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Research paper

Neural correlates of human somatosensory integration in tinnitus

C.P. Lanting [a,b,*], E. de Kleine [a,b], R.N. Eppinga [a,b], P. van Dijk [a,b]

[a] Department of Otorhinolaryngology/Head and Neck Surgery, University Medical Center Groningen, The Netherlands
[b] Faculty of Medical Sciences, School of Behavioral and Cognitive Neurosciences, University of Groningen, The Netherlands

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ABSTRACT

Possible neural correlates of somatosensory modulation of tinnitus were assessed. Functional magnetic resonance imaging (fMRI) was used to investigate differences in neural activity between subjects that can modulate their tinnitus by jaw protrusion and normal hearing controls. We measured responses to bilateral sound and responses to jaw protrusion. Additionally we studied multimodal integration of somatosensory jaw protrusion and sound. The auditory system responded to both sound and jaw protrusion. Jaw responses were enhanced in the cochlear nucleus (CN) and the inferior colliculus (IC) in tinnitus patients. The responses of the auditory brain areas to jaw protrusion presumable account for the modulation of tinnitus as described by the patients. The somatosensory system responded to jaw protrusion and not to sound. These responses occurred both in subjects with tinnitus and controls. Unexpectedly, the cerebellum responded to sound in normal hearing subjects, but not in tinnitus patients. Together, these results provide a neurophysiological basis for the effect of jaw protrusion on tinnitus.

1. Introduction

Tinnitus is an auditory sensation without the presence of an external acoustic stimulus. Almost all adults have experienced some form of tinnitus, mostly transient in nature. The exact etiology of tinnitus remains unknown but may involve increased spontaneous neural activity, increased neural synchrony or reorganized tonotopic maps as a neural substrate of tinnitus in humans (Eggermont, 2006).

Tinnitus is affected in complex ways by somatosensory influences. Somatic maneuvers can elicit tinnitus or modulate the psychoacoustic attributes of tinnitus (e.g., the loudness or pitch). Examples of these somatosensory modulators are forceful head and neck contractions (Levine, 1999; Levine et al., 2003, 2008; Abel and Levine, 2004), oral facial movements like jaw clenching or jaw protrusion (Chole and Parker, 1992; Rubinstein, 1993; Lockwood et al., 1998; Pinchoff et al., 1998), electrical stimulation of the median nerve (Møller et al., 1992; Møller and Rollins, 2002) and cutaneous stimulation (Cacace et al., 1999a,b). In a remarkable case, finger movement evoked tinnitus (Cullington, 2001). A change of gaze is also known to modulate tinnitus in some patients with a vestibular schwannoma removed (Cacace et al., 1994a,b; Giraud et al., 1999; Coad et al., 2001; Lockwood et al., 2001; Herraiz et al., 2003; Albuquerque and Bronstein, 2004; Baguley et al., 2006), which is possibly caused by somatosensory neural signals.

Somatic modulation or induction of tinnitus may be considered a special case of multisensory integration – a phenomenon, in which one (sensory) modality influences another. Examples of this multisensory integration are visual stimuli that modulate activity measured in the auditory cortex (Pekkola et al., 2005) and audio-visual speech or communication signals that modulate activity in the auditory cortex (Calvert et al., 1999; Ruytjens et al., 2006, 2007). In addition to auditory-visual integration, there are studies that specifically assess multisensory integration between the auditory system and the somatosensory system. One illustrative example is a study of Jousmaki and Hari (1998) showing that auditory input can modulate touch sensation. Subjects were asked to rub their hands, and the evoked sounds were played back to them. When the high-frequency content of this auditory signal was increased in loudness, subjects felt the skin under their palms becoming dry – the parchment-skin illusion.

Abbreviations: AAC, auditory association cortex; BA, Brodmann area; BOLD, blood oxygen level dependent; CN, cochlear nucleus/nuclei; EPI, echo planar imaging; fMRI, functional magnetic resonance imaging; HL, hearing level; IC, inferior colliculus/colliculi; MGB, medial geniculate body of the thalamus; PAC, primary auditory cortex; Put, putamen; ROI, region of interest; SII, secondary somatosensory cortex; SPM, statistical parametric map; TE, echo time; TR, repetition time; VL, ventrolateral.

[*] Corresponding author at: MRC Institute of Hearing Research, University Park, NG7 2RD Nottingham, United Kingdom. Tel.: +44 (0)115 922 3431; fax: +44 (0)115 951 8503.

E-mail addresses: cris@ihr.mrc.ac.uk (C.P. Lanting), e.de.kleine@med.umcg.nl (E. de Kleine), p.van.dijk@med.umcg.nl (P. van Dijk).

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Somatosensory stimulation can also influence auditory perception. The fact that subjects with somatosensory tinnitus can modulate their tinnitus is an example of this somatosensory-auditory modulation, and might be explained by changes in normal multisensory integration. Noise-induced hearing-loss, for example, has been reported to alter the normal somatosensory input. The somatosensory input to the cochlear nucleus (CN) is increased after hearing loss (Shore et al., 2008). This change in balance in somatosensory and auditory input at the level of the brainstem might thus be the neural correlate of somatosensory modulation of tinnitus.

Functional magnetic resonance imaging (fMRI) methods have been used to study multisensory integration of auditory and somatosensory input in the auditory cortex of the macaque monkey. Kayser et al. (2005) showed multisensory integration of tactile stimuli of the palm and the foot, and auditory stimuli in the belt area (caudal medial and caudal lateral belt area) of the auditory cortex. Supra-additive effects were demonstrated in the belt area, showing voxels with a response to the multisensory stimuli that was larger than the sum of the unisensory stimuli. Foxe et al. (2002) used an fMRI design to assess multisensory integration in humans. The unisensory response to sound and somatosensory stimulation was determined. There were voxels that showed overlap in activity between the two conditions. A cluster showing overlap was determined as the posterior part of the left superior temporal gyrus (Brodmann area (BA) 22 and 39) and the right auditory association cortex (BA22). Within the left-hemisphere a small area was found where the bimodal response exceeded the summed unimodal responses (e.g., a supra-additive effect). Schurmann et al. (2006) later used vibrotactile, pulsed tactile and white noise auditory stimuli in an fMRI design to assess human multisensory integration. In the posterior auditory belt area, bilateral areas were found that showed overlap in activity between the unisensory conditions. These were the same area as found by Foxe et al. (2002), showing voxels with overlap between tactile and auditory stimuli.

Multisensory integration and spatial overlap of auditory and somatosensory input was also shown in several parts of the auditory system using anatomical labeling methods and electrophysiological measurements. Sites of neurophysiologic auditory-somatosensory integration were identified in the lower brainstem (the dorsal and ventral CN) and the inferior colliculus (IC) in guinea pigs (see review by Dehmel et al. (2008)). In addition, multisensory areas (i.e., areas that receive both auditory and somatosensory input, but not necessarily exhibit multisensory integration) were found in macaque monkeys using anatomical labeling methods. These areas were identified as the medial geniculate complex and the caudal medial belt area of the auditory cortex (Schroeder et al., 2001; Smiley et al., 2007; Hackett et al., 2007a,b). These studies suggest that somatosensory-auditory integration may already take place at the brainstem auditory nuclei.

In this work we investigated the phenomenon of somatic modulation of tinnitus. For this purpose, we studied two groups of subjects: normal controls and subjects with tinnitus. The subjects in the tinnitus group were included based on their ability to change the psychoacoustical characteristics of their tinnitus by jaw protrusion. We hypothesize that this may be based on somatosensory-auditory interaction already in the brainstem.

