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Research report

Dissociable contributions of the prefrontal and neocerebellar cortex to time perception

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Abstract

We report a series a three psychophysical experiments designed to differentiate the contributions of the neocerebellar and prefrontal cortex to time perception. Comparison of patients with focal, unilateral neocerebellar or prefrontal lesions on temporal discrimination of 400-ms and 4-s intervals (Expt. 1) indicated that neocerebellar damage impaired timing in both millisecond and seconds ranges, whereas prefrontal damage resulted in deficits that were robust only at the longer duration. Patients with prefrontal lesions, however, also exhibited working memory deficits on a non-temporal task (Expt. 2), biases in point of subjective equality indicative of attentional deficits, and were disproportionately sensitive to strategic manipulations in a long-duration discrimination task (Expt. 3). In contrast, the pervasive timing deficits of cerebellar patients were relatively insensitive to strategic support and could not be readily explained by general deficits in working memory or attention. These findings support the hypothesis that neocerebellar regions subserve a central timing mechanism, whereas the prefrontal cortex subserves supportive functions associated with the acquisition, maintenance, monitoring and organization of temporal representations in working memory. Such functions serve to bridge the output of the central timing mechanism with behavior. Together, these regions appear to participate in a working memory system involved in discrimination of durations extending from a few milliseconds to many seconds.

Keywords: Time perception; Frequency perception; Internal clock; Attention; Working memory; Cerebellum; Prefrontal cortex

1. General introduction

1.1. Overview

Time perception is an adaptive function that facilitates the ability to predict and anticipate events, as well as organize and plan sequences of actions. The relative accuracy with which human and non-human animals are able to perceive temporal duration is accomplished by a complex system involving multiple component processes that engage multiple neural regions [1,25,39,99]. Fundamental to this system is a neural mechanism capable of representing real-time information—the internal clock. Yet, to fully explain timing behavior, it is necessary to place this neural timer within a larger framework that includes non-temporal components, such as attention, memory and decision processes. Brain regions underlying these processes work together with the neural timer as part of a network subserving time perception. In the present study, we investigate the complimentary roles of two brain regions putatively involved in this network—the neocerebellum and prefrontal cortex.

1.2. Cerebellum as an internal clock

1.2.1. Empirical evidence

The cerebellum has been hypothesized to operate as an internal clock that serves to time precise temporal relationships between events in both motor and perceptual domains (reviewed in Ref. [42]). In the motor domain, neocerebellar lesions have been shown to result in increased variability on a repetitive tapping task in which the participants are asked to produce periodic movements to match a target frequency. This increased variability has been attributed to increased noise in an internal timing system

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[22,46,47]. A disruption in timing also provides a functional account of prominent cerebellar signs such as dysmetria or intentional tremor. Deficits in the precise timing of muscle flexors and extensors could cause patients to over- or undershoot a target [37,41].

The most compelling evidence for the cerebellar timing hypothesis, however, comes from research on a simple form of sensorimotor learning–eyeblink conditioning. For learning to be adaptive, an animal must not only learn that a previously neutral stimulus (e.g., a tone) consistently predicts an aversive stimulus (e.g., an airpuff), but also must learn the precise temporal relationship between the two events [42,87]. Careful neurophysiological stimulation and lesion studies in the rabbit have isolated the critical associative processes to the cerebellum (see Ref. [96]), and demonstrated that the cerebellar neocortex is essential for timing the interval between the stimulus and learned response [84]. Furthermore, eyeblink conditioning is impaired, if not absent, in patients with cerebellar lesions [16,97,102].

Perceptual studies suggest a generalized role for the cerebellum in the representation of temporal information. Patients with lesions of the neocerebellum were found to be impaired in their ability to judge the duration of an auditory stimulus [46], but performed comparably to control subjects on a second perceptual task involving judgments of the intensity of the stimuli. Thus, perceptual deficits appeared to be specific to the temporal dimension. Similarly, cerebellar patients have difficulty on visual tasks requiring the analysis of motion information even in the absence of eye movements [44,74]. These perceptual problems suggest that the neocerebellum is critical for any task that requires the precise representation of dynamic information (see Ref. [87] for a related account of the cerebellum in the vestibular–ocular reflex).

1.2.2. Temporal bounds of the clock mechanism

The evidence cited above has been obtained in tasks in which the extent of temporal processing is quite limited, spanning only up to about 500 ms. Evidence for neocerebellar contributions to timing in the range of seconds to minutes is less clear. Clarke et al. [13] trained rats on two duration discrimination tasks, one involving durations in the millisecond range and the other involving durations centered around 30 s. Cerebellar lesions produced a selective deficit on the millisecond task, suggesting an upper bound on the neocerebellar timing system. This view is consistent with current theoretical proposals concerning how real-time information might be represented in the neocerebellar cortex [7,18].

It is possible, however, that relatively short intervals form the building blocks for the representation of long intervals. This idea is central to clock–counter theories of internal timing [26,53] in which a counter mechanism tallies the outputs of a periodic process. Information processing models based on clock–counter mechanisms have provided an excellent account of the data obtained in a wide range of temporal processing tasks generally spanning many seconds. Investigations of the neural correlates of the component operations have focused on a basal ganglia–frontal–hippocampal circuit (see reviews in Refs. [27,65]), with little attention being devoted to the cerebellum. Recent evidence, however, suggests that cerebellar damage in humans can impair discrimination of durations as long as 21 s [63,76].

Nichelli et al. [76], however, suggested that impaired long-duration timing in patients with cerebellar damage did not result from a damaged internal timer, but rather, was secondary to deficits in cognitive components of time perception, such as sustained attention and strategic processing. They suggested that these cognitive processes, typically associated with functions of the prefrontal cortex, were impaired in cerebellar patients via the anatomical connection between the neocerebellum and prefrontal cortex. Although intriguing, this interpretation rests upon two controversial assumptions: (1) that neocerebellar damage necessarily leads to frontal lobe dysfunction and, (2) that frontal lobe damage results in timing deficits secondary to primary deficits in sustained attention and strategic processing. In the following sections, we outline the basis for these assumptions, including inconsistencies in the relevant evidence, and describe how the present study addresses these issues.

1.2.3. Anatomical and functional connections between the cerebellum and prefrontal cortex

The assumption of a functional link between neocerebellar cortex and prefrontal cortex has its basis in anatomical and neuroimaging studies. Middleton and Strick [69] identified an afferent pathway in non-human primates connecting the ventral portion of the cerebellar dentate nucleus to Broadmann's area 46 of the prefrontal cortex. Neuroimaging studies with normal subjects have also demonstrated that cognitive tasks associated with frontal lobe function, such as word generation and retrieval from episodic memory, typically co-activate regions in cerebellar cortex contralateral to the region of activated prefrontal cortex (see Ref. [8] for review). Nonetheless, it is unclear how to interpret the functional role of cerebellum on the basis of neuroimaging findings. In general, it is difficult to link particular mental operations with specific neural loci using this type of methodology [19,43].

Research with brain-damaged patients, although more suited to addressing such questions, has led to much controversy concerning the role of the cerebellum in higher cognition. Patients with neocerebellar lesions have been found to exhibit deficits on tests associated with frontal lobe function, such as tasks requiring planning (e.g., Tower of Hanoi [34]), mental fluency (e.g., FAS letter fluency task [2]), control of interference (e.g., Stroop interference

task [5]), and strategic retrieval from episodic memory (e.g., free recall [2]). Yet, other studies have failed to find any pattern of frontal-like deficits in patients with cerebellar lesions [6,9]. Moreover, Daum et al. [15] found that deficits on memory, planning and WCST tests were only evident in patients whose cerebellar degeneration extended to brainstem structures [e.g., olivopontocerebellar atrophy (OPCA)], suggesting that frontal dysfunction may only emerge in atrophic cerebellar syndromes resulting in concomitant damage to brainstem nuclei or widespread deficits in cholinergic innervation of the cerebral cortex [54]. Notably, the study of long duration timing by Nichelli et al. [76] included cerebellar patients with OPCA.

1.3. The role(s) of the prefrontal cortex in time perception

Determining the functional relationship between the cerebellum and prefrontal cortex in the perception of duration also requires an understanding of how the prefrontal cortex alone contributes to this ability—an issue over which there is currently considerable disagreement. In various theories, this region has been proposed to be the locus of a counting mechanism accumulating pulses from an oscillating pacemaker [68,78], an attentional mechanism responsible for gating pulses of a pacemaker to an accumulator (i.e., switch) [33], a memory mechanism involved in storage and retrieval of time information [76], or even the complete internal clock mechanism itself (i.e., pacemaker and accumulator) [103].

This lack of agreement regarding frontal lobe contributions to time perception is not surprising, given that lesions in this area can result in deficits of attention, memory and strategic processing [31,73,91]. Indeed, it is possible that damage to this region would not impair time perception at a single stage, but rather would affect multiple components. Nonetheless, although the prefrontal cortex has been implicated in nearly every aspect of time perception, there is relatively little direct empirical evidence to date concerning the specific contributions of this region.

Theories of prefrontal cortex as a clock or counter mechanism are based primarily on single-unit recordings in nonhuman primates during delayed response tasks [55,78]. These studies have identified a subset of cells in the principal sulcus of monkeys that demonstrate a sustained neural response during the delay between a stimulus and response cue, but abruptly cease firing at initiation of a response. Niki and Watanabe [78] suggested that this pattern of neural discharge may serve to time the duration of the delay interval. In a related view, Miall [68] focused not on the firing rates of single neurons in prefrontal cortex, but on the gradual increase in averaged activity over the neuronal population, suggesting that the accumulation of activity in prefrontal cortex during a delay may reflect an internal counting mechanism.

A more general view, however, is that these neural discharges are related to active maintenance of an internal representation in working memory, thus allowing organisms to bridge gaps between sensory input and motor output, rather than provide an explicit representation of the duration of these gaps (e.g., Refs. [23,31]). This view would argue that cells in prefrontal cortex are only involved in the on-line representation of temporal information when duration serves as a type of information that must be maintained in working memory. In other words, the primary representation of duration might be generated elsewhere in the brain and, as with other types of information, the prefrontal cortex serves to keep this representation active and free from interference during a delay period (see also Ref. [17]).

Rat models of time perception support the role of frontal cortex in memory and attention components of time perception [17,66,80,81] (see Ref. [65] for review). In the peak-interval procedure [88], animals are reinforced for the first response emitted after a target interval such as 30 s. In rats with frontal cortex lesions, the peak of the response function was shifted to longer intervals, indicating that on the probe trial, they expected the reward later than when it was provided during training [66,80,81]. This shift was interpreted as a distortion of reference memory for the target interval. In addition, this series of studies demonstrated that frontal lesions resulted in reduced attentional resources that limited the ability of lesioned rats to divide their attention across multiple temporal stimuli.

Research with animal models has implicated frontal cortex in clock, memory and attentional aspects of time perception. Evidence concerning the effects of prefrontal lesions on time perception in humans is more limited. Timing deficits observed in patients with Korsakoff's amnesia [90] or closed head injury [67] have been associated with frontal lobe damage, yet such findings provide only indirect evidence, given that pathology in these patients (typically) is not restricted to prefrontal cortex. Most studies of temporal processing using patients with focal frontal lesions have focused on memory for the temporal relationships among items [64,72,92], rather than the duration of temporal intervals, despite evidence that these processes may be related [71].

Recently, however, time perception deficits in both the milliseconds (100–900 ms) and seconds (8–32 s) range were reported in patients with focal frontal lesions [77]. In this study, subjects classified test intervals as to whether they were more similar to either a short or long reference interval that had been presented at the start of a test block. The test intervals, however, differed from the reference intervals by relatively large step sizes (i.e., 100 ms and 4 s for the short- and long-duration tasks, respectively). Such large increments may not provide very sensitive indices of time perception. Instead, the requirement to maintain the reference intervals in working memory throughout presentation of multiple test intervals may have made this task

very sensitive to frontal lobe deficits in working memory and control of proactive interference (e.g., Ref. [17]). As of yet, however, the relationship between deficits in time perception and specific cognitive processes, such as working memory, strategic processing and inhibitory control, has not been assessed more systematically in patients with frontal lobe lesions.

1.4. Current objectives

The present study attempts to clarify the contributions of the prefrontal cortex and cerebellum to the perception of duration by directly comparing patients with lesions in these regions across a series of temporal and non-temporal tasks. Although both regions may contribute to time perception, previous studies suggest that cerebellar neocortex primarily subserves basic clock functions in the temporal range useful for motor control, whereas prefrontal cortex modulates time perception through supportive functions related to sustained attention, working memory and strategic organization. As such, we predict that their respective roles may be distinguished by varying the scale of the duration (i.e., milliseconds vs. seconds) (Expt. 1) and cognitive factors related to maintenance and control in working memory. These factors include the requirement to maintain stimulus information in working memory for an extended period of time (Expt. 2) and the ability to engage in strategic processing (e.g., counting) (Expt. 3).

2. Expt. 1: range of duration

2.1. Introduction

Recent models suggest that timing in the millisecond and second range may be dissociated behaviorally [86] and neurally [45,65,86]. Behaviorally, timing in the millisecond range may be achieved relatively automatically through direct read-out from an internal timing system. At ranges exceeding the neural limitations of this system, the contributions of other processes, such as those associated with counting and memory, may become relatively more important. Neurally, timing in the range of milliseconds—the range associated with motor control—has been linked to the cerebellum [45]. Currently, it is unclear whether its role also extends to longer durations [13,63,76]. However, Meck [65] and Gibbon et al. [27] have argued that the representation of temporal information up to the minutes range is subserved not by the cerebellum, but by a network involving the basal ganglia and frontal cortex. Whether the frontal cortex plays a significant role in timing of intervals in the millisecond range is also unclear [77].

Expt. 1 evaluated temporal discrimination in patients with neocerebellar or frontal lobe damage using temporal intervals centered around 400 ms and 4 s. Performance on these time perception tasks was compared to performance on a frequency perception task. The frequency perception task was included as a control condition to evaluate whether the patients had generalized problems on psychophysical tasks. It was designed to involve the same general discrimination and response requirements as the time perception tasks without requiring an explicit timing component.

2.2. Methods

2.2.1. Participants

2.2.1.1. Patients with frontal lobe lesions. Seven right-handed patients with unilateral frontal lobe lesions were identified by review of medical records and CT or MRI scans (see Fig. 1). Patients had unilateral lesions in the region of prefrontal cortex resulting from a single cerebral vascular accident (CVA) in the territory of the precentral branch of the middle cerebral artery. Although lesion site within the prefrontal cortex was somewhat variable, the region of greatest overlap corresponded to lateral prefrontal cortex. CVA occurred between 1980 and 1989. Average lesion volume was estimated from quantitative analyses of neuroimaging data to be 40.1 cm^3. Five patients had left hemisphere lesions (4 men, 1 woman) and two patients had right hemisphere lesions (1 man, 1 woman).

