

Working Memory–Specific Activity in Auditory Cortex: Potential Correlates of Sequential Processing and Maintenance

André Brechmann¹, Birgit Gaschler-Markefski¹, Mandy Sohr¹, Koichi Yoneda^{1,2}, Thomas Kaulisch¹ and Henning Scheich¹

¹Non-Invasive Brain Imaging, Leibniz Institute for Neurobiology, D-39118 Magdeburg, Germany and ²Faculty of Medicine, Kagoshima University, Sakuragaoka 4-3-1-2654, Kagoshima City 891-0175, Japan

Working memory (WM) tasks involve several interrelated processes during which past information must be transiently maintained, recalled, and compared with test items according to previously instructed rules. It is not clear whether the rule-specific comparisons of perceptual with memorized items are only performed in previously identified frontal and parietal WM areas or whether these areas orchestrate such comparisons by feedback to sensory cortex. We tested the latter hypothesis by focusing on auditory cortex (AC) areas with low-noise functional magnetic resonance imaging in a 2-back WM task involving frequency-modulated (FM) tones. The control condition was a 0-back task on the same stimuli. Analysis of the group data identified an area on right planum temporale equally activated by both tasks and an area on the left planum temporale specifically involved in the 2-back task. A region of interest analysis in each individual revealed that activation on the left planum temporale in the 2-back task positively correlated with the task performance of the subjects. This strongly suggests a prominent role of the AC in 2-back WM tasks. In conjunction with previous findings on FM processing, the left lateralized effect presumably reflects the complex sequential processing demand of the 2-back matching to sample task.

Keywords: fMRI, hemispheric specialization, *n*-back, planum temporale, task performance

Introduction

The basic concept of working memory (WM) refers to “a brain system that provides temporary storage and manipulation of the information necessary for cognitive tasks” (Baddeley 1992). In a general functional sense WM has been characterized as “providing an interface between perception, long-term memory, and action” (Baddeley 2003).

When WM content becomes engaged in tasks, several operational components are conceivable, originally proposed for the role of WM in language processing (Baddeley and Hitch 1974). This multicomponent view has been substantiated by human and animal research identifying specific brain regions instrumental in WM tasks. These studies typically employ either delayed response tasks that focus on the maintenance aspect of WM or *n*-back WM tasks that focus more on the manipulation aspect of WM.

The neural correlate of WM has been proposed to be the sustained activity of neurons that maintain stimulus-related activation long outlasting the eliciting event and was initially observed in prefrontal cortex (Fuster and Alexander 1971) but later also in other brain areas (for recent reviews, see Constantinidis and Procyk 2004; Passingham and Sakai 2004; Ranganath and D’Esposito 2005). The brain structures of key importance for WM are prefrontal cortex and other multimodal

brain areas (e.g., Goldman-Rakic 1995; Smith and Jonides 1998; Fletcher and Henson 2001; Fuster 2001; Romanski 2004).

The role of sensory cortex in WM processes to date is unclear, but there is increasing evidence for a specific involvement of the visual cortex (Constantinidis and Procyk 2004; Pasternak and Greenlee 2005). Evidence for a similar involvement of auditory cortex (AC) in WM is sparse and mainly comes from animal studies describing sustained activity (Gottlieb et al. 1989; Sakurai 1994) or WM deficits after auditory cortical lesions (Stepien et al. 1960; Colombo et al. 1990, 1996; Fritz et al. 2005). To our knowledge, there are only 2 studies in humans suggesting an involvement of AC in WM, namely, an magnetoencephalography study investigating the physiological lifetime for the memory of the loudness of a tone in AC that correlated with behavioral measures (Lü et al. 1992) and a behavioral study revealing deficits of patients with right but not left temporal lobe damage in a pitch memory task but only when interfering tones were presented between the target and comparison tone (Zatorre and Samson 1991). However, imaging studies similarly testing pitch memory with interfering tones did not observe WM-specific activation in AC but in the frontal cortex and middle temporal gyrus of the right hemisphere (Zatorre et al. 1994) and in the supramarginal gyrus (Gaab et al. 2003).

A number of other imaging studies used delayed matching to sample tasks to compare brain activation between different types of information to be maintained in memory (Alain et al. 2001; Rämä et al. 2004; Anurova et al. 2005; Arnott et al. 2005; Rämä and Courtney 2005). However, the findings of these studies do not allow conclusions about WM-specific activation because any difference in activation between the 2 delayed matching to sample tasks may be due to differences in stimulus properties, especially in AC.

An approach that allows to control for activation effects due to stimulus identification is to compare activation between *n*-back and 0-back WM tasks. In the auditory domain, such comparisons have been made using letters (Schumacher et al. 1996; McAllister et al. 1999, 2001; Jaeggi et al. 2003), single digit numbers (Menon et al. 2001; Crottaz-Herbette et al. 2004; Wei et al. 2004), or a name with different prosodic expressions (Rämä et al. 2001). However, none of these studies revealed WM-specific activation in AC. One reason for this may be the use of subtraction designs in direct contrasts of experimental conditions in these studies that have been shown to differ from results obtained when individual tasks are compared with a baseline condition (Sidtis et al. 1999).

