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Analysis Of Fine Motor Skills in Chronic Neurodegenerative Models of Huntington's Disease and Amyotrophic Lateral Sclerosis

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Abstract : Motor impairment is an inherent phenotypic feature of several chronic neurodegenerative diseases, and pharmacological therapies aimed to counterbalance the motor disability have a great market potential. Animal models of chronic neurodegenerative diseases display a number deteriorating motor phenotype during the disease progression. There is a wide array of behavioral tools to evaluate motor functions in rodents. However, currently existing methods to study motor functions in rodents are often limited to evaluate gross motor functions only at advanced stages of the disease phenotype. The most commonly applied traditional motor assays used in CNS rodent models, lack the sensitivity to capture fine motor impairments or improvements. Fine motor skill characterization in rodents provides a more sensitive tool to capture more subtle motor dysfunctions and therapeutic effects. Importantly, similar approach, kinematic movement analysis, is also used in clinic, and applied both in diagnosis and determination of therapeutic response to pharmacological interventions. The aim of this study was to apply kinematic gait analysis, a novel and automated high precision movement analysis system, to characterize phenotypic deficits in three different chronic neurodegenerative animal models, a transgenic mouse model (SOD1 G93A) for amyotrophic lateral sclerosis (ALS), and R6/2 and Q175KI mouse models for Huntington's disease (HD). The readouts from walking behavior included gait properties with kinematic data, and body movement trajectories including analysis of various points of interest such as movement and position of landmarks in the torso, tail and joints. Mice (transgenic and wild-type) from each model were analyzed for the fine motor kinematic properties at young ages, prior to the age when gross motor deficits are clearly pronounced. Fine motor kinematic Evaluation was continued in the same animals until clear motor dysfunction with conventional motor assays was evident. Time course analysis revealed clear fine motor skill impairments in each transgenic model earlier than what is seen with conventional gross motor tests. Motor changes were quantitatively analyzed for up to ~80 parameters, and the largest data sets of HD models were further processed with principal component analysis (PCA) to transform the pool of individual parameters into a smaller and focused set of mutually uncorrelated gait parameters showing strong genotype difference. Kinematic fine motor analysis of transgenic animal models described in this presentation show that this method isa sensitive, objective and fully automated tool that allows earlier and more sensitive detection of progressive neuromuscular and CNS disease phenotypes. As a result of the analysis a comprehensive set of fine motor parameters for each model is created, and these parameters provide better understanding of the disease progression and enhanced sensitivity of this assay for therapeutic testing compared to classical motor behavior tests. In SOD1 G93A, R6/2, and Q175KI mice, the alterations in gait were evident already several weeks earlier than with traditional gross motor assays. Kinematic testing can be applied to a wider set of motor readouts beyond gait in order to study whole body movement patterns such as with relation to joints and various body parts longitudinally, providing a sophisticated and translatable method for disseminating motor components in rodent disease models and evaluating therapeutic interventions.

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