Four of the five patients with left hemisphere lesions were mildly dysfluent and had some difficult in word finding, but scored 85 or higher on the Western Aphasia Battery [51] (norm = 100), indicating that they did not have moderate to severe aphasia. Patient JC, however, was severely dysfluent and did not attempt the verbal subtests of the Weschler Adult Intelligence Scale-Revised (WAIS-R). Patients had no history of other significant medical disease such as psychiatric disorder, dementia [Mini-Mental Status Exam (MMSE) > 25], substance abuse, or additional neurological events. They averaged 68.3 years of age and had an average of 14.1 years of education.

2.2.1.2. Patients with neocerebellar lesions. Nine male, right-handed patients with unilateral lesions that included regions of the neocerebellum or dentate nucleus were identified by CT or MRI review and chosen by the same general criteria as the patients with frontal lobe lesions. Although two patients (CB and JD) had previous histories of substance abuse, they had been substance-free for extended periods of time when tested. Reconstruction of these cerebellar lesions on a set of horizontal templates are shown in Fig. 2. Estimates of lesion volume were unavailable.

A neurologist (RK) and/or one of the authors (RI) assessed motor dysfunction in these patients using a clinical evaluation that included ratings of posture, gait, eye movements and volitional movements with the upper and

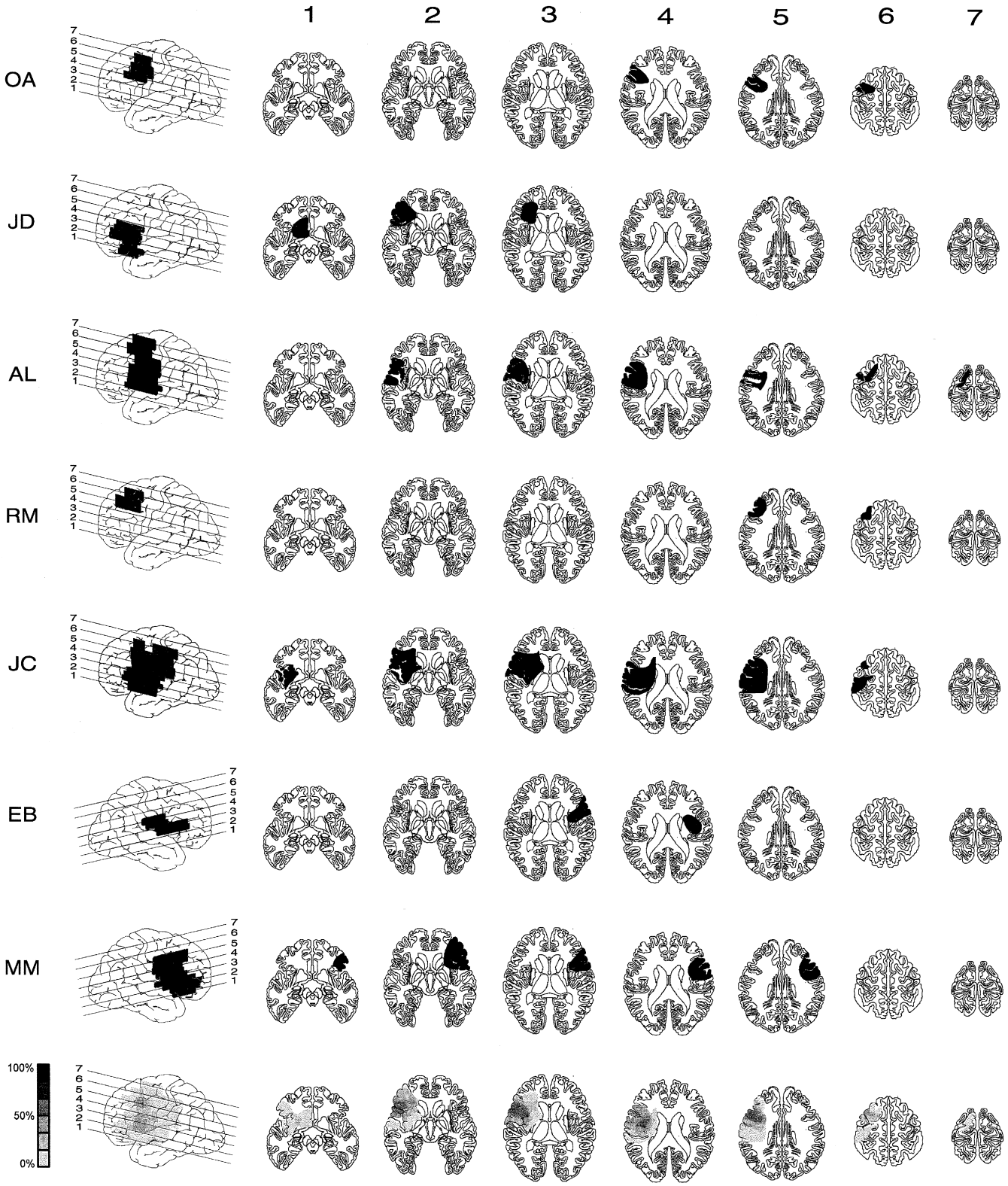

Fig. 1. Lesion reconstructions of patients with frontal lobe damage. Lesions were reconstructed from computer tomography scans and magnetic resonance images. The numbered lines on the lateral view indicate the corresponding axial cuts from the most inferior cut (1) to the most superior cut (7).

lower extremities on a five-point scale (0–4). Overall clinical rating of motor signs ranged from 0 (no evidence of cerebellar dysfunction) to 3 (moderate to severe) (see Table 1). All patients exhibited some asymmetry on a repetitive movement task; movements made with the ipsilesional hand were more variable than movements made

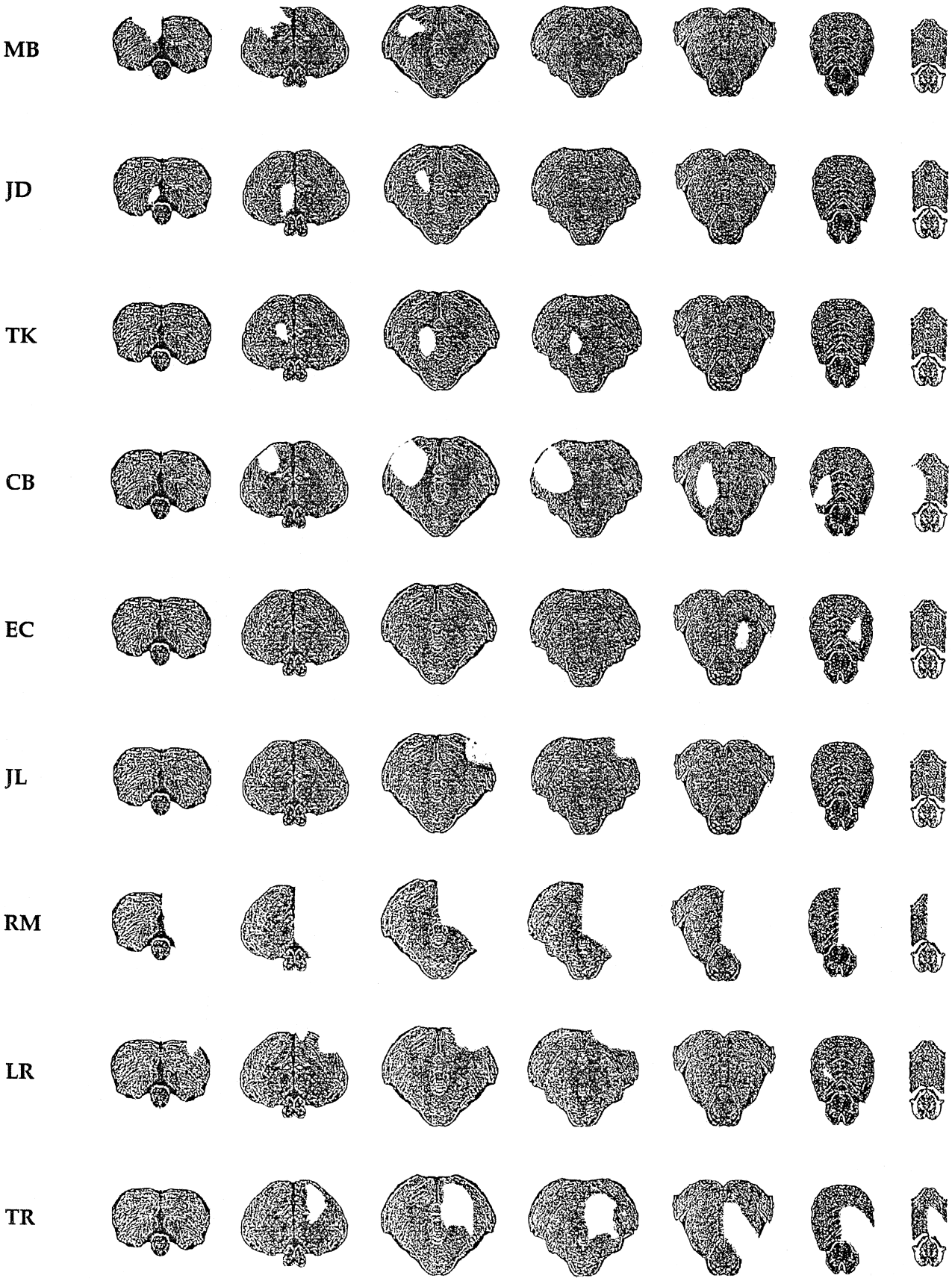
MB
JD
TK
CB
EC
JL
RM
LR
TR

Table 1
Participant characterization

Group	Sex	YOB	ED	Lesion				WAIS-R subtests (scaled)				WCST		
				Etiology	Side	Vol/Clin	Onset	Info	Voc	DgSp	DgSy	FAS	Categ	%PerErr
Frontal						*Volume*								
1. OA	M	1932	14	Stroke	L	17.5	1984	12	12	10	11	29	1	25.8
2. JC	M	1925	16	Stroke	L	102.6	1987	–	–	–	10	7	6	17.0
3. JD	M	1927	20	Stroke	L	30.8	1986	10	6	5	9	8	6	16.3
4. AL	F	1929	13	Stroke	L	51.2	1980	13	11	5	7	21	4	28.1
5. RM	M	1925	12	Stroke	L	10.3	1989	8	7	11	10	24	6	13.8
6. EB	F	1917	12	Stroke	R	17.3	1983	10	9	11	15	48	4	25.0
7. MM	M	1925	12	Stroke	R	51.2	1984	9	9	10	9	12	0	71.9
Cerebellar						*Clinical*								
1. CB	M	1949	11	Stroke	L	3.0	1996	9	13	15	7	34	4	28.9
2. MB	M	1962	12	Stroke	L	0.5	1995	9	11	10	9	41	6	10.8
3. JD	M	1944	12	Tumor	L	2.0	1990	8	10	15	6	22	6	14.5
4. TK	M	1920	3	Stroke	L	0.0	1991	9	–	–	5	19	2	26.6
5. EC	M	1936	16	Stroke	R	2.5	1991	12	15	11	10	33	6	9.0
6. JL	M	1927	10	Stroke	R	1.0	1990	7	9	9	7	26	2	53.1
7. RM	M	1942	16	Tumor	R	2.5	1966	11	13	11	6	25	6	11.2
8. LR	M	1927	16	Stroke	R	1.0	1987	13	8	8	6	29	1	51.6
9. TR	M	1925	16	Stroke	R	1.5	1992	16	19	11	10	24	6	20.2
Means														
Frontal						*Volume*								
Expts. 1 and 3	5M, 2F	1926	14.1	–	5L, 2R	40.1	1985	10.3	9.0	8.7	10.1	21.3	3.9	28.2
Expt. 2	4M, 2F	1926	14.5	–	5L, 1R	38.3	1985	10.6	9.0	8.4	10.3	22.8	4.5	20.9
Cerebellar						*Clinical*								
Expt. 1	9M	1937	12.4	–	4L, 5R	1.6	1988	10.4	12.3	11.3	7.3	28.1	4.3	25.1
Expt. 2 and 3	8M	1938	12.0	–	4L, 4R	1.6	1988	10.1	12.9	11.7	7.5	28.0	4.8	21.8
Controls														
Expt. 1	10M,4F	1928	15.1	–	–	–	–	13.4	13.1	12.1	12.1	45.1	5.3	16.3
Expt. 2	8M,3F	1929	14.6	–	–	–	–	12.9	12.5	12.6	12.5	44.5	5.3	16.4
Expt. 3	8M,4F	1928	14.9	–	–	–	–	13.1	13.0	12.5	12.7	47.0	5.3	15.7

YOB = year of birth.
ED = years of formal education.
Vol (frontal patients only) = Volume of lesion in cubic centimeters (cm^3) estimated from CT scans.
Clin (cerebellar patients only) = Overall clinical rating of motor signs, range: 0 (no impairment) to 4 (severe impairment).
Onset = year stroke/tumor resection occurred.
WAIS-R = Weschler Adult Intelligence Scale-Revised.
Info = Information Subtest, Voc = Vocabulary Subtest, DgSp = Digit-Span Subtest (total of Digit-Span Forward and Backward), DgSy = Digit-Symbol Subtest.
FAS = Total number of words produced in 3 min on the FAS Letter Verbal Fluency Test.
WCST = Wisconsin Card Sort Test: Categ = Number of categories attained, % PerErr = Percent perseverative errors.
– = score not applicable or available.

with the contralesional hand. This asymmetry corresponds to a pattern observed in patients with lateral cerebellar damage [47].

Seven of these patients sustained a single CVA in one hemisphere of the cerebellar neocortex (3 left hemisphere, 4 right hemisphere), and two patients had portions of cerebellar neocortex removed during tumor resection (1 left hemisphere, 1 right hemisphere). There was no evidence of neural damage beyond the cerebellum, with the exception of two patients (LR, JD). Specifically, cortical scans of patient LR revealed a small lesion in right calcarine cortex that would not be expected to influence

Fig. 2. Lesion reconstructions of patients with unilateral neocerebellar damage. Lesions were reconstructed from computer tomography scans and magnetic resonance images. Cuts are shown from the most inferior (left) to the most superior (right) and are oriented such that the posterior portion of the cerebellum is positioned toward the top of the page.

performance on the auditory tasks in the present studies. Patient JD appeared to have a small white matter lesion in area 4 (motor strip) corresponding to the region controlling movement of the lower extremities. Such lesions are typically asymptomatic, however, and all motor symptoms demonstrated by JD were consistent with cerebellar dysfunction.

In four patients (CB, TK, RM, TR), the lesions appeared to encompass the regions containing the dentate nucleus (i.e., at the level of the 3rd and 4th columns from the left in Fig. 2). For patient TK, however, the lack of motor symptoms suggests that the dentate nucleus was spared. Notably, the CT for patient TK was obtained during the acute period, and the abnormality at this level may have been from a perfusion of blood that subsequently resolved. In two patients (JD, EC), dentate involvement was somewhat unclear, but considered highly probable by the consulting neurologist (RK).