Therefore, we tested the specific involvement of AC areas in WM processes by comparing activation during a 2-back and a 0-back condition each contrasted with a “silence” condition.

To avoid possible interference of functional magnetic resonance imaging (fMRI) scanner noise pulses with the serial auditory 2-back WM task (Novitski et al. 2003; Tomasi et al. 2005), we used a low-noise scanning procedure (Scheich et al. 1998). Sequences of upward- and downward-modulated tone sweeps (frequency-modulated [FM]) served as stimuli, the representation of which was studied in detail in previous fMRI experiments (Brechmann et al. 2002; Behne et al. 2005; Brechmann and Scheich 2005). The insights of these studies that served as a basis for the search of WM-specific activities in AC were 1) a right AC specialization for the processing of FM tone direction and 2) evidence for a specific involvement of the left AC in the processing of the relative duration of the FM tone sweeps. These 2 findings have different implications for the present study. On the one hand, the 2-back WM task also required the evaluation of FM tone direction suggesting a specific involvement of the right AC. On the other hand, the 2-back task required sequential comparison of items that was also necessary to evaluate the relative duration of FM tone in a sequence used in the study by Brechmann and Scheich (2005). The latter may imply a specific involvement of the left AC. Specialization of the left hemisphere for sequential processing has long been suggested (Bradshaw and Nettleton 1981), and a recent study of our laboratory (Deike et al. 2004) showed, rather unexpectedly, that the sequential nature of the task can lead to left lateralized activation even though the stimulus property on which the task was based was timbre, which is widely believed to be processed in the right hemisphere.

The aim of the present study was to answer 2 specific questions. 1) Does the comparison of a 2-back and a 0-back WM task each contrasted against a common baseline condition reveal WM-specific activation in the AC and 2) does the 2-back WM task, which involves the processing of FM tone direction, lead to right or left lateralized activation? A region of interest (ROI) analysis in each individual subject served to reveal possible correlations between fMRI activation and task performance as recently shown by Brechmann and Scheich (2005).

Materials and Methods

Subjects

The experiment included 13 right-handed subjects (assessed by the Edinburgh Handedness Inventory) (7 males, 6 females, age range 20–33

years, mean 26 ± 4). All subjects had normal hearing and extensive fMRI experience from previous studies. They gave written informed consent to the experiments which were approved by the Ethics Committee of the Otto-von-Guericke University, Magdeburg.

Data Acquisition

Subjects were scanned in a Bruker 30/60 3-Tesla head scanner equipped with a birdcage coil and an asymmetric gradient system. The system and scanning procedures are specialized for low continuous noise generation allowing stimulus presentation with low background masking at the expense of acquisition of complete brain volumes (Scheich et al. 1998). In this and a previous study on sequential auditory processing during a stream segregation task (Deike et al. 2004), it was particularly important to avoid pulselike gradient noise interference with sequential stimulus presentation as occurs with some scanning techniques. Therefore, we used a FLASH-based gradient echo sequence with longer gradient rise times (2500 μ s) producing low continuous noise (54 dB) (Scheich et al. 1998). Two contiguous slices of 8 mm thickness each were oriented in parallel to the Sylvian fissure covering the superior temporal gyrus of both hemispheres. Functional volumes (field of view: 18 cm², in-plane resolution: 2.8 mm², echo time/repetition time/flip = 38 ms/109 ms/15 deg) required a scan time of approximately 6 s each. In both studies, the flip angle was set to a low value to avoid functional mismatches due to inflow artifacts (Frahm et al. 1994). In order to obtain anatomical landmarks, functional imaging was followed by the acquisition of a high-resolution T1-weighted volume (modified driven equilibrium fourier tomography) with the same orientation. The subject's head was fixed with a vacuum cushion. During the whole fMRI session, the subjects were instructed to keep their eyes closed.

Acoustic Stimulation

Six different linear FM tones of 500-ms duration each were used both for the 2-back task and the 0-back task (Fig. 1). The frequency ranges of these stimuli were 0.5–1, 1–2, 2–4 kHz, and the reverse. The interstimulus interval (ISI) varied randomly between 1, 2, and 3 s to avoid periodic expectancy of the stimuli in the tasks. The stimuli in pseudorandom order were presented in blocks of 49 s.

For stimulus presentation and recording of behavioral responses, the software Presentation (Neurobehavioral Systems, Inc., San Francisco, CA) was used. The acoustical stimuli were presented binaurally through electrodynamic headphones, specially modified for use in the scanner and integrated into earmuffs with liquid-filled rims (Baumgart et al. 1998). The presentation level of the stimuli was adjusted to a comfortable level of about 70 dB SPL.