2. Materials and methods

2.1. Subjects

Thirteen subjects (12 males and one female, age 28–68 years, median 52 years) with tinnitus were recruited at the University Medical Center Groningen in the multidisciplinary tinnitus outpatient clinic, all with no known neurological and psychiatric history. The subjects with tinnitus were selected based on their ability to alter the loudness or pitch of their tinnitus by performing a protrusion of the jaw. Additionally, twenty control subjects (18 males and two females, age 20–59 years, median 31 years) without tinnitus were recruited. A selection criterion for all subject comprised the hearing levels for both ears better than 30 dB hearing levels (HL) for frequencies 250, 500 and 1000 Hz, with the average difference between the left and right ear not exceeding 10 dB.

In the patient group, the perceived tinnitus frequency and loudness level were determined by a matching procedure. The frequency matching was performed with an external tone presented at the non-tinnitus ear or at the ear where the tinnitus was weakest, at a comfortable level. The loudness level was then determined by adjusting the level of this tone to match the tinnitus loudness.

Somatosensory modulation of tinnitus was assessed using a questionnaire as described in Table 2. In this questionnaire—presented here as a translated version of the original Dutch version, the loudness of the tinnitus and loudness of the tinnitus during jaw protrusion was assessed using a visual analog scale. In addition to these loudness values, subjects were asked to rate the duration (in seconds) of the period that subject could pertain the jaw protrusion that lead to a change of their tinnitus. Subjects reported loudness values prior to the fMRI study (see Fig. 4). Subjects without tinnitus were also asked to report any perceptual change corresponding to jaw protrusion but no changes were reported.

The handedness of each subject was determined using a translated version of the Edinburgh inventory (Oldfield, 1971). Details of most subject characteristics are shown in Table 1 and the assessment of the somatosensory modulation can be found in section 2. The study was approved by the local medical ethics committee and written informed consent was obtained for each participant.

2.2. MRI protocol

All imaging experiments were performed on a 3T MRI system (Philips Intera, Philips Medical Systems, Best, The Netherlands)

Table 1
Subject characteristics.

Characteristics	Controls ($n = 20$)	Subjects with tinnitus ($n = 13$)
Age (years)		
Average	32.8	51.8
Standard deviation	10.5	10.4
range	20–59	28–68
Gender		
Male	18 (90%)	12 (82%)
Tinnitus		
Lateralization (left/right/non-lateralized)	–	1/1/11
Average pitch (Hz)	–	6400
Range (Hz)	–	750–12,000
Average loudness (dB SL)	–	16.7
Range (dB SL)	–	10–25
Modulation of tinnitus		
Changes in frequency	–	2 (15%)
Changes in loudness	–	10 (77%)
Changes in frequency and loudness	–	1 (8%)
Handedness		
Right handed	19 (95%)	11 (85%)
Left handed	1 (5%)	1 (8%)
Ambidextrous	–	1 (8%)

with an eight-channel phased-array head coil (SENSE head coil). First, a T1-weighted fast-field echo scan was acquired for anatomical orientation (TR 11.1 ms; TE 4.6 ms; flip-angle 15°; matrix $256 \times 256 \times 9$; voxel-size $1.0 \times 1.0 \times 2.0$ mm^3).

The functional scans consisted of 2179-ms single-shot T2*-sensitive echo planar imaging (EPI) sequences with 41 2-mm thick slices (TR 10 s; TE 22 ms; flip-angle 30°; matrix 128×128, field of view 224 mm, SENSE reduction factor 2.7) and were acquired using a coronal orientation, aligned to the brainstem when viewed on a midsagittal cross-section. The influence of acoustic scanner noise was reduced using a sparse sampling strategy (Hall et al., 1999) in which auditory stimuli were presented during a 7.8-s gap of scanner silence between two successive acquisitions. For each subject three runs of 61 acquisitions were performed. An additional 3D T1-weighted fast-field echo scan (TR 25 ms; TE 4.6 ms; flip-angle 30°; matrix $256 \times 256 \times 160$; voxel-size $0.94 \times 0.94 \times 1.0$ mm^3) was acquired with the same orientation as the functional scans to serve as anatomical reference.

2.3. Experimental paradigm

Each functional run consisted of the acquisition of 61 volumes with 3 experimental conditions that were contrasted against a baseline condition: [1] a condition in which a temporally and spectrally modulated noise (Langers et al., 2003) was presented to both ears, [2] a condition in which subjects protruded their jaw (protrusion of the mandible) and [3] a bimodal condition including both protrusion of the jaw and presentation of sound. Each condition was presented 15 times per functional run, the baseline condition was presented 16 times.

During the experiment, subjects were looking at the instruction as projected on a screen mounted in the bore of the scanner. The instruction consisted of words describing the jaw protrusion task (either ‘rest’ or ‘protrude jaw’). Subjects were instructed to attend to the sound stimuli, but were not required to perform any task related to the sound stimuli.

The noise stimuli had a frequency-range of 125–8000 Hz with a spectral modulation density of one cycle per octave, a temporal modulation frequency of two cycles per second and a modulation amplitude of 80%. These stimuli were generated using Matlab 6.5 (The Mathworks Inc., Natick, MA) and were saved as wave files. These stimuli were chosen to evoke large sound-evoked responses in the auditory cortex based on the experience with these stimuli in our group (see e.g., Langers et al., 2003 and Lanting et al., 2008).

A PC setup equipped with a digital-analogue card (National Instruments 6052E, National Instruments Corporation, Austin, TX) in combination with Labview (National Instruments Corporation, Austin, TX) was used to present the auditory stimuli bilaterally at 70 dB (SPL) to the subjects through an MR compatible electrodynamic system (MR Confon GmbH, Baumgart et al., 1998).

The experimental paradigm was not randomized and the jaw protrusion condition was performed alternating with either baseline or presentation of sound to prevent fatigue of jaw muscles as was reported by subjects in initial pilot measurements.

In order to minimize the within-scan movement, the protrusion started 4s after the beginning of the acquisition and ended 1.5 s before the next acquisition (see Fig. 1). Due to the long latency of the hemodynamic response of the blood oxygen level dependent (BOLD) effect (typically about 4–5 s, although latencies vary between subjects and brain areas; see Neumann et al., 2003 and Langers et al., 2005), we were still able to measure the jaw-related neural activity. Since the jaw was always fully relaxed during the MRI acquisitions, the jaw protrusion task did not degrade the quality of the data. In addition, our timing paradigm ensured the reliable response of subjects to the visual instructions.

