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## Sustained blood oxygenation and volume response to repetition rate-modulated sound in human auditory cortex

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### Abstract

The blood oxygen level-dependent (BOLD) signal time course in the auditory cortex is characterized by two components, an initial transient peak and a subsequent sustained plateau with smaller amplitude. Because the  $T_2^*$  signal detected by functional magnetic resonance imaging (fMRI) depends on at least two counteracting factors, blood oxygenation and volume, we examined whether the reduction in the sustained BOLD signal results from decreased levels of oxygenation or from increased levels of blood volume. We used conventional fMRI to quantify the BOLD signal and fMRI in combination with superparamagnetic contrast agent to quantify blood volume and employed repetition rate-modulated sounds in a silent background to manipulate the response amplitude in the auditory cortex. In the BOLD signal, the initial peak reached 3.3% with pulsed sound and 1.9% with continuous sound, whereas the sustained BOLD signal fell to 2.2% with pulsed sound and to 0.5% with continuous sound, respectively. The repetition rate-dependent reduction in the sustained BOLD amplitude was accompanied by concordant changes in sustained blood volume levels, which, compared to silence, increased by ~30% with pulsed and by ~10% with continuous sound. Thus, our data suggest that the reduced amplitude of the sustained BOLD signal reflects stimulus-dependent modulation of blood oxygenation rather than blood volume-related effects.

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### Introduction

The blood oxygen level-dependent (BOLD) response in the auditory cortex is often characterized by spatially and temporally dissociable signal patterns (Gaschler-Markefski et al., 1997; Robson et al., 1998; Jäncke et al., 1999; Giraud et al., 2000; Di Salle et al., 2001; Harms and Melcher, 2002). Its temporal profile falls into at least two broad independent classes, an initial transient and a subsequent sustained component (Seifritz et al., 2002). The amplitude of the sustained component is typically considerably smaller

than the amplitude of the initial transient. However, it is unclear whether the reduction during the sustained period represents underlying neural activity-related changes in oxygenation or results from other hemodynamic mechanisms. The  $T_2^*$ -weighted signal recorded with functional magnetic resonance imaging (fMRI) depends on at least two counteracting factors, blood oxygenation and volume. During neural activation, regional levels of blood flow (Fox and Raichle, 1984) and volume (Belliveau et al., 1991) increase to an extent that the oxygen supply exceeds the actual demand of the activated neurons (Fox and Raichle, 1986; Hoge et al., 1999). The relative change in concentrations of oxygenated and deoxygenated hemoglobin leads to a decrease in the local magnetic susceptibility, which results in an increase of the  $T_2^*$ -weighted BOLD signal (Ogawa et al.,

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1990; Kwong et al., 1992). In turn, increased blood volume per se decreases the  $T_2^*$  signal due to increased absolute concentrations of the paramagnetic deoxygenated hemoglobin. This interaction plays a role in the  $T_2^*$  signal undershoot, which is typically observed after the offset of a stimulus (Frahm et al., 1992; Kwong et al., 1992; Ogawa et al., 1992, 1993; Bandettini et al., 1997; Fransson et al., 1998) and which is believed to result from a temporal mismatch between blood flow and blood volume (Buxton et al., 1998; Mandeville et al., 1999a, 1999b).

Here we addressed the question of whether the reduction in amplitude of the sustained BOLD signal during auditory stimulation is related to lowered levels of neural activity-related oxygenation or to blood volume-dependent signal depression. We have explored two alternative predictions: (a) if a reduced sustained BOLD signal amplitude results from a prolonged blood volume-related undershoot after the initial response peak, small sustained native  $T_2^*$  signals should be accompanied by large sustained blood volume levels; and (b) if a reduced sustained BOLD signal amplitude represents decreased oxygenation from neural activity, the corresponding blood volume levels should be small.

## Materials and Methods

### Subjects, imaging, and stimulation procedures

Healthy subjects (3 females and 5 males; mean age and standard deviation,  $27 \pm 5.3$  years) participated in experiment 1, and one male subject (36 years) was studied repeatedly in experiments 2 and 3. After approval by the local ethics committee, subjects gave written informed consent after the procedures had been fully explained.

