Cerebellar and basal ganglia contributions to interval timing

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0. ABSTRACT

Previous studies have suggested that the cerebellum and basal ganglia may play a critical role in interval timing. In the first part of the chapter, we review this literature, focusing on production and perception tasks involving intervals in the hundreds of millisecond range. Overall, the neuropsychological and neuroimaging evidence consistently points to the involvement of the cerebellum in such tasks; the evidence is less consistent with respect to the basal ganglia. In the second half of the chapter, we present an experiment in which patients with either cerebellar or basal ganglia pathology were tested on a repetitive tapping task. Unlike previous studies, a pacing signal was provided, allowing an evaluation of variability associated with internal timing, motor implementation, and error correction. The results suggest a dissociation between the two groups: the patients with cerebellar lesions exhibited noisy internal timing while the gain in error correction was reduced in Parkinson patients. In combination with previous work, these results indicate how the cerebellum and basal ganglia may make differential contributions to tasks that require consistent timing.

1. INTRODUCTION

Accurate timing is a ubiquitous aspect of mental processes. How does the central nervous system solve the demands involved in the temporal aspects of information processing? One solution would be that timing is handled by subsystems specialized for domain specific processing. For example, the timing required for producing well-articulated speech would be solved by areas involved in speech production, whereas the

timing demands for the coordination of manual actions would be controlled by brain areas that also control the force and spatial aspects of these movements. Alternatively, humans are capable of producing rather arbitrary behaviors that exhibit accurate timing. We can produce periodic movements over a considerable range of durations. These actions can be achieved with different parts of the body, and indeed, do not even require overt actions; we can covertly maintain an internal beat. We can also detect and judge rhythmicity in a wide variety of sensory signals. While our sense of rhythm may be most accurate for auditory events, we can readily detect temporal perturbations in a sequence of visual or tactile events. Thus there likely exists some general system specialized to represent temporal information, a system that is recruited for tasks that require this form of computation.

There is ample evidence that temporal acuity correlates across different domains and behaviors.[1] Furthermore, a direct relationship is observed between interval duration and temporal accuracy over a wide variety of intervals, organisms and tasks (for a review, see[2]). These observations suggest at least one common underlying system for the representation of temporal information.

Three major challenges for research on temporal processing then become apparent. The first is primarily psychological, involving the distinction and characterization of different timing systems. What behaviors and perceptual skills share a common system and which functional domains engage domain specific processes? For example, it has been proposed that a distinction can be made between repetitive movements for which timing is explicitly represented and repetitive movements in which temporal regularities are an emergent property.[3,4] A second distinction that has been

considered is based on the idea that different systems may be engaged, depending on the temporal extent of the timed intervals.[2,5]

The second challenge is to generate a process model or models that make explicit the component operations involved in tasks that require temporal processing. For example, the scalar timing model specifies a series of component parts associated with the accumulation of clock pulses and the comparison of this sum to stored representations in long-term memory.[2,6] Similarly, the Wing-Kristofferson model postulates distinct processes that contribute to the variability observed during repetitive tapping tasks.[7] In this chapter, we consider models of this latter type, analyzing the psychological processes involved in synchronizing an internal timing mechanism to external, rhythmic events.

The last and ultimate challenge is to provide a mapping between psychological operations and neural circuits. This mapping need not be in a one-to-one correspondence. While some operations may be localized to particular neural structures, it is possible that the operations we describe at a computational level of explanation are implemented in a distributed manner within the brain. Exploring this mapping not only provides a first step towards developing a mechanistic explanation at the neural level, but also can help shape our understanding of the psychological operations.

We will focus on the contribution of two subcortical structures that have been proposed to be the cornerstone of an internal timing system, the cerebellum and the basal ganglia.[8,9] Both structures form reciprocal loops with many cortical areas[10-12], which would enable them to provide the precise representation of temporal information across a range of different task domains. We first review neuropsychological studies that investigate the role of the cerebellum and basal ganglia in the production and perception

of timed events. We then report a new experiment, examining the contribution of these structures to synchronization behavior.

2. REVIEW OF EXISTING STUDIES

While temporal regularities are manifest at many time scales, our review will be restricted to tasks involving intervals in the hundreds of milliseconds range. We opt for this limited range for two reasons. First, given the role of the cerebellum and basal ganglia in motor control, this range reflects the temporal extent of the component movements that form human actions such as walking, reaching, or speech. Second, similar methodologies have been applied in studies looking at timing in this range, providing an empirical basis for comparison. By restricting our review to short intervals, we do not imply that the timing of intervals in the range of multiple seconds does not entail similar processes and neural structures as timing in the millisecond range. At present, we see this issue as one in need of further study (for discussion of this issue, see[5,13-15]).

2.1. THE PRODUCTION OF TIMED SEQUENCES

Time production studies in this time span that have involved patients with either cerebellar lesions or Parkinson's disease (PD) are summarized in Table 1. The Parkinson patients have been generally viewed as a model for studying basal ganglia dysfunction. Most of these studies have used a continuation task introduced by Wing and Kristofferson.[7] Trials begin with the presentation of a periodic signal, usually an auditory metronome. After an initial synchronization phase, the metronome is terminated and the

participants are asked to continue tapping, attempting to separate each response by the interval specified by the metronome.

This task is appealing for its simplicity. The instructions are intuitive and comprehensible by people with a range of neurological or psychiatric disorders. The motor requirements are minimal. More important, this task has provided a process model for evaluating component sources of temporal variability in performance.[7] The model postulates two component sources of noise: A central clock that provides the timing signals for the series of successive responses and a motor system that implements these responses. Based on a small set of assumptions, namely that the component sources are independent of each other and that feedback mechanisms do not play a role in producing the next tap, estimates of the two components can be obtained from the autocovariance function of the inter-tap intervals (ITIs). The assumptions of the model have received substantial empirical support.[1,16]

Ivry and Keele[17] provided the first large-scale study in which the performance of patients with different neurological disorders was assessed with the Wing-Kristofferson continuation task. Patients with lesions of the cerebellum exhibited significant increases in variability on this task. The increase was especially marked in the estimate of the clock component and in a more detailed analysis of a subgroup of patients, the clock deficit was found to be associated with damage to the lateral regions of the neocerebellum.[18] In contrast, lesions centered in the medial cerebellum were associated with increases in the estimate of motor implementation noise. This double dissociation is in agreement with the anatomical projections of the output pathways of the cerebellum: The lateral regions primarily ascend to motor, premotor, and prefrontal regions of the

cerebral cortex while the medial regions innervate brainstem and spinal cord regions of the descending motor pathways. The finding of a clock deficit in patients with neocerebellar lesions has been replicated.[4,19]

The results from experiments involving PD patients yield a more ambiguous picture. Two studies have reported that medicated PD patients perform similar to age-matched controls in terms of overall variability during the continuation phase[17,20], whereas one study has shown a deficit in performance similar to that observed with cerebellar patients.[21] An earlier study had also pointed to a deficit in non-medicated PD patients.[22] However, each participant completed only a single trial per interval, rendering estimates of the variability components suspect. O'Boyle et al.[23] found significant increases in both estimates of clock and motor implementation estimates for patients tested off L-dopa medication. On the other hand, Ivry and Keele[17] reported no change in performance as a function of medication level.

