

Emotional Voice Areas: Anatomic Location, Functional Properties, and Structural Connections Revealed by Combined fMRI/DTI

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We determined the location, functional response profile, and structural fiber connections of auditory areas with voice- and emotion-sensitive activity using functional magnetic resonance imaging (fMRI) and diffusion tensor imaging. Bilateral regions responding to emotional voices were consistently found in the superior temporal gyrus, posterolateral to the primary auditory cortex. Event-related fMRI showed stronger responses in these areas to voices-expressing anger, sadness, joy, and relief, relative to voices with neutral prosody. Their neural responses were primarily driven by prosodic arousal, irrespective of valence. Probabilistic fiber tracking revealed direct structural connections of these "emotional voice areas" (EVA) with ipsilateral medial geniculate body, which is the major input source of early auditory cortex, as well as with the ipsilateral inferior frontal gyrus (IFG) and inferior parietal lobe (IPL). In addition, vocal emotions (compared with neutral prosody) increased the functional coupling of EVA with the ipsilateral IFG but not IPL. These results provide new insights into the neural architecture of the human voice processing system and support a crucial involvement of IFG in the recognition of vocal emotions, whereas IPL may subserve distinct auditory spatial functions, consistent with distinct anatomical substrates for the processing of "how" and "where" information within the auditory pathways.

Keywords: connectivity, diffusion, probabilistic fiber tracking, prosody, superior temporal gyrus

Introduction

Speech melody (prosody) provides important cues about the emotional state of our conversational partners during social interactions. Previous functional magnetic resonance imaging (fMRI) studies have provided consistent evidence that the middle part of the human associative auditory cortex holds a temporal voice area (TVA; Belin et al. 2000; Ethofer, Kreifelts, et al. 2009), which exhibits stronger responses to utterances spoken in an emotional rather than neutral tone (Grandjean et al. 2005; Ethofer, Anders, Wiethoff, et al. 2006; Beaucousin et al. 2007). These fMRI results converge with electrophysiological data demonstrating a differentiation of neutral and emotional vocal stimuli over temporal cortical areas as early as 200 ms after stimulus onset (Paulmann and Kotz 2008). The increases observed in this area occur for a broad range of emotional categories and cannot be explained on the basis of single acoustic parameters (Wiethoff et al. 2008). Furthermore, an increased activation to voices spoken in alluring prosody by speakers of the opposite (but not same) sex indicates that

these modulations reflect a particular sensitivity to the behavioral relevance of voices for the listener (Ethofer et al. 2007).

However, the recognition and appraisal of affective signals in voices implicate widespread brain networks beyond auditory areas. Explicit judgment of prosody type or intensity consistently activates the inferior frontal gyrus (IFG; e.g., Buchanan et al. 2000; Wildgruber et al. 2005; Ethofer, Anders, Erb, et al. 2006; Ethofer, Kreifelts, et al. 2009). In addition, lesions of the IFG lead to impaired comprehension of vocal emotions (Hornak et al. 1996, 2003; Rymarczyk and Grabowska 2007). Accordingly, models of prosody processing have long postulated a role for important interactions between temporal and frontal regions of the right hemisphere, similar to the networks associated with language functions in the left hemisphere (Ross and Mesulam 1979). In the latter case, strong connections between the posterior part of the left superior temporal gyrus (STG) and left IFG via the arcuate fasciculus have been identified using diffusion tensor imaging (DTI) in humans (Catani et al. 2005). Furthermore, a strong left-right asymmetry for connections between phonological areas in STG and frontal areas has been demonstrated, with more consistent fiber bundles in the left than right hemisphere (Glasser and Rilling 2008). However, the anatomical substrates mediating interactions between temporal and frontal cortices for comprehension of emotional prosody still remain unknown.

This study was designed to clarify the following 3 questions: First, we wanted to determine the precise location of the emotion-sensitive auditory cortices in relation to other anatomical structures, particularly the primary auditory cortex (PAC) and the voice-sensitive associative auditory cortex in the TVA. Voice-sensitive areas were defined using a validated fMRI localizer experiment (Belin et al. 2000). Second, we wanted to systematically investigate any differential influence of valence and arousal on emotional responses in these areas. Third, we aimed at determining the structural and functional connectivity between the emotion-sensitive auditory areas and other distant regions in the brain. To this end, we combined fMRI and DTI measures in the same volunteers. Sentences spoken in neutral and various emotional categories were presented during an event-related fMRI experiment with a 2 × 2 factorial design including valence (positive vs. negative emotions) and arousal (low- vs. high-arousing emotions) as within-subject factors. The fMRI activations were subsequently employed as seed areas to examine not only how the network underlying prosody perception is modulated by the emotional content of voices (effective connectivity) but also how areas within this network are structurally interconnected (using probabilistic

fiber tracking). Based on previous neuroimaging studies in humans (Buchanan et al. 2000; Meyer et al. 2004; Wildgruber et al. 2005; Ethofer, Anders, Erb, et al. 2006; Ethofer, Kreifelts, et al. 2009) as well as anatomical data obtained in human primates (Hackett et al. 1998; Romanski et al. 1999), we hypothesized strong connections of the emotional voice areas (EVA) with inferior frontal regions that are modulated by emotional information expressed by prosody.