Imaging data were acquired on a 1.5-Tesla Vision scanner (www.siemens.de) using a standard circularly polarized head coil. After acquisition of structural  $T_1$ -weighted volumes, nine contiguous transversal functional slices (single shot gradient recalled echo planar imaging sequence; TE, 70 ms; field of view;  $219 \times 250$  mm<sup>2</sup>; matrix,  $108 \times 128$ ; slice thickness, 4 mm; slice acquisition time, 200 ms) covering the auditory and surrounding temporal cortex were used for fMRI (further details below). Images were postprocessed using Brainvoyager (www.brainvoyager.de). The fMRI time series were corrected for slice acquisition time, realigned with their corresponding  $T_1$  volumes, warped into standard space, resampled into 3 mm isotropic voxels, motion-corrected using least square fit for six spatial parameters, and corrected voxelwise for linear drifts.

All auditory stimuli consisted of sine tones at a carrier frequency of 1 kHz and a sound pressure level of 95 dB and were delivered using the scanner's piezoelectric loudspeaker connected to a pneumatic headphone system. Repetition rate was varied by amplitude modulation using a square-wave envelope with smoothed 5-ms on- and offset ramps and a 50% duty cycle (except for the continuous

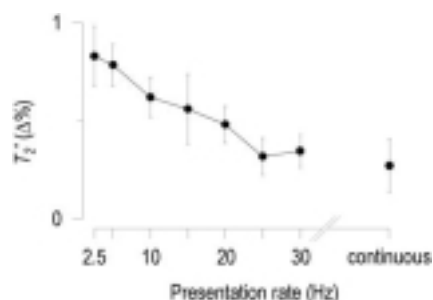


Fig. 1. Dependence of BOLD signal response bilaterally in the core and belt of the auditory cortex on sound repetition rate [ $N = 8$  subjects, mean, and standard error;  $F(7,49) = 4.2$ ,  $P < .001$ ]; note, the mean difference between BOLD signal response to the 2.5- and 5-Hz repetition rates was statistically not significant [ $F(1,7) = .14$ ].

sound). Subjects were asked to passively listen to the stimuli but not to carry out any output task.

## Experiments 1–3

In experiment 1, we examined the sound repetition rate dependence of BOLD response in the auditory cortex using an fMRI sampling method (Scheffler et al., 1998; Edmister et al., 1999; Hall et al., 1999), which allowed us to avoid activation by scanner noise (Bandettini et al., 1998) and which consisted of 30 scans with a short scan duration of 1.8 s and long interscan delays of 13.2 s. In a boxcar stimulation protocol (stimulation was switched on and off alternately every five scans), we assessed the BOLD response to stimulus repetition rates of 2.5, 5, 10, 15, 20, 25, and 30 Hz and continuous carrier sound presented in randomly permuted order. The continuous carrier sound stimulus was used as the limiting case for infinite repetition rate. Using a fixed effects general linear model analysis (Friston et al., 1995) considering all subjects and sound repetition rates as different regressors, areas common to all conditions in terms of significant main effects ( $P \leq 0.05$ , corrected voxelwise for multiple comparisons) were identified and yielded a pattern of bilateral activity, which covered the core and belt of the auditory cortex (Wessinger et al., 2001; Zatorre and Belin, 2001). The BOLD signal amplitudes (fractional difference between on- and off-scans) were computed as a function of sound repetition rate and compared using repeated-measures analysis of variance (Fig. 1).

In experiment 2, we examined the time course of the BOLD signal response to a 60-s stimulation with 5-Hz pulse-modulated and continuous sound in the auditory cortex region described in experiment 1. We used an event-related averaged single trial approach to present the stimuli without background scanner noise (Ernst and Hennig, 1994; Robson et al., 1998; Belin et al., 1999). Thereby, the timing of functional image acquisition was parametrically shifted relative to the stimulus onset, which allowed us to reconstruct a composite signal profile as a function of timing