Greater convergence is found in studies involving PD patients with unilateral symptoms either taking L-dopa medication[23] or tested in a drug-naive state.[17,24] In these cases, the patients showed consistent increases in the estimate of clock variability when tapping with their impaired hand; the motor estimate was not significantly changed. For example, Keele and Ivry[25] tracked one patient over a two-week period during which he began L-dopa therapy. His performance showed a marked improvement over the test sessions with the decrease in variability solely associated with a reduction in the estimate of clock variability.

In sum, the neuropsychological studies suggest that disorders of the cerebellum and basal ganglia can result in increased variability during repetitive tapping. The

increase may be isolated to either of the two component processes proposed in the Wing-Kristofferson model. The source of the increase following cerebellar pathology appears to be dependent on lesion location within the cerebellum. In PD, the deficit is less consistently observed, but when present, is almost always restricted to the clock component. Ivry and Hazeltine[1] point out that the term "clock" is misleading in the W-K model since this estimate refers to all sources of variability other than that associated with motor implementation. As such, they propose that the term "clock" variability should be replaced by "central" variability, encompassing all aspects of motor planning and preparation that occur prior to movement initiation. In this view, the cerebellum and basal ganglia might both add to central variability, but in distinct ways.[17]

Four studies have used functional imaging to investigate neural regions involved in the production of rhythmic movements. We defer our review of two of these to Section 3.2. In the third study[26] participants reproduced a sequence of isochronous intervals with the right hand, with the target pace indicated by either an auditory or visual metronome. Compared to just listening to the metronome, increased activation in the auditory condition was observed in left globus pallidus and right anterior cerebellum (Lobules V/VI). In the visual condition, activation was observed in the left lateral cerebellum (VIIa) in addition to the anterior cerebellar site. No basal ganglia activation was found in the visual condition. Another set of comparisons involved conditions in which participants produced either novel or well practiced rhythmic patterns. Prominent cerebellar activation was found for the novel conditions, spanning left and right cerebellar hemispheres (VIIa,b) and anterior and posterior vermal areas (III/IV and VIIIa,b). This pattern was similar for both auditory and visual stimulus conditions. The

basal ganglia also showed a bilateral increase in activation during novel rhythms, but again, this increase was limited to the auditory condition. Kawashima et al.[27] recently reported congruent results, in which they compared visually triggered and memory-timed finger taps. Again, this comparison was significant for the anterior cerebellum, but not for the basal ganglia. These results point to a consistent involvement of the cerebellum in the processing of temporal information. In contrast, the results are less consistent for the basal ganglia and are restricted to one sensory domain.

2.2. THE PERCEPTION OF TIMED EVENTS

Table 2 summarizes the performance of cerebellar and PD patients on time perception tasks. The table is restricted to studies in which participants judged the duration of a stimulus; we excluded papers in which the temporal judgment was based on gap detection or simultaneity.[28] Temporal acuity on duration discrimination tasks is conventionally assessed by varying the difference between a standard and a comparison stimulus. The participant's responses are fitted with a logistic distribution function to estimate the point of subjective equality (PSE) and variability, typically quantified as correct performance on 75% of the trials (corresponding to +- 1 SD of the logistic distribution). The table also shows the variability data in a normalized form in which the SD has been divided by the PSE. Interestingly, the results indicate a considerable range in the Weber fractions across the studies, probably reflecting the different methodologies used to make the threshold estimates.

Deficits for cerebellar patients were reported by Ivry and colleagues in three studies.[17,29,30] Note that many of the same patients were tested in the 1998 and 1999

papers, and thus, do not constitute independent samples. Nichelli et al.[31] also reported elevated thresholds for intervals ranging from 100 to 600 ms. However, their group of patients with cerebellar degeneration performed comparable to controls for intervals ranging from 100 to 325 ms. As with the tapping data, the PD results are less consistent. Ivry and Keele[17] observed no increase in the difference threshold in a group of medicated PD patients. In contrast, Harrington et al.[21] observed a significant impairment in a different group of medicated PD patients with intervals of 300 ms and 600 ms.

Jueptner and colleagues have conducted two PET studies to investigate the neural correlates of duration discrimination, one with auditory stimuli[32] and a second with tactile stimuli.[33] In both studies activation of the left inferior cerebellum (hemisphere of Lobule VII) and vermis (VI,VII) was found during the duration discrimination task compared to a control task in which the same stimuli were presented but the responses simply required alternating key presses. Increased blood flow was also seen bilaterally in the basal ganglia, but only in the experiment with auditory stimuli.

In summary, the patient and imaging studies of time production and perception yield a somewhat unsatisfying picture. The existing data indicates that cerebellar lesions are consistently associated with deficits on both production and perception tasks. While the initial studies involving PD patients reported no impairments, more recent reports have shown that PD patients also exhibit increased variability on time production and perception tasks. Thus, while Ivry and colleagues had argued that the dissociation between cerebellar and PD patients provided evidence of a specialized role for the cerebellum in the representation of temporal information, the current literature does not offer strong support for this dissociation.

Nonetheless, the fact that both groups can be impaired on similar tasks need not lead to the conclusion that temporal processing involves a distributed network that includes both the cerebellum and basal ganglia (as well as other structures such as the prefrontal cortex[34,35]). It may well be that the analytic power of the tasks used in these studies is insufficient. As noted above, the estimate of "clock" variability in the Wing-Kristofferson model is really a composite of all non-motor implementation sources of variability. Similarly, the perception tasks used in the patient studies have generally failed to provide a means for evaluating different sources of variability.[1] Two exceptions are Mangels et al.[29] and Casini and Ivry[30] in which an attempt was made to separate the effects of timing from those associated with attention and/or working memory. In both studies, the results from the cerebellar group were consistent with an impairment in timing whereas patients with prefrontal lesions were primarily influenced by the attentional demands of the tasks, temporal or non-temporal. It would be useful to apply a similar strategy in a direct comparison of cerebellar and PD patients.

3. SYNCHONIZATION

Studying the synchronization of repetitive finger taps with a stream of regular external events has a long history in experimental psychology.[36,37] Synchronization requires the ability to control motor output based on the prediction of external events.[38,39] It is thought to entail both open- and closed-loop processes: the former in that the responses are generated in advance of the metronome signals and the latter in that an error signal associated with the asynchrony between the responses and metronome signals are used to modify future responses. We first outline a general model of the

hypothetical processes required for synchronized tapping and then turn to a review of previous attempts to link these processes to neural structures.

