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

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showed that the mean number of years after stroke did not differ between the two points at which the subject made no more than one error in 1 sec. The smallest distance of the subject's index finger with either one or two points, and 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 (a circle), or a combination 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 tone pairs was 1 sec, 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 method for deriving thresholds.

**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 hemisphere damage, and patients were tested a minimum of 3 months after onset. A Mann–Whitney U test was used to determine the relationship of attention and time perception in patients with focal left or right hemisphere lesions.

**Table 1. Demographic characteristics of the control and stroke groups**

<table>
<thead>
<tr>
<th>Right control</th>
<th>Left control</th>
<th>Right hemisphere damage</th>
<th>Left hemisphere damage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>24</td>
<td>24</td>
<td>18</td>
</tr>
<tr>
<td>Age</td>
<td>66.7 (8.3)</td>
<td>63.5 (9.1)</td>
<td>64.6 (12.2)</td>
</tr>
<tr>
<td>Education</td>
<td>14.5 (3.0)</td>
<td>14.7 (2.4)</td>
<td>13.9 (3.0)</td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>71</td>
<td>71</td>
<td>50</td>
</tr>
</tbody>
</table>

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

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 hemiparetic 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 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 procedures (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 tone pairs was 1 sec, 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 method for deriving thresholds.

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 lower duration thresholds and dividing that 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 frequency of the comparison tones in the standard 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. 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
Lesion volume did not differ significantly 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 RHD groups (mean = 10.7; SD = 5.3) relative to the controls (mean = 8.3; SD = 6.5 for all control subjects) \( F_{(1,85)} = 6.23, p < 0.025 \). 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 group) or with right hemisphere anterior lesions (i.e., one
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 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.
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).

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.

**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 3a displays the duration thresholds for all subjects on the duration perception task. The figure shows
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 \( \times \) 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 \( F_{1,39} = 28.70; p < 0.001 \), whereas there was only a trend for difference thresholds to be elevated in the LHD group in comparison to their controls \( F_{1,31} = 18.14; p < 0.001 \), but there was no difference between the LHD group and their controls \( F_{1,285} < 1.0 \). There was also an interaction of group \( \times \) hand \( \times \) 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 \( \times \) 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 \( \times \) 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 \( \times \) 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) \( F_{1,31} = 14.16; p < 0.01 \), 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 \( \times \) 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. 3b), 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 \(F_{(1,100)} = 6.69; p < 0.025\) 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. 4a,b) or posterior lesions (Fig. 4c,d) in the left and right hemispheres. Figure 4a shows that 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 4b 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. 4b), and the other (patient 2) had damage to the motor and caudal portion of the premotor cortex on Section 9 (Fig. 4b), as well as somatosensory cortex (Section 8). Figure 4a,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. 4a), and all three of the LHD patients with normal duration perception (Fig. 4b) 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. 4b). 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 4c 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).
formance and posterior damage involved the supramarginal gyrus (SMG; BA 40) on Section 9 and rostral portions of the angular gyrus. In contrast, Figure 4d 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 4c,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. 4c), 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. 4d).

**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 repre-

sented 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 (Seelen 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).

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