2.4. Data analysis

MR images were analyzed using Matlab 7.1 (R14) (The Mathworks Inc., Natick, MA) and SPM5 (Functional Imaging Laboratory, The Wellcome Department of Imaging Neuroscience, London, UK, http://www.fil.ion.ucl.ac.uk/spm/). The functional images were corrected for motion using realignment of all images to the first acquired volume of each subject and were spatially coregistered with the T1-weighted high-resolution anatomical image. The high-resolution anatomical image was segmented in gray matter, white matter and cerebral spinal fluid (CSF) segments. The gray-matter segment of the anatomical image was normalized to a custom normalization template (for more details, see Lanting et al., 2008) and the resulting transformation parameters were also applied to the functional data. Functional data were spatially smoothed using an isotropic Gaussian kernel with a full width at half maximum of 4 mm, to improve signal-to-noise ratio characteristics while retaining the ability to discern small auditory structures (e.g., the

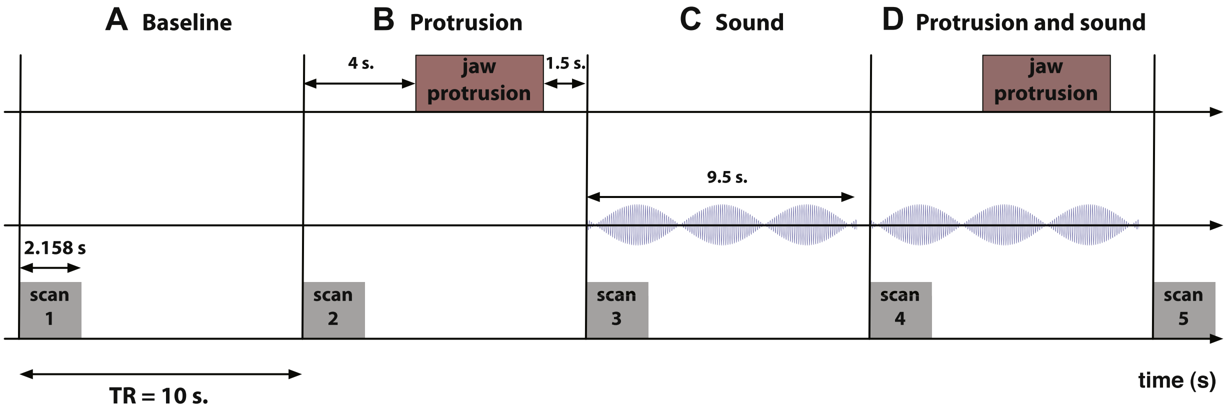

Fig. 1. The experimental design. The design consisted of 4 conditions: a baseline condition (panel A: baseline) to which all other conditions were contrasted, two unisensory conditions (panel B: jaw protrusion and panel C: sound) and one multisensory condition (panel D: jaw protrusion combined with sound). Presentation of the sound stimulus started with scanning and ended 0.5 s prior to the next scan. The instruction for jaw protrusion was projected on a screen 4 s after the beginning of a scan until 1.5 s prior to the next. Note that the data acquisition of each condition started after the stimulus presentation or instruction was finished (e.g. the unisensory jaw protrusion condition (B) corresponds to hemodynamic fMRI responses that are measured during scan 3 and the multisensory condition (D) corresponds to the fMRI responses measured during scan 5). The sequence of the four conditions was repeated 15×3 times.

cochlear nuclei). Functional images were interpolated to voxel dimensions of 2.0 × 2.0 × 2.0 mm^3.

2.4.1. *Statistical parametric mapping*

For each subject, a general linear model was set up to analyze the relative contribution of each condition to the measured response. The multiple regression model included three covariates of interest (one for each condition with the exception of the baseline condition), and for each run one constant factor to model the mean and a linear term to correct for drift in the scanner signal. The model was applied to the data of all individual voxels and contrast images were created, one for each condition (i.e., sound vs. baseline, jaw protrusion vs. baseline and sound combined with jaw protrusion vs. baseline).

The three contrast images obtained per subject as based on the general linear model were further analyzed in a random effects analysis using a repeated measures ANOVA implemented as a factorial design in SPM5. Three factors were defined to model the responses. One factor was a subject factor; one factor was defined as group factor (i.e., subjects with tinnitus or controls) and one factor was a within-subjects stimulus factor (i.e., the experimental conditions). Using such a design, several main effects could be tested. First we assessed which voxels responded significantly to sound only, to jaw protrusion only and to the bimodal condition that combined both modalities. This was achieved by pooling the data of all subjects. In addition, a contrast was defined showing voxels that have a significant larger response to the bimodal condition than to the sum of the unimodal conditions. This last contrast can be thought of as a measure of multisensory integration.

2.4.2. *Probability maps*

A drawback of a random effects analysis is that, when the between-subject variability is high and the mean response is weak, it can prove rather unreliable and insensitive (Thirion et al., 2007). An alternative method to represent a response that is common within a particular subject group is to make use of a map containing a descriptive statistic like an incidence or probability (Hall and Plack, 2009). This method depicts a percentage of subjects that exhibit (significant) activity at a certain voxel.

In the present study we used a probability threshold of $p < 0.001$, uncorrected for multiple comparisons, for the unisensory conditions (i.e., sound vs. baseline and jaw protrusion vs. baseline). If now, in a single subject, the response measured at a certain voxel exceeded threshold in both unimodal conditions, it was given a value of one. If it did not exceed threshold, it was given a value of zero. Next, the values were summed over all subjects and divided by the number of subjects to create a probability map. This map now shows the percentage of subjects that exhibit overlap in activation between the unisensory conditions at a certain voxel (Schurmann et al., 2006).

2.4.3. *Region of interest analysis*

In addition to the second level analysis and the analysis of the probability maps we performed a region of interest (ROI) analysis, assessing sound-evoked responses in 13 anatomical areas comprising parts of the auditory pathway and parts of the somatosensory pathway. The ROIs were defined based on anatomical atlases. The left and right primary auditory cortices (PAC) were defined as the combination of the TE1.0, TE1.1 and TE1.2 areas using the SPM5 Anatomy toolbox (Morosan et al., 2001; Rademacher et al., 2001; Eickhoff et al., 2005, 2007). For the left and right auditory association cortices (AAC) we used the left and right superior temporal gyrus as defined by Brodmann (BA 22) based on the AAL template in MRIcron (http://www.sph.sc.edu/comd/rorden/mricron/).

Both the ROIs of the primary and auditory association cortices were first normalized to match our anatomical template in order to have a corresponding image space. The left and right part of the medial geniculate body of the thalamus (MGB), the left and right inferior colliculi (IC) and the left and right cochlear nuclei (CN) were manually drawn based on an anatomical atlas (Woolsey, 2003; Martin, 2003). In addition to these auditory areas, the left and right somatosensory cortices were manually drawn approximately coinciding with BA 6 and SII. Also, the left and right ventrolateral (VL) nucleus of the thalamus were manually drawn based on an anatomical atlas (Woolsey, 2003; Martin, 2003). Finally, the vermis of the cerebellum was taken as a region of interest since it showed aberrant responses in subjects with tinnitus in a previous study (Lanting et al., submitted for publication). Fig. 2 shows the location of the ROIs of the primary auditory cortex, the auditory association cortex, the medial geniculate body and the somatosensory cortex.

Based on a *t*-test comparing the responses to the bimodal condition to a baseline condition, the 10% of the voxels that responded most strongly (i.e., with the highest t-value) within each ROI were selected. A percent signal change compared to baseline was calculated for each condition based on the (averaged) regression coefficients within each ROI. For each subject we calculated a percent signal change for all 13 ROIs. Box plots were used to visualize the data and show for each ROI the distribution of the percent signal change values for each condition within each group.

Next, we determined if there were significant differences between the percent signal change in the left hemisphere ROI compared to the right hemisphere ROI using a two-sample *t*-test where the data was pooled over all subjects. This excluded the vermis of the cerebellum since we made no distinction between the left and right hemisphere.