Tasks

Learning a Reference FM Tone

In the first 294 s of the fMRI session, the subjects learned a reference FM tone inside the magnetic resonance imaging scanner: first, the reference

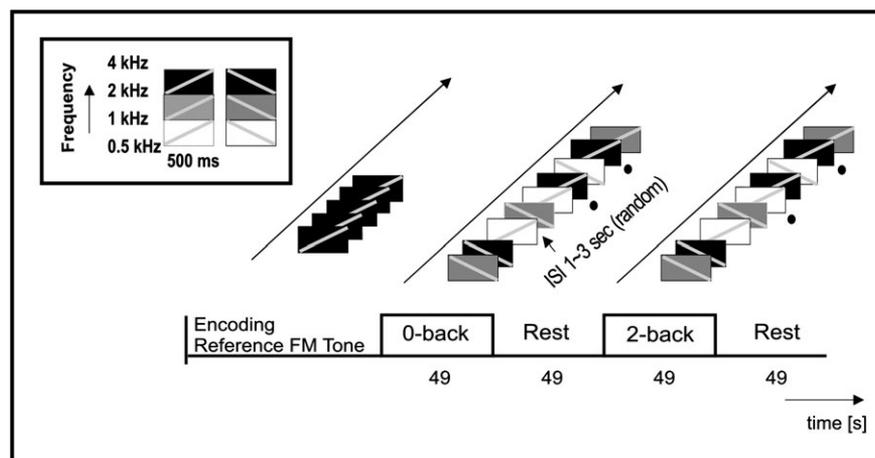


Figure 1. Experimental design. The frequency–time dimensions of the FM stimuli are shown in the inset. Blocks with 0-back and 2-back matching to sample tasks alternated. The time between the onset of 2 FM tone sweeps (ISI) was 1, 2, or 3 s. Filled circles indicate correct targets for the respective tasks.

FM tone (2–4 kHz) was presented 8 times with an ISI of 1 s. Afterward in 2 practice blocks of 49 s separated by a 49-s resting condition, the subjects were instructed to identify the learned FM tone among the other tones and to press the response button with the right index finger when it was recognized. When the subject's hit rate for this task was at least 80%, the fMRI session was continued.

The 0-Back Matching Task

A 0-back task (identifying the reference FM tone) served as a control for the 2-back task with respect to auditory perception, attention toward the stimuli, and motor response. The stimuli were assembled in the same way in both tasks. Subjects were instructed to indicate a match of a current FM tone with the learned reference by pressing the response key.

The 2-Back Matching to Sample Task

For each FM tone, the subjects had to decide by key pressing whether it matched the FM tone 2 back in the sequence (matching in FM tone direction and pitch). The number of possible matches was the same as in the 0-back tasks. The subjects were experienced and familiar with the categorization of FM tone direction because they already participated in a different study involving this task.

Task Sequence

The 2-back and the 0-back tasks were presented alternately in blocks of 49 s separated by a resting period of equal length. Each condition was repeated 6 times. At the beginning of each stimulus block, a verbal cue (2-back or "reference") was given as current task indicator. Each stimulus block contained 5 randomly distributed targets that were not known to the subjects. The subject's response was recorded (number of hits, false alarms, misses, and correct rejections of the targets) and was analyzed with a 2-by-2 frequency table to test the performance in each task (1-sided χ^2 Test, $P = 0.01$; $u > 2.33$).

The fMRI Data Preprocessing

Each functional data set was subjected to a quality check: subject's 3-dimensional (3D) movement was monitored using the AIR package (Woods et al. 1998). Continuous movements exceeding one voxel in at least one direction or continuous rotation of more than 1 degree were used as criteria for data exclusion. Furthermore, the mean gray value of the temporal lobe defined in 2 slices was computed for each volume. Images with percentage deviation of gray values from the mean gray value larger than 2.5% were excluded from further analysis. This procedure was derived in former studies that showed that gray value deviations of more than 2.5% reliability extract volumes in which the subjects made strong transient head movements as confirmed by visual inspection of each single brain volume.

All 13 functional data sets, met these criteria, were corrected for 2D movement using the AIR package and were analyzed with the software package KHORFu (Gaschler et al. 1996). The matrix size of each slice was increased to 128×128 by pixel replication followed by in-plane spatial smoothing with a Gaussian filter (full width half maximum = 2 pixel [2.8 mm], Kernel = 5 pixel [7 mm]). This ensured that data further away than 2.8 mm are not used for spatial smoothing. Then we applied a moving average temporal smoothing using a kernel width of 2 time points.

