Spontaneous, synchronized, and corrective timing behavior in cerebellar lesion patients

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Research report

Spontaneous, synchronized, and corrective timing behavior in cerebellar lesion patients

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HIGHLIGHTS

- Cerebellar patients and controls performed self-paced and paced sensorimotor tasks.
- The results confirm a temporal processing dysfunction in cerebellar lesion patients.
- Lesions increase asynchronies, decrease tempo sensitivity, impair error correction.
- The results are compatible with a sensory predictive account of cerebellar function.

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ABSTRACT

To successfully navigate through and interact with a dynamic environment it is necessary to acquire and use adequate temporal information to guide behavior. Apart from several areas in the cerebral cortex and cortico-striatal networks, the cerebellum has been proposed to engage in the processing of temporal information. Damage to the cerebellum can impair precise event-based temporal processing in motor and non-motor behavior. To further substantiate cerebellar contributions to temporal processing and to explore its specific role in adapting to a dynamic environment, we investigated sensorimotor temporal processing in ten patients with cerebellar lesions and a corresponding number of healthy matched controls. Experimental tasks included simple self-paced repetitive finger-tapping (spontaneous motor tempo), temporally non-adaptive (isochronous pacing) and adaptive (tempo-changing pacing) sensorimotor synchronization with auditory sequences (synchronization-continuation tapping), and a perceptual tempo judgment. The results indicate that patients' performance diverges systematically from controls on several measures. Cerebellar patients demonstrate more variable self-paced tapping, larger negative asynchronies when synchronizing with isochronous pacing sequences, altered automatic error correction responses to tempo changes (phase correction), and decreased perceptual sensitivity to these perturbations, especially for small accelerations. These findings confirm imprecise temporal processing in cerebellar patients, and hint at a specific impairment in the tens-of-milliseconds range preceding critical events, in line with a temporally predictive account of cerebellar function. Moreover, this cerebellar profile complements previous findings concerning dysfunctional temporal processing in basal ganglia patients assessed with the same experimental setup, suggesting structural and functional differentiation within an integrative temporal processing network.

1. Introduction

Reciprocal polysynaptic connections between the cerebellum, thalamus, cerebral cortex, and subcortical areas establish the structural basis for functional interactions, and an active role of the cerebellum in motor and non-motor behavior [1–6]. A common denominator in cerebellar function across these domains is *temporal processing*, conceived as the ability to encode, decode, and evaluate the temporal structure of sensory and sensorimotor

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events. In addition to the basal ganglia, prefrontal-, and supplementary motor areas, the cerebellum is among the brain regions consistently associated with temporal processing [7–11]. More specifically, the *cerebellar timing hypothesis* suggests that the cerebellum generates a precise internal representation of the temporal relation between salient events in the subsecond range [12–14].

Another denominator in cerebellar function is a conglomerate of related functions, namely the interplay of preparation, prediction, and attention, conceived as a dynamic process of constant adaptation to internal and external variation [15]. Cerebellar circuitry involved in predicting sensory consequences of action ("forward-modelling" [16]) has been suggested to generate a temporal signal, which, potentially in concert with pre-supplementary motor cortices, guides sensory prediction and the temporal orienting of attention [17]. This mechanism is reminiscent of a more general concept of attention and the allocation of attention in time as formulated in the framework of *dynamic attending theory* [18]. This theory considers naturally occurring internal variations (fluctuations) of attention directly sensitive to the temporal structure of external stimulation. Modelled as a complex of adaptive oscillations (attending rhythms), these fluctuations may establish a stimulus-driven, synchronized attending mode, which allows prediction of the temporal locus of future events. From this perspective, the temporal structure of events determines efficient allocation of attention and thereby the quality of integrated percepts [18].

The question arises whether the precise representation of event timing, forward-modelling, and the efficient allocation of attention converge into a generalizable function in behavior that requires or at least benefits from real-time prediction [19,20]. This assumption is essentially a variant of the idea that the cerebellum contributes to precise sensory discrimination and integration, and controls the acquisition of sensory data to increase the efficiency of processing in cerebral cortex [21]. These cerebellar contributions to temporal aspects of behavior are perhaps most evident (but not limited to) tasks, in which sensory processing concurs in conjunction with movement [22,23]. Notwithstanding functional specialization within specific cerebellar subregions, the cerebellum as a whole may thus instantiate a sensorimotor structure, which modulates activity in cerebral cortex to optimize behavior in terms of temporal precision and coherence, synchronization, and temporal prediction as facets of ongoing interactions with a dynamic environment. On this account, damage to the cerebellum should reduce the efficiency of these operations, leading to suboptimal temporal precision, which may cascade into a broad range of motor and non-motor behaviors.

In the current study, we compared the performance of patients with cerebellar lesions and healthy controls in a set of sensorimotor tasks that require a relatively high degree of temporal precision. Self-paced generation of temporal regularity (spontaneous motor tempo, SMT), paced synchronization and unpaced reproduction, as well as adaptation and perceptual sensitivity to tempo changes were assessed using previously established adaptive finger-tapping paradigms in combination with a modelling approach that has been shown to differentiate between automatic and attention-dependent forms of error correction in adaptive sensorimotor synchronization [24,25]. Firstly, we expected patients' performance to diverge systematically from controls in all domains tested: spontaneous, paced, and perceptual behaviour, and to exhibit a profile of dysfunctions that would be compatible with the proposed role of the cerebellum in precise subsecond temporal processing in production and perception as suggested by the *cerebellar timing hypothesis*. Secondly, based on the current modelling approach we also expected this profile to reflect dysfunctional automatic mechanisms, thus differing from the previously obtained profile of basal ganglia patients, who demonstrated dysfunctional attention-dependent error correction in adaptive sensorimotor synchronization [25]. The emergence of such a pattern would substantiate the notion of cerebellum and basal ganglia as nodes within an integrative temporal processing network, and specify this global function on the basis of a differential engagement of attention.

