Chapter 4

Time estimation in Parkinson’s disease and degenerative cerebellar disease

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4.1 Abstract

With functional MRI, we recently identified fronto-cerebellar activations in predicting time to reach a target and basal ganglia activation in velocity estimation, that is, small interval assessment. We now tested these functions in patients with Parkinson’s Disease (PD) and degenerative cerebellar ataxia. They watched a ball that repeatedly appeared, moved, and disappeared. Velocity, stop locations, and predicted target locations as well as time to reach a target were indicated. Compared with controls, PD patients showed impaired velocity estimation (momentary mode) whereas temporal prediction was selectively impaired in cerebellar ataxia patients. The latter highlights feedforward processing within frontocerebellar circuitry. Impaired velocity estimation in PD fits the concept of a basal ganglia clock function.
4.2 Introduction

Actions take place in a dynamic environment. The preparation of purposeful movements, for example, catching a ball, thus requires adjustment to these dynamics. To that end, spatial and temporal parameters are extrapolated from direction and velocity of perceived movements, thus enabling accurate temporospatial tuning in the preparation of movements to be executed. The estimation of present as well as future spatial changes implies the assessment of a short temporal interval, with minimal spatial change, as well as the extrapolation of such an interval to a longer one, enabling the prediction of a future spatial state at a distinct moment in time.

With functional MRI (fMRI), we have recently been able to distinguish activation patterns related to the assessment of the two above mentioned classes of temporal intervals (Beudel et al., 2009). Predicting the time a moving ball needs to reach a given target, that is, estimating a longer interval of spatial changes, revealed (fronto)cerebellar activation. Estimating the velocity of a moving ball, that is, estimating a short interval with minor changes revealed bilateral caudate activation when this condition was contrasted with assessment of the actual ball position at a given moment. In estimating the virtual place of arrival, that is, spatial prediction, neither cerebellum nor caudate was activated.

These findings were consistent with the previously described role of the cerebellum in predicting future sensory (Blakemore et al., 2001; Bares et al., 2007) and motor (Miall et al., 1993; Nixon and Passingham, 2001; Spencer et al., 2003) events. A contribution of the striatum to specifically estimating short (minimal) intervals, which we inferred from the temporal component in velocity assessment, is less evident. Although behavioral (Artieda et al., 1992), neuropharmacological (Meck, 1983), and fMRI (Elsinger et al., 2003) studies have reported a relationship between disturbances in different domains of time based cerebral processing and dopamine based striatal pathology, a specific role of the striatum in estimating such short intervals has not been convincingly documented. On the other hand, disturbances in continuous motor timing have been reported in Parkinson’s Disease (PD) (Spencer and Ivry, 2005) and frontostriatal circuitry has long been associated with an (attention driven) clocklike measurement of time (Meck and Benson, 2002). Taken together, these findings may imply that the striatum is involved in processing small intervals of time and the cerebellum is involved in predicting longer in-
to test this hypothesis, we examined patients with dysfunction of the striatum, that is, patients with PD, and patients with neurodegenerative Cerebellar Ataxia (CA). They had to estimate velocity of a moving ball, which includes small interval assessment, as well as predict the time it takes a ball to abridge longer intervals. Considering the previous arguments, we expected that PD patients would perform worse on velocity estimation and CA patients would perform worse on temporal prediction, both compared with age matched controls. Moreover, owing to the previously described contribution of the cerebellum in learning (Mauk et al., 2000), we expected to find a reduced improvement of performance over time in CA patients.

4.3 Materials & Methods

The group of PD patients included 11 participants (two females) with a mean age (±SD) of 62 (±10) years. Twelve age-matched controls (seven females) had a mean age of 59 (±8) years. The CA patient group, mean age 40 (±7) years, consisted of eight participants (three females) affected by primary neurodegenerative disease (seven Friedreich’s ataxia and one primary cerebellar degeneration of unknown origin). Their eight age matched controls (four females) were 39 (±14) years. None of the control participants had neurologic, ophthalmologic, or upper extremity disorders. This was also the case for the two patient groups, except for the symptoms related to their PD and CA. All participants signed an informed consent to a protocol approved by the local medical ethics committee. Procedures and task instructions were practiced briefly until the tasks were understood. Such practice was 1 or 2 days before the experiment as well as immediately before the experiment.