All patients were tested a minimum of 6 months following CVA or surgery. These patients averaged 57.0 years of age, which was marginally younger than the patients with frontal lobe lesions ($P < 0.06$). Their average level of education (12.4 years), however, did not differ from the frontal patients' ($P = 0.4$). Patient TK did not perform the verbal subtests of the WAIS-R.

2.2.1.3. Control subjects. Fourteen healthy, right-handed volunteers from the Martinez, CA community (10 men, 4 women) participated as control subjects. They were matched to the patients with frontal lobe lesions with respect to age (66.3 years) and education (15.1 years). Compared to patients with neocerebellar damage, however, control subjects were significantly older ($P < 0.05$) and had achieved a marginally higher level of education ($P = 0.08$) (see Table 1).

2.2.2. Procedures

2.2.2.1. General procedure (PEST). Participants were given a series of two duration perception (short and long) tasks and a frequency perception task in a counterbalanced sequence. Each series of three tasks was tested in two sessions separated by a minimum of 1 h of neuropsychological or unrelated testing. An adaptive psychophysical procedure, Parametric Estimation by Sequential Testing (PEST) [56,83,93], was used to estimate the difference thresholds for all three tasks (see Ref. [46] for a more detailed description of this method).

On each trial, participants first saw a visual cue to 'listen', then 600 ms later heard a sequence of two tones produced by the internal speakers of an IBM/PC computer at approximately 60 dB. Tones were separated by a silent 1000-ms inter-stimulus-interval (ISI). The first tone was always a constant duration and frequency, and was designated as the standard. Depending on the task condition, either the duration or frequency of the second tone was varied. This stimulus was designated as the comparison. At the start of each task, participants were given 10 practice trials in which the duration or frequency of the comparison tone was set to be highly discriminable (fixed at > 2 S.D. shorter or longer than the standard, based on pilot work). For the remaining 50 trials, the duration or frequency of the comparison stimulus was determined on a trial-by-trial basis using the PEST procedure. This adaptive procedure used the participant's previous response to re-estimate the psychophysical function from which the comparison value for the next trial was determined (25 trials for each threshold).

2.2.2.2. Duration perception. The duration of the standard was 400 ms in the short-duration task and 4 s in the long-duration task. The duration of the comparison was set to the current estimate of the participant's difference threshold. Separate estimates were made for the thresholds corresponding to the comparison interval at which the participant responded longer on approximately 75% of the trials (upper threshold), and the threshold corresponding to the comparison interval at which the participant responded longer on approximately 25% of the trials (lower threshold). The two thresholds were estimated within the same block of 50 trials. Participants pressed the 'S' on the computer keyboard if they perceived the comparison tone as shorter than the standard, and pressed the 'L' on the keyboard if they perceived the comparison tone as longer than the standard. The next cue to 'listen' was shown 500 ms following the subject's response. Subjects were informed that their responses were not timed.

2.2.2.3. Frequency perception. Participants heard sequences of two tones presented in the same manner as in the duration perception task. Both tones were presented for 400 ms each. For the majority of participants, the frequency of the standard was 600 Hz. Due to a programming error, the standard was 400 Hz for a minority of the participants in each group (1 frontal patient, 2 cerebellar patients, and 4 control subjects). The second tone of each pair was either higher or lower in frequency than the standard. The PEST procedure was used to select the test value in the same manner as described above. Participants pressed the 'H' on the computer keyboard if they perceived the comparison tone as higher in pitch than the standard, and pressed the 'L' on the keyboard if they perceived the comparison tone as lower in pitch than the standard. Separate estimates were obtained for the lower and higher thresholds, with the 25 trials per threshold being presented in a mixed block.

2.2.2.4. Neuropsychological tests. Information, Vocabulary, Digit-Span and Digit-Symbol subtests of the Weschler Adult Intelligence Scale-Revised (WAIS-R) were administered as measures of general intellectual ability. Subjects

were also given two tests considered to be sensitive to frontal lobe function, the FAS letter fluency test [4] and Wisconsin Card Sort Test (WCST [40]).

2.2.3. Data analysis

The PEST procedure provides a measure of difference threshold and, when bi-directional thresholds are obtained, bias. The difference threshold, or acuity measure can be expressed as a standard deviation score. Assuming a standard psychophysical function, the sampled threshold corresponds to one standard deviation unit, or point at which the subject is correct on approximately 75% of the trials. The standard deviation was calculated as the difference between the upper and lower thresholds divided by 2 given that each threshold was 1 S.D. from the subject's point of subjective equality (PSE). Thus, a large value would indicate that the subject needed a large difference between the standard and comparison in order to correctly classify the comparison. The PSE is equal to the average of the upper and lower thresholds and reflects the point at which participants were equally likely to make either of the two responses (e.g., 'shorter'/'longer' or 'higher'/'lower'). This measure estimates the duration or frequency that participants perceived to be equal to the standard. It should be noted that the current application of the PEST procedure provides only a limited assessment of bias. The standard was presented on all trials, and thus, any systematic distortion in clock speed would apply to both the standard and comparison stimuli.

Performance (S.D. and PSE) on the test sessions was averaged for each of the three discrimination tasks (short duration, long duration, frequency). The distribution of standard deviation scores for the three groups were non-normal (Kolmogorov–Smirnov goodness-of-fit test, $P < 0.05$); therefore, we first normalized these scores using a logarithmic transform. For the frequency task, some participants were tested at 600 Hz and others were tested at 400 Hz. To compensate for this difference, standard deviation scores first were converted to a Weber fraction, or coefficient of variance (CoV = S.D./PSE), then normalized in the manner described above.

Normalized standard deviation (S.D.) scores were analyzed for each task separately using one-way ANOVAs. Significant overall analyses were pursued with planned comparisons between each patient group and the control subjects. Given that average age and education differed across patient groups, these characteristics were entered into the analyses as covariates (ANCOVA) if the relationship between these characteristics and the dependent measure was significant ($P \leq 0.05$). Neuropsychological test performance was evaluated in a similar manner.

PSE was evaluated using a one-group *t*-test comparing the mean of each group to the target value for that task [e.g., 400 (short duration), 4000 (long duration), 600 (frequency)]. Only participants receiving the 600-Hz tone were entered into the analysis of PSE for the frequency task.

Alpha levels were set at 0.05; however, marginally significant P values (0.06–0.10) will be reported, given the trade-off between power and variability inherent in small sample sizes of homogeneous patient groups.

2.3. Results

2.3.1. Neuropsychological tests

Table 1 lists individual patient performance and group means on the neuropsychological tests described below.

Traditionally, the Information and Vocabulary subtests of the WAIS-R have been considered to be good measures of premorbid intelligence. Yet, patients with frontal lobe lesions were significantly impaired on both subtests relative to control subjects ($P < 0.04$), despite an average Full Scale score within the normal range (mean = 101.7, norm = 100) (see Ref. [64] for a full description of WAIS-R scores in these patients). Relative to the control group, patients with cerebellar lesions were impaired on the Information subtest ($P < 0.02$), but were unimpaired on the Vocabulary subtest ($P = 0.6$). Although we cannot rule out the possibility of premorbid differences in intellectual ability between patients and control subjects, it is also likely that performance on these verbal subtests was sensitive to general deficits in word-finding ability, such as those evidenced on the FAS test of verbal fluency.

Indeed, both patient groups produced significantly fewer words than controls on the FAS letter fluency task (frontal patients: $P < 0.0001$; cerebellar patients: $P < 0.001$). Word retrieval deficits in patients with frontal lobe or neocerebellar damage most likely do not reflect a simple motor impairment, as poor word fluency can be observed even in non-aphasic patients [70].

On the WCST, patients with frontal lobe lesions exhibited only marginal deficits in comparison to control subjects on both the number of categories achieved ($P = 0.1$) and percentage of perseverative errors ($P = 0.1$). Patients with focal cerebellar lesions demonstrated a similar pattern with regard to number of categories achieved ($P = 0.08$) and percentage of perseverative errors ($P = 0.1$). As illustrated in Table 1, however, performance on this task was quite variable in both patient groups, with some patients demonstrating clear evidence of a perseverative deficit [i.e., MM (front), JL (cere), LR (cere)] and others showing essentially normal performance [i.e., RM (front), EC (cere), RM (cere)].

Although frontal and cerebellar patients performed similarly on classic tests of frontal lobe function ($P > 0.6$), they were differentially impaired on the Digit-Span and Digit-Symbol subtests of the WAIS-R. Performance on the Digit-Span subtest, which requires subjects to hold and manipulate information in working memory, was impaired in patients with frontal lobe lesions ($P < 0.03$), but not in

patients with cerebellar lesions ($P = 0.5$) (frontal vs. cerebellar patients: $P = 0.1$). In contrast, performance on the Digit-Symbol subtest, a time-limited task that is sensitive to speed of information processing, was significantly impaired in patients with neocerebellar damage relative to control subjects ($P < 0.0001$). Patients with frontal lobe damage were only marginally slower on the Digit-Symbol subtest than controls ($P = 0.1$) (frontal vs. cerebellar patients: $P < 0.02$).

Thus, patients with neocerebellar damage performed similarly to frontal patients on neuropsychological tests assessing initiation, fluency and perseveration, but unlike frontal patients, demonstrated reduced processing speed in the presence of preserved working memory function.

2.3.2. Duration perception

Table 2 lists untransformed difference thresholds (S.D.) and PSE scores for the short- and long-duration perception tasks.

2.3.2.1. Difference threshold. Analysis of time perception acuity yielded a marginally significant effect of group on the short duration task [$F(2,27) = 3.1$, $P = 0.06$], and a significant effect of group on the long-duration task [$F(2,27) = 6.7$, $P < 0.005$]. Planned comparisons, however, revealed different patterns of timing deficits across the two patient populations. Patients with neocerebellar lesions exhibited larger difference thresholds than control subjects on both the short- [$F(1, 21) = 5.8$, $P = 0.03$] and long-duration tasks [$F(1, 21) = 10.9$, $P < 0.003$], whereas patients with frontal lobe lesions only demonstrated significantly larger difference thresholds on the long-duration task [$F(1, 19) = 8.2$, $P < 0.01$]. On the short-duration task, patients with frontal lobe lesions performed comparably to controls [$F(1, 19) = 1.8$, $P = 0.2$]. However, given that frontal patients' performance also did not differ from that of the cerebellar patients [$F(1, 14) = 0.6$, $P > 0.5$], this single dissociation should be interpreted with caution.

2.3.2.2. Point of subjective equality. Lesions to prefrontal or neocerebellar cortex also had contrasting affects on the PSE of the short and long durations. Relative to the standard durations, patients with prefrontal lesions demonstrated an increase in the PSE at the 400-ms duration [$t(6) = 3.5$, $P < 0.02$], but no bias at the 4-s duration [$t(6) = 10.0$, $P = 0.4$]. Cerebellar patients demonstrated the opposite pattern; they showed no bias at the shorter duration ($P = 0.4$), but a significant decrease in PSE at the longer duration [$t(8) = 3.6$, $P < 0.008$]. This pattern was similar to that of the control subjects, who also showed a significant decrease in PSE at the longer duration [$t(13) = 4.8$, $P < 0.001$], but only a marginal effect at the shorter duration [$t(13) = 1.9$, $P = 0.08$].

The biases of cerebellar patients and control subjects were not atypical. Reproduction of durations exceeding 3 s are typically underestimated, whereas durations under 3 s are more veridically estimated [86]. Thus, the PSEs of patients with frontal lobe lesions could be interpreted as reflecting a rightward shift of the psychophysical function in both the short- and long-duration tasks. Regardless of stimulus duration, the frontal patients were more likely to classify the comparison interval as 'short' compared to both the control subjects and neocerebellar patients.

2.3.3. Frequency perception

Table 3 lists difference thresholds for the frequency task, expressed as an untransformed Weber fraction (i.e., coefficient of variance [CoV]) to take into account different target values across subjects, and untransformed PSE scores of subjects receiving the 600-Hz target tone.

2.3.3.1. Difference threshold. Analysis of mean S.D.'s across all three groups did not reach conventional levels of significance [$F(2, 27) = 2.6$, $P = 0.1$]. Planned comparisons between each patient group and control subjects also yielded only marginally significant impairments in patients with frontal lobe [$F(1, 19) = 3.0$, $P = 0.1$] or neocerebellar [$F(1, 21) = 3.2$, $P = 0.09$] damage.

Given these marginal significance levels, we cannot confidently state that patients with neocerebellar or prefrontal damage were unimpaired in their ability to discriminate pitch. Larger group differences may have been obscured by low power due to small sample size. More importantly for the purposes of the current study, however, is the question of whether time and frequency perception performance in patients with frontal lobe or neocerebellar lesions can be accounted for by a common deficit in acoustic perception or sequential stimulus discrimination.

Although audiograms were not obtained for these subjects, we are relatively confident that impaired perfor-

Table 2
Expt. 1: Mean difference threshold (S.D.) and point of subjective equality (PSE) for short and long duration tasks, as a function of patient type

Patient group	*N*	Difference threshold (ms)		PSE (ms)	
		Short (400 ms)	Long (4000 ms)	Short (400 ms)	Long (4000 ms)
Frontal	7	39.6 (5.2)	315.7 (52.1)	431.0 (9.0)	3854.3 (145.1)
Cerebellar	9	44.9 (5.0)	323.3 (47.1)	412.9 (15.3)	3676.7 (89.4)
Control	14	31.5 (3.3)	189.3 (19.2)	418.2 (6.7)	3650.0 (60.0)

Standard errors of the mean are shown in parentheses.

Table 3
Expt. 1: Mean difference threshold, expressed as a coefficient of variation (CoV = S.D./PSE), and point of subjective equality (PSE) for the frequency discrimination task, both as a function of patient type

Patient group	*N*	Difference threshold (Hz) (CoV)	*N*	PSE (Hz) (600 Hz)
Frontal	7	0.012 (0.002)	6	598.8 (1.2)
Cerebellar	9	0.013 (0.003)	7	603.3 (2.0)
Control	14	0.009 (0.003)	10	600.4 (1.5)

Mean PSE for frequency judgments is based only on individuals receiving the 600 Hz tone.
Standard errors of the mean are shown in parentheses.

mance across auditory discrimination tasks was not merely the result of poor hearing. First, the patients did not have any known pathology in the auditory system. Second, all tones were in the low-frequency range (400–600 Hz), which is relatively unaffected by normal age-related changes in hearing level [79]. Third, when linear differences in pitch perception were removed using the difference thresholds (S.D.) for the frequency task as a covariate, the pattern of results on the duration discrimination tasks was unchanged. Thus, it appears that impaired temporal discrimination in patients with frontal lobe or neocerebellar damage cannot be attributed simply to fundamental deficits in auditory perception or judging sequential stimuli.