Materials and Methods

Subjects, Stimulus Material, and Experimental Design

Twenty-two right-handed healthy subjects (13 females; 26.3 ± 7.7 years) participated in the fMRI experiment. The study was approved by the local ethical committee. The stimulus material (Banziger et al. 2009) consisted of recordings of 10 actors expressing the pseudosentence “Ne kalibam sout molem” in angry (high-arousing negative), sad (low-arousing negative), joyful (high-arousing positive), relieved (low-arousing positive), and neutral prosody. These recordings were normalized to the same mean sound intensity and evaluated by 24 subjects (12 females; 28.5 ± 4.5 years) to ensure that the intended emotion was recognized by at least 70% of the subjects. In addition, all stimuli were evaluated by another 14 subjects (7 females; 28.6 ± 4.6 years) with respect to valence and arousal expressed by prosody using a 9-point Likert scale. For each stimulus, the mean pitch (F0) was determined with Praat software (<http://www.praat.org>). Mean F0 and mean duration, as well as valence and arousal ratings, are presented in Supplementary Table 1. During fMRI, these stimuli were presented twice in pseudorandomized order and jittered relative to scanning in steps of 850 ms (intertrial interval: 6.8–10.2 s). Subjects were instructed to identify the gender of the speaker as accurately and quickly as possible.

Prior to the main fMRI experiment, a voice localizer was also run in each participant using a passive-listening block design with 32 stimulation and 16 silent epochs (each 8 s), as validated in previous research (Belin et al. 2000; Kreifelts et al. 2009). These stimuli included 16 blocks with human voices (HV; e.g., speech, sighs, laughs, etc.), 8 blocks with animal sounds (cries of various animals), and 8 blocks with environmental sounds (ES; e.g., doors, telephones, cars, etc.).

Image Acquisition

Structural T_1 -weighted images (time repetition [TR] = 1900 ms, time echo [TE] = 2.32 ms, time to inversion [TI] = 900 ms, voxel size: $0.9 \times 0.9 \times 0.9$ mm³) and functional images (30 axial slices, slice thickness 4 + 1 mm gap, TR = 1.7 s, TE = 30 ms, voxel size: $3 \times 3 \times 5$ mm³) were acquired with a 3-T scanner (Siemens TIM TRIO, Erlangen, Germany). Time series consisted of 509 images for the main experiment and 242 images for the voice localizer. For correction of image distortions, a field map (36 slices, slice thickness 3 + 1 mm gap, TR = 400 ms, TE(1) = 5.19 ms, TE(2) = 7.65 ms, voxel size: $3 \times 3 \times 4$ mm³) was acquired. Diffusion-weighted images were acquired using a “Skejskal-Tanner” sequence (TR = 8.3 s, TE = 82 ms, flip angle = 90°, 64 axial slices, 2 acquisitions) with a voxel size of $2 \times 2 \times 2$ mm³ along 30 independent directions. The b value for these images was 1000 s/mm². Additionally, an image with a b value of 0 s/mm² was acquired for coregistration with the fMRI data.

Conventional fMRI Analysis

Images were analyzed with statistical parametric mapping software (SPM5, Wellcome Department of Imaging Neuroscience, London, UK). Preprocessing comprised realignment, unwarping, slice time correction, normalization into Montreal Neurological Institute space (MNI, resampled voxel size: $3 \times 3 \times 3$ mm³), and smoothing with a Gaussian filter (10 mm full width at half maximum). In the main fMRI experiment, statistical analysis was based on a general linear model with the 5 prosodic intonations as distinct event-related regressors defined by a stick function, convolved with the hemodynamic response function (hrf), in SPM5. Events with missed responses (<1% of trials)

were excluded from analysis. For the voice localizer experiment, responses to HV, AV, and ES were separately modeled using a boxcar function of 8 s duration convolved with the hrf. For both experiments, data from the individual first-level models were employed to create contrast images for each subject that compared brain responses with emotional prosody (all categories together) versus neutral prosody in the main experiment and voices versus other sounds (animals and environmental) in the voice localizer experiment. These contrast images were then submitted to a second-level random effect to enable population inference for localization of emotion-sensitive voxels (emotional > neutral prosody) and voice-sensitive voxels (HV > AV and ES) at the group level. To ensure that only voxels with a reliable response were included in the subsequent DTI analysis (see below), a conservative threshold of $P < 0.05$, family-wise error (FWE) corrected for the whole brain was applied for our analysis of both experiments.

To examine more subtle effects of valence and arousal on neural activity in the emotion-sensitive areas, a region-of-interest (ROI) analysis was conducted. Using an ROI approach was most appropriate given our main focus on EVA and the 2×2 factorial distribution of our stimulus conditions. To this end, beta estimates averaged across all significant voxels of each emotion-sensitive cluster were submitted to a 2-by-2 factorial analysis of variance (ANOVA) with valence (positive and negative) and arousal (high and low) as within-subject factors.

The optimal strategy for defining activation seed masks for subsequent fiber tracking critically depends on the signal-to-noise ratio (SNR) of the differential responses (i.e., emotional vs. neutral prosody). While individual seed masks might accommodate differences in functional anatomy across subjects, averaging across subjects can suppress noise, which can be crucial for measures with a low SNR such event-related fMRI. Hence, to formally determine the average ROI activation strength to auditory stimulation as well as the effect size of response enhancements due to emotion, we evaluated the SNR of all event-related responses versus baseline and the differential contrast emotional versus neutral prosody averaged across the EVAs for each subject. To this end, the corresponding beta or contrast estimates were divided by the standard deviation of the noise (as calculated by the square root of the residual mean square image created during estimation of the first-level statistical model in SPM). SNRs are given in mean \pm standard error.

Effective Connectivity Analysis of fMRI Data

A psychophysiological interaction (PPI; Friston et al. 1997) analysis was conducted to identify brain areas showing a modulation of their functional coupling with the EVAs as a function of vocal emotional information. To this end, subject-wise PPI models were run, which contained 3 regressors for the physiological variable, the psychological variable, and the PPI, respectively. The physiological variable was defined as the time course of activity in the EVA clusters as obtained by the conventional SPM analysis above. The psychological variable was defined by the contrast emotional > neutral prosody. The PPI was obtained by deconvolving the hemodynamic time course of the physiological variable, multiplying it with the psychological variable, and then reconvolving it with the hrf. This deconvolution-reconvolution procedure was specifically developed for measures of effective connectivity using PPI analyses in event-related designs (Gitelman et al. 2003). Significance was assessed at a voxel level of $P < 0.05$, FWE corrected for multiple comparisons across the whole brain.

