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► To cite this version:

Simon Baumann, Timothy D Griffiths, Li Sun, Christopher I Petkov, Alexander A Thiele, et al..
Orthogonal representation of sound dimensions in the primate midbrain. *Nature Neuroscience*, 2011,
10.1038/nn.2771 . hal-00619270

HAL Id: hal-00619270

<https://hal.science/hal-00619270>

Submitted on 6 Sep 2011

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Orthogonal representation of sound dimensions in the primate midbrain

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Abstract

Natural sounds are characterised by their spectral content and the modulation of energy over time. Using fMRI in awake macaques, we report topographical representations of these spectral and temporal dimensions in a single structure, the inferior colliculus, the principal auditory nucleus in the midbrain. These representations are organised as a map with two approximately perpendicular axes: one representing increasing temporal rate and the other increasing spectral frequency.

A general organising principle of sensory systems is the representation of their peripheral receptor arrays as topographic maps in the brain. Systematic representations of where light falls on the retina or a haptic stimulus touches the skin occur at several levels of their brain pathways. Likewise in hearing, the receptor array in the cochlea is represented in a frequency, or tonotopic, map at all levels of the mammalian auditory pathway, including the inferior colliculus (IC) ¹⁻³. However, in addition to their spectral frequency content, a second fundamental acoustic dimension, the modulation of energy over time is crucial for the characterisation and perceptual analysis of biologically significant sounds like speech and animal vocalisations ⁴. A systematic map of this second, temporal or periodotopic dimension in the auditory pathway has proved more elusive. Electrophysiological studies sampling the electrical activity of single neurons or clusters in the IC have not been consistent in reporting a topographical representation of temporal stimulus dimensions⁵⁻¹⁰.

Here we address the topographical representation of spectral and temporal information using functional magnetic resonance imaging (fMRI) in rhesus monkeys (*Macaca mulatta*). This technique allows activity to be sampled across the whole structure and so has the important advantage of being relatively free from ascertainment bias compared to the electrophysiological sampling of single neurons.

We mapped neural activity in the IC at high spatial resolution (1 mm x 1 mm in-plane) by measuring the blood oxygenation level dependent (BOLD) signal to sound stimuli in two separate experiments. The first served to identify a tonotopic gradient, and in the second we tested for an analogous temporal (periodotopic) gradient. The stimuli for the tonotopy experiment consisted of narrow bands of noise containing spectral frequencies ranging from 0.5 – 16 kHz. In the periodotopy experiment we presented broad band noise with amplitude modulation rates ranging from 0.5 – 512 Hz (see Suppl. Mat. and Suppl. Fig. S1 for stimulus details). We obtained data in multiple sessions from each of three different animals for both experiments. All experimental procedures were approved by UK Home Office (see details in Suppl. Methods). The orientation and location of the imaged slices within the brain are shown in Fig. 1a.

Consistent with our previous study in macaques ¹¹, the sounds evoked robust BOLD responses in the IC with maximal t-values > 30 when contrasting the combined sound stimulation versus a silent baseline (Fig 1b). We analysed the BOLD response to the different spectral frequencies by identifying areas in the IC that responded best to either low (lf), mid-range (mf) or high frequencies (hf). The analysis revealed a consistent response pattern in all three animals (Suppl. Fig. S2, left column). Areas preferring low spectral frequencies clustered along the dorso-lateral border of the IC while areas responding best to high spectral frequencies were located along the ventro-medial border. The mid-range frequencies predominated mostly between the areas for low and high spectral frequencies. This topographic representation of frequency is consistent with the tonotopic organisation **along the dorso-lateral to ventro-medial axis** established electrophysiologically in primates and other mammals ^{1, 2}.

An analysis to identify areas in the IC responding to temporal modulation rates also revealed a consistent organisation. In this case, the low rates (lr) clustered at the dorso-medial side of the IC, approximately perpendicular to the axis of the spectral frequencies (Suppl. Fig. S2, right column), with the high temporal rates (hr) represented along the ventro-lateral border.

