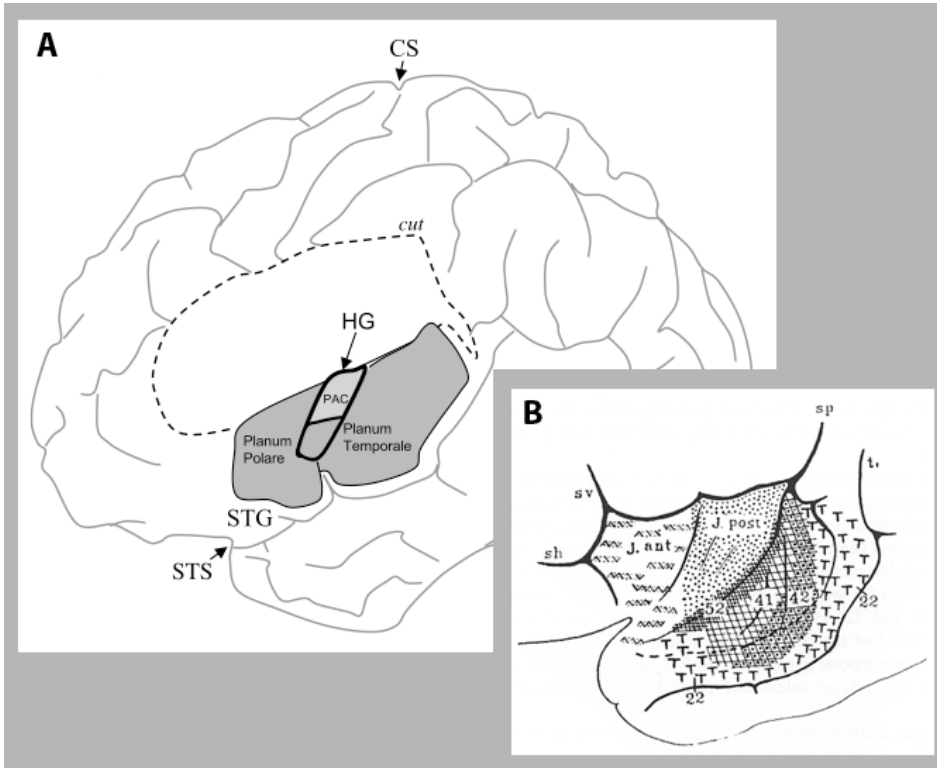


Figure 1.4 Panel A: Lateral view of the human auditory cortex exposing the superior temporal gyrus (STG). It shows Heschl's gyrus (HG), of which the medial two-third part corresponds to the primary auditory cortex (PAC). The areas surrounding the PAC include the planum polare and the planum temporale. The central sulcus (CS) and superior temporal sulcus (STS) are indicated as major anatomical landmarks; adapted from: [Hall *et al.* \(2003\)](#). Panel B shows the cytoarchitectonic organization of the same area as in panel (A), now according to [Brodmann \(1909\)](#). Indicated are the parainsular area (BA 25), the anterior or medial transverse temporal area (BA 41) and posterior or lateral temporal posterior area (BA 42). Surrounding these areas is the superior temporal area known as BA 22. The superior temporal sulcus is indicated as tr.

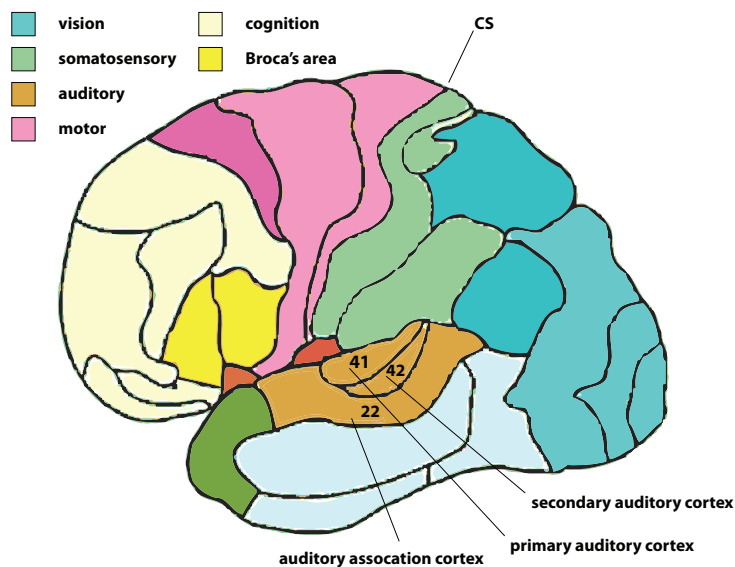


Figure 1.5 The lateral view of the cytoarchitectural areas in the brain according to Brodmann (1909). In addition to auditory areas (BA 41, 42 and 22), areas that correspond with vision, motor function, somatosensory perception and cognition are depicted. Adapted from Mark Dubin, <http://spot.colorado.edu/~dubin/talks/brodmann/brodmann.html>

