Chapter 7

Concluding remarks and future perspectives

With functional neuroimaging techniques, functions of the human brain can be assessed in vivo. These tools contributed in a significant way to our understanding of the functional organization of the human brain in general and, of particular interest for this thesis, the central auditory system. Among these techniques, positron emission tomography has proven its merit over the last two decades.

This thesis started with an introductory review on functional neuroimaging of the central auditory system, with a focus on the PET technique. The basic anatomy of the auditory pathways was described, followed by the principles of brain activation studies and the highlights of their findings in auditory brain research. In chapter 3 and 4 we investigated brain activation induced by auditory stimulation with music and noise and the influence of sex and sexual orientation on this brain activity. In chapter 3 we found differences in how male and female brains process a noise stimulus. Females displayed higher activation in the primary auditory cortex during noise and the male group had a significant deactivation in the prefrontal cortex. We explained this difference in activation of the auditory cortex by functional sex differences in the auditory-prefrontal network, which is engaged in auditory attention. This experiment showed that sex can influence brain activity already at the primary level of a sensory cortex. For the first time, a sex difference in the functioning of the primary auditory cortex was
shown. Chapter 4 extended these results by showing that not only the sex of the volunteers affects auditory activation, but also sexual orientation. The main finding of the experiment described in this chapter was the fact that the variables sex and sexual orientation are not independent in brain activation studies. This means that investigating sex differences in brain activation depends on the sexual orientation of the groups and vice versa and that mixing groups can have a significant influence on the outcome. The results showed that sex and sexual orientation are important variables to take into account in (auditory) functional neuroimaging research. Hence, a clear description of the experimental groups in terms of sex and sexual orientation is essential in brain activation studies.

In the two subsequent chapters, the influence of sex on the central auditory system as part of a multimodal network was explored. We used silent lipreading, i.e. visual speech images without the speech sounds, in normal hearing subjects to detect how the human brain processes visual stimuli that are normally accompanied by speech sounds. In chapter 5, we examined the possible role of the primary auditory cortex in silent lipreading, a role that was previously debated in the literature. We discovered that only females activated this region during silent lipreading, which explains previous seemingly inconsistent results since no differentiation for sex was made before. Our results show that, at least in females, the primary auditory cortex also processes stimuli that are not auditory in nature. This shows that the traditional view on primary sensory cortices, which states that, in healthy subjects, these areas only process stimuli of that particular sensory modality and that the information of different modalities is integrated in the higher order associative areas is too simple. It also shows that activation of the primary auditory cortex by visual stimuli depends on the sex of the experimental group. Apparently, males and females use different neural strategies to come to the same result. We hypothesized that females make a connection with the auditory speech sound, which normally goes along with the moving lips, whereas males focus more on the visual image itself.
These different ways of processing the same stimuli was further investigated in chapter 6. In that chapter, we did not focus on the auditory areas alone, but we explored regions distributed throughout the whole brain. The overall activation pattern differed between males and females, including differences in integration areas in which females displayed higher activation. This is consistent with our previous hypothesis of the female brain associating the visual speech image to its auditory counterpart as opposed to the male brain. Hence, male and female brains process visual speech stimuli differently without differences in overt lipreading ability.

Overall this thesis raises one major point, namely that sex can have a considerable influence on neuroimaging results even in experiments that are thought of as basic. In the past, possible sex differences were often neglected in fundamental neuroscience research. Nevertheless, many clinical disorders are known to vary with the sex of the patients. For example in some neurodevelopmental disorders such as autism, hyperactivity and mental retardation males have a disadvantage (Gualtieri and Hicks, 1985). In order to understand these disorders, it is important to know how the healthy brain functions, including normal variations in its function and variables that influence this function. Sex can influence the normal brain function, as shown in this thesis. Therefore, in future neuroscience research, sex should be considered as a variable of influence and a detailed description of the experimental groups is essential.

The present results also generate new questions for future central auditory system research. Chapters 3 and 4 clearly show that activation induced by well-known auditory stimuli can be affected by sex and sexual orientation. But these experiments concentrate on a small part of the auditory process. Firstly, we focussed mainly on the primary auditory cortex. Subcortical and other cortical areas were not extensively investigated. Secondly, only a small set of auditory stimuli was used. To further understand the relationship between sex and auditory processing, other auditory stimuli and tasks need to be explored.
Chapter 5 presents information about visual processing in the primary auditory cortex and the influence of sex on this processing. These new findings might be important when studying subjects with hearing deficits, who rely on visual cues for speech comprehension. It has been thought that when a sensory modality is lost, the corresponding primary region gets involved in processing other modalities. We showed that even in normal functioning, other modalities are processed in a primary sensory region. This is important to take into account when studying subjects with sensory deficits. Especially for patients with cochlear implants it is interesting to investigate if sex influences the outcome of the revalidation process. Among the factors that predispose implanted children to higher levels of language development is female sex, regardless of the modality of speech (Geers et al., 2003). Chapters 5 and 6 allow us to hypothesize that because females have a stronger association between the visual and auditory modalities, they have an advantage for language output. Furthermore, these two chapters present new research topics for further research in the multimodal integration field. We hypothesized that males focus more on the primary sensory modality (in this thesis vision) and that females have stronger associations with other related modalities (in this case audition). It indicates that females might be more susceptible to situations in which the information of different modalities does not match, like in the McGurk effect. Research in this field is important for clinical studies on deficits in integration of different information streams. For example in schizophrenia, female patients display more auditory hallucinations (Leung and Chue, 2000), which can be linked to the present results.

We used positron emission tomography to study the function of the central auditory system. As discussed in chapter 2, other techniques exist to investigate brain function in vivo, each with their own (dis-)advantages. In functional neuroimaging studies, fMRI is gaining support as the imaging tool of preference, because of its noninvasiveness and better temporal resolution. Even in auditory research, fMRI is overtaking PET, since solutions for the
loud scanner noise have been proposed. However, PET remains an important tool to study the function of the central auditory system especially in relation to clinical issues. Therefore we will conclude this thesis by highlighting the possibilities of PET in auditory functional neuroimaging research.

The major advantage of PET is the possibility to use equipment that is not magnetic compatible during scanning. PET has proven its clinical value in the study on brain reorganization after cochlear implantation (Truy et al., 1995; Truy, 1999) and there are still questions left unanswered. In this respect, PET will become more important since several new implant devices are developed to treat centrally located disorders. One exciting development is the use of electrical stimulation of (sub)cortical structures to temporarily reduce tinnitus (Plewnia et al., 2003; De Ridder et al., 2005). In an attempt to permanently treat tinnitus, neurostimulative devices around the cochlear nerve (Holm et al., 2005) or extradural (De Ridder et al., 2004) were implanted. However, these studies are still in their infancy. With functional neuroimaging studies in the implanted patients we might better understand the effects of the neurostimulation and the neural base of tinnitus itself. Moreover, PET might also have a diagnostic value to select candidates for cochlear or neurostimulative implantation. When used simultaneously with transcranial magnetic stimulation, PET might predict the outcome of the implant. In general, the future use of PET in functional neuroimaging studies will probably focus on studies in which fMRI can not be applied, like studies which use equipment that is not magnetic compatible.

In conclusion, the present thesis contributes to our basic understanding of how the central auditory system functions and how this function can be influenced. New findings on auditory and visual processing in auditory cortical areas are presented. By contributing to basic knowledge of the central auditory system inspiration for future research, fundamental as well as clinical, is given.
References


