Words in melody: an $H_2^{15}O$ PET study of brain activation during singing and speaking

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We used $H_2^{15}O$ PET to characterize the interaction of words and melody by comparing brain activity measured while subjects spoke or sang the words to a familiar song. Relative increases in activity during speaking *vs* singing were observed in the left hemisphere, in classical perisylvian language areas including the posterior superior temporal gyrus, supramarginal gyrus, and frontal operculum, as well as in Rolandic cortices and putamen. Relative increases in activity during singing were observed in the right hemisphere: these were maximal in the right anterior superior temporal gyrus and contiguous portions of the insula; relative increases associated with singing were also detected in the right anterior middle temporal gyrus and superior temporal sulcus, medial and dorsolateral prefrontal cortices, mesial temporal cortices and cerebellum, as well as in Rolandic cortices and nucleus accumbens. These results indicate that the production of words in song is associated with activation of regions within right hemisphere areas that are not mirror-image homologues of left hemisphere perisylvian language areas, and suggest that multiple neural networks may be involved in different aspects of singing. Right hemisphere mechanisms may support the fluency-evoking effects of singing in neurological disorders such as stuttering or aphasia. *NeuroReport* 14:749–754 © 2003 Lippincott Williams & Wilkins.

Key words: Brain; Music; Lateralization; Right hemisphere; Singing

INTRODUCTION

Clinical investigations in the nineteenth century led to the concept of lateralization of cerebral function, the superior capacity of each side of the brain to perform distinct classes of skilled behaviors [1]. Evaluation of patients with focal brain lesions led to the notion that regions supporting core language functions (lexical semantics, syntax, and phonology) are located in the left hemisphere. It was subsequently shown that the right hemisphere may play a greater role in processing the prosodic, rhythmic, intonational, or melodic characteristics of speech [2] and song [3].

Indeed, a number of neuropsychological and neuroimaging studies support the notion that the right hemisphere may play a dominant role in musical processing. Patients with right hemisphere lesions are likely to be impaired in musical perception and imagery [4–9]. In contrast, aphasic patients with left hemisphere lesions often show extraordinarily well-preserved musical and vocal capabilities [10]. Neuroimaging studies of the intact human brain have also generally supported this idea of the predominant role of the right hemisphere in music [11–13]. However, the majority of these studies have evaluated musical perception; neuroimaging studies of musical production have been limited [14], and only a few have examined singing [15–17].

A more complete understanding of the brain mechanisms underlying singing, particularly the singing of words, may help clarify mechanisms that play a role in the pathophysiology and treatment of disorders such as developmental stuttering and certain types of aphasia, in which singing may enable fluent articulation. The means by which this interaction of word and melody generates a beneficial effect is unclear, although it has been hypothesized that right hemisphere mechanisms may play a compensatory role, making it possible to articulate lexical items in these conditions [18]. Such hypotheses are unproven, and the issue remains controversial.

The generation of words in song, i.e. the interaction of words and melody, has not yet been evaluated with neuroimaging methods. Wildgruber *et al.* [17] examined covert rather than overt singing; Perry *et al.* [16] evaluated overt singing of a single pitch rather than a melody; and Riecker *et al.* [15] studied the production of melody, but in the absence of words. In order to complement and extend these studies, we used $H_2^{15}O$ PET to directly compare patterns of cerebral activity in subjects speaking and singing the words to a familiar song.

Use of the same lexical material in each case controls for linguistic features such as syntax or semantics, assuring that generation of melody, and any potential interaction between words and melody in singing, remains the principal variable. We used PET in order to allow continuous vocal production without confounding artifacts associated with changes in vocal tract airway volume and resultant susceptibility effects that can complicate the interpretation of blood oxygenation level dependent contrast (BOLD) fMRI studies. Subjects were allowed to sing and speak using natural rate, rhythm, and intonation, and speech and singing rates were measured and used as covariates in these analyses. The direct contrast between singing and speaking was used in order to highlight relative differences in activity (rather than shared features) in order to test the following hypotheses: (1) that regions in the left hemisphere will be more active during speaking, and regions in the right hemisphere more active during singing, (2) that the latter will not simply represent homologous portions of the right perisylvian cortex, but include non-homologous regions specifically associated with musical production; (3) that these will include, in addition to more anterior portions of the auditory association cortices, additional cortical (prefrontal, parietal, insular) and subcortical regions (basal ganglia, cerebellum) that may contribute to the production of words in song; and finally (4) since our singing task required subjects to generate complex over-learned melodies, we predicted that additional areas would be recruited, particularly in the superior temporal gyrus and medial prefrontal cortex, regions that appear to be involved in auditory long-term memory.