1.3 Tinnitus

The main theme of this thesis is tinnitus and its potential neural correlate. It is thus important to introduce tinnitus and explain some basic features of tinnitus. Tinnitus can be differentiated into subjective and objective tinnitus. In objective tinnitus, sound from the body leads to an auditory percept via normal hearing mechanisms, i.e. by stimulation of the hair cells in the inner ear. Consequently, objective tinnitus is not a true hearing disorder in the sense that the hearing organ is affected. Rather, normal perception of an abnormal sound source in the body (somatosound) causes the complaint. Typically, sources of objective tinnitus are of vascular or muscular origin. Due to vascular anomalies (Chandler, 1983), vibrations due to pulsatile blood flow near the middle or inner ear (Weissman and Hirsch, 2000; Liyanage *et al.*, 2006; Sonmez *et al.*, 2007) can become audible. Also, involuntary contraction of muscles in the middle ear (Abdul-Baqi, 2004; Howsam *et al.*, 2005) or in palatal tissue (Fox and Baer, 1991) may cause objective tinnitus. Objective tinnitus is rare and has been described only in case reports.

Subjective tinnitus is far more common than objective tinnitus. In contrast to objective tinnitus, there is no (overt) acoustic stimulus present in cases of subjective tinnitus. Yet, the distinction between objective and subjective tinnitus (Møller, 2003; Lockwood *et al.*, 2002) remains debatable (Jastreboff, 1990) in the sense that the definition is based on whether a somatosound can be detected or objectified by an external observer, rather than on the possible underlying mechanisms.

Almost all adults have experienced some form of tinnitus, mostly transient in nature, at some moments during their life. However, in 6–20% of the adults, tinnitus is chronic and for 1–3% tinnitus severely affects the quality of life. Tinnitus is more prevalent in men than in women and its prevalence increases with advancing age (Axelsson and Ringdahl, 1989; Lockwood *et al.* (2002); see figure 1.6).

Subjective tinnitus has many different forms and varies in character and severity (Stouffer and Tyler, 1990). It can be perceived as an intermittent or a continuous sound (Lockwood *et al.*, 2002; Henry *et al.*, 2005) and can be perceived unilaterally, bilaterally or in the head (Axelsson and Ringdahl, 1989). Although subjects rate their tinnitus as very loud, the tinnitus is typically matched at levels of 5–10 dB sensation level (SL, i.e. the level compared to subjects' own threshold; Vernon and Meikle, 2003)). In order to fully classify chronic subjective tinnitus, subjects need proper otological examination, audiological assessment and, in addition, need psychological profiling assessing the severity of the tinnitus and the accompanying distress and influence on the quality of life (Bartels, 2008).

Subjective tinnitus is often associated with peripheral hearing loss (Eggermont and Roberts, 2004; Nicolas-Puel *et al.*, 2006), although tinnitus with no or minor hearing loss has also been reported (Stouffer and Tyler, 1990; Jastreboff and Jastreboff, 2003). Many patients describe tinnitus as a sound in one or both ears. Therefore, it has been thought for many years that the tinnitus-related neural activity must also originate from a peripheral source, i.e. the cochlea.