Multisubject Analysis

Initial data analysis was performed with the software package BrainVoyager™. After manual alignment of the preprocessed fMRI data to the corresponding 3D anatomical data set parallel to the Sylvian fissure, the data were transformed into Talairach coordinate space. By using a cortex-based spatial independent component analysis (ICA) implemented in BrainVoyager™ (Formisano et al. 2002), 30 spatial components were derived from the grand average of these spatially transformed data. ICA is a data driven statistical technique that has been shown to be a powerful method for the analysis of fMRI data (e.g., McKeown et al. 1998) and that does not require an a priori hypothesis about the time course of the activated voxels. We used this method to locate spatially independent components (clusters of activation) in the

AC without assuming that the blood oxygen level-dependent (BOLD) response in these clusters during the blocks of 49 s, in which the subjects had to solve the n -back WM tasks, strictly follows the on/off characteristics usually assumed in correlation analyses. The time series of voxels belonging to a 3D cluster of at least 6 voxels with a $|z|$ value >3 were then further analyzed with a linear regression analysis (general linear model [GLM]) using the 0-back and the 2-back conditions as the 2 predictors. This was done to ensure that these clusters were significantly activated compared with the common baseline. Then the Talairach coordinates of the activated voxel with the highest significance of the linear contrast (2 back = 1, 0 back = -1) were determined.

Individual ROI Analysis

Functional activation was analyzed by correlation analysis to obtain statistical parametric maps. A trapezoid function served as correlation vector, roughly modeling the expected BOLD response. Pearson's correlation analysis tested the 2-back and the 0-back conditions versus the following resting conditions ($P = 0.05$). Only those voxels that belonged to a cluster of at least 8 significant contiguous voxels were accepted as significantly activated. As previously described (Scheich et al. 1998) and discussed in detail in Brechmann et al. (2002), these clusters in each slice were attributed to 1 of 4 ROI of AC. These ROIs form comparable adjacent territories in each hemisphere of individual brains in relation to the anatomical landmarks Heschl's gyrus and Heschl's sulcus. T1 follows the course of Heschl's gyrus on its anterior rim and extends laterally on the superior temporal gyrus. TA covers the planum polare anterior to Heschl's gyrus; T2 follows the course of and is centered to Heschl's sulcus; T3 covers the posterior planum temporale and includes the adjacent superior temporal gyrus. For each territory in each subject and each condition versus rest, the total number of significantly activated voxels was multiplied by their averaged relative BOLD signal change resulting in intensity-weighted volumes (IWs). By using a 2-way analysis of variance (ANOVA) with repeated measurements (task, hemisphere), the IWV of each territory was tested across subjects (F -test, $P = 0.05$). Post hoc, the IWV were tested for differences between tasks across subjects (dependent samples, 2-tailed paired t -test, $P = 0.05$).

Results

Behavioral Performance

The statistical analysis of sensitivity index d' (Swets et al. 1961) showed that the 13 subjects were well above chance in both tasks. Identification of matching FM tone was significantly better (dependent samples, 2-tailed paired t -test, $P < 0.01$) in the 0-back task ($d' 3.51 \pm 0.25$) than in the 2-back task ($d' 2.34 \pm 0.18$). Most subjects reported not to have a specific strategy but that they just compared the FM tone sweeps acoustically. However, some subjects used a visual strategy, for example, imagined a line going up or down, and one subject gave each of the 6 different tones a number and made his decision on the pattern of these numbers.

Multisubject Analysis

The ICA of signal time course of voxels identified 30 spatial activation components in the Talairach transformed brain of the 13 subjects. In the AC, 2 separate components were located. One on the left planum temporale (Talairach coordinates: -51/-30/10) and one on the right planum temporale laterally extending on the upper bank of the superior temporal sulcus (Talairach coordinates: 59/-35/14). These clusters of activation were tested for significant differences between the 2 conditions using a GLM with the direct contrast 2-back = 1 and 0-back = -1. Only the spatial component on the left side showed a significant difference between the 2 conditions with a larger 2-back than 0-back response ($P = 0.03$). The component on the right lateral

planum temporale showed no significant difference between the 0-back and 2-back response ($P = 0.24$) (Fig. 2).

Individual ROI Analysis

The ICA served to identify candidate areas for WM-related activation effects. For 2 reasons, this was followed by an individual analysis of AC areas. First, individual performance differences in the tasks (d') may potentially be related to individual activation differences. This information is largely lost in grand average analyses of all transformed data sets. Second, because of the multiplicity of auditory fields in the region of the Sylvian fissure and of the known inaccuracies of Talairach

localizations of activity on the superior temporal plane, the exact localization and spatial extent of activations have to be scrutinized. The individual reanalysis was performed with a previously developed scheme of landmark-oriented ROIs (see Materials and Methods) that serves to parcellate AC into areas with known differential activation (Gaschler-Markefski et al. 1998; Scheich et al. 1998; Baumgart et al. 1999; Brechmann et al. 2002; Deike et al. 2004; Behne et al. 2005; Brechmann and Scheich 2005).

