Abstract. The term ‘central auditory processing disorder’ (CAPD; in German-speaking countries: ‘auditive Verarbeitungs- und Wahrnehmungsstörung’, AVWS) embraces various complex disorders of central auditory function. The purpose of this preliminary study was to develop a functional magnetic resonance imaging (fMRI) test set in order to extend the diagnostic work-up to include imaging, and thus to improve both diagnostic performance and the monitoring of treatment outcome. fMRI was performed in 11 healthy children ranging in age from 7 to 10 years and in 11 healthy adults (age range: 23 to 31 years). Three tests, used for diagnosis of CAPD, served as the basis for fMRI paradigms: the Hannover phoneme discrimination test (HPDT); the auditory memory span test (MST) and the dichotic listening test (DLT). In the HPDT, activations in the dorsal part of the superior temporal gyrus (STG) were found on both sides, in the Broca area and in the left middle temporal gyrus, typical for phonemic tasks. The MST showed bilateral activations of the STG, typical for processing of pseudo-words. In addition, bilateral activation of the hippocampus was found. However, there was no clear activity in the left supramarginal gyrus, where the phonological store is thought to be located. The DLT showed activations of the bilateral STG and of the left inferior frontal gyrus. Predominantly, the paradigms showed typical activation patterns of the examined central auditory functions. These results can serve as a reference for future examinations in children with AVWS/CAPD.

In the German-speaking countries, the term ‘auditive Verarbeitungs- und Wahrnehmungsstörung’ (AVWS) embraces various complex central auditory disorders. According to a German consensus statement (1), these disorders can relate both to the level of processing and perception, and to higher cognitive functions. In contrast, following the definition in the English-speaking countries, auditory disorders resulting from higher cognitive dysfunction do not meet the criteria of (central) auditory processing disorders (CAPD) (2). Despite these different criteria, there is agreement that the underlying complex dysfunction necessitates careful differential diagnosis. AVWS/CAPD is predominantly suspected and diagnosed at an early school age, in 7- to 8-year-old children.

Besides detailed anamnesis, the diagnostic work-up includes extensive testing of hearing acuity and the central auditory functions. For the evaluation of central auditory performance, test sets exist which can examine particular aspects of processing and perception. The standard central auditory tests for children in German-speaking countries include the three tests used in this study: the Hannover phoneme discrimination test (HPDT), the auditory memory span test (MST) and the dichotic listening test (DLT). In the HPDT, activations in the dorsal part of the superior temporal gyrus (STG) were found on both sides, in the Broca area and in the left middle temporal gyrus, typical for phonemic tasks. The MST showed bilateral activations of the STG, typical for processing of pseudo-words. In addition, bilateral activation of the hippocampus was found. However, there was no clear activity in the left supramarginal gyrus, where the phonological store is thought to be located. The DLT showed activations of the bilateral STG and of the left inferior frontal gyrus. Predominantly, the paradigms showed typical activation patterns of the examined central auditory functions. These results can serve as a reference for future examinations in children with AVWS/CAPD.
To date, no imaging is used in the diagnosis of CAPD. Functional magnetic resonance imaging (fMRI) is able to localise centres of neural processing and perception in the brain. Our aim was to analyse if fMRI is suitable for inclusion in the diagnostic work-up of CAPD.

For this, we pursued a novel strategy for fMRI in children. Existing standardized auditory tests were adapted and modified for fMRI and the resulting activation patterns were analysed. This strategy would be suitable for clinical application. Provided the contraindications are taken into consideration, fMRI without contrast material is a safe method, suitable also for use in children (4-6).

Answers were sought to the following questions: 1. Can children ranging in age from 7 to 10 years be scanned at all and evaluated with these three tests? 2. Are there evaluable patterns of activation in the auditory cortex, and do these activation patterns show typical responses depending on each hearing task?

Patients and Methods

Study participants. Eleven healthy adults (7 female), ranging in age from 23 to 31 years, and 14 children (4 female), ranging in age from 7 to 10 years (age; years; months): mean 9; 01, median: 9; 03), with normal hearing participated in this study. The definition of normal hearing was that thresholds of all tested frequencies (250 and 500 Hz, 1, 2, 4 and 8 kHz) did not exceed 20 dB. Additionally, the children were submitted to the auditory tests for the purpose of familiarization and showed normal results. The experimental protocol was approved by our institutional Ethics Committee for human studies, and informed consent was obtained from all participants (in the case of children, from the parents) before experiments. Those with a history of any psychiatric, neurological or significant medical illness, a history of substance abuse, or contraindications for fMRI were excluded from participation in the study. Three out of the 14 children decided not to go through with the fMRI examination, but none of the adults withdrew. All participants were right-handed and native speakers of German.