2.3.3.2. Point of subjective equality. No consistent biases were observed on the pitch perception task. None of the group mean values for PSE significantly differed from 600 Hz ($P > 0.1$).

2.4. Discussion

2.4.1. Frontal–cerebellar dissociations

To summarize the primary findings of this experiment, both neocerebellar and frontal patient groups demonstrated impaired performance on time perception tasks. Yet, the results were ambiguous with regard to the hypothesis that temporal range might be one way to distinguish the contributions of these two brain regions. Compared to the control subjects, the patients with neocerebellar lesions were impaired on both short- (400 ms) and long- (4 s) duration discrimination tasks. Thus, these results replicate previous findings of perceptual timing impairment within the range of milliseconds [46], but also demonstrate that cerebellar timing deficits extend to the range of seconds. In contrast, the frontal patients only exhibited a significant timing deficit when judging 4-s intervals. Nonetheless, the mean S.D. of the frontal patients on the 400-ms task was numerically larger than that of the control subjects, and was not significantly different from that of the neocerebellar patients. Thus, although these results suggest that the prefrontal cortex is less critical for millisecond timing than the neocerebellum, they also raise the possibility that the contribution of the prefrontal cortex to discrimination performance simply increases with the temporal extent of the task. We will return to this issue in Expt. 2.

The two patient groups could be more clearly distinguished on the basis of PSE scores. Patients with prefrontal lesions exhibited a significant rightward shift in PSE not observed in neocerebellar patients or control subjects. Frontal cortex lesions in rats produce a similar rightward shift in expected time of reinforcement that may reflect a systematic lengthening of the duration stored in reference memory [65,66,80,81]. By this view, the rightward shift observed in the current paradigm could reflect a systematic distortion in memory for the remembered duration of the standard interval. Yet, given that the standard was presented on each trial, and that the delay between the standard and comparison stimuli was relatively short (1 s), this interpretation seems less tenable.

Deficits in attention seem to provide a more reasonable explanation for the bias of the frontal patients. In normal individuals, disruptions of attention have been shown to affect perception of intervals ranging from very brief durations (100–500 ms) to durations of many seconds [11,35,36,70,95,103]. Specifically, subjects produce longer time intervals when temporal processing is conducted concurrently with a secondary task, as opposed to when it is conducted under full attention, presumably because diverting attention from temporal processing interrupts the accumulation of temporal information in working memory [21,103]. During the presentation of the comparison interval, subjects not only had to attend to the interval itself, but also had to keep the standard duration in mind in order to make a subsequent decision. Due to this increased demand on working memory, patients with frontal lobe lesions may have required that the second tone be played slightly longer in order for it to be perceived as equal to the standard.

2.4.2. Frontal–cerebellar interactions

Although frontal and neocerebellar patient groups could be differentiated on the basis of PSE and discrimination of the 400-ms duration, the variability of the two groups on the 4-s duration task was quite similar. What relationship is there, if any, between the increased variability observed for these patient groups on the long-duration task? In the following section, we describe three possible ways in which these regions might interact.

First, neocerebellar and prefrontal cortex may interact directly at the level of the internal clock, subserving timer and accumulator mechanisms, respectively. Indeed, the normal PSE scores for the neocerebellar patients coupled with their poor discrimination ability is consistent with the hypothesis that neocerebellar damage increased the variability of a central timing mechanism. Nonetheless, durations in the range of seconds may exceed the capacity of

millisecond interval timers in the neocerebellum and necessitate involvement of an accumulator, or counter mechanism, in the frontal cortex. It has been suggested that a counter mechanism such as this may be an intrinsic property of prefrontal neurons [68].

Alternatively, the cerebellar neocortex, along with other subcortical regions such as the neostriatum, may be wholly responsible for providing clock-counter-based representations necessary for timing durations in the seconds range. By this view, the prefrontal cortex, rather than functioning as a neural counter, may primarily subserve memory, attention and strategic processes that are involved in, but not exclusive to, time perception. In other words, the prefrontal cortex would contribute to the maintenance, monitoring and organization of temporal information—perhaps represented in the neocerebellum and/or basal ganglia—in the same way it participates in the executive control of other, non-temporal types of information. It is likely that these cognitive processes would be more critical for discriminating durations in the range of seconds, as compared to milliseconds. Specifically, in the long-duration task, not only must attention be sustained on-task for a longer period of time, but there is also a greater amount of information accumulating in working memory that must be kept free from interference, yet available for on-line comparison.

Finally, Nichelli et al. [76] suggested that impaired long-range timing in both neocerebellar and frontal patients resulted from common deficits in executive control processes. In patients with neocerebellar damage, deficits in these processes could potentially arise from frontal lobe dysfunction caused by 'reversed cerebellar diaschisis'–hypometabolism in cerebral cortex subsequent to cerebellar damage [29,30,49]. Comparison of frontal and neocerebellar patient groups on neuropsychological tests of frontal lobe function yielded inconclusive results regarding this hypothesis, however. Although verbal fluency was impaired in both patient groups, working memory, as measured by the WAIS-R Digit-Span subtest, was only impaired in frontal patients, and neither group exhibited consistent deficits on the WCST. Furthermore, correlations between performance on timing and neuropsychological tests revealed only a significant relationship between long-range timing variability (S.D.) and the percentage of perseverative errors on the WCST in patients with prefrontal lesions [$r = 0.75$ (Spearman's rank–order correlation), $P = 0.05$].

The results of the present experiment do not easily distinguish between the hypotheses outlined above. To further explore the reasons why lesions of prefrontal cortex or the neocerebellum disrupt temporal discrimination acuity in the seconds range, we attempted to separate the demands for accurate representation of temporal information per se, from the demands imposed on a working memory system as the temporal extent of a task is increased. In the following experiment, we focused on the contributions of prefrontal cortex and neocerebellar regions to working memory for non-temporal information.

3. Expt. 2: maintenance in working memory

3.1. Introduction

In this experiment, two frequency discrimination tasks were administered, differing only with respect to the length of time that information had to be maintained in working memory: (1) a 'short-range' task in which standard and comparison pitches were presented for 400 ms with a 1-s ISI, and (2) a 'long-range' task in which standard and comparison pitches were presented for 400 ms with a 4-s ISI.

Based on previous findings (e.g., Ref. [31]), we predicted that the difference thresholds of patients with prefrontal lesions would be affected by the length of the delay between standard and comparison tones (i.e., demonstrating an increase in mean S.D. from the short-range to long-range task) due to deficits in maintaining information about the standard in working memory. Such a finding would parallel the results of Expt. 1 in which the frontal group only showed a significant impairment when the duration of each stimulus spanned approximately 4 s.

The performance of patients with neocerebellar lesions will provide insight into the nature of their deficit on the 4-s duration perception task in Expt. 1. If the neocerebellum, along with the prefrontal cortex, supports general working memory functions, cerebellar patients should demonstrate a range-related increase in variability that is similar to that of patients with prefrontal lesions. Alternatively, if the underlying cause of long-duration timing deficits in neocerebellar patients is a specific deficit in the explicit representation of temporal information, we would not expect patients to show an increased deficit as working memory demands increased in a non-temporal task.

In addition, this experiment offers the opportunity to replicate the frequency control task used in Expt. 1 with a more controlled procedure. Parameters of the short-range task were identical to the frequency task from Expt. 1, except that all subjects were tested with the 400 Hz standard.

3.2. Method

3.2.1. Participants

Six patients with prefrontal lesions and eight patients with neocerebellar lesions from Expt. 1 were tested. Patients MM (frontal) and LR (cerebellar) were not available for testing in this experiment. Eleven control subjects (8 male, 3 female) participated. Ten of these subjects (7 male, 3 female) had been in Expt. 1.

Subject characteristics and neuropsychological test performance for patient and control groups for this experi-

ment are described in Table 1. Statistical analyses were conducted on the neuropsychological tests described in Expt. 1, but restricted to those subjects participating in Expt. 2. Overall, the pattern of performance of patients with frontal or neocerebellar lesions was similar to Expt. 1, with the exception that patients with neocerebellar lesions, who had shown marginal deficits on the Vocabulary subtest and number of categories achieved on the WCST, were more clearly unimpaired on these tests when compared to the current control group ($P > 0.1$).

3.2.2. Procedure

Participants received two sessions each of the short- and long-range frequency tasks in a counterbalanced order. The short-range frequency task was identical to the frequency control task in Expt. 1, except that all subjects were tested with a 400-Hz standard. Specifically, subjects were presented with two computer-generated tones, a standard and comparison tone, separated by a silent 1-s ISI. The standard tone was always 400 Hz, and the comparison tone was higher or lower in frequency than the standard. Subjects indicated whether they perceived the comparison tone as higher or lower by pressing the appropriate button on the computer keyboard or pointing up or down with the index finger of their least impaired hand. The procedure for the long-range frequency task was identical to the short-range task, except that the silent interval separating standard and comparison tones was 4 s.

3.2.3. Data analysis

Measures of the difference threshold (standard deviation of the psychophysical function) and bias (point of subjective equality) were obtained with the PEST procedure, as described in Expt. 1. Performance (S.D. and PSE) on the two discrimination tasks (short-range and long-range) was averaged across the two test sessions. For both short-range and long-range tasks, the distributions of S.D. scores for the control group were non-normal (K–S test for normality, $P < 0.02$). Therefore, prior to analysis, these scores were normalized using a logarithmic transform. Because the untransformed S.D. score of one subject was 0.0, however, it was necessary to add a constant of 1.0 to the raw data for each subject before performing this transform.

We were primarily concerned with relative changes in variability as the temporal extent of the task increased. Therefore, analyses were performed on the difference between the mean S.D.'s of the short-range and long-range tasks. Single-group *t*-tests were performed on this measure to determine whether the change in S.D. across the two tasks differed from zero in each of the subject groups. Single-factor (group) ANOVAs were also conducted to assess between-group differences. Performance on the short-range frequency task was analyzed separately as a replication of Expt. 1. PSE scores for each frequency task were analyzed for each subject group using single-group *t*-tests with 400 as the target value.

3.3. Results

Untransformed S.D. and PSE scores for the short-range and long-range frequency perception tasks, as well as the difference between these tasks, are listed in Table 4.

3.3.1. Difference threshold

Single-group *t*-tests revealed that patients with prefrontal lesions were differentially sensitive to the temporal extent of the task. These patients demonstrated a mean increase in difference threshold of 89.9% between the short-range and long-range frequency discrimination tasks, [$t(5) = 3.8,\ P < 0.02$]. Increasing ISI had a reduced effect on the other two groups. Specifically, the increase in difference threshold across the two tasks was 8.9% and 31.7% for the neocerebellar and control subjects, respectively. For the neocerebellar group, this value was not significantly different than zero, [$t(7) = 0.5,\ P = 0.7$]. For the control group, the increase was marginally significant, [$t(10) = 2.0,\ P = 0.07$].

Direct comparisons between groups on this measure further supported this dissociation between patients with prefrontal or neocerebellar lesions. Patients with prefrontal lesions exhibited a larger increase in difference threshold from the short-range to long-range task than patients with neocerebellar damage, [$F(1,\ 12) = 9.5,\ P < 0.01$]. Yet, neither patient group differed from the control group [cerebellar vs. control: $F(1,\ 17) = 1.6,\ P = 0.2$; frontal vs. control: $F(1,\ 15) = 2.2,\ P = 0.2$], reflecting the trend toward an increase in difference threshold in control subjects.

Consideration of the short-range frequency task alone revealed a larger difference threshold in the patients with

Table 4
Expt. 2: Mean difference threshold (S.D.) and point of subjective equality (PSE) for short-range (1 s ISI) and long-range (4 s ISI) frequency tasks, as a function of patient type

Patient group	*N*	Difference threshold (Hz)			PSE (Hz)	
		Short-range (1 s ISI)	Long-range (4 s ISI)	Diff. (SR-LR)	Short-range (1 s ISI)	Long-range (4 s ISI)
Frontal	6	7.8 (1.5)	13.9 (2.6)	6.1 (1.5)	402.4 (2.4)	398.8 (1.8)
Cerebellar	8	9.7 (2.2)	9.8 (1.9)	0.1 (1.3)	401.0 (3.2)	400.6 (1.8)
Controls	11	4.9 (1.9)	5.9 (2.0)	1.0 (0.6)	398.0 (4.9)	398.0 (1.6)

Standard errors of the mean are shown in parentheses.

cerebellar lesions compared to control subjects [$F(1, 17) = 4.8$, $P < 0.05$], and a marginally significant difference between the patients with prefrontal lesions compared to control subjects, [$F(1,15) = 3.4$, $P = 0.09$]. Although these comparisons had failed to reach significance in Expt. 1, the pattern was quite similar.

3.3.2. Point of subjective equality

None of the subject groups exhibited a PSE in either the short-range or long-range tasks that significantly deviated from 400 Hz ($P > 0.2$).

3.4. Discussion

The main finding in this experiment is that patients with prefrontal lesions were disproportionately impaired on the long-range frequency task, indicating that discrimination deficits in these patients become more evident as the temporal extent of processing increases. These patients demonstrated similar range-related increases in difference threshold in the duration discrimination tasks of Expt. 1. Thus, discrimination deficits in patients with prefrontal lesions appear to be dependent on the duration that information must be maintained in working memory, but independent of whether the task requires a temporal or non-temporal judgment. The trend toward poorer long-range discrimination in the elderly control subjects suggests that 'subclinical' deficits in working memory may have been present in this group. Normal aging is associated with neurophysiological and neuropharmacological decline that is somewhat selective for frontal regions (see Ref. [100] for review).

The performance of the patients with neocerebellar damage, in contrast, was not sensitive to the length of the delay between standard and comparison pitches. From these results, it is possible to infer that the contribution of the neocerebellum to long-duration timing in Expt. 1 was related to the specific operations of an internal timing system, rather than to the operations of a non-specific working memory system. Notably, the neocerebellar patient group was marginally younger in age than either the frontal patients or control subjects ($P < 0.08$) and thus, was also less likely to have sustained any general age-related decline in working memory.

Fiez [19,20] has argued that the cerebellum does play a role in working memory, but that this role is specifically related to the articulatory loop component, and thus, supports maintenance rehearsal of verbal information (see Ref. [3]). Such a deficit may not have been apparent in the current experiment, given that it is unlikely that working memory for pitch entails verbal rehearsal. Verbal rehearsal, however, may contribute to counting strategies that could be used to optimize performance on a long-duration timing task. The issue of strategic processing will be explored in Expt. 3.

When considered together, Expts. 1 and 2 form a 2×2 factorial combination of task dimension (duration or pitch) and temporal extent (short-range or long-range). As illustrated in Fig. 3, lesions in either the cerebellum or prefrontal cortex produce changes in performance along different axes. For the neocerebellar group, the key factor is the task dimension, with these patients showing an impairment on the two duration discrimination tasks. For the prefrontal group, the key factor is the temporal extent, with these patients showing an impairment whenever the interval between the stimulus presentation and response is sufficiently long enough that maintenance or monitoring demands exceed a certain threshold.

