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Research Report

Cognitive timing: Neuropsychology and anatomic basis

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ABSTRACT

We report data from 31 subjects with focal hemisphere lesions (15 left hemisphere) as well as 16 normal controls on a battery of tasks assessing the estimation, production and reproduction of time intervals ranging from 2–12 s. Both visual and auditory stimuli were employed for the estimation and production tasks. First, ANOVAs were performed to assess the effect of stimulus modality on estimation and production tasks; a significant effect of stimulus modality was observed for the production but not the estimation task. Second, accuracy was significantly different for the 2 s interval as compared to longer intervals. Subsequent analyses of the data from 4–12 s stimuli demonstrated that patients with brain lesions were more variable than controls on the estimation and reproduction tasks. Additionally, patients with brain lesions but not controls exhibited significant differences in performance on the different tasks; patients with brain lesions under-produced but over-estimated time intervals of 4–12 s but performed relatively well on the reproduction task, a pattern of performance consistent with a “fast clock”. There was a significant correlation between impaired performance and lesions of the parietal lobe but there was no effect of laterality of lesion or correlation between lateral frontal lobe lesions and impairment on any task.

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1. Introduction

Gibbon et al. (1997) noted that “Time is the primordial context”. A similar view on the centrality of time for human understanding was expressed by Kant (1787/1934) who argued that space and time represent the two elementary dimensions of experience. The critical role in behavior played by temporal processing may also be illustrated by the fact that basic mechanisms involved in timing appear to have developed early in evolution and been conserved. A well-developed capacity for timing has been demonstrated in goldfish, starlings, rats, primates and humans (Gibbon et al., 1997; Matell and Meck, 2000).

Despite its central role in human cognition, temporal processing has received relatively little attention in contem-

porary neuroscience. One possible explanation for this is that there are no neural structures dedicated to temporal processing. Whereas much of the posterior third of the primate brain is intimately involved in the representation of space for perception and action, comparable specialization for temporal processing is not readily identified. Similarly, although clinical syndromes attributed to a disruption of spatial processing are well known (e.g., neglect, simultanagnosia, optic ataxia, topographic disorientation), disorders characterized by a primary impairment in temporal processing have not been described.

A number of models of the processes underlying interval timing have been proposed (see Gibbon et al., 1984a,b; Mangels and Ivry, 2001; Matell and Meck, 2000; Ivry and Richardson, 2002; Staddon and Higa, 1999). Many models incorporate

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elements that provide a representation of temporal duration, a “clock mechanism” (e.g., [Gibbon et al., 1984a,b](#)). Attention and working memory are also involved in temporal processing ([Macar et al., 1994](#); [Zakay and Block, 2004](#); [Papagano et al., 2004](#); [Chaston and Kingstone, 2004](#)).

More than one hundred years ago, [Musterberg \(1889\)](#) argued for a fundamental distinction between the processing of time intervals of less than 500 ms as compared to longer intervals. Although there has been disagreement regarding the precise boundary between “short” and “long” time intervals, the hypothesis that timing of short intervals is “automatic” whereas the processing of longer time intervals is under “cognitive” control and that these processes have different neural bases has been supported by a number of investigators ([Rammsayer and Lima, 1991](#); [Lewis and Miall, 2003](#); [Kagerer et al., 2002](#); but see [Macar et al., 2002](#) for a dissenting view). As our interest in the present context is cognitive timing, here we restrict our analysis to multi-second durations.

The anatomic basis of temporal processing remains controversial, in part because a variety of different paradigms has been employed in both normal and brain lesion subjects. Investigations involving brain lesion subjects have explored the effects of subcortical damage to the basal ganglia (e.g., [Harrington et al., 1998](#); [Shin et al., 2005](#)) and cerebellum (e.g., [Malapani et al., 1998](#); [Nichelli et al., 1996](#); [Ivry et al., 2002](#); [Spencer et al., 2003](#); [Harrington et al., 2004b](#)). Additionally, several investigators have explored the cortical basis of the processing of short intervals (often known as “automatic” timing) in subjects with hemispheric lesions. [Mangels et al. \(1998\)](#) administered a task in which subjects with frontal lobe or cerebellar lesions were asked to determine if a stimulus was shorter or longer than a reference stimulus; in different blocks of trials, the reference stimulus was either 400 or 4000 ms. They found that subjects with neocerebellar lesions performed abnormally at both intervals whereas patients with frontal lesions performed abnormally only at the longer interval. They concluded that the frontal lobe supports the working memory elements crucial to the maintenance and monitoring of temporal information whereas the neocerebellum was crucial for core timing procedures. [Nichelli et al. \(1995\)](#) also explored the effects of frontal lobe lesions on temporal processing using a temporal bisection task. They found that patients with frontal lesions exhibited greater variability in performance but were not less accurate than controls. [Harrington et al. \(1998\)](#) reported data from subjects with right or left hemisphere cortical lesions on a duration perception task in which subjects were asked to judge whether a tone was shorter or longer than a preceding standard tone of 300 or 600 ms. Whereas both right and left hemisphere lesion subjects were impaired on the time duration task, only subjects with right hemisphere lesions were impaired after controlling for frequency perception deficits. The authors emphasized the role of the right frontal and parietal cortices in the processing of temporal information.