First, global activation in terms of IWV across the 4 ROIs was subjected to an ANOVA that covered task (0-back, 2-back) and hemisphere. We found a significant main effect of hemisphere

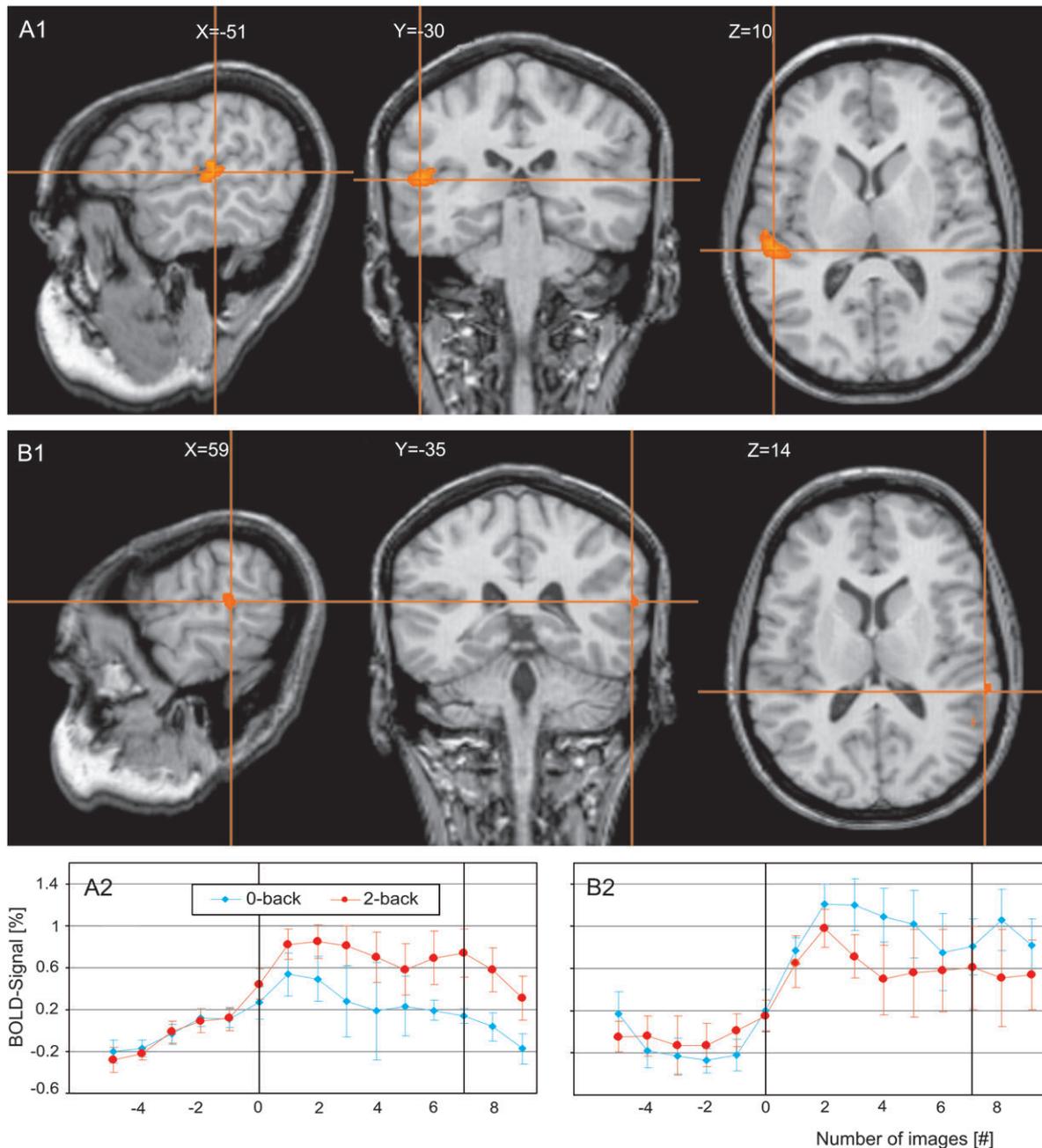


Figure 2. Multisubject analysis. (A1) shows the spatial component in left posterior AC of Talairach transformed data sets that exhibited stronger activation during the 2-back task. (A2) shows the corresponding time courses averaged over 0-back and 2-back blocks. Images 0–7 cover the stimulation epochs. (B1) shows the spatial component in right posterior AC that did not reveal significant differences between the 0-back and 2-back conditions. (B2).

with larger left AC activation during the 2-back task ($F(1,12) = 5.32$; $P = 0.04$) (Fig. 3A). IWVs in each of the predetermined ROIs in both hemispheres were also subjected to an ANOVA. A significant main effect of task ($F(1,12) = 10.44$; $P = 0.007$) and (as a trend) a main effect of hemisphere was found in T3 on the planum temporale ($F(1,12) = 4.47$; $P = 0.056$) (Fig. 3B). This result corresponds to the multisubject analysis that identified a component with 2-back > 0-back response on left but not right planum temporale.

Correlation of Activity with Performance

Pearson's correlation between the fMRI activation in terms of IWV and the sensitivity index d' was determined for each task and each territory. Among all ROIs analyzed in AC, only activation in the left T3 showed a significant correlation with the sensitivity index d' of performance and only in the 2-back task (F -test; $r = 0.72$, $F(1,12)$, $P = 0.006$) (see Fig. 4). Thus, good performers in the WM task showed stronger activation in left T3 than poor performers.