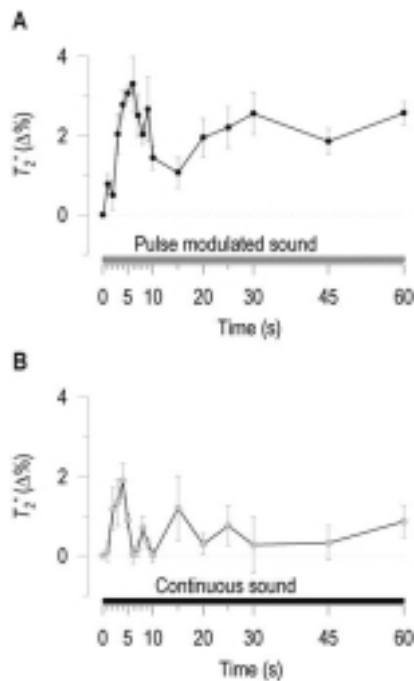


Fig. 2. Event-related averaged single trial-derived BOLD signal time course in the core and belt of the auditory cortex (mean and standard error; normalized to silent baseline at stimulus onset) of one subject, (A) during 60 s stimulation with 5-Hz pulse-modulated 1-kHz sound, and (B) during 60 s stimulation with continuous 1-kHz sound. The mean transient peak reached 3.3% (at ~5–6 s) during the pulsed sound and 1.9% (at ~3–4 s) during the continuous sound. The amplitude of the sustained component, defined as averaged signal between 20 and 60 s, was 2.2% (or 67.4% relative to the transient amplitude) during presentation of the pulsed sound and 0.5% (or 26.4% relative to the transient amplitude) during presentation of the continuous sound.

relative to stimulus onset (Fig. 2). Because this strategy requires long periods of time for data acquisition, 5 sessions with acquisition of 4 repeated measurements per time point (resulting in 10 repeated measurements per time point and repetition rate) and preceding reference scans to define the region of interest as described in experiment 1 were carried out. In order to arrive at resting state baseline levels at the initiation of stimulation, we used a delay between scan offset and onset of a new stimulus of 45 s. Delay-specific BOLD signal amplitudes relative to stimulus onset were calculated bilaterally in the auditory cortex, which comprised core and belt as functionally defined by linear correlation analysis (Bandettini et al., 1993) using a simple box car stimulation protocol with a 5-Hz repetition rate ( $P \leq 0.05$ , corrected).

In experiment 3, we used the same silent acquisition scheme with short scan times (1.8 s) and long silent inter-scan times (13.2 s) and the same region of interest as described in experiment 1 and determined the changes in blood volume associated with the native  $T_2^*$  response to a repetition rate of 5 Hz and to a continuous sound. We employed fMRI in combination with intravenous infusion of the intravascular superparamagnetic contrast agent En-

dorem, a suspension with dextran-coated iron oxide nanoparticles 60–150 nm in diameter, and serial venous blood sampling. The details of this “titration” procedure have been described in detail elsewhere (Scheffler et al., 1999). In brief, a 30-scan boxcar stimulation scheme (as described in experiment 2) using a sound stimulus with a 5-Hz repetition rate was used to define the auditory cortex region of interest from which the signal was extracted. Then, 15  $\mu\text{mol Fe/kg}$  body wt diluted in 100 ml glucose 5% solution was infused over a period of 17 min intravenously during fMRI and auditory stimulation alternating every five scans among 5-Hz pulsed and continuous sound and silence. Venous blood samples (3 ml) were collected at the end of each acoustic stimulation block (every 150 s) during the infusion of the contrast agent. Absolute iron blood concentrations were quantified using a  $T_2$ -weighted rapid acquisition with relaxation enhancement (RARE) sequence and specific calibration curves. Because the relaxation rate decays as a function of intravascular iron concentration, the  $T_2^*$  signal time course in the auditory cortex could be used to quantify blood volume changes (Fig. 3A). The change in relaxivity was plotted as a function of iron blood concentration for the resting state, and for the 5-Hz pulsed- and continuous-sound activation states, whereby the slopes determined using a linear fit represented condition-specific blood volume levels (Fig. 3B). Time-of-flight angiography was used to exclude large vessels within the activation area.