Although studies in which subjects are selected according to lesion site help to elucidate the role of the brain region in question they cannot provide information about the contributions of other brain regions to the faculty in question. For this purpose subjects with brain lesions distributed across multiple brain regions may be most informative. We are aware of

two such studies of the cortical contribution to temporal processing involving longer intervals (often known as “cognitive” timing). [Rubia et al. \(1997\)](#) reported an investigation of subjects with right or left middle cerebral artery infarcts on time estimation and production tasks; they found that both right and left hemisphere lesion subjects were inaccurate. The patterns of performance of the right and left hemisphere lesion subjects differed, however, in that the former group behaved as if the clock was running too fast whereas the left hemisphere lesion subjects did not demonstrate a consistent effect on “clock speed”. Furthermore, they suggested that a lesion in the posterior portion of the supralenticular white matter provided the anatomic basis of the temporal processing deficit. [Kagerer et al. \(2002\)](#) reported a study in which subjects with focal brain lesions involving the right or left hemisphere were tested on a temporal reproduction task; they found that subjects performed well with stimuli lasting up to 2 s but that subjects with right hemisphere lesions were impaired with stimuli greater than 3 s.

Finally, it should be noted that several single subjects with temporal processing abnormalities caused by cortical lesions have been reported. [Koch et al. \(2002\)](#) reported a patient with a right prefrontal lesion who underestimated longer intervals; for example, he estimated 90 s intervals to be approximately 40 s. [Binkofski and Block \(1996\)](#) reported a patient with a left frontal tumor whose performance on a time production task was abnormal; when asked to produce a 60 s interval, his mean production was 286 s. [We \(Wiener and Coslett, 2008\)](#) recently reported a subject with probable fronto-temporal dementia with bilateral frontal lobe abnormalities on PET scan whose performance was strikingly abnormal on a variety of temporal processing tasks. She performed well on reproduction tasks but under-produced and over-estimated time; with auditory stimuli she estimated a 12 s stimulus to be 144 s and when asked to produce a 12 s interval generated a 4 s response.

The anatomic basis of temporal processing has also been explored with functional imaging in humans and animals (e.g., [Onoe et al., 2001](#)). Unfortunately, these studies have often reported inconsistent results (for review see [Harrington and Haaland, 1999](#); [Lewis and Miall, 2003](#); [Macar et al. 2002](#)). Some functional imaging work (see [Lewis and Miall, 2006](#)) and Transcranial Magnetic Stimulation studies (e.g., [Jones et al., 2004](#); [Koch et al., 2003](#)) have implicated the dorsolateral prefrontal cortices whereas other studies have emphasized the role of the SMA (e.g., [Macar et al., 2002, 2004](#); [Coull et al., 2004](#)). In a similar vein, there is no unanimity with respect to the lateralization of temporal processing. Many functional imaging (see [Rubia and Smith, 2004](#), [Lewis and Miall, 2006](#)) and Transcranial Magnetic Stimulation (e.g., [Jones et al., 2004](#)) studies suggest that the right hemisphere is of particular relevance to temporal processing but, once again, there are a number of discrepant findings. [Jech et al. \(2005\)](#), for example, reported an increase in BOLD signal in the left but not right dorsolateral cortex that exhibited properties consistent with the hypothesis that this region served to measure stimulus duration. Additionally, a number of other investigators have reported left prefrontal activation in timing tasks ([Hinton and Meck, 2004](#); [Harrington et al., 2004a](#); [Rubia et al., 1998](#); [Kawashima et al., 2000](#); [Schubotz et al., 2001](#)).

We report data from a series of investigations in which 31 subjects with focal brain lesions and 16 normal controls were assessed on a range of tasks that included time production, time estimation and time reproduction with both visual and auditory stimuli. This study is unique in several respects. To the best of our knowledge this represents the first investigation in which subjects with a wide distribution of brain lesions were assessed on a battery of tasks assessing temporal estimation, production and reproduction in the same subjects. Second, previous investigations have not administered temporal processing tasks using both auditory and visual stimuli.

2. Results

Subjects included 31 patients with focal, unilateral brain lesions (16 right, 15 left hemisphere), and 16 age-matched control subjects. Five tasks were administered to all subjects and controls. In the two time estimation tasks subjects were presented either a visual or auditory stimulus for an interval of 2, 4, 6, 8, 10 or 12 s and asked to indicate the duration of the stimulus. In the two time production tasks, subjects were shown a number (2, 4, 6, 8, 10 or 12) and asked to produce a visual or auditory stimulus corresponding to that duration (in seconds) by depressing a response key to initiate and terminate the trial. Finally, in the time reproduction task, subjects were shown a visual stimulus and asked to generate a stimulus of the same duration by depressing a response key to initiate and terminate the trial. A time reproduction task with auditory stimuli was not performed because of time constraints.

For all tasks, both accuracy and variability were assessed. Accuracy was measured by subtracting the target duration from the subject's response duration for all tasks; using this method, responses shorter than the target produced negative numbers whereas responses longer than the target duration generated positive numbers. In order to compare performance across different duration lengths, this difference was then divided by the stimulus duration. Using this procedure, a perfect response would be scored as 0. Variability was assessed by calculating each subject's standard deviation at each duration length for each task.

