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Cortical Networks Underlying Mechanisms of Time Perception

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Precise timing of sensory information from multiple sensory streams is essential for many aspects of human perception and action. Animal and human research implicates the basal ganglia and cerebellar systems in timekeeping operations, but investigations into the role of the cerebral cortex have been limited. Individuals with focal left (LHD) or right hemisphere (RHD) lesions and control subjects performed two time perception tasks (duration perception, wherein the standard tone pair interval was 300 or 600 msec) and a frequency perception task, which controlled for deficits in time-independent processes shared by both tasks. When frequency perception deficits were controlled, only patients with RHD showed time perception deficits. Time perception competency was correlated with an independent test of switching nonspatial attention in the RHD but not the LHD patients, despite attention deficits in both groups. Lesion overlays of patients with RHD and impaired timing showed that 100% of the patients with anterior damage had lesions in premotor and prefrontal cortex (Brodmann areas 6, 8, 9, and 46), and 100% with posterior damage had lesions in the inferior parietal cortex. All LHD patients with normal timing had damage in these same regions, whereas few, if any, RHD patients with normal timing had similar lesion distributions. These results implicate a right hemisphere prefrontal–inferior parietal network in timing. Time-dependent attention and working memory functions may contribute to temporal perception deficits observed after damage to this network.

Key words: timing; hemispheric asymmetry; prefrontal cortex; inferior parietal cortex; basal ganglia; cerebellum; frequency perception; attention; working memory

Current interest in neural systems underlying timing processes emanates from studies of Parkinson's disease or cerebellar damage in which motor timing abnormalities have been reported (Ivry et al., 1988; O'Boyle et al., 1996; Harrington et al., 1998), consistent with the traditional view of the basal ganglia and cerebellum as motor systems. However, patient, animal, and functional imaging studies (Ivry et al., 1988; Jueptner et al., 1995; Meck, 1996; Harrington et al., 1998) also implicate both systems in perceptual timekeeping processes. The focus on the basal ganglia and cerebellum contrasts with the limited attention paid to the role of the cerebral hemispheres, although both systems have multiple cortical connections that could play a direct role in time-dependent computations or an indirect role in nontemporal operations, such as attention and working memory, which support timing (Gibbon et al., 1984; Meck, 1984).

The present study investigated the role of the cerebral hemispheres in time perception by studying individuals with focal left (LHD) or right (RHD) hemisphere cortical lesions. A duration perception task measured perceptual timing acuity, and a frequency perception task controlled for impairments in processes common to both paradigms, to better separate deficits specific to timing. Although frontal cortex damage disrupts time discrimination in rats (Olton, 1989; Meck, 1996), the findings in humans are discrepant (Ivry and Keele, 1989; Lacruz et al., 1992; Nichelli et al., 1995) and have not delineated specific neural networks that could advance explanations of the cognitive processes underlying time perception. We hypothesized that cortical systems with reciprocal pathways to the basal ganglia [e.g., supplementary motor area (SMA), frontal eye fields (FEF), and dorsolateral prefrontal (DLPF) cortex] (Alexander et al., 1986) would be candidates for supporting time perception, given the role of the striatum in interval timing. Similarly, the cerebellar dentate nucleus, which also has been implicated in timing, projects to the DLPF and premotor cortex (Strick et al., 1993; Middleton and Strick, 1994). Some of these cortical sites may directly mediate interval timing (SMA) (Rao et al., 1997) or support timing because of their putative role in working memory (DLPF) and attention (Posner and Dehaene, 1994). The role of other cortical areas has not been studied, but the inferior parietal cortex might mediate time perception because it has strong, bilateral projections to the putamen and caudate nucleus in monkeys (Cavada and Goldman-Rakic, 1991) and is typically damaged in patients with limb apraxia who show disruptions in timing gestures (Poizner et al., 1995).

We also investigated whether there were hemispheric asymmetries in time perception. One study using positron emission tomography (PET) did not uncover a hemispheric bias for interval discriminations (Jueptner et al., 1995), whereas another PET study found a right hemispheric bias for interval, but also illumination intensity discriminations (Maquet et al., 1996), possibly attributable to the emphasis on sustained attention and working memory. Therefore, we correlated an independent measure of

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Table 1. Demographic characteristics of the control and stroke groups

	Right control	Left control	Right hemisphere damage	Left hemisphere damage
Sample size	24	24	18	19
Age	66.7 (8.3)	63.5 (9.1)	64.6 (12.2)	64.3 (9.9)
Education	14.5 (3.0)	14.7 (2.4)	13.9 (3.0)	13.0 (3.4)
Sex (% male)	71	71	50	84

Tabled values represent means with SDs in parentheses, except where specified otherwise.

switching attention with duration perception performance to determine the relationship of attention and time perception in patients with focal left or right hemisphere lesions.

MATERIALS AND METHODS

Subjects

Table 1 describes the four subject groups. All subjects were right-handed, and *t* tests showed that there were no significant differences among the patient groups and their respective control groups in age, education, or gender. The etiology of hemispheric damage was stroke, and patients were tested a minimum of 3 months after onset. A Mann–Whitney *U* test showed that the mean number of years after stroke did not differ significantly between the LHD group (mean = 3.8; SD = 4.3) and the RHD group (mean = 4.1; SD = 3.9). Lesion location was assessed using magnetic resonance imaging (MRI) or computed tomography (CT), which was conducted at least 3 months after onset. All lesions were confined to one hemisphere and did not extend into the cerebellum or brain stem. The right control and right hemisphere damaged (RHD) stroke groups performed all tasks using their right hand, and the left control and left hemisphere damaged (LHD) groups performed the tasks using their left hand.

All subjects were administered a battery of neuropsychological tests to document their language, visuospatial, motor, and somatosensory skills. The Western Aphasia Battery (WAB) (Kertesz, 1982) was used to evaluate the main clinical features of language function, including spontaneous speech, auditory comprehension, and repetition. Spontaneous speech (e.g., response to examiner questions, describing a picture) is evaluated in terms of information content and fluency. Auditory comprehension assesses the ability to follow one-, two-, and three-step commands. Repetition assesses the ability to repeat high- and low-probability words, phrases, or sentences of increasing difficulty and has been used clinically to identify patients with conduction aphasia. These three measures are used to derive an aphasia quotient that reflects aphasia severity. Table 2 shows that, as anticipated, the LHD group was significantly impaired on all measures of language function, whereas the RHD group was only mildly impaired on the repetition test and had a slightly lower aphasia quotient. Pearson correlations (one-tailed significance tests) showed that severity of aphasia was not related to performance on the experimental tasks. Visuospatial function was assessed using the Block Design subtest from the Wechsler Adult Intelligence Scale–Revised (WAIS-R) (Wechsler, 1981), which assesses the ability to construct designs of increasing complexity using blocks that are colored red on two sides, white on two sides, and red and white on the remaining two sides. Both the RHD and the LHD groups were impaired on this test. Grip strength, which is assessed using a hand dynamometer, was normal in both stroke groups in the hand ipsilateral to the lesioned hemisphere and impaired in the contralateral hand. The contralateral hand was hemiplegic in five RHD patients and was hemiparetic in four LHD patients. Somatosensory function (two-point discrimination) was evaluated using a two-point aesthesiometer, which has a single point on one end and two points on the other end that can be adjusted to various widths. A screen conceals the subject's hand, the examiner touches the tip of the subject's index finger with either one or two points, and the subject indicates whether one or two points were felt. The smallest distance between the two points at which the subject made no more than one error is scored. Somatosensory deficits were found in the contralateral hand of both stroke groups, and the LHD group also showed some mild somatosensory impairments in the ipsilateral hand. Visual fields testing used the double simultaneous visual fields test and the gross confrontation procedure (Lezak, 1995). Two RHD patients showed contralateral visual field cuts, and two other patients showed neglect. Visual fields were normal in all LHD patients, and none showed neglect.