Experimental design and acoustic stimulation. Brain activation in response to listening central auditory hearing tasks was examined by means of fMRI. The fMRI examination was performed while speech signals were delivered to each individual binaurally using a high-fidelity MRI-compatible headset (Institute of Psychology, University of Zurich, Switzerland). Participants were instructed to listen attentively to the speech sounds. The three hearing tests (HPDT, MST and DLT) were performed on a 1.5 T, 20 cm, 30 cm and 0.7 T, respectively, machine with a head coil (Magnetom Sonata, Siemens AG Medical Solutions, Forchheim/Erlangen, Germany). Firstly, axial T1-weighted 3D images were generated with magnetization-prepared rapidly acquired gradient echoes (MPRAGE) to depict the individual anatomy. Imaging parameters were as follows: 52 slices, 3-mm slice thickness, repetition time (TR) 1900 ms, echo time (TE) 4.38 ms, field of view (FOV) 250x220, inversion time (TI) 1100 ms, flip angle 15°. Secondly, fMRI was performed as blood oxygenation level-dependent (BOLD) imaging using EPI sequences with the following parameters: 20 slices, 3-mm slice thickness with a pixel width of 3 mm in each direction, TR 5000 ms, delay in TR 3000 ms, scan time 2000 ms, TE 50 ms, FOV 192x192. The acquired EPI sequences covered the auditory cortex of the temporal gyrus and the inferior portions of the frontal cortex. The total duration of each MRI examination was approximately 30 minutes.

Data processing. Using the OSIRIS (Unité d’Imagerie Numérique, Service d’Informatique Médical, Département de Radiologie et d’Informatique Médical, Hôpitaux Universitaires de Genève, Switzerland) and MRIcon (7) programs, MRI data were converted into the analysing format, which can be read with the Statistical Parametric Mapping program (SPM2; Functional Imaging Laboratory Methods Group, University College, London, UK). The data pre-processing (realignment/motion correction, spatial normalization on the Montreal Neurological Institute (MNI) Reference brain implemented in SPM2, spatial smoothing using a Gaussian kernel of 8 mm field width at half maximum) and statistical data analysis were performed with SPM2. Considering the short scan time and the block design used, slice time correction was unnecessary. After the statistical analysis of the data from each individual participant (first-level analysis using a fixed-effect model with adapted p-thresholds), there followed a group analysis (second-level analysis using a random-effect model with adapted p-thresholds), excluding first-level results in which no clear activation patterns could be obtained. Thus, six groups were analysed regarding the occurrence of clusters: HPDT – adults, MST – adults, DLT – adults, HPDT – children, MST – children, DLT – children. A cluster was required to have a volume of at least 30 voxels. Depending on the strength of activation, different statistical levels [correction of false-positive results by means of false discovery rate (FDR), implemented in SPM2, or no correction] were used in the second-level analysis.
Anatomical localization of the clusters was achieved by means of the anatomical atlas Automatic Anatomical Labelling (AAL) according to Tzourio-Mazoyer et al. (8) and the MRlcrro program (7). In addition, the SPM Anatomy Toolbox according to Eickhoff et al. (9) was employed to establish the exact anatomical location of clusters.

Results

HPDT – adults. The HPDT was evaluated in 11/11 adults. Group analysis with an FDR-corrected p-threshold of 0.01 revealed five clusters (Figure 1). 

Left hemisphere: We found evaluable BOLD responses in the superior temporal gyrus (STG) including the primary auditory cortex; in the inferior frontal gyrus (IFG) with Brodmann area (BA) 44 and branches running to the insula and the IFG. The smaller cluster was located in the capsule interna. 

Right hemisphere: The two clusters showed activations of the STG and middle temporal gyrus (MTG).

MST – adults. The MST was evaluated in 10/11 adults. With an FDR-corrected p-value of 0.05, there were four clusters (Figure 2). 

Left hemisphere: The larger of the two clusters present was located in the STG, with extensions running to the MTG, the end of the temporal cortex, the insula and the IFG. The smaller cluster was located in the capsule interna. 

Right hemisphere: The larger cluster extended over the STG, the MTG and the insula; the smaller one was located in the thalamus.