2. Material and methods

2.1. Participants

10 chronic-stage right-handed patients with cerebellar lesions (mean age: 45.0, SD: 14.0, range: 25–70 years; 3 women) and 10 healthy matched controls (mean age: 46.8, SD: 13.1 years) participated in the experiment (Table 1, Fig. 1). All participants provided informed written consent with the study. Individual control-patient pairings were matched in terms of handedness, gender, age (+/− 2 years), and education (in years). None of the participants had professional musical expertise. Both groups were recruited via databases at the Max Planck Institute for Human Cognitive and Brain Sciences in Leipzig, Germany. None of the participants had prior experience with finger-tapping in an experimental setup. The study was conducted in accordance with the World Medical Association Declaration of Helsinki and was approved by the ethics committee of the University of Leipzig.

2.2. Structural magnetic resonance imaging

High-resolution T1-weighted magnetic resonance scans were obtained for each patient on Bruker BioSpin (BioSpin GmbH, Rheinstetten, Germany) or Siemens TrioTim (Siemens Healthcare, Erlangen, Germany) magnetic resonance systems at 3 T using a 32-channel phased-array head array coil and an MP-RAGE sequence [26]. The resulting images were segmented and spatially normalized to Montreal Neurological Institute (MNI) space by means of a unified segmentation approach [27] in *SPM* (SPM8, Wellcome Department of Imaging Neuroscience, London, http://www.fil.ion.

Table 1
Patient characteristics. Abbreviations: cen. = center of mass (stereotactic coordinates provided by MRIcron), hem. = hemisphere, l = left, r = right, m/f = male or female, vol. = lesion volume in cc.

no.	m/f	age	vol.	cen. (x,y,z)	hem.	aetiology
1	m	25	48.0	77,38,35	l,r	arteriovenous malformation, intracranial haemorrhage
2	m	30	30.1	52,53,46	l	superior cerebellar artery aneurysm, intracranial haemorrhage
3	m	45	4.9	84,64,47	l,r	basilar artery aneurysm, superior cerebellar artery infarction
4	m	70	1.6	63,31,35	l	posterior inferior cerebellar artery infarction
5	m	59	7.1	89,37,26	r	posterior inferior cerebellar artery infarction
6	f	38	0.3	121,48,27	r	posterior inferior cerebellar artery infarction
7	f	45	7.9	62,41,24	l,r	posterior inferior cerebellar artery infarction
8	m	55	14.5	57,40,24	l	posterior inferior cerebellar artery infarction
9	f	33	8.8	84,49,37	r	medulloblastoma resection
10	m	50	2.4	88,52,15	r	posterior inferior cerebellar artery infarction

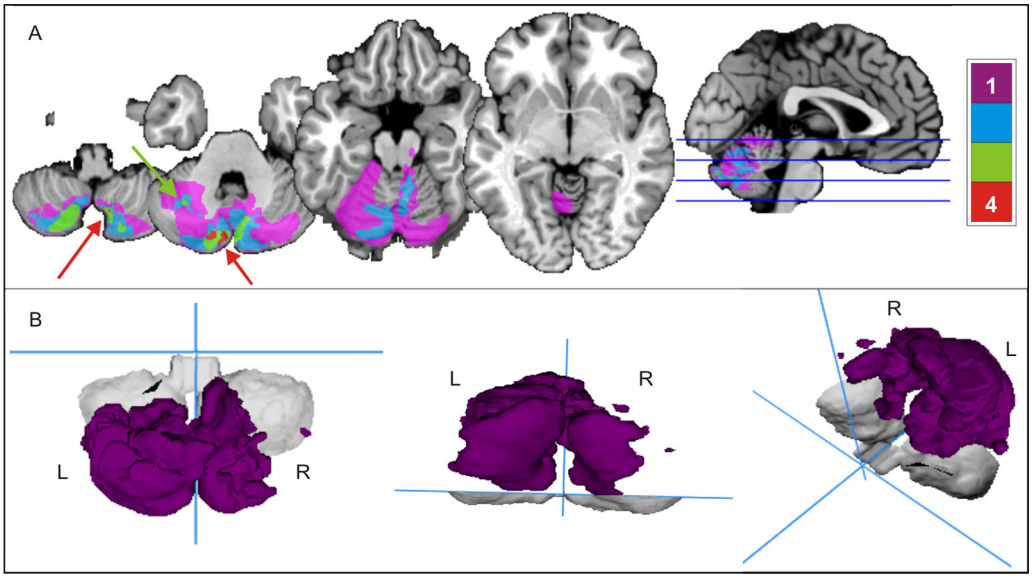

Fig. 1. Lesion characteristics. An illustration of the location and the overlap of the cerebellar lesions was created in MRIcron (http://www.mccauslandcenter.sc.edu/mricro/mricron/). Purple shades indicate regions of minimal overlap (N = 1), while red shades indicate regions of maximal overlap (N = 4, indicated by red arrows) (A). A 3-D "shape" representation of the damaged regions was generated in Mango (http://ric.uthscsa.edu/mango) to depict the volume information for the whole group (B). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