Procedures

Duration perception task. Subjects completed two duration perception tasks in which they judged the relative duration of two tone pairs. Tones were 75 dB and 50 msec in duration. A standard tone pair was presented and followed 1 sec later by a comparison tone pair. Subjects indicated by pressing a key whether the interval between the comparison tone pair was longer or shorter than the standard. In one condition the interval between the two tones in the standard pair was always 300 msec, and in the other condition it was 600 msec. There were 30 possible longer and 30 possible shorter intervals that varied in step sizes of 6 msec. The presentation order of the target intervals was counterbalanced across subjects.

The Parameter Estimation by Sequential Testing (PEST) procedure was used to derive a criterion threshold (Pentland, 1980; Lieberman and Pentland, 1982). The PEST procedure is similar to staircase procedures used in psychophysical experiments and has been shown to be a reliable shortcut for assessing thresholds. The PEST procedure operates by producing a maximum-likelihood estimate of the independent variable that will result in the maximum amount of information about the position of the threshold on each trial, based on all previous responses (Lieberman and Pentland, 1982). The procedure establishes a probability array based on a normal sigmoid-shaped psychophysical function and then uses this to determine the next best current estimate of a subject's upper (i.e., longer than the standard duration) or lower (i.e., shorter than the standard duration) threshold point. This is done for each trail, so that the selection of a stimulus value for a particular trial represents the highest probability, given all previous responses. Thus, a revised estimate of a subject's threshold point is made after each response. The test threshold was set to equal 1 SD from the point of subjective equality (PSE), which is the interval at which subjects are equally likely to respond shorter or longer. The PEST procedure does not produce data that can be averaged across individuals within a group to systematically evaluate the relationship between values of an independent variable (e.g., duration) and the probability of classifying it as longer or shorter than the standard because each subject receives a different subset of stimuli, and the number of trials for a particular stimulus value also differs across subjects, depending on their response distribution.

Ten practice trials were presented and followed by 50 experimental trials consisting of 25 judgments each for the upper and lower thresholds. A difference threshold was computed by taking the difference between the upper and the lower duration thresholds and dividing this value by 2.

Frequency perception task. A frequency perception task was included as a control for the general auditory processing requirements of the duration perception task. Subjects judged the relative pitch of two tone pairs, which were 75 dB and 50 msec in duration. The interval between the two tones in the standard and comparison pairs was fixed at 550 msec, and the two tone pairs were separated by a 1 sec interval. The frequency of the standard tones was 1000 Hz, and the comparison tones consisted of higher or lower frequencies. Subjects indicated by pressing a key whether the pitch of the comparison tone pair was higher or lower than the standard pair. There were 30 possible higher and 30 lower frequencies that varied in step sizes of 1 Hz. Ten practice trials were followed by 50 experimental trials, which consisted of 25 judgments each for the upper and lower thresholds. The PEST procedure was used to derive a criterion threshold. As for the duration perception data, a difference threshold was calculated by taking the difference between the upper and lower frequency thresholds and dividing this value by 2.

Attention task. A nonspatial attention task was used to measure the subject's ability to disengage attention. Subjects made an index or middle finger key press in response to a stimulus, which was a circle or a triangle. The stimulus was preceded by either a neutral cue (a cross), a valid cue (circle or triangle), or an invalid cue. At the beginning of each trial, a 50 msec warning tone sounded, followed by the cue, which appeared at the center of the monitor. After a random delay of 200, 350, or 500 msec, the response stimulus appeared at the center of the monitor, just below the cue, and subjects were instructed to make a key press as quickly and accurately as possible. The intertrial interval was 1 sec. Reaction time (RT) was measured from the onset of the response stimulus to the completion of the key press. Two blocks of experimental trials were given, each containing a random presentation of 63 neutral cue trials (21 trials at each delay), 78 valid cue trials (26 at each delay), and 21 invalid

Table 2. Cognitive, motor, and somatosensory status of the control and stroke groups

	Right control	Left control	Right hemisphere damage	Left hemisphere damage
Speech[a]	20.0 (0.0)	20.0 (0.0)	19.7 (0.7)	16.8* (4.3)
Comprehension[a]	79.5 (1.3)	80.0 (0.0)	78.7 (4.3)	68.5* (16.5)
Repetition[a]	98.0 (3.4)	98.7 (1.5)	95.5 (4.3)	83.6* (17.7)
Aphasia quotient[a]	98.8 (1.2)	99.2 (0.7)	96.9** (3.0)	84.7* (17.8)
Block design[b]	9.2 (1.8)	8.8 (2.5)	6.1** (2.3)	7.0* (2.7)
Grip strength[c]				
Right hand	48.5 (9.4)	49.7 (7.3)	46.9 (12.9)	37.8* (13.7)
Left hand	51.6 (9.4)	52.2 (7.6)	35.9** (25.4)	49.9 (11.6)
Two-point discrimination[d]				
Right finger	0.46 (0.21)	0.41 (0.16)	0.61 (0.42)	0.69* (0.45)
Left finger	0.45 (0.28)	0.43 (0.16)	0.78** (0.45)	0.56* (0.23)

Tabled values represent means with SDs in parentheses.

[a]The Western Aphasia Battery (WAB) (Kertesz, 1982) was used to derive the aphasia quotient and assess spontaneous speech, auditory comprehension, and repetition. The maximum score was 20 for spontaneous speech, 80 for auditory comprehension, 100 for repetition, and 100 for the aphasia quotient. Data were missing on five right control subjects.

[b]Block Design subtest scaled scores from the WAIS-R (Wechsler, 1981).

[c]Grip strength is expressed as a standardized T-score. Data were missing on five right control subjects.

[d]Two-point discrimination was tested on the index finger of each hand. Data were missing on five right control subjects and six RHD patients with contralateral somatosensory deficits that were too severe to measure using this task.

*A *t* test or Mann–Whitney *U* test showed that the left hemisphere stroke group was impaired ($p < 0.05$) relative to the left control group.

**A *t* test or Mann–Whitney *U* test showed that the right hemisphere stroke group was impaired ($p < 0.05$) relative to the right control group.

cue trials (7 at each delay). The experimental trials were preceded by 18 practice trials. A measure of cost, which reflects disengagement of attention (Posner et al., 1984), was calculated by subtracting the valid from the invalid RTs for a particular condition.

Lesion reconstruction. Computer reconstructions of lesion size and location were derived from MRI scans in the majority of subjects. MRI scans were performed using a Siemens or a Picker 1.5 Tesla scanner, with a slice thickness of 5 mm. Reconstructions based on CT scans (5 mm slice thickness) were performed in three LHD and four RHD patients, who for medical reasons could not undergo an MRI scan (e.g., pacemaker). All scans were obtained at least 3 months after onset. Lesions were transcribed onto corresponding axial templates derived from the atlas of DeArmond et al. (1989), using procedures developed at the Veterans Affairs Medical Center (Martinez, CA) (Knight et al., 1988; Singh and Knight, 1993). The software allowed for reconstruction of the lesion volume, projections of the lesion onto the lateral surface of the brain, and averaging of group lesions by superimposing subjects' lesions on each horizontal slice. Figures 1 and 2 show the axial reconstructions for each subject in the LHD and RHD groups. A *t* test showed that there was not a significant difference in lesion size between the LHD group (mean = 35.7 cc; SD = 21.5; range, 13.3–89.9 cc) and the RHD group (mean = 39.3 cc; SD = 25.4; range, 7.1–102.2 cc). In some analyses, subjects were also separated into those with primarily anterior damage or those with posterior damage (Figs. 1, 2). The anterior group included patients whose lesions were mainly anterior to the central sulcus, but also could involve damage to the sensorimotor cortex or temporal lobes, and in three subjects (Fig. 1, cases *3* and *4*; Fig. 2, case *4*), a lesion that extended slightly into the supramarginal gyrus (SMG). The posterior group consisted of patients whose lesions were mainly posterior to the central sulcus, but also could involve damage to the primary motor cortex or temporal lobes, and one subject had a small lesion in the prefrontal cortex (Fig. 1, case *11*). Figures 1 and 2 show that there were nine RHD and six LHD patients in the anterior groups, and 10 RHD and 12 LHD patients in the posterior groups. A *t* test showed that there was no difference in lesion volume between the LHD (mean = 34.8 cc; SD = 21.2) and RHD (mean = 39.0 cc; SD = 34.3) groups with anterior lesions. Similarly, lesion volume did not differ significantly between the LHD (mean = 36.6 cc; SD = 22.9) and RHD (mean = 39.4 cc; SD = 21.4) groups with posterior lesions.