Discussion

The experiment aimed at clarifying the contribution of sensory mechanisms in AC to the solution of WM tasks and to determine which BOLD activation in left and right AC reflects distinguishable components of the specific 2-back WM task. The study was based on previous research carried out with other cognitive tasks but the same class of stimuli, namely, FM tone sweeps varying in direction and frequency range (Brechmann et al. 2002; Behne et al. 2005; Brechmann and Scheich 2005). Thus, in a broader sense, the experiment served to obtain a more comprehensive view of task-specific representations of stimuli to substantiate the hypothesis that it is the type of conceptualization of the stimuli and not stimulus properties per se that determines the spatiotemporal representations in AC (Brechmann and Scheich 2005; Ohl and Scheich 2005). In this respect, it seemed important to determine how the continuous sequential comparisons inherent in the execution of the 2-back WM task influence the stimulus representation in AC.

Evidence for a specific involvement of sensory cortical areas in WM processes is increasing (Pasternak and Greenlee 2005) but mostly comes from research in the visual domain. This includes specific fMRI activation in visual cortical areas in 2-back compared with 0-back tasks (e.g., Carlson et al. 1998; Druzgal and D'Esposito 2001). Similar activation differences in AC were not found in previous studies using auditory n -back tasks (Schumacher et al. 1996; McAllister et al. 1999, 2001; Rämä et al. 2001; Jaeggi et al. 2003; Crottaz-Herbette et al. 2004; Wei et al. 2004). This may be due to methodological differences, for example, using direct contrast designs (for a discussion, see Sidtis et al. 1999) or using much louder echo planar imaging that may have led to confounding effects. However, in the present study, we found a significant increase in activation in the 2-back compared with the 0-back condition in the left planum temporale (T3). This evidence for a specific involvement of AC in WM is especially supported by the fact that the activation of left T3 in the 2-back WM task showed a significant positive correlation with task performance. These results could reflect one or several of the underlying processes that are distinct from the 0-back condition and necessary to solve the 2-back task: 1) potential differences of feature analysis of stimuli, 2) differences of matching the actual with the memorized items,

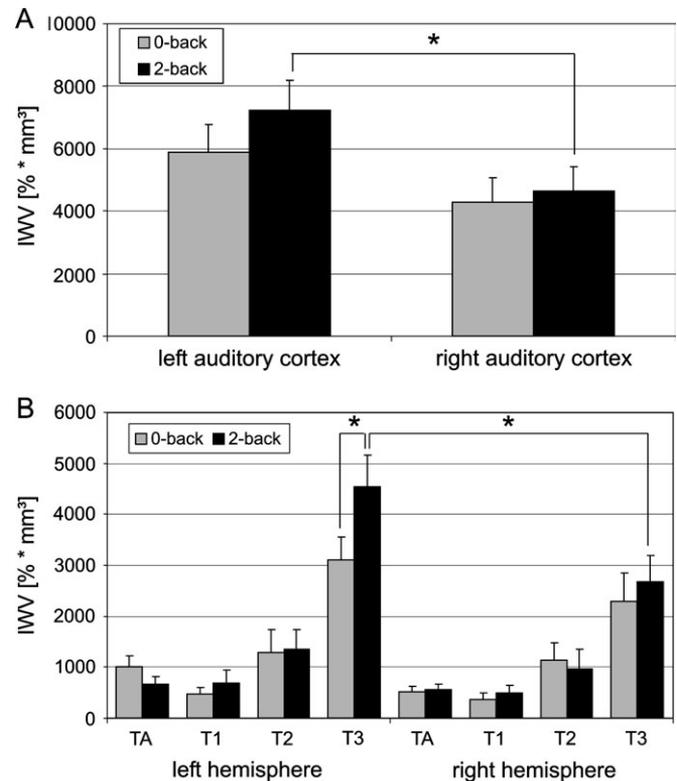


Figure 3. ROI analysis. Total activation in left and right AC (A) and in the individual auditory territories (B) in the 0-back and 2-back conditions each compared with a "silent" resting condition.

3) differences of sequential processing, and 4) WM maintenance differences.

First, during both the 0-back and 2-back tasks, the subjects had to identify the pitch range and direction of FM tone sweeps and had to compare each of them with memorized reference stimuli all belonging to the same stimulus set. Thus, reasons for the difference in activation are not likely found in the realm of basic feature analysis of the presented items.

Second, the number of comparisons of actual with memorized items to be made were the same in the 2 conditions as well as the number of possible matches. Even if this matching led to a difference in activation due to the fact that in the 0-back condition it was always the same memorized item, the stronger activation during the 2-back task would not be expected in the left T3. In our previous study (Brechmann and Scheich 2005) in which an even larger set of FM stimuli had to be matched to the upward and downward directional categories of FM tone, a classification based on the same auditory feature analysis of stimuli as in the present study, we found right T3 dominance. In the same vein, most studies using simple comparisons and discriminations of stimuli distinguishable by pitch and melodic contour found right AC dominance or bilateral involvement but not left AC dominance, for example, after temporal lobe lesions (Zatorre 1985; Samson and Zatorre 1988; Zatorre and Halpern 1993; Johnsrude et al. 2000). Thus, the left T3 dominance in the 2-back task must have other reasons. One reason could be that the subjects used a verbal strategy to identify and compare the FM tone sweeps. If such a strategy was used (which was mostly not the case), it is very likely that naming would have occurred in both of the alternating conditions 0-back and 2-back WM.