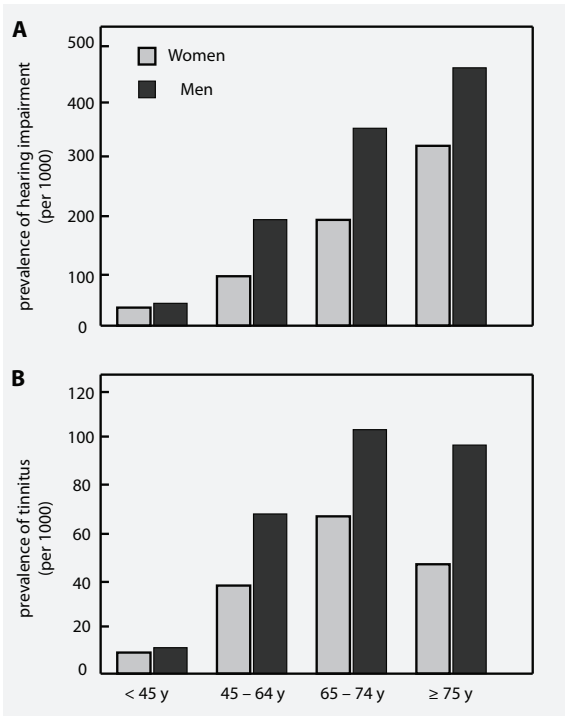


Figure 1.6 The prevalence of hearing impairment (panel A) and tinnitus (panel B); Adapted from: [Lockwood *et al.* \(2002\)](#)

Some clinical observations indicate however, that a peripheral origin of tinnitus cannot account for all forms of tinnitus. In patients that underwent sectioning of the eighth cranial nerve as part of retro-cochlear tumor surgery, tinnitus arose in 34% of the cases ([Berliner *et al.*, 1992](#)). Apparently, tinnitus may arise by disconnecting the cochlea from the brain. Sectioning of the eighth cranial nerve has also been applied in tinnitus patients in an effort to provide relief of the tinnitus. This was however not successful in 38–85% of cases (varying from 38% as reported by [Barrs and Brackmann \(1984\)](#) to 85% as reported by [House and Brackmann \(1981\)](#); reviewed earlier by [Kaltenbach *et al.* \(2005\)](#)). Clearly, in these cases, where the cochlea is disconnected from the brain, central mechanisms must be responsible for the tinnitus.

Changes in the central auditory system may be responsible for tinnitus. A popular hypothesis describes tinnitus as a change in the balance between excitatory and inhibitory input which may cause hyperactivity. The cochlea not only provides excitatory input to the cochlear nucleus but provides also abundant inhibitory input. Now, if the cochlea is impaired, both excitatory and inhibitory input to central auditory structures are reduced, but often inhibitory input is reduced more than the excitatory input ([Kim *et al.*, 2004](#)). This causes a shift in the balance between inhibition and excitation. Tinnitus is often associated with loss of hearing (due to injuries to inner and outer hair cells). Such injuries

now reduce the input to central auditory structures, causing disinhibition—a potential basis for neural hyperactivity (Eggermont, 2007b).

Causes of tinnitus are only in rare cases known and often relate to injuries to cochlear hair cells. Ototoxic agents such as certain antibiotics, salicylate and quinine, and intense sound may lead to tinnitus (Jastreboff and Sasaki, 1986; Jastreboff *et al.*, 1988; Kaltenbach, 2000; Eggermont and Kenmochi, 1998). Also, disorders of the central auditory system, such as meningitis and stroke, are known to cause tinnitus, accompanied by the disturbed perception of sound.

Tinnitus may also be influenced by the somatosensory modality (presumably via the so-called non-classical, or extralemniscal, auditory pathway; (Møller *et al.*, 1992)) and by changes in gaze (Cacace *et al.*, 1994a; Baguley *et al.*, 2006). Also, chemical substances, such as lidocaine are known to modulate characteristics of tinnitus (Melding *et al.*, 1978). These forms of modulation have been used in combination with functional imaging experiments as reviewed in chapter 2.

Summarizing, it should be noted that there is no single form of tinnitus and it is thus of great importance to distinguish several types of tinnitus since, in principle, each of these forms may have a different etiology and therapeutic approach.

1.4 Functional magnetic resonance imaging

Physics

Magnetic resonance imaging (MRI) techniques all exploit nuclear magnetic resonance and make use of a quantum mechanical property called nuclear spin. This spin characteristic can be, in a classical approach, regarded as the rotation of a particle around its own axis. Associated with this spin characteristic is a magnetic property and represents the angular momentum that charged rotating nuclei possess. When these nuclei are placed in a strong external magnetic field (B_0) they precess around the axis along the direction of the field (often called the z -axis) since the quantum mechanical restrictions prevent an exact alignment along the main field. The frequency of this precession is called the Larmor frequency and depends on the strength of the magnetic field.