4.3.1 Patient Characteristics

PD and CA patients were selected from an outpatient population meeting the following criteria: score on Mini Mental State Examination (MMSE, scale 0-29) was >26, motor ability on the Hoehn and Yahr score in PD (scale 0-5) was <3, and relevant comorbidity was absent. After initial selection, participants were instructed and they practiced briefly. They were included when they showed the ability to perform the tasks. The mean disease duration (±SD) of the PD group was 5.8 (±7.6) years and in the CA group 19.3 (±5.5) years. The mean MMSE score was 27.0 (±0.9) in the PD group, 27.9 (±0.3) in the
PD control group, and 27.1 (±0.7) in the CA group. In the CA control group of healthy young participants, no MMSE score was obtained. To overcome a potential bias between test results and disturbed motor execution (Ivry and Keele, 1989), all PD patients continued to use their dopaminergic medication, administrated on average 2.5 (±1.1) h before the experiment. No wearning-off or levodopa-induced dyskinesias occurred during the experiment. The control participants of the PD and CA groups were selected on cognition (MMSE>26) and age.

4.3.2 Experimental task equipment

Participants watched a visual display of a ball moving on a gray screen with constant speed (Fig. 4.1). After judging specific temporospatial characteristics of the ball’s behavior (see description of experimental conditions), responses were made by pressing a button on a response box. Participants did not receive feedback about their judgment. Response choices and reaction times were logged. An arrowhead marked the middle of the bottom edge of the screen. With blank intervals, the ball appeared at an uncued location and moved until it disappeared. It moved along a straight line, which continued in a new direction after bouncing from either the upper or one of the side edges of the screen (Fig. 4.1).

4.3.3 Experimental procedure

The experimental paradigm was constituted by four stimulus-response conditions and one rest block. In the conditions 1 and 2, participants were instructed to extrapolate the ball’s trajectory after its disappearance until it virtually touched the bottom edge of the screen. In condition 1 (‘place ahead’), participants had to estimate whether the ball touched either the left side or the right side of the bottom edge, whereas in condition 2 (‘time ahead’), they had to estimate whether this edge was reached either within or after 3 s. Responses to such a two-choice demand were made by pressing one of two buttons with either the index finger or middle finger of the dominant hand and in the case of the PD and CA groups the least affected hand. In condition 3 (‘speed’), participants had to distinguish between high speed and low speed, which was relative to their perception of average speed inferred from the previous stimuli. The subsequent response had to be given in a similar way as in conditions 1 and 2. In a fourth condition (‘place at stop’), the ball’s stop position had to be indicated left or right. This condition required less additional cognitive processing
Figure 4.1: Display of the Stimulus Presentation. The solid line indicates one trajectory of the moving ball. The three balls point at the successive locations of uncued appearance, stop, and disappearance, respectively, and virtually touching the bottom edge of the screen. The dotted line indicates the extrapolated trajectory guessed by the participants to make either a temporal (1) or a spatial (2) prediction. The solid arrowhead (triangle) demarcates the middle of the screen. In condition 1, participants predicted whether the ball would touch either the left or right side of the bottom edge. In condition 2, participants estimated whether the bottom edge was reached either within or after 3 s. Responses were made by pressing one of two buttons of a response box.

