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Imaging in hearing using radiotracers

Abstract: Radiotracers offer unique options for brain imaging of functional and molecular processes related to hearing. Such imaging can be applied in a broad spectrum of situations from preclinical research to clinical patient care. Functional imaging to assess activation in brain regions and networks involved in auditory processing uses markers of blood flow or energy-metabolism in well-defined conditions with and without auditory stimulation. Molecular markers can be used in hearing research for example to study changes in inhibitory neurotransmission systems related to hearing loss. For imaging either positron emission tomography (PET) or single-photon emission computed tomography (SPECT) are employed. Data analysis can encompasses voxel-wise statistical analysis of activation and calculation of quantitative parameters like receptor binding-potentials based on bio-kinetic modeling. Functional imaging has been frequently used in the context of auditory implantation. Before implantation it aims to assess intactness of the central auditory pathway and prognosis. After implantation it is used to improve understanding of the outcome with respect to auditory function and finally speech understanding, e.g. by measuring correlates of central auditory processing and neuroplasticity.

Keywords: Radiotracer imaging, PET, SPECT, cochlear implant, auditory brainstem implant, neuroplasticity.

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1 Procedures

1.1 Radiotracer

Brain regions and networks involved in processing of simple or complex auditory stimuli – e.g. like tones or speech – can be studied using radioactively labelled markers of neuronal activity. Specifically markers of blood flow like ^{15}O-water or ^{99m}Tc-HMPAO and energy metabolism i.e. ^{18}F-flurodeoxyglucose (^{18}F-FDG) can be employed. Studies are performed during silence to measure baseline activity and typically during well-defined stimulation of the auditory system as well. Tracers labelled with short living isotopes – like ^{15}O with a physical half-life of 2 min – allow repeated applications multiple times for later statistical analysis. The radiation exposure of a typical activation study ranges between 4 mSv (^{15}O-water) and 10 mSv (^{99m}Tc-HMPAO) effective Dose.

Furthermore, molecular structures involved in auditory processing like neuro-receptors can be measured using radiotracers. This is of particular interest for inhibitory neurotransmission systems. Changes of these in auditory regions e.g. due to hearing loss or reflecting neuroplasticity are suggested by experimental data. One example is the inhibitory GABAergic system. The radiotracer ^{18}F-flumazenil allowing to measure $GABA_A$ receptor binding has already been employed in hearing research.

1.2 Imaging devices

The radiotracer distribution e.g. in the brain can be measured by emission tomography. Depending on the type of isotope used for labelling either single-photon emission computed tomography (SPECT, for gamma emitters) or positron emission tomography (PET, for positron emitters) is employed. In comparison to functional magnetic resonance imaging (fMRI) both devices have the advantages to be relatively quite imaging modalities and the option of measuring patients with implants without safety concerns.

PET scanners have been fundamentally improved technically in the last two decades [1]. A spatial resolution down to 2 mm (full width at half maximum), and sensitivity up to 9.5 cps/kBq has been achieved. This is considerably superior to SPECT devices, with about 4-5 times lower spatial resolution and up to 100 fold lower sensitivity.

1.3 Data analysis

The simplest form to assess functional activations in the auditory system is based on always one image obtained

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during silence and one during stimulation of the auditory system (see Figure 1). Images of subtraction (stimulation – silence) as well as percent activation of normalized counts registered for auditory regions can be calculated.

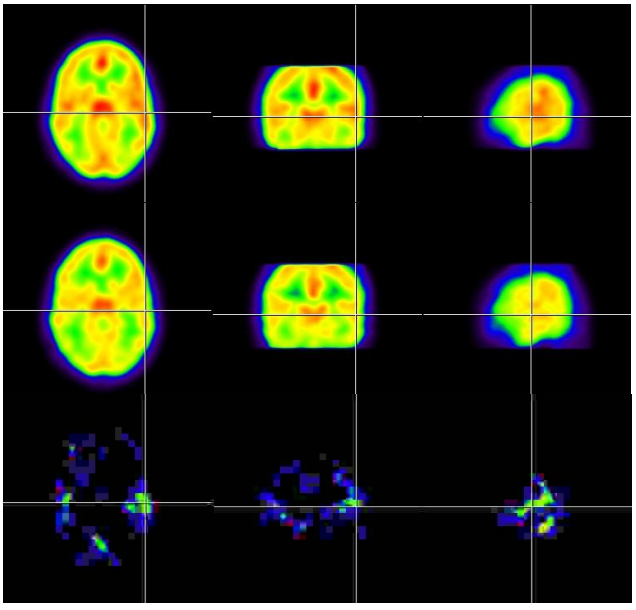

Figure 1: Sectional tomograms (transaxial, coronal and sagittal) of 15O-water uptake obtained with (upper row) and without (middle row) stimulation of the auditory system. The subtraction image "stimulation – silence" is shown in the lower row. Activation within the upper temporal cortex (temporal voice area) can be seen.