In an additional analysis we mapped the trends of these preferences for frequency and temporal modulation rate by subtracting the response strengths (beta-values) to the low from the high frequencies and modulation rates, respectively. The resulting maps revealed two gradients, characterised by a decreasing response to low frequencies or rates and an

increasing preference for high frequencies or rates, that run dorso-lateral to ventro-medial for the spectral frequencies (Fig. 1c, first column), and dorso-medial to ventro-lateral for the temporal rates (Fig. 1c, second column). The axes of these tonotopic and periodotopic gradients are approximately perpendicular to one another.

To quantify these gradients we analysed the subtraction maps of the IC using multiple regression analysis (Fig. 2). A 2-dimensional gradient plane was fitted to the values of the subtraction map (see Suppl. Methods). The resulting values represent the direction of the gradients, and the correlation coefficients and significance of the regression analysis are summarised in Suppl. Table 1. The gradients showed correlation coefficients (r^2) between 0.56 – 0.89 and significance levels of $p < 0.0005$. The orthogonality of the two gradients is evident by comparing the average angle between the axes of the tonotopic and periodotopic gradients which was 97.5 degrees (± 17.9 S.D.) for the left IC and 103.1 degrees (± 35.1) for the right IC (see Suppl. Methods Table 1).

The significance and consistency of the gradients apparent in both ICs of all tested animals (Suppl. Fig. S3) demonstrate that the two fundamental sound dimensions, frequency and modulation rate, are represented topographically in the IC of macaques. The arrangement takes the form of a map in which the axes for increasing spectral frequency and increasing temporal rate lie perpendicular to one another. **Because we collapsed the two fMRI slices in the rostro-caudal dimension (see Suppl. material) the curvature of the frequency-band laminae revealed by electrophysiology in the rostro-lateral region ² is represented in a flat 2-dimensional map in our data. This may lead to some loss of resolution in the frequency and modulation rate representations, which could conceal a systematic representation, however, in our data their orthogonality is clear nevertheless.** The organisation shown in our data gives independent support to electrophysiological evidence in other species ⁵⁻⁷, and by extending it to primates suggests that an orthogonal arrangement of tonotopy and periodotopy in the IC is a governing organising principle in the auditory system of mammals.

The midbrain is the first level in the auditory pathway where significant neuronal selectivity for AM rate is evident in the average firing rate as well as the response synchronised to the temporal waveform ¹⁰. This is consistent with the IC being the structure where the temporal pattern of neuronal activity is converted into a topographical representation. That the axis of

such a representation is orthogonal to the tonotopic axis would facilitate the independent processing of these fundamental sound dimensions.

The systematic representation of temporal envelope information in the inferior colliculus is an organising principle that could facilitate the subsequent analysis of this important cue for identification and segregation of sound objects. In speech perception, for example, the amplitude envelope of a small number of frequency bands carries sufficient information for intelligibility⁴. Envelope fluctuations also provide important cues for segregating sound in situations where multiple sound sources are present with overlapping frequency components^{12, 13}. The identification and grouping of components sharing the same temporal envelope is one of the cues the brain uses to parse or stream information into distinct sources.

These data represent the first demonstration of a spectro-temporal map in the midbrain of a primate. The systematic representation of frequency and modulation rate in perpendicular gradients demonstrated in this study suggests an organisation for the analysis of temporal rate independent of spectral frequency. Furthermore, the data also represent a major advancement in non-invasive brain imaging. Until recently it was challenging to record BOLD responses from brainstem nuclei, especially in humans^{14, 15}. These high-field fMRI data demonstrate for the first time the detailed organisation within a primate brainstem nucleus.

Acknowledgments

This research was funded by the Wellcome Trust. The authors wish to thank David Hunter for his assistance in animal handling and data recording.