compared with the other conditions and was included to evaluate performance constancy during the experiment. The experiment consisted of a practice block (3 min) followed by two 12-min runs of task performance. The two runs contained six blocks each. Each block contained the four stimulus-response conditions grouped in four segments, whereas the rest block was placed in between the task blocks. The order of conditions was randomized and balanced. Each 21-s block segment contained six repeated stimulus-response trials of the same condition, and was preceded by a visually presented task instruction (2000 ms) and a blank screen (1000 ms). A stimulus-response trial consisted of stimulus observation (1000 ms) and an interval (2000 ms) in which a response had to be given by button press. In total, 72 stimuli were designed with different ball directions and trajectory lengths. They were balanced for both the time to virtually reach the bottom of the screen and the target side of arrival.
4.4. RESULTS

Owing to the constant 1000 ms presentation time, differences in trajectory lengths resulted in speed differences. The stimulus presentation was designed such that making the ball to move over different parts of the basic trajectories and in opposite directions, the virtual arrival time at the bottom edge of the screen was dissociated from direction, trajectory length, and speed. Indeed, a bias between particularly speed of the ball and the estimated time to virtually reach the bottom edge of the screen was avoided.

4.3.4 Data Analysis

Response accuracy was established by calculating the percentage of correct answers of single participants for each condition and run. Accuracy differences between the temporal and spatial prediction conditions, within groups, were used as a timing-specific measure (regarding long intervals) for the comparison between groups. Accuracy of velocity estimation was compared directly between groups. Accuracy differences between the first run and second run within conditions and within groups were used to compare effects with time between groups. Analyses between groups were conducted using one-sided independent t-tests. Bonferroni correction was applied for multiple comparisons.

4.4 Results

When the two patient populations were compared with their age-matched controls, we found disease-specific differences particularly in performing the time-based tasks. In the CA group, the decrease of accuracy in temporal prediction (condition 2) compared with the accuracy in spatial prediction (condition 1) was 7% more than the difference between these two conditions in its control group (P=0.02, Fig. 4.2A). In this control group of younger participants, accuracy (±SD) of temporal prediction was 77% (±14), whereas it was 80% (±12) for spatial predictions. For CA, these values were 68 (±15) and 78% (±8), respectively. In the PD group, the accuracy difference between temporal and spatial predictions was similar to that of their age-matched controls (P=0.40, Fig. 4.2A). The accuracy values in temporal and spatial predictions were 72 (±14) and 77% (±9), respectively, in the elder controls, whereas for PD they were 68 (±12) and 74% (±10), respectively. Velocity (condition 3) was estimated 6% less accurately by the PD patients when compared with their age-matched controls (P=0.02, Fig. 4.2B). For this parameter, a nonsignificant difference of 3% was found between the CA patients and their controls.
The assessment of differences between the two successive sessions revealed that for all four groups the accuracy in the control condition 4 (indicating where the ball actually stopped) did not change (1% decrease, NS). For spatial prediction, a 10% (±2) decrease in session 2 also pointed at similarity in between the four groups. The only time effect that was significantly different between the two patient groups was the improvement of temporal prediction in the PD group, which did not occur in the compared CA patients (19% difference between groups; P=0.03) (Fig. 4.2c). With regard to velocity estimation, the time effects did not differ between the two patient groups (P=0.30). The experimental conditions 1 and 2 were negatively correlated with age. The correlation coefficient was -0.38 for spatial prediction (P<0.05) and -0.37 for temporal prediction (P<0.05). Such correlation was not found for sex, MMSE score, and the disease durations of PD and CA.

### 4.5 Discussion

The present study revealed specific differences in velocity estimation and temporal prediction between patients with PD, CA, and healthy controls. The most important difference between the two patient groups was that compared to their controls, PD patients performed significantly worse in velocity estimation, whereas CA patients performed significantly worse in temporal prediction relative to spatial prediction. The specific impairment of PD patients in velocity estimation is consistent with models of striatum-based timekeeping, whereas the specific impairment in CA patients in temporal prediction is consistent with the role of the cerebellum in predictive timing. These relations were further highlighted by the absence of a learning effect in both velocity estimation and temporal prediction in the CA, whereas in PD such absence of learning was restricted to velocity estimation.

