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Genotype specific age related changes in a transgenic rat model of Huntington's disease

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ABSTRACT

We aimed to characterize the transgenic Huntington rat model with in vivo imaging and identify sensitive and reliable biomarkers associated with early and progressive disease status. In order to do so, we performed a multimodality (DTI and PET) longitudinal imaging study, during which the same TgHD and wildtype (Wt) rats were repetitively scanned. Surprisingly, the relative ventricle volume was smaller but increased faster in TgHD compared to Wt animals. DTI (mean, axial, radial diffusivity) revealed subtle genotype-specific aging effects in the striatum and its surrounding white matter, already in the presymptomatic stage. Using ^{18}F-FDG and ^{18}F-Fallypride PET imaging, we were not able to demonstrate genotype-specific aging effects within the striatum. The outcome of this longitudinal study was somewhat surprising as it demonstrated a significant differential aging pattern in TgHD versus Wt animals. Although it seems that the TgHD rat model does not have a sufficient expression of disease yet at the age of 12 months, further validation of this model is highly beneficial since there is still an incomplete understanding of the early disease mechanisms of Huntington's disease.

Introduction

Huntington's disease (HD) is a dominantly inherited human neurodegenerative disorder, caused by a CAG trinucleotide repeat expansion (≥ 39 repeats) within the HD gene. As with other polyglutamine diseases, HD is marked by the expression of neuronal intranuclear and cytoplasmic inclusions, containing aggregated expanded huntingtin (htt) and other proteins (Gil and Rego, 2008; Heng et al., 2008). The median age at which HD occurs, is around the age of 40 and the disease progresses over time and is invariably fatal 15–20 years after the onset of the first symptoms (Gil and Rego, 2008). Traditionally, the clinical diagnosis of HD relies upon the presence of abnormal motor signs in a person at risk for HD by virtue of having an affected parent (Aylward, 2007). Currently, the formal diagnosis of HD is confirmed by gene testing (Tabrizi et al., 2009). However, to date, it remains challenging to define early biomarkers that predict the onset of the disease.

Since the discovery of the HD gene in 1993, a variety of genetic models, such as transgenic mice (Ferrante, 2009; Heng et al., 2008), a lentiviral rat model (de Almeida et al., 2002) and recently a lentiviral non-human primate model (Lundberg et al., 2008) have been generated (Heng et al., 2008; Ramaswamy et al., 2007). While no animal model replicates all features of HD, they provide an alternative approach to study the molecular pathogenesis of the disease. Moreover, they provide valuable tools in the development of existing and novel therapeutic strategies. Consequently, the choice of the animal model depends on the scientific questions being asked. However, the small size of the mouse brain, limits its use for non-invasive imaging studies, such as MRI and PET. Both techniques are translational imaging tools, and exquisitely suited to study neuronal substrate changes preceding and underlying the behavioral and pathological phenotype in a non-invasive manner.

Recently, a transgenic rat model of HD has been developed, carrying 51 CAG repeats (von Horsten et al., 2003). This model exhibits an adult-

Abbreviations: TgHD, transgenic Huntington; Wt, wild-type; HD, Huntington's Disease; htt, huntingtin; MRI, magnetic resonance imaging; DTI, Diffusion Tensor Imaging; PET, positron emission tomography; RARE, Rapid Acquisition with Relaxation Enhancement; AD, axial diffusivity; MD, mean diffusivity; RD, radial diffusivity; FA, fractional anisotropy; GP, globus pallidus; cc, corpus callosum; ec, external capsula; ic, internal capsula; BP, binding potential.

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onset neuropathological phenotype, characterized by motor deterioration and emotional, cognitive decline, starting at the age of 7 and 9 months respectively (Kantor et al., 2006; Nguyen et al., 2006; von Horsten et al., 2003). Interestingly, transgenic HD (TgHD) rats show a significant better motor performance at the age of 1 month, followed by a slow decline of motor function with increasing age (Nguyen et al., 2006). Histopathological alterations include htt aggregation foci in nuclei, cytoplasm, dendrites and spines, axons, synaptic terminals, and mitochondria at the earliest age of 6 months (Bode et al., 2008; Cao et al., 2006; Kantor et al., 2006; Nguyen et al., 2006; Petrasch-Parwez et al., 2007) (Fig. 1).