The most abundant nuclei in the human body are the protons that form the hydrogen atom. When placed in an external field, they will align to the field, forming a distribution of either parallel or anti-parallel to the external field. Since the parallel alignment is energetically favorable, a greater fraction will align parallel. The net alignment of the nuclei together form a net steady state magnetization M_0 . Note however that the overall behavior of large number of nuclei can be described in a classical fashion (Jezzard *et al.*, 2001) but the individual nuclei need a quantum-mechanical approach (Haacke *et al.*, 1999).

By means of 90° radio frequent (RF) pulses of the right frequency (i.e. the Larmor frequency, the resonance frequency that gives the most efficient energy transfer), the magnetic moment can be tilted into the transverse (xy)-plane. As a result, the component of the magnetization parallel to the applied magnetic field (i.e. the longitudinal magnetization, M_z) will decrease, and the component perpendicular to the field (the transverse magnetization, M_{xy}) will develop. A receiver can now detect the precession in the transversal plane.

Once the RF pulse ends, the return to the favored (parallel) state begins—called relaxation. First, the longitudinal component will grow back to its steady state magnetization by an exponential (longitudinal) relaxation process with a time constant T_1 , involving spin-lattice interaction (see figure 1.7). For brain tissue, this T_1 time constant is of the order of 1 s.

Second, the transverse component will decrease to zero magnitude, characterized by two simultaneous complex effects. First, there are spin-spin interactions: interactions of individual spins that influence each other in such a way that the initial coherent phase becomes dephased. This dephasing is characterized by a time constant T_2 . Furthermore, transverse spins also dephase due to inhomogeneities in the main magnetic field (B_0) resulting in a dispersion in Larmor frequencies, corresponding to a dispersion of the precession frequency. The combined effect of spin-spin relaxation and B_0 -field inhomogeneities is characterized by a time constant T_2^* .

In summary, RF causes the longitudinal magnetization to flip to the transversal plane.

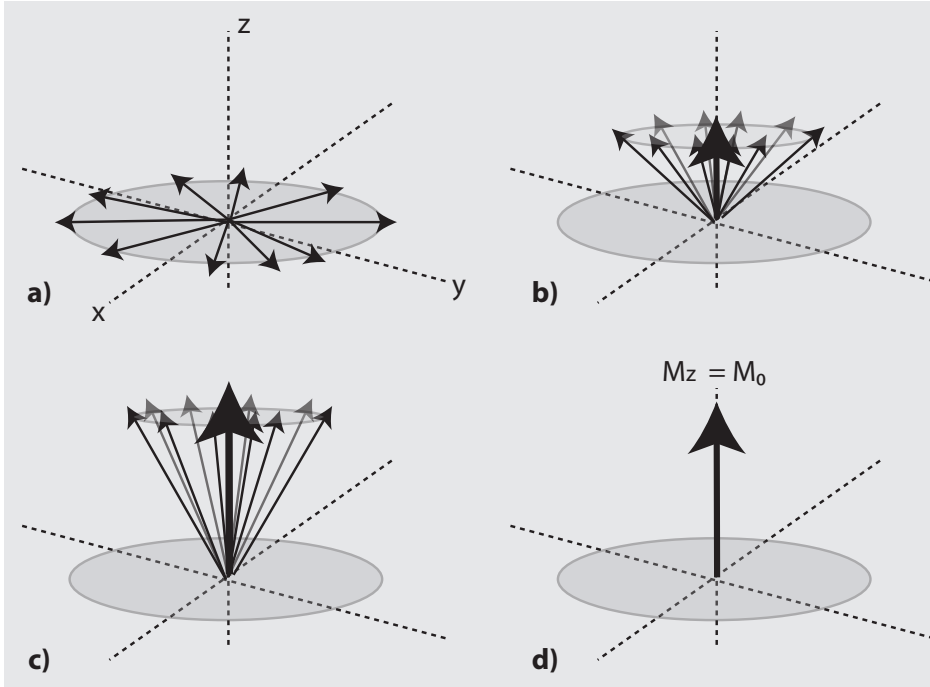


Figure 1.7 T_1 relaxation. After an 90° RF pulse has flipped all magnetization in the xy-plane (a), the magnetization relaxes back (b–d) to its equilibrium condition (d). Together they form a net steady state magnetization vector M_0 . The longitudinal component slowly relaxes back according to an exponential relationship $M_z = M_0 \cdot (1 - \exp(-t/T_1))$.