RESULTS

Frequency perception

The frequency perception data were analyzed using ANOVA, which tested the between-subject effects of group (control, stroke) and hand (left, right) and their interaction. The PSE data were first analyzed, and the results showed that there were no significant effects of group, indicating that the response criterion was similar across all groups. However, frequency perception (difference threshold) was impaired in the LHD (mean = 13.7; SD = 9.0) and the RHD groups (mean = 10.7; SD = 5.3) relative to the controls (mean = 8.3; SD = 6.5 for all control subjects) [$F_{(1,81)} = 6.23$; $p < 0.025$]. No other effects were significant. The results indicated that some aspect of auditory processing (e.g., discrimination processes, sensory processing, temporal ordering of stimulus events, pitch perception) was deficient in both stroke groups. This raised the possibility that deficits in duration perception might be attributable to more primary problems in processing sequential auditory stimuli, because of the similarity between the frequency and duration perception tasks in the sequence of trial events. Therefore, analyses of the duration perception data were conducted first by analyzing all subjects' data and then by analyzing the data of only those whose performance was within normal limits on the frequency perception task (i.e., within 1 SD of the control group). The latter procedure excluded four right controls, three left controls, three RHD patients, and eight LHD patients.

Figures 1 and 2 depict the lesions of all stroke patients, including those with frequency perception deficits. The incidence of frequency perception deficits was low for patients with left or right hemisphere posterior lesions (i.e., two patients in each stroke groups) or with right hemisphere anterior lesions (i.e., one

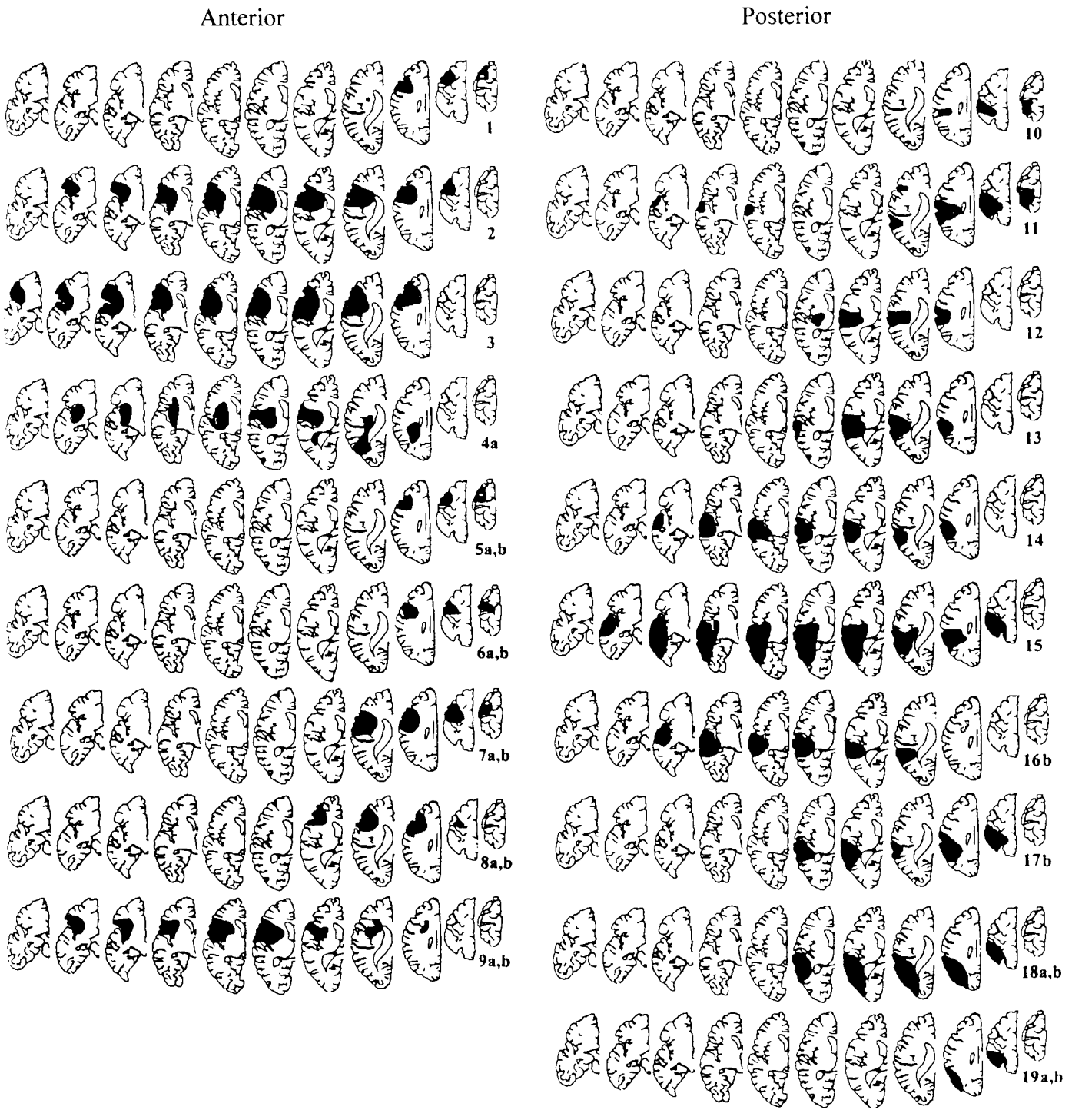

Figure 1. Axial sections showing the location of lesions in 19 individuals with left hemisphere damage. Case numbers are displayed beneath each series of sections and are ordered according to whether lesions were largely anterior or posterior to the central sulcus. The letter *a* refers to individuals with impaired frequency perception, and the letter *b* refers to individuals with impaired duration perception.

patient). This contrasted with the high incidence of frequency perception deficits associated with left hemisphere anterior lesions (i.e., six patients), which could not be explained by any particular lesion focus (Fig. 1) (see below) or subject characteristic (e.g., age, neuropsychological test performance). Additionally, temporal lobe lesions were not associated with frequency perception deficits, which was consistent with a study of patients with temporal lobe excisions (Zatorre and Samson, 1991) but contrasts with functional imaging work showing activation of the left and right superior temporal lobes during pitch discriminations of linguistic or nonlinguistic stimuli (Zatorre et al., 1996; Rao et al., 1997). Bilateral hemispheric activation of the middle and inferior frontal gyri have also been associated with pitch discrimination, putatively because of the role of short-term mem-