DTI Analysis

Voxelwise estimates of fiber orientations and their uncertainty were calculated using Oxford Centre for Functional MRI of the Brain Diffusion Toolbox (part of FSL 4.1, <http://fsl.fmrib.ox.ac.uk/fsl/>) on the basis of a model that accounts for the possibility of crossing fibers within each voxel (Behrens et al. 2003, 2007). The 2 most probable directions within each voxel of the white matter were determined for each individual subject.

Two different seed masks were generated using activation clusters: The first included the emotion-sensitive voxels in auditory cortex that were obtained from the main fMRI experiment. The second included

the voxels in auditory cortex that showed significant voice sensitivity in the localizer experiment ($HV > AV \cap HV > ES$) but no significant emotion sensitivity (emotional $>$ neutral prosody) in the main fMRI experiment. These 2 seed masks contained only voxels within the gray matter (determined by segmentation of the high-resolution anatomical images, Ashburner and Friston 2005), which overlapped with activation clusters obtained in the fMRI group analysis, and were then transferred to individual DTI space (resampled voxel size: $2 \times 2 \times 2 \text{ mm}^3$). A small exclusion mask consisting of the temporal pole gray matter in the STG and middle temporal gyrus was used to avoid spurious fiber shortcuts from the temporal pole to the inferior frontal lobe. Otherwise, probabilistic fiber tracking was not restricted by target or waypoint masks. The results were then corrected for the size of the masks (i.e., divided by the number of seed voxels), and connectivity maps of the emotion- and voice-sensitive cortices were compared using a paired *t*-test. To ascertain that the comparison of tracking results were not influenced by the fact that the EVA was localized in the central part of the auditory cortex whereas the region with more general responses to voices (TVA) was more widespread across the temporal lobe (see Results), we performed additional fiber tracking separately for each of 3 subparts of the TVA that were situated anterior, posterior, and at the same level as the EVA. To locate fibers that were specifically connected to EVA, we statistically compared the tracking results for each of these 3 subparts of the voice area with those obtained for the emotion area using a minimum *T*-statistic (conjunction null hypothesis, Nichols et al. 2005).

Results

Location of Emotional Voice Areas

Comparing brain responses to emotional and neutral prosody ($P < 0.05$, FWE corrected) yielded stronger activation in the right (Z score = 6.34; $k = 316$ voxels; MNI coordinates: $x = 51, y = -24, z = 9$) and left ($Z = 5.93$; $k = 165$ voxels; MNI coordinates: $x = -45, y = -33, z = 9$) auditory cortices (see Fig. 1*a-c*) in 21/22 participants. Voxels with differential responses to emotional voices were partly embedded within the voice-sensitive temporal areas, which were defined at the same statistical threshold of $P < 0.05$, FWE corrected (overlap with TVA: 103 and 68 voxels for right and left EVA, respectively), although a substantial proportion extended into earlier auditory areas outside TVA. In our subsequent analyses, we therefore considered all emotion-responsive voxels as a single region (EVA; red in Fig. 1*d*), partly distinct from the TVA proper (in blue in Fig. 1*d*).

In both hemispheres, the EVA was situated mainly posterolateral to the PAC in Heschl's gyrus, extending medially to the most dorsal sectors of these early auditory areas, particularly in the right hemisphere (see white frame area in Fig. 1*d*, as well as more laterally onto the surface of the STG). The activation