3.1. Components involved in synchronization

A schematic of the component operations involved in synchronized tapping is presented in Figure 1. A clock-like system that represents the predicted interval emits a timing signal ($\underline{t_k}$) for the next motor command. The timing of this command is set such that the resulting tap occurs approximately at the same time as the stimulus tone ($\underline{s_k}$). The internal timing signal triggers a motor implementation process that adds a random motor-delay component $\underline{M_k}$ conceptualized as a independent noise source.[7]

To ensure that the taps occur in simultaneity with the metronome, the system must contain a closed-loop component. Two types of mechanisms have been proposed.[40,41] In period correction, the internal representation of the interval t is adjusted when a significant and consistent mismatch is detected between the metronome and the produced responses. This mechanism is thought to be relatively slow and dependent on a conscious perception of the mismatch of expected and perceived tempo.[42]

The other process, phase correction, ensures that the error of the central clock does not accumulate over a number of taps. Such accumulation would lead to a loss of phase stability between the metronome signals and the responses. Phase correction uses information about the asynchrony between the action and the external event to adjust the time of the next central command, thus compensating for this discrepancy. The simplest and normative method is a first order linear correction, in which some fraction, α, of this synchronization error is used to adjust the interval before the next tap. Random errors are

rapidly corrected when α is large, although the system would be overcompensating should α be greater than 1. Under some conditions, the adjustment process may take into account more than just the last asynchrony. In such cases, second-order error-correction models are more appropriate. Futhermore error correction may not always be linear (see[43]).

Because the "real" asynchrony $\underline{A_k}$ is not readily available, the phase correction process has to estimate the time of occurrence of the metronome signals and the time of occurrence of the tap.[37] For the time of the tap, proprioceptive reafferences from the action and the perceived consequences of the action such as an audible click produced by the response key or the sound of the finger striking the table surface could suffice. However, even without tactile, proprioceptive, visual, or auditory feedback, stable synchronization between actions and an auditory pacing signal can be accomplished. Billon, Semjen, Cole, and Gauthier[44] examined synchronization in a patient with a severe sensory neuropathy that rendered him functionally deafferented. This patient could maintain a stable phase relationship and correct for perturbations in a relatively normal manner. Thus, the estimate of the time at which an action occurs may be also include the copy of the efferent signals.[45]

Alternative models have been proposed in which the clock is reset on every trial by a combination of the perceived tap and metronome signal rather than through a modification process based on the perceived asynchrony, e.g.[38]. However, the former model has the advantage of capturing many characteristics of human performance in a parsimonious way[41], and is more readily consistent with widespread evidence of tempo constancy in musical contexts. For example, humans tend to precede the pacing signal

with the action by a constant amount of approximately 50 ms.[36,46] From the framework of the model outlined in Figure 1, the phase lead of the taps over the metronome signals can be accounted for by longer delays in the perception of the action than in the perception of the pacing signal. This would lead to a perceived asynchrony that is close to zero, even though the actual asynchrony is negative.[37,47]

3.2. Neural structures underlying synchronization and timing

In the context of this chapter, two neuroimaging papers are of special interest[48,49] since they included a synchronization phase and a continuation phase during repetitive tapping. Both studies observed activation in right anterior cerebellum (hemisphere of Lobule I-VI) during the two phases, with the degree of activation approximately equal. A second cerebellar focus in the right inferior lateral hemisphere (H VIII-IX) was reported by Jaenke et al.[49] when the participants were paced by an auditory metronome. These authors failed to observe any activation in the basal ganglia. In contrast, Rao et al.[48] reported significant activation in the putamen during the continuation phase, only. Cortical areas were identified in both studies, especially during the synchronization phase, although these tended to be modality specific (e.g., primary or secondary auditory or visual regions).

Unfortunately, the design of these studies makes it difficult to draw strong conclusions. Rao et al.[48] argue that neural correlates of an internal timing mechanism should be most activated during the continuation phase. Based on this, they argue that their results are consistent with a basal ganglia locus for timing and propose that the cerebellar activation reflects general contributions of this structure to sensorimotor

control, consistent with the idea that the movements are similar during synchronization and continuation.

The assumption that internal timing is most pronounced during the continuation phase is suspect. All models of synchronization assume that the internal clock is engaged during paced and unpaced tapping. Indeed, it is difficult to see how participants would tap in advance of the metronome signals if they were not engaging in anticipatory timing. Mates et al.[50] have shown that such anticipatory behavior holds for intervals up to around 2 s. Beyond this duration, tapping does become reactive, now following rather than anticipating the tones.

If the demands on an internal timer are similar during the synchronization and continuation phases, then the cerebellar activation profile matches that expected of an internal timing process. However, this finding provides only weak support for a timing interpretation. As noted above, similar activation during both phases would also be expected of areas associated with the planning and execution of the finger movements, independent of whether or not these movements requiring the operation of an internal timing system. In sum, the cerebellar activation pattern during repetitive tapping is consistent with what would be expected if neural activity within this structure was involved in determining when each response should be produced whereas activation within the basal ganglia is not consistent with a timing account. But the cerebellar activity could also be accounted for by hypotheses that do not involve internal timing.

4. EXPERIMENTAL STUDY

To investigate the role of the cerebellum and basal ganglia in sensorimotor synchronization, we conducted a study in which patients with cerebellar lesions or Parkinson's disease were asked to tap along with an auditory metronome. Unlike previous studies of tapping with these patient groups, we only included a paced phase and the number of taps per trial (200) was considerably longer than in previous work. These long runs were essential for examining how the participants adjusted their behavior based on an error signal generated through the comparison of their own performance and the metronome signals. While previous studies have focused on component processes that are assumed to operate during unpaced tapping, the focus here was on the ability of these patients to use error correction during paced tapping.

We based our analysis on a linear error-correction model.[51] To separate the influence of the phase correction process from noise coming from the internal clock component and noise arising at stages of the motor implementation, we express the asynchrony on tap k+1 relative to the perceived asynchronies on the last two taps (see Figure 1):

$$A_{k+1} = A_k - \alpha A_k - \beta A'_{k-1} + (T_k - P) + (M_{k-1} - M_k) \quad (1)$$

While this formulation includes a second order term based on the asynchrony two taps pervious to the adjusted tap, the first order (AR1) forms of the models proved to be sufficient with most of the data sets. With a few exceptions discussed in the result section, the estimates for beta were close to zero. Thus, we will limit our focus to the first-order model.

Because the perceived asynchrony A' is the sum of the measured asynchrony A and the difference of the perceptual delays for the perception of the motor event (the tap), F_k, and auditory signal, S_k, Formula 1 becomes

$$A_{k+1} = (1-\alpha)A_k - \alpha(F_k - S_k) + (T_k - P) + (M_{k+1} - M_k) \quad (2)$$

We can solve for a stationary solution of the expected asynchrony, by taking expected values, yielding

$$\bar{A} = \frac{\bar{T} - P}{\alpha} - (\bar{F} - \bar{S}) \quad (3)$$

where the bar denotes the average or expected value.

Thus the expected asynchrony is a direct function of the difference between mean perceptual delays[37], the deviation of the mean interval of the clock from the pacing interval, and the error-correction parameter α. The stochastic properties of this and related models have been described extensively in several publications, along with different methods for estimating these parameters.[51-55] To estimate the parameters, we established the equivalence between the first-order synchronization model and an ARMA(1,1)-process of the asynchronies (see Appendix). This approach, based upon earlier work by Vorberg and Wing[51], allows the estimation of the error-correction parameter α, as well as of the motor and central variances with standard estimation methods. In addition, second-order models (AR2) were also fit to the data and the relative adequacy of the AR1 form of the model was tested against AR2 optional formulations.