This conclusion is tempered somewhat by the fact that both patient groups tended to perform more poorly than

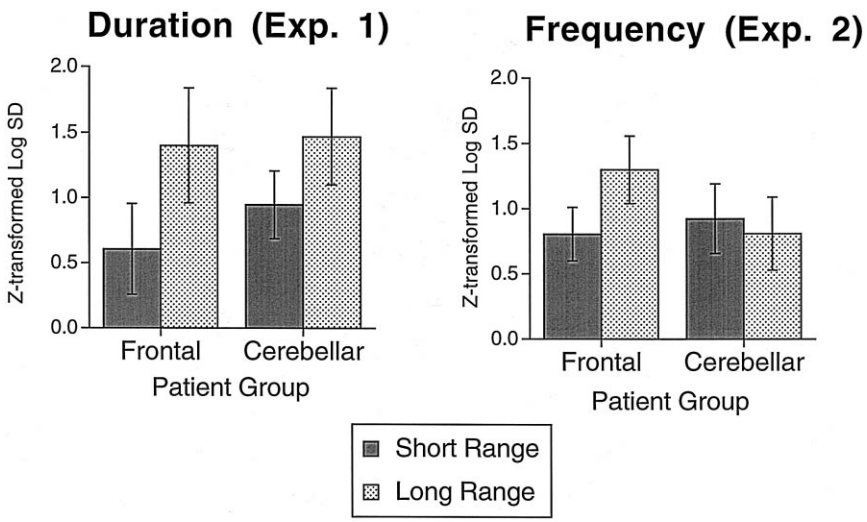

Fig. 3. Performance of patient groups on short-range and long-range duration and frequency tasks. Normalized and *z*-transformed difference thresholds (S.D.s) of patients with prefrontal or cerebellar lesions, as a function of temporal range, in duration discrimination (Expt. 1) and frequency discrimination (Expt. 2) tasks.

the controls on the short-range pitch discrimination task in Expts. 1 and 2. As discussed in Expt. 1, it is unlikely that time perception deficits in the patient groups can be attributed simply to basic deficits in auditory discrimination. Nonetheless, the reasons for the poorer performance on what had been included as a 'control' task are unclear. One possibility is that this deficit may reflect a generalized problem that our patient groups have on psychophysical tasks [89]. Arguing against this interpretation, however, is the finding that such generalized deficits do not appear to be a typical aspect of cerebellar dysfunction. In previous studies, cerebellar patients have been shown to perform normally on other types of psychophysical tasks such as a line length discrimination [76] and loudness discrimination [46].

Alternatively, patients with prefrontal or neocerebellar damage may have task-specific deficits in pitch perception. Zatorre et al. [105] found activation in right prefrontal cortex related to pitch discrimination in a positron emission tomography (PET) study of speech processing. Although cerebellar involvement in pitch perception has not been noted in the literature, it is worth mentioning that one model of pitch perception proposes that frequency is encoded by timing cycles of neural pulses in the acoustic nerve as they synchronize with the period of the signal [38]. By this view, frequency perception would require a level of precision in temporal representation similar to that required to control movement and thus, may also involve millisecond interval timers within the neocerebellum.

Regardless of the underlying cause of these deficits in pitch perception however, the use of two different ISIs in the current experiment revealed that working memory deficits were selective for the prefrontal group independent of any main effects between the difference thresholds in the three populations.

4. Expt. 3: influence of strategy

4.1. Introduction

Expt. 2 succeeded in differentiating the performance of patients with prefrontal or neocerebellar lesions by manipulating the duration over which non-temporal information had to be maintained in working memory. As such, one possible explanation for the similar performance of these patient groups on the long-duration task in Expt. 1 has been eliminated. Despite its connections with prefrontal cortex, neocerebellar damage does not simply induce a syndrome of frontal lobe dysfunction. Rather, the evidence supports the hypothesis that the neocerebellum serves a specific role as an internal clock, and that this timing property is invoked for intervals spanning less than half a second, as well as intervals of 4 s. The prefrontal cortex appears to be more essential for tasks in which information must be kept active in working memory over a period of a few seconds—one requirement for the 4-s duration discrimination task.

In the seconds-to-minutes range, a number of other cognitive processes exert their influence on the variability of temporal perception in addition to the working memory requirements discussed above. It is well established that timing variance in this range can be minimized significantly by counting strategies that serve to subdivide a longer interval into multiple shorter intervals [28,52,53,99]. Clock–counter models of timing formally describe the beneficial effects of counting, demonstrating that the summed variance of timing shorter subdivisions is typically less than the variance associated with timing the interval as a whole [53]. Counting is likely to be especially beneficial when the counting process itself adds little variance.

In Expt. 1, subjects were not given any explicit instructions regarding whether or not to use a counting strategy. Nonetheless, the control group exhibited the hallmark of an underlying counting strategy [53,99]—a significant decrease in the coefficient of variation (CoV) as the interval to be timed increased [$F(1, 13) = 14.7$, $P < 0.003$]. Patients with neocerebellar damage also demonstrated a significantly smaller CoV in the long-duration task as compared to the short-duration task [$F(1, 8) = 5.6$, $P < 0.05$], despite overall deficits on both tasks. Only the patients with prefrontal lesions failed to demonstrate any change in CoV from the 400-ms to the 4-s duration task [$F(1, 7) = 0.3$, $P = 0.6$]. These results suggest that deficits in use of a counting strategy may be a contributing factor to the long-duration timing impairment of patients with prefrontal lesions. This hypothesis is in line with results showing that patients with frontal lobe damage are impaired in self-initiated strategy use across a variety of cognitive tasks [24,60,64].

The present experiment explored the extent to which long-duration timing deficits of patients with prefrontal or neocerebellar lesions were related to a failure in self-initiated strategy use. To this aim, we varied the level of external strategic support across a series of five long (4 s) duration perception tasks (see Fig. 4). These tasks were presented across two separate test sessions.

In the first of these sessions, subjects were tested on two tasks. First, they performed a 4-s duration perception task in which no strategic support was provided. This is essentially a replication of the long-range duration condition of Expt. 1. In the second task, the 4-s standard was divided into 10 isochronous subintervals by the presentation of brief, 50-ms tones every 400 ms. Although these subdivisions could provide support for a counting strategy, no instruction was provided on how to use these markers. In the second session, there were three tasks. As in the first session, the basic 0-s duration perception task was tested first. In the next task, external support was provided by again subdividing the standard into 400-ms subintervals,

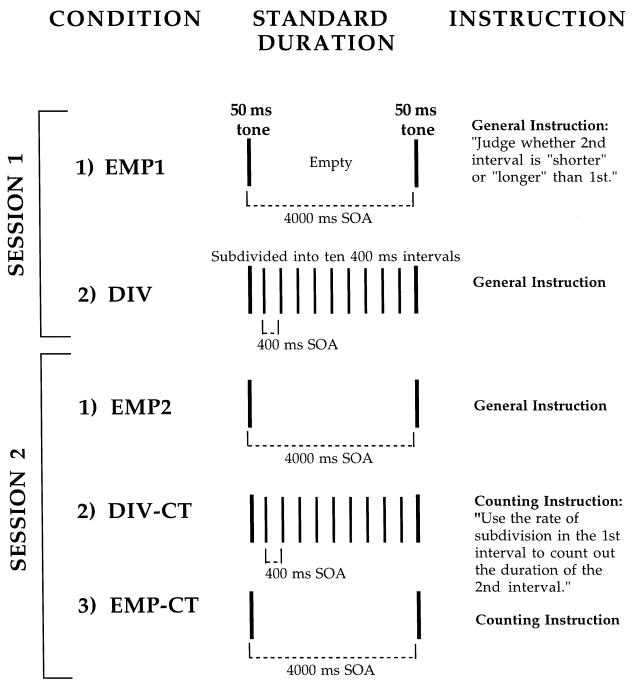

Fig. 4. Schematic description of test conditions used in Expt. 3.

and by explicitly instructing the subjects to use the subdivision as a rhythm for regulating a counting strategy. In the final task, subjects were presented with the undivided 4-s standard interval, but were now explicitly encouraged to use the counting strategy that they had practised in the prior condition. This final 'transfer' condition assessed whether training with external support transferred to situations in which support was no longer externally available.

To the extent that deficits in the use of strategic processes underlie the impaired long-range timing performance in patients with prefrontal lesions, timing problems should be ameliorated when strategic support is provided. Furthermore, the type of strategic support necessary to improve performance may provide an index of the level at which processing is impaired. Specifically, it is possible that patients are attempting to implement a counting strategy, but due to deficits in attention or articulatory processes, they implement this strategy in a sub-optimal manner, thereby increasing the variance associated with the counting process. If so, the inclusion of the subdividing markers, regardless of whether explicit instruction is provided or not, should produce a beneficial effect by providing external cues for counting. Subintervals of 400 ms were chosen based on previous studies showing that subintervals between 250 and 500 ms provide optimal timing performance for intervals in the range of 1 to 5 s [35,53]. Alternatively, if the patients simply do not implement a self-initiated counting strategy of any kind, they may not find the markers beneficial unless given explicit instruction regarding their strategic utility. Indeed, if the markers are not utilized in a strategic manner, they may function as a source of interference and impair the performance of frontal patients [12,104].

4.2. Methods

4.2.1. Participants

Patients with prefrontal lesions were the same as in Expt. 1. Patients with cerebellar damage were the same as in Expt. 2. Twelve control subjects (8 males, 4 females) participated in this experiment. Nine had been in both Expts. 1 and 2, one had only been in Expt. 1 and two had only been in Expt. 2.

The means of participants in Expt. 3 on the neuropsychological tests described in Expt. 1 are listed in Table 1. Compared to the current group of control subjects, patients with prefrontal lesions exhibited a significantly greater number of perseverative errors ($P < 0.04$) and marginally worse performance on the digit symbol subtest of the WAIS-R ($P = 0.07$). The pattern of performance of cerebellar patients did not differ from Expt. 2.

4.2.2. Procedure

Subjects received five 4-s duration perception tasks across two test sessions separated by a minimum of 1 week (see Fig. 4). At the start of each test session, subjects performed a duration perception task using an empty interval that served as a baseline [Condition EMT1 (session 1), Condition EMT2 (session 2)]. This task was identical to the 4-s duration task in Expt. 1 with the following modifications: (1) standard and comparison intervals were empty intervals (as opposed to filled intervals) bounded by two 400-Hz, 60-dB tones lasting 50 ms each, and (2) the ISI between standard and comparison tones was extended from 1 s to 1.6 s to provide adequate perceptual separation between the second tone of the standard and first tone of the comparison. For the standard interval, the interval between the two markers was 4 s. As in Expts. 1 and 2, the PEST procedure was used to select the duration of the comparison interval. Instructions for Conditions EMT1 and EMT2 were the same as for the duration tasks in Expt. 1.

Following a brief rest period, the baseline task was followed by a task in which the standard 4-s interval was divided into 10 isochronous subintervals by eleven 50-ms tones. The comparison interval in these tasks was not subdivided, but was presented as an empty interval. In the first session, subjects were given this 'subdivided' task with the simple instruction that they would hear the standard interval broken up into a series of short intervals, but should still 'measure the duration bounded by the first and last tones in the series'. Thus, in this condition (Condition DIV), subjects were given no explicit instruction regarding how to use the markers as part of a counting strategy. In the second session, however, the subdivided standard was combined with specific instruction to use the markers as part of a counting strategy (Condition DIV-CT). Specifi-

cally, subjects were told that they should learn the rhythm of the subintervals during the standard (by counting to 11) and then count at this rate during the comparison, judging 'short' if their count came to less than 11 and 'long' if their count came to greater than 11.

The fifth task, Condition EMP-CT, was given shortly after subjects completed Condition DIV-CT. This condition was identical in all respects to the baseline task (i.e., Condition EMP2), except that subjects were asked to use the counting strategy that they had practised when the external markers had been present (i.e., Condition DIV-CT).

4.2.3. Data analysis

The PEST procedure was used to obtain difference thresholds (S.D.) and bias (PSE) for each of the five duration discrimination tasks. The distributions of S.D. scores for the control group were non-normal (K–S test for normality, $P < 0.02$). Therefore, prior to analysis, these scores were normalized using a logarithmic transform.

Data analysis focused on a subset of critical comparisons. First, to evaluate the effects of subdividing the standard in the absence of explicit strategy instruction, 3 (group) $\times$ 2 (condition) mixed-design ANOVAs were conducted that compared the S.D. and PSE scores of each group across Condition EMP1 (empty standard, no strategy) and Condition DIV (subdivided standard, no strategy). To assess the combined effects of subdivision and strategic support, similar ANOVAs were conducted, comparing performance across Condition EMP2 (empty standard, no strategy) and Condition DIV-CT (subdivided standard, strategy). Finally, the potential for transfer of training with these external supports to an unsupported condition was evaluated by comparing performance on Condition EMP-CT (empty standard, strategy training) with Condition DIV-CT (subdivided standard, strategy) and Condition EMP2 (empty standard, no strategy). In addition, for each group, bias (PSE) in each condition was evaluated using a single-group *t*-test with 4000 as the target value.

4.3. Results

Table 5 lists untransformed difference thresholds (i.e., S.D.'s) and point of subjective equality (PSE) for the five experimental conditions, as a function of subject group.

4.3.1. Effect of subdivisions alone: session 1

4.3.1.1. Difference threshold. Relative to the empty standard (EMP1), the subdivided standard (DIV) did not affect overall performance [$F(1, 24) = 1.2$, $P = 0.3$]. There was, however, an overall difference in performance between groups [$F(2, 24) = 5.7$, $P < 0.01$]. Specifically, control subjects exhibited a smaller difference threshold across these conditions than patients with prefrontal lesions [$F(1, 17) = 8.3$, $P < 0.02$], or neocerebellar damage [$F(1, 18) = 6.9$, $P < 0.02$]. In addition, the interaction of group by condition was marginally significant [$F(2, 24) = 2.5$, $P = 0.1$]. We opted to pursue this finding using interaction contrasts given that inclusion of multiple groups may have obscured more robust differences.