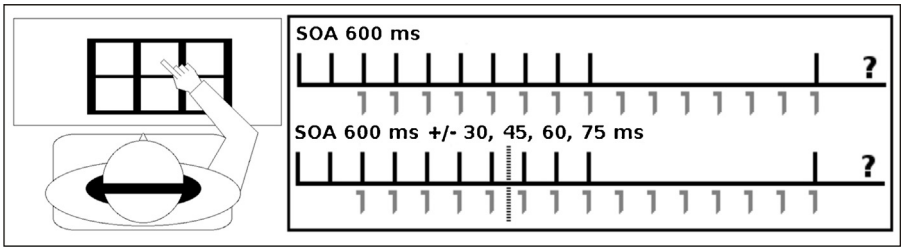

Fig. 2. Experimental setup. The study comprised three parts, corresponding to an initial assessment of spontaneous motor tempo (SMT; 31 taps), an intermediate (adaptive) sensorimotor synchronization task, followed by a second assessment of SMT. Participants were asked to tap as regularly as possible at a self-chosen rate during the SMT recordings. In the synchronization task, participants aligned taps to tonal pacing sequences, which either contained or did not contain (control sequences) a tempo change relative to an initial stimulus-onset-asynchrony (SOA) of 600 ms. If the sequence contained a tempo change, then participants had to adapt their tapping to that change. The sequences consisted of 10 tones, and participants continued tapping at the final sequence tempo until they heard a single tone, which marked the end of a trial. Afterwards, they reported whether they had perceived the sequence as getting faster, slower, or as maintaining a constant tempo.

ucl.ac.uk/spm). Volumes of interest corresponding to individual lesions were delineated manually on axial slices of the normalized images in *MRIcron* [28] and plotted onto a scalp-stripped T1-weighted single subject template (Colin27_T1_seg_MNI.nii, available via http://brainmap.org/ale/index.html; Fig. 1). Finally, the total volume (cm^3) and the center of mass (cartesian coordinates) of each lesion as provided by *MRIcron* were extracted for subsequent use in correlational analyses, providing information about lesion size and a form of approximation of lesion location in terms of the anterior-posterior (x), lateral (y), and superior-inferior (z) dimensions of the center of mass.

2.3. Data collection and analysis

The current protocol was the same as in previous work ([25]; Fig. 2). Stimulus presentation and data recording was controlled by custom software written in *MAX* (cycling74.com) running on a PC. The SMT of each participant was assessed before (SMT1) and after (SMT2) the adaptive synchronization task. Participants sat on a chair and tapped for 31 taps (30 inter-tap-intervals, ITIs) on the rubber surface of an electronic percussion pad (Roland SPD-6) connected to the Musical Instrument Digital Interface (MIDI) port of the PC. They were asked to tap as regularly as possible at a self-chosen rate until they heard a single tone (E7) presented via headphones (Sennheiser HD 202). All participants were allowed to familiarize themselves with the setup and to test different styles of tapping on different locations on the pad, but the experimenter did not demonstrate the task to avoid potential influences on individual performance. All participants elected to tap with the index finger of their right hand and to rest their hand on the pad. For SMT, variables of interest were tapping rate (mean inter-tap-interval (M_ITI)) and tapping variability (coefficient of variation (CV_ITI), obtained by dividing the ITI standard deviation by M_ITI).

The same technical setup was used during the adaptive synchronization task. In this case, participants were asked to synchronize their taps with an auditory pacing sequence (600 ms stimulus-onset asynchrony) consisting of 10 piano tones (C8, 4176 Hz), to adapt to any tempo change that might occur, and to continue tapping in the last perceived tempo after the end of the sequence until they heard a single lower pitch tone (E7), which signalled the end of the trial. All participants completed 100 pseudo-randomized trials in 10 blocks distributed over 9 conditions. Each block consisted of eight sequences that contained a tempo change relative to the 600 ms base tempo (+/− 30, 45, 60, and 75 ms) and two sequences without a tempo change that served as control sequences. All tempo changes occurred between the 7th and the 8th tone of the sequence. The order of the sequences was counterbalanced across the blocks. Participants were instructed to start tapping with the third tone of

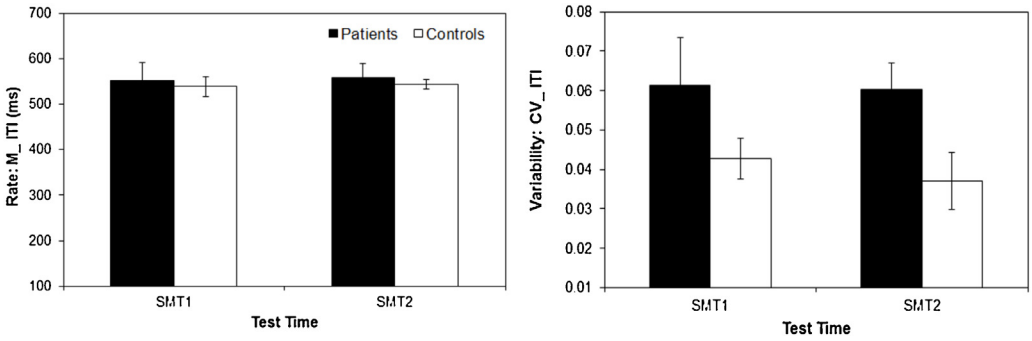

Fig. 3. Spontaneous motor tempo. Self-paced spontaneous regular tapping was assessed before (SMT1) and after (SMT2) the adaptive synchronization task in terms of rate (mean inter-tap-interval, M_ITI) and variability (coefficient of variation of the mean inter-tap-interval, CV_ITI). Patients and controls did not differ significantly in their tapping rates but patients displayed significantly increased tapping variability in comparison to controls in both assessments.

the pacing sequence. After they stopped tapping, participants indicated whether they had perceived an acceleration, deceleration, or no tempo change. An additional block of 10 trials served as training. There was a short break of approximately 5 min after block 5.