Diffusion-based MRI techniques are the only non-invasive techniques that can be applied for studying the pathways and connections of not only the human brain, but also of the rodent brain (Bohanna et al., 2008; Douaud et al., 2009; Rosas et al., 2006; Van Camp et al., 2009, 2010). As it is known that many developmental, aging, and pathological

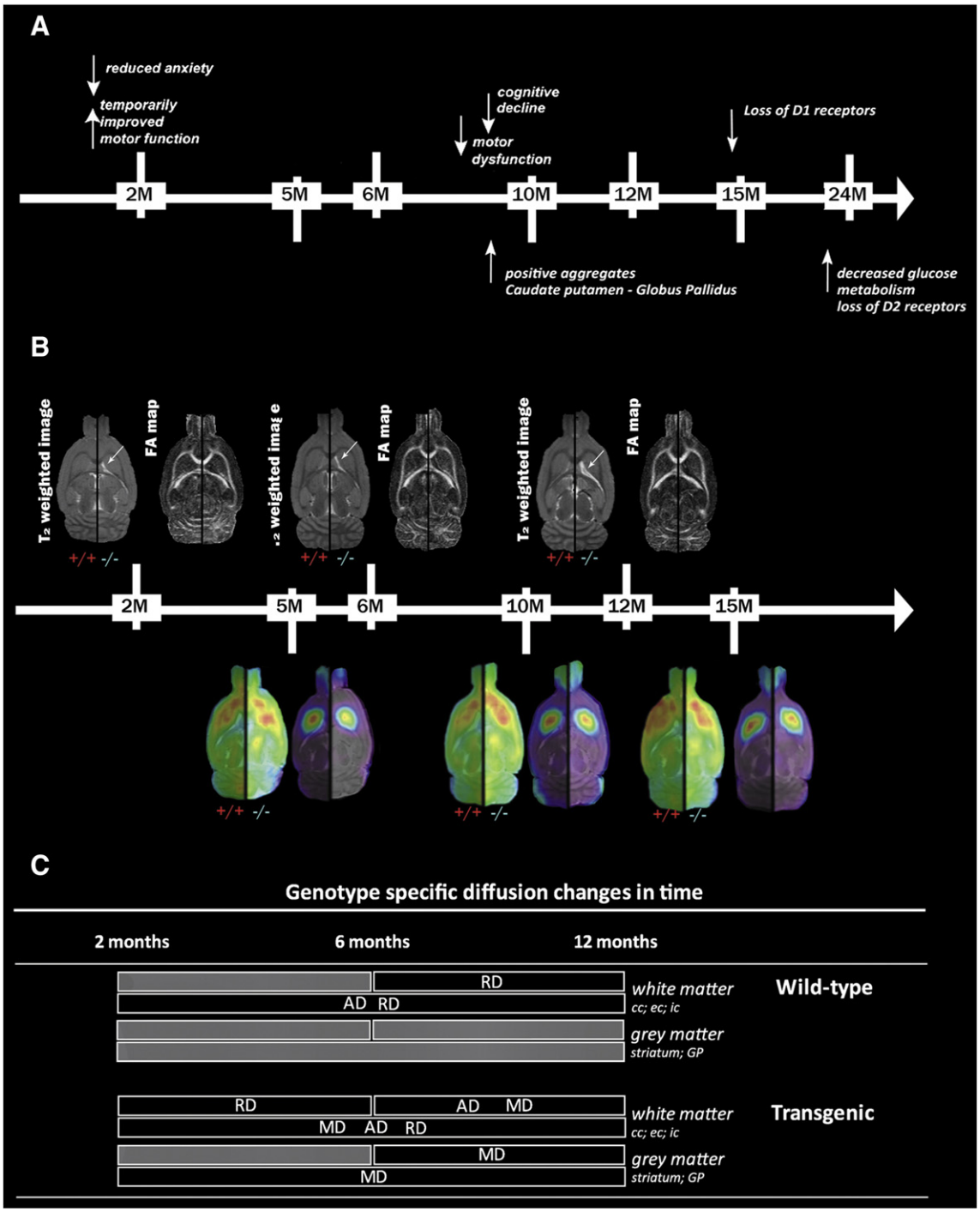

Fig. 1. (A) Timeline adapted from (Nguyen et al., 2006). Onsets of behavioral and cognitive abnormalities are shown. At 1 month of age, a reduced anxiety in TgHD rats was found, as well as an improved motor performance. At 7 months of age, a reduced motor performance was found in TgHD rats, compared to Wt animals. Cognitive impairment was seen in 9-month-old TgHD rats. A reduction in striatal D_1-receptor density was found at the age of 14 months (Bode et al., 2008). A decrease in glucose metabolism as well as decreased D_1 and D_2 receptor binding was reported at the age of 24 months (Bauer et al., 2005; von Horsten et al., 2003). (B) Timeline indicates different repeated measures for both Wt (−/−) and TgHD (+/+) rats. DTI (B_0 and Fractional Anisotropy) maps are illustrated at the top of the time line. PET images are illustrated beneath the timeline. Note the larger ventricle volumes of Wt rats, compared to TgHD animals (arrow). (C) Schematic overview of the genotype specific age related changes of TgHD and Wt animals. The timing at which significant changes (the start of age related genotype specific changes) were observed for the first time is shown in the bars. Gray bars indicate the absence of a significant difference.