## Results and discussion

In experiment 1, we examined the stimulation rate dependence of the BOLD response in the auditory cortex using a 1-kHz sine tone carrier with repetition rates ranging between 2.5 and 30 Hz and a fixed duty cycle of 50%, as well as a nonpulsed continuous 1-kHz sine tone carrier. We found that the sustained BOLD response amplitude in the core and belt of the auditory cortex monotonically decayed as a function of increasing repetition rates of sounds presented in a silent background (Fig. 1). In contrast, Tanaka et al. (2000) found a nonmonotonic relationship between repetition rate and BOLD response, which peaked at 5 Hz across the studied rates ranging between 0.5 and 20 Hz. Their data were also acquired in silence; however, the sound energy of the stimuli covaried systematically with repetition rate. Similarly, Harms and Melcher (2002) found a nonmonotonic repetition rate dependence of the sustained BOLD response amplitude in Heschl’s gyrus, which peaked at 10 Hz across the studied rates ranging between 1 and 35 Hz. However, their findings were based on cardiac gated image acquisition that resulted in an irregular temporal pattern of scanner noise and on rate-specific sound energy variation, both of which can lead to unpredictable interactions in the auditory cortex (Hall et al., 2001). On the other hand, Giraud et al., (2000) used energy-equated sound repetition rates between 4 and 256 Hz in the presence of regular

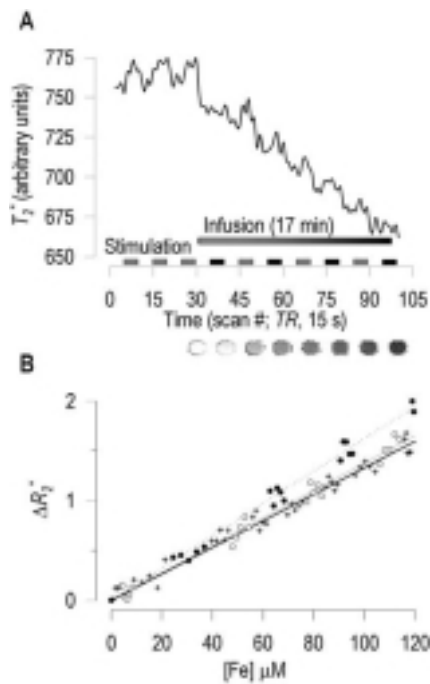


Fig. 3. (A)  $T_2^*$ -weighted signal time course during stimulation with pulse-modulated sound (5-Hz repetition rate, dashed boxes) and continuous sound (black boxes) during intravenous infusion of superparamagnetic intravascular contrast agent (Endorem) in the auditory cortex of one subject. Below the ordinate are the  $T_2$ -weighted RARE images of the venous blood samples taken at the end of each stimulation block. (B) Changes in relaxation rate ( $\Delta R_2^*$ ) in auditory cortex as a function of venous iron concentration during Endorem infusion for the resting state in silence (+; slope,  $[1.3 \pm .23] \times 10^3$ ), for 1-kHz sound with a repetition rate of 5 Hz [●; slope,  $(1.7 \pm .32) \times 10^4$ ], and continuous 1-kHz sound [○; slope,  $(1.4 \pm .25) \times 10^4$ ]. The corresponding fractional blood volume increased from a resting state level of  $4.00 \pm 0.72\%$  to  $5.26 \pm 1.01\%$  with 5-Hz pulse-modulated sound and to  $4.44 \pm .79\%$  with continuous sound (mean and standard deviation).

scanner noise and found, consistent with our data, a largely monotonic sustained response decrease with increasing rates.

Because the silent fMRI sampling procedure sacrifices temporal resolution in favor of presenting the stimuli against a silent background, in experiment 2 we examined the time course of the BOLD signal response to long-lasting sound stimuli at those repetition rates that produced great and robust differences in the sustained BOLD signal amplitudes. There was no statistically significant difference between the 2.5- and 5-Hz rate (Fig. 1), thus we selected the 5-Hz rate because this represents a robust common denominator of producing great BOLD response amplitudes both in our experiment 1 and in the previous reports by Tanaka et al., Giraud et al., and Harms and Melcher. In addition, the interstimulus interval of 200 ms during the 5-Hz repetition rate falls within the boundaries of the so-called temporal window of integration within which sequentially presented discrete auditory events tend to be associated, or integrated, to a coherent perceptual unit (Cowan, 1984; Näätänen, 1992; Yabe et al., 2001; Mustovic et al., 2003). As shown in