Although the equations are linear, their application to real data requires considerable care for three main reasons. First, it is necessary to circumnavigate certain

parameter ranges that exhibit near-indeterminacy of a solution.[53-55] This effect was kept to a minimum by excluding trials in which the autocovariance function showed no significant deviation from zero for lags one through five since the model fit for these data would fall in the area of near-indeterminacy. We also acquired converging results using the method of bins[53]. This method yields a more robust estimate of the error-correction parameter, but requires that the size of the motor delay variance be specified a priori.

Second, the validity of the estimates is related to the number of intervals produced on each trail. Without error correction, stable estimates of clock and motor variability variability can be obtained with short runs of 20-40 taps.[7] However, such lengths are completely inadequate when error correction is involved. An order of magnitude longer is essential (at least 200 taps, depending on the consistency of the performer's control.) Our run lengths were chosen with this in mind.

Third, the data analysis presumes that the same control process is used over the course of the run, a phenomenon that is described as stationarity. If a run is markedly non-stationary, then the estimation technique may exhibit significant biases. This is not a significant problem with younger control groups, but patient groups are selected precisely due to problems in their control processes, and non-stationarity can be more likely with them.[56] This issue can be handled in part by comparing parameter estimates in different sections of each run and discarding runs that are inconsistent. Runs with a notably poor model fit are also likely to be non-stationary.

4.1. METHOD

Participants. Three groups were tested. One group consisted of five patients with Parkinson's Disease (Age = 68.9 years, SD = 3.9; Education = 16 years, SD = 1.5; Time since diagnosis = 11.4 years, SD = 5.9). All patients were rated to have mild to severe (2-4) Parkinson's symptoms on the Hohn & Yahr scale. They were all on their regular dopaminergic replacement medication program at the time of testing.

The cerebellar group (N = 7; Age = 65.9, SD= 10.1. Education = 13.6, SD = 2.4) consisted of two patients with bilateral cerebellar degeneration and five patients with unilateral lesions due to either stroke (2) or tumor (3). Three of the unilateral patients had left-sided lesions and two had right-sided lesions. These patients were tested in a chronic condition, at least 2 years after their neurological incident.

A control group of six elderly control participants was also tested (Age = 69.5, SD = 5.2, Education = 14.0, SD = 1.8). These individuals reported no history of significant neurological disease or injury and were selected to match the patients in terms of age and education.

Procedure. Responses were made on a peripheral response device linked to a PC. The taps required flexion movements of the right or left index fingers on a piano-type key (2 x 10 cm), mounted parallel to the top surface of the response device. The tone generator in the PC was used to create the auditory metronome, with the pitch of the pacing tones fixed at 500 Hz.

The experimenter initiated the trial, triggering the onset of the auditory metronome. Participants were instructed to begin tapping when they had a good sense of the target pace, attempting to tap along with the metronome. Once the first response was

detected, the metronome continued until it had completed another 200 cycles. At this point, the tones ceased. Feedback was then provided, indicating the target interval, the mean interval produced, and the variability of the inter-response intervals. The next trial began after a short rest period.

Two independent variables were manipulated. First, the target rate was either 500 ms or 900 ms. Second, participants used either the right hand alone, left hand alone, or tapped bimanually. This chapter will only report data from the unimanual conditions.

The conditions were tested in separate blocks of four trials each and the participants completed two blocks for each of the six conditions. Thus, the data set for the analyses consists of eight trials of approximately 200 intervals each. The order of the blocks was randomized across participants, although a complete counterbalancing was not possible given the small number of participants in each group. Rate was manipulated across sessions with half of the participants starting with testing at 500 ms and the other half starting with 900 ms. A short practice trial consisting of 20 paced intervals was included prior to the first block of each condition.

4.2. Data Analysis

The first 10 taps were excluded to allow performance during synchronization to stabilize. The raw data were examined to screen for places in which a tap was missing or an extra response was recorded and only intact segments of each trial were used for parameter estimation. Trial in which the asynchronies showed sudden drifts of the mean (for example to an anti-phase pattern) were excluded. These exclusions were far more frequent for the two patient groups (16%) than for the controls (3%). Parameter

estimates from trials in which the autocorrelation-function was degenerative, yielding indeterminacy of the model, were also excluded (9%). These trials were as frequent for the control and patient groups. Another effect to be considered is inconsistency between runs. Given the likelihood of stochastic variations in process control parameters, moderate effects of this kind are normative and can be addressed by averaging across runs. However, it is possible that performance changes over time due to learning. For example, with practice, Pressing[43] observed an increase in the utilization of error correction and a decrease in the estimate of central variability. However, these effects occurred over a period of years. We assume that learning-related changes are minimal with the current design.

4.3. RESULTS

Separate ANOVAs were performed to compare the performance of each patient group to that of the control participants for each of the dependent variables. The factors in these analyses were tempo (500 ms and 900 ms) and participant group. Based on preliminary analyses, we averaged the results over the two hands for the controls, Parkinson patients, and two cerebellar degeneration patients. For the cerebellar patients with unilateral lesions we compared performance with the impaired, ipsilesional hand to that of the control participants. We also ran a separate analysis in which we compared the performance of the ipsilesional and contralesional hands for the unilateral patients. Surprisingly, none of these within-subject comparisons were significant. These null results likely reflect two factors. First, the number of participants with unilateral cerebellar lesions was small (n=5). Second, a couple of the patients showed little

impairment on the task, consistent with their marked clinical recovery. Thus, our focus here is on the comparison of the patient groups to the controls.

As an overall measure of performance we assessed the SD of the intervals (Figure 2a). This measure was significantly increased in the cerebellar group, $F(1,11)=7.11$, $p = .022$, but not in the Parkinson group, $F(1,9) = .44$, $p = .52$. The decomposition of the variance revealed that the SD of the motor delays (Figure 2b) were not different between the control group and the two patient groups: $F(1,11) = .001$, $p = .981$, for the cerebellar, $F(1,9) = 0.10$, $p = .753$, for the PD patient group. The effect of pace and the group by pace interaction were not significant in either comparison.

In contrast, the estimates for the SD of the clock intervals (Figure 2c) were significantly elevated for the cerebellar group, $F(1,11) = 7.43$, $p = .019$. No such deficit was found for the Parkinson patients, $F(1,9) = .443$, $p = .52$. As expected from a linear increase of clock SD with interval length[1], the effect of pace on the clock SD was significant in both comparisons. $F(1,11) = 36.6$, $F(1,9) = 110.8$, $p<.001$. The Group x Pace interaction was not significant for either comparison, $F(1,11) = 0.5$, $F(1,9)=2.6$. These results are congruent with the idea that the higher variability of the performance of cerebellar patients is due to deficits in a central timing mechanism.