First, ANOVAs that included both normal and brain lesions subjects were conducted to examine the effect of stimulus modality on subject accuracy in both the visual and auditory versions of the estimation and production tasks. Results showed a significant interaction between task and modality (Wilkes' = .853, $F(1, 45) = 7.724$, $p = .008$). Separating the tasks showed a significant effect of modality in the production task ($p = .003$); consistent with some (Meck, 1984; Penney et al., 2000; Droit-Voilet et al., 2007) but not all (Macar et al., 2002) previous observations, productions were shorter for auditory as compared to visual stimuli. No difference as a function of sensory modality was observed for the estimation task ($p = .26$). In light of these findings, data for the visual and audio version of the estimation task were combined whereas the visual and audio versions of the production task were analyzed separately.

Next, accuracy was assessed with a repeated measures ANOVA in which stimulus duration (2, 4, 6, 8, 10, and 12 s) and task (production – visual, production – auditory, estimation,

and reproduction) served as within subject factors and subject type (patient, control) served as a between subjects factor. (See Fig. 1).

A main effect of duration length (Wilks' $\Lambda = .726$, $F(5, 41) = 3.10$, $p = .02$) was noted. There was no effect of subject type or task; there were no interactions. Post hoc testing using paired-sample t-tests with an alpha level set at $p = .003$ to correct for multiple comparisons revealed that accuracy was significantly worse at 2 s than at all other intervals (all p 's $< .001$). As previously noted, many investigators have proposed that there is a fundamental difference in the processes underlying timing in the sub-second to second range as compared to the procedures employed in "cognitive" timing involving longer intervals. In light of these data, the demonstration that performance at 2 s differed substantially from all other intervals was surprising. The finding was not, however, unprecedented. Kagerer et al. (2002) reported that subjects with brain lesions performed differently with stimuli less than 3 s in duration as opposed to longer durations. As cognitive timing is the focus of the present investigation and, at least for subjects with brain lesions, the 2 s duration differs substantially from longer durations, we subsequently analyzed the data from the 2 s interval and the 4–12 s intervals separately. We return to this issue in the General discussion.

The repeated measures ANOVAs were repeated for both accuracy and variability using 5 duration lengths (4, 6, 8, 10, and 12 s). For the accuracy ANOVA, the effect of duration length was no longer present ($p = .13$) but a main effect of task was obtained (Wilkes' = .658, $F(3, 43) = 7.45$, $p < .001$). Paired sample t-tests revealed that both estimation ($M = .03$, $p = .03$) and reproduction ($M = .00$, $p < .001$) accuracy was significantly better than the production audio accuracy ($M = -.15$) while the production visual task fell between these scores ($M = -.06$).

There was a marginal interaction between task and subject type ($p = .09$). To further evaluate this relationship, a series of one-sample t-tests was conducted comparing mean scores for the audio production, visual production, reproduction and estimation tasks (collapsed across 4 to 12 s durations; see Fig. 2). Mean accuracy for controls did not differ in the four tasks. In contrast, significant differences between all tasks were noted for patients ($p \leq .03$) with the exception of visual and audio production comparison, for which a trend was noted ($p = .06$). Thus, patients, but not controls, over-estimate and under-produce time intervals, but perform well on the reproduction task. As will be discussed below, one interpretation of these findings is that "clock speed" is increased in subjects with brain lesions (see also Wiener and Coslett, 2008).

The ANOVA for variability revealed a main effect of task (Wilkes' = .71, $F(3, 43) = 5.869$, $p = .002$). As in the accuracy analysis, both the estimation ($M = .20$, $p = .005$) and reproduction ($M = .21$, $p = .002$) tasks were significantly more variable than the audio production task ($M = .08$). The mean for visual production task fell between these scores ($M = .14$). A significant interaction of task and subject type (Wilkes' = .82, $F(3, 43) = 3.25$, $p = .03$) was also obtained. A one-way ANOVA revealed that patients were significantly more variable than controls on the estimation ($p = .005$) and reproduction ($p = .009$) tasks, but no group differences were found on either production task ($p > .15$).