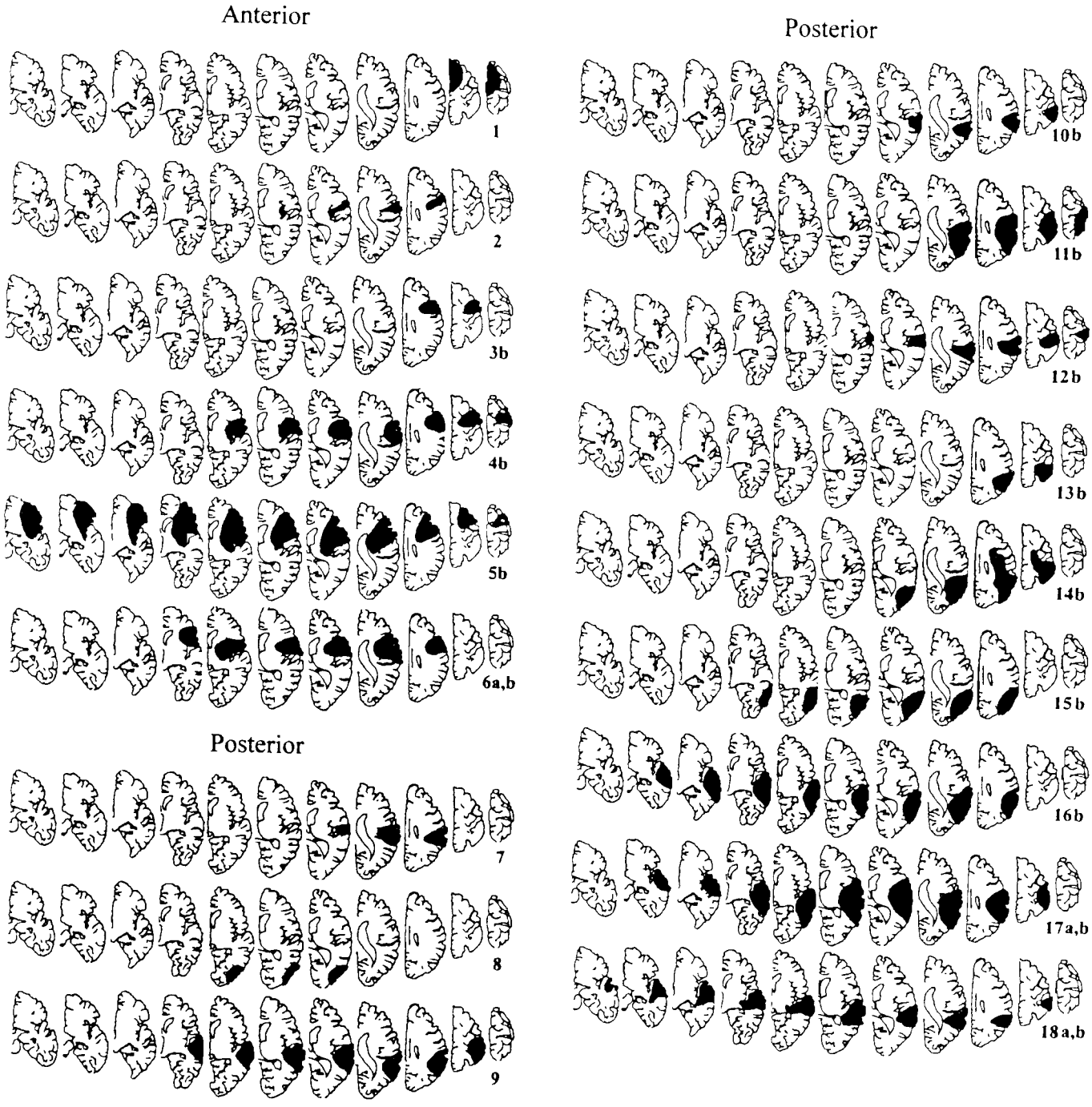

Figure 2. Axial sections showing the location of lesions in 18 individuals with right hemisphere damage. Case numbers are displayed beneath each series of sections and are ordered according to whether lesions were largely anterior or posterior to the central sulcus. The letter *a* next to the case number refers to individuals with impaired frequency perception, and the letter *b* refers to individuals with impaired duration perception.

ory in linguistic processing (Zatorre et al., 1994, 1996). Our frequency perception task appears to have short-term memory requirements similar to those in the latter studies, yet few patients with RHD showed pitch discrimination deficits. Rather, deficits were most associated with LHD to the frontal cortex, which raises the possibility that our findings, and perhaps those of others (Zatorre et al., 1994, 1996), may reflect left hemispheric specialization for other processes ostensibly involved in frequency discrimination, such as serial ordering (Von Steinbuchel, 1995).

Duration perception

The duration perception data were analyzed using a mixed-model ANOVA with repeated measures, wherein the between-subject factors were group and hand and the within-subject factors were target interval (300 msec, 600 msec) and order (testing order of the 300 and 600 msec conditions). The PSE data were first analyzed, and no significant effects of group or interactions with group were obtained. Figure 3*a* displays the duration thresholds for all subjects on the duration perception task. The figure shows

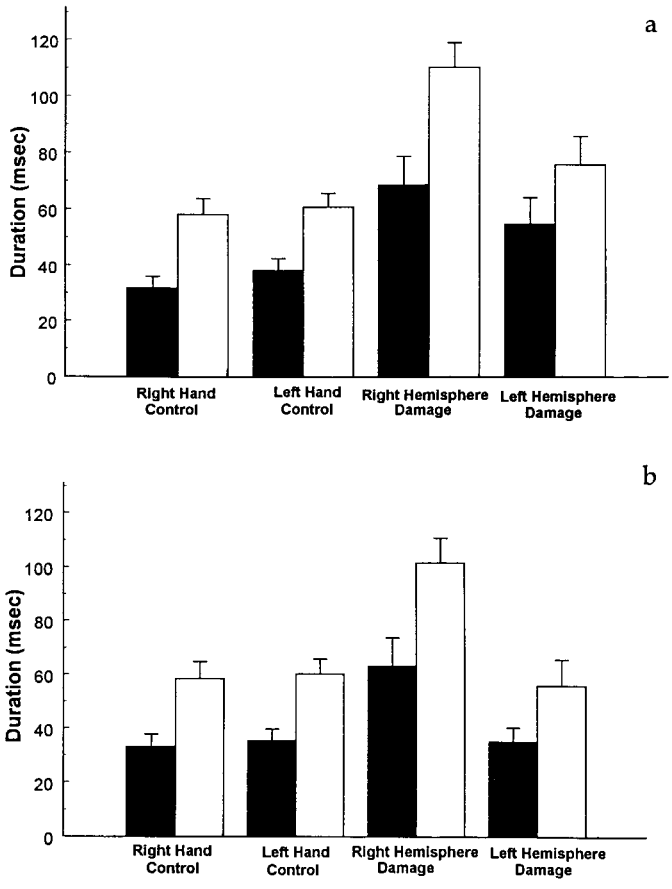

Figure 3. Mean (SE) difference thresholds for the 300 msec (*black bars*) and 600 msec (*white bars*) conditions of the duration perception task. The top graph (*a*) displays the data from all subjects, and the bottom graph (*b*) includes data only from subjects who performed within normal limits on the frequency perception task.

that judgments of duration were less accurate when the interval between the standard tone pair was 600 msec than when it was 300 msec [$F_{(1,77)} = 58.72$; $p < 0.0001$]. Most importantly, judgments of duration were less accurate in both stroke groups, especially in the RHD stroke group. This observation was confirmed by the significant effects of group [$F_{(1,77)} = 25.95$; $p < 0.001$] and the group × hand interaction [$F_{(1,77)} = 4.49$; $p < 0.05$]. Simple effects analyses showed that duration perception was significantly impaired in the RHD group relative to their control group [$F_{(1,38)} = 28.70$; $p < 0.001$], whereas there was only a trend for difference thresholds to be elevated in the LHD group in comparison to their controls [$F_{(1,39)} = 4.05$; $p = 0.051$]. There was also a significant main effect of order [$F_{(1,77)} = 4.76$; $p < 0.05$], indicating that for all subjects duration perception was more accurate when the 600 msec interval was tested first (mean = 39.9, SD = 30.6 for the 300 msec interval; mean = 69.2, SD = 33.7 for the 600 msec interval) than when the 300 msec interval was tested first (mean = 54.56, SD = 35.6 for the 300 msec interval; mean = 79.1, SD = 42.4 for the 600 msec interval). No other significant effects were obtained.

Next, the same analyses were conducted on the duration threshold data after excluding subjects with difference thresholds on the frequency perception task that were >1 SD of the control group mean (i.e., >15). These data are displayed in Figure 3*b*, which suggests that judgments of duration were impaired only in the RHD group. This observation was supported by the group × hand interaction [$F_{(1,59)} = 12.61$; $p < 0.002$], in which difference thresholds were elevated in the RHD group in comparison to their controls [$F_{(1,31)} = 18.14$; $p < 0.001$], but there was no difference between the LHD group and their controls [$F_{(1,28)} < 1.0$]. There was also an interaction of group × hand × order [$F_{(1,59)} = 4.94$; $p < 0.05$], which was attributable to an order effect only in the RHD group. In this group, duration thresholds were more accurate, albeit still impaired, when patients performed the 600 msec condition first. As for the previous analyses, duration thresholds were more accurate for the 300 than the 600 msec target interval [$F_{(1,59)} = 41.38$; $p < 0.0001$]. No other significant effects were found.

