Automated tracking of motor behavior as a means to assess severity of symptoms in the 6-OHDA marmoset model of Parkinsons disease

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Abstract

We present a method for analyzing locomotive behavior of marmosets in two experimental setups used for the analysis of severity of symptoms in a primate model of Parkinsons disease. A characterization of changes in motor behavior following experimental manipulations based on automatic tracking procedures is here presented.

1. Introduction

To be able to develop new therapies for the treatment of Parkinsons disease (PD) researchers critically depend on valid animal models of the disease that allows for repeated testing of motor disabilities over extended time periods. Motor symptoms in PD typically involve rigidity, tremor and an overall reduction and slowing of movements. However, because of the technical challenges involved in tracking detailed motor behavior in freely moving animals the sensitivity and robustness of the assessment methods used in characterization of motor deficits often turn out to be a key limiting factor in this field of research. To this aim we have developed methods for tracking of freely moving animals and present a first characterization of a range of motor symptoms tested over several months in a primate model of PD marmoset monkeys (Callithrix Jacchus) that have been exposed to the neurotoxin 6-OHDA causing lesions to dopaminergic cell groups in the midbrain. To validate the developed methods, scores obtained by automatic methods have also been verified using manual scoring protocols based on the rating scales applied by neurologists to evaluate severity of symptoms in PD patients that were here adapted to suit the motor behavior of marmoset monkeys (that is so called UPDRS scores). Importantly, through the use of automated quantitative motion tracking procedures we are now able to assess the severity of motor deficits in different testing set-ups of spontaneous motor behavior in freely moving animals. In addition, the new screening methods will allow us to investigate more subtle deficits that until now have been hard to evaluate, such as the gradual slowing of certain movements or a reduced ability to combine a sequence of motor components into compound actions.

Analyses of the first set of experiments suggest that: first, the current methodological approach indeed seems to generate reliable tracking data from freely moving primates suitable for long-term analysis of motor behavior. Second, robust motor symptoms lasting for several months could be induced when using a two-stage neurotoxic lesioning procedure involving one hemisphere of the brain at a time, indicating that this non-human primate model of PD may be well suited for long-term evaluation of novel therapies for treatment of PD.

Here we present the methods developed for tracking of spontaneous motor behavior and outline ongoing and future work aimed at obtaining more detailed and reliable characterizations of the kinematics of compound motor acts.

2. Methods

The experiments in this study are comprised of two different experimental setups to be able to observe a range of different behaviors and impairments.

The first setup, the tower experiment (Fig. 1A-E), is designed to capture the natural locomotive behavior of the common marmoset, including jumps. The setup

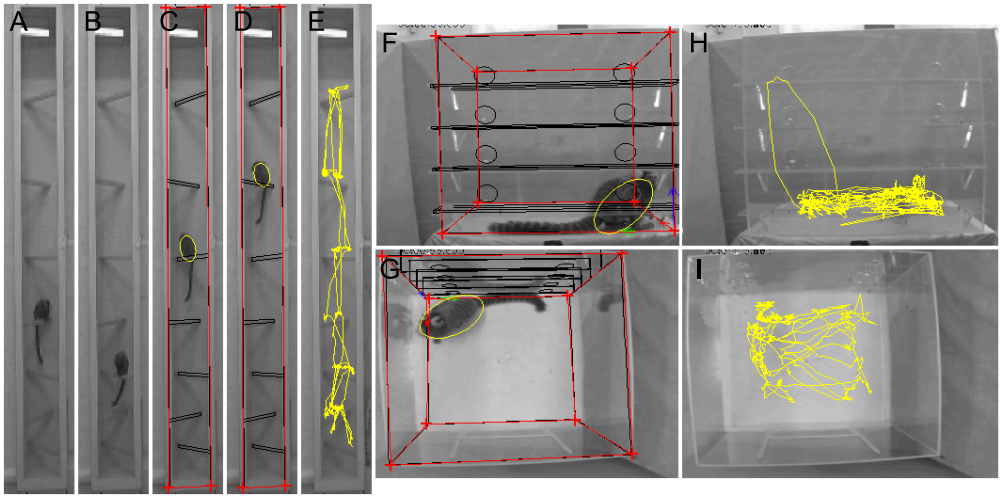

Figure 1. Video data in grayscale from the tower experiment (A-B). Tracking data for two images (yellow) and tower calibration (red and black) drawn on video data (C-D). Movement trace for the whole experiment drawn on the background image (E). Tracking data (yellow) and box calibration (red and black) drawn on video data for the two tower cameras (F-G). Movement trace for the whole experiment drawn on the background images for the two cameras (H-I).

is a 2.3 meter high tower with 7 bars (levels) that are further separated at the top of the tower. Experiments are filmed by a 640x480 pixel color camera generating video as in Fig. 1A-E.