One measure of the quality of error correction is the mean synchronization error (Figure 3). Similar to previous reports, the mean asynchrony for the control participants was negative, indicating that their taps anticipated the onset of the tones. The magnitude of this asynchrony was similar for the patients with cerebellar lesions and controls, $F(1,11) = 0.09$, $p = .77$. The PD patients showed a greater negative asynchrony compared to the controls, $F(1,9) = 7.99$, $p = 0.02$. That is, the responses of the PD

patients preceded the tones to a greater extent than the responses of the controls. The effect of pace was significant in both the control/cerebellar ANOVA, $\underline{F}(1,11) = 9.23$, $\underline{p} = .011$, and control/Parkinson ANOVA, $\underline{F}(1,9) = 6.4$, $\underline{p} = .031$. In both, the negative asynchrony was greater in the 900 ms condition than in the 500 ms condition. The Group x Pace interaction was not significant in either case.

The estimates for the error-correction parameter α are shown in Figure 4. The analyses indicate that the estimates for the cerebellar patients were not different from those obtained for the controls, $\underline{F}(1,11) = .67$, $\underline{p} = .80$. The error-correction values were lower in the PD patients than in the controls, although this comparison did not reach significance, $\underline{F}(1,9) = 3.73$, $\underline{p} = .085$. The error-correction estimate increased in size from the faster to the slower pace, an effect which was significant when considering all three groups, $\underline{F}(2,15) = 6.83$, $\underline{p} = .019$. The group factor did not interact with this effect (both $\underline{F}$'s <1).

We also compared the error-correction strategies in the groups by comparing the fraction of runs for which the linear, AR1 model provides a satisfactory fit in relation to the AR2 model. In the control group, 84.9 % ($\underline{SE} = 2.8$) of the runs were well fit by the AR1 model. This proportion did not significantly decrease in either the cerebellar group (79.4 %, $\underline{SE} = 3.9$) or the Parkinson group (82.5 %, $\underline{SE} = 5.5$). Thus, based on the assessment of correction strategy as inferred by the validity of the AR1 model, it appears that the patients groups engaged in error correction in a way that was comparable to the control participants. The estimates of the α-parameter and the higher mean asynchrony suggest that the PD patients might exhibit a quantitative deficit in error correction.

5. DISCUSSION

In this chapter, we have sought to evaluate the contribution of the basal ganglia and cerebellum to temporal processing, focusing on behaviors that require precise timing in the range of hundreds of milliseconds. As shown in our review of the existing literature, it has been difficult to dissociate the functions of these regions based on patient and neuroimaging studies. While cerebellar damage is consistently linked to deficits on both time production and time perception tasks, similar deficits are reported in some studies involving patients with Parkinson's disease.

At least three issues should be kept in mind when evaluating this state of affairs. First, the inferential nature of science is strengthened by considering results from various task domains and methodologies. Our evaluation should encompass a broad range of behavioral tasks, and should also include computational, anatomical, pharmacological, and physiological evidence. Ivry[8] has argued that the case for a cerebellar timing system provides a parsimonious account of the functions of this structure in a wide range of tasks, including many in which the demands on precise timing are more subtle than in tapping or time perception tasks. Computational models based on a detailed analysis of the architecture and physiology of the cerebellar cortex are also consistent with a specialized role of this structure in representing the temporal relationships between successive events.[57,58] The case for a basal ganglia role in internal timing has not been developed to the same extent. With the exception of the PD studies reviewed above, it has been primarily been based on pharmacological and lesion studies in rats, and for the most part, this work has been conducted on tasks involving intervals that span many seconds, (reviewed by Meck[9]).

Second, there are limitations in inferring basal ganglia function from studies solely involving PD patients. While this degenerative disorder clearly produces a characteristic change in basal ganglia function, the loss of dopaminergic cells also has direct and indirect effects on other neural regions including the frontal lobes. We have recently begun testing patients with unilateral basal ganglia lesions on time production tasks[59] and our preliminary results suggest that their performance is normal in repetitive tapping. It is possible, however, that this group, while seemingly better matched for comparison to patients with unilateral cerebellar lesions, will fail to provide insight into basal ganglia function due to recovery and reorganization following unilateral basal ganglia damage.

Third, many neuropsychological studies have been limited to either PD or cerebellar patients. There have been few efforts to directly compare the two groups of patients within the same experiment (but see [17]). Such comparisons offer the best opportunity to test specific hypotheses concerning the differential contributions of neural structures, which collectively are recruited in the performance of specific tasks.[29,30] In this way a mapping may be established between components of a psychological process model and the underlying neural substrates. In the current study, we compared two patient groups on investigated one aspect of performance involved in paced tapping, namely the ability to use error-correction processes in order to keep responses in synchrony with a pacing signal.

5.1. VARIABILITY

Consistent with earlier reports, the cerebellar group exhibited increased variability of the inter-tap intervals for both the 500 ms and 900 ms conditions. In contrast, we failed to observe a significant increase in the PD group at either rate. The PD patients were medicated and previous results have suggested that the impairment in this group is especially marked when tested off medication or during the early stages of the disease process.[17,24] Nonetheless, despite their medication, the PD patients did exhibit clinical evidence of PD disease at the time of testing.

Estimates of clock and motor implementation variability were obtained through decomposition of the overall variability. All three groups exhibited similar estimates of motor variability, consistent with earlier work on these patient populations.[17,18,20,21] Notably, the increased variability in the cerebellar group was attributed to the clock component. Thus, these results again point to a central role for the cerebellum in the generation of the central signals related to the production of consistently timed responses.[17,19]

5.2. ERROR-CORRECTION PROCESS.

As a first step toward analyzing error correction in these patients, it is necessary to establish that a first-order linear error-correction model provides an adequate account of the patients' performance. Given their neurological impairments and hypotheses concerning the role of the basal ganglia and/or cerebellar in online error correction[60-62], we considered it possible that a qualitatively different strategy might characterize the performance. A second-order error-correction model has been shown to provide a better

fit under certain circumstances. For example, these higher order models are more appropriate when expert musicians tap at a fast pace.[52] In our study, the proportion of runs that were adequately accounted for by a first-order error-correction model was roughly equivalent across the groups. Thus, we infer that, qualitatively, both patient groups used a similar strategy as the control participants in how they used asynchrony information to adjust their performance. However, the results indicate a quantitative deficit in error correction for the PD patients. The estimates for the first-order parameter α tended to be lower for this group, although the result was only marginally significant. If this finding was to replicate, it would suggest that a dopamine-related deficit in the striatum reduces the gain at which the error signal influences the next outgoing motor-command.

5.3. Asynchrony.

Another dissociation between the Parkinson and cerebellar patients was observed in the asynchrony results. As is typically observed for synchronized tapping at intervals below 1 s [37,46], the taps for all of the participants occurred prior to the tones. However, this asynchrony was greater for the Parkinson patients (overall mean of 136 ms) compared to both the controls and cerebellar patients (62 and 70 ms, respectively).

As outlined in the Introduction, three different factors could contribute to the increase in the asynchrony (see Formula 3). First, the increased asynchrony may be due to the fact that PD patients perceive their taps to have occurred later than healthy individuals. The difference in perceptual delays for the perception of the tone and the tap influences the average asynchrony directly. For example, it has been shown that when

participants tap with their foot, they precede the pacing tones by 50 ms more than when they tap with their finger.[37] This effect may also be related to how PD patients integrate different sources of information to estimate the time at which the tap has occurred. A number of researchers have proposed a role for the basal ganglia in sensory integration, even though PD patients do not show obvious sensory impairments. To fully account for the observed difference between groups, one would have to posit that the PD patients perceived their taps to have occurred 66 ms later than the age-matched controls.