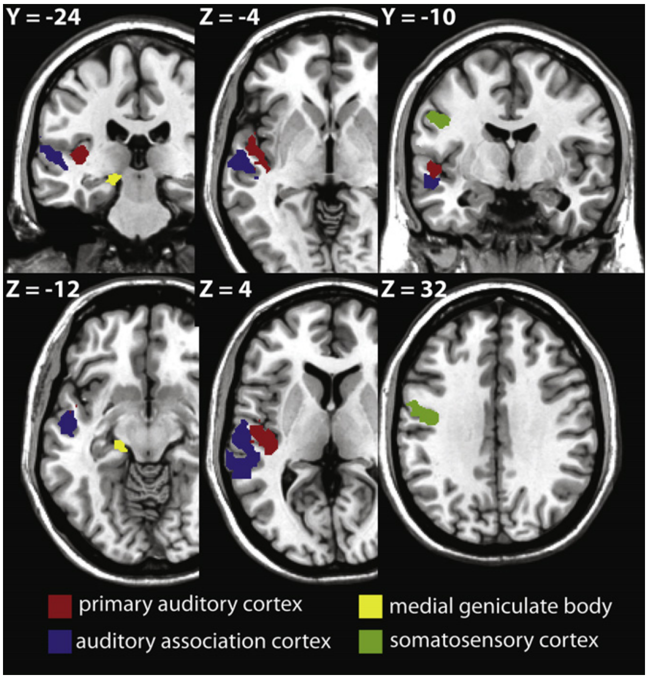

Fig. 2. Regions of interest (ROIs). Four ROIs are displayed as colored overlays over a gray-scale anatomical image. Shown in red is the ROI of the primary auditory cortex, in blue the auditory association cortex, in yellow the medial geniculate body, and in green the ROI corresponding to the somatosensory cortex (see text for definition of ROIs). Note that, for visualization purposes, only the left hemisphere ROIs are shown. The ROIs of the inferior colliculus (IC), cochlear nucleus (CN), ventrolateral (VL) nucleus of the thalamus and cerebellum (vermis) are not shown in this figure.

The responses of both unimodal conditions, each compared to a baseline signal level were tested for statistical significant deviation from zero using a one-sample *t*-test. The bimodal condition was not tested, since the voxels used in the ROI analysis were determined based on the strength of the responses in the bimodal condition and is therefore biased (Kriegeskorte et al., 2009). Next, a two-sample *t*-test was used for each condition and each ROI to assess potential differences between subject groups.

Finally, the bimodal condition (jaw protrusion combined with the presentation of sound) was compared to the unimodal conditions. This comparison was based on the difference between the multisensory condition and the sum of the unisensory conditions (Calvert et al., 2001; Kayser et al., 2005). A difference that was larger than zero was considered evidence for multisensory integration.

3. Results

3.1. Audiometry

Pure tone audiometry (250–8000 Hz) was performed prior to the functional session. The mean audiogram and the standard deviation around the mean are displayed per group in Fig. 3. For the control group, hearing threshold was 13 ± 8 dB hearing level (HL), averaged over both ears and over frequencies of 250–8000 Hz (mean ± standard deviation across subjects). In subjects with tinnitus, this average was 25 ± 20 dB HL. For the frequency-range of 250–2000 Hz, average hearing thresholds were determined at 11 ± 2 and 15 ± 8 dB HL for, respectively, the controls and subjects with tinnitus. The frequency-range of 4000–8000 Hz showed larger (and significant) differences between the two subject groups with an average of 17 ± 11 and 39 ± 23 dB for, respectively, the controls and subjects with tinnitus (see Fig. 3).

Table 2 shows the questions that subjects with tinnitus were asked. The last column shows the incidence (in % of all subjects with tinnitus) that a maneuver changed the perceptual characteristics of the tinnitus. All tinnitus subjects were able to alter their tinnitus by protrusion of the jaw. Upon protrusion of the jaw, two subjects (15%) reported only a change in pitch of their tinnitus or the appearance of another sound and ten (77%) subjects reported only a loudness change of their tinnitus. One subject reported both a change in frequency and loudness. The change in loudness varied from −9 to +4 units on a visual analog scale, where a negative number indicates a loudness decrease (two subjects) and a positive number an increase of the loudness (eight subjects). Fig. 4 shows the loudness of the tinnitus during jaw protrusion as function of the loudness as measured during rest. In all tinnitus subjects, the modulation effect of jaw protrusion was stable and persisting throughout the maneuver. Question 7 and 8 of the questionnaire were asked specifically since subjects had to perform the maneuver without excessive head movement while in a supine position (i.e., lying in the MR scanner).

Table 2
Somatosensory modulation of tinnitus questionnaire.

	Question		Percentage
1.	Does the tinnitus changes by performing the following manipulations?		
a.	Protrusion of the jaw (mandible)	y/n	100%
b.	Movement of the mandible to the right	y/n	77%
c.	Movement of the mandible to the left	y/n	62%
d.	Retraction of the mandible	y/n	46%
e.	Touching of/pressure on the skin of the face	y/n	62%
f.	Touching of/pressure on the neck area	y/n	31%
g.	Touch of/pressure on the left hand/making fist	y/n	23%
h.	Touch of/pressure on the right hand/making fist	y/n	8%
i.	Turn head left	y/n	54%
j.	Turn head right	y/n	69%
k.	Gaze to the left (hold head fixed in normal position)	y/n	0%
l.	Gaze to the right (hold head fixed in normal position)	y/n	8%
m.	Gaze upwards (hold head fixed in normal position)	y/n	8%
n.	Gaze downwards (hold head fixed in normal position)	y/n	0%
2.	Describe the effect of the manipulations in 1.)		
a.	Change in pitch		15%
b.	Change in loudness		77%
c.	Another sound		8%
d.	Any other effect		8%
3.	Is this modulation persistent if you hold the manipulation in a fixed position	y/n	
4.	Does the loudness of the tinnitus change?	y/n	
5.	What is the loudness of your tinnitus (visual analog score 0–10)?		Average: 6.0
6.	What is the loudness of your tinnitus if you perform any of the manipulations in 1.)		Average: 6.6
7.	Can you manipulate your tinnitus without movement of the head	y/n	
8.	Can you manipulate your tinnitus while in a supine position	y/n	

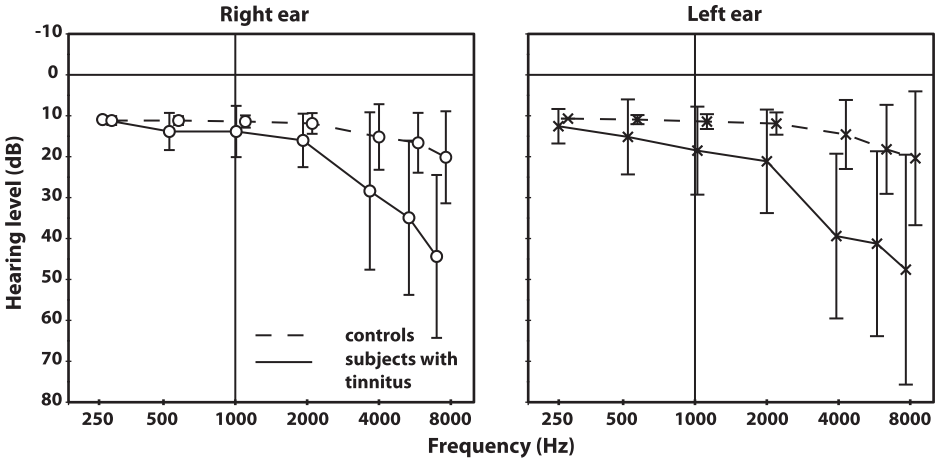

Fig. 3. Average hearing thresholds for the right and left ear of the two subject groups. The solid lines represent hearing thresholds of subjects with tinnitus and the dashed lines represent hearing thresholds of the controls. The thresholds were normal in the control group (i.e. better than 20 dB hearing level). For the high frequency range (4.0–8.0 kHz), thresholds in subjects with tinnitus were elevated as compared to controls. The error bars indicate the group standard deviation around the mean.