MATERIALS AND METHODS

Subjects: Subjects included eight females 36 ± 10 (mean ± s.d.) years of age, range 24–50, and 12 males 33 ± 8, range 23–47. All subjects were right handed and free of medical or psychiatric illness on the basis of history and physical examination, baseline laboratory evaluation, and structural MRI. None had received music theory or formal voice training. Written informed consent was obtained from all subjects. The study was approved by the NIDCD/NINDS Institutional Review Board.

Speech and singing tasks: Subjects were scanned while (1) reciting and (2) singing words to a familiar song. The sequence of scans was randomized across subjects, all of whom underwent practice prior to the PET study. Subjects selected an overlearned song (e.g. happy birthday), and sang it at a comfortable rate and volume. When the same song was spoken, subjects were instructed to speak at a natural rate, keeping rhythm and intonation approximately the same as during conversational speech. Scanning sessions were recorded and transcribed, a computer-generated signal identifying the start of the scan. One-minute samples, from 15 s prior to 45 s after the start of scan, were used to calculate speech and singing rates (syllables/s).

Scanning methods: PET scans were performed on a Scanditronix PC2048-15B tomograph (Uppsala, Sweden) with axial and in-plane resolution of 6.5 mm. Subjects' eyes were patched, and head motion was restricted with a thermoplastic mask that permitted free movement of the oral articulators. For each scan, 30 mCi of $H_2{}^{15}O$ were injected intravenously. Speech and singing tasks were initiated 30 s prior to injection of the radiotracer and were continued throughout the scanning period. Scans commenced automatically when the count rate in the brain reached a threshold value (~20 s after injection) and continued for 4 min. Studies were separated by 10 min intervals. Emission data were corrected for attenuation by means of a transmission scan.

PET data analysis: PET scans were registered and stereotaxically normalized using Statistical Parametric Mapping software (Wellcome Department of Cognitive Neurology, London, UK). Images were smoothed with a Gaussian filter (15 × 15 × 9 mm in x, y and z axes) to accommodate intersubject differences in anatomy, and spatially normalized to produce images in a common stereotaxic (Talairach) space. Differences in global activity were controlled for by proportional normalization.

Using SPM, we contrasted singing and speaking conditions using a multiple subjects with conditions and covariates design with rate entered as a confounding covariate. Tests of significance based on the size of the activated region [19] were performed; local maxima from the task contrast were considered most reliable when these were included with a cluster of significant spatial extent (instances in which differences did not satisfy this criterion are so indicated in Table 1).

RESULTS

Speech and singing rates differed significantly (speaking, 3.05 ± 0.55 syllables/s; singing, 2.61 ± 0.81 syllables/s, $p = 0.01$, paired t-test). In order to eliminate the contribution of rate to apparent task-related differences, it was included in the SPM contrasts as a confounding covariate.

These contrasts demonstrated that, in general, regions within the left hemisphere were more active for speaking and regions in the right were more active for singing. This hemispheric dissociation was observed both in homologous and non-homologous regions (Fig. 1; Table 1).

In the prefrontal cortex, the left operculum was more active for speaking. The left and right medial prefrontal cortices and contiguous right superior dorsolateral prefrontal cortex were more active for singing.

In Rolandic cortices, the secondary somatosensory area (SII) was more active on the left for speaking, on the right for singing. Other portions of the left Rolandic cortex, including both pre- and postcentral gyri, were also more active for speaking.