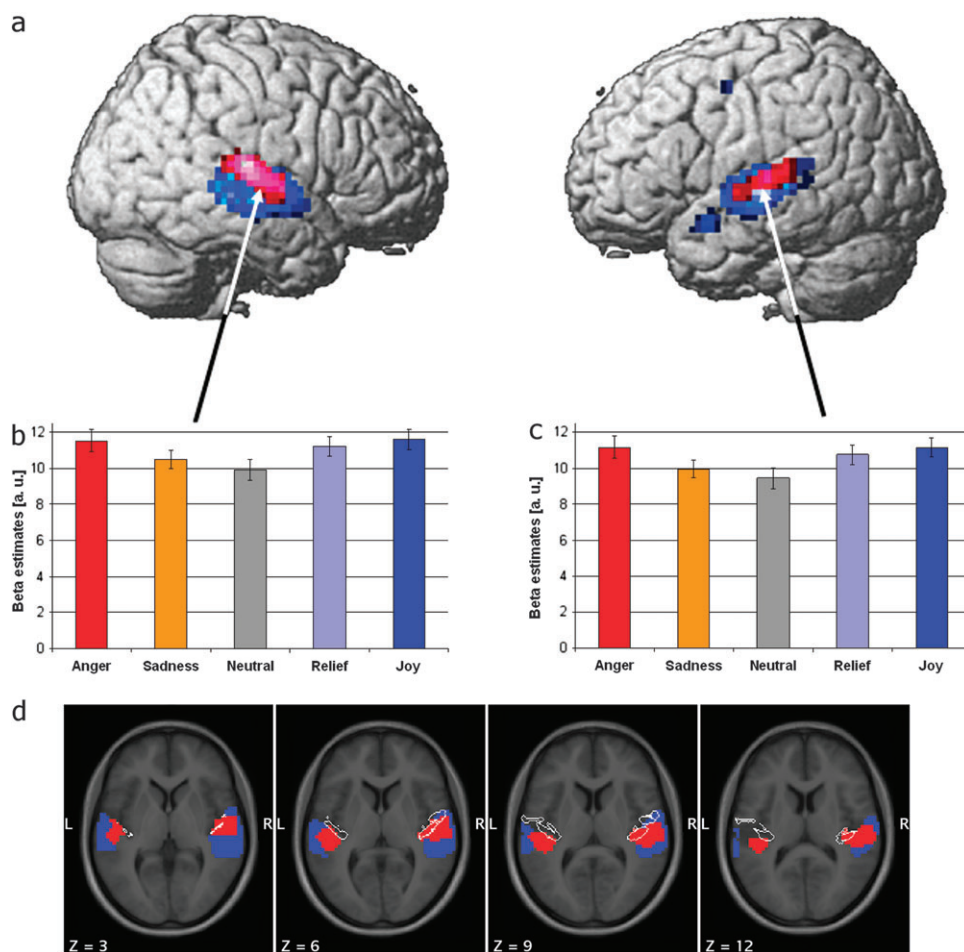


Figure 1. (a) Overlap of activation selective to voices (temporal voice area, TVA: voices $>$ animal and ES, blue) and activation selective to emotional prosody (emotional voice area, EVA: emotional $>$ neutral prosody, red) rendered on a standard brain template (group data, $P < 0.05$, FWE corrected). (b, c) Beta estimates for each of the 5 prosody categories averaged across the right (b) and left (c) EVA. (d) Position of EVA (red) relative to TVA (blue) and Heschl's gyrus (white) displayed on horizontal brain slices.

maxima were located in the middle part of the STG on both sides (see Table 1). Individual activation maps revealed a high spatial congruency of this organization for the contrast emotional versus neutral prosody across subjects. The most significant activation was situated within, or in voxels directly adjacent to, the cluster obtained in the SPM group analysis for 17/22 participants in the right hemisphere and for 19/22 participants in the left hemisphere.

Taken together, these data indicate that emotional effects in auditory cortex arose partly in the voice-selective cortex but also extended to earlier auditory stages on the right more than on the left side.

Functional Properties of Emotional Voice Areas

In both hemispheres, the EVA exhibited a robust main effect of auditory stimulation, with positive responses in all subjects and a mean SNR of 11.0 ± 0.6 and 11.5 ± 0.6 for the right and left EVA, respectively. Stronger responses to emotional than neutral prosody were found bilaterally in all but one subject, with an average SNR of 1.3 ± 0.1 (right EVA) and 1.4 ± 0.2 (left EVA). Post hoc paired *t*-tests on the beta estimates averaged across the whole EVA clusters indicated that responses to emotional categories were significantly stronger than responses to neutral stimuli (for right EVA, anger vs. neutral: $t_{21} = 7.0$, sadness vs. neutral: $t_{21} = 2.8$, relief vs. neutral: $t_{21} = 6.4$, joy vs. neutral: $t_{21} = 9.8$; and for left EVA, anger vs. neutral: $t_{21} = 9.0$, sadness vs. neutral: $t_{21} = 2.4$, relief vs. neutral: $t_{21} = 5.5$, joy vs. neutral: $t_{21} = 8.7$; all $P < 0.05$, see Fig. 1*b,c*).

A 2-factorial ANOVA on neural responses of the EVA demonstrated a significant main effect for both valence and arousal, as well as an interaction between these 2 factors for both sides (right EVA—main effect of valence: $F_{1,21} = 4.7$, $P < 0.05$; main effect of arousal: $F_{2,21} = 12.2$, $P < 0.01$; interaction valence \times arousal: $F_{1,21} = 4.4$, $P < 0.05$; left EVA—main effect of valence: $F_{1,21} = 5.6$, $P < 0.05$; main effect of arousal: $F_{1,21} = 23.4$, $P < 0.001$; interaction valence \times arousal: $F_{1,21} = 6.6$, $P < 0.05$). To test whether the observed effects of valence and the interaction between valence and arousal were due to the fact that sad prosody expressed lower arousal than relief prosody (see Supplementary Table 1), we removed the variance correlated with arousal ratings from fMRI responses and

submitted the regression residuals of this new analysis to a 2-factorial ANOVA again. Neither the left nor the right EVA now showed any significant main effect for valence or interaction between valence and arousal (all $F_{1,21} < 3.0$, all $P > 0.05$). Conversely, removing the variance correlated with valence ratings did not change significance of the main effect of arousal or the interaction of valence and arousal (right EVA—main effect of arousal: $F_{2,21} = 10.8$, $P < 0.01$, interaction valence \times arousal: $F_{1,21} = 6.5$, $P < 0.05$; left EVA—main effect of arousal: $F_{1,21} = 22.1$, $P < 0.001$, interaction valence \times arousal: $F_{1,21} = 8.6$, $P < 0.01$). These findings indicate that arousal was the main factor influencing EVA responses.

Effective Connectivity of Emotional Voice Areas

A PPI analysis performed on activity of the right and left EVA separately showed that emotion enhanced the functional coupling of these auditory areas with a widespread network of distant brain regions. Remarkably, a very similar set of regions was found in the 2 hemispheres (Fig. 2 and Table 2), including bilateral frontal and parietal areas such as the supramarginal gyrus (SMG), frontal operculum, and IFG, which all showed higher connectivity with both the right and the left EVA during perception of emotional prosody. Vocal emotions also increased effective connectivity of both EVAs with bilateral posterior thalamus, bilateral visual areas, left middle frontal gyrus, right putamen, and right cerebellum (see Table 2 and Fig. 2*a-f*). In addition, for the right EVA, we also found an increased effective connectivity with the left cerebellum and left IFG, whereas the left EVA exhibited an enhanced coupling with the right posterior middle temporal gyrus and right medial prefrontal cortex.