Direct comparison of patients with neocerebellar lesions and control subjects did not demonstrate a significant group by condition interaction [$F(1, 18) = 1.5$, $P = 0.2$]. The main effect of condition also failed to reach conventional significance levels [$F(1, 18) = 2.4$, $P = 0.1$] In contrast, when patients with prefrontal lesions were compared directly to control subjects, a significant interaction between group and condition emerged [$F(1, 17) = 9.2$, $P < 0.009$]. The performance of control subjects significantly improved when the standard was subdivided, as compared to when it was empty [$F(1, 11) = 13.1$, $P < 0.005$]. The performance of patients with prefrontal lesions was not significantly improved by subdivision of the standard [$F(1,$

Table 5
Expt. 3: Mean difference threshold (S.D.) and point of subjective equality (PSE), as a function of condition and patient type

Patient group	*N*	Session 1		Session 2		
		EMP1	DIV	EMP2	DIV-CT	EMP-CT
		Empty; no	Subdiv; no	Empty; no	Subdiv; yes	Empty; yes
Difference threshold (ms)						
Frontal	7	328.6 (36.2)	408.6 (55.7)	408.6 (56.2)	280.0 (51.6)	385.7 (90.7)
Cerebellar	8	375.0 (63.1)	350.0 (49.3)	332.5 (37.4)	295.0 (19.2)	370.0 (50.7)
Control	12	290.0 (28.8)	206.7 (21.2)	228.3 (35.2)	165.0 (21.1)	178.3 (28.2)
Point of subjective equality (ms)						
Frontal	7	3922.9 (196.3)	4231.4 (133.3)	3962.9 (185.3)	4211.4 (95.3)	3985.7 (100.1)
Cerebellar	8	3767.5 (67.3)	4305.0 (149.1)	3732.5 (122.9)	4525.0 (112.2)	4000.0 (171.8)
Control	12	3810.0 (82.8)	4146.7 (92.2)	3831.7 (63.8)	4121.7 (102.0)	3888.3 (67.3)

Listed below each condition name is a description of the interval [empty vs. subdivided (subdiv)] and indication of whether a counting strategy was provided by the experimenter (yes) or not (no).
Standard errors of the means are shown in parentheses.

6) = 1.4, $P = 0.3$]. Indeed, the trend was in the opposite direction; the difference threshold for the prefrontal group increased by 35.5% when the standard interval was subdivided.

These findings indicate that patients with prefrontal lesions did not use the markers in a strategic way, and that, if anything, the markers were more a source of interference than aid. Previous studies of auditory working memory suggest that prefrontal lesions result in increased sensitivity to interference from irrelevant sensory input [12,104]. Thus, for the patients with prefrontal lesions, deficits resulting from failure to use the markers as part of a self-initiated counting strategy may have been exacerbated by an impaired ability to inhibit interference from what had essentially become irrelevant auditory stimuli.

4.3.1.2. Point of subjective equality. There was a significant increase in PSE when the standard was subdivided relative to when it was empty, [$F(1, 24) = 23.5$, $P < 0.0001$]. This effect did not interact with group [$F(2, 24) = 0.73$, $P = 0.5$], nor was there a significant overall effect of group [$F(2, 24) = 0.3$, $P = 0.8$]. This tendency to perceive the subdivided standard as longer than the empty standard is most likely an instance of the filled duration illusion (e.g., Ref. [94]).

In condition EMP1, the mean PSE of control subjects and neocerebellar patients was significantly lower than the target value of 4000, indicating a tendency in these subjects to classify the second intervals as 'long' [control subjects: $t(11) = 2.3$, $P < 0.05$; cerebellar patients: $t(7) = 3.5$, $P < 0.02$]. This bias was not observed in patients with prefrontal lesions [$t(6) = 0.4$, $P = 0.7$]. Similar patterns of bias were observed across the three groups on the long-duration task in Expt. 1. When the standard was subdivided, all groups demonstrated a marginally significant tendency to classify the second interval as 'long' [controls: $t(11) = 1.6$, $P = 0.1$; cerebellar patients: $t(7) = 2.1$, $P = 0.08$; frontals: $t(6) = 1.7$, $P = 0.1$].

4.3.2. Effect of subdivisions with strategy instruction: session 2

4.3.2.1. Difference threshold. When subjects were instructed to use the markers to establish a reference interval for a counting strategy (i.e., DIV-CT), there was an overall improvement in discrimination performance relative to the baseline condition (i.e., EMP2) [$F(1, 24) = 9.4$, $P < 0.006$]. This improvement did not interact with subject group [$F(2, 24) = 1.2$, $P = 0.3$], indicating that both patients and control subjects were able to benefit from the external markers when instruction was provided. Importantly, these results demonstrate that patients with prefrontal lesions were capable of using the subdivisions in a strategic manner when given explicit instruction to count, even though they did not appear to do so spontaneously.

Nonetheless, as indicated by a significant overall effect of group [$F(2, 24) = 7.9$, $P < 0.003$], experimenter-provided counting strategies were not able to compensate completely for discrimination deficits in the patient groups. As in previous conditions, control subjects exhibited a significantly smaller difference threshold than either frontal patients [$F(1, 17) = 9.1$, $P < 0.009$] or neocerebellar patients [$F(1, 18) = 11.7$, $P < 0.004$].

4.3.2.2. Point of subjective equality. Similar to session 1, subdivision of the standard produced a significant overall increase in PSE relative to when the standard was empty [$F(1, 24) = 28.0$, $P < 0.0001$]. However, the magnitude of this increase differed across groups, as indicated by a significant interaction between group and condition [$F(2, 24) = 4.3$, $P < 0.03$]. Specifically, the increase in PSE from EMP2 to DIV-CT conditions was significant in both control subjects and cerebellar patients [control subjects: $F(1, 11) = 5.8$, $P < 0.04$; cerebellar patients: $F(1, 7) = 37.0$, $P < 0.0005$], but did not reach significance in frontal patients [$F(1, 6) = 1.9$, $P = 0.2$].

Comparison of the target PSE (4000) with group mean PSEs in condition EMP2 revealed effects that essentially replicate those from condition EMP1. Control subjects and patients with neocerebellar lesions demonstrated a tendency toward classifying the second interval as 'long' [controls: $t(11) = 2.6$, $P < 0.03$; cerebellar patients: $t(7) = 2.2$, $P = 0.07$], whereas patients with prefrontal lesions did not exhibit a significant bias in either direction [$t(6) = 0.4$, $P = 0.8$]. For condition DIV-CT, however, both patient groups exhibited a tendency toward classifying the second interval as 'short' [cerebellar patients: $t(7) = 4.7$, $P < 0.003$; frontal patients: $t(6) = 2.2$, $P = 0.07$]. In contrast, the mean PSE of control subjects did not differ significantly from the target value [$t(11) = 1.2$, $P = 0.3$].

4.3.3. Transfer of training: session 2

4.3.3.1. Difference threshold. The previous analysis demonstrated that subdivision of the standard interval, when combined with explicit instruction to count at that prescribed rate, successfully improved performance in all groups. It was less clear, however, whether patients and control subjects were as effective at implementing this counting strategy in the absence of external support from the markers.

Comparison of EMP-CT and DIV-CT conditions provides an indication of how well subjects were able to maintain a counting strategy in the absence of the subdividing markers. This comparison only revealed a significant effect of group [$F(2, 24) = 7.9$, $P < 0.003$]. Both patient groups were impaired relative to control subjects [frontal patients vs. control subjects: $F(1, 17) = 6.5$, $P < 0.03$; cerebellar patients vs. control subjects: $F(1, 18) = 18.5$, $P < 0.0001$]. However, there was no difference over-

all in performance across the two conditions [$F(1, 24) = 1.5$, $P = 0.2$] and no interaction between group and condition [$F(2, 24) = 0.3$, $P = 0.7$].

If strategy training had been successful, however, we would have expected performance in the transfer task (i.e., EMP-CT) to be superior to performance in the baseline task (i.e., EMP2). Comparison of these conditions yielded only a significant overall effect of group [$F(2, 24) = 9.3$, $P < 0.001$], with both patient groups performing more poorly than control subjects [frontal patients vs. control subjects: $F(1, 17) = 10.9$, $P < 0.005$; cerebellar patients vs. control subjects: $F(1, 18) = 18.5$, $P < 0.0004$]. Performance did not differ across conditions [$F(1, 24) = 1.1$, $P = 0.3$], and group did not interact with condition [$F(2, 24) = 0.7$, $P = 0.5$].

4.3.3.2. Point of subjective equality. Comparison of the subdivided and empty conditions (DIV-CT vs. EMP-CT) yielded a significant effect of condition [$F(1, 24) = 29.3$, $P < 0.0001$], replicating the increase in PSE associated with the subdivided standard that was found in the previous analyses. In addition, although there was no difference between subject groups [$F(2, 24) = 1.9$, $P = 0.2$], there was a marginally significant group by condition interaction [$F(2, 24) = 2.6$, $P = 0.09$]. Specifically, patients with neocerebellar lesions exhibited a larger decrease in PSE from the subdivided to empty standard interval than control subjects [$F(1, 18) = 6.8$, $P < 0.02$] or patients with prefrontal lesions [$F(1, 13) = 4.4$, $P = 0.05$]. Across the two empty conditions (EMP2 vs. EMP-CT), however, there was only a trend toward a slightly higher PSE in the final condition [$F(1, 24) = 3.1$, $P = 0.09$]. In the EMP-CT condition, patients' estimates of the target interval were equivalent to 4000 [cerebellar patients: $t(7) = 0$, $P = 1.0$; frontal patients: $t(6) = 0.1$, $P = 0.9$]. Control subjects, however, demonstrated a trend toward underestimation in this condition [$t(11) = 1.7$, $P = 0.1$].

4.4. Discussion

The findings from this study confirm that strategic processing deficits in patients with prefrontal lesions contribute to their impaired performance on duration discrimination tasks spanning several seconds. Unlike control subjects, the frontal patients failed to benefit when the standard interval was partitioned into a set of isochronous subintervals and no explicit strategy instructions were provided. These patients did improve on the task, however, when given explicit instructions to use the markers as a strategic aid in establishing a counting rate. Performance on the transfer condition, however, suggests that patients with prefrontal lesions may have had difficulty maintaining an optimal counting strategy when regulating markers were removed. Given that the transfer task in the present experiment was the last task in a session containing three relatively long, monotonous tasks, it is also possible that positive effects of training were mitigated by fatigue. With the current design, we could not control for order effects.

In addition, it is important to note that strategic support did not eliminate timing deficits in patients with prefrontal lesions. There are a number of possible reasons for their persistent impairment. First, although counting may have aided processing of the long intervals in this experiment, working memory load may still have been relatively high, given the temporal extent over which information must be maintained in this task. Second, although the standard was divided into subintervals of 400 ms, a duration over which the frontal patients' timing performance was within normal bounds (see Expt. 1), they may not have been able to maintain their internal counting at this rate during the comparison interval, perhaps due to problems in attention or internal articulation. Third, although counting variability is assumed to make minimal contributions to duration discrimination tasks, this contribution may be disproportionately large for frontal patients, especially if this region of the brain is critical for processes involved in counting [68]. These hypotheses are, of course, not mutually exclusive. Consistent counting is likely to require sustained attention, as well as working memory to keep track of the running tally.

Nonetheless, in contrast to patients with prefrontal lesions, whose performance was strongly modulated by strategic manipulations, duration discrimination in patients with neocerebellar lesions was relatively unaffected by the level of external support. For example, the combination of markers and strategy instruction (DIV-CT) produced a mean improvement of 32.4% over baseline (EMP2) in patients with prefrontal lesions. Control subjects demonstrated a mean improvement of 13.3% across these conditions. Patients with neocerebellar lesions, however, only demonstrated an average 2.1% change in performance. Thus, patients with neocerebellar damage appeared to demonstrate the least influence of strategy overall, suggesting that their deficits stem from a fundamental impairment in a basic timing mechanism.

In summary, the results of this experiment provide an additional dissociation between the time perception performance of patients with prefrontal or neocerebellar damage. Although both patient groups were impaired relative to control subjects, the deficits of patients with prefrontal lesions were strongly influenced by strategic manipulations, whereas the deficits of patients with neocerebellar lesions were not. The pervasive discrimination deficits of patients with neocerebellar lesions lend further support for the hypothesis that impaired duration discrimination in the seconds range results from fundamental deficits in an internal clock component, rather than deficits secondary to cognitive dysfunction, and the sensitivity of patients with prefrontal lesions to strategic manipulations supports the hypothesis that timing deficits in these patients are due, in part, to deficits in the executive control of working memory.

5. General discussion

5.1. Summary

Physiological and behavioral evidence suggests that both the dorsolateral prefrontal cortex and neocerebellum contribute to the perception of time [46–48,75,76,80,81]. Yet, their contributions to temporal processing tasks have been studied in relative isolation, using very different methodologies and dependent variables, despite increasing evidence suggesting functional interactions between these two neural systems [14,58,59]. The aim of the current study was to compare directly the performance of patients with either cerebellar or prefrontal lesions on a series of temporal and non-temporal tasks. In this way, we could potentially identify dissociations that would provide evidence for the specialized contributions of each neural region to time perception, as well as similarities that might elucidate the manner in which they interact.

In Expt. 1, we found that only the patients with neocerebellar damage were impaired in discriminating intervals in the millisecond range, but that both patient groups were impaired in discriminating intervals in the seconds range. Importantly, long-duration timing deficits in cerebellar patients were established using individuals with focal, unilateral damage who did not demonstrate evidence of frontal dysfunction as indexed by standardized neuropsychological tests such as the WCST and Digit-Span subtest of the WAIS-R. To date, the only previously published study of long-duration timing deficits in patients with cerebellar damage had included patients with OPCA [76], leaving open the possibility that long-duration timing deficits in that study arose from concomitant frontal lobe dysfunction, rather than directly from cerebellar damage.

Although patients with either prefrontal or neocerebellar damage were impaired on the long-range duration discrimination task, these groups could be dissociated on the cognitive factors known to contribute to performance on this task. Patients with prefrontal lesions exhibited a bias in PSE consistent with an attentional deficit (Expts. 1 and 3), greater sensitivity to strategic manipulations in the context of the long-duration discrimination task (Expt. 3), and a disproportionate impairment on a non-temporal long-range task indicative of a general deficit in maintaining information in working memory (Expt. 2). In contrast, duration discrimination deficits in patients with neocerebellar damage were relatively insensitive to strategic support, and could not be readily explained by general deficits in working memory or sustained attention.

These findings support the hypothesis that the cerebellum serves as the critical locus of a central timing mechanism, whereas the prefrontal cortex provides working memory functions necessary to bridge the output of the cerebellar timing mechanism with behavior. It is reasonable to assume that the prefrontal cortex subserves these functions in both millisecond and second timing, but that timing deficits associated with lesions to this area become more robust as the temporal extent of a task increases beyond a certain threshold. Thus, our results would suggest that the prefrontal and neocerebellar cortex participate in a working memory system involved in discrimination of durations extending from a few milliseconds to many seconds.

5.2. The cerebellar timing system

There are a number of possible ways in which the cerebellum might provide the temporal representation required in these tasks. One conceptualization of an internal clock assumes that temporal information is provided by a supramodal pacemaker. This pacemaker could be accessed by various perceptual channels, with its output directed to the relevant component processes required for a particular task. In a motor task, the output of the pacemaker might be directed to a counter that, when a criterion value is reached, triggers the next movement on a repetitive tapping task. In a perceptual task, the output might be compared to reference values in memory to judge the duration of a stimulus. Pacemaker models have been proposed in which the basic oscillatory process operates at a fixed rate (e.g., Ref. [57]) or is adjustable (e.g., Ref. [98]). A core assumption of either model, however, is that a common mechanism is invoked to represent a range of intervals. For example, if the oscillator operates at 40 Hz, 300-ms intervals would require 12 cycles of the mechanism, 400-ms intervals would require 16 cycles, and 4-s intervals would require 160 cycles.