The second setup, the box experiment (Fig. 1F-I), is designed to capture gross aspects of forelimb reaching movements, horizontal locomotion and rotational behavior (which is sometimes seen in lesioned animals). The setup is a transparent box with dimensions 45x45x45 cm. One of the walls has four shelves attached to it, where food rewards can be placed (Fig. 1F, H). This allows for detailed studies of how test subjects reach out and grasp food objects when retrieving the rewards (for details see [3]). The experiments are filmed by two cameras one placed above the box, filming straight down (top view) and one filming head on the shelves (front view).

UPDRS scores include 16 different aspects of motor behavior that are each scored from 0 (normal) to 3 (severely parkinsonian). Summed scores are presented in this paper giving a total scale ranging from zero to 84.

2.1. Extraction of kinematic parameters

Motion tracking in the two setups was performed using similar methods. Constant light conditions during each recording sessions as well as a high contrast between the subjects and the background eliminated the need for advanced background-models. Hence, a simplified mixture of Gaussians model [4] was employed with two components. That is, each pixel is modeled to belong to either one of two Gaussian distributions. After an initiation procedure, the background is estimated by randomly selecting a number of frames, and then for each pixel in each of the frames decide which component it most likely belongs to. The expectation value of the most probable component is updated using that pixel value. Consequently, an estimate of the video without the subject is contained in the brighter pixels, as the animals in this set of experiments were always darker than the experimental setup. Thus, a binary foreground image can be estimated for each frame in the video by, for each pixel checking whether it is likely to belong to the background component or not. The binary foreground images are used in the shape analysis.

By assuming that the two-dimensional image of the monkey in each camera plane is approximately elliptically shaped, the position and orientation of the animal can be estimated from the position and orientation of the ellipse that best fits the binary foreground images. Given a binary foreground image F and a hypothetical foreground image M, generated by an ellipse (x, y, θ), matching quality is defined as the Jaccard index

$q = \frac{|M \cap F|}{|M \cup F|}$.

The definition means that the quality measure is given by the number of pixels with coinciding foreground classifications divided by the total number of pixels classified as foreground. Notice that the fore-

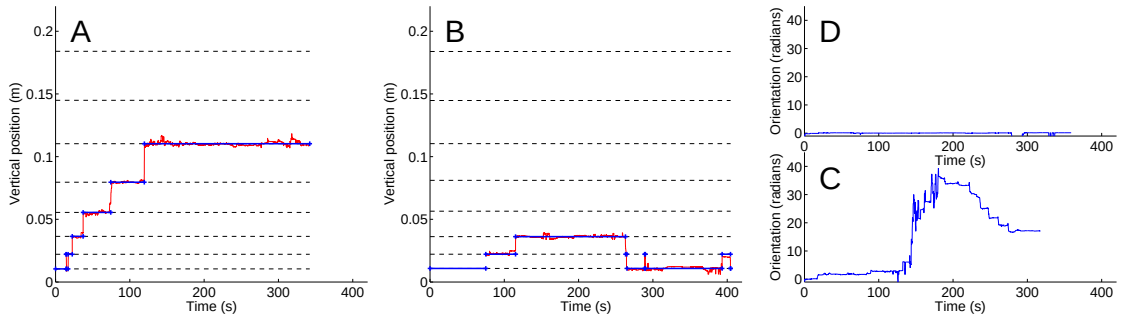

Figure 2. Characterization of motor behavior in a hemi-parkinsonian animal. Baseline experiments (A,C) and after pharmacological blockade of dopamine synthesis (B,D). In (A,B), the tracked y-coordinate is presented for the tower experiment. In (C,D) the rotation (given in radians) of the subject is plotted over time. Notice that the dopamine depletion affects how high the animal reaches in the tower and how many jumps it makes. In the box experiment the animal turns both left and right in the baseline recording, but after treatment it does not rotate as much and only to the left.

ground image M is not actually computed, but instead the quality measure is computed using the conic matrix for the ellipse.

Movement tracking in time is then carried out by using the last known location to initiate estimation for a given frame, followed by step-wise improvement of the matching quality by gradual adjustment of the parameters of the estimated ellipse. In practice, a set of hypothetical ellipses are generated randomly, and the matching quality is computed for each of them. The ellipse yielding the highest matching quality is chosen as the result of estimation. Due to the sometimes relatively high movement speed of the marmoset, the empirically set values for maximum change in position is 50 pixels in any direction and change in rotation is 45 degrees. These calculations are performed for every frame in the video, resulting in the vectors (x, y, θ, q), each of length N, where N is the number of frames in the video and q is the quality measure given above.