Taken together, these PPI results reveal that processing of emotional (compared with neutral) voice prosody enhanced the synchronization of neural activity in EVA with a distributed and bilateral network of cortical and subcortical regions, including the IFG and SMG on both sides.

Structural Connectivity of Emotional Voice Areas

Fiber connections originating in emotion-sensitive auditory areas are presented in Fig. 3 (yellow/red areas in Fig. 3*a-f,g-l* for the left and right EVA, respectively). Consistent connections across subjects (voxel-by-voxel overlap $\geq 50\%$) were found with the ipsilateral IFG via the superior longitudinal fasciculus (SLF) and the external capsule (EC, see Fig. 3*a-d,g-j*) in both hemispheres, as well as with the ipsilateral medial geniculate body (MGB) via the acoustic radiation (AR, see Fig. 3*a,g*). Additional connections with the ipsilateral occipital cortex (Fig. 3*a,g*) and bilateral inferior parietal lobe (IPL, Fig. 3*c-e,i-k*) were also observed. Connections of right and left EVA toward the contralateral IPL crossed the corpus callosum within its posterior part (see Fig. 3*f,l*).

The projections of the EVA were further assessed by a voxel-by-voxel statistical comparison of fiber connections originating in the EVA proper against those originating in the surrounding TVA (light blue/blue areas in Fig. 3*a-f,g-l* for the left and right EVA, respectively). This analysis revealed that the connections with ipsilateral IFG via the EC (but not SLF), as well as those to ipsilateral MGB via the AR, and the projections to ipsilateral IPL were significantly stronger when tested from the EVA than from the TVA, in both the right and the left hemispheres ($P < 0.05$, corrected at the level of spatial extent). All these

Table 1

Location of activations (emotional > neutral prosody) used to define the right and left emotional voice area (EVA)

	MNI coordinates	Z score	Cluster size
Right EVA	$x = 51 \ y = -24 \ z = 9$	6.34	316
Composition of right EVA	% Cluster	% Region	Number of voxels
Right STG	47.1	31.5	149
Right Heschl's gyrus	4.75	56.8	15
Right Rolandic operculum	2.53	3.70	8
White matter	45.3		
	MNI coordinates	Z score	Cluster size
Left EVA	$x = -45 \ y = -33 \ z = 9$	5.93	165
Composition of left EVA	% Cluster	% Region	Number of voxels
Left STG	31.5	14.4	52
Left middle temporal gyrus	8.48	1.28	14
Left Rolandic operculum	1.21	1.43	2
Left Heschl's gyrus	1.21	9.03	2
White matter	57.5		

Note: Percentage of cluster denotes the contribution of white matter and different gray matter structures to the activation clusters (emotional > neutral prosody). Percentage of regions denotes the fraction of different gray matter structures as defined by automatic anatomic labeling covered by the activation clusters (emotional > neutral prosody).

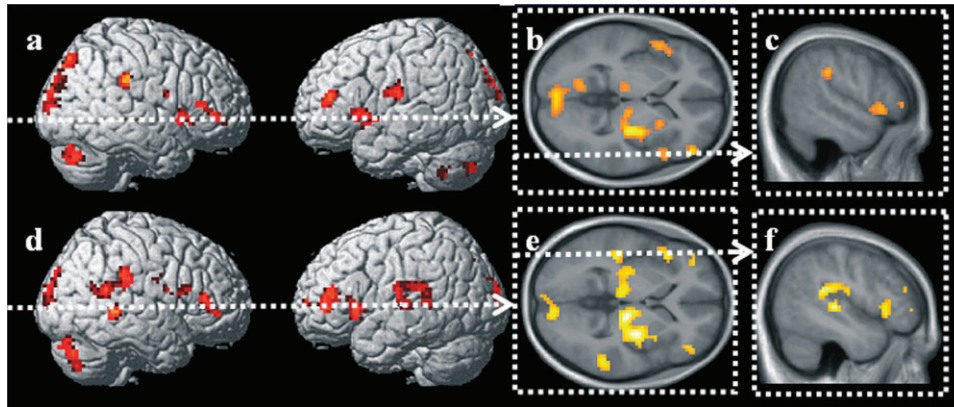


Figure 2. Brain regions showing an increase of functional connectivity ($P < 0.05$, FWE corrected) with the right EVA (a–c) and left EVA (d–f) rendered on a standard brain template (a, d) and on transversal (b, d, $z = 0$) and sagittal slices (c, $x = 45$; f, $x = -54$).

Table 2

Brain regions showing increased effective connectivity with right and left EVA during perception of emotional stimuli (PPI: emotional > neutral)

	MNI (x)	MNI (y)	MNI (z)	Z score
Brain areas modulated from right EVA				
Left posterior thalamus	−6	−18	6	5.52
Right posterior thalamus	6	−15	6	5.34
Left visual cortex	−3	−93	24	5.97
Right visual cortex	9	−93	27	5.67
Left IFG	−51	12	0	4.92
Right IFG	51	42	0	5.20
Left SMG	−54	−12	21	5.24
Right SMG	63	−33	30	5.02
Left cerebellum	−21	−60	−42	5.45
Right cerebellum	42	−72	−33	5.12
Right putamen	27	3	18	6.28
Left middle frontal gyrus	−36	45	15	5.09
Brain areas modulated from left EVA				
Left posterior thalamus	−9	−18	6	5.85
Right posterior thalamus	15	−18	0	5.77
Left visual cortex	−9	−93	12	5.44
Right visual cortex	15	−90	6	5.38
Left IFG	−45	21	0	5.02
Right cerebellum	39	−75	−33	5.14
Right putamen	30	−9	0	5.85
Right SMG	45	−48	18	5.44
Left middle frontal gyrus	−33	39	9	5.17
Right posterior middle temporal gyrus	57	−42	0	5.08
Right medial prefrontal cortex	0	45	21	5.00

connections of EVA were also significantly stronger when separately compared with those originating in different TVA subparts anterior, lateral, or posterior to the EVA (see Supplementary Fig. 1). Taken together, these data indicate that connections with both the IFG and the IPL predominated with auditory regions exhibiting significant emotion effects rather than with more widespread auditory areas showing voice-selective responses but no emotion effects.