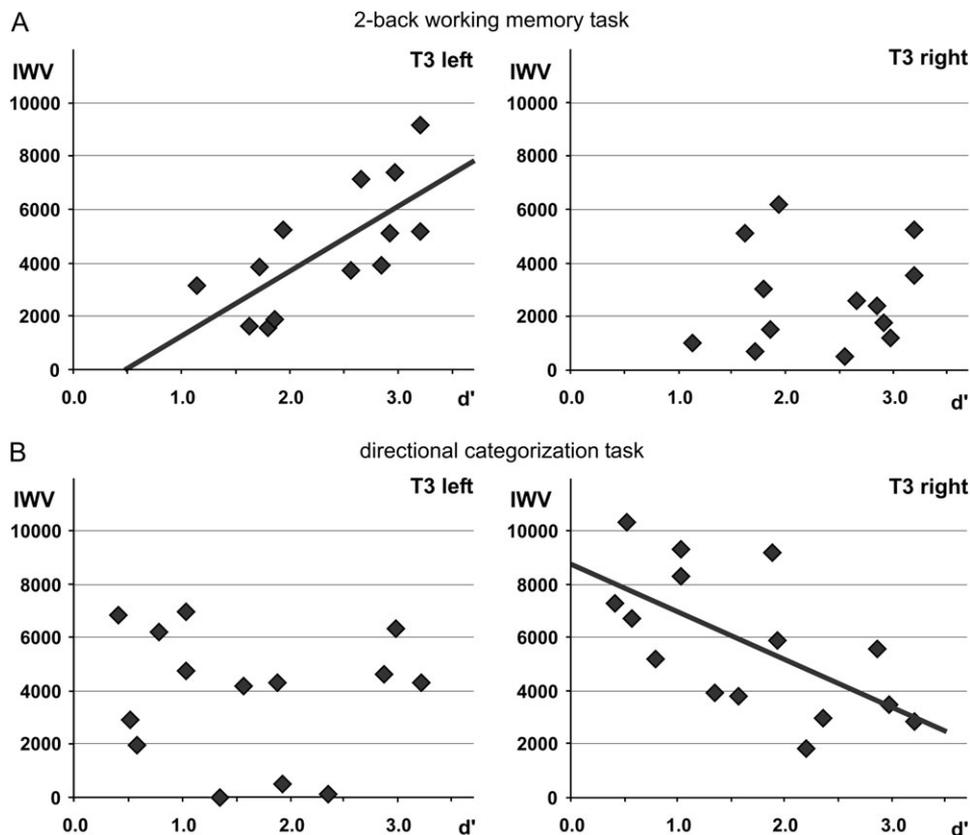


Figure 4. Correlation between task performance and activation in left and right T3 during the 2-back WM condition (A). Note positive correlation in left T3 but no significant correlation in right T3. For comparison, the data of the study by Brechmann and Scheich (2005) during discrimination of FM tone direction is plotted in (B). Here the activation of right but not left T3 showed an inverse correlation.

Another rather unlikely possibility is that attention effects per se have produced the left T3 dominance. Attentional modulation of activity produced by presented stimuli is usually found in the cortex areas where the stimulus cues are selectively processed (Posner 1995). Thus, attentional effects would also be expected in the right T3. Right T3 is also activated in the present experiment but not differently in the 2 tasks as revealed both by multisubject and ROI analyses. This is in accordance with the idea that the specific auditory cues for the identification of target stimuli, namely, frequency and direction of FM tone that were the same in the 2 conditions, are processed in right T3 (Brechmann and Scheich 2005).

Third, we have to consider whether the stronger left T3 activation during the 2-back task can be related to the task-inherent complexity, namely, the sequential analysis of stimuli in contrast to the 0-back task in which the sequence of stimuli was not important. Dominant left AC activation has been found reliably with speech material and has been related to the high demands of temporal feature analysis inherent at all levels of speech from voice onset times in phonemes to syllable, word, and sentence segmentation (for review, see Zatorre et al. 2002). Left AC dominance in response to nonspeech sounds might occur if such stimuli have similar demands on temporal pattern analysis. In the present case, stimuli in the 2 conditions were the same. Thus, there was no difference of temporal complexity of the material. As an alternative, evidence should be taken into account that left AC is not merely specialized for the bottom-up temporal feature analysis. Top-down influences can make