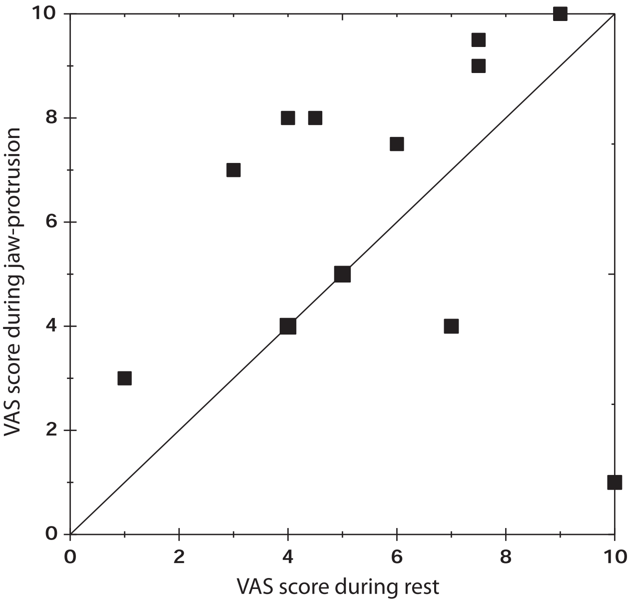

Fig. 4. Tinnitus loudness during rest and jaw protrusion. Visual analogue scores (VAS) show for each subject the loudness of their tinnitus during jaw protrusion vs. the loudness during rest. Eight subjects reported an increase, two subjects reported a decrease and two subjects reported no change in the loudness as a result of jaw protrusion. The latter two subjects described a change in the pitch of their tinnitus.

3.2. *Statistical parametric mapping and probability maps*

Fig. 5 shows a statistical parametric map (SPM) obtained through the random-effects analysis, across all (33) subjects for the contrast sound vs. baseline and jaw-protrusion vs. baseline. The contrast sound vs. baseline (indicated as 'sound') showed part of the auditory pathway consisting of the CN, IC, MGB, PAC and AAC. The contrast jaw-protrusion vs. baseline (indicated as 'jaw') showed the following structures: the ventrolateral nucleus of the thalamus (VL), the putamen (Put) and the secondary somatosensory cortex (SII). Activation patterns obtained exceeded the voxel-wise threshold, showing significant responses. A small area in the primary auditory cortex responded to both sound and jaw protrusion.

Fig. 6 shows a probability map indicating overlap between the two unisensory conditions and additionally shows a measure of multisensory integration. In blue/red colors it shows the probability-map indicating the incidence that a voxel shows a significant response to both jaw-protrusion and sound at the level of single subjects (thresholded at $p < 0.001$, uncorrected for multiple comparisons). Voxels with more than 5% overlap across subjects are shown. These areas include the bilateral BA 41 and 22. Similarly, it shows in orange/yellow colors, the voxels for which the sum of the jaw and sound responses was smaller that the response to the combined jaw plus sound stimulation. These areas are considered to exhibit multisensory integration. They include the bilateral middle temporal gyrus (including BA 21) and the inferior temporal gyrus. The coronal cross-section shows voxels that exhibit multisensory integration in the cingulate gyrus, which is part of the limbic lobe.

3.3. *Region of interest analysis*

A region of interest analysis was performed in all subjects using ROIs comprising parts of the auditory pathway (the CN, the IC, the MGB, the PAC and the AAC) and the somatosensory areas including the somatosensory cortex, the ventrolateral nucleus of the thalamus and the vermis of the cerebellum. Within each ROI, the 10%

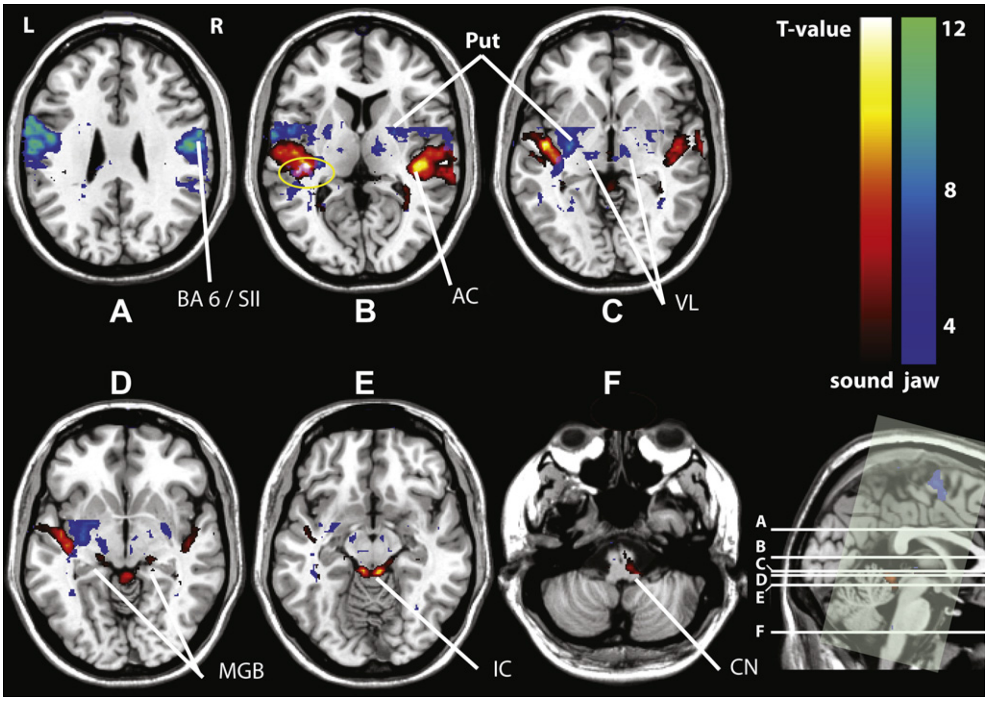

Fig. 5. Group responses to sound stimuli and jaw protrusion. The group analysis (random effects analysis) shows the spatial distribution of voxels that have a significant large ($p < 0.01$ FDR; $T > 3.43$) response to sound (red/yellow colored overlay) and jaw protrusion (blue/green colored overlay). The responding voxels are displayed over a gray-scale anatomical image. The bottom-right midsaggittal cross-section shows (semi-transparent) the imaging volume and the slices of interest (A–F). These slices include the following structures: (A) BA6/SII, Brodmann area 6/somatosensory cortex; (B) AC, auditory cortex; Put, Putamen; (C) VL, ventral lateral nucleus of the thalamus; (D) MGB, medial geniculate body; (E) IC, inferior colliculus and (F) CN, cochlear nucleus. The yellow circle in panel B indicates an area in the primary auditory cortex that shows overlap of activity between the two conditions (sound and jaw protrusion). This overlap is visible by the purple color; mixing red (sound) and blue (jaw protrusion).