Although these results were similar to those obtained in the analyses of all subjects, the analyses of the PSE data showed an interaction of group × target interval [$F_{(1,59)} = 6.58$; $p < 0.025$], wherein the PSE was lower in the stroke (mean = 313.0, SD = 25.6; mean = 589.9, SD = 43.7) than in the control groups (mean = 309.5, SD = 38.3; mean = 612.1, SD = 46.6), but only for the 600 msec target interval. This effect was attributable to an asymmetry in the upper and lower thresholds of the RHD group for the 600 msec target interval. Specifically, the upper threshold (mean = 625) of the LHD group was more accurate than that of the control group (mean = 672) or the RHD group (mean = 706), whereas both stroke groups showed a more accurate lower threshold (mean = 508) than the controls (mean = 553). Consequently, the difference threshold data were also analyzed by controlling for PSE (i.e., the difference threshold was divided by the PSE and then multiplied by 100), and the analysis produced similar findings. There was an interaction of group × hand [$F_{(1,59)} = 8.54$; $p < 0.01$] wherein no difference in duration perception was found between the LHD group (mean = 11, SD = 2, and mean = 10, SD = 2, for the 300 and 600 msec intervals, respectively) and their controls (mean = 11, SD = 1, and mean = 10, SD = 1, for the 300 and 600 msec intervals, respectively), but the RHD group (mean = 20, SD = 4, and mean = 17, SD = 2, for the 300 and 600 msec intervals, respectively) was impaired relative to their controls (mean = 11, SD = 1, and mean = 10, SD = 1, for the 300 and 600 msec intervals, respectively) [$F_{(1,31)} = 13.09$; $p < 0.01$].

We also conducted similar analyses, normalizing the data by dividing the difference threshold by the standard interval to determine whether accuracy was scalar across the two intervals (Gibbon et al., 1997). The results from these analyses were similar to the ones above, showing an interaction of group × hand [$F_{(1,59)} = 10.53$; $p < 0.01$], such that in proportion to the standard interval the RHD group still was less accurate (mean = 0.21, SD = 0.14, and mean = 0.17, SD = 0.06, for the 300 and 600 msec intervals, respectively) than their controls (mean = 0.11, SD = 0.07, and mean = 0.10, SD = 0.05, for the 300 and 600 msec intervals, respectively) [$F_{(1,33)} = 14.16$; $p < 0.01$], but there were no differences between the LHD group (mean = 0.12, SD = 0.06, and mean = 0.09, SD = 0.05, for the 300 and 600 msec intervals, respectively) and their controls (mean = 0.12, SD = 0.06, and mean = 0.09, SD = 0.05, for the 300 and 600 msec intervals, respectively). However, the main effect of interval was significant [$F_{(1,59)} = 5.22$; $p < 0.05$], showing that timing accuracy was nonscalar in all subjects. Most importantly, the interaction of group × interval was not significant, indicating that although accuracy was lower in proportion to the standard interval in the RHD group, timing efficiency remained the same across the two intervals.

Finally, we compared the two stroke groups to determine whether duration thresholds differed in patients with anterior or posterior lesions. Only patients with normal frequency thresholds were included in the analyses, which were similar to the previous ones except that the between-subject factors were stroke group (RHD, LHD) and lesion location (anterior, posterior). The order effect was not tested because of the limited cell size. Although duration thresholds were higher in the RHD than in the LHD group [$F_{(1,22)} = 8.72$; $p < 0.01$] (Fig. 3*b*), thresholds did not differ between patients with anterior (mean = 63.6, SD = 34.6, and mean = 93.0, SD = 33.2, for the 300 and 600 msec intervals in the RHD group; mean = 30.0, SD = 16.7, and mean = 42.0, SD = 13.7, for the 300 and 600 msec intervals in the LHD group) or posterior lesions (mean = 62.7, SD = 46.7, and mean = 105.9, SD = 37.5, for the 300 and 600 msec intervals in the RHD group; mean = 36.8, SD = 18.2, and mean = 60.8, SD = 36.7, for the 300 and 600 msec intervals in the LHD group), nor were there interactions of lesion location with stroke group or interval.

Attention

The dependent measure, cost, was analyzed using a mixed-model ANOVA with repeated measures, in which the between-subject factors were group and hand and the within-subject factor was stimulus onset asynchrony (SOA) (200, 350, and 500 msec). Only the tests involving the group and hand factors are reported, because they were of main interest. All subjects were included in the analyses to have sufficient sample sizes for subsequent correlations with the main experimental measures. There was a main effect of hand [$F_{(1,80)} = 6.69$; $p < 0.025$) showing that cost was greater for subjects performing with their left than their right hand. Most importantly, both stroke groups showed greater cost (mean = 122.6, SD = 52.8 for the RHD group; mean = 284.6, SD = 352.1 for the LHD group) than the control groups (mean = 92.5, SD = 30.7 for the right controls; mean = 119.5, SD = 42.4 for the left controls). There were no significant interactions of group, hand, or SOA. The results indicate that both stroke groups showed similar deficits in disengaging nonspatial attention. Moreover, a separate ANOVA focusing on the effect of lesion location revealed no difference in cost between stroke patients with anterior or posterior lesions, nor did lesion location interact with stroke group.

Correlations among tasks

Pearson correlations (one-tailed significance tests) were conducted to examine the interrelationships among the experimental tasks in all stroke patients, regardless of frequency perception performance. Duration perception was positively correlated with frequency perception, but the relationship was stronger for the LHD group ($r = 0.77$; $p < 0.001$) than the RHD group ($r = 0.41$; $p < 0.05$). This suggests that the LHD group may have had greater deficits in time-independent processes common to both tasks than the RHD group. This speculation was also supported by the greater incidence of frequency perception deficits in the LHD group (see above). Cost was not related to frequency perception in either stroke group ($r = 0.16$), whereas it was positively correlated with duration perception, but only in the RHD group ($r = 0.43$; $p < 0.05$). These results suggest that the attention demands of frequency perception were not as great or perhaps different from those for duration perception, despite the similarity of the paradigms. Additionally, competency in switching attention was associated with perceptual timing processes only in the RHD group, consistent with their greater incidence of timing deficits, which could not be attributed to nontemporal processes shared with frequency perception.

Analyses of lesion reconstruction data

Patients' lesions were next averaged by superimposing them on each horizontal slice to determine whether there were regions within the right hemisphere essential for duration perception. Patients were separated into those with and those without duration perception deficits (i.e., >1 SD above the control group mean at either or both target intervals), and then averages were constructed for subjects with lesions that were predominantly anterior or posterior to the central sulcus. Lesion averages were constructed using only subjects with normal frequency perception. Brodmann areas (BAs) corresponding to the regions of 100% overlap were determined using the sulci landmarks from the templates (DeArmond et al., 1989) and the projections of the lesion overlays onto the lateral surface of the brain (Frey et al., 1987; Knight et al., 1988).

Figure 4 contrasts the averages for patients with anterior (Fig. 4*a,b*) or posterior lesions (Fig. 4*c,d*) in the left and right hemispheres. Figure 4*a* shows that for the three patients with anterior RHD and impaired duration perception, the one common area of infarction, in which there was 100% lesion overlap (i.e., *yellow*), was the lateral premotor area, including the FEF (BA 6; *Section 9* and *Section 10*) and the middle and superior gyri of the DLPF area (BA 9 and 46 on *Section 9* and BA 8 on *Section 9* and *Section 10*) (Rajkowska and Goldman-Rakic, 1995a,b). By comparison, Figure 4*b* shows that only two RHD patients with anterior damage showed normal duration perception and the location of their lesions was different. One of these patients (i.e., *blue*) had a lesion in the SMA (patient 1; *Section 10* of Fig. 4*b*), and the other (patient 2) had damage to the motor and caudal portion of the premotor cortex on Section 9 (Fig. 4*b*), as well as somatosensory cortex (*Section 8*). Figure 4*a,b* also illustrates the hemispheric asymmetry in duration perception for patients with anterior lesions. None of our LHD patients with anterior lesions showed impaired duration perception (Fig. 4*a*), and all three of the LHD patients with normal duration perception (Fig. 4*b*) had lesions in the same areas as those that were associated with impaired duration perception in the RHD group.