In the temporal lobe, posterior portions of the left superior temporal gyrus (STG), in the vicinity of the planum temporale were more active for speaking. For singing, activity was greater in anterior regions on the right, prominent in the anterior middle temporal gyrus (MTG) and superior temporal sulcus (STS) and maximal in the anterior STG and contiguous insula.

Speaking was also associated with relative increases in activity in the left supramarginal gyrus, and singing with increases in the right fusiform and parahippocampal gyri, caudal orbital and posterior cingulate cortices, midline anterior cerebellum, and bilateral increases in the lingual gyri and cerebellar vermis.

In the basal ganglia, relative increases in activity in the left putamen (extending to the anterior insula) and the right nucleus accumbens were seen during speaking and singing respectively.

Analysis of spatial extent for speaking−singing revealed a single cluster of significant spatial extent: cluster 1: 1861 voxels; $p\,(\text{nmax} = \text{k}) = 0.00002$; (left perisylvian, inferior parietal, rolandic cortices). Analysis of spatial extent for singing−speaking revealed three significant clusters: cluster

Table 1. Regions in which normalized rCBF rates are greater during speaking *vs* singing or during singing *vs* speaking are shown, along with Z scores representing local maxzima, and Talairach coordinates.

Region	Brodmann area	Speaking								Singing							
		Left hemisphere				Right hemisphere				Left hemisphere				Right hemisphere			
		Z score	x	y	z	Z score	x	y	z	Z score	x	y	z	Z score	x	y	z
Subcortical																	
Cerebellum																	
Cerebellar vermis		–	–	–	–	–	–	–	–	3.03	−10	−72	-8^{b}	3.12	2	−52	-8^{b}
Anterior cerebellum		–	–	–	–	–	–	–	–	–	–	–	–	3.09	16	−36	-20^{b}
Basal ganglia																	
Putamen/insula		2.99	−28	16	4^{a}	–	–	–	–	–	–	–	–	–	–	–	–
Nucleus accumbens		–	–	–	–					–	–	–	–	3.52	8	16	−8
Prefrontal																	
Middle frontal operculum	45	3.19	−44	24	8^{a}	–	–	–	–	–	–	–	–	–	–	–	–
Superior frontal operculum	44/6	3.40	−50	6	24^{a}	–	–	–	–	–	–	–	–	–	–	–	–
Dorsolateral prefrontal cortex	8	–	–	–	–	–	–	–	–	–	–	–	–	3.37	26	36	40^{d}
Medial prefrontal cortex	9/10	–	–	–	–	–	–	–	–	3.65	−6	58	20^{d}	3.39	18	52	32^{d}
Perirolandic																	
SII	43	3.16	−52	−10	20^{a}	–	–	–	–	–	–	–	–	3.68	46	−18	16^{c}
Postcentral gyrus	3,1,2	3.68	−48	−22	32^{a}	–	–	–	–	–	–	–	–	–	–	–	–
Precentral gyrus	6	3.03	−48	−2	24^{a}	–	–	–	–	–	–	–	–	–	–	–	–
Temporal																	
Anterior STG/insula	22	–	–	–	–	–	–	–	–	–	–	–	–	4.20	48	−6	0^{c}
Anterior MTG/STS	21	–	–	–	–	–	–	–	–	–	–	–	–	3.34	58	−8	-4^{c}
Posterior STG/PT	22	3.13	−54	−50	20^{a}	–	–	–	–	–	–	–	–	–	–	–	
Basal temporal, occipital																	
Fusiform/parahippocampal gyrus	37	–	–	–	–	–	–	–	–	–	–	–	–	3.03	20	−52	-4^{b}
Cuneus/lingual gyrus	18	–	–	–	–					2.99	−2	−84	4^{b}	3.09	2	−88	8^{b}
Parietal																	
Supramarginal gyrus		3.34	−60	−38	24^{a}	–	–	–	–	–	–	–	–	–	–	–	–
Proisocortical																	
Posterior cingulate	23/31	–	–	–	–	–	–	–	–	–	–	–	–	3.17	14	−52	16^{b}
Caudal orbital cortex	25/32	–	–	–	–	–	–	–	–	–	–	–	–	3.09	2	16	−8

Superscripts indicate clusters of significant spatial extent (see text) in which local maxima are included.
^{a}Cluster 1, 1861 voxels; $p(\text{nmax} \geq \text{k}) = 0.0002$;
^{b}Cluster 2, 1854 voxels; $p(\text{nmax} \geq \text{k}) = 0.0002$.
^{c}Cluster 3, 661 voxels; $p(\text{nmax} \geq \text{k}) = 0.04$;
^{d}Cluster 3, 817 voxels; $p(\text{nmax} \geq \text{k}) = 0.01$.