DLT – adults. The DLT was evaluated in 11/11 adults. With an FDR-uncorrected p-value of <0.001 we found four clusters (Figure 3).

Left hemisphere: The largest of three clusters present was located in the STG, with extensions running to the end of the temporal cortex and the insula; two smaller clusters were detected in the left hemisphere of the cerebellum and in the IFG. 

Right hemisphere: The cluster was located in the MTG and STG.

HPDT – children. The HPDT was evaluated in 10/11 children. With an FDR-uncorrected p-value of <0.001 evaluable BOLD responses were found comprising seven clusters (Figure 1). 

Left hemisphere: The largest of three clusters present was located in the MTG, incorporating parts of the STG with the primary auditory cortex. The second cluster was found in the IFG and the left insula, activating parts of BA 44 and 45. The third cluster was in the STG. 

Right hemisphere: Two of the four clusters found were located in the STG, the other two in the white matter running to the insula.

MST – children. The MST was evaluated in 9/11 children. With an FDR-uncorrected p-value of <0.001, there were 14 clusters (Figure 4). 

Left hemisphere: Two out of a total of eight clusters were located in the temporal lobe, in the STG and MTG. Three clusters were found in the frontal lobe, each activating parts of the IFG, including BA 44 and 45. One cluster was detected in the tegmentum mesencephali, another in the left pallidum. The last cluster activated the hippocampus. 

Right hemisphere: One large cluster (1440 voxels) was located in the STG and MTG, another at the end of the temporal lobe. Other evaluable BOLD responses were clustered in the tegmentum mesencephali, the pallidum and the hippocampus. Furthermore, one cluster was detectable in the right hemisphere of the cerebellum.

DLT – children. The DLT was evaluated in 6/11 children. With an FDR-uncorrected p-value of <0.001, two clusters were found (Figure 3): one in the left STG, the other in the right STG.

Discussion

Can this test set be used to evaluate children aged from 7 to 10 years?

Careful introduction of children to the examination reduces their anxieties and results in an improved compliance, with fewer and less marked motion artefacts. This is a crucial point because motion artefacts in fMRI studies are more frequent in children than in adults (10).

We found evaluable activation patterns with all three hearing tasks. However, the frequency of such patterns decreased with increasing duration of the examination. It was possible to evaluate the HPDT in 10 out of 11 children, the MST in 9 children, and the DLT in only 6 children. One possible explanation is that the childrens’ levels of concentration decreased and with it their performance. Thus, the original idea of presenting the simplest test first, the HPDT, to accustom the children to the test conditions has to be reconsidered. More evaluable results might be obtained if in fact the most difficult-appearing test, the DLT, were presented first. In the adults, there was no such decrease in evaluable activation patterns.

Another important aspect of fMRI testing in children is the problematic statistical evaluation of the data. Anatomical factors are a major source of errors in interpretation of fMRI data from this age group. The relative extents of various areas of the cortex differ between adults and children. In addition, the relation between white and grey matter changes with increasing age (11-13). In paediatric studies, one has to identify a suitable reference brain (template) to serve as the basis for spatial normalization. In the opinion of Wilke et al. (4-6), the use of adult templates for children can lead to false spatial localisations of activations. However, Burgund et al. (14) and Kang et al. (15) do not regard the use of adult templates as problematic provided a resolution of no more than 5 mm is used, as is the case in fMRI studies.
We decided in favour of the adult templates. This facilitated the comparison between children and adults and enabled observer-independent classification of activations with the aid of the AAL atlas (8). In addition, the SPM2 program can be used in children over 6 years of age (16).

Are there evaluable activation patterns in the auditory cortex, and do these show typical responses for each hearing test?

HPDT. When interpreting the activation pattern of the HPDT, it must be considered that the task predominantly tests the ability to discriminate phonemes. In addition, the phonological working memory and, to a certain extent, semantic processing are involved (17). In children, the temporal lobe showed activations in the posterior-superior parts of both hemispheres. Similar patterns of activation have been reported in other studies of phonemic processing; however, they were mostly regarded not as phoneme-specific responses, but either as general speech perception responses (18, 19), or as showing the spatial localisation of the analysis of rapid changing temporal properties of auditory input (20, 21).
Figure 3. Clusters for the DLT in adults (n=11) and in children (n=6) on selected axial T1-weighted images and the lateral view of the brain. Result of second-level analysis. Adults (left side): in the left hemisphere, the largest of the clusters present was located in the STG, with extensions running to the end of the temporal cortex and the insula (clusters 1 and 4); one smaller cluster was detected in the IFG (arrow, left lateral view). In the right hemisphere, the cluster was located in the MTG and STG (cluster 2). Children (right side): two clusters were found (clusters 1 and 2), one in the left STG, the other in the right STG.