Recall, however, that six LHD patients with abnormal frequency perception, five of whom also had abnormal duration thresholds (Fig. 1), were excluded from the analyses. To determine whether this exclusion criterion biased the hemispheric findings, we constructed overlays of the LHD patients with anterior lesions who had both frequency and time perception deficits. The overlays showed that the maximum percentage lesion overlap (66%) was in BA 9 of Section 9 and in motor cortex of Section 10. By comparison, 100% of the LHD patients with anterior lesions who showed normal frequency and time perception also had damage to BA 9 on Section 9 (Fig. 4*b*). These results indicate that, unlike time perception deficits after RHD, frequency or time perception deficits after LHD were not strongly associated with damage to a particular neuroanatomical region, although there was clearly a left hemisphere asymmetry for pitch perception processing. Nevertheless, it is still possible that time discriminations are dependent on unspecified left hemisphere-dependent processes that are also common to frequency perception, because more than half of our subjects with anterior LHD showed deficits on both types of discriminations.

Figure 4*c* shows that the area of 100% lesion overlap in the seven RHD patients with abnormal duration perception perfor-

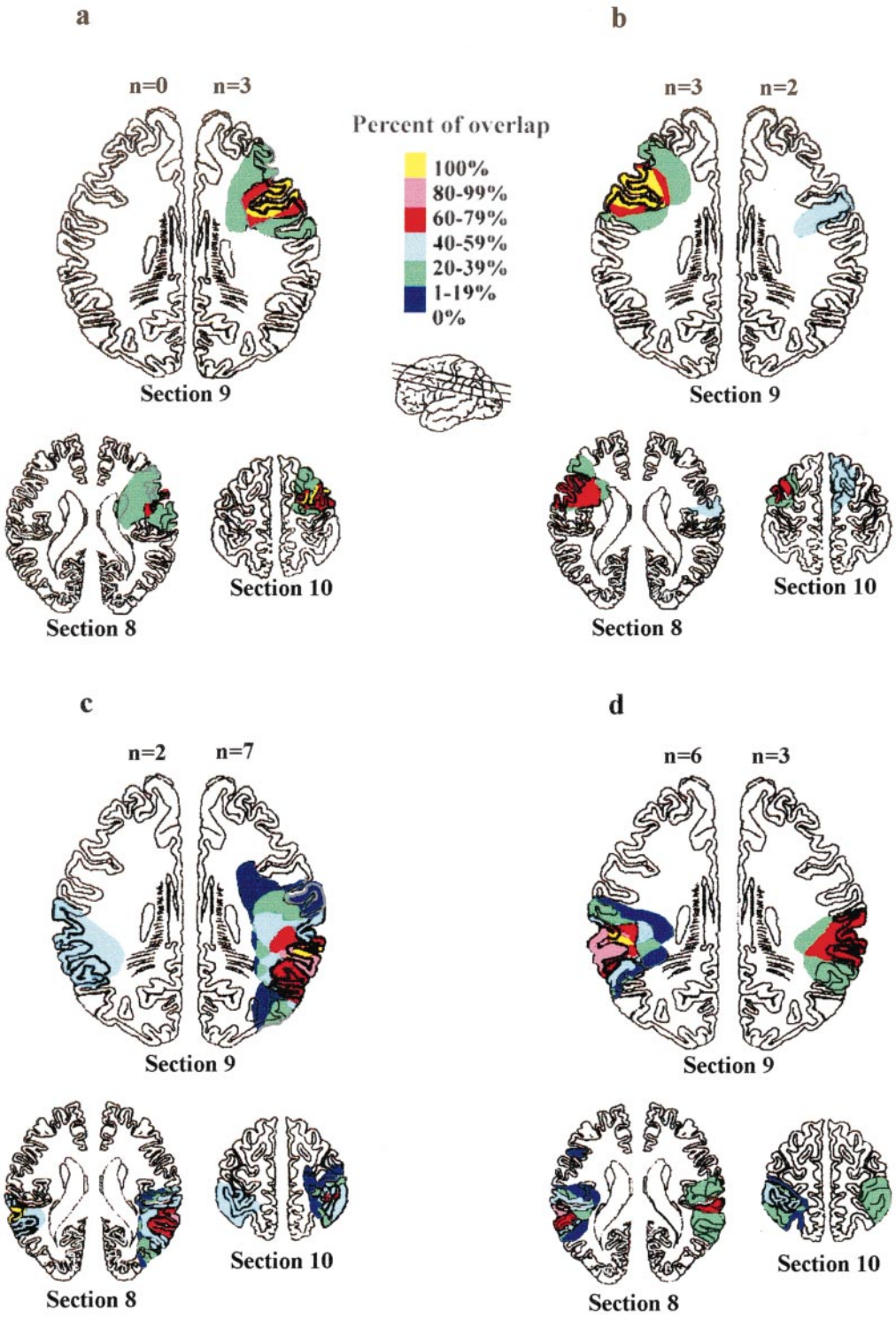

Figure 4. Lesion overlap in individuals with damage primarily anterior or posterior to the central sulcus. Axial sections show overlap for left hemisphere (on the *left* of each section) and right hemisphere (on the *right* of each section) lesions in individuals with intact frequency perception. The *lines* on the lateral view show the location of the corresponding axial sections. The *color scale* indicates the percentage of patients within a particular group with damage in an area. *a*, Overlapping lesions in patients with anterior lesions and *impaired performance* on the duration perception task. Only three patients with RHD were impaired on this task, and the common areas of infarction (*yellow*) were found on *Section 9* (*top row*) and *Section 10* (*bottom row*). No individuals with LHD were impaired on duration perception. *b*, Overlapping lesions in patients with anterior lesions and *normal performance* on the duration perception task. A region on *Section 9* shows 100% overlap in the three patients with LHD. There were no common areas of infarction in the two RHD patients (i.e., *blue* indicates a lesion from one patient). *c*, Overlapping lesions in patients with posterior lesions and *impaired performance* on the duration perception task. Seven patients with RHD were impaired on this task, and the common area of infarction (*yellow*) was found on *Section 9* (*top row*). Only two LHD patients were impaired on this task, and the common area of infarction is seen on *Section 8* (*bottom row*). *d*, Overlapping lesions in patients with posterior lesions and *normal performance* on the duration perception task. *Section 9* shows 100% overlap in six patients with LHD. There were no common areas of infarction in the three RHD patients (i.e., *green* and *red* signify lesions from one and two patients, respectively).

mance and posterior damage involved the supramarginal gyrus (SMG; BA 40) on Section 9 and rostral portions of the angular gyrus. In contrast, Figure 4*d* shows that only three posterior RHD patients had normal duration perception. The lesion of one patient (8) was occipital and is not shown on these sections. The lesion of the other two (7 and 9) involved damage to BA 40 and 39 (i.e., *red*), as well as other parietal regions. Duration perception performance was clearly within normal limits for both target intervals in patients 7 and 8, whereas the performance of patient 9 was borderline normal in the 600 msec condition (i.e., 81 msec). Hence, damage in the region of the SMG was associated with duration perception deficits in the large majority of patients, but there were two exceptions, one of which could be explained by borderline abnormal performance on this task. Figure 4*c,d* also illustrates the hemispheric asymmetry in duration perception for patients with posterior lesions. Only two posterior LHD patients (16 and 17) showed deficits on this task (Fig. 4*c*), and although BA 40 was damaged in both patients, it was more ventral (*yellow* area on slice 8). Moreover, 100% of the six LHD patients who showed normal duration thresholds had damage in the region of the SMG on slice 9 (Fig. 4*d*).

DISCUSSION

Hemispheric asymmetry in timing mechanisms

This is the first study to show directly that the right hemisphere is essential for timekeeping mechanisms. Despite the similarity between the stroke groups in lesion loci and size, only RHD was associated with a disruption in time discriminations, when deficits in frequency perception were controlled. In contrast, the left hemisphere does not appear to play a role in these operations, at least in the analysis of nonlinguistic acoustic stimuli. This is consistent with the finding that aphasia severity was not correlated with duration perception. Our lesion analyses of LHD patients with impaired frequency and duration perception also failed to uncover evidence of a left hemisphere network underlying timing, although it is still possible that the left hemisphere supports nontemporal mechanisms used in time and frequency discriminations that were not identified in this study.

