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BRIEF COMMUNICATION

Tonotopic Gradients in Human Primary Auditory Cortex: Concurring Evidence From High-Resolution 7 T and 3 T fMRI

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Abstract The tonotopic representations within the primary auditory cortex (PAC) have been successfully mapped with ultra-high field fMRI. Here, we compared the reliability of this tonotopic mapping paradigm at 7 T with 1.5 mm spatial resolution with maps acquired at 3 T with the same stimulation paradigm, but with spatial resolutions of 1.8 and 2.4 mm. For all subjects, the mirror-symmetric gradients within PAC were highly similar at 7 T and 3 T and across renderings at different spatial resolutions; albeit with lower percent signal changes at 3 T. In contrast, the frequency maps outside PAC tended to suffer from a reduced BOLD contrast-to-noise ratio at 3 T for a 1.8 mm voxel size, while robust at 2.4 mm and at 1.5 mm at 7 T. Overall, our results showed the robustness of the phase-encoding paradigm used here to map tonotopic representations across scanners.

Keywords Auditory areas · Tonotopy · Heschl's gyrus · Human fMRI · 7 T · 3 T

Introduction

Tonotopic gradients have been repeatedly demonstrated with fMRI in the human primary auditory cortex (PAC), albeit with varying interpretations of their spatial orientation. Mirror-symmetric gradients of high-low–high frequencies were described along (1.5 T: Seifritz et al. 2006; 3 T: Schönwiesner et al. 2002; 7 T: Formisano et al. 2003) or across the long axis of Heschl's gyrus (HG; 1.5 T: Talavage et al. 2004; Woods et al. 2010; 3 T: Humphries et al. 2010; Striem-Amit et al. 2011; Langers and Dijk Langers and van Dijk 2012; 7 T: Da Costa et al. 2011). It is currently unclear to what extent these discrepancies are due to inter-individual variability of HG and PAC configuration (Rademacher et al. 1993; Viceic et al. 2009; Clarke and Rivier, 1998; Morosan et al. 2001; Rademacher et al. 2001; Rivier and Clarke 1997) or to differences in magnetic field strength and spatial resolutions used in these studies.

Mapping of small functional subunits, such as ocular dominance columns in the human visual cortex (Yacoub et al. 2007) or tonotopic organization in human PAC (Da Costa et al. 2011) and inferior colliculus (De Martino et al. 2013), requires high spatial resolution which is more easily achieved with fMRI at ultra-high magnetic field strengths, due to the combination of increased signal-to-noise ratio and BOLD signal allowing smaller voxel sizes. Furthermore, the short venous T_2* reduces venous blood signal and restricts the BOLD signal more to cortical gray matter, thus increasing spatial specificity (van der Zwaag et al. 2009).

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As a gold standard for tonotopic mapping, ultra-high field fMRI is currently of limited use, because of the small number of 7 T scanners available for human studies. The majority of cognitive investigations which would benefit from tonotopic mapping (including studies of speech processing, sound recognition, auditory spatial functions, and audioneurological disorders), both in normal subjects and in patients, are carried out with 3 T scanners. Here, we compare the high-resolution 7 T mapping from (Da Costa et al. 2011), with standard-resolution maps acquired at 3 T in five normal subjects to evaluate consistency of the tonotopic gradients at different field strengths and resolutions. Each subject underwent tonotopic mapping sessions at both 7 T (1.5 mm spatial resolution) and 3 T (1.8 and 2.4 mm resolution, with other parameters (TE/bandwidth/flip angle) optimised per field strength.. For detailed methods see Supplementary Material). The ethics Committee of the Faculty of Biology and Medicine of the University of Lausanne approved all experimental procedures.

Results and Discussion

The tonotopic gradients visualized on HG were very similar at 7 T and at either spatial resolution at 3 T as shown for one subject in (Fig. 1), as well as across subjects (Fig. S1 and S2 in Supplementary Material). Tonotopic gradients ran antero-posteriorly across the long axis of HG, as suggested in previous studies (1.5 T: Talavage et al. 2004; Woods et al. 2010; 3 T: Humphries et al. 2010; Striem-Amit et al. 2011; Langers and van Dijk 2012; 7 T: Da Costa et al. 2011, 2013). Although, 3 T—1.8 mm tonotopic maps showed fewer activated voxels at a p value of 0.05 ($r > 0.13$, uncorrected). Tonotopic gradients outside PAC were less robust at 3 T (outside the dotted regions indicating PAC, Fig. S1), especially for the 1.8 mm spatial resolution and voxels tended also to be less frequency-specific.