Missing taps, e.g., due to insufficient tapping force, and misplaced taps (defined as lying outside a −150 ms to +130 ms time-window relative to the expected target position) were excluded from all further analyses. For sequences without a tempo change, variables of interest were the mean asynchrony between the tones and the taps (M_ASYN) and the corresponding variability (CV_ASYN), as well as M_ITI, and CV_ITI, calculated separately for synchronization and continuation tapping. The ability to adapt the tapping to an actual tempo change was assessed by means of several additional variables, i.e., adaptation indices computed separately for accelerations and decelerations, as well as phase- and period-correction estimates computed on the basis of five intervals (positions) of interest (s0, s1, s2, s3, c). Position s0 corresponds to the interval terminated by the tap that coincided approximately with the first tone at the new sequence tempo, immediately followed by positions s1, s2, and s3. Thus, s3 corresponds to the interval initiated by the tap that coincided approximately with the last tone of the pacing sequence. Position c reflects the average interval produced during continuation tapping. These parameters were then submitted to a *MATLAB* (The Mathworks) implementation of the *two-way error-corrective mechanism* as originally proposed in a model by Mates ([29]; for a detailed description of the mathematical procedures applied for fitting data to this model see Ref. [24]) in order to obtain estimates for phase correction (compensation for gaps between the central availability of internal stimulus representations and response feedback) and period correction (compensation for discrepancies between an internal reference interval and an actual inter-stimulus-onset interval). Finally, perceptual sensitivity to the tempo changes was assessed in terms of individual d' scores computed separately for the various step changes. All variables of interest were analysed by means of repeated-measures ANOVA with a primary focus on the between-subject factor *group* (patients vs. controls).

3. Results

All patients and controls were able to complete the experimental tasks without apparent signs of fatigue or needing additional breaks.

3.1. Spontaneous motor tempo

The spontaneous tapping rate (Fig. 3) in the patient group was similar for SMT1 (M_ITI: 551 ms, SD: 124) and SMT2 (M_ITI: 557 ms, SD: 99) and comparable to the rates observed in the control group for SMT1 (M_ITI: 539 ms, SD: 44) and SMT2 (M_ITI: 544 ms, SD: 35). This was substantiated by significant correlations between SMT1 and SMT2 in patients ($r = 0.632$, $p = 0.050$) and in controls ($r = 0.785$, $p = 0.007$), while a 2×2 ANOVA with the between-subject factor *group* (patients vs. controls) and the within-subject factor *test time* (SMT1 vs. SMT2) on M_ITI revealed no significant differences. However, the same type of ANOVA conducted for CV_ITI yielded a significant main effect of *group* ($F(1,18) = 5.037$, $p = 0.038$, $\eta_p^2 = 0.219$), indicating generally more variable performance in patients.

In order to further explore structure-function relations within the patient group, M_ITI and CV_ITI for SMT1 and SMT2 were correlated first with lesion size and then with the three anatomical dimensions reflected by the center of mass for individual lesions. To address the problem of multiple comparisons, the sequentially rejective Holm-Bonferroni adjustment method [30] was applied in these and similar correlation analyses reported in the following. As each experimental variable of interest was correlated with four lesion-related variables, this procedure resulted in adjusted alpha levels of 0.0125 for the most significant test, 0.017 and 0.025 for the following, and 0.05 for the least significant test. This type of analysis yielded a significant positive correlation between the anterior-posterior dimension and M_ITI for SMT1 ($r = 0.772$, $p = 0.009$) but not for SMT2 ($r = 0.172$, $p = 0.635$). Subsequent exclusion of one patient whose performance fell outside a range of two standard deviations of the mean for SMT2 (311 ms) confirmed a similarly strong correlation between M_ITI for SMT1 and SMT2 in patients ($r = 0.822$, $p = 0.007$) as in controls and yielded significant correlations between the anterior-posterior dimension and M_ITI for SMT1 ($r = 0.923$, $p = 0.000$) as well as SMT2 ($r = 0.884$, $p = 0.002$), while it did not change the pattern of results for the corresponding ANOVAs. For the whole patient group, there were positive correlations between lesion size and CV_ITI for SMT1 ($r = 0.821$, $p = 0.004$) and SMT2 ($r = 0.792$, $p = 0.006$), suggesting that more anterior centers of mass for the respective lesions are associated with slower tapping rates, while larger lesions are generally associated with more variable tapping.

3.2. Synchronization: sequences without tempo changes

Trials in which the tempo of the pacing sequence remained constant served as a control for trials that required adaptation of the tapping rate to a changing pacing tempo. Patients and controls seemed to differ in several of the measures (Table 2).

To compare the group performance for the control sequences, independent-samples *t*-tests were conducted for the mean and the CV of the asynchronies between taps and pacing tones. Patients produced substantially larger ($t(18) = -7.919$, $p = 0.000$, $d = 3.535$) and also more variable ($t(18) = 4.115$, $p = 0.001$, $d = 1.803$) nega-

Table 2
Control sequences. Tapping performance for sequences without a tempo change was assessed in terms of the mean asynchrony (M_ASYN) and the coefficient of variation (CV_ASYN) between the tones of the pacing sequence and the corresponding taps. In addition, mean inter-tap-intervals (M_ITI) and coefficients of variation (CV_ITI) were computed separately for the paced synchronization (Syn) and the unpaced continuation (Con) phase.