Figure 4. Main clusters for the MST in children (n=9) on selected axial T1-weighted images and the lateral view of the brain. Result of second-level analysis. There were clusters present located in the temporal lobe, including the STG and MTG (clusters 1, 2, 5, and 7). In addition, clusters were found in the frontal lobe, each activating parts of the IFG, including BA 44 and 45 (clusters 6 and 12), and with extensions running to the insula (cluster 6). Note the activation of the limbic system (hippocampal area) of both hemispheres (clusters 8 and 9). Furthermore, one cluster was detectable in the right hemisphere of the cerebellum (cluster 4).
Ashtari et al. (22) reported phoneme-specific activations in the left MTG. In agreement, in our study the MTG was activated in children and adults; in children the global maximum was located in the left MTG.

Besides activations of the temporal lobe, in children the left IFG is also activated, including parts of the Broca area. Such activations, when registered, are predominantly regarded as phoneme independent (18, 21). Another possible explanation is activation of the IFG by working memory processes (23, 24).

As well as these classical spatial localisations of speech processing and perception, other brain regions were activated during the HPDT task. One of these was the left anterior insula, co-activated by the cluster with its local maximum in the IFG. The left insula plays a role in initiation, articulatory planning and coordination of the muscles used in speech (25-28). However, in our study, the participants did not repeat the presented words, but instead pressed a button. Possibly they repeated the words silently; this can lead to activation of the insula (29). Additionally, in children, the right insula is activated, an activation rarely found in speech perception studies. Kato et al. (30) found similar right-sided activation of the insula during prearticulatory processes, supporting the theory that the children silently repeated the words.

The cerebellar activations found in adults have been interpreted predominantly as reflecting the cerebellum’s participation in motor speech production. However, this would not explain activation of the vermis of the cerebellum. Alternatively, Ackermann et al. (31) suggested, especially for the vermis, that activations were caused by trigeminal input from the orofacial system. Since, however, the words were not repeated, an adequate explanation of this activation is lacking.

Whether the areas activated during the HPDT include phoneme-specific localisations remains open to debate, and our study was not designed or intended to answer this question. The left MTG, containing the global maximum of responses, can be regarded as a possible localisation. In our opinion, it is important that these activations showed typical, albeit non-specific, patterns in tasks with phonemic processing. The activation patterns can therefore serve as reference for studies in children with AVWS.

MST. The following discussion focuses on the phonological working memory. According to the modified model of Baddeley (32), the working memory comprises four components: the central executive and the three slave subsystems: the visuospatial sketchpad, the phonological loop and the episodic buffer. The phonological loop, comprising the phonological store and the articulatory subvocal rehearsals, is important for the MST. The vocal rehearsal of pseudo-words places stress on the phonological loop. Thus, the function of the phonological loop is reflected clearly in MST performance. The phonological store component of the phonological loop is located in the left supramarginal gyrus, the subvocal rehearsal component in the Broca area (23, 33). In our study, neither the children nor the adults showed significant activations in the supramarginal gyrus. However, in children we found notable BOLD responses in the bilateral hippocampus. Particularly long-term memory processes are attributed to the hippocampus. An involvement of the hippocampus in working memory processes during phonological tasks has been ruled out by some authors (34), but others consider it possible (35). Given that the children had already performed the hearing tests before the fMRI, long-term memory registration seems possible, even if subconsciously. In adults, there was no hippocampal activation. This supports the notion that long-term memory registration may be involved because the adults performed the tasks for the first time during the fMRI examination. As an alternative explanation, technical data acquisition may not have fully included the supramarginal gyrus. However, modified technical data acquisition used in another trial (data in processing) supported the lack of significant responses.

The left IFG was activated in children, albeit at a low level, indicating involvement of working memory processes. Activation by vocal rehearsal also seems feasible, but the simple vocal rehearsal of words does not necessarily lead to activations of the Broca area, as shown previously (36).

As with the HPDT, on the MST the adults displayed activations in the bilateral insula. This can be associated with preparatory processes of speech production (27, 28, 30, 37) or with coordination of the speech muscles (25).

The activations of the basal ganglia found in children and adults may be explained by the hypothesis of involvement of these entities in motor control of speech production and perception (38). Since, however, the activations were nearly symmetrical and the local maxima in adults were located in the white matter, these activations could represent artefactual responses.