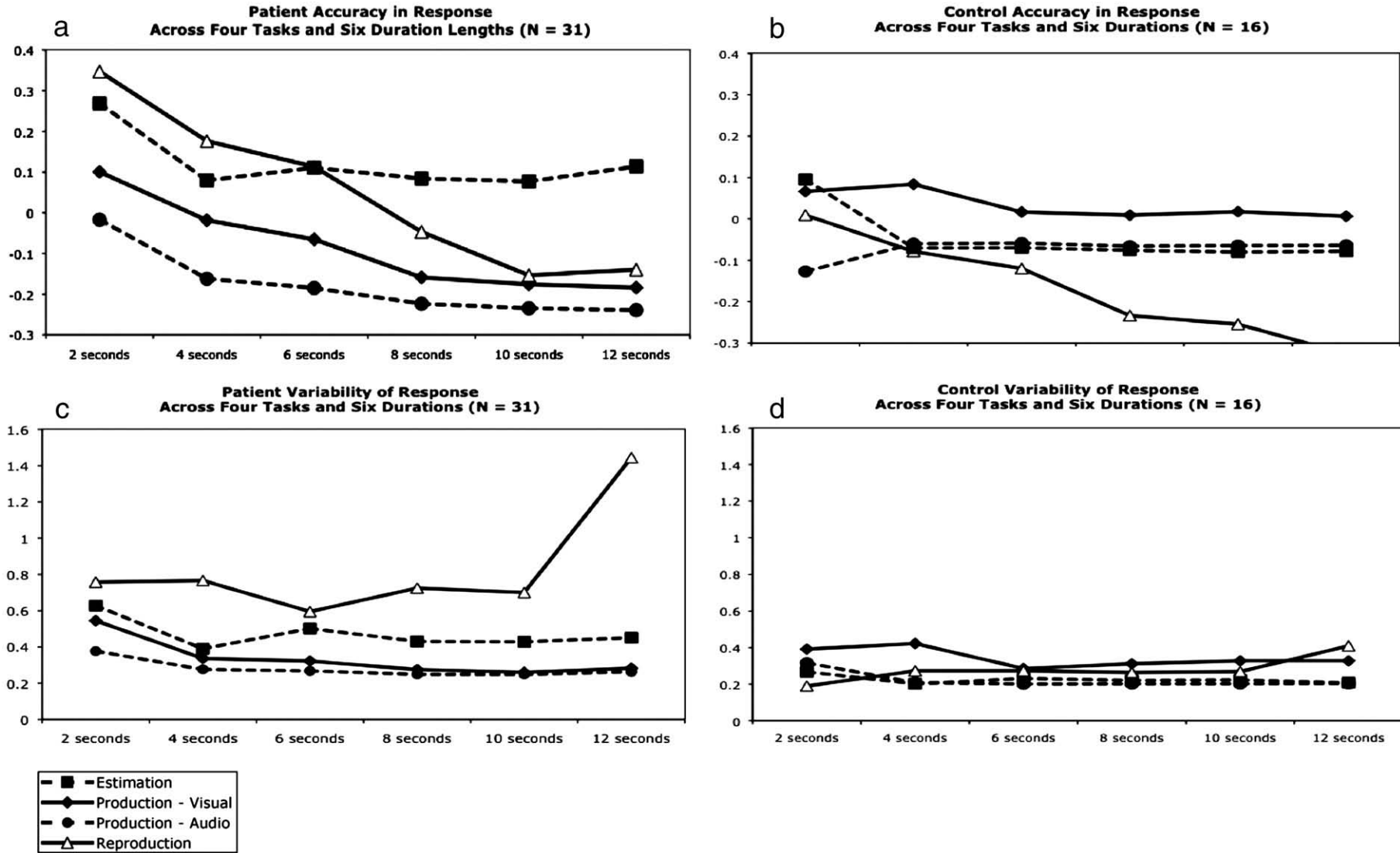


Fig. 1 - (a) Accuracy data for patients for the estimation, reproduction, auditory production and visual production tasks for the six durations; (b) Accuracy data for controls; (c) Variability data for patients for four tasks across the six durations; (d) Variability data for controls.

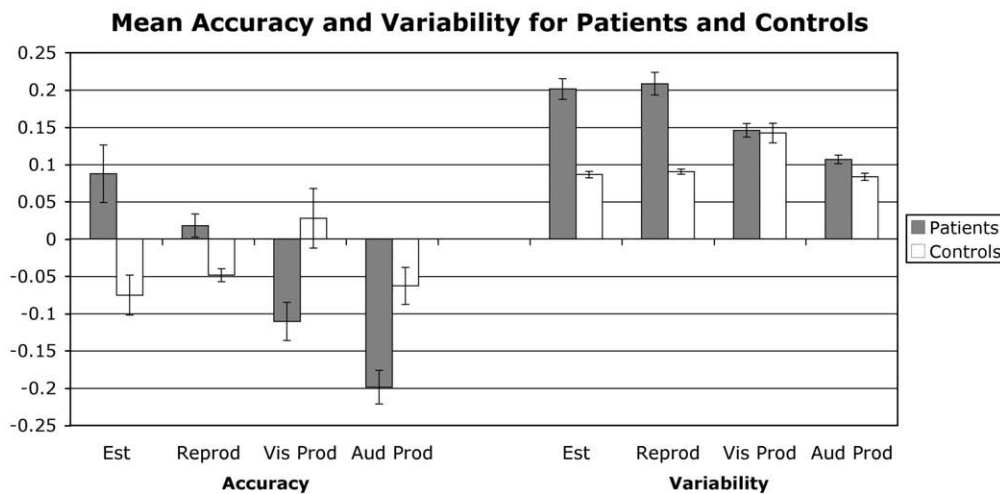


Fig. 2 – Mean accuracy and variability data for patients and controls for the estimation, reproduction, visual production and auditory production tasks collapsed across the 4–12 s intervals.

Two additional repeated measures ANOVAs were repeated for both accuracy and variability at 2 s. For the accuracy ANOVA, there were no main effects of task or group; additionally, there were no interactions with subject type (Wilkes'=.966, $F(3,43)=.497$, $p=.686$). For the variability ANOVA, there was no main effect of task (Wilkes'=.889, $F(3, 43)=1.798$, $p=.162$) or interaction with subject type (Wilkes'=.974, $F(3, 43)=.386$, $p=.764$).

2.1. Anatomic basis of interval timing effects

A series of repeated measure ANOVAs was performed to examine the anatomic bases of the behavioral differences described above. Separate analyses were performed for accuracy and variability at the 2 s duration and the 4–12 s durations on all four tasks. First, the effect of hemisphere of lesion (right, left) was assessed; there was no effect of hemisphere of lesion on any of the four tasks with respect to accuracy or variability at either time interval (all $p>.27$). As four subjects were left-handed, a similar analysis was performed in which the data were analyzed with respect to dominant/non-dominant hemisphere; once again, no significant effects were identified for any comparison ($p>.16$).