At present, there is little evidence showing oscillatory activity in the cerebellum. Although Llinas [61] and Llinas and Welch [62] have suggested that the olivo-cerebellar circuit provides a 10-Hz oscillatory signal that could be coupled to volitional movements, the spiking activity of cerebellar Purkinje cells fails to show prominent periodicities [50]. Moreover, it is not clear how a pacemaker operating at 10 Hz would provide sufficient resolution for discriminating intervals that differ by 30 ms.

Alternatively, the cerebellar timing system may be conceptualized as a network of interval-based timers [45]. By this view, there is no pacemaker per se, but rather distinct microcircuits across the cerebellar cortex capable of representing different intervals. For example, activity in one set of units may represent intervals of 300 ms, while activity in another set of units represents intervals of 400 ms. At a functional level, this representational scheme corresponds to a form of chronotopic coding. The anatomy and physiology of the cerebellar cortex, however, may only be capable of supporting intervals within a limited temporal range [7,18]. Additional neural systems may be required when tasks require longer intervals. For example, a functional clock–counter system might be established, linking a particular interval microcircuit with a counter process when the overall interval exceeds this limited temporal extent.

Although the current results demonstrate that the neocerebellum is integral to time perception over a relatively wide temporal range, perhaps enlisting counter mechanisms in other regions at longer durations, they provide little insight into what particular regions within the neocerebellar hemispheres are most critical for timing processes. An analysis of the relationship between the discrimination performance and lesions of the individual patients failed to reveal any consistent findings. Furthermore, there was only a modest correlation between lesion volume and clinical motor symptoms in the current study ($r = 0.34$). In general, a fine-grained analysis of cerebellar subregions is difficult with human lesion studies. Patients with large hemispheric lesions may be relatively asymptomatic after extended recovery periods, whereas small lesions of the deep nuclei may produce lasting deficits. Although neuropsychological studies can provide important information regarding the functional specialization of the cerebellar cortex within larger subcortical and cortical networks, future neurophysiological studies in primates, and perhaps functional neuroimaging studies in humans will serve to elucidate the precise neural organization within the cerebellar timing system.

5.3. The prefrontal cortex and working memory for time

Working memory deficits resulting from reduced attentional resources provide a parsimonious account of frontal patients' pattern of discrimination deficits and bias. In the present study, accurate time perception requires dynamic updating of information regarding the duration of the comparison interval while simultaneously maintaining an on-line representation of the standard interval. As the duration of both the standard and comparison intervals increases, this dual-processing requirement may tax the limited attentional resources of patients with prefrontal lesions to the point where both maintenance and encoding are impaired. Specifically, reduced resources to the maintenance of the standard interval in subcortical regions may result in a degraded representation of this interval which, in turn, would lead to an increase in timing variability (i.e., difference threshold). Reduced resources for attending to the comparison interval may increase the likelihood of distraction, interrupting the accumulation of temporal information and requiring the comparison to be presented for a longer period of time to be judged equal to the standard.

In addition, basic reductions in processing capacity may be compounded by impaired strategic and inhibitory control. Specifically, patients with prefrontal lesions did not appear to spontaneously organize the longer interval into subintervals—a strategy that could have reduced demands on attentional resources—and appeared to be distracted by the markers when no explicit counting strategy was provided. The working memory model of Baddeley [3] divides attention into two distinct aspects: total processing capacity and control processes. Our findings indicate that the patients with frontal lobe lesions sustained damage to both aspects, and that both aspects influence temporal processing.

Thus, the current study indicates that the human prefrontal cortex is involved in the active maintenance, monitoring and organization of time-based representations in working memory, thereby extending its more well-established role as part of a working memory system for object identity and location [23,31,32,85]. This is not to say that a single set of neurons within the prefrontal cortex simultaneously responds to the identity, location and temporal features of a given stimulus. Indeed, current views of the prefrontal cortex regard this region as heterogeneous with regard to both structure and function. For example, Goldman-Rakic and her colleagues [32,101] have delineated regions within the primate prefrontal cortex that selectively respond to feature and location information (i.e., the inferior prefrontal convexity and dorsolateral regions of the principal sulcus, respectively). Petrides [85] also argues that regions within the lateral prefrontal cortex subserve different cognitive functions, but divides them by process, rather than domain. By his view, ventrolateral regions support basic maintenance in working memory, and dorsolateral regions conduct higher-level organization of this information.

What specific subregions of the prefrontal cortex might underlie working memory processes necessary for time perception? Duration, like color and shape, could be considered a feature of a stimulus, and thus, during on-line maintenance, may engage inferior regions associated with object identity. Yet, unlike dimensions of color and shape, temporal representations appear to be acquired dynamically in relation to a fixed point, and thus, during encoding, may require the type of higher-level processing associated with dorsolateral regions. Although the lesion area of greatest overlap among the present group of frontal patients was dorsolateral, the lesions of these patients often extended into more ventral prefrontal areas (see Fig. 1), hampering a more precise localization of function. Thus far, single-neuron studies, capable of providing a more precise answer to this localization question, have not attempted to map the activity of prefrontal neurons during a task in which time must be explicitly monitored. Indeed, the association of prefrontal neuronal activity with internal clock functions has been based solely on delayed response tasks with the assumption that passing time is implicitly encoded during a stimulus–cue delay [78].

The question also remains as to whether changes in activity across populations of prefrontal neurons might actually function as a counter mechanism, directly accumulating temporal information that exceeds the limitations of interval timers (see Ref. [68]), or whether this activity simply reflects the active maintenance and monitoring of temporal information as it accumulates in subcortical regions. It is difficult to evaluate this hypothesis within the context of the present experiment, as we addressed count-

ing only at a strategic level in Expt. 3. Nonetheless, although the frontal patients in this experiment were clearly impaired in generating a self-initiated counting strategy, this could not fully account for their discrimination deficit. They exhibited a residual impairment that could be attributed to an attentional deficit, damage to an internal counter mechanism, or both.

Isolation of a neural counter is also difficult given that, at the current stage of theoretical development, models of human clock–counter processes do not easily distinguish between counting at a neural or strategic level [53]. Indeed, the ubiquitous nature of counting strategies for timing intervals over 500 ms has caused some to question whether such a distinction would even be theoretically useful [53,99]. Nonetheless, even if these processes could be distinguished anatomically and/or functionally, neural and strategic counting are likely to be interrelated. Strategic (explicit) counting may serve to reduce timing variability by regulating a neuronal counter and conversely, the physiological limitations of a neural counter may serve to define the optimal rate of strategic (explicit) counting. Furthermore, the neural counter mechanism would be under the strategic and attentional control of the prefrontal cortex, regardless of whether the prefrontal cortex is additionally the locus of a neural counter or not.

5.4. A neural network for time perception

The findings from the present study, along with those of others [10,80,81], converge on the prefrontal cortex as a region important for managing attentional resources necessary for acquiring temporal representations and actively maintaining those representations in working memory. The current results are less amenable to an interpretation in which prefrontal cortex is assumed to operate as part of the internal clock itself, involved in generating the primary temporal representation. Our findings suggest that a more suitable candidate for producing this primary temporal representation would be the interval timers within the cerebellar neocortex. Other researchers, however, have focused on the neostriatum and substantia nigra, arguing that these structures are key components of a dopamine-regulated internal clock [27,65].

Meck and his colleagues (see Ref. [65] for review), drawing upon neuropharmacology and ablation studies with rats, hypothesize that the dorsal striatum serves as a counter mechanism that accumulates clock (pacemaker) pulses generated in the substantia nigra. In support of this model, Parkinson's disease (PD), a neurodegenerative disorder affecting neostriatal regions via dopaminergic cell loss in the substantia nigra pars compacta, also results in deficits in the reproduction of temporal intervals suggestive of an impaired clock mechanism. For example, Pastor et al. [82] demonstrated that patients with PD overestimated a target interval when instructed to reproduce a time interval by counting out intervals at a prescribed rate. Interestingly, the magnitude of the patients' deficits was largest when the rate of counting was faster (i.e., 5 vs. 1.6 Hz), but the actual duration to be timed was shorter (i.e., 3 s vs. 9 s), suggesting that the locus of the deficit was an impaired counting mechanism.

At first, it might appear that basal ganglia and cerebellar contributions to time perception could be distinguished on the basis of interval range; the cerebellum maintaining temporal representations in the millisecond range, and the basal ganglia serving as neural counter engaged at longer durations [45] (but see Ref. [27]). A recent positron emission tomography (PET) study by Jueptner and colleagues, however, suggests that both the cerebellum and basal ganglia contribute to a network underlying perception of durations less than 1 s [48]. In this study, activity during a time perception task centered around 400 ms was compared to a control task involving similar perceptual and motor components. Increases in rCBF specific to timing were found in the superior parts of the cerebellar vermis and adjacent hemispheres, but also in the globus pallidus, putamen and caudate nucleus. Additionally, timing-specific activity was found in the thalamus and cingulate cortex, bilaterally. Although dorsolateral prefrontal cortex (area 46) was active during the timing task, it was equally active when the control condition was compared to a rest condition, supporting the hypothesis that it makes a more general contribution to task performance.

The cortical and subcortical regions activated in the PET study by Jueptner et al. [48] suggest a network for time perception. By comparing neuropsychological populations with circumscribed lesions across a range of temporal and non-temporal tasks, we have demonstrated that the prefrontal and neocerebellar regions perform dissociable functions within this network. A similar comparative approach is currently underway to investigate the relative contributions of the basal ganglia and cerebellum to the processes involved in time perception with the aim of integrating functions of the frontal lobe, basal ganglia and cerebellar neocortex into a complete neural model of this complex cognitive process.

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References

[1] L.G. Allan, The internal clock revisited, in: F. Macar et al. (Eds.), Time, Action and Cognition, Vol. 22, Kluwer Academic Publishers, Netherlands, 1992, pp. 59–83.

[2] I.M. Appollonio, J. Grafman, V. Schwartz, S. Massaquoi, M. Hallett, Memory in patients with cerebellar degeneration, Neurology 43 (1993) 1536–1544.

[3] A. Baddeley, Working memory, Oxford Univ. Press, Oxford, 1986, 289 pp.

[4] A.L. Benton, K. Hamsher, The Multilingual Aphasia Examination, Univ. of Iowa Press, IA, 1978.

[5] M.I. Botez, T. Botez, R. Elie, E. Attig, Role of the cerebellum in complex human behaviour, Ital. J. Neurol. Sci. 10 (1989) .

[6] R. Bracke-Tolkmitt, A. Linden, A.G.M. Canavan, B. Rockstroh, E. Scholz, K. Wessel, H.C. Diener, The cerebellum contributes to mental skills, Behav. Neurosci. 103 (1989) 442–446.

[7] D. Buonomano, M. Mauk, Neural network model of the cerebellum: temporal discrimination and the timing of motor responses, Neural Comput. 6 (1994) 38–55.

[8] R. Cabeza, L. Nyberg, Imaging cognition: an empirical review of PET studies with normal subjects, J. Cogn. Neurosci. 9 (1997) 1–26.

[9] A.G.M. Canavan, R. Sprenglemeyer, H.-C. Diener, V. Homberg, Conditional associative learning is impaired in cerebellar disease in humans, Behav. Neurosci. 108 (1994) 475–485.

[10] L. Casini, R. Ivry, Effects of divided attention on time perception in patients with lesions of the cerebellum or frontal lobe, Neuropsychologia (submitted).

[11] L. Casini, F. Macar, S. Grondin, Time estimation and attentional sharing, in: F. Macar, V. Pouthas, W.J. Friedman (Eds.), Time, Action and Cognition: Towards Bridging the Gap, Kluwer Academic Publishers, Netherlands, 1992, pp. 177–180.

[12] L.L. Chao, R.T. Knight, Human prefrontal lesions increase distractibility to irrelevant sensory inputs, NeuroReport 6 (1995) 1605–1610.

[13] S. Clarke, R. Ivry, J. Grinband, S. Roberts, N. Shimizu, Exploring the domain of the cerebellar timing system, in: M.A. Pastor, J. Artieda (Eds.), Time, Internal Clocks and Movement, Vol. 115, Elsevier, Amsterdam, 1996, pp. 257–280.

[14] I. Daum, H. Ackermann, Cerebellar contributions to cognition, Behav. Brain Res. 67 (1995) 201–210.

[15] I. Daum, H. Ackermann, M.M. Schugens, C. Reimold, J. Dichgans, N. Birbaumer, The cerebellum and cognitive functions in humans, Behav. Neurosci. 107 (1993) 411–419.

[16] I. Daum, M.M. Schugens, H. Ackermann, W. Lutzenberger, J. Dichgans, N. Birbaumer, Classical conditioning after cerebellar lesions in humans, Behav. Neurosci. 107 (1993) 748–756.

[17] A. Diamond, The development and neural bases of memory functions as indexed by the A not-B and delayed responses tasks in human infants and infant monkeys, in: A. Diamond (Ed.), The Development and Neural Bases of Higher Cognitive Functions, Academy of Sciences, New York, 1990, pp. 267–317.

[18] J.C. Fiala, S. Grossberg, D. Bullock, Metabotropic glutamate receptor activation in cerebellar Purkinje cells as substrate for adaptive timing of the classically conditioned eye blink response, J. Neurosci. 16 (1996) 3760–3774.

[19] J. Fiez, Cerebellar contributions to cognition, Neuron 16 (1996) 13–15.

[20] J. Fiez, A positron emission tomography study of short-term maintenance of verbal information, J. Neurosci. 16 (1996) 808–822.

[21] C. Fortin, R. Breton, Temporal interval production and processing in working memory, Percept. Psychophys. 57 (1995) 203–215.

[22] E.A. Franz, R.B. Ivry, L.L. Helmuth, Reduced timing variability in patients with unilateral cerebellar lesions during bimanual movements, J. Cogn. Neurosci. 8 (1996) 107–118.

[23] J.M. Fuster, Role of the prefrontal cortex in delay tasks: Evidence from reversible lesion and unit recording in the monkey, in: H.S. Levin, H.M. Eisenburg, A.L. Benton (Eds.), Frontal Lobe Function and Dysfunction, Oxford Univ. Press, New York, 1990, pp. 59–71.

[24] F.B. Gershberg, A.P. Shimamura, The role of the frontal lobes in the use of organizational strategies in free recall, Neuropsychologia 13 (1995) 1305–1333.

[25] J. Gibbon, R.M. Church, W. Meck, Scalar timing in memory, in: J. Gibbon, L. Allan (Eds.), Timing and Time Perception, Ann. NY Acad. Sci., Vol. 423, 1984, pp. 52–77.