A more sophisticated approach is based on repeated measures of conditions – e.g. always 6 times alternating silence and stimulation. This enables analysis using statistical parametric mapping. For this analysis 3D data sets are first transferred into an anatomical stereotaxic standard space and thereafter all scaled in the same way e.g. by normalization to the respective average counts in the brain. Finally a statistical test (e.g. t-test) is performed for each resolution element (voxel) of the 3D data sets to obtain statistical parameter values reflecting the magnitude of the difference between studies obtained during stimulation vs. those obtained during silence (i.e. activation). Finally, relevant activations are recognized, by applying an adequate threshold of significance (e.g. $p<0.001$, uncorrected for multiple comparisons).

For quantification of neuro-receptor studies, bio-kinetic modeling is used. Receptor binding potentials are calculated based on radiotracer input functions (measured from blood samples or reference tissue measured in the scanner) and tissue response curves (measured in the scanner for tissue with specific tracer binding) [2].

2 Results

2.1 Assessment before implantation

Resting state ^{18}F-FDG PET studies have been performed in deaf children before cochlear implantation to assess the prognosis with respect to the achieved speech comprehension A significant negative correlation has been demonstrated between tracer uptake in auditory regions and the performance in a sentence comprehension test achieved 3 years after implantation. This has been explained by a cross modal occupation of auditory regions by visual functions. The data indicate a prognostic relevance of resting metabolism in auditory regions before implantation [3].

Functionality of the central hearing pathway can be assessed using a trans-tympanic needle electrode placed at the promontory (adjacent to the cochlear). The electrode induces direct stimulation of the spiral ganglion / auditory nerve. Promontory simulation has been shown to induce about 20% of increase in blood flow in the auditory cortex (as measured by ^{99m}Tc-HMPAO SPECT), if the central auditory pathway is intact [4].

2.2 Plasticity after cochlear Implantation

After successful cochlear implantation resting activity in auditory regions in the temporal cortex (temporal voice area) decreases because compensatory visual activity is gradually replaced by speech related activity [5]. Moreover, with time after implantation activation in the inferior frontal cortex (Broca area) increases reflecting the auditory rehabilitation process in this region relevant for speech perception and production [6].

Furthermore, improved activation in auditory networks has been demonstrated together with bilateral in contrast to unilateral cochlear implantation. Bilateral implantation recruited more equally auditory cortices in both hemispheres [7]. Finally, binaural vs. monaural discrimination of voice vs. non-voice stimuli revealed, that binaural implant stimulation is associated with activation in right fronto-parietal networks contributing to improved task performance [8].

2.3 Results after brainstem implantation

This subchapter shows exemplarily the potential of ^{15}O-water PET to reflect speech processing in patients with new types of auditory implants. Due to the post cochlear cause of deafness (loss of the auditory nerve due to vestibular

schwannoma) hearing could not be restored by a cochlear implant in these patients (n=7). Instead auditory midbrain implants (ABIs) to the cochlear nucleus were applied. Table 1 outlines the test procedure for the speech performance achieved in these patients applied after a mean period of 8 months.

Table 1: Grading of speech performance in ABI users.

Grade	Speech tracking test (audio-visual)	Understanding of consonants
1 (very good)	> 25 words / min	> 40%
2 (good)	< 25 words / min	25%-40%
3 (moderate)	< 20 words / min	< 25%
4 (poor)	no understanding of speech	differentiation of noises

The quality of speech understanding was strongly correlated to the percentage of activation observed in the temporal voice area with ^{15}O-water PET using a standardized speech activation paradigm (r^2=0.83, p<0.0042, see Table 2).

Table 2: Grade of speech understanding and percent of activation in PET in ABI users.

Grade	Ipsilateral activation in temporal voice area [%]	Contralateral activation in temporal voice area [%]
1 – 2	21 (19-22)	23 (21-25)
2 – 3	12 (12-12)	0
3 – 4	0	0

2.4 Relevance of stimuli

Timing and type of stimulus used in auditory activation studies with radiotracers is of major importance. This can be exemplified e.g. in studies of loudness adaptation, a phenomenon observed in auditory implant users, which is characterized by a loss of loudness perception with a continuous multi-tone stimulus after a particular time period. The phenomenon is associated with lacking activation in auditory regions and additional activation in networks of auditory processing including the ventral frontal cortex [9]. These correlates of deficient processing cannot be observed if e.g. speech instead of a muti-tone complex is used even with identical timing.

3 Neurotransmission

Experimental ex vivo data indicates a relevance of inhibitory neurotransmission systems like the GABAergic system in various alterations of the hearing system like: age related hearing loss, tinnitus and neuro-plastic changes in the central auditory system. Preliminary preclinical studies indicate that at least in profound hearing loss a reduction in $GABA_A$ receptor binding can be detected in vivo in longitudinal studies using ^{18}F-flumazenil PET [10].

4 Conclusion

Radiotracer imaging provides a broad spectrum of methods useful to detect with respect to hearing from basic functionalities – like the intactness of the central auditory pathway up to complex issues – like neuro-plastic changes occurring after auditory implantation. Furthermore the methodology is a research tool for further studies aiming to reveal the neurotransmission of hearing in vivo.

Author's Statement

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