As Rubia et al. (1997) reported differences in subjects with anterior as compared to posterior lesions, an additional analysis was performed in which subjects were categorized

according to this dimension; those subjects whose lesion was predominantly anterior to the central sulcus or involved the anterior two-thirds of the temporal lobe were included in the anterior group; No significant effects of location were found within the hemisphere on any task with respect to either accuracy or variability (all $p>=.18$).

In order to examine a possible relationship between lesion size and behavioral performance, a series of bivariate correlations was conducted for each task between lesion size and either mean accuracy or variability at the 2 s duration or the 4–12 s mean score (collapsed). No results were significant ($-.14<r<.18$, $p>.21$).

Next, to investigate potential relationships between task performance and damage to specific cortical structures, the number of voxels lesioned (1 voxel=1 mm³) was determined in 4 anatomical regions using MRICron software (<http://www.sph.sc.edu/comd/rorden/mricron/>; see Fig. 3 for lesion overlay of subjects). The regions of interest were selected on the basis of previous investigations; they included the lateral frontal lobe (inferior and middle frontal gyri), the middle temporal gyrus, the inferior parietal lobule (the supramarginal gyrus and angular gyrus), and the superior parietal lobule. The regions of interest were identified using the AAL atlas that is provided with MRICron (see supplementary Fig. 1). The number of lesioned voxels in each region was divided by the total number of voxels in each region, in order to generate a

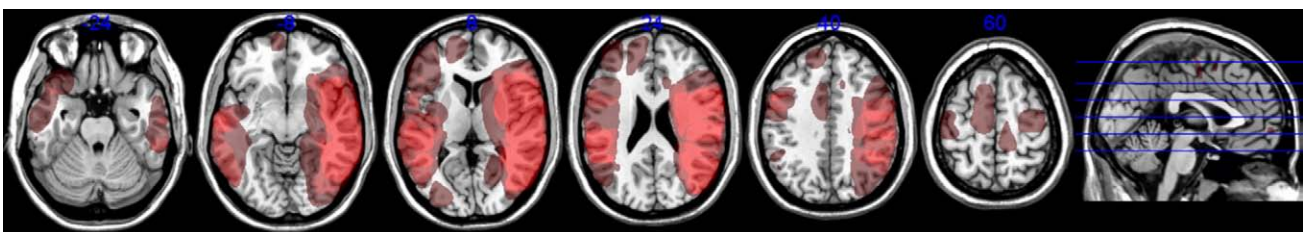


Fig. 3 – An overlay of the 31 lesions transposed to a common template using MRICron. Brown represents a single lesion whereas the reddest areas represent eight overlapping lesions. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1

ID	Sex	Age	Handedness	Lesion type	Aphasia	Lesion vol (cc)	Lesion side	Posterior/ Anterior	Lateral frontal	Middle temporal	Inferior parietal	Superior parietal
1	M	58	R	I	13	165.1	L	Anterior	15.2	0.0%	0.3%	0.0%
2	M	64	R	I	23	10.6	L	Anterior	0.0%	0.0%	0.0%	0.0%
3	F	54	L	I	N/A	25.1	R	Anterior	30.6%	0.0%	0.0%	0.0%
4	F	73	R	I	N/A	14.8	R	Posterior	0.0%	0.1%	11.6%	0.0%
5	F	80	R	I	N/A	69.6	R	Posterior	0.0%	0.0%	52.8%	79.0%
6	M	49	R	I	N/A	38.8	R	Posterior	0.0%	2.0%	35.3%	0.1%
7	M	54	L	I	18	68.1	L	Posterior	18.5%	19.4%	14.7%	0.0%
8	M	54	L	I	21	15.3	L	Posterior	0.0%	0.0%	24.2%	1.3%
9	F	68	R	T	N/A	34.5	R	Anterior	2.9%	0.0%	0.0%	0.0%
10	F	41	R	I	18	44.5	L	Anterior	9.0%	3.5%	0.0%	0.0%
11	F	69	R	I	N/A	6	R	Posterior	0.0%	0.2%	19.8%	0.0%
12	M	79	R	I	22	49.2	L	Posterior	0.0%	2.1%	33.4%	18.5%
13	F	76	R	I	N/A	31.2	R	Anterior	19.6%	0.0%	0.0%	0.0%
14	M	51	R	I	N/A	18.8	R	Posterior	0.0%	1.7%	0.0%	0.0%
15	F	42	R	I	N/A	88.4	R	Posterior	8.7%	64.2%	11.3%	0.0%
16	M	50	R	I	15	59.4	L	Posterior	0.0%	35.3%	53.0%	0.0%
17	F	57	R	I	N/A	2.5	R	Anterior	0.0%	0.0%	0.0%	0.0%
18	M	58	R	I	8	302.6	L	Posterior	48.3%	81.3%	85.1%	1.7%
19	F	51	R	I	N/A	64.8	R	Posterior	1.1%	23.6%	6.1%	0.0%
20	F	77	L	I	21	21.5	L	Posterior	0.0%	20.3%	15.5%	0.0%
21	F	76	R	I	N/A	6.9	R	Anterior	0.0%	0.0%	0.0%	0.0%
22	F	64	R	I	N/A	8.2	R	Anterior	7.8%	0.0%	0.0%	0.0%
23	F	61	R	I	19	31.5	L	Anterior	13.8%	0.0%	2.1%	0.0%
24	M	62	R	I	10	71.8	L	Posterior	0.0%	51.8%	42.6%	0.2%
25	F	59	R	I	N/A	75.6	R	Posterior	0.0%	82.8%	4.4%	0.0%
26	F	44	R	I	N/A	16.1	R	Posterior	0.0%	0.4%	24.3%	0.0%
27	F	54	R	T	N/A	43.2	R	Anterior	10.5%	0.0%	0.0%	0.0%
28	F	69	R	I	13	60.5	L	Posterior	0.0%	59.4%	4.6%	0.0%
29	M	42	R	I	21	85.1	L	Anterior	24.9%	3.3%	4.5%	0.0%
30	M	65	R	I	25	57.1	L	Posterior	0.0%	0.0%	30.5%	60.3%
31	F	51	R	I	22	74.7	L	Anterior	1.5%	6.4%	0.0%	0.0%