2: 1854 voxels; $p(\text{nmax} = \text{k}) = 0.00002$; (mesial, basal temporal cortex, midline cerebellum); cluster 3: 661 voxels; $p(\text{nmax} = \text{k}) = 0.04$; (right anterior temporal, Rolandic cortices); cluster 4: 817 voxels; $p(\text{nmax} = \text{k}) = 0.01$; (right dorsolateral prefrontal cortex, medial prefrontal cortices).

DISCUSSION

Our results demonstrate clear differences in the contributions of the left and right hemispheres to sung and spoken language: the left hemisphere is relatively more active for speech, the right more active for singing. Beyond confirming hemispheric lateralization, we observed conspicuous differences in the functional nature of regions associated with either condition.

Clinical correlations: Previous neuropsychological studies have demonstrated that areas in the right hemisphere are involved in the perception, imagery, and memory of pitch, timbre, and melody [5–9], and neuroimaging studies also emphasize the importance of frontal and temporal areas in the right hemisphere during musical perception [11–13]. Our results are in agreement with these studies, while indicating greater activation in areas related to motor function and vocal self-monitoring during the production of song. Clinical evidence also supports the notion that the right hemisphere plays an important role in musical production, since singing is impaired following lesions, anesthesia, or transcranial stimulation of the right hemisphere [3,18,20,21].

Previous neuroimaging studies of singing: The design of the present study differs from earlier neuroimaging studies that evaluated overt singing [15,16]; but our design also complements these studies, and our findings both confirm and extend their results. Perry *et al.* [16] evaluated singing of a sustained pitch, comparing this to tone perception. The use of a perceptual baseline in this contrast effectively isolates the motor features of singing. In the present study, the direct comparison of speech and song production selectively isolates the generation (and self monitoring) of melody, since essential motor features such as vocalization and articulation are common to both conditions.

Riecker *et al.* [15] studied overt production of melody, but in the absence of words, comparing recitation of months of the year to production of a non-lyrical tune. In our study we