Discussion

We provide novel findings on the exact location, functional properties, and connectivity of EVA within the auditory cortex, which show preferential increases to affective prosody information and partly overlap with the TVA. We employed both structural and functional neuroimaging methods to characterize the connectivity of this cortical region. Structural connectivity approaches are well suited to reveal the anatomical

connection profile of brain regions but cannot determine which of these connections are active during processing of certain stimulus types or tasks. Effective connectivity analyses, on the other hand, provide information on networks showing an increased coupling of functional activity but cannot determine whether the enhancement of connectivity occurs directly or via one or several other mediating neural nodes (Friston et al. 1997). Here, by combining both structural fiber tracking and effective connectivity analysis, we were able not only to uncover the direct structural fiber connections of the EVAs but also pinpoint their functional recruitment during the perception of emotional prosody.

Anatomical Location of Emotional Voice Areas

It has been consistently replicated across different studies and laboratories that responses within the auditory cortex situated in the middle part of STG are modulated by the emotion expressed in the voice of humans (Grandjean et al. 2005; Ethofer, Anders, Wiethoff, et al. 2006; Beaucousin et al. 2007; Ethofer et al. 2007; Dietrich et al. 2008; Wiethoff et al. 2008; Ethofer, Kreifelts, et al. 2009; Ethofer, Van De Ville, et al. 2009) or animals (Belin et al. 2008). However, the exact location of emotion-sensitive areas in relation to anatomical landmarks and other auditory areas has not been precisely defined yet. Here, we demonstrate that the majority of the emotion-sensitive cortex is located posterolateral to the PAC and situated within Brodmann's area (BA) 22, which covers the posterior two-thirds of the free surface of the STG (Brodmann 1909). In the right hemisphere, the emotion-sensitive areas additionally comprised a large part of the PAC itself, suggesting a lateralized involvement of early auditory processing stages and thus providing a possible explanation for the typical left-ear superiority observed for emotionally relevant information in dichotic listening tasks (Erhan et al. 1998). These findings also accord with electrophysiological data demonstrating a modulation of early event-related potentials within the first 200 ms, which occurs more consistently in the right than in the left hemisphere (Paulmann and Kotz 2008). Enhanced responses of early sensory cortices to emotionally relevant information are a well-known phenomenon in the visual modality, as it has been shown that emotional cues in scenes (Lang et al. 1998) and faces (Pourtois et al. 2004; Vuilleumier and Pourtois 2007) modulate responses in the primary visual cortex (see also Vuilleumier 2005). Thus, our fMRI findings provide new evidence for the

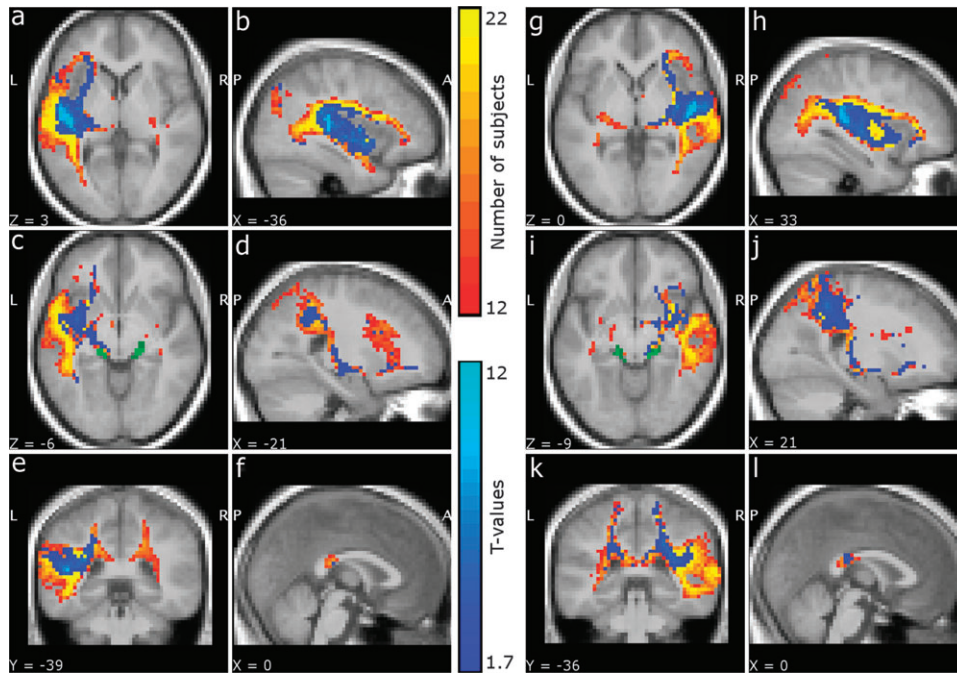


Figure 3. Fiber connections from the right (a–f) and left (g–l) EVA as determined by either the degree of overlap ($\geq 50\%$) across subjects (red/yellow) or a direct pairwise statistical comparison ($P < 0.05$) of tracking probabilities from EVA versus TVA (EVA > TVA, blue/light blue). The MGBs in the posterior thalamus as determined by probabilistic cytoarchitectonic maps are marked in green.

suggestion that increased activation within primary areas might contribute to efficient processing of behaviorally relevant information across different sensory modalities.