Author contributions

S.B., T.D.G and A.R. designed the experiment. A.T. provided the animals and supervised their handling. L.S. provided the EPI sequences and optimised them for each animal. S.B. recorded the data. S.B. analysed the data with contribution from C.I.P. S.B. and A.R. prepared the manuscript with contributions from T.D.G., A.T., C.I.P and L.S.

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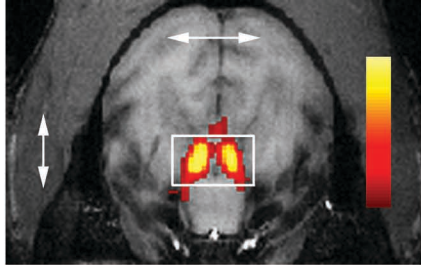
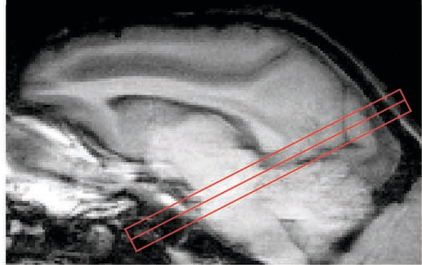
Figure legends

Figure 1

BOLD response maps in the inferior colliculus (IC). A. Location of the analysed MRI slices (in red) on a sagittal structural MRI from one animal. V and D indicate the ventral and the dorsal edges of the slice. B. t-value map of all sound stimuli versus no-sound for one of the slices in A (t-value shown by scale on right). Robust responses from the inferior colliculi are clearly visible. C. Subtraction maps for the white framed area in B. These show the BOLD responses to high spectral sound frequencies (hf, left column) or temporal rates (hr, right column) vs. the low spectral frequencies (lf) or temporal rates (lr) respectively for three animals. Change towards blue indicates increasing dominance of high frequencies or rates. Change towards red indicates increasing dominance of low frequencies or rates. Minimal and maximal response estimate coefficients (beta-values) are displayed above and below respectively the colour scale. Letters in upper left corner of left column indicate animal ID.

Figure 2

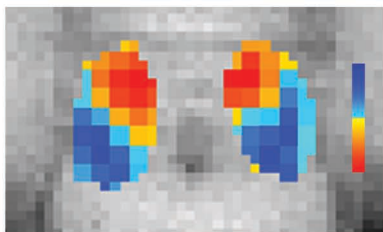
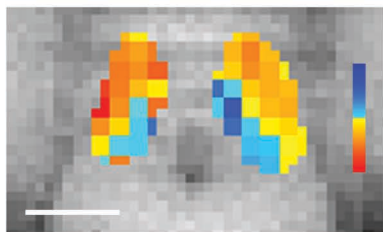
Estimation of gradient directions by two dimensional regression analysis. These are shown for the spectral experiment (left) and the temporal experiment (right) in the left IC of animal Ws. Above: subtraction maps for the response estimates. Middle: The fitting of a plane to the values of the response-estimate coefficients (black dots). Below: gradient direction is displayed by the contours of the subtraction maps. Gradient directions are indicated relative to the dorsal-ventral axis. The angle between the axes of the tonotopic and periodotopic gradients is shown below the figure.



C

Tonotopy

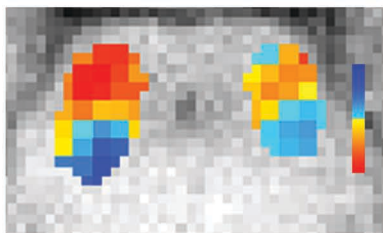
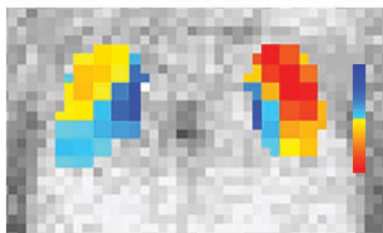
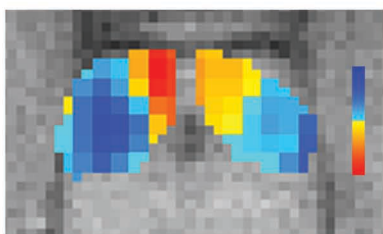
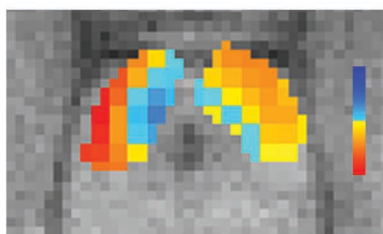
Periodotopy