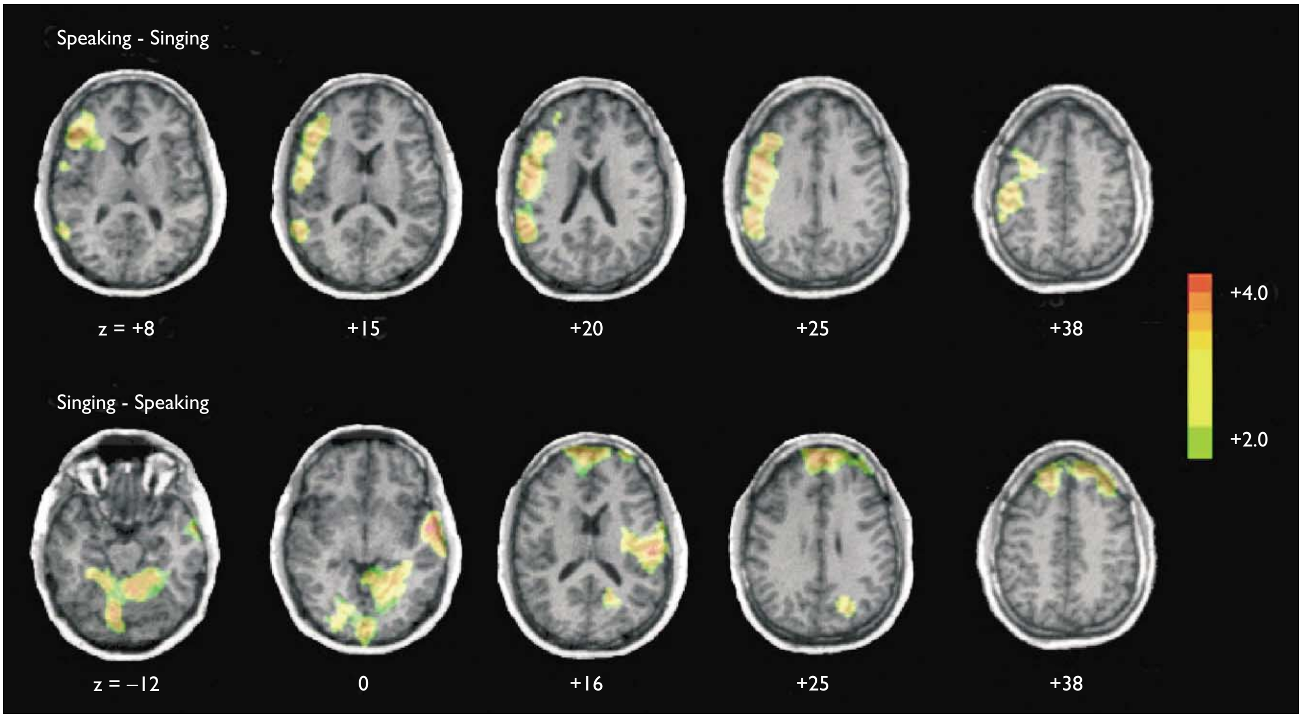

Fig. 1. Brain maps depicting differences in regional cerebral blood flow (rCBF) during speaking and singing the words to a familiar song. The top row illustrates significant elevations in rCBF during speaking (*vs* singing); the bottom row, elevations during singing (*vs* speaking). Statistical parametric maps resulting from these analyses are displayed on a standardized MRI scan, which was transformed linearly into the same stereotaxic (Talairach) space as the SPM **{z}** data. Scans are displayed using neurological convention (left hemisphere is represented on the left). Planes of section relative to the anterior commissural-posterior commissural line are indicated for each contrast. Values are Z-scores representing the significance level of voxel-wise changes in normalized rCBF for each contrast. The range of scores is coded in the accompanying color tables. Significant differences correspond to local maxima summarized in Table 1.

evaluate the production of song in words. Use of the same lexical material in both conditions insures that differences in brain activation do not reflect task-related linguistic features, but are due instead to the interaction of word and melody. As noted earlier, this may have clinical relevance for disorders in which singing words enables fluent articulation.

Hemispheric lateralization: Regions more active during speaking *vs* singing words were lateralized to the left hemisphere and include areas that are constituents of the classical perisylvian language system, i.e. left frontal operculum, posterior superior temporal gyrus and planum temporale [22,23]. Speaking was also associated with increased activity in the left supramarginal gyrus, which may constitute an auditory motor interface for spoken language production [24].

Singing, on the other hand, was associated with greater activity in a wide array of regions within the right hemisphere. Some of these represent homologues of left hemisphere areas in which activity was greater during speech. However, the majority, e.g., right prefrontal, temporal, paralimbic, and subcortical areas, do not, and may instead constitute elements of a functionally distinct system within the right hemisphere.

These patterns may be interpreted in a number of ways. The relative increases in left hemisphere perisylvian activity may not simply reflect enhanced activity in these regions during speaking of words, but may instead represent relative decreases in activity manifest when words are sung. That is, singing may involve selective activation of right hemisphere regions and concomitant suppression of activity in left hemisphere perisylvian areas that are normally more active during speech production. Conversely, activity in the right hemisphere system may be suppressed when the left hemisphere is more strongly engaged in the production of spoken language [25].

Lateralization in homologous brain regions: The homologous regions within left and right hemispheres that were more active for speaking or singing are most closely associated with sensorimotor function.