The EVAs were functionally defined by contrasting activity to emotional and neutral prosody. Note that this approach allowed us to assess sensitivity to emotional information but does not imply that this area exclusively subserves the representation of vocal emotions. Indeed, posterior lateral regions of the auditory cortex are also implicated in other auditory functions including speech perception, particularly in the left hemisphere (for review, see Price et al. 2009). Posterior auditory areas also participate in the representation of auditory space and motion (for review, see Recanzone and Sutter 2008). Thus, it is likely that the EVA regroups primary and higher order auditory regions that operate as a computational hub (Griffiths and Warren 2002) underlying several discriminatory functions among which processing of prosodic emotions is just one. Further research investigating different auditory functions in the same group of participants is needed to examine to what extent these processes share overlapping representations within posterior auditory areas or can instead be spatially segregated using high-resolution fMRI.

Functional Response Profile of Emotional Voice Areas

In both hemispheres, the activation of EVA was significantly stronger for all emotional categories (i.e., anger, sadness, joy, and relief) than neutral prosody. This confirms previous observations that this area is sensitive to a broad range of emotional information (Ethofer et al. 2007; Wiethoff et al. 2008), an effect that may occur irrespective of spatial attention (Grandjean et al. 2005) or task instructions (Ethofer, Anders, Wiethoff, et al. 2006). Again, these effects are reminiscent of those found in the visual domain, where various facial expressions are known to modulate the fusiform face area (FFA; see Vuilleumier et al. 2002;

Surguladze et al. 2003; Sato et al. 2004). This similarity in neural response profiles may suggest equivalent functional roles for these 2 areas in the analysis of facial and vocal affect, respectively (Campanella and Belin 2007).

Our study sought to disentangle effects due to the emotional arousal and valence of prosody on EVA using a 2×2 factorial design. As expected, a conventional ANOVA revealed a strong main effect of arousal. In addition, we also found a significant main effect of valence and an interaction between valence and arousal, suggesting at first glance that this area may respond stronger to positive than to negative emotions and that arousal-related enhancement is stronger for negative than positive emotions. Further inspection of activation to the different emotional categories revealed, however, that these effects can be explained by the different levels of arousal elicited by positive and negative low-arousing emotions (i.e., sadness and relief). When correcting for arousal-related activity by regression analysis, both the main effect of valence as well as the interaction between valence and arousal were completely abolished, indicating that arousal was the most important factor modulating EVA. Likewise, in the visual modality, responses of the FFA increase linearly with the intensity of computer-morphed facial expressions of fear, disgust, happiness, and sadness (Surguladze et al. 2003), although the strongest enhancement is often observed for fearful faces—a finding that may reflect greater sensitivity to signals of imminent danger or greater arousing value of fear compared with other emotion categories. However, direct comparisons between sensory modalities might be hampered by many differences in stimulus properties across studies, and future studies with high-resolution techniques and multivoxel analysis might be valuable to investigate more subtle differences in the cortical representation of different emotions expressed by voices (Ethofer, Van De Ville, et al. 2009) or faces (Peelen et al. 2010).

Modulation of Connectivity of Emotional Voice Areas

We found that emotion expressed by prosody did not only activate the EVA but also modulated its connectivity with a widespread and bilateral network, including downstream areas in the auditory processing pathway, such as bilateral posterior thalamus, but also occipital, parietal, motor, and—most critically—inferior frontal areas. All these regions may reflect distinct facets of the impact of salient emotional prosody on cognitive processes. The interplay between auditory and visual regions during the perception of emotional prosody might constitute the neural substrate of enhanced cross-modal representations of behaviorally relevant auditory stimuli (Sander et al. 2005; Kayser et al. 2010). Increased connectivity between the EVA and the frontoparietal opercular areas could reflect an engagement of the audio-motor loop to evoke representations that covertly simulate the perceived vocal emotions (Vigneau et al. 2006; Warren et al. 2006), whereas the enhanced coupling with the SMG might have mediated a stronger activation of the phonological working memory system (Vigneau et al. 2006; Buchsbaum and D'Esposito 2008) during perception of emotionally relevant information. Modulation of connectivity with core components of the motor system (cerebellum and putamen) converges with electrophysiological findings (Paulmann et al. 2008) and clinical observations, indicating that emotional prosody is impaired in Parkinson's disease (Pell and Leonard 2003) or after cerebrovascular lesions in the basal ganglia (Cancelliere and Kertesz 1990; Starkstein et al. 1994).

More critically, in agreement with our hypothesis, we found that vocal emotions produced a distinctive pattern of enhanced connectivity with inferior frontal regions that were also found to activate during prosody recognition in previous work (Ethofer, Kreifelts, et al. 2009). Very similar effects were observed in both hemispheres. Importantly, the current study indicates that the same areas in IFG showed direct fiber connections with the ipsilateral EVA, as demonstrated by our DTI fiber tracking results (see Fig. 3). Thus, our findings provide novel and converging evidence for both structural and functional interactions between auditory and inferior frontal areas that are typically associated with the “how” auditory pathway (Belin and Zatorre 2000).

Structural Connection Profile of the Emotional Voice Areas

To our knowledge, our study is the first investigating structural fiber connections within the network underlying emotional voice processing. Probabilistic fiber tracking revealed that both the right and the left EVA were directly connected with the ipsilateral MGB, ipsilateral IFG, and bilateral IPL. To further determine the specificity of these connections, we statistically compared the structural connection profile of the EVA with those of adjacent cortex (in TVA) that was more generally sensitive to voices but did not show any significant enhancement to emotional prosody. These different analyses converged to show a strong selectivity of these connections in both hemispheres.