What is the nature of the computations performed by the right hemisphere? One interpretation is it regulates timekeeping operations. Although the duration perception paradigm did not separate timing from other processes, the frequency perception paradigm controlled for deficits in at least some nontemporal processes, so that duration thresholds could reasonably reflect right hemisphere deficits in a central timekeeper, at least for the intervals studied here. Interestingly, right hemisphere activation of prefrontal and inferior parietal cortex has been found for rhythm discriminations, which have a time-dependent component (Roland et al., 1981). This interpretation contrasts with animal research that favors the basal ganglia for a timekeeper or clock (Gibbon et al., 1997). Although these studies use different paradigms and longer intervals (typically 2 sec or more), they have been more successful in isolating hypothetical timing operations than most patient studies have. Still, human studies are crucial for delineating specific neural networks and hemispheric biases in timekeeping mechanisms, which the present study uncovered.

Although our study controlled for some extraneous variability in time perception by partialing out deficits in unspecified processes, nonspatial attention ability was correlated with duration thresholds only in patients with RHD, suggesting another interpretation of the results. Specifically, judgments of duration may engage attentional operations that are asymmetrically represented in the cerebral cortex. This proposal is consistent with the role of attention in interval timing (Gibbon et al., 1997), although there have been few studies of its neurobiology. Attention may also be required to operate a timekeeper or clock, such that the clock is not continually activated when attention is disrupted (Macar et al., 1994). Importantly, despite attention deficits in both stroke groups, attention was not correlated with frequency perception, suggesting that attentional abnormalities were specific to time-dependent discriminations. This possibility extends the prevailing view of the right hemisphere as biased for switching and sustaining spatial attention (Knight et al., 1981; Posner et al., 1984; Heilman et al., 1985; Pardo et al., 1991; Corbetta et al., 1993; Smith et al., 1996) to include the domain of time perception.

The prospect that the right hemisphere supports time-dependent attentional mechanisms is compatible with findings in RHD individuals with and without neglect (Husain et al., 1997). Subjects were presented a rapid, serial sequence of letters, and identified one (control task) or two target letters (dual task) that varied in their temporal proximity to one another. The dual task required shifts in nonspatial attention between the two targets, and in healthy individuals identification of a second target is impaired, relative to the control task, if it appears within 400 msec of the first target. This phenomenon is called the "attentional blink" and was increased (to 1440 msec) only in RHD patients with unilateral neglect. This prolongation was not attributable to a disruption in sustaining attention, because these same individuals showed normal performance on the control task. Although hemispheric asymmetries and perceptual acuity for time were not assessed directly, the findings of this study, together with ours, raise the intriguing possibility that deficits in attentional shifts after RHD have a significant temporal component.

Intrahemispheric networks in timing

Evidence for intrahemispheric specialization of timing was also found that implicated the inferior parietal lobe and areas of the prefrontal cortex, including the FEF (BA 6) and DLPF cortex (BA 8, 9, and 46). Few RHD patients with normal duration perception had damage to these regions, and lesions in the same regions in LHD patients were associated with normal timing. The results imply a role for anterior and posterior regions of the right hemisphere in temporal computations, which is compatible with the reciprocal connections between the inferior parietal cortex and corresponding frontal cortical areas in monkeys (Selemon and Goldman-Rakic, 1988).

Prefrontal cortex

Most investigations of frontal cortical mechanisms in timing have been conducted in animals and suggest that the frontal cortex supports working memory, which underlies timing (Gibbon et al., 1997). Therefore, our findings associating time perception competency with the prefrontal cortex could reflect the roles of one or more of these areas in sustaining on-line representations of a standard interval for comparison with an immediately after-target interval, a working memory function. Duration perception deficits were associated with damage in the middle and superior frontal gyri [some investigators designate these areas 9 and 46 (Goldman-Rakic, 1987; Rajkowska and Goldman-Rakic, 1995b)], which are critical for working memory. These areas and the FEF have direct access to an internal clock, assuming that the basal ganglia regulate a timekeeper (Gibbon et al., 1997; Harrington et al., 1998), through reciprocal connections with the caudate nucleus (Alexander et al., 1986). However, different frontal areas

have been associated with working memory (Pardo et al., 1991; Paulesu et al., 1993), and cytoarchitectonic maps of some areas (9 and 46) vary considerably (Rajkowska and Goldman-Rakic, 1995a).

Our findings contrast with a PET study that reported right inferior frontal gyrus (BA 45) activation for duration and intensity discriminations (Maquet et al., 1996). However, in both tasks subjects had to remember a standard interval or illumination intensity for several minutes to compare with target intervals during imaging trials. In our task, the standard interval was presented on every trial, placing minimal demands on retrieval or rehearsal processes. Hence, our results are more compatible with a working memory interpretation of prefrontal cortex function, although it is possible that one or more of these areas might also support a central timekeeper.

We reported previously that the right inferior frontal gyrus (BA 44) was activated in a motor timing task wherein a retained interval (300 or 600 msec) was reproduced continuously over an 18 sec trial (Rao et al., 1997). This region appears to form a network involving the superior temporal gyrus that is important for the retrieval and rehearsal of nonlinguistic auditory images (Zatorre et al., 1996). In the present study, damage to the inferior frontal gyrus was not associated with time perception deficits, possibly because maintenance of a standard interval was necessary for only a brief period (1 sec). We also previously attributed activation of the basal ganglia–SMA circuit to a timekeeper for movement (Rao et al., 1997). In the present study, the one patient with a right hemisphere SMA lesion showed normal duration perception, which may imply that different neural systems support motor and perceptual timekeepers, although additional case studies are clearly needed.

Parietal cortex

Our findings extend spatial attention theory (Posner and Dehaene, 1994) by suggesting that the parietal cortex is essential for covert shifts of attention to temporal stimuli. Although impairments in disengaging nonspatial attention were comparable between patients with frontal and posterior lesions, attention is intricately linked to working memory functions, possibly because of frontal–parietal interconnections (Selemon and Goldman-Rakic, 1988). Interestingly, neglect patients who showed prolonged attentional blink frequently had right inferior parietal lesions (Husain et al., 1997), consistent with the prospect that temporal aspects of stimuli are processed in this area. Most importantly, the inferior parietal cortex has an avenue for transmitting processing to a timekeeper through its bilateral projections to the basal ganglia (Cavada and Goldman-Rakic, 1991). We should mention that speculations of a time-specific mechanism supported by the parietal cortex is inconsistent with the previously described PET study (Maquet et al., 1996), in which duration and illumination intensity discriminations both activated right inferior parietal cortex (BA 40). Again, this study requires further verification using paradigms that more clearly distinguish temporal from nontemporal processes.

Concluding remarks

The present results extend existing knowledge of right hemisphere function, designating an essential role in supporting time-dependent discriminations within specific areas of frontal and parietal cortex. One intriguing speculation is that right hemisphere specialization for timing might underlie the visuospatial functions of this hemisphere, because the ability to time switches between multiple sensory streams could be crucial for the selection or binding of spatial features (Husain et al., 1997). In contrast, attention to time-related information such as speed activates the left inferior parietal cortex (Corbetta et al., 1991). This may illustrate the analog of the time-dependent perceptual processes of the right hemisphere, reflecting the dominance of the left hemisphere for the representation of movement (Haaland and Harrington, 1996). In fact, damage to the left inferior parietal cortex is commonly associated with limb apraxia, a disruption in the spatiotemporal patterning of movements (Poizner et al., 1995; Harrington and Haaland, 1997).

REFERENCES

Alexander GE, DeLong MR, Strick PL (1986) Parallel organization of functionally segregated circuits linking basal ganglia and cortex. In: Annual review of neuroscience (Cowan WM, ed), pp 357–381. Washington, DC: Society for Neuroscience.

Cavada C, Goldman-Rakic PS (1991) Topographic segregation of corticostriatal projections from posterior parietal subdivisions in the macaque monkey. Neuroscience 42:683–696.

Corbetta M, Miezin FM, Dobmeyer S, Shulman GL, Petersen SE (1991) Selective and divided attention during visual discriminations of shape, color, and speed: functional anatomy by positron emission tomography. J Neurosci 11:2383–2402.