We manually identified the two primary gradients ("high-to-low-to-high") running across the medial 2/3rds of HG as PAC (dotted lines, Fig. 1). The distribution of preferred-frequencies within PAC followed a bell-shaped curve (Fig. 2 top). The percentage of PAC voxels devoted to a given frequency was analyzed with fourteen 3 × 2 ANOVA (one for each frequency) with factors "Protocol" (7 T—1.5, 3 T—1.8, 3 T—2.4 mm) and Hemisphere (right, left), showing no significant main effects or interactions ($p > 0.05$, Bonferroni corrected). Independently of the resolution, the proportion of voxels dedicated to a specific frequency did not differ, reflecting the reproducibility of the tonotopic maps at both resolutions and magnetic field strengths. A non-significant main effect of

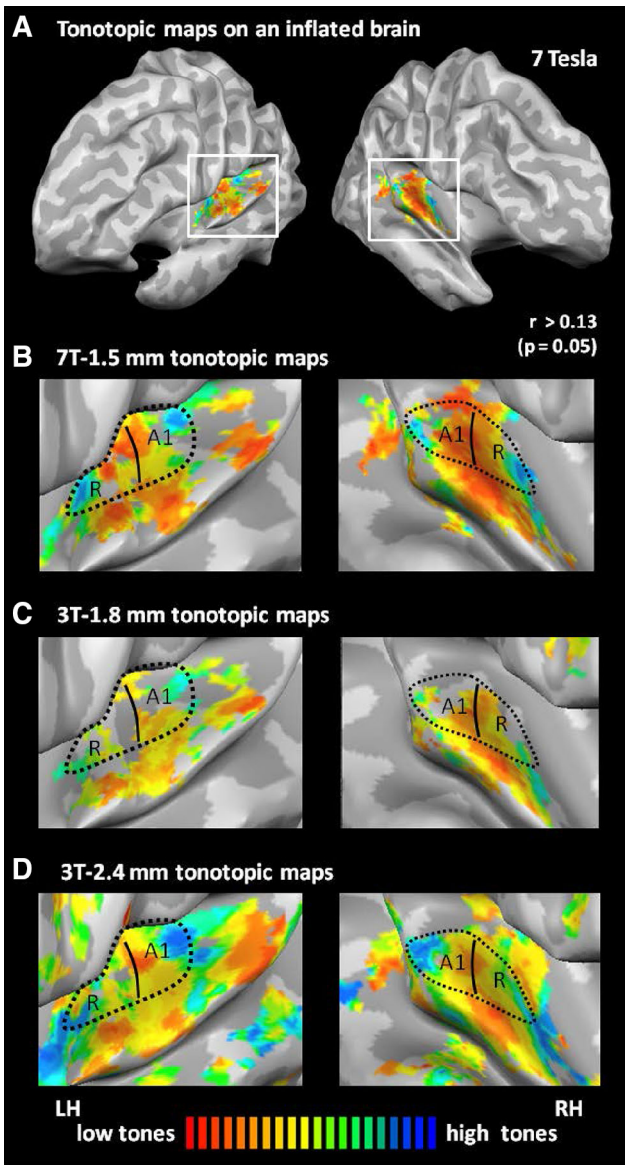

Fig. 1 Tonotopic maps in the human primary auditory cortex. **a** Color-coded tonotopic maps were projected onto each subject's cortical surface meshes (minimally inflated). **b–c** Enlargement of the region delimited by the white square. Individual tonotopic maps in left and right hemispheres ($r > 0.13$, $p = 0.05$, uncorrected) at 7 T (**b**) and 3 T (**c**) of the same subject. *RH* right hemisphere; *LH* left hemisphere

Protocol ($p < 0.05$, uncorrected) was found for the 250 and 4,000 Hz bins, where the 7 T—1.5 mm protocol differed by approximately 5 % from the other two.