Direct fiber bundles connected the EVA and the MGB via the AR as verified by comparison with probabilistic maps for these brain structures (Burgel et al. 2006). Our finding that these connections were significantly stronger for EVA than surrounding TVA accords with the fact that EVAs were located in the central section of the auditory cortex and also comprised

parts of the PAC. The MGB represents the dominant source of auditory afferents to PAC (Burton and Jones 1976), although several other posterior thalamic nuclei also provide inputs to higher order posterior auditory areas in nonhuman primates (Hackett et al. 2007).

In agreement with our hypothesis, strong connections were found between the EVA and the inferior frontal cortex, running through the EC. These connections were also significantly stronger for seeds originating in EVA than surrounding TVA and terminated mostly in the cortex of BA 44–46, which has previously been found to activate during working memory for emotional prosody (Mitchell 2007) and explicit judgments of affective information expressed in the voice (Wildgruber et al. 2005; Ethofer, Anders, Erb, et al. 2006). The finding of direct structural connections between these areas accords with data obtained from tracer studies in rhesus monkeys (Seltzer and Pandya 1989; Padberg et al. 2003) and lends new support to the hypothesis of a how pathway for voice processing in the human brain (Belin and Zatorre 2000).

The third, and among the strongest and most consistent, fiber bundle originating in EVA terminated in bilateral IPL. This result agrees with tracing studies in the macaque monkey demonstrating strong connections between posterior auditory areas and IPL (Lewis and Van Essen 2000; Rozzi et al. 2006; Smiley et al. 2007). However, it is important to note that we did not observe any modulation of the IPL during the perception of vocal emotions, unlike the PPI results for IFG. Therefore, it seems that this pathway was not actively engaged during identification of emotional information in the voice. Results obtained in a dichotic listening paradigm using emotional utterances, however, suggest that the IPL might be involved in directing spatial auditory attention to emotional voices (Sander et al. 2005). This interpretation is also consistent with single-cell recordings demonstrating auditory responses within the cortex of the IPL in macaque monkeys (Mazzoni et al. 1996; Cohen et al. 2004; Gifford and Cohen 2004), as well as human fMRI data during auditory spatial tasks (Griffiths et al. 1998; Zatorre et al. 2002).

Finally, fibers originating in EVA also included a posterior bundle projecting toward the occipital cortex. However, these fibers were equally found for the surrounding TVA and thus not specific for the EVA. These findings might reflect the observation made in anatomical studies of nonhuman primates that both PAC and higher order auditory cortex are reciprocally connected with early visual areas (Falchier et al. 2002; Rockland and Ojima 2003) and thus represent a possible neural substrate for cross-modal integration in early auditory cortices, as evidenced by electrophysiological studies (Ghazanfar et al. 2005).

Taken together, our DTI results highlight several important direct pathways through which emotion processing in auditory cortex may influence cognition and behavior and converge with our effective connectivity analysis to demonstrate how some of these pathways with prefrontal areas are differentially recruited by the current task demands.

Methodological Considerations

Combining data obtained across different imaging modalities can help interpret results from each modality and thus greatly advance our understanding of the functional brain architecture (for review, see Bandettini 2009). However, it is important to keep several methodological issues in mind when interpreting fMRI-guided fiber tracking results based on DTI data.

In our study, seed areas for probabilistic fiber tracking were defined on the basis of fMRI activation maps using a conservative threshold that controls for false positives for each and every included voxel (i.e., FWE correction at the voxel level). While this approach guarantees that the whole seed area shows significant fMRI activation for the effect of interest (i.e., stronger responses to emotional than neutral prosody), it is possible that the true extent of emotional effects in auditory cortex is underestimated. However, this is a general problem in functional imaging as it is impossible to determine the exact spatial extent and borders of functional areas responding to a certain type of stimulus based on statistical parametric maps.

Increased activity in EVA in response to vocal emotions was a very consistent phenomenon across subjects (21 out of 22 participants showed stronger responses to emotional than neutral prosody within both the right and the left EVA), with a high spatial congruency across subjects (at least 75% of them showed an activation peak within or voxels directly adjacent to the cluster defined by the random-effect group analysis). However, peaks in a statistical parametric map may not necessarily reflect the true activation maximum for an individual subject given that the difference in activation amplitude between conditions (emotional and neutral prosody) was only slightly larger than the average noise level (SNR of 1.3–1.4). Therefore, here we preferred a definition of seed areas based on group rather than individual activation data, since it would not have been possible to select a constant statistical threshold to identify the EVA for each and every subject and at the same time reliably control for false positives.

Conclusions

By combining structural and functional neuroimaging approaches, our study yields novel insights on neural networks engaged by the perception of vocal emotions. We demonstrate that emotion-sensitive areas in auditory cortex are situated posterolateral to the PAC but also partially include primary auditory areas. Neural activity in the EVA is mainly driven by the arousal expressed by vocal emotions, with less or no influence of valence. These findings suggest a key role for this area in detection of acoustic information with high behavioral relevance irrespective of emotion category.

Both right and left EVAs were found to be directly connected with the MGB, presumably reflecting the main input source of early auditory areas. In both hemispheres, EVAs were also strongly connected with the ipsilateral IFG and bilateral IPL, consistent with an important role of these areas in higher level processing of the emotional nature and spatial position of auditory information, respectively. These connections might constitute the anatomical substrates of the “where” and how processing streams activated by voices and be differentially modulated depending on stimulus characteristics and task demands.

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Supplementary Material

Supplementary material can be found at <http://www.cercor.oxfordjournals.org/>

Notes

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