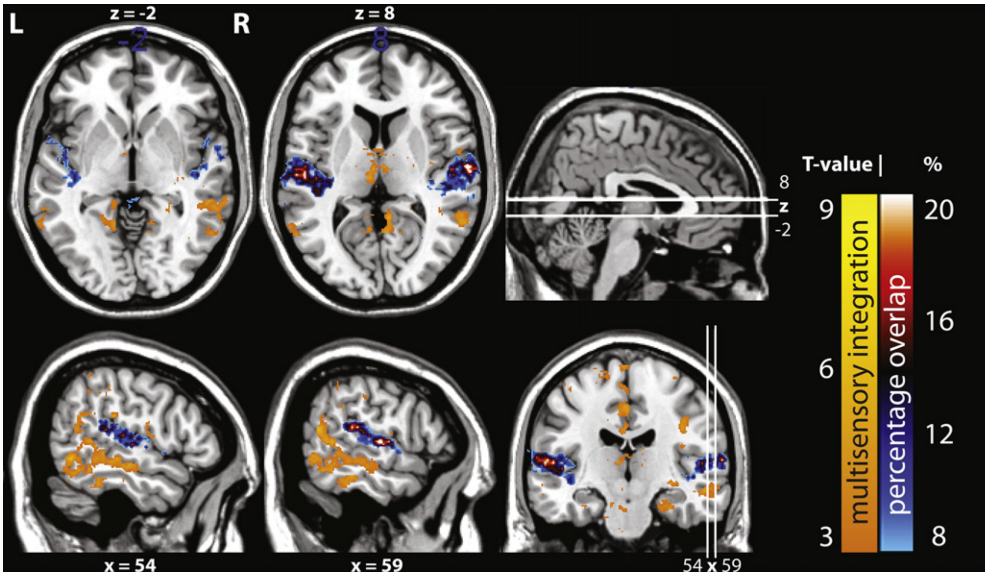

Fig. 6. Probability map showing the incidence, in percent overlap between all subjects (thresholded at 5% and coded in blue–black–red colors), that a voxel showed significant responses to both jaw protrusion and sound (each thresholded at the single subject level of $p < 0.001$, *F*-test, uncorrected for multiple comparisons). Areas that showed overlap include the primary auditory cortex (PAC, BA 41) and the auditory association cortex (AAC, BA 22). In addition, orange/yellow colors show voxels that exhibited multisensory integration (i.e. when the bimodal condition showed a larger response than the sum of the unimodal stimuli; $p < 0.05$ FDR, $T > 2.58$). Areas that showed multisensory integration included the bilateral middle temporal gyrus (including BA 21) and the inferior temporal gyrus. The coronal cross-section (bottom-right) shows also multisensory integration in the cingulate gyrus, which is part of the limbic lobe.

best responding voxels to the bimodal condition were selected and the mean signal change compared to baseline was calculated. Since the responses of each left and right ROI were not statistically significant different from each other, the average value of the left and right ROI was taken.

The box plots in Fig. 7 show the distribution of ROI-responses for controls (white) and subjects with tinnitus (gray) for the different ROIs. For each ROI, it shows the distribution of measured percent signal changes for the three experimental conditions, sound, jaw protrusion and the combined (bimodal) condition – all compared to baseline. In addition, a measure for multisensory integration is shown in each rightmost box plot, where the distribution of values of the multisensory response minus the sum of the two unisensory responses for each single subject is represented. Summary statistics on the experimental conditions are presented in Table 3 and summary statistics on the group differences are presented in Table 4.

3.3.1. *Response to sound*

All nuclei of the auditory pathway (Fig. 7A–E) showed a significant ($p < 0.001$) response to sound in both subject groups. The somatosensory cortex (Fig. 7F) did not show a significant response to sound stimuli ($p = 0.06$ and $p = 0.93$ for, respectively, the controls and subjects with tinnitus). The ventrolateral nucleus of the thalamus (Fig. 7G), in contrast, showed a small, but significant response to sound ($p = 0.004$ and $p = 0.008$ for, respectively, the controls and subjects with tinnitus). The vermis responded significantly to sound in controls ($p = 0.001$). In tinnitus subjects the response of the vermis to sound was not significant ($p = 0.06$). When comparing groups (controls vs. subjects with tinnitus) no significant differences in sound-evoked responses were observed (see Table 4).

3.3.2. *Response to jaw protrusion*

While the somatosensory cortex (Fig. 7F) did not show a response to sound, it did show a significant ($p < 0.001$) response to jaw-protrusion as can also be observed at the voxel-wise group analysis in Fig. 5. The ventrolateral nucleus of the thalamus and the cerebellum also showed a significant response to jaw-protrusion in both subject groups (Fig. 7G–H). Interestingly, almost all ROIs in the auditory pathway responded significantly to jaw-protrusion, except for the IC in the control group ($p = 0.48$). Evidently, somatosensory input enhances activity in the auditory pathway, even in the absence of sound stimuli.

3.3.3. *Multisensory integration*

For each ROI we determined whether the multisensory response exceeded the sum of both unisensory responses. A positive difference is considered strong evidence of multisensory integration Calvert (2001). The difference was positive in the MGB and the IC of controls (Fig. 7CD and Table 4). The patient group did not show evidence of multisensory integration at this level. Also the somatosensory cortex (both groups) and the ventrolateral nucleus of the thalamus in the control group showed some integration. Note, however, that the effects of this integration were small (Fig. 7F–H).

3.3.4. *Group differences*

The responses measured in several ROIs allow for a comparison between both subject groups. Although there no significant differences at cortical levels, there are differences of importance in the midbrain and the brainstem that relate to tinnitus (see Fig. 7). At the level of the CN (Fig. 7E), the subjects with tinnitus showed a larger response to jaw protrusion than the controls (tinnitus – controls: 0.35 ± 0.24; mean difference ± 95% CI). Also, the IC (Fig. 7D) showed larger jaw responses in tinnitus subjects than in controls ($p = 0.014$; tinnitus – controls: 0.28 ± 0.22; mean difference ± 95% CI). The other ROIs did not show significant differences between the subject groups.

So, although motor activity or sensory activity caused by jaw-protrusion was not expected to generate responses in the auditory pathway, we measured extensive responses to jaw-protrusion throughout the auditory pathway in both subject groups. The only significant differences between the responses of subjects with tinnitus and controls were found in the CN and the IC, for which the