[26] J. Gibbon, R. Church, Representation of time, Cognition 37 (1990) 23–54.

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

[28] A.R. Gilliland, R. Martin, Some factors in estimating short time intervals, J. Exp. Psychol. 27 (1940) 243–255.

[29] S. Gilman, K. Adams, R.A. Koeppe, S. Berent, K.J. Kluin, J.G. Modell, P. Kroll, J.A. Brunberg, Cerebellar and frontal hypometabolism in alcoholic cerebellar degeneration studied with positron emission tomography, Ann. Neurol. 28 (1990) 775–785.

[30] S. Gilman, R.A. Koeppe, L. Junck, K.J. Kluin, M. Lohman, R.T. St Laurent, Patterns of cerebral glucose metabolism detected with positron emission tomography differ in multiple system atrophy and olivopontocerebellar atrophy, Ann. Neurol. 36 (1994) 166–175.

[31] P.S. Goldman-Rakic, Circuitry of the primate prefrontal cortex and regulation of behavior by representational memory, Handbook of Physiology—The Nervous System, 5, 1987, pp. 373–417.

[32] P.S. Goldman-Rakic, The prefrontal landscape: implications of functional architecture for understanding human mentation and the central–executive, Philos. Trans. R. Soc. Lond. B Biol. Sci. 351 (1996) 1445–1453.

[33] J. Grafman, Plans, actions and mental sets: managerial knowledge units in the frontal lobes, in: E. Perecman (Ed.), Integrating Theory and Practice in Clinical Neuropsychology, Lawrence Erlbaum Associates, Hillsdale, NJ, 1989, pp. 93–138.

[34] J. Grafman, I. Litvan, S. Massaquoi, M. Stewart, A. Sirigu, M. Hallett, Cognitive planning deficit in patients with cerebellar atrophy, Neurology 42 (1992) 1493–1496.

[35] S. Grondin, Production of time intervals from segmented and nonsegmented inputs, Percept. Psychophys. 52 (1992) 345–350.

[36] S. Grondin, F. Macar, Dividing attention between temporal and nontemporal tasks: A performance operating characteristic–POC–analysis, in: F. Macar, V. Pouthas, W.J. Friedman (Eds.), Time, Action and Cognition: Towards Bridging the Gap, Vol. 66, Kluwer Academic Publishers, Netherlands, 1992, pp. 119–128.

[37] M. Hallett, B. Shahani, R. Young, EMG analysis of patients with cerebellar lesions, J. Neurol. Neurosurg. Psychiatry 38 (1975) 1163–1169.

[38] W.M. Hartmann, Pitch, periodicity and auditory organization, J. Acoust. Soc. Am. 100 (1996) 3491–3502.

[39] E. Hazeltine, L.L. Helmut, R.B. Ivry, Neural mechanisms of timing, Trends Cogn. Sci. 1 (1998) 163–169.

[40] R.K. Heaton, Wisconsin card sorting test manual, Psychology Assessment Resources, Odessa, FL, 1981.

[41] J. Hore, B. Wild, H.C. Diener, Cerebellar dysmetria at the elbow, wrist and fingers, J. Neurophysiol. 65 (1991) 563–571.

[42] R. Ivry, Cerebellar involvement in the explicit representation of temporal information, Ann. NY Acad. Sci. 682 (1993) 214–230.

[43] R. Ivry, Cerebellar timing systems, Int. Rev. Neurobiol. 41 (1997) 555.

[44] R. Ivry, H.C. Diener, Impaired velocity perception in patients with lesions of the cerebellum, J. Cogn. Neurosci. 3 (1991) 355–366.

[45] R.B. Ivry, The representation of temporal information in perception and motor control, Curr. Opin. Neurobiol. 6 (1996) 851–857.

[46] R.B. Ivry, S. Keele, Timing functions of the cerebellum, J. Cogn. Neurosci. 1 (1989) 136–152.

[47] R.B. Ivry, S.W. Keele, H.C. Diener, Dissociation of the lateral and

medial cerebellum in movement timing and movement execution, Exp. Brain Res. 73 (1988) 167–180.
[48] M. Jueptner, M. Rijntjes, J.H. Faiss, D. Timmann, S.P. Mueller, H.C. Diener, Localization of a cerebellar timing process using PET, Neurology 45 (1995) 1540–1545.
[49] L. Junck, S. Gilman, J.R. Rothley, A.T. Betley, R.A. Koeppe, R.D. Hichwa, A relationship between metabolism in frontal lobes and cerebellum in normal subjects studied with PET, J. Cereb. Blood Flow Metab. 8 (1988) 774–782.
[50] J.G. Keating, W.T. Thatch, Nonclock behavior of inferior olive neurons: interspike interval of Purkinje cell complex spike discharge in awake behaving monkey is random, J. Neurophysiol. 73 (1995) 1329–1340.
[51] A. Kertesz, Western Aphasia Battery, Grune and Stratton, New York, 1982.
[52] P.R. Kileen, Counting the minutes, in: F. Macar, V. Pouthas, W.J. Friedman (Eds.), Time, Action and Cognition: Towards Bridging the Gap, Kluwer Academic, Netherlands, 1992, pp. 203–214.
[53] P.R. Kileen, N.A. Weiss, Optimal timing and the Weber function, Psychol. Rev. 94 (1987) 455–468.
[54] S.J. Kish, M. El-Awar, L. Schut, L. Leach, M. Oscar-Berman, M. Freedman, Cognitive deficits in olivopontocerebellar atrophy: implications for the cholinergic hypothesis of Alzheimer's dementia, Ann. Neurol. 24 (1988) 200–206.
[55] S. Kojima, P.S. Goldman-Rakic, Delay-related activity of prefrontal neurons in Rhesus monkeys performing delayed response, Brain Res. 248 (1982) 43–49.
[56] B. Konigsmark, L. Weiner, The olivopontocerebellar atrophies: a review, Medicine (Baltimore) 49 (1970) 227–241.
[57] A.B. Kristofferson, Quantal and deterministic timing in human duration discrimination, Ann. NY Acad. Sci. 423 (1984) 3–15.
[58] H.C. Leiner, A.L. Leiner, R.S. Dow, The human cerebro–cerebellar system: its computing, cognitive and language skills, Behav. Brain Res. 44 (1991) 113–128.
[59] H.C. Leiner, A.L. Leiner, R.S. Dow, The underestimated cerebellum, Hum. Brain Mapping 2 (1995) 244–254.
[60] B. Levine, D.T. Stuss, W.P. Milberg, M. Alexander, M. Schwartz, R. Macdonald, The effects of focal and diffuse brain damage on strategy application: evidence from focal lesions, traumatic brain injury and normal aging, J. Int. Neuropsychol. Soc. (in press).
[61] R.R. Llinas, The intrinsic electrophysiological properties of mammalian neurons: insights into central nervous system function, Science 242 (1988) 1654–1664.
[62] R.R. Llinas, J.P. Welch, On the cerebellum and motor learning, Curr. Opin. Neurobiol. 3 (1993) 958–965.
[63] C. Malapani, C. Khati, B. Dubois, J. Gibbon, Damage to cerebellar cortex impairs precision of time estimation in the seconds range, 4th Annual Meeting of the Cognitive Neuroscience Society, Boston, MA, 1997.
[64] J.A. Mangels, Strategic processing and memory for temporal order in patients with frontal lobe lesions, Neuropsychology 11 (1997) 207–221.
[65] W.H. Meck, Neuropharmacology of timing and time perception, Cogn. Brain Res. 3 (1996) 227–242.
[66] W.H. Meck, R.M. Church, G.L. Wenk, D.S. Olton, Nucleus basalis magnocellularis and medial septal area lesions differentially impair temporal memory, J. Neurosci. 7 (1987) 3505–3511.
[67] C.A. Meyers, H.S. Levin, Temporal perception following closed head injury, Neuropsychiatry Neuropsychol. Behav. Neurol. 5 (1992) 28–32.
[68] C. Miall, Models of neural timing, in: M.A. Pastor, J. Artieda (Eds.), Time, Internal Clocks and Movement, Vol. 115, Elsevier, Amsterdam, 1996, pp. 69–94.
[69] F.A. Middleton, P.L. Strick, Anatomical evidence for cerebellar and basal ganglia involvement in higher cognitive function, Science 266 (1994) 458–461.
[70] E. Miller, Verbal fluency as a function of a measure of verbal intelligence and in relation to different types of cerebral pathology, Br. J. Clin. Psychol. 23 (1984) 53–57.
[71] R.R. Miller, R.C. Barnet, The role of time in elementary associations, Curr. Direct. Psychol. Sci. 2 (1993) 106–110.
[72] B. Milner, M. Petrides, M.L. Smith, Frontal lobes and the temporal organization of memory, Hum. Neurobiol. 4 (1985) 137–142.
[73] M. Moscovitch, Models of consciousness and memory, in: M.S. Gazzaniga (Ed.), The Cognitive Neurosciences, MIT Press, Cambridge, MA, 1994, pp. 1341–1356.
[74] M. Nawrot, M. Rizzo, Motion perception deficits from midline cerebellar lesions in human, Vision Res. 35 (1995) 723–731.
[75] P. Nichelli, Time perception measurements in neuropsychology, in: M.A. Pastor, J. Artieda (Eds.), Time, Internal Clocks and Movement, Vol. 115, Elsevier, Amsterdam, 1996, pp. 187–204.
[76] P. Nichelli, D. Alway, J. Grafman, Perceptual timing in cerebellar degeneration, Neuropsychologia 34 (1996) 863–871.
[77] P. Nichelli, K. Clark, C. Hollnagel, J., Grafman, Duration processing after frontal lobe lesions, in: J. Grafman, K.J. Holyoak, F. Boller (Eds.), Ann. NY Acad. Sci., Vol. 769, New York Academy of Sciences, New York, 1995, pp. 183–190.
[78] H. Niki, M. Watanabe, Prefrontal and cingulate unit activity during timing behavior in the monkey, Brain Res. 171 (1979) 213–224.
[79] L.W. Olsho, S.W. Harkins, M.L. Lenhardt, Aging and the auditory system, in: J.E. Birren, K.W. Schaie (Eds.), Handbook of the Psychology of Aging, Van Nostrand-Reinhold, New York, 1985, pp. 332–377.
[80] D.S. Olton, Frontal cortex, timing and memory, Neuropsychologia 27 (1989) 121–130.
[81] D.S. Olton, G.L. Wenk, R.M. Church, W.H. Meck, Attention and the frontal cortex as examined by simultaneous temporal processing, Neuropsychologia 26 (1988) 307–318.
[82] M.A. Pastor, J. Artieda, M. Jahanshahi, J.A. Obeso, Time estimation and reproduction is abnormal in Parkinson's Disease, Brain 115 (1992) 211–225.
[83] A. Pentland, Maximum likelihood estimation: the best PEST, Percept. Psychophys. 28 (1980) 377–379.
[84] S. Perret, B. Ruiz, M. Mauk, Cerebellar cortex lesions disrupt learning dependent timing of conditioned eyelid responses, J. Neurosci. 13 (1993) 1708–1718.
[85] M. Petrides, Frontal lobes and working memory: evidence from investigations of the effects of cortical excisions in nonhuman primates, in: F. Boller, J. Grafman (Eds.), Handbook of Neuropsychology, Vol. 9, Elsevier, Amsterdam, 1994, pp. 59–82.
[86] E. Pöppel, Reconstruction of subjective time, in: M.A. Pastor, J. Artieda (Eds.), Time, Internal Clocks and Movement, Vol. 115, Elsevier, Amsterdam, 1996, pp. 165–185.
[87] J.L. Raymond, S.G. Lisberger, M.D. Mauk, The cerebellum: a neuronal learning machine?, Science 272 (1996) 1126–1131.
[88] S. Roberts, Isolation of an internal clock, J. Exp. Psychol. Anim. Behav. Process 7 (1981) 242–268.
[89] R.J. Seitz, Cerebellar timing processes, Neurology 47 (1996) 306–370.
[90] C. Shaw, J.P. Aggelton, The ability of amnesic subjects to estimate time intervals, Neuropsychologia 32 (1994) 857–873.
[91] A.P. Shimamura, Memory and frontal lobe function, in: M.S. Gazzaniga (Ed.), The Cognitive Neurosciences, MIT Press, Cambridge, MA, 1994, pp. 803–814.
[92] A.P. Shimamura, J.S. Janowsky, L.R. Squire, Memory for the temporal order of events in patients with frontal lobe lesions and amnesic patients, Neuropsychologia 28 (1990) 803–813.
[93] M. Taylor, C. Creelman, PEST: Efficient estimates of probability functions, J. Acoust. Soc. Am. 41 (1967) 782–787.
[94] E.A.C. Thomas, I.J. Bown, Time perception and the filled-duration illusion, Percept. Psychophys. 16 (1974) 449–458.
[95] E.A.C. Thomas, W.B. Weaver, Cognitive processing and time perception, Percept. Psychophys. 17 (1975) 363–367.
[96] R. Thompson, Neuronal mechanisms of classical conditioning in

mammals, Philos. Trans. R. Soc. Lond. B Biol. Sci. 329 (1990) 161–170.
[97] H. Topka, J. Valls Sole, S.G. Massaquoi, M. Hallett, Deficit in classical conditioning in patients with cerebellar degeneration, Brain 116 (1993) 961–969.
[98] M. Treisman, A. Faulkner, P.L. Naish, On the relation between time perception and the timing of motor action: evidence for a temporal oscillator controlling the timing of movement, Q. J. Exp. Psychol. A 45 (1992) 235–263.
[99] J.H. Wearden, Do humans possess an internal clock with scalar timing properties?, Learn. Motiv. 22 (1991) 59–83.
[100] R.L. West, An application of prefrontal cortex function theory to cognitive aging, Psychol. Bull. 120 (1996) 272–292.
[101] F.A.W. Wilson, S.P. ó Schalaidhe, P.G. Goldman-Rakic, Dissociation of object and spatial processing domains in primate prefrontal cortex, Science 260 (1993) 1955–1958.
[102] D. Woodruff-Pak, M. Papka, R. Ivry, Cerebellar involvement in eyeblink classical conditioning in humans, Neuropsychology 10 (1996) 443–458.
[103] D. Zakay, R.A. Block, The role of attention in time estimation processes, in: M.A. Pastor, J. Artieda (Eds.), Time, Internal Clocks and Movement, Vol. 115, Elsevier, Amsterdam, 1996, pp. 143–163.
[104] R.J. Zatorre, S. Samson, Role of the right temporal neocortex in retention of pitch in auditory short-term memory, Brain 114 (1991) 2403–2417.
[105] R.J. Zattore, A.C. Evans, E. Meyer, A. Gjedde, Lateralization of phonetic and pitch discrimination in speech processing, Science 256 (1992) 846–849.