	M_ ASYN	CV_ASYN	M_ITI Syn	M_ITI Con	CV_ITI Syn	CV_ITI Con
Patients	–91 ms	0.065	595 ms	585 ms	0.053	0.072
Controls	–21 ms	0.035	599 ms	599 ms	0.043	0.048

tive mean asynchronies than controls. In the latter case Levene's test for equality of variances proved significant ($F(1,18) = 11.524$, $p = 0.003$), with equal variances not assumed changing the result to ($t(10.150) = 4.115$, $p = 0.002$). On average, the observed difference in the mean asynchronies corresponds to an additional 70 ms, by which the taps in the patient group preceded the pacing stimuli relative to the 21 ms observed for the control group. Two separate 2 × 2 ANOVAs with the between-subject factor *group* (patients vs. controls), and the within-subject factor *phase* (synchronization vs. continuation) were conducted for M_ITI and CV_ITI. The ANOVA on M_ITI did not identify any significant differences. However, for CV_ITI this procedure yielded significant effects of *group* ($F(1,18) = 5.652$, $p = 0.029$, $\eta_p^2 = 0.239$) and *phase* ($F(1,18) = 31.226$, $p = 0.000$, $\eta_p^2 = 0.634$), as well as an interaction of these factors ($F(1,18) = 11.177$, $p = 0.004$, $\eta_p^2 = 0.383$). Subsequent direct comparisons revealed a group difference during the continuation phase ($t(18) = 2.985$, $p = 0.008$, $d = 1.372$) but not during the synchronization phase, indicating increased variability for self-paced tapping in patients. Again, Levene's test for equality of variances was significant ($F(1,18) = 11.271$, $p = 0.004$), with equal variances not assumed changing the result to ($t(10.164) = 2.985$, $p = 0.013$).

There were significant positive correlations between lesion size and CV_ITI for the synchronization phase ($r = 0.818$, $p = 0.004$) and the continuation phase ($r = 0.825$, $p = 0.003$), essentially replicating findings for SMT concerning the relation of larger lesion extent and high tapping variability.

3.3. Synchronization: sequences with tempo changes

Performance for trials containing a tempo acceleration or deceleration was assessed on the basis of adaptation indices calculated separately for each participant and for each position of interest and type of tempo change. To this end, M_ITIs were plotted as a function of final sequence tempo (Fig. 4).

The slope of a linear regression line fitted to these functions was then taken as a measure of the ability to adapt to the final sequence tempo and to maintain this tempo during the continuation phase [25]. Adaptation indices (Fig. 5) were then analyzed by means of a 2 × 2 × 4 ANOVA with the between-subject factor *group* (patients vs. controls), and the within-subject factors *tempo* (faster vs. slower) and *position* (s1 vs. s2 vs. s3 vs. c). When applicable, Greenhouse-Geisser corrected values are reported here and for similar analyses described below. While there was only a tendency for a main effect of *group* ($F(1,18) = 3.314$, $p = 0.085$, $\eta_p^2 = 0.155$), there was a significant effect of *position* ($F(3,54) = 7.802$, $p = 0.000$, $\eta_p^2 = 0.302$) and an interaction of *group x position* ($F(3,54) = 3.523$, $p = 0.021$, $\eta_p^2 = 0.164$).

Subsequent analyses revealed a group difference for position s1 only ($t(18) = -3.126$, $p = 0.006$, $d = 1.409$), i.e., the first interval for which a reaction to the tempo change occurring during the preceding interval (position s0) can be expected. This result indicates the lack of initial overcorrection in the patient group contrary to behavior typically observed in healthy participants [31,32]. This phenomenon has been linked to the perceptual sensitivity towards the tempo change ([24]; see also Section 3.4). Visual inspection of the data showed that the lack of overcorrection at the group level was primarily due to four patients with adaptation indices <0.9 (indicating atypical undercorrection), whereas such behavior was entirely absent in the control group (all adaptation indices >1.1). To further explore the potential anatomical correlates of these particular profiles, we looked for overlap in lesion locations in the respective patients. There was a single small area of overlap for three out of four overlays, located in the left cerebellar crus I (Fig. 1, green arrow).

Informed by the findings of the preceding ANOVA, correlation analyses with lesion size and location were performed on the basis of averaged adaptation indices for each position of interest, i.e., disregarding the direction of tempo change. There was a significant positive correlation between the lateral dimension and adaptation indices on s1 ($r = 0.934$, $p = 0.000$), which further substantiates the link between lesions with more left-lateralized centers of mass and the lack of initial overcorrection (Fig. 5).

The differential contribution of phase- and period correction mechanisms to the adaptation to the tempo changes was analyzed by means of two separate 2 × 2 ANOVAs with the between-subject factor *group* (patients vs. controls), and the within-subject factor *tempo* (faster vs. slower). For phase correction estimates, this procedure identified a main effect of *group* ($F(1,18) = 4.617$, $p = 0.046$, $\eta_p^2 = 0.204$), indicating less efficient phase correction in patients relative to controls, independent of the direction of the tempo change, while the same type of ANOVA on period correction estimates yielded no significant results.

Correlations with lesion size and location were performed on the basis of averaged phase and period correction estimates, again disregarding the direction of tempo change. There was a significant positive correlation ($r = 0.825$, $p = 0.003$) between the lateral dimension and period correction estimates, indicating that more

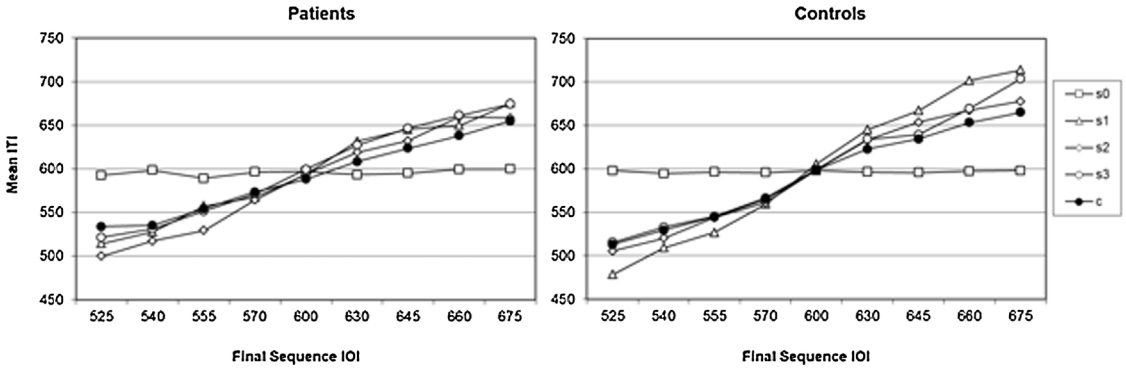

Fig. 4. Mean inter-tap-intervals (ITI) for patients and controls as a function of the final sequence inter-onset-interval (IOI).

