



Computational Neuroscience

Three-dimensional rodent motion analysis and neurodegenerative disorders



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HIGHLIGHTS

- We have constructed and fully presented a three-dimensional rodent kinematic model.
- The mouse consists of three segments, the rear body, the anterior body and the head.
- The unique description of each segment in space does not require long transformation matrices.
- The rotations are not sequence-dependent.
- The results are translatable to patients with Parkinsonism, demonstrating the models' translational efficacy.

ARTICLE INFO

Article history:

Received 2 June 2013

Received in revised form 8 September 2013

Accepted 9 September 2013

Keywords:

Movement disorders

Parkinson's disease

Aging

Motion analysis

Movement function

Kinematics

ABSTRACT

Background: Three-dimensional (3D) motion analysis is established in investigating, human pathological motion. In the field of gait, its use results in the objective identification of primary, and secondary causes of deviations, many current interventions are the result of pre- and post-testing, and it was shown recently that it can result in decreased number of surgeries and overall cost of care. Consequently, recent attempts have implemented 3D motion analysis using rat models to study, parkinsonism. However, to-date, a 3D user friendly analytical approach using rodent models to, identify etiologies of age-related motor impairment and accompanying pathologies has not been, implemented.

New method: We have developed and presented all aspects of a 3D, three body-segment rodent model, to analyze motions of the lower, upper and head segments between rodents of parkinsonism-type and, normal aging during free walking. Our model does not require transformation matrices to describe the, position of each body-segment. Because body-segment positions are not considered to consist of three, rotations about the laboratory axes, the rotations are not sequence dependent.

Results: Each body-segment demonstrated distinct 3D movement patterns. The parkinsonism-type, genotype walked slower with less range of motion, similarly to patients with parkinsonism.

Comparison with existing methods: This is the first model considering the rodent's body as three, distinct segments. To the best of our knowledge, it is the first model to ever consider and report the 3D, head motion patterns.

Conclusions: This novel approach will allow unbiased analysis of spontaneous locomotion in mouse, models of parkinsonism or normal aging.

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1. Introduction

The ability to perform the function of walking safely and smoothly requires the integration of intact visual, vestibular, proprioceptive and musculoskeletal systems to allow the appropriate neuromechanical processes to maintain postural control. However, declines in all systems and all three stages of processing, including sensory processing, sensorimotor integration and motor

output, and, therefore, balance, are found with aging (Light, 1990; Shumway-Cook and Woollacott, 2007). Because the integration of processed input and motor output takes place at the cortical level, increasing evidence from clinical research and practice, epidemiological studies, and clinical trials shows that gait and cognition, or executive function, are interrelated in terms of reduced function in older adults (Montero-Odasso et al., 2012). Recent studies suggest that early changes in gait and gait stability may predict deficiencies in attention and working memory, and possibly also predicting future loss of movement function paralleled with cognitive impairment eventually leading to dementia (for review, see Montero-Odasso et al., 2012). Because of this connection between aging-related movement dysfunction and cognitive impairment, quantitative gait and movement assessment may be utilized as a sensitive and measurable tool for determining potential risk for frailty and progression to dementia in older adults (Karakostas et al., 2013).

Parkinson's disease (PD) is one of the aging-related neurological disorders that afflicts an increasing number of individuals in Western cultures. If the wider complex of extrapyramidal symptoms referred to as parkinsonian syndrome (PS) is included, the incidence is near 50% of the population over 80 years of age (Bennett et al., 1996). Currently there are no treatment paradigms that will stem the degenerative aspect of the disease, and the etiology is still unknown, although it is well recognized that age is the number one risk factor for PD (Eggers, 2009). To date, the most accurate measurement scales for PD and other movement disorders have been qualitative assessment scales, such as the Hoehn and Yahr scale, or the more recently adopted UPDRS scale (Universal Parkinson's Disease Rating Scale) (Martinez-Martin, 2013). These movement assessment scales are objective and do not provide a quantitative and unbiased analysis of movement. Although these scales have been developed specifically to provide low inter-rater variability, the outcome is subjective and to a great extent depends on the person performing the test (Schrage et al., 2009). It has been suggested that a comprehensive evaluation of all different symptoms of movement disorders of aging is possible using a combination of measures completed by health professionals, patients and/or caregivers. However, until recently, no quantitative assessment of movement using motion capture systems has been employed in patients.