I = Ischemic stroke.
T = Tumor resection.

value for percent of total structure damaged (see Table 1). For each task, the percentage of structure damaged was correlated with the patients' mean accuracy or variability score at either the 2-second duration or the 4–12 s durations (collapsed) for all four tasks. To correct for multiple comparisons the alpha level was set to $p = .004$. We note that for this analysis we collapsed across hemisphere; that is, to explore the effect of lesions of the superior parietal lobule, for example, we included subjects whose lesion involved either the right or left superior parietal lobule. We did not perform an ROI-based analysis restricted to either the right or left hemisphere because we believed that we would not have sufficient power to detect an effect with our sample size (Kimberg et al., 2007).

The only significant findings at the corrected p value involved the superior parietal lobule. For the reproduction task accuracy scores were significantly correlated with percent damage at the 2-second duration ($r = .63$, $p < .001$), and variability at the 4–12 s duration ($r = .50$, $p = .004$); the variability score at the 2 s duration was also correlated with percent damage ($r = .42$, $p = .02$) but this was not significant at the corrected p value. Finally, although not significant given the corrected p value, variability at the 4–12 s duration on the reproduction task was correlated with percent of the inferior parietal lobe damaged ($r = .38$, $p = .04$).

2.2. Effect of aphasia on timing

A similar analysis was conducted to examine the effects of aphasia on performance. To this end, the fifteen subjects with left hemisphere lesions were categorized as aphasic ($N = 5$) or not ($N = 10$) on the basis of the tasks described previously. ANOVAs were performed in which the performance of aphasic and non-aphasic subjects were contrasted with respect to accuracy and variability for each of the four tasks at 2 s and 4–12 s. There was no difference between the aphasic and non-aphasic groups in any analysis (all p 's $> .33$).

3. General discussion

We report the first study of which we are aware in which both visual and auditory stimuli were employed and the production, estimation and reproduction of supra-second intervals was assessed in subjects with focal brain lesions. Several interesting and important findings emerge.

The first point is that, like a number of other investigators (e.g., Nichelli et al., 1996), we find differences between brain lesion and normal subjects with respect to variability; abnormal variability has been found on temporal bisection

tasks (Melgire et al., 2005), the peak procedure (Malapani et al., 1998), a PEST task (Mangels et al., 1998), timed tapping tasks (Ivry et al., 1988), and reproduction and production tasks (Pouthas and Perbal, 2004). Our subjects with brain lesions exhibited significantly greater variability than controls on estimation and reproduction tasks. This is evident in the ANOVA that demonstrated effects of variability on estimation and reproduction.

Consistent with some previous investigations (e.g., Harrington et al., 1998), we did not observe a significant main effect of subject (patients versus controls) on accuracy. There was, however, a trend ($p=.09$) for an interaction between subject and task. Additional analyses demonstrated that patients with brain lesions but not controls exhibited significant differences in accuracy across all 4 tasks. In particular, patients with brain lesions overestimated, under-produced, but accurately reproduced intervals. There are several possible explanations for this pattern of performance (see Wiener and Coslett, 2008). Many accounts of temporal processing postulate a “clock” mechanism consisting of a pacemaker that generates “beats” and an accumulator that registers or counts the beats (e.g., Wearden, 1999; Gibbon et al., 1984a,b). On such a model, a “fast” clock characterized by too rapid production or counting of beats could explain this pattern of performance. If the metric for converting beats to seconds is preserved, a fast clock should be associated with overestimation of time intervals because the total number of beats registered would be too high. In contrast, subjects would be expected to under-produce time because the pathologically rapid accumulation of beats would lead subjects to reach the target number more quickly. This pattern can be illustrated by assuming that a normal clock beats at 100 Hz but a “fast clock” is beating at 130 Hz. In this situation, a subject would estimate a 10 s stimulus as 13 s as in this interval they would have accumulated 1300 rather than 1000 beats. Similarly, if asked to produce a 10 s stimulus, the subject would respond after the accumulator had registered 1000 beats; at the accelerated rate of accumulation this would occur after 7.7 s. Subjects with a fast clock would be expected to perform normally on a reproduction task, however, as the same clock that recorded the number of beats during the target presentation would be used to generate that same number of beats for the response.

An alternative explanation for this pattern of performance is that memory of time intervals is disrupted. If, for example, the 10 s corresponds to a mental representation of 7.7 s, subjects would estimate a 10 s stimulus as 7.7 s but when asked to produce a 10 s stimulus, would respond at 13 s. Once again, subjects would be expected to perform well on a reproduction tasks because the same corrupted mental representations of duration would be implicated in both registering the target duration and producing the response.

It should be noted that these accounts are not mutually exclusive; in light of the diversity of the size and location of the lesions one might speculate that the same pattern of performance reflects different processing impairments in different subjects.