The observed association between cerebellar dysfunction and reduced temporal prediction fits the proposed properties of cerebellar circuitry to anticipate and process input with high temporal precision (Ivry et al., 2002). This is further demonstrated by stimulus-locked neural oscillations that have shown anticipatory enhancement related to somatosensory input (Tesche and Karhu, 2000). The absence of learning effects on both velocity estimation and temporal prediction in patients with cerebellar disease also provides an argument
Figure 4.2: Accuracy differences. (a) Accuracy reduction in temporal prediction compared with spatial prediction in the four groups. This difference is expressed in the percentage correct responses in spatial prediction minus this value in temporal prediction. (b) Mean accuracy (and SD) in velocity estimation in the four groups. (c) Changes in accuracy between the two runs (percentage correct responses in run 2 - this value in run 1) assessed for the two time-dependent conditions in the two patient populations. CA = cerebellar ataxia; Con = control; PD = Parkinson’s disease.
for particularly time-dependency in normal cerebellar learning (Mauk et al., 2000), in which feed-forward-based prediction is regulated by feedback-based associative learning (Miall et al., 1993).

The disturbed velocity estimation in PD is in line with earlier findings pointing at impaired time perception in the milliseconds range (Harrington et al., 1998a) based on an increased temporal discrimination threshold in PD patients (Artieda et al., 1992). The absence of a learning effect in specifically velocity estimation in PD, whereas temporal prediction over longer intervals improved, provides an argument that the striatum is indeed only involved in short interval assessment. The distinction between the perception of short and long interval estimation, representing two separate classes of timing, fits the distinction that has previously been made between smooth and interrupted movements, which were proposed to reflect emergent and event-based timing, respectively (Ivry et al., 2002). In the latter, the event of interruption provides a marking point for interval assessments. Our main findings, acquired with perceptual instead of motor timing tasks, are thus consistent with the data of Spencer et al. (2003) and Spencer and Ivry (2005) in CA and PD populations. This not only indicates similarity between perceptual and motor timings (Keele et al., 1985), but also further supports the role of disturbed event-based timing in CA and emergent timing in PD.

In contrast to prediction paradigms that have previously been applied in patients with CA (Bares et al., 2007), we were able to demonstrate a time-specific deficit by the comparison with spatial prediction. In our recent fMRI study, both spatial and temporal predictions were related with increased parietal activation, whereas additional cerebellar increase only occurred in temporal prediction (Beudel et al., 2009). The fact that in CA temporal prediction was more disturbed than spatial prediction indicates that although both cerebellum and parietal cortex have been proposed to play a role in action prediction (Blakemore and Sirigu, 2003), the unwinding of future temporal relations is indeed facilitated particularly by the cerebellum. This might imply that the parietal contribution to such action prediction supports the unwinding of future spatial relations.

The task-related differences between groups were not caused by nonspecific movement handicaps in two patient groups. A possible response bias related to such movement disturbances was circumvented by using dichotomous instead of reaction time-dependent responses. With regard to a cerebellar role in visually guided tracking (Miall et al., 2000), a possible bias related to stim-
ulus observation in our paradigm was overcome by measuring the difference between two conditions with the same stimuli and similar attention demand, that is, spatial and temporal predictions. As visually guided tracking is not required for observing small intervals, velocity estimation was directly compared between groups. Owing to the constant performance of all groups in indicating the actual stop position of the ball, as well as recent literature demonstrating that patients with cerebellar damage do not show disturbed attention (Haarmeier and Thier, 2007), we have no arguments for a bias introduced by differences in attention between groups. Thereby, correlational analyses indicated that no covariant except for age (which was corrected for by using appropriate control groups) showed a significant correlation with the results.

4.6 Conclusion

Taken together, our present findings are consistent with the results of our previously conducted fMRI experiment, and further support a concept of two stages in temporal processing, that is, ‘momentary’ timing (minimal interval assessment implicated in speed estimation) and predictive timing (large interval assessment).