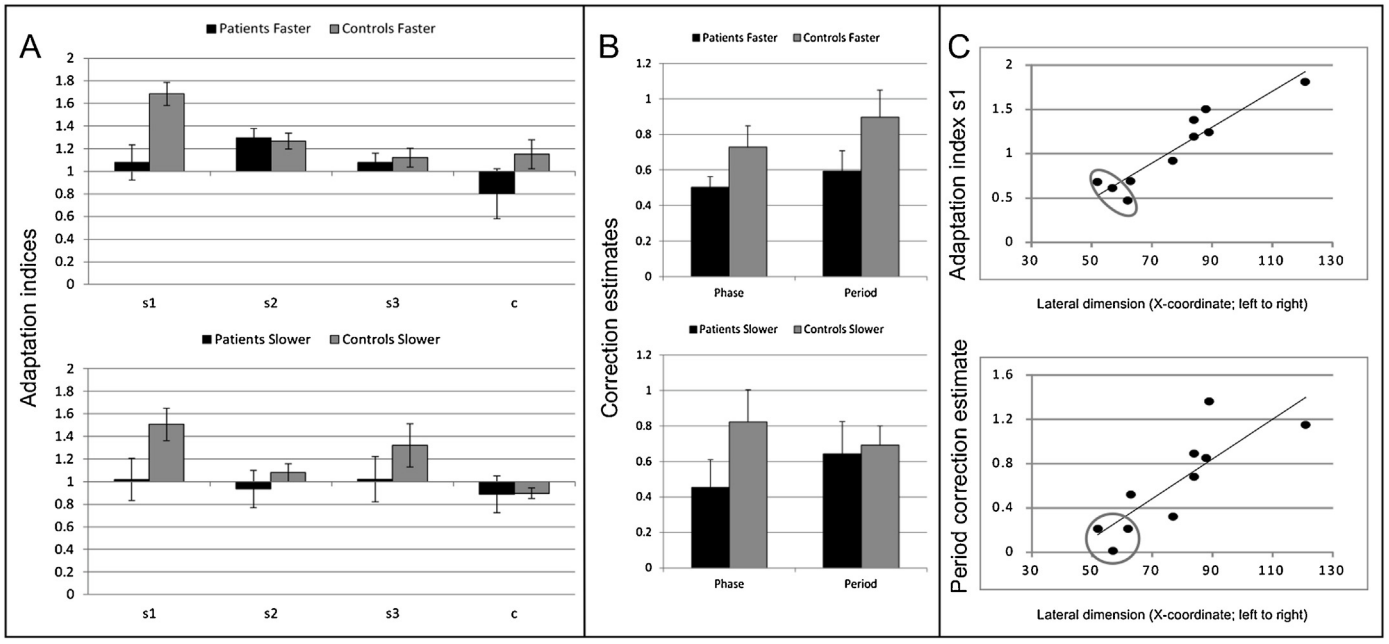

Fig. 5. Adaptation to tempo changes. Adaptation indices were computed for each participant and for each position of interest (corresponding to the inter-tap-intervals following the tempo change: s1, s2, s3, and the average inter-tap-interval during the continuation phase: c) by plotting mean inter-tap-intervals as a function of the final sequence tempo and fitting a linear regression line to these functions. The slope of this function served as an index for the degree of adaptation, with values below 1 indicating undercorrection, and values above 1 indicating overcorrection (A). Note, that the time-course of the correction response is typically characterized by initial overcorrection and subsequent stabilization at the new rate. This initial response overshoot was largely absent in the patient group. Modelling and analysis of the differential contribution of phase and period correction mechanisms to overall error correction demonstrated generally less efficient phase correction in patients (B). More left-lateralized lesions were associated with a lack of initial overcorrection and smaller period correction estimates (centers of mass). Circles indicate a subgroup of participants with overlapping lesions in the left cerebellar crus I (C).

left-lateralized centers of mass were associated with smaller period correction estimates (Fig. 4).

3.4. Detection of tempo changes

To assess the ability to detect changes in the tempo of the pacing sequences, d' scores were computed for each participant (corresponding to the difference between z-transformed false alarm rates, i.e., the proportion of "no change" and "deceleration" responses for acceleration trials or "no change" and "acceleration" responses for deceleration trials, and hit rates, i.e., "acceleration" responses for tempo increases and "deceleration" responses for tempo decreases). Although d' scores for patients and controls appeared similar for tempo decreases, the performance of the two groups differed markedly for tempo increases, especially for smaller increments (Fig. 6).