Activations in the right hemisphere of the cerebellum as found in the children studied have been reported in other studies on speech processing and perception. There is no consensus, however, on the role played by the cerebellum. Some authors attribute cognitive or higher linguistic functions to the cerebellum (39, 40). Xiang et al. (41) regard the cerebellum as a metasystemic entity providing important support functions for speech task, while other authors emphasise perceptional and articulatory functions of the cerebellum (31). Ravizza et al. (42) assumed participation of the cerebellum in the initial phonological coding and in the strengthening of memory traces. Of course, our study cannot resolve this controversy. However, we have demonstrated that activation of the cerebellum in working memory tasks during speech and listening to pseudo-words is not unusual and can be regarded as a typical finding. In contrast, the activation of the mesencephalon in children is probably an artefact.
In summary, only in part did the MST, reflecting working memory processes during speech and listening to pseudo-words, show typical activations. Activations of the left IFG, of the cerebellum and of the bilateral STG were typical, but activations of the supramarginal gyrus, representing the spatial localisation of the phonological store component of the phonological loop, were broadly absent or showed responses at a very low level. In contrast, bilateral responses were found in the hippocampus.

However, these data could still be used for comparison with children with AVWS/CAPD, since the latter also undergo a pretask before the fMRI, so that the conditions are the same.

**DLT.** In the DLT different words were delivered simultaneously to the right ear and the left ear. This task represents an abstraction and simplification of the normally complex acoustic environmental situation, where the necessity also exists to discriminate among simultaneous acoustic signals. As long ago as the 1960s, Feldmann (43) stated that coping with such situations must be regarded as a high-level central auditory task.

In children, there were only two clusters, one on each side of the brain in the STG. Most previous DLT studies used target polysyllables or words and individuals had to identify the target stimuli and then, usually, press a button (44-48). Thus, these studies are only partially comparable with ours, since we delivered different polysyllabic words to the two ears and the participants were asked to repeat the words. However, most of the earlier studies also reported bilateral activations of the STG (44, 45, 47, 49). Jäncke and Shah (46) reported that the right auditory cortex showed more activations than the left one during concentrated listening to the input to both ears. In agreement with these findings, the global maximum of activations was found to be located in the right STG in our study. According to Jäncke and Shah (46), this might be explained by increased demands on the processing capacity of the right hemisphere, resulting either from transfer of phonetic information to the left hemisphere or from top-down processes directing attention to the right hemisphere in order to increase the effectiveness of the auditory pathway from the left ear.

The responses in the IFG that are usually found in DLT studies were not detected in the children we investigated. However, this may be explained by the small size of the group: in only 6 out of 11 children could the DLT be evaluated. In contrast, the adults showed activations in the IFG. In addition, the adults displayed activations in the left hemisphere of the cerebellum. As mentioned above for the MST, activations of the left cerebellar hemisphere have often been reported in speech studies.

In summary, bilateral activations in the STG are typical for dichotic listening tasks. Despite the small group size, the results can serve as a basis for comparison with children with AVWS/CAPD in future studies. The findings in the adult group (activations in the IFG, cerebellum) should be taken into account in evaluating the responses.

**Methodological concerns.** Although the questions asked were successfully tested, there are possible methodological issues that can be addressed better in future work. Firstly, despite normal results of the children in the pre-fMRI familiarisation test set, it is possible that a child did not meet the criteria for a normal result within the fMRI testing. In future work, an fMRI-compatible microphone recording the participants utterances may be used to prove the correctness of answers. Secondly, we found no significant age-dependent alterations within the children and adult groups. Considering the reports of age-dependent BOLD responses (50), in future studies, subject-specific hemodynamic response functions or alternative designs of data acquisition may be used to generate a better model. Thirdly, despite the use of an MRI-compatible headset, the BOLD responses in auditory aereas can be compromised by the scanner noise. In future work, modelled data acquisition such as sparse-sampling, clustered acquisition (51) or sparse-sampling EPI acquisition (52) may be used to improve the model.

**Conclusion**

In view of the overall good results and the good compliance of the children, fMRI seems appropriate for the examination of children.

The activation patterns of each hearing test can predominantly be regarded as typical for individual components of auditory processing and perception. Thus, the activation pattern could serve as basis for comparison of children with AVWS/CAPD.

**Conflict of Interest**

The authors declare that they have no conflict of interest.

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