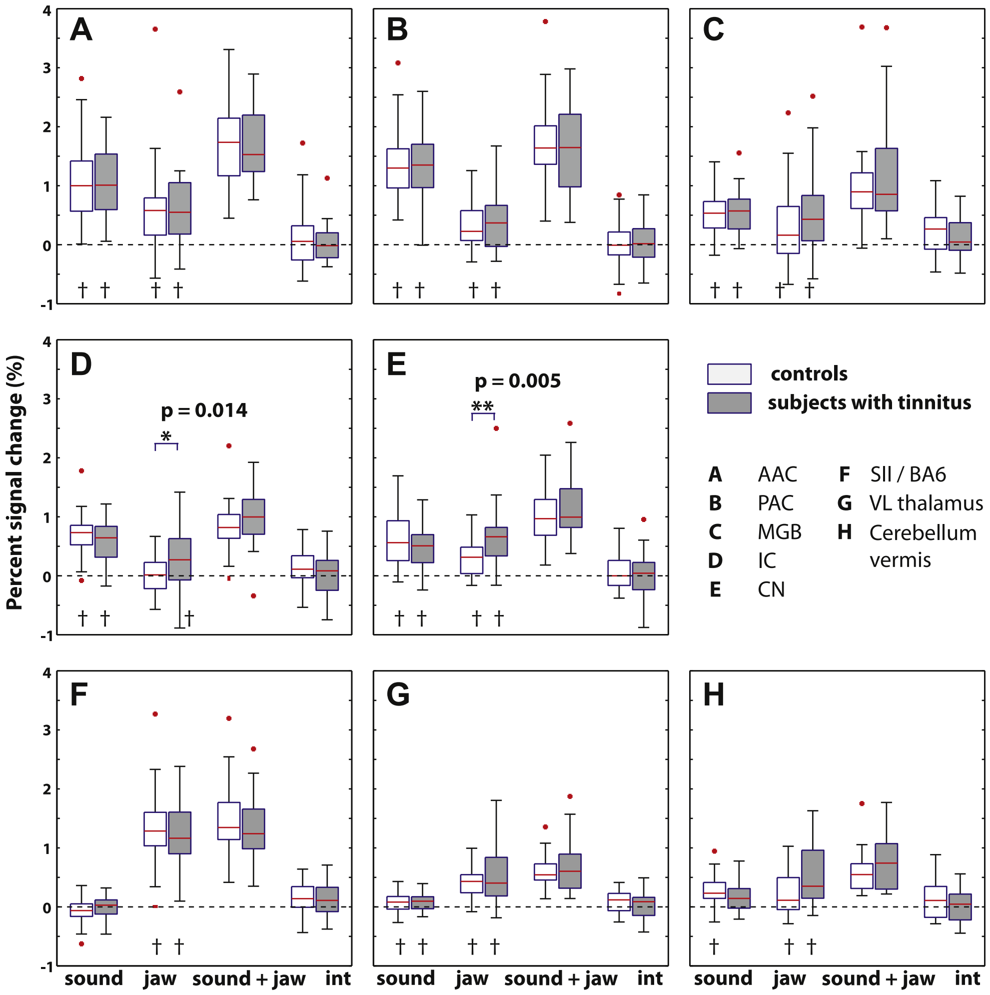

Fig. 7. Region of interest (ROI) responses in (A) the auditory association cortex (BA 22), (B) the primary auditory cortex (BA41), (C) the medial geniculate body, (D) inferior colliculus and (E) the cochlear nucleus. In addition, the responses in (F) the somatosensory cortex, (G) the ventral lateral nucleus of the thalamus and the (H) cerebellum (vermis) are shown. Responses are shown for controls (white) and subjects with tinnitus (gray) as box plots (showing smallest observation, 25th, 50th and 75th percentile, and largest observation). The responses are given in percent signal changed compared to baseline. For each ROI, the responses for three conditions are displayed: the response to sound ('Sound'), the response to jaw-protrusion ('Jaw'), and the response to both conditions together ('Sound + Jaw'). In addition a measure for multisensory integration is shown ('Int', defined as the difference between the multisensory condition and the sum of the unisensory condition). The symbol † indicates that the response is significantly different from zero for each group separately.

responses to jaw protrusion were larger in subjects with tinnitus. This implies, that jaw protrusion, in addition to a subjective difference in the loudness of tinnitus, causes differential levels of activity between the subject groups in early stages of auditory processing. The change in loudness of tinnitus by jaw-protrusion, may thus tentatively, occur due to changes in the normal function of early auditory processing.

4. Discussion

Many patients with tinnitus describe that their tinnitus is modulated by somatic maneuvers (Levine et al., 2003). We studied the effect of one maneuver, jaw protrusion, on activity in the central auditory system. We studied the effects of jaw-protrusion using an experimental paradigm where jaw protrusion was alternated with

Table 3
Significance values (p-values, t-test) of the region-of-interest (ROI) responses to sound, jaw and integration in both subject groups; significant values ($p < 0.05$) are typeset in bold. The responses were averaged over the left and right hemisphere ROIs at each level.

Region of interest	Controls			Subjects with tinnitus		
	Sound	Jaw-protrusion	Integration	Sound	Jaw-protrusion	Integration
AAC	<**0.001**	<**0.001**	0.08	<**0.001**	<**0.001**	0.41
PAC	<**0.001**	<**0.001**	0.66	<**0.001**	<**0.001**	0.80
MGB	<**0.001**	**0.002**	**0.01**	<**0.001**	**0.001**	0.22
IC	<**0.001**	0.48	**0.005**	<**0.001**	**0.012**	0.47
CN	<**0.001**	<**0.001**	0.27	<**0.001**	<**0.001**	0.83
SII	0.06	<**0.001**	<**0.001**	0.93	<**0.001**	**0.049**
VL thalamus	**0.004**	<**0.001**	**0.006**	**0.008**	<**0.001**	0.22
Cerebellum vermis	**0.001**	**0.022**	0.10	0.06	**0.003**	0.80

Table 4
Differences between subject groups; significant differences (two-sided t-test; $p < 0.05$) are typeset in bold. For each ROI, the table shows the mean difference (a positive difference indicates that the responses in patients are bigger than those in controls subjects), the 95% confidence interval (CI) and the corresponding significance level (p-value). The responses, denoting the percent signal change compared to baseline, were averaged over the left and right hemisphere ROIs at each level.

Region of interest	Sound			Protrusion			Integration		
	Mean	±CI	p-value	Mean	±CI	p-value	Mean	±CI	p-value
AAC	0.02	0.31	0.89	−0.04	0.36	0.81	−0.09	0.24	0.44
PAC	−0.02	0.22	0.90	0.08	0.22	0.44	0.00	0.19	0.93
MGB	0.04	0.18	0.66	0.20	0.37	0.30	−0.09	0.20	0.35
IC	−0.09	0.17	0.28	**0.28**	**0.22**	**0.014**	−0.08	0.16	0.30
CN	−0.13	0.22	0.23	**0.35**	**0.24**	**0.005**	−0.07	0.18	0.46
SII	0.07	0.10	0.13	−0.12	0.33	0.47	−0.05	0.13	0.45
VL thalamus	0.09	0.08	0.75	0.09	0.18	0.29	−0.03	0.10	0.57
Cerebellum vermis	−0.10	0.21	0.34	0.33	0.35	0.06	−0.12	0.24	0.33

either a rest condition or a condition with sound stimulation (rather than a randomized approach) to prevent fatigue of the jaw muscles.

We showed that jaw protrusion extensively activates the auditory system. A remarkable result is that for the majority of auditory brain areas, the response to jaw protrusion is similar between normal hearing subjects and the selected tinnitus patients (see Fig. 7). The only significant difference between normal hearing and tinnitus subjects was the increased responsiveness to jaw motion in the brainstem nuclei in tinnitus patients (see Fig. 7D and E). The fact that there were significant differences in hearing levels between the two subject groups in the frequency-range of 4–8 kHz, may contributed to these differences. In other words, it is possible that the hearing loss, rather than the tinnitus, caused the differences we found between the subject groups.