After the RF has stopped, the magnetization will relax back to the steady state magnetization. The magnetization will precess around the z -axis and will emit RF electromagnetic radiation and can be detected. These two types of relaxation, in addition to the number of protons in tissue, together comprise the contrast mechanisms in MR imaging.

Image formation

The Larmor frequency is essential in the detection of spin properties. The emission of RF from the rotating transverse magnetization is used to extract information about the location of the nuclei. Because the amount of RF is proportional to the density of protons (hydrogen nuclei), which differs between tissue types, anatomical images can be constructed by detecting the power of the RF that is emitted from a certain location. The magnitude can, however, not be determined directly, since signals from other locations that contain protons will interfere. By now adding gradients to the main magnetic field, a spatial distribution of signals, each with a different resonance Larmor precession frequency, can be detected. Thus a spatial variation in the magnetic field strength alters the resonance frequency and can be used to form images.

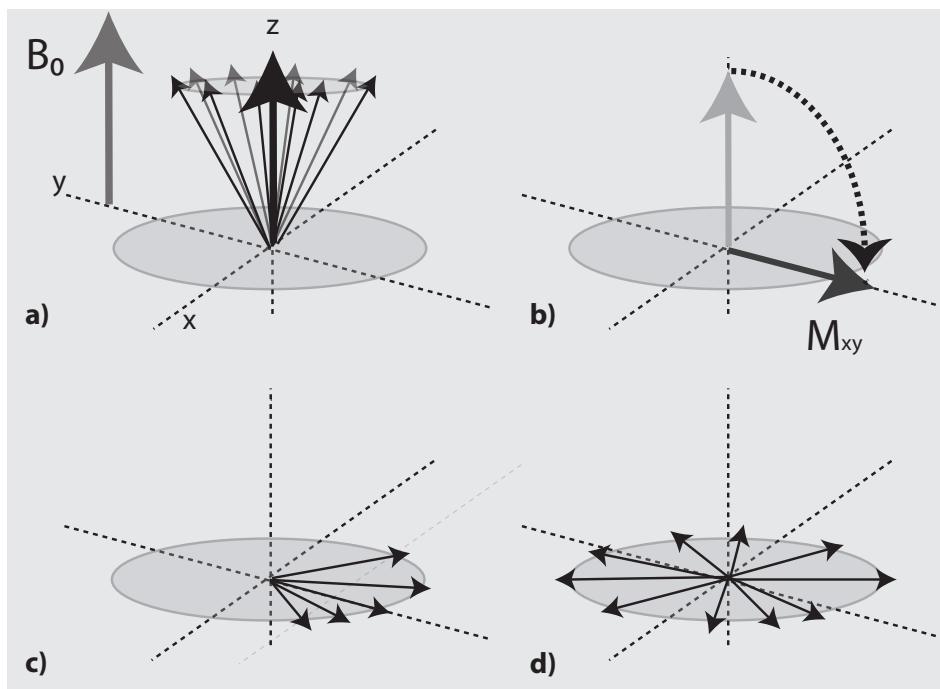


Figure 1.8 The application of an RF pulse and T_2 relaxation. After an 90° RF pulse has flipped all magnetization in the xy -plane (b), dephasing starts and decreases the transversal magnetization vector (c) to its equilibrium condition of a net transversal magnetization of zero (d). The transverse component of the magnetization decreases according to $M_{xy} = M_0 \cdot \exp(-t/T_2)$

In short, a pulse sequence contains the following items (Haacke *et al.*, 1999): First, the magnetization is given a chance to fully relax (figure 1.7d). Next, a 90° RF pulse is applied, flipping the magnetization into the transverse plane (figure 1.8b). The magnetization in the xy -plane precesses around the z -axis with the Larmor frequency that codes the location of the protons. The signal-emitting transverse magnetization will shrink (T_2 relaxation, figure 1.8c) and simultaneously, the longitudinal magnetization grows slowly back to its steady-state magnitude. The gradients will cause an additional dephasing, since protons at different locations will have different resonance frequencies, causing increased spin-spin interactions and lower T_2^* time constant. To recover signal losses, often another RF pulse is applied. This 180° pulse flips all magnetization 180° . This causes all spins with a phase lag to be turned into a phase lead and the magnetic moment refocusses again. This will, in turn, yield an RF pulse which can be detected—a spin echo.