Fig. 2, we found a fundamental difference in the response time course during pulsed versus continuous sounds. Pulsed sound produced a biphasic temporal pattern of response that was characterized by an initial peak (3.3%) at approximately 5–6 s after stimulus onset and a subsequent sustained plateau (2.2%). This response pattern was consistent with data obtained in a previous study using 10 Hz pulse-modulated sounds against a silent baseline (Seifritz et al., 2002). In contrast, continuous sound produced a temporal response pattern that was characterized by an initial peak (1.9%) and a subsequent sustained component that remained largely at the level of the silent baseline (0.5%). Compared to the pulsed-sound response, the initial peak during the continuous sound occurred approximately 2 s earlier (Fig. 2C). This was temporally reminiscent of the response to a short single acoustic event reaching its maximum approximately 3 s after stimulus onset (Belin et al., 1999). In addition, our data are consistent with previous studies showing that not only the sustained but also the initial component in the auditory cortex response is subject to sound repetition rate-dependent modulation (Giraud et al., 2000; Harms and Melcher, 2002). Notably, however, the study design of our experiment 2 did not allow us to make inferences about the spatial distribution of the different temporal response components of activity, because we examined the signal time course in a predefined region; in addition, the data do not allow us to quantify the differential contribution of the various underlying hemodynamic parameters, especially of transient blood volume changes, but also of blood flow, oxygenation and metabolic rate, and their specific interactions and role in the conformation of the initial peak (Buxton et al., 1998, 2001; van Zijl et al., 1998; Mandeville et al., 1999a, 1999b; Mildner et al., 2001; Miller et al., 2001). However, the biphasic pattern of response found in this and other fMRI studies (Jäncke et al., 1999; Giraud et al., 2000; Harms and Melcher, 2002; Seifritz et al., 2002) converges, on a different temporal scale, with electrophysiological findings obtained in the human and animal auditory cortex (Pantev et al., 1991; Kilgard and Merzenich, 1998; Recanzone, 2000; Atzori et al., 2001; Lu et al., 2001; Eggermont, 2002; Nagarajan et al., 2002).

To examine the contribution of blood volume changes in shaping the sustained response component, in experiment 3, we employed a “titration” procedure combining intravenous infusion of iron oxide nanoparticle-based intravascular superparamagnetic contrast agent and serial venous blood sampling. In addition, we used auditory stimulation alternatingly consisting of pulsed and of continuous sound to modulate the amplitude of the sustained response component. As shown in Fig. 3A, increasing iron concentration produced a decrease in the overall  $T_2$  and  $T_2^*$  signal intensity in the blood samples and in the brain. The differences in relaxivity as a function of iron concentration (Fig. 3B), in combination with appropriate calibration curves, allowed us to determine stimulus-dependent sustained blood volume fractions (for details and quantitative equations see Schef-

fler et al., 1999). Our calculations yielded a mean blood volume fraction in the auditory cortex of 4.00% during silence, which increased to 5.26% during stimulation with the 5 Hz pulsed sound and to 4.44% during the continuous sound.

We acknowledge that the data obtained in experiments 2 and 3 are based on single-subject studies, which bear the principal risk of individual idiosyncrasies. However, the biphasic pattern of response (experiment 2) as well as the quantitative blood volume changes (experiment 3) associated with pulsed sound stimuli are very consistent with our previous findings (Scheffler et al., 1999; Seifritz et al., 2002). Keeping this limitation in mind, our data demonstrate that the repetition rate-dependent dissociation of the native  $T_2^*$  signal response was paralleled by concordant changes in blood volume response ( $\sim 30\%$  vs  $\sim 10\%$ ). This finding is not compatible with the hypothesis that a prolonged blood volume effect in response to the initial peak would explain the reduction in the sustained BOLD signal component found in experiments 1 and 2 and in previous fMRI studies, because a prolonged undershoot would be expected to be associated with increased rather than decreased blood volume levels. Thus, our data suggest that the repetition rate-dependent modulation of the  $T_2^*$  signal in the auditory cortex during the sustained phase of response reflects modulation of neural activity-related oxygenation rather than merely a blood volume-dependent signal decrease.

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