A $2 \times 2 \times 4$ ANOVA with factors *group*, *tempo*, and *magnitude* ($\pm$30 vs. 45 vs. 60 vs. 75 ms) was conducted to verify these observations. There were significant effects of *group* ($F(1,18) = 7.753$, $p = 0.012$, $\eta_p^2 = 0.301$), *tempo* ($F(1,18) = 6.655$, $p = 0.019$, $\eta_p^2 = 0.270$), *magnitude* ($F(3,54) = 69.606$, $p = 0.000$, $\eta_p^2 = 0.795$), and a significant interaction of these factors ($F(3,54) = 7.589$, $p = 0.001$, $\eta_p^2 = 0.297$). Subsequent step-down analyses revealed an interaction of *group* $\times$ *magnitude* ($F(3,54) = 8.730$, $p = 0.001$, $\eta_p^2 = 0.327$) for faster tempi only. Direct comparisons yielded group differences for the -30 ms ($t(18) = -4.140$, $p = 0.001$, $d = 1.852$) and -45 ms ($t(18) = -4.076$, $p = 0.001$, $d = 1.824$) step changes and a non-significant trend for the -60 ms step change ($t(18) = -1.930$, $p = 0.070$, $d = 0.864$). The time-range (-30 to about -60 ms), in which the perceptual dysfunction was present, appeared similar to the temporal shift in patients' negative mean asynchronies observed for the control sequences. Post-hoc correlation analyses between adaptation indices for s1 and d' for acceleration step changes yielded a significant correlation for -45 ms ($r = 0.751$, $p = 0.012$), indicating that smaller adaptation indices are associated with reduced perceptual sensitivity. A similar outcome for -60 ms ($r = 0.689$, $p = 0.027$) was rejected on the basis of Holm-Bonferroni adjustment. Detection accuracy for faster tempi was negatively correlated with negative mean asynchronies in patients, i.e., the larger the asynchronies, the smaller the detection accuracy for accelerations ($r = -0.725$, $p = 0.018$). However, this was also the case in the control group ($r = -0.662$, $p = 0.037$), suggesting a more fundamental relation between these measures, while the same correlations conducted for the relation between asynchronies and detection accuracy for decelerations did not yield any significant result.

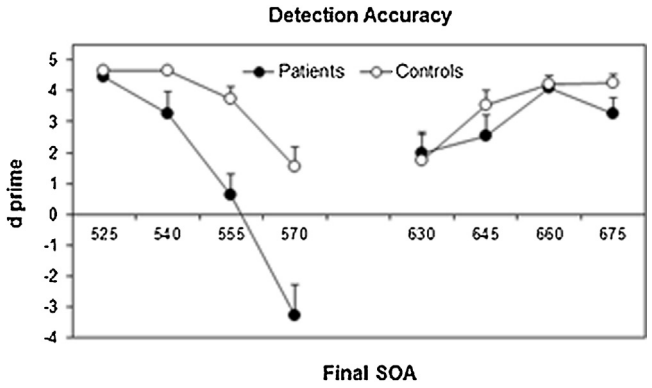

Fig. 6. Perceptual judgement. The ability to detect a tempo change in the pacing sequence was assessed on the basis of d' scores computed for each participant and each condition. In comparison to controls, patients showed marked differences in the detection of tempo accelerations. Statistical analyses confirmed a selective dysfunction to detect the -30 ms (570 ms final SOA) and -45 ms (555 ms final SOA) step changes and a trend in a similar direction for -60 ms.

In line with these findings and the results of the preceding ANOVA, the correlation analyses with lesion size and location were

restricted to d' for faster tempi. Some potential indications of lower detection accuracy with more left-lateralized centers of mass for −45 ms ($r = 0.640$, $p = 0.046$) and −60 ms ($r = 0.707$, $p = 0.022$) step changes were found but rejected following Holm-Bonferroni adjustment.

4. Discussion

Cerebellar lesions can impair sensorimotor temporal processing although the manifestation of this overall effect depends on anatomical features (extent and location of damage), on (temporal) task characteristics and temporal processing requirements (e.g., implicit, automatic, event-based as opposed to attention-dependent, continuous, interval-based), as well as on the methods employed in the data analyses [13,33–37]. Research on this topic has hence to consider under what specific circumstances a temporal processing dysfunction emerges. However, notwithstanding functional specialization within specific cerebellar subregions, the cerebellum may instantiate a structure, which modulates activity in cerebral cortex to optimize sensory and sensorimotor behavior in terms of temporal precision and coherence, synchronization, and temporal prediction as facets of ongoing interactions with a dynamic environment.

On this account, damage to the event-based cerebellar timing system was expected to reduce the efficiency of these operations, leading to suboptimal temporal precision, which may cascade into a broad range of motor and non-motor behaviors. The current study employed self-paced spontaneous and paced finger-tapping paradigms to investigate the impact of cerebellar lesions on behavioral performance. We used a setup that places relatively high demands on sensory and sensorimotor temporal precision [24] and fitted data to a *closed-loop timing model* [29] that extends classical open-loop models [38] by implementing error correction mechanisms that control the temporal relationship between an internal timekeeper and external pacing events. The adaptive synchronization task in the current study employed abrupt tempo changes as opposed to gradual changes and continuously applied error correction over longer timespans, which is relatively well preserved in cerebellar and basal ganglia patients [37]. In line with the basic assumption that damage to the cerebellum modulates performance by decreasing temporal precision and leads to suboptimal behavior, we observed a number of characteristic differences between the patient and the control groups. Although some of these differences could be interpreted as instances of impaired motor function, this is not the case for all observations, especially for those that relate to reduced perceptual accuracy. Furthermore, the profile obtained for cerebellar patients differs substantially from the temporal processing dysfunction observed in basal ganglia patients tested in the same experimental setup [25].

SMT results indicate more variable self-paced generation of temporally regular events but similar tapping rates for patients as compared to healthy controls. This finding is further substantiated by more variable tapping in patients during the continuation phase of the isochronous control trials, for which the target tempo was set during the synchronization phase, but which required the self-paced generation of regular events during the continuation phase. Both forms of variability co-vary with overall lesion size. Specifically, more extensive structural damage is associated with increased variability. However, in contrast to observations in basal ganglia patients, cerebellar patients did not show indications for decreased tapping variability for SMT2 relative to SMT1, which could be interpreted as a stabilizing influence of task repetition or of the global temporal context of the intermediate sensorimotor task on variability measures [25]. This seems to suggest that the problem and the mechanism underlying increased variability in cerebellar patients is of a more persistent nature and potentially reflects damage to an automatic temporal processing system [36].