D

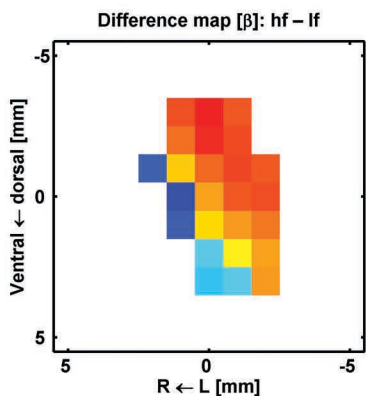


V

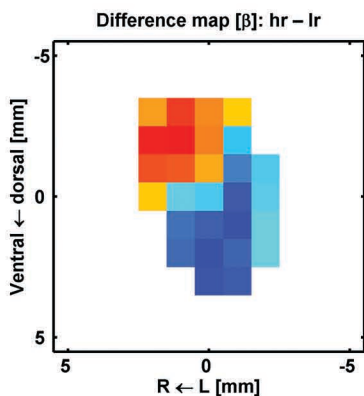


R \longleftrightarrow L

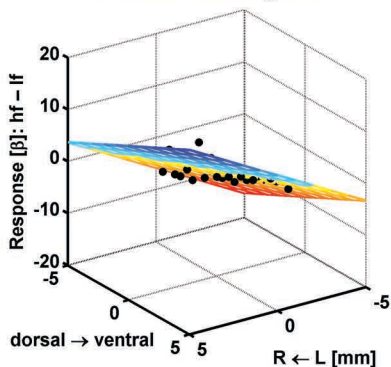
Tonotopy



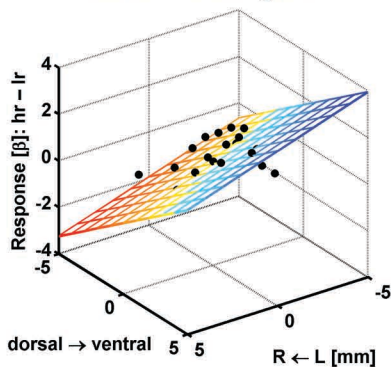
Periodotopy



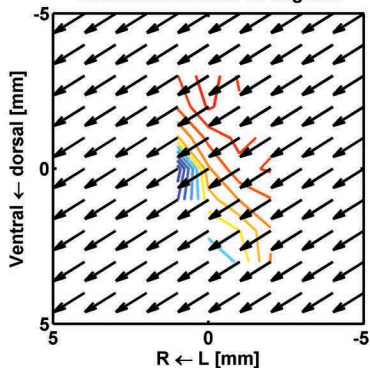
Two dimensional regression



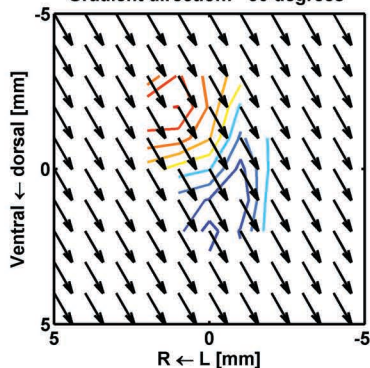
Two dimensional regression



Gradient direction: 58 degrees



Gradient direction: -30 degrees



Resulting relative angle: 88 degrees