sequence information selectively available in percepts. Mainly based on psychophysical and lesion-related impairment data, it has long been hypothesized that sequential analysis is a domain of the left hemisphere that may explain several aspects of left hemisphere-related speech and music processing (Bradshaw and Nettleton 1981). Regarding top-down influences, it is noteworthy that a sequential pattern of sounds is conceptual and not necessarily determined by the physical description of events following one another. A good example is the temporal binding of phonemes and words from one speaker in the cocktail party situation that must disregard interfering voices from other speakers. A simple model of this is “streaming” of sequences of alternating sounds (ABAB), namely, the capability to sequentially group those sounds according to their similarity (AA vs. BB) in preference to their immediate succession (Bregman 1990). It was recently shown by fMRI that a task of segregating sequences of alternating harmonic tones only distinguishable by their timbre selectively activates left T3 areas (Deike et al. 2004). Because of the spectral cue for distinguishing these alternating sounds, one would expect a dominance of right T3 activity but obviously the selective sequential analysis is so demanding that the left T3 is more challenged.

In terms of sequential tasks, there is also some similarity to a pitch memory task in which the subjects had to compare always either the first and the last note or a melody (Zatorre et al. 1994) or the first with the last or the penultimate note depending on a visual prompt after the end of the melody (Gaab et al. 2003, 2006). The latter may pose a higher demand

on sequential processing due to the equivocality of the rule of comparison that was disambiguated only after the end of the melody. Although speculative, this may explain the left lateralized activation found by Gaab et al. (2003, 2006) compared with the right lateralized activation found by Zatorre et al. (1994).

Following all these considerations, it appears that in our experiment, it was the execution of the complex sequential aspect of the 2-back task that lateralized activity to the left. However, this hypothesis needs further support, for example, by showing that a lower demand on sequential processing, for example, in a 1-back WM task, would lead to reduced activation of the left side.

The fourth question is whether there are aspects of the results that may be related to the memory component of the WM task, specifically which activation differences between the 2 conditions could reflect the need to maintain WM content in the 2-back condition for serial comparisons. We propose that the positive direction of the correlation of activity in left T3 with the performance of subjects (d') is a correlate of memory maintenance. This finding is particularly relevant not only because correlations of performance with BOLD activation are considered signs of specific involvement of brain structures in a task (Parker and Newsome 1998; Ohl and Scheich 2005) but also because positive or negative correlations of BOLD activity are found in different tasks that may allow different interpretations of the underlying process (Jonides 2004). For instance, in T3 on the right side, a negative correlation with performance was found for directional categorization of similar FM stimuli as used in the present study (Brechmann and Scheich 2005). This negative correlation was interpreted as a sign of variable proficiency in solving this classification task, namely, that a high performance in processing depends on a restriction to specialized neurons that clearly distinguish the direction of FM tone at the expense of less specific neurons that may be involved in an initial, less proficient stage of the experiment. A theoretical concept (Desimone 1996) for this is that the specificity of stimulus representation can be improved by suppressing neurons that have a low stimulus selectivity.

In contrast, a positive correlation of performance and BOLD activation was found in AC for a phoneme discrimination task with graded binaural noise masking (Binder et al. 2004). Because the highest discrimination performance and the largest BOLD signal were found for the best signal-to-noise ratio of presented stimuli, the result may be explained by changed discriminability of sensory representations of stimuli. Thus, more salient representation of stimuli may allow better performance leading to the positive correlation. Compatible with this idea is that stimulus-specific fMRI activation must be upregulated if the perceptual salience of a stimulus is low due to masking noise. Such an improved representation was suggested by experiments in which FM stimuli were monaurally presented for directional categorization and white noise was presented to the contralateral ear (Behne et al. 2005).

In the case of the positive correlation found in the present WM task, improved performance may also be achieved by improved central representation of stimuli but of a different type. It was already shown in a visual WM task that high fMRI signal intensity in frontoparietal areas was a predictor of successful performance (Pessoa et al. 2002; Olesen et al. 2004). Similarly, Gaab et al. (2006) found stronger fMRI activation in left supramarginal gyrus of subjects who strongly improved performance after training of a pitch memory task compared

with subjects who did not improve very much after training. In principle, to solve a 2-back WM task, neuronal activations from 2 stimuli must be maintained in memory, whereas for the 0-back task, immediate comparisons with one memorized item can be used. This could be accomplished by WM signature neurons described by Sakurai (1994) in AC, which in the 2-back task guarantee a high and lasting representation of past stimuli. This recruitment or higher activity of recruited neurons would allow successful comparison and match of the actual and the memorized stimuli and therefore better performance. Such comparisons could be performed efficiently if not only the actual but also the memorized stimulus is represented in the AC. We would therefore hypothesize that such comparisons are indeed performed in AC, however, presumably orchestrated by prefrontal areas using anatomical feedback connections (Petrides and Pandya 2006).

Notes

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Address correspondence to André Brechmann, Leibniz Institute for Neurobiology, Brennekestrasse 6, 39118 Magdeburg, Germany. Email: brechman@ifn-magdeburg.de.

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