A few research groups have recently evaluated novel quantitative gait and motion analysis systems in order to measure motor dysfunction associated with movement disorders and effects of drug treatment or disease progression. For example, Das et al. (2011) performed full-body motion capture of PD patients with deep brain stimulator off-drugs and with stimulators on and off (Das et al., 2011). Their results suggested that their motion capture system was capable of measuring distinctive differences between mild and severe symptoms of the disease. Data obtained from the Support Vector Machine (SVM) classifier used demonstrated discrimination of mild vs. severe symptoms with an average accuracy of approximately 90%. Thus, their data supported the notion that motion capture and related technology could potentially be an accurate, reliable and effective tool for tracking progression of PD, as well as potential beneficial effects of surgical or pharmaceutical treatment paradigms. In other studies, investigators have shown validity of optical capture-related measurements for either tremor (Rigas et al., 2009) or gait (Esser et al., 2012) in patients with movement disorders, again showing that novel methods for motion capture can be utilized for quantification. In Esser et al. (2012), investigators used both inertial measurement units (IMU) or optical motion capture systems (OMCS) to objectively measure gait in patients with Parkinson's disease. They found no differences between the OMCS and IMU in terms of stride length, step time or walking speed, suggesting that these optimized measurement systems could be utilized to objectively evaluate gait in this

patient group. These recently developed methods can enhance the accuracy of research studies and provide better predictions of disease progression. However, since most drug trials for PD involve pre-assessment in models of the disease, translatable and accurate motion capture methods also have to be developed for mouse and rat models.

The use of instrumented motion analysis with cameras for the purpose of studying different pathologies and respective treatment paradigms on rats or rodents, such as for spinal cord injury, is well established (Bouyer, 2005; Jung et al., 2009; Leblond et al., 2003; Snigdha et al., 2011). Even though most studies implement video-based motion capture systems because of their processing flexibility, OMCS have an advantage with respect to the speed of processing. However, whether a video-based or an optoelectronic camera motion capture system is used, the data collection process and system output is the same. Markers need to be placed on selected body landmarks which are tracked by the cameras of the system, each camera capturing two-dimensional (2D) images of each marker. When more than one camera is used and the system software implements the appropriate algorithms, then the three-dimensional (3D) coordinates of each marker in space are produced. However, for this information to have any functional meaning, there needs to exist a kinematic model implementing the correct transfer functions to transform the 3D marker coordinates to the position, and ultimately the motion, of the body segment in 3D space. For example, if a body is modeled as a line, even though one can have the 3D coordinates of the markers representing that body, the kinematic information that can be obtained will be motion in only two of the three planes of movement (Thota et al., 2005).

Similar problems regarding the identification of ways to express angles in 3D space for the analysis of human motion have existed in the past for engineers. The most common approach used to be to establish a fixed global or laboratory coordinate system and measure rotations about these axes. However, such an approach does not produce a unique set of angles that can describe the orientation of the body because the values can change based on the order of rotations. In other words, the angles are sequence-dependent. Attempts to circumvent this problem have been implemented, at the expense, however, of the anatomical interpretation of the results (Kinzel et al., 1972; Patriarco et al., 1981; Soutas-Little and Inman, 1999). Euler (1776) with his study of the motion of the spinning top provided insights to this problem, which later were implemented in the description and quantification of human movement (Grood and Suntay, 1983). While the position of the spinning top could be completely described by a transformation matrix between the coordinates of the laboratory and top systems, if the rotational position is considered to be made up of three rotations about the laboratory axes, then the amounts of these rotations are sequence dependent. However, Euler showed that the position and rotations can be measured about one axis in each system and the third rotation measured about a line of nodes. These angles do not have to be expressed in a form of a transformation matrix while at the same time their power is underlined by their ability to uniquely describe the position of the object. In engineering, these angles are referred to as the yaw, pitch and roll (Goldstein, 1960).

To the best of our knowledge, our group was the first to report on the feasibility of using an OMCS to study aging-related changes on a mouse while walking (Karakostas et al., 2008). Madete et al. (2010) also utilized an OMCS to investigate movement dysfunction during gait on different types of beams, of rats with a unilateral 6-hydroxydopamine (6-OHDA) lesion, a common model for PD. The conclusion was that marker-based motion capture could provide a novel approach to quantifying temporal-spatial gait parameters for rat models of PD (Madete et al., 2010). This group also followed up with another manuscript, in which they used the same marker protocol to investigate the postural adaptations of the body of the

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