Second, negative asynchronies could result from an internal clock that is operating at a faster rate than the external pacing signal. A phase-correction process would then prevent the error from accumulating across successive taps, but the faster rate of the internal clock would result in taps occurring prior to the tones. In contrast to the perceptual-delays hypothesis, this explanation offers a parsimonious account of why the asynchronies were larger in the 900 ms condition for all of the groups. The mean error of the clock is likely to be proportional to the length of the timed interval, causing larger asynchronies for longer intervals.

Pharmacological studies in humans [63] and rats [9] have suggested that the rate of an internal pacemaker may be altered by dopamine levels. However, in this work, the clock has been hypothesized to slow down when dopamine levels are low, not to speed up. Of course, we did not monitor dopamine levels nor did we attempt a within-subject comparison in which the patients were tested both on and off their medication. It would be interesting to see if the mean asynchrony lead varied with medication level.

While the relationship of the asynchrony to dopamine is unclear, this behavioral change is reminiscent of the speeding up that is observed in PD patients when engaged in

an extended action. For example, PD patients tend to speed up during unpaced, repetitive tapping.[17,23] Similarly, although they have difficulty initiating locomotion, once started their steps become smaller and marked by a faster cycle time. Such changes could be interpreted as reflecting a bias for an internal clock to operate faster when engaged repetitively.

Ivry and Richardson[64] offer an alternative model that could account for the reduced cycle time. In their view, the basal ganglia operate as a threshold device, gating when centrally generated responses are initiated. They conceptualize the loss of dopamine as an increase in the threshold required to initiate a response. If we assume that this threshold drifts toward more normal levels with repetitive use, then the same input pattern will trigger a response at shorter latencies over successive cycles. Thus, the increased negative lag could reflect a change in a thresholding process rather than a disturbance of sensory integration times or a change in the operation of an internal timing process.

Third, as shown in Formula 3, the observed asynchronies caused by a difference between clock speed and the pacing rate will be modulated by α. Lower gains of the error-correction process would allow the error to accumulate to a larger degree, resulting in larger asynchronies. Assuming that the internal timing mechanism runs too fast in all groups, the differences in α alone potentially could account for a substantial part of the observed differences between groups. In the current study, we can estimate the differences between internal clock speed and pacing signal for each group, given the values of the error-correction parameter. It turns out that the differences in error correction can only partly explain the group differences in asynchronies. To fully

account for this effect, we would have to posit an additional difference in clock speed, being on average 20 ms faster for the PD patients.

At present, the results do not allow us to discriminate between accounts based on changes in perceptual delays or inaccuracies in the internal timing signal (caused by different clock speed or changes in threshold). Moreover, the relative contribution of reduced error correction to the increased asynchrony depends on the assumption that error correction behaves linearly. When the asynchronies deviate substantially from zero, as is the case for the PD patients, this assumption is likely to be violated.[43] Thus, converging evidence from independent methods is needed to distinguish between these factors.

5.4. Final comments

The current experiment points to differential contributions of the cerebellum and basal ganglia in the performance of synchronized tapping. Lesions in the cerebellum appear to perturb the internal timing mechanism, manifest as an increase in the noise of this system. In terms of overall variability, as well as the estimates of clock and motor noise, medicated PD patients performed comparable to the control participants.

Nonetheless the PD patients differed from the controls on two measures, the error-correction parameter α and mean asynchrony. Together these findings suggest that these patients have difficulty in adjusting their movements based on sensory information. In contrast, no differences were observed between the cerebellar patients and controls on the measures of error correction. This null finding is rather surprising given the frequently suggested role of the cerebellum in the comparison of expected and actual

sensory information for rapid error correction,[60] but see [62,65]. Our results indicate that the cerebellar contribution is more of a feedforward signal, indicating when the next response should be emitted. On-line modulations of these timing signals may come from extracerebellar structures.

The role of the basal ganglia in error correction has been suggested in a very broad sense.[61] One important distinction is between online adjustments that are used to ensure that the current movement is executed accurately and trial-by-trial information that is used to develop stable internal models for the production of future movements. Neither of these ideas have been extensively tested. Smith et al.[62] provide evidence of the role of the basal ganglia in online error correction of reaching movements, demonstrating that patients with Huntington's disease and asymptomatic HD gene-carriers are impaired in correcting for external and self-generated perturbations of reaching movements. It remains to be seen how best to characterize error-correction processes in synchronized tapping. While the adjustments appear to occur over time spans that are comparable to online error correction, the discrete nature of the taps and pacing signals may create conditions more akin to trial-by-trial error correction.

6. FOOTNOTES

1. For purposes of parameter estimation we consider the perceptual delays F and S to be constants. Schulze and Vorberg[55] showed that if F and S are regarded as random variables, the variance attached to these delays would inflate the variance estimations of motor delays. However, the main stationary characteristics of the model remain equivalent to the simplified model used here.

7. TABLES

Table 1

Summary of studies involving human participants with damage to the cerebellum or Parkinson's Disease on repetitive finger tapping. N: number of participants. CD, MD: standard deviation of clock and motor components estimated with the Wing-Kristofferson model. Sig: * indicates that the difference between the experimental and control group is statistically reliable.

Study (pace)	Group	Condition	N	CD	Sig	MD	Sig	Sympt.
Ivry et al.[18] (550 ms)	Cerebellar, Hemisphere	Imp	4	37.0	*	17.8		
		Unimp		21.0		14.3		
	Cerebellar, Vermal	Imp	3	27.0		25.3	*	
		Unimp		23.0		13.0		
Franz et al.[19] (400 ms)	Cerebellar	Imp	4	22.0	*	12		
		Unimp		13.0		8.0		
Ivry & Keele[17] (550 ms)	Control		21	24.3		11.0		
	Cerebellar		27	38.1	*	14.0		11 focal, 16 deg.
	Parkinson		29	27.7		9.3		On medication
	Parkinson	Imp	4	46.5	*	11.5		
		Unimp		25.6		9.4		
	Parkinson	On	7	28.4		10.7		
		Off		27.7		11.8		

Pastor et al.[22] (400ms)	Control		20	9.0		6.1		
	Parkinson		42	34.8	*	19.6	*	Off medication
Ducheck et al.[20] (550 ms)	Control		30	21.1		14.0		
	Parkinson		20	24.2		10.4	*	HY= 1-2 On medication
O'Boyle et al.[23] (550 ms)	Control		12	15.4		8.2		
	Parkinson	Unimp	12	17.8		8.5		HY=1.5
		Imp		23.7	*	11.9	*	On medication
	Parkinson	On	12	17.9		8.1		HY=1.8
		Off		24.3	*	13.5	*	
Harrington et al.[21] (600 ms)	Controls		24	27		15		
	Parkinson		34	42	*	20	-	HY=2.4, On medication

Table 2.

Summary of studies with human participants with damage to the cerebellum or Parkinson's Disease on perceptual tasks involving duration discrimination. Thresholds are one SD of a logistic distribution fit to the observers response. K: Weber-fraction of 1 SD / PSE (point of subjective equality). Sig: * indicates that a statistically reliable difference between the experimental and control groups.