Striatal Beat Frequency (Matell and Meck, 2000, 2004) as well as other non-monotonic accounts of temporal processing may also provide an account of the increased variability and tendency to exhibit a “fast clock” (leftward shift) demon-

strated by brain lesion subjects. This account postulates a prominent role of the cerebral cortex in timing; more specifically, by virtue of widespread projections from cortical neurons, spiny neurons of the striatum serve as coincidence detectors. Damage to the cortex would be expected to alter the network’s input to the coincidence detectors disrupting their capacity to generate a match between a previously observed or expected pattern of input and the observed pattern of input. As responses would be made on an impoverished cortical input, one might expect greater variability in performance. Striatal beat frequency may also explain the tendency to observe a fast clock (leftward shift) in patients with brain injury. One possible response to a degraded network input would be to relax the criteria for defining a “match”, thereby increasing the likelihood of an early coincident signal.

The most noteworthy finding with respect to the anatomic basis of temporal processing is a significant correlation between extent of damage to the superior parietal lobule and several measures of performance. This finding is at least broadly consonant with a number of studies involving monkeys (Leon and Shadlen, 2003) and humans (Rubia et al., 1997). Janssen and Shadlen (2005), for example, identified neurons in LIP in macaques for which the spike rate varied over several seconds as a function of the likelihood that a response will be required. As noted by these investigators, the fact that the firing rate of these neurons was sensitive to both elapsed time and the probability that a response would be required, suggests that the parietal lobe may represent the time structure of external stimuli.

We did not replicate a number of previously reported findings from lesion studies regarding the anatomic basis of timing. For example, unlike Kagerer et al. (2002) and Harrington et al. (1998), we did not find temporal processing deficits to be associated with right hemisphere lesions. Similarly, we did not replicate the report of Rubia et al. (1997) that timing deficits were associated with posterior lesions. The explanation for these discrepancies is not clear. As our sample size was comparable to studies that have reported significant lesion site correlations, it is not clear that this factor alone can explain the discrepancy.

Whereas a number of studies have implicated the dorso-lateral frontal lobe (Lewis and Miall, 2006; Jones et al., 2004; Koch et al., 2003) we did not find an association between lesions at this location and impaired temporal processing. Although this finding must be interpreted with caution given our sample size, it is noteworthy that significant associations were identified for parietal structures; as the number of subjects with lesions at the two regions was at least approximately the same, a limitation in power because of a small sample size is unlikely to be the sole explanation for the failure to demonstrate an effect of dorsolateral frontal lesions on temporal processing.

A number of functional imaging studies have implicated the medial frontal cortex in temporal processing (e.g., Macar et al., 2002, 2004; Coull et al., 2004). Unfortunately, our data do not permit us to address the role of this region in temporal processing. As our sample included only one subject with a lesion in this region, our ability to identify effects of lesions at this site was extremely limited (Kimberg et al., 2007). In light of this, we did not include the medial frontal cortex in our

analysis; our data do not permit us to draw any conclusions regarding its role in temporal processing. Collectively, our data as well as the data reviewed briefly in the introduction regarding the anatomic bases of temporal processing is consistent with the view that multiple, widely distributed structures may be implicated in temporal processing. For example, the clock mechanism may be critically dependent on sub-cortical structures such as the cerebellum (Mangels et al., 1998; Ivry and Spencer, 2004) or basal ganglia (Matell and Meck, 2004); other faculties that are crucial for timing such as working memory, attention, and motor planning may be distributed across multiple cortical regions. The degree to which specific brain regions appear to be implicated in timing tasks may be a reflection of complex and interacting variables such as the length of the interval, the degree to which attention and working memory are required and the extent to which the response requires motor planning (see Buhusi and Meck, 2005 and Lewis and Miall, 2006). As noted by Lewis and Miall (2003), inconsistencies across studies may be, at least in part, attributable to the degree to which the tasks drawn on these different faculties.

Our data are, in part, consistent with previous observations that interval timing is influenced by stimulus modality. Penney et al. (2000) and Droit-Volet et al. (2004, 2007) reported that the clock rate is 10% slower for visual as compared to auditory stimuli; this was only observed on a temporal bisection task in which the standard and target differed with respect to modality (e.g., the standard interval was a visual stimulus whereas the target was auditory); trials on which both the stimulus and standard were presented in the same modality (e.g., both visual) did not exhibit this effect. Although we did not observe an effect of stimulus modality on the estimation task, we found that subjects with brain lesions but not normal controls produced shorter responses to visual as compared to auditory stimuli; this finding is consistent with the claim that a clock mechanism is faster for visual as compared to auditory stimuli. Data from a patient with probable Fronto-temporal dementia investigated with the same battery of tasks is also relevant (Wiener and Coslett, 2008). This patient (MN) exhibited striking effects of stimulus modality on both estimation and production tasks; productions were longer for visual stimuli whereas her estimates of time intervals were shorter for visual as compared to auditory stimuli. Once again, these data are consistent with the hypothesis that different mechanisms are used for interval processing for visual as compared to auditory stimuli. We are unaware of other data from patients with brain lesions that address this issue. Clearly, a more adequate account of stimulus modality differences in interval timing will require additional investigations.

