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Title: Eye movement symptoms in Huntington's disease: evidence from a large international collaboration

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Introduction:

Huntington disease (HD) is a genetic, degenerative disorder of the brain, characterised by purposeless, involuntary movements, or chorea, as well as psychiatric and cognitive symptoms. It is typically diagnosed at around forty years of age. Early in the disease, symptoms are usually mild and not severe enough to significantly impair the functioning and independence of most patients. However, the disease persists and relentlessly progresses until death. While there is currently no treatment, as potential treatments become trialed and available, there is going to be an increasing need for markers to monitor the disease progression in response to new therapies.

One of the earlier signs to appear in HD is disordered eye movements; eye movements are controlled by many of the same brain areas affected in HD. Types of eye movements include saccades, the jerky, rapid movements of the eyes from one point to another, and smooth pursuit, when the eyes are tracking a moving object without jerks. In HD, it is generally considered that eye movements in the vertical direction are more slowed and take longer to begin than movements in the horizontal, but this is only supported by small, laboratory studies. And so, to definitively determine what features of eye movements are affected sooner and to a greater extent, particularly in the horizontal versus vertical plane, there is a need for a large sample of data on HD patients. Fortunately, this exists in the form of ENROLL-HD, a study collecting ongoing data from HD patients all over the world.

Aim:

The aim of this study is to determine how different types of eye movements are differently in early HD, and conclusively determine whether horizontal or vertical eye movements are more affected.

Impact:

The impact of this study is that eye movement dysfunction in the early stages of HD may provide information regarding the rate of disease progression, as well as provide suitable markers for monitoring response to any future therapies as they emerge.

Method:

Data was collected from the ENROLL-HD database, a large, international, prospective study, which has been running since 2012 and includes over 200 data collection sites around the world, including Christchurch.

Participants are recruited into the ENROLL-HD database through Huntington disease clinics. All provide written informed consent for anonymised use of their clinical data, and all contributing data-collection sites were required to obtain and adhere to local ethics committee approvals.

Participants were excluded if they had any brain disease other than HD, or participants were under the age of 18 years (unless consent was provided by parent or legal guardian).

There were 8174 participants in the database at the time of analysis (including controls and presymptomatic carriers); 4752 of these had been diagnosed with manifest HD.

ENROLL-HD collects a wide range of clinical information about HD, including six eye movement measures: horizontal and vertical smooth pursuit, horizontal and vertical saccade velocity, and horizontal and vertical saccade latency. These measures are scored by evaluation on a scale of 0 to 4 by a clinical examiner (0 being normal, 4 being completely unable to perform the task).

For analysis, longitudinal changes of the eye movement measures were analysed by plotting the years since diagnosis of HD against the mean of all the scores for each of the eye measures, and a linear model for the first 8 years of HD duration was made with the statistical programming language, R.

Results:

We analysed data over the first 8 years of HD duration, where impairment at the population level increased in a linear fashion. For horizontal smooth pursuit, at onset the expected eye measure score was 0.726 points (95