In addition to pathological spontaneous activity in auditory brain areas due to induced hearing loss (Seki and Eggermont, 2003), a recent study related tinnitus to changes in normal somatosensory integration, in that a peripheral hearing loss enhanced the somatosensory input to the (dorsal) cochlear nucleus (Shore et al., 2008). Moreover, after cochlear damage they found increased levels of the glutamate transporters VGLUT2, associated with somatosensory input (Zeng et al., 2009). The main idea is that these changes represent a compensatory response to deafening leading to undesirable increased spontaneous rates in neurons of the CN and may cause modulation of tinnitus by increased levels of somatosensory input to the CN. The findings in our tinnitus subjects are thus in general agreement with the findings in animal studies: the degree of hearing loss and tinnitus corresponded to enhanced brainstem responses to jaw protrusion. In the next sections we relate our findings to the hypothesis of changes in somatosensory-auditory integration as a functional and neurophysiologic basis for tinnitus.

4.1. Somatosensory integration in the auditory system and tinnitus

The effect of jaw protrusion on tinnitus is straightforward behavioral evidence for a specific form of multisensory integration: it represents a clear example of a somatosensory event that influences an auditory percept. Obviously, the behavioral observation must have a corresponding neural representation of multisensory integration. In the following, we will discuss to what extent the fMRI responses we measured, reflect some basic principles of sensory integration.

There are many different measures for multisensory integration. Multimodal integration refers to the responsiveness of a single neuron to stimulation of different sensory modalities, or the modulation of the response to one sensory modality by another sensory modality. Typically, this influence has been described in terms of firing rates of the neuron, being either enhancing or suppressive (Stein and Meredith, 1993).

Our work provides several types of evidence for multisensory processing in the brainstem and cortex using functional MRI. We considered I) the spatial overlap in activity patterns between the unisensory modalities, II) multisensory integration in individual voxels, and III) the response levels to unisensory stimuli and multisensory integration in regions of interest (ROIs).

4.1.1. Spatial overlap of activation patterns

Spatial overlap of activation patterns (i.e. voxels that show a significant response to two distinct sensory modalities) can be visualized using probability maps (Fig. 6). We found overlap between the auditory modality and the somatosensory modality in the primary auditory cortex (BA 41) and the auditory association cortex (BA 22).

Previously, Foxe et al. (2002) and Schurmann et al. (2006) also showed overlap of responses to somatosensory (touch) and auditory stimuli in the human auditory cortex. Foxe et al. (2002) argued that this area coincides with the CM belt area that was found earlier to show bimodal responses in cellular recordings in macaque monkeys (Foxe et al., 2000). In addition to these studies, Beauchamp et al. (2008) located an area on the human superior temporal sulcus that showed overlap in responses to auditory input, somatosensory (tactile) input and visual input.

Although spatial overlap of the patterns of activity to different modalities is indicative for integration, it may not be the best way to describe integration. An additive response (i.e., when the bimodal response equals the sum of the unimodal responses) could simply reflect linear summation of the responses of two sets of sensory-specific neurons that happen to fall within the same individual MRI voxel (Calvert, 2001) and could therefore (wrongly) be interpreted as a functional multimodal integration.

4.1.2. Voxel-wise multisensory integration

The second level of evidence for multisensory processing comes from voxel-wise analyses. Multisensory integration was investigated by testing for supra-additivity in each individual voxel separately. Several areas, in addition to regions that were selected for the ROI analyses, were identified as exhibiting multisensory integration. Fig. 6 shows the middle temporal gyrus, the inferior temporal gyrus and the cingulate gyrus. These areas showed significant responses to the multimodal stimulus as compared to the sum of the unimodal responses.

4.1.3. ROI analysis: response levels to unisensory stimuli and markers of multisensory integration

Finally, we looked at the response levels of regions of interest (ROIs). All auditory ROIs showed responses to both sound and jaw movement (Fig. 7A–E). Interestingly, the only differences between subjects with tinnitus and controls were found in the CN and IC. In both ROIs, jaw protrusion evoked a larger response in subjects with tinnitus compared to controls. This may indicate an abnormal somatic input to the auditory system in the tinnitus subjects.

Additionally, we specifically looked for supra-additivity of the combined response-strong evidence for multisensory integration (Calvert, 2001) – which was present in the MGB and the IC (at least, in the control group; this was not detected in the patient group). The somatosensory cortex and the ventrolateral nucleus of the thalamus also showed some supra-additivity, although the effects of this integration were small; presumably since in all ROIs one of the unisensory modalities gave a large response (and could be detected without the use of the other modality). Thus, the ROI analysis provides no clear evidence for multisensory integration in terms of supra-additivity of unimodal responses.

4.2. Auditory and somatosensory integration: neurophysiologic and histological evidence

Whereas we so far only reviewed our findings on somatosensory auditory integration and tinnitus, this section is aimed at understanding this integration from a neurophysiologic and histological perspective.

Somatic sensation of the head, including the oral cavity is conveyed by four cranial nerves, of which the trigeminal nerve is most important. The trigeminal ganglion (TG), receiving information from the branches of the trigeminal nerve, in turn projects to the brainstem trigeminal complex. This pathway conveys proprioceptive information from the jaw and the temporomandibular joint (see e.g. Dehmel et al., 2008).

Anatomical labeling and electrophysiological measurements in animals have shown that nuclei of the trigeminal ganglion and trigeminal nucleus project to the ventral cochlear nucleus (VCN) and dorsal cochlear nucleus (DCN) (Zhou and Shore, 2004). In addition, the dorsal column nuclei and the spinal trigeminal nucleus (Sp5) also project to the ventrolateral border region of the IC (Zhou and Shore, 2006).

Smiley et al. (2007) and Hackett et al. (2007a) showed that in macaque monkeys there are corticocortical (Smiley et al., 2007) and thalamocortical (Hackett et al., 2007a) somatosensory connections to the caudal medial auditory area (presumably secondary auditory cortex or association cortex in humans). Additionally, there is evidence for integration based on the modulatory effect of one modality (e.g. somatosensory or visual input) on responses to auditory stimuli (see e.g., Meredith and Allman, 2009; Allman et al., 2009).

So, in addition to the CN and the IC, which receive (and integrate) both somatosensory and auditory signals, there are cortical auditory areas that exhibit multisensory processing. This indicates that multisensory integration is widely present along the auditory pathway. A change in the normal function of this multisensory integration may thus be key to understanding somatic tinnitus.

4.3. Responses in the cerebellum

Interestingly, the vermis of the cerebellum showed a small but significant sound-evoked response in the normal hearing subjects. The role of the cerebellum in purely auditory processing has previously been reviewed by Petacchi et al. (2005). The vermis appears to have a specific auditory function and auditory responses were mapped previously by Huang and Liu (1990). Aitkin and Boyd (1975) found binaural processing in the vermis, and suggested that this processing may be related to the motor function of the cerebellum. In other words, the cerebellum may include binaural auditory cues in its control of motor functions, especially in controlling the neck muscles to move the head towards a sound source. In contrast to normal hearing subjects, the vermis response to sound was not significant in tinnitus subjects (Fig. 7H). Thus, the auditory processing of the cerebellum may be different between tinnitus subjects and controls (although there is no significant difference between the subject groups). One may speculate that this may be related to the fact that the tinnitus subjects were selected on the basis of the perceived effect of jaw protrusion (a motor function) on the auditory perception of their tinnitus.

5. Conclusion

In conclusion, we showed responses to jaw protrusion throughout the auditory pathway. These responses occurred in both tinnitus patients and control subjects. The somatosensory responses of the auditory brain areas to jaw protrusion presumable account for the modulation of tinnitus by jaw protrusion. The response to jaw protrusion of the CN and the IC was larger in subjects with tinnitus than in healthy controls, suggesting an abnormal auditory-somatic interaction in the patient group.

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