In the Rolandic cortices, maximal differences were found in the secondary somatosensory cortex (SII, BA 43) in which activity was greater in the left hemisphere for speaking, in the right for singing. The idea that lateralization for speech and singing is manifest at the level of primary sensorimotor cortices is consistent with all three of the neuroimaging studies cited above [15–17]. Task related differences were also seen in homologous portions of the insula, with the right more active for singing, the left more active for speech. Both Riecker *et al.* [15] and Perry *et al.* [16] reported differences in insular activity related to singing: Perry *et al.* reported bilateral insular activation when simple singing was compared with complex tone perception, consistent with a contrast highlighting motor activity *per se*. Our results, on the other hand, are more consistent with those of

Reicker *et al.*, who also reported left insular activation for speech and right insular activation for singing.

The insula is an important convergence zone, that appears to be involved in relatively direct processing of auditory input and serves as a parallel relay from temporal to frontal motor and other higher order association areas [26]. One such projection, to the frontal operculum, may, in the left hemisphere, subserve the role proposed for the insula in speech planning and articulation [27]. Our results suggest that the right insula might similarly participate in coordination of the oral-articulatory and laryngeal musculature for the generation of words in melody.

The possibility that singing words is associated with more direct control of oral motor processes by the right hemisphere could account for the fact that singing can enable fluent articulation in developmental stuttering (there is evidence that a shift to right insular activation may underlie fluent speech production in these individuals [28]) as well as in patients with Broca's aphasia resulting from left perisylvian lesions that include the insula.

Lateralization in non-homologous brain regions: Lateralized differences between singing and speaking were more numerous in non-homologous regions of the brain. For example, such differences were manifest in distinct areas along the anterior-posterior axis of the temporal lobe. While activity in the left posterior superior temporal regions was greater for speaking, right anterior temporal regions, including both STG, MTG, and intervening STS, were more active for singing. These observations are consistent with Parsons [14], who reported activation of right anterior temporal areas during musical (keyboard) performance. In addition, Perry *et al.* [16] reported right lateralized activity in the auditory cortices during simple singing, although the local maxima in that study were more posterior than we observed here.

The anterior portions of temporal cortex, including the STS (lateralized to the right hemisphere, in approximately the regions we report) have been shown to be activated for voice perception [29,30]. However, since voice is produced in both of our conditions, our results suggest that right anterior temporal regions may be more actively involved in self-monitoring of sung as opposed to spoken words, perhaps playing a role in the intricate feedback control of pitch and rhythmic phrasing during the production of melody.

A similar left-right dichotomy was detected in non-homologous, functionally distinct portions of the prefrontal cortex. While left opercular areas were more active for speaking, their homologues in the right hemisphere did not appear to be more active for singing (unlike the results of the Perry *et al.* study). Instead, we found that singing words was associated with increased activity in the medial prefrontal cortex (MPF) and contiguous portions of the right superior dorsolateral prefrontal cortex.

The dorsolateral prefrontal cortex plays a role in temporal sequencing of behavior [31] and, in the right hemisphere, could support a timing mechanism for production of words in song. With respect to the medial prefrontal cortex, it is interesting that the adjacent paramedian cortices, with which the MPF may share certain functional characteristics, have been implicated in control of phonation: the anterior cingulate cortex, for example, appears to regulate elicitation of species-specific calls in lower mammalian species [32] and stimulation of the contiguous pre-supplementary motor area produces vocalization in humans [33,34]. If the MPF plays a similar role in humans, relative increases in activity in this region may be related to more precise control of phonation required during singing. In this context it is interesting that the MPF receives dense auditory projections from the anterior STG [35], which we have shown is also significantly more active during singing. In addition, both regions have been implicated in auditory memory [36]. Hence another possibility is that the activation of the MPF may reflect its role in auditory memory for the familiar melodies chosen by our subjects. Interestingly, this portion of the prefrontal cortex also has the richest connections with the limbic system [37].

Involvement of the limbic system in singing is also supported by findings in the basal ganglia. In these nuclei, which have been shown to play a role in speech motor control [38], we observed relative elevations in the left hemisphere for speech, and in the right for singing. However, for speech, relative increases were found in the left dorsal putamen, which lies at the center of the motor circuit [39]. Singing was associated with increases in activity, not in the contralateral putamen, but in the right ventral striatum, particularly in the nucleus accumbens, at the center of the cortico-limbic circuitry. This area has been shown to be activated during pleasurable emotional states induced by familiar, self-selected musical passages [40] which may have been evoked by the songs chosen by our subjects.