For functional imaging of brain activity, a T_2^* -weighted sequence is most often used since it is sensitive to changes in the oxygen concentration in blood—a marker of neural

activity.

From neural activity to differences in T_2

Functional MRI is an indirect method for measuring brain activation (Jezzard *et al.*, 2001). It does not measure electrical or magnetic activity that is generated by signal conduction mechanisms of neurons, like electro- and magneto-encephalography (EEG and MEG) or evoked potential (EP) methods. Rather, it measures changes in the magnetic properties of the blood. Figure 1.9 shows schematically the events that underly PET and fMRI signal intensity changes that may relate to task related changes.

Although there are some functional MR imaging methods that specifically measure changes in blood volume (VASO, vascular space occupancy; Lu *et al.* (2003)) or cerebral blood flow (Golay *et al.*, 2004; Petersen *et al.*, 2006), most fMRI methods make use of the blood oxygen level dependent (BOLD) contrast. This technique is based on the increase in signal intensity caused by an increase in oxygen concentration of blood (Ogawa *et al.*, 1990).

Synaptic activity in neurons, both excitatory and inhibitory, correspond to the consumption and increase in metabolic rate of oxygen (Logothetis *et al.*, 2001). The metabolic reserve within neurons and neighboring glia cells is limited and additional oxygen is needed to fulfill the oxygen need. As a response, vascular dilation takes place—the increase in diameter of blood vessels, which in turn leads to an increased cerebral blood volume (CBV) and cerebral blood flow (CBF). The corresponding increase in oxygen level now exceeds the need for it, causing an increase in oxygen-rich blood on the venous side of the neural activity. As a result, the ratio of deoxygenated hemoglobin to oxygenated hemoglobin will drop.

If oxygen is bound to hemoglobin (oxyhemoglobin), the ferrous core is diamagnetic similar to the surrounding (brain) tissue, causing hardly any disturbance of the local magnetic field homogeneity. Deoxyhemoglobin, on the contrary, is paramagnetic and differs strongly from the surrounding tissue and deforms the local magnetic field (susceptibility artifacts). This inhomogeneity now leads to a dephasing of the nuclear magnetic moments, reducing the net transverse magnetization. In summary, deoxygenated blood has a shorter T_2^* than oxygenated blood and forms the basis of the BOLD effect.

Regions of the brain that are active will show an increased CBV and CBF, leading to an increase of the local oxygenation level. This, in turn, will reduce the local field inhomogeneities, and will increase the T_2^* . If an MR imaging sequence is used that is sensitive to T_2^* changes, like with an echo planar imaging (EPI) sequence, this effect will show as a local increase in signal intensity and is called the hemodynamic response signal. By now performing acquisitions during two or more conditions of which one will act as a baseline and the other during some experimental condition (the performance of a certain task), the resulting difference in intensity can be detected and presumably related to the task that is contrasted to the baseline condition.