Corbetta M, Miezin FM, Shulman GL, Petersen SE (1993) A PET study of visuospatial attention. J Neurosci 13:1202–1226.

DeArmond SJ, Fusco MM, Dewey MM (1989) Structure of the human brain: a photographic atlas. New York: Oxford UP.

Frey RT, Woods DL, Knight RT, Scabini D, Clayworth C (1987) Defining functional areas with averaged CT scans. Soc Neurosci Abstr 13:1266.

Gibbon J, Church RM, Meck WH (1984) Scalar timing in memory. Ann NY Acad Sci 423:52–77.

Gibbon J, Malapani C, Dale CL, Gallistel CR (1997) Toward a neurobiology of temporal cognition: advances and challenges. Curr Opin Neurobiol 7:170–184.

Goldman-Rakic PS (1987) Circuitry of primate prefrontal cortex and regulation of behavior by representational memory. In: The nervous system, higher functions of the brain, Vol 5, Handbook of physiology (Mountcastle V, Plum F, eds), pp 373–417. Washington, DC: American Physiological Society.

Haaland KY, Harrington DL (1996) Hemispheric asymmetry of movement. Curr Opin Neurobiol 6:796–800.

Harrington DL, Haaland KY, Hermanowicz N (1998) Temporal processing in the basal ganglia. Neuropsychology 12:1–10.

Harrington DL, Haaland KY (1997) Representations of actions in ideomotor limb apraxia: clues from motor programming and control. In: Apraxia: the neuropsychology of action (Gonzalez Rothi LJ, Heilman KM, eds), pp 111–147. East Sussex, UK: Psychology Press.

Heilman KM, Watson RT, Valenstein E (1985) Neglect and related disorders. In: Clinical neuropsychology (Heilman KM, Valenstein E, eds), pp 243–293. New York: Oxford UP.

Husain M, Shapiro K, Martin J, Kennard C (1997) Abnormal temporal dynamics of visual attention in spatial neglect patients. Nature 385:154–156.

Ivry RB, Keele SW (1989) Timing functions of the cerebellum. J Cognit Neurosci 1:136–152.

Ivry RB, Keele SW, Diener HC (1988) Dissociation of the lateral and medial cerebellum in movement timing and movement execution. Exp Brain Res 73:167–180.

Jueptner IH, Rijntes M, Weiller C, Faiss JH, Timmann D, Mueller SP, Diener HC (1995) Localization of a cerebellar timing process using PET. Neurology 45:1540–1545.

Kertesz A (1982) Western Aphasia Battery. New York: The Psychological Corporation.

Knight RT, Hillyard SA, Woods DL, Neville HJ (1981) The effects of frontal cortex lesions on event-related potentials during auditory selective attention. Electroencephalogr Clin Neurophysiol 52:571–582.

Knight RT, Scabini D, Woods DL, Clayworth C (1988) The effects of lesions of superior temporal gyrus and inferior parietal lobe on temporal and vertex components of the human AEP. Electroencephalogr Clin Neurophysiol 70:499–509.

Lacruz F, Artieda J, Pastor MA, Obeso JA (1992) The anatomical basis

of somaesthetic temporal discrimination in humans. J Neurol Neurosurg Psychiatry 54:1077–1081.
Lezak M (1995) Neuropsychological assessment. New York: Oxford.
Lieberman H, Pentland A (1982) Microcomputer based estimation of psychophysical thresholds: the best PEST. Behav Res Methods Instrum 14:21–25.
Macar F, Grondin S, Casini L (1994) Controlled attention sharing influences time estimation. Mem Cognit 22:673–686.
Maquet P, Lejeune H, Pouthas V, Bonnet M, Casini L, Macar F, Timsit-Berthier M, Vidal F, Ferrara A, Degueldre C, Quaglia L, Delfiore G, Luxen A, Woods R, Mazziotta JC, Comar D (1996) Brain activation induced by estimation of duration: a PET study. NeuroImage 3:119–126.
Meck WH (1984) Attentional bias between modalities: effect on the internal clock, memory, and decision stages used in animal time discrimination. Ann NY Acad Sci 423:528–541.
Meck WH (1996) Neuropharmacology of timing and time perception. Cognit Brain Res 3:227–242.
Middleton FA, Strick PL (1994) Anatomical evidence for cerebellar and basal ganglia involvement in higher cognitive function. Science 266:458–461.
Nichelli P, Clark K, Hollnagel C, Grafman J (1995) Duration processing after frontal lobe lesions. Ann NY Acad Sci 769:183–190.
O'Boyle DJ, Freeman JS, Cody FWJ (1996) The accuracy and precision of timing of self-paced, repetitive movements in subjects with Parkinson's disease. Brain 119:51–70.
Olton DS (1989) Frontal cortex, timing and memory. Neuropsychologia 27:121–130.
Pardo JV, Fox PT, Raichle ME (1991) Localization of a human system for sustained attention by positron emission tomography. Nature 3:61–64.
Paulesu E, Frith CD, Frackowiak RS (1993) The neural correlates of the verbal component of working memory. Nature 362:342–345.
Pentland A (1980) Maximum likelihood estimation: the best PEST. Percept Psychophysics 28:377–379.
Poizner H, Clark M, Merians AS, Macauley B, Rothi L, Heilman K (1995) Joint coordination deficits in limb apraxia. Brain 118:227–242.
Posner MI, Dehaene S (1994) Attentional networks. Trends Neurosci 17:75–79.
Posner MI, Walker JA, Friedrich FJ, Rafal RD (1984) Effects of parietal injury on covert orienting of attention. J Neurosci 4:1863–1874.
Rajkowska G, Goldman-Rakic PS (1995a) Cytoarchitectonic definition of prefrontal areas in the normal human cortex: I. Remapping of areas 9 and 46 using quantitative criteria. Cereb Cortex 5:307–322.
Rajkowska G, Goldman-Rakic PS (1995b) Cytoarchitectonic definition of prefrontal areas in the normal human cortex: II. Variability in locations of areas 9 and 46 and relationship to the Talairach coordinate system. Cereb Cortex 5:323–337.
Rao SM, Harrington DL, Haaland KY, Bobholz JA, Cox RW, Binder JR (1997) Distributed neural systems underlying the timing of movements. J Neurosci 17:5528–5535.
Roland PE, Skinhoj E, Lassen A (1981) Focal activations of human cerebral cortex during auditory discrimination. J Neurophysiol 45:1139–1151.
Selemon LD, Goldman-Rakic PS (1988) Common cortical and subcortical targets of the dorsolateral prefrontal and posterior parietal cortices in the rhesus monkey: evidence for a distributed neural network subserving spatially guided behavior. J Neurosci 8:4049–4068.
Singh J, Knight RT (1993) Effects of posterior association cortex lesions on brain potentials preceding self-initiated movements. J Neurosci 13:1820–1829.
Smith EE, Jonides J, Koeppe RA (1996) Dissociating verbal and spatial working memory using PET. Cereb Cortex 6:11–20.
Strick PL, Hoover JE, Mushiake H (1993) Evidence for "output channels" in the basal ganglia and cerebellum. In: Role of the cerebellum and basal ganglia in voluntary movement (Mano N, Hamada I, DeLong MR, eds), pp 171–180. New York: Elsevier Science.
Von Steinbuchel N (1995) Temporal systems states in speech processing. In: Supercomputing in brain research: from tomography to neural networks (Herrmann HJ, Wolf DE, Poppel E, eds), pp 75–81. Singapore: World Scientific.
Wechsler D (1981) Wechsler Adult Intelligence Scale–Revised. New York: Psychological Corporation.
Zatorre RJ, Samson S (1991) Role of the right temporal neocortex in retention of pitch in auditory short-term memory. Brain 114:2403–2417.
Zatorre RJ, Evans AC, Meyer E (1994) Neural mechanisms underlying melodic perception and memory for pitch. J Neurosci 14:1908–1919.
Zatorre RJ, Halpern AR, Perry DW, Meyer E, Evans AC (1996) Hearing in the mind's ear: a PET investigation of musical imagery and perception. J Cognit Neurosci 8:29–46.