Lateralized increases in activity selectively associated with singing: A role for limbic structures is also supported by activation of paralimbic regions, including the right parahippocampal gyrus, during singing. In the monkey, this region is known to receive the largest auditory cortical input of all the mesial temporal areas [41]. It is interesting in this context that the hippocampus and parahippocampal gyri may play a role in the detection of musical consonances and dissonances [42,43], suggesting that they may participate in self-monitoring during the production of song. Relative increases associated with singing were found in other limbic-related regions, including the right posterior cingulate cortex which, in the monkey has been shown to receive a large projection from secondary auditory association areas as well [44].

It should be noted that a subset of the mesial temporal regions in which relative increases were detected during singing, i.e. fusiform and lingual gyri, also constitute extrastriate visual association areas, consistent with extrastriate activations reported by Perry *et al.*, who suggest that cross-modal processes might be involved in the production of song.

The importance of the cerebellum in singing has been established clinically: patients with cerebellar lesions often demonstrate unsteady vocal pitch and impairments in the perception of temporal features of auditory stimuli [45]. Our results indicate that the cerebellar vermis was selectively more active during singing, an observation consistent with the findings of Perry *et al.* (but inconsistent with Riecker *et al.*, who observed reciprocal activations for singing and speaking in more lateral portions of the cerebellum).

It has been suggested [46] that the vermis provides a circuitry though which sensory systems extract temporal information, enabling precisely timed motor responses. The singing of words (rather than the generation of melody alone as in the Riecker *et al.* study), requires continuous alteration of voiced and voiceless segments and precise adjustments of stress, pitch, volume, and rhythm, features that may be mediated by, and place greater demands upon, the cerebellar circuitry.

Multiple networks for singing: The various cortical and subcortical regions that are activated during singing may in fact represent elements of large-scale, distributed networks that support the production of words in melody. Although the present analysis does not demonstrate that regions are functionally coupled in such a fashion, they can be heuristically grouped into systems that appear to play a role in: (1) fine motor control of intonation, pitch and volume during the generation of melody (medial prefrontal cortex, Rolandic cortices, anterior insula, and cerebellum) [14–17,26,32]; (2) auditory feedback for self-monitoring of pitch, volume and rhythmic phrasing (parahippocampal and anterior middle temporal cortices, anterior STG, STS, and cerebellum) [15,16]; (3) melodic memory (anterior STG, parahippocampal and other mesial temporal cortices, medial prefrontal cortex, and posterior cingulate cortex) [7,35,36,41]; (4) emotional responses generated during song production (parahippocampal gyrus, nucleus accumbens, and associated limbic regions) [40,43]. Additional studies will be necessary to test the validity and generality of the hypothesis that these regions operate as functional networks underlying the production of song.

CONCLUSION

Singing words and speaking words are associated with lateralized differences in cerebral activity: regions in the right hemisphere are more active during singing, regions in the left hemisphere more active during speaking. Relative increases are detected in homologous portions of the left and right hemispheres, in regions typically associated with sensorimotor function. These asymmetries suggest that oral-laryngeal motor activity may be more directly controlled by regions in the right hemisphere (including Rolandic and insular cortices) when words are sung. This pattern may provide insight into the nature of neurological conditions such as stuttering and aphasia in which singing can induce fluency. Singing also appears to engage right hemisphere systems that are not homologues of left hemisphere motor or language areas. For example, while speaking is associated with greater activity in left perisylvian regions, singing is associated with increased activity in right anterior temporal, prefrontal, and paralimbic cortices (regions which are also anatomically interconnected). Thus, functionally distinct networks within the right hemisphere may underlie production of words in melody. Regions such as the right anterior STS and cerebellar vermis may be involved in self-monitoring and feedback guided regulation of singing, which may require more precise adjustments of vocal pitch, volume and rhythmic phrasing. Activation of these regions may also support the fluency-inducing effects of words produced in melody.

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