fMRI reveals altered auditory sensory integration in manifest and premanifest Huntington's disease

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Introduction

Huntington's disease (HD), is a progressive neurodegenerative disorder with cognitive decline and mood disturbance. Depending on the stage of disease alterations in striatal and thalamic structure as well as striatal function, even before first motor symptoms occurred, were reported. Since neuronal dysfunction rather than neuronal loss is discussed to be an early feature in HD, fMRI may be more sensitive to early changes in pathophysiology of HD than structural studies. We used an already established paradigm of auditory integration and processing by repeated presentation of sine tones in presymptomatic HD gene carriers (pHD) and manifest HD to investigate the involvement of basal ganglia-thalamic circuits in sensory integration. Our hypothesis was that patients with HD and even premanifest gene carriers will show altered auditory sensory integration depending on the progression of the pathogenetic alterations.

Methods

Subjects: 18 pHD and 16 clinically manifest HD and age and gender-matched controls were included in this study. Patients with severe hyperkinesia or pronounced cognitive problems interfering with test performance were excluded. pHD patients were defined by a positive gene test and absence of clinical and motor symptoms were recruited from our HD center. The pHD group was divided into two subgroups close (cpHD; < 10 years), respectively far pHD (fcHP; >10 years), according to their estimated age of disease onset (eAO). Staging was performed according to the Unified Huntington's Disease Rating Scale.

fMRI measurements, paradigm and data analysis: MRI protocol: 60 GE-EPI-images, matrix: 64X64, FOV=210 mm, 16 oblique slices, slice thickness = 3.6 mm., TE = 55ms at 3 T (Philips, NL).A TR of 11.5 sec was used ("sparce" imaging. Auditory paradigm: the whole fMRI sequence consisted of 3 stimulation cycles A1-A3 (digitally generated pulsed (ν = 5 Hz) 800 Hz sine tones of 2 min duration), which alternated with rest periods R1-R3 (1 min duration). Subjects were binaurally stimulated and acoustic stimuli were delivered by pneumatic headphones. For all subjects the hearing threshold was determined within the magnet and all were stimulated with the same sound pressure level of 85 dB. Image Processing and statistical analysis of the fMRI images were done by SPM2 first and second level standard routines and templates (www.fil.ion.ucl.ac.uk/spm) and SPSS 13.0.

Results and discussion: We found a distinctly altered activation in all areas of the secondary auditory cortex, putamen, anterior cingulate, prefrontal cortex, middle temporal gyrus and thalamus in HD and/or pHD compared to controls. i) Predominantly up-regulated processes were observed in the fpHD and HD (fig. 2), whereas the cpHD group presented predominantly down-regulated processes. ii) HD and fpHD presented stronger bilateral activation of the putamen (Fig. 2). iii) We obtained several correlations between clinical data, impaired motor function and the activation intensities in sensory auditory areas. iiii) A shift to activation of relatively more right hemispherical areas in the progression of the disease can be observed (Fig. 1). ad i) Our findings seem to reflect an altered activation pattern to auditory stimulation depending on the progression of neuronal dysfunction in HD and pHD. Ad ii) These findings stress the involvement of the basal ganglia-thalamic circuits in processing of sensory auditory stimuli. Ad iii) This clearly demonstrates the involvement of basal ganglia-thalamic circuits in sensorimotoric integration. Ad iiii) Left sided lateralisation of tone processing is disturbed in manifest HD. This is presumably due to a disturbed top-down regulation and resulting compensatory mechanisms.

Figure 1

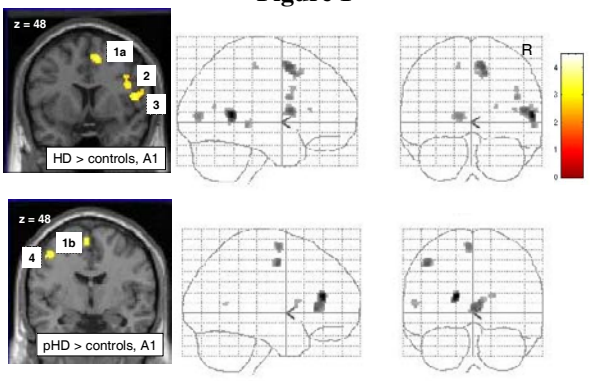

Figure 2

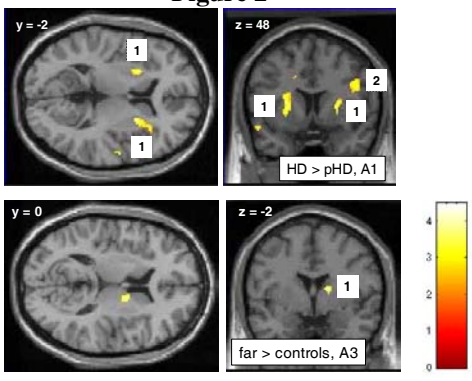

Fig.1: Activation after first auditory stimulation cycle with sine tones, ΔA1R1, and corresponding glass brain (p (uncorrected) = 0.001). Upper row: HD > controls, 1a = right BA 32 (ACC), 2: right BA 22, 3 = right BA 44. HD exhibited mainly higher right lateralized brain areas compared to controls. Lower row: pHD > controls. 1b = left BA 32, 4 = left BA 6. Remarkably, pHD –in contrast to HD exhibit stronger left lateralized activations compared to controls. Figure 2: upper row: Activation after ΔA1R1 (p (uncorrected) = 0.001). HD > pHD, 1 = bilateral putamen, 2 = BA 22. Symptomatic patients presented a higher activation of the bilateral putamen when sine tones are presented compared to premanifest HD. Lower row: Activations are shown at x = 20, y = 0, z = -28). Activation after third auditory stimulation cycle with sine tones, ΔA3R3 (second levels spm2, two sided t-test: k = minimum 4 voxels, p (uncorrected) = 0.001). fpHD > controls, 1 = right putamen. fpHD revealed a distinct higher activation of the right putamen after processing of repeated presentation of sine tones compared to age and gender matched controls.