Cerebellar patients produced not only larger but also more variable negative mean asynchronies in the control sequences compared to healthy participants. The negative asynchronies allow participants to gain the subjective impression of tapping in synchrony with the pacing and therefore people are usually not aware of it [39,40]. The substantially larger negative mean asynchronies produced by the patients may indicate a pathological widening of the time-window in which temporal integration of the tap and the external pacing event occurs. Patients' subjective impression of being in synchrony may be the same as in controls but this effect seems to objectively reduce temporal precision in the tens-of-milliseconds range preceding a critical event and it leads to inefficient task performance in the current setting.

Although the (neuro-)functional mechanisms underlying the negative mean asynchrony are still unclear [32], it has been linked to the synchronization of internal action simulation with a pacing signal [39,40]. Considering its role in forward-modelling and temporal processing, the cerebellum seems a likely candidate for a neural implementation of this mechanism. The current results may indicate dysfunctional matching between forward modelling and sensory input following cerebellar lesions. In this context, cerebellar "filtering" of salient events (e.g., onsets, offsets or increases in the energy-level of a stimulus) occurring in close temporal proximity (up to about 30 ms) into a single temporal marker may be important to obtain distinct temporal event markers [20]. This mechanism also offers an explanation for the finding that the negative mean asynchrony is sensitive to stimulus rise-time and that people seem to use the so-called *perceptual center* (p-center) rather than the physical onset as a reference point for synchronization [41–43]. For this specific aspect, the current findings relate to more recent proposals concerning the functional relevance of rise-time sensitivity and the p-center in complex sensorimotor behaviors such as speech processing [44,45].

Transmitted from the cerebellum via the thalamus to targets in the cerebral cortex, successive temporal markers may instantiate the precise temporal signal, which guides sensory prediction and the temporal orienting of attention [17,20]. In other words, these successive temporal markers may drive oscillatory activity in the sense of *dynamic attending theory* and/or in cortico-basal ganglia circuits implicated in interval timing and working memory [7,18,46]. Furthermore, one may speculate that interaction of the cerebellar mechanism with thalamic and cortical oscillatory activity imposes a fundamental constraint to the acquisition of sensory data, which is treated as "co-temporal" if it occurs within 30 ms [47].

In the patient and the control group, negative mean asynchronies predicted detection accuracy for tempo accelerations. The proposed role of successive cerebellar temporal event markers in the generation of sensory predictions may explain the highly asymmetrical pattern for detection accuracy in the patient group, i.e., why problems surfaced in response to events occurring during a period of anticipation as opposed to events occurring during a period of delay.

Impaired phase correction and a lack of initial overcorrection were observed for both tempo accelerations and decelerations. Phase correction is associated with registering violations of temporal expectations [32] and according to the *two-way error-corrective mechanism*, it is directly implemented by a motor control unit [29]. Although the position of a tempo change within a trial was in principle predictable, such knowledge seems not have been sufficient to compensate for the dysfunction observed in the patients. Cerebellar connections to early stages of sensory processing may provide the necessary temporal precision and allow for rapid (direct or automatic) implementation of phase correction [20,48]. Phase

correction only depends on the intention to synchronize with the pacing sequence, while period correction depends also on attention and awareness of the tempo change [24]. In line with this dissociation, subliminal error correction in sensorimotor synchronization has been found to engage the cerebellar dentate nucleus, whereas supraliminal error correction recruits additional cerebellar areas as well as right inferior parietal and frontal areas [49]. Whereas basal ganglia patients had shown selectively impaired period correction [25], this type of attention-dependent error correction was spared in cerebellar patients. Period correction may hence compensate for erratic performance once dysfunctional phase correction leads to an accumulation of response discrepancies beyond a certain threshold corresponding to multiples of the actual step change over two or more subsequent ITIs (i.e., once the error magnitude becomes supraliminal). This threshold may be reflected in limits in detection accuracy (from impaired performance at −30 and −45 ms, and a similar trend at −60 ms, to preserved function at −75 ms). Compensatory engagement of attention-dependent period correction may potentially stabilize performance in patients to the extent that it becomes comparable to that of healthy controls over the course of the following taps but it seems that it cannot compensate for the dysfunctional initial (subliminal) phase correction response. Correlation analyses performed at the group level and for a subset of the patients with particularly small adaptation indices suggested a critical role of the left cerebellar crus I in the divergent pattern of results for the initial correction response. Although the functional interpretation of these results remains speculative due to the small number of participants, it is noteworthy that damage to this area in the left cerebellum had the most deteriorating effect despite the fact that all participants chose to perform the task with their right hand. This area has previously been linked to basic auditory processing [50] and resting-state functional connectivity imaging suggests that it is part of a "cognitive" network comprising the ventral cerebellar dentate and prefrontal areas [51]. Convergence of sensory and cognitive aspects in this area may suggest that these patients have the most pronounced problems with converting the auditory pacing signal into a precise temporal signal transmitted to frontal areas, including supplementary motor cortices in order to guide the stimulus-driven allocation of attention in time [52].

5. Conclusions

Taken together, the findings of the current study confirm a temporal processing dysfunction in patients with cerebellar lesions. The results are in line with the proposed role of the cerebellum in precise automatic, event-based temporal processing and establish a link between previous work in cerebellar patients and a sensory predictive account of cerebellar function. The specific pattern of results seems compatible with the proposal of a general cerebellar function in optimizing the temporal component of ongoing interactions with a dynamic environment.

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