Percent signal change (PSC) between the maximum and the minimum of the frequency-related time courses tended to be larger at 7 T than 3 T (Fig. 2 bottom), as expected (van der Zwaag et al. 2009). PSCs were analyzed with fourteen 3 × 2 ANOVA with factors Protocol (7 T—1.5, 3 T—1.8, 3 T—2.4 mm) and Hemisphere (right, left), which showed a significant main effect of Protocol for all

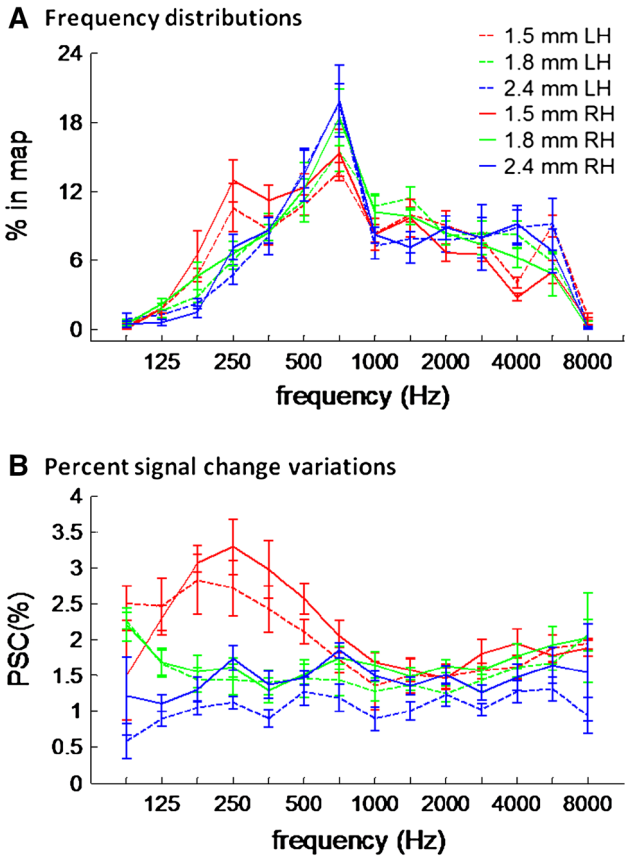

Fig. 2 **a** Frequency distributions. Tonotopic maps were quantified in percentages of best-fitted frequency per total number of voxels (percentage of voxels dedicated to a specific frequency within PAC; *error bars* = std across subjects and runs). Frequency distributions peak around 707 Hz in all resolutions, field strengths and hemispheres. **b** Percent signal changes variations. Amplitude variations from frequency-related time courses are displayed in percent signal changes (PSC) variations per frequency bin (*error bars* = std across subjects). PSCs tended to be larger at 7 T (*red lines*) than at 3 T (*green and blue lines*)

frequency bins from 125 to 500 Hz (125 Hz: $F(2,4) = 16.55$; 177 Hz: $F(2,4) = 29.23$; 250 Hz: $F(2,4) = 19.18$; 354 Hz: $F(2,4) = 18.38$; 500 Hz: $F(2,4) = 18.16$ $p < 0.05$, Bonferroni corrected) and of Hemisphere for the 1,000 Hz ($F(1,4) = 190.95$; $p < 0.05$, Bonferroni corrected), but no interaction for any frequency bin. Post-hoc analysis suggests that the main effects of Protocol were driven by differences between 7 T—1.5 and 3 T—2.4 mm maps for 88 and 354 Hz ($p = 0.001$ and 0.002, respectively, Bonferroni corrected), whereas the main effect of Hemisphere was driven by difference between hemispheres in the 3 T—2.4 mm map for the 354 Hz response ($p = 0.001$, Bonferroni corrected).

These dissimilarities could be attributed to (1) larger voxel sizes at 3 T and (2) differences in overall gradient design and available readout bandwidth in the EPI and the resulting acoustic resonance of the scanners used. These latter two aspects could explain the discrepancies between tonotopic studies which reported varying spatial arrangements.

Overall, our results showed clear, highly similar tonotopic gradients across scanners with no or minor significant differences in the observed frequency distributions and PSCs, respectively. They illustrated the robustness of the phase-encoding paradigm used to map tonotopic representations independently of the scanner, provided sufficient spatial resolution and limited interference of scanner acoustical noise with the tonotopic stimuli.

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