Software tools were is developed in MATLAB and includes a few mex-implementations (MATLAB compiled c-code).

3. Results

In the first experiment, a hemi-parkinsonian animal was experimentally dopamine depleted through pharmacological blockade of dopamine synthesis. As expected, the subjects movements are greatly impaired by the drug (Fig. 2). Firstly, it is unable to reach higher than the second level and secondly, it does not make as many jumps as in the baseline experiment. Two animals with bilateral lesions were then tested in the box experiment over a prolonged period involving multiple recording sessions over many months. In these subjects, a slowing of movements bradykinesia could be detected even in moderately parkinsonian animals (Fig. 3). It should be noted that moderate bradykinesia is particularly challenging to detect using manual qualitative scoring procedures. In the two animals analyzed bradykinesia was however still correlated to the total UPDRS score.

3.1. Tracking evaluation

To estimate how well the system performs, ground truth-ellipses were manually entered for 100 random

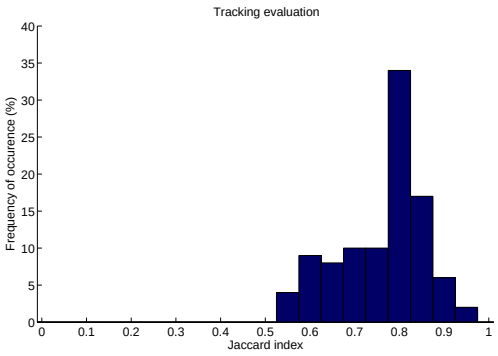

Figure 4. A comparison of tracking data to ground truth for 100 random frames.

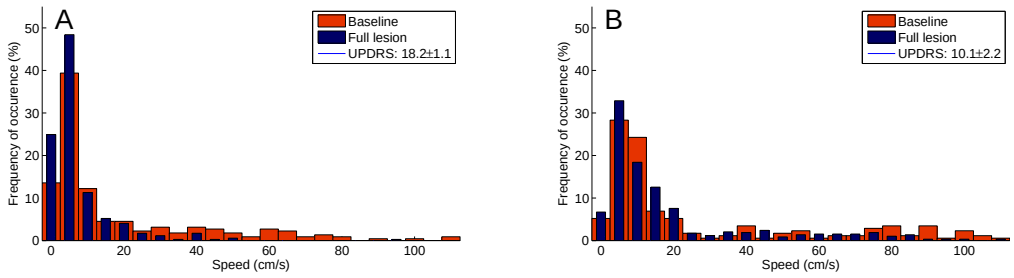

Figure 3. Evidence of bradykinesia (slowing of movements) in spontaneous motor behavior was observed in two bilaterally lesioned animals. Data was provided by the automatic tracking in the box testing set-up. A threshold (20 cm/s) was used to classify movement bouts into two groups; fast and slow. The group-size quota was modeled as a binary distribution, and a two-proportion z-test of the data showed that there is a 0.001% significant similarity between the distributions for test subject A, and 12% significance in subject B. The number of recording sessions pooled for each animal and condition is denoted over each panel. In the rightmost panels the mean $\pm$ SD of UPDRS scores after lesioning are inserted (as assessed during the same days as the box tests were performed). Note that even though these two animals were only moderately parkinsonian a slowing of movements could still be detected.

frames. For each of the frames, tracking data was compared to ground truth using the Jaccard index on the corresponding ellipses. The results are presented in figure 4. Furthermore, a subjective evaluation of tracking quality was done by scoring tracking quality as 1 (good), 0.5 (decent), 0 (bad), for each of the 100 frames. The resulting total score out of the 100 frames was 85.

4. Future work

The system works well enough in practice, although more advanced techniques could be applied, for example condensation [1], Kalman filters, etc. Furthermore, modelling the subjects as ellipses has proved to be a source for errors in certain poses of the subjects.

Along with each experiment there is also a Unified Parkinson's Disease Rating Scale (UPDRS) score, which allows for further analysis. The primary goal is not to replace the UPDRS score, but rather to create a method to complement it (indeed, UPDRS assessment gives some data that cannot be measured by our video system - for example presence of tremors). In future work the strengths and weaknesses of the two assessment methods will be further evaluated.

To our knowledge, this is the first published description of an automated system for tracking of spontaneous motor behavior in marmosets in the used testing set-ups. However in previous studies, 3D tracking of the movement trajectories of freely moving rhesus monkeys performing outdoor spatial navigation tasks has been performed using related techniques [2]. Attempts have also been made to perform more detailed tracking of head movements in marmoset monkeys performing specific motor tasks but in this case manual tracking was chosen [5].

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