Study	Group	N	Standard interval	Threshold (1 SD)	K	Sig	Sympt
Ivry & Keele[17]	Controls	21	400	19.2	0.05		
	Cerebellar	27		30.5	0.08	*	
	Parkinson	28		21	0.05	-	
Mangels et al.[29]	Controls	14	400	31.5	0.08		
	Cerebellar	9		44.9	0.11	*	unilateral lesions
Casini & Ivry[30]	Control		`	27	0.07		
	Cerebellar			38.8	0.10	*	unilateral lesions
Nichelli et al.[31]	Controls	13	100-600[1]	29.6	0.11		
	Cerebellar	12		48.9	0.17	*	CCA , 2 OPCA
	deg,						
Harrington et	Controls	24	300 &	53	0.09		

al.[21]		600				
	Parkinson	34	80	0.13	*	HY=2.4

1. This task required the participants to classify single intervals as "short" or "long"; a standard interval was not presented on each trial. The PSEs were 274 and 282 for controls and cerebellars, respectively.

8. APPENDIX

For the estimation of parameters, the linear first-order error-correction model

$$A_k = A_{k=1} + (T_k - P + M_k - M_{k-1}) - \alpha A_{k-1} \tag{4}$$

was reformulated as an ARMA(1,1) process based on a gaussian white noise series $w_1,...,w_N$ with variance σ_w^2.

$$A_k = \phi A_{k-1} + w_k + \theta w_{k-1} \tag{5}$$

The asymptotic autocovariance function of the process described in Equation 4 can be derived as[51,54]

$$\gamma(k) = \begin{cases} \dfrac{\sigma_T^2 + 2\alpha\sigma_M^2}{1-(1-\alpha)^2} & ;k = 0 \\ \left[\dfrac{(1-\alpha)\sigma_T^2 + 2(1-\alpha)\alpha\sigma_M^2}{1-(1-\alpha)^2} - \sigma_M^2\right](1-\alpha)^{k-1} & ;k > 0 \end{cases} \tag{6}$$

and the asymptotic autocovariance function for the ARMA(1,1) model, described in Equation 5[66]

$$\gamma(k) = \begin{cases} \sigma_w^2 \dfrac{1+2\theta\phi+\theta^2}{1-\phi^2} & ;k = 0 \\ \sigma_w^2 \dfrac{(1+\theta\phi)(\phi+\theta)}{1-\phi^2}\phi^{k-1} & ;k > 0 \end{cases} \tag{7}$$

From this we can extract the three equivalences

$$\phi = 1-\alpha \tag{8}$$

$$\theta = \sqrt{r(2+r)} - r - 1 \quad ;with \quad r = \frac{\sigma_T^2}{2\sigma_M^2} \tag{9}$$

$$\sigma_w^2 = -\frac{\sigma_M^2}{\theta} \tag{10}$$

and conversely

$$\sigma_T^2 = \sigma_w^2(1+\theta)^2 \tag{11}$$

$$\sigma_M^2 = -\sigma_w^2\theta \tag{12}$$

This reformulation has two important advantages. First the estimation of parameters of the linear first-order error-correction model can be accomplished using the standard methods for ARMA (1,1) models. In practice this was accomplished by using the ARMAX routine in MATLAB™ (System Identification Toolbox), which implements an iterative Newton-Raphson algorithm that minimizes the quadratic next-step prediction error. The second advantage is that the characteristics of the model only vary with ϕ and θ, but are homogenous across different levels of the parameter σ_w^2. For example, whereas optimal error correction α_{OPT} is a non-linear function of σ_M^2 and σ_T^2 [51], it is a linear function of θ and independent of σ_w^2.

$$\alpha_{OPT} = 1+\theta \tag{13}$$

The region of parameter space encompassing and near the region of optimal error correction is of importance in the estimation process since the model becomes unidentifiable here. The time series under this model becomes Gaussian white noise with autocovariance function

$$\gamma(k) = \begin{cases} \sigma_w^2 & ;k=0 \\ 0 & ;k>0 \end{cases} \tag{14}$$

Monte-Carlo studies of this method have shown that the parameter values for α, σ_M^2, and σ_T^2 can be validly estimated from simulated time-series data produced following Formula 4. However, in the region surrounding the line of indeterminacy (Formula 13) the estimates become unreliable.[55] In practice we avoid this region by

excluding trials in which $\hat{\gamma}(k)$ does not significantly deviate from zero for the lags $0<k<6$.

9. FIGURE CAPTIONS

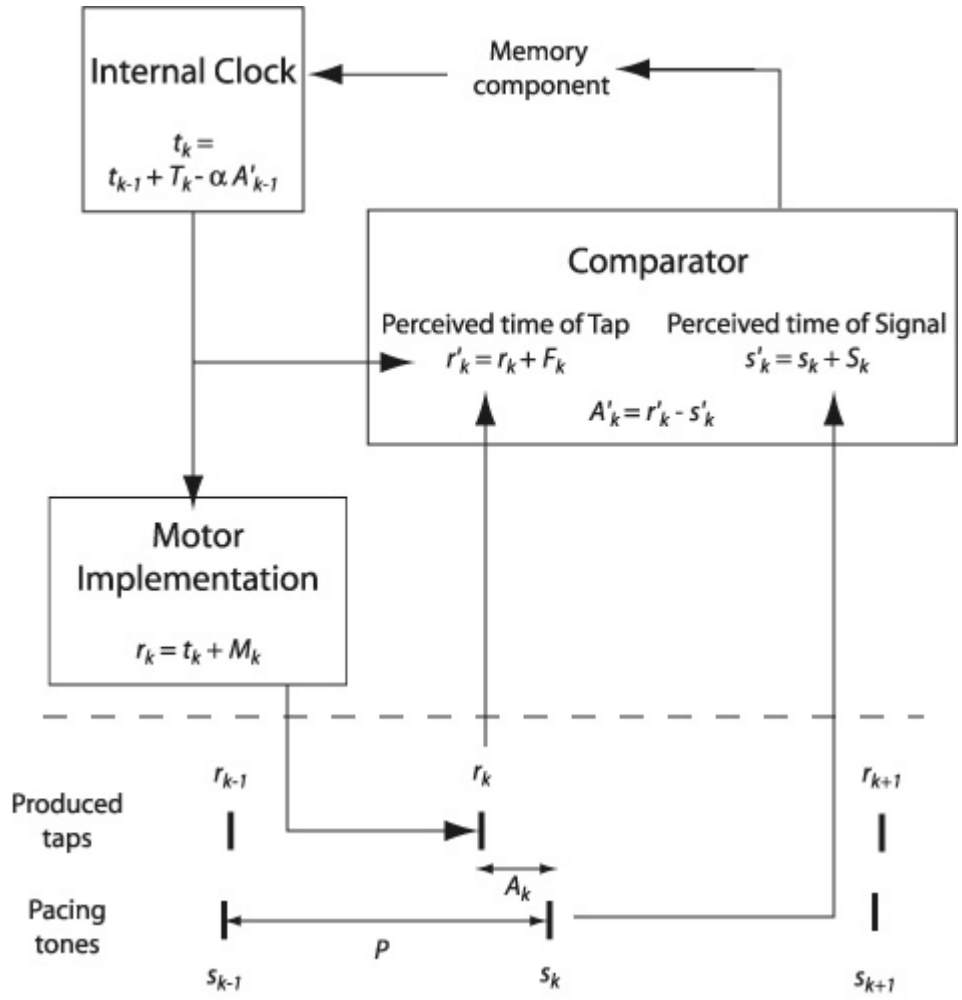

Figure 1. Process model of synchronization.[51,54] Lower-case variables indicate time-points of events, upper case variables indicate the length of the intervals between events, and subscripted variables are conceptualized as random variables (see Footnote 1).