Finally, one factor that may have influenced the performance of our subjects is chronometric counting. Several studies have demonstrated that a strategy of counting may produce deviations from the scalar property of temporal processing (Hinton and Rao, 2004; Clement and Droit-Volet, 2006; Wearden and Lejeune, 2008). We asked subjects not to count during the testing but do not have information regarding the degree to which they complied with this strategy. We were reluctant to add a secondary task to interfere with counting as brain lesions in different locations

may differentially affect performance in dual task paradigms, thereby introducing a different confound (Coslett et al., 1987).

There is, however, at least one finding that suggests that counting did not substantially influence performance. As previously described, the performance of subjects with left hemisphere lesions with and without aphasia did not differ. On the assumption that chronometric counting is likely to be language-based (cf., Hinton and Rao, 2004), one might expect aphasic subjects to be impaired in counting. If aphasic subjects were unable to count but subjects without language impairment employed a strategy of chronometric counting and this strategy significantly influenced performance, one would expect aphasic and non-aphasic subjects to differ. The lack of a difference between these groups suggests that counting was not a major determinant of performance in our subjects.

Finally, we suggest that our data may have implications for the distinction between automatic and cognitive timing. As previously described, we found significant differences between performance at 2 s as compared to all longer intervals. This finding is at least broadly consistent with the results of Kagerer et al. (2002) who reported that subjects with right brain lesions exhibited different performance with intervals of 3 s or less as compared to 3.5 s or more. Thus, these data are consistent with our finding that performance at 2 s differed from that at 4 s and longer. Collectively, these findings raise several possibilities regarding the relationship between automatic and cognitive timing. One possible account is that the temporal boundary between automatic and cognitive timing may be longer than the 1 s interval that has been suggested by some investigators (Lewis and Miall, 2003; Ivry and Spencer, 2004; Buhusi and Meck, 2005). An alternative speculation is that there may be a transitional interval during which processing is not clearly automatic or cognitive but which employs either or both routines in response to task demands, the range of intervals assessed in the task or other factors. Additional research would be needed to address these and alternative possibilities.

4. Experimental procedures

Brain lesion subjects were at least 6 months removed from the time of infarction ($N=29$) or tumor resection ($N=2$). Brain lesion ($M=60\pm 11$ years) and control subjects ($M=56\pm 11$ years) did not differ with respect to age ($t(45)=1.21$, $p=0.23$).

No subject exhibited neglect on line bisection or line cancellation tasks. Aphasia was assessed in all left hemisphere damage (LHD) patients using three measures: a picture naming task (8 items), a verbal repetition task (12 items), and a lexical comprehension task (6 items). An aphasia score was computed for each LHD subject by adding the patient's score on each task, resulting in a value between 0 and 26, with a lower score indicating a higher severity of aphasia; based on previous observations in our laboratory, a score of 15 or less is indicative of aphasia (see Table 1).

MRI or CT scans were available for all brain-lesion subjects. For each patient, the lesion locus was transcribed onto a standard digital template using MRicro software [www.MRicro.com] by a neurologist (HBC) who was naïve with

respect to the behavioral data. As lesions were rendered on a standard brain, we are unable to calculate absolute lesion volume; relative lesion volumes were calculated for each subject, however, using MRICro (see Table 1).

Stimuli were presented in either the visual or auditory modality. For all tasks, the visual stimulus consisted of a red square that measured 4 cm on each side, presented in the center of the screen. The auditory stimulus consisted of a 250 Hz tone, presented over headphones; the volume was adjusted to a comfortable level for each subject. The tasks were administered to all subjects in the sequence in which they are described below. Subjects were asked not to count during the tasks.

4.1. Duration estimation

This task was administered to assess the ability to estimate a specific interval in either the visual or auditory modality. For each trial, a fixation point was presented in the middle of the screen for 1 s. Subjects initiated each trial with a keypress. In different trials the square or tone persisted for 2, 4, 6, 8, 10 or 12 s; for this and all other tasks, trials of different durations were presented in random sequence. After the end of each stimulus the subject indicated the estimated duration of the stimulus in seconds by typing the number on a keyboard. For both the visual and auditory versions of the task there were five trials at each duration, for a total of 30 trials. In all tasks subjects were not told the range of stimulus durations and were not given feedback regarding accuracy.

4.2. Duration production

This task was administered to assess the ability to produce a specified interval in either the visual or auditory modality. For each trial, a fixation point was presented in the middle of the screen for 1 s. For both tasks, the fixation point was immediately replaced by a number (2, 4, 6, 8, 10, 12) representing the duration (in seconds) of the interval that the subject was to generate. The subject initiated the stimulus presentation by depressing the space bar on the keyboard to initiate the presentation of the visual (red rectangle) or auditory (250 Hz. tone) stimulus; when the subject believed the specified time had elapsed they pressed the space bar a second time to terminate the trial. For both the visual and auditory versions of the task, there were five trials at each of the six durations for a total of 30 trials.

4.3. Duration reproduction

This task was administered to assess the ability to reproduce a visual stimulus. In each trial, a fixation point was presented in the middle of the screen for 1 s. After the trial was initiated with a keypress, the fixation point was immediately replaced by a red square. In different trials the square persisted for 2, 4, 6, 8, 10 or 12 s. After the end of each stimulus the subject attempted to reproduce the immediately preceding duration by pressing the space bar on a keyboard once to initiate a presentation of the red square, and then pressing the space bar a second time to terminate the stimulus. There were five trials at each duration for a total of 30 trials.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.brainres.2008.11.015](https://doi.org/10.1016/j.brainres.2008.11.015).

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