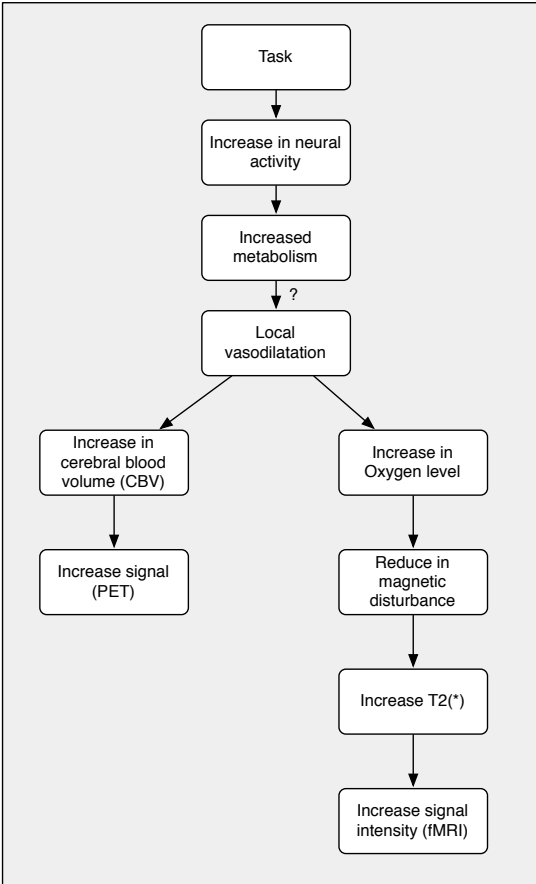


Figure 1.9 A flow chart that describes the events that underly BOLD fMRI signal contrast and PET signal contrast. An experimental task leads to a local increase in neural activity. This leads to increased metabolism for which oxygen is needed. As a consequence, vasodilation takes place leading to increased cerebral blood volume (CBV) and cerebral blood flow (CBF). This in turn can be measured with PET and MRI methods based on arterial spin labeling. The oxygen increase exceeds the actual need and forms an oxyhemoglobin overshoot. This leads to smaller difference in the magnetic disturbances with the surrounding tissue resulting in an increase of T_2^* which can be detected as an increase in signal intensity in the image. The exact neurovascular coupling remains partly unknown, which is depicted by the question mark (?).

From data-acquisition to statistical parameter maps and beyond

In a T_2^* weighted fMRI sequence the hemodynamic response amplitudes have typically a magnitude of only a few percent of the baseline signal level. Measurement noise and physiological fluctuations have a similar magnitude. As a consequence, signals can only be discriminated from noise by taking many acquisitions, and by applying statistical methods to determine which voxels in the brain contain significant contribution from the hemodynamic response.

Before actual signal detection can be performed, a number of (pre)processing steps are needed. Some of these steps are necessary while others may be omitted. The steps as presented here form a basis of processing steps that are considered standard. First, spatial realignment has to be performed to correct for subject movement, and involves estimating the six parameters of an affine, rigid-body transformation that minimizes the difference between each successive scan and a reference scan (usually the first of all scans acquired).

After realignment of the functional data (and optionally, the co-registration of the functional data and an anatomical image), the mean image of the series is used to estimate warping parameters that map onto a canonical standard anatomical space (e.g. [Talairach and Tournoux \(1988\)](#)). This is in most cases a 12-parameter affine transformation followed by non-linear deformations. The primary use of this stereotactic spatial normalization is to facilitate inter-subject averaging.

Next, the functional data can be smoothed by means of convolution with a Gaussian kernel. This improves the signal-to-noise ratio, while on the downside, it reduces the spatial resolution.

After these preprocessing steps, the acquired data may be analyzed on a voxel-by-voxel basis. Functional mapping studies generally use some form of statistical parameter mapping. Statistical parameter maps (SPMs) are images with values that are, under the null hypothesis, distributed according to a known probability density function, usually the Student's t or F -distribution. In general, a general linear model (GLM) is set-up that incorporates the expected time courses of the responses to each of the modeled conditions (X). Using (multiple) linear regression analysis, the amplitude of the coefficients (β) are fitted ([Turner *et al.*, 1998](#)).

Statistics are then performed on the regression coefficients to determine the significance of the response to each condition, or a linear combination of these (so-called contrasts that e.g. compare two responses against a baseline level). Analysis of variances (ANOVA) can be performed on the data and assesses whether inclusion of a certain condition (i.e. column in the model X) decreases the residual variance and thus describes part of the data. The resulting significance levels from individual voxels are combined into a SPM, which can be thresholded at a certain p-value (or, equivalently, a t or F -value). Thresholds can be chosen to restrict the statistically expected family-wise error (FWE) rate or the false discovery rate (FDR) below an acceptable level (e.g. 5 %).

Results from multiple subjects can be combined into an analysis on the group level. A fixed effects analysis assumes the effect of interest to be present in all subjects in equal fashion. This makes it very sensitive to activation but may also be vulnerable to outliers in the data. Moreover, given the assumptions underlying this analysis, it is not possible to make inferences regarding the significance of the detected effects in the population as a whole. A random effects analysis, on the contrary, does not assume equal activation patterns and allows the strength of effect to be different between subjects (i.e. the effect of each subject is treated as a random variable). This allows population inferences at the cost of sensitivity.

Although the data analysis in functional neuroimaging had been dominated by the use of multiple linear regression models, novel analysis methods have been introduced that are based on blind source separation techniques (Langers, 2009). Examples of these techniques are methods like principal component analysis (PCA), in combination with independent component analysis (ICA, Hyvarinen and Oja (2000)), which decompose functional neuroimaging data into components with a meaningful neurophysiologic interpretation in the absence of prior information about the experimental paradigm (or even in the absence of an experimental condition, so-called resting state experiments).