An external pacing signal occurs with period P at the time points s_k. An internal clock is emitting signals to the motor system at times t_k. In absence of error correction, the clock produces timing signal separated by the clock intervals T_k. The motor implementation process produces the k^{th} taps at time r_k by adding a random motor delay M_k to the time of the internal timing signal. The real synchronization error A_k between the tap and the pacing signal is perceived (A'_k) by a comparator system. The perceived

asynchrony is influenced by the perceptual delays, with which the comparator perceives the occurrence of the tap ($\underline{F}_k$) and of the pacing signal ($\underline{S}_k$). This asynchrony is then used to correct the next timing signal send by the internal clock with error-correction parameter alpha.

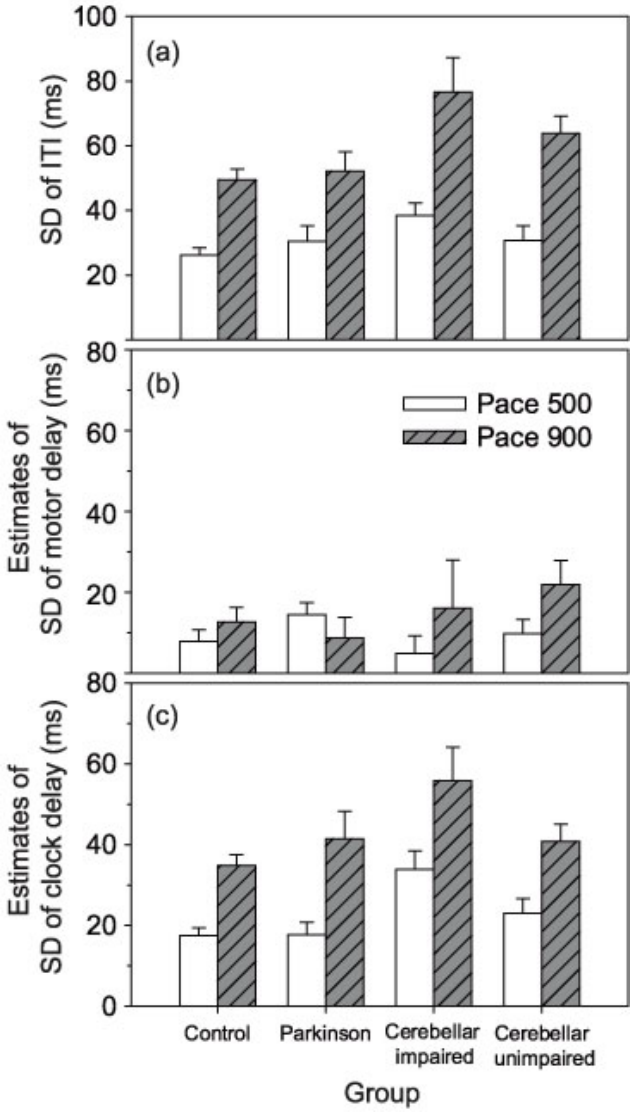

Figure 2. Variability of the intertap intervals for the control, Parkinson and cerebellar groups. For the unilateral cerebellar patients, separate values are shown when performing with the ipsilesional hand (impaired) or contralesional hand (unimpaired). A single value is included for the patients with bilateral cerebellar degeneration, based on the average of the two hands (and included in the impaired bar). (a) SD of the intertap intervals for the fast (500 ms) and slow (900 ms) pacing tones. The bottom two figures show the decomposition of the variability into estimates of the motor (b) and clock delay (c) components. Error-bars indicate between-subject standard error.

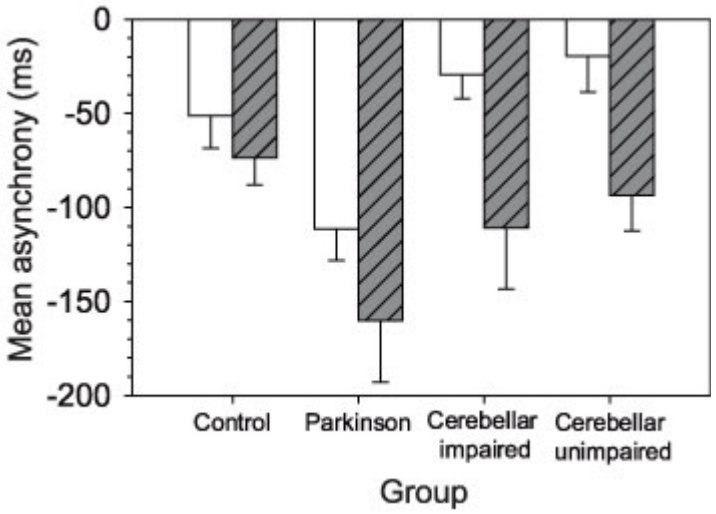

Figure 3. Mean asynchrony between the produced taps and the external pacing tone for the 500 ms (white bars) and 900 ms (gray bars) conditions. Negative values indicate that the taps occurred in advance of the tones. Conventions as in Figure 2.

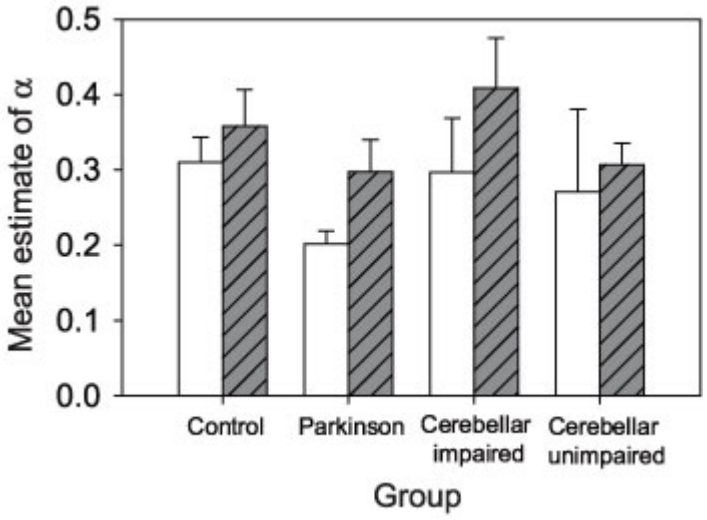

Figure 4. Mean estimates of the error-correction parameter α for the 500 ms (white bars) and 900 ms (gray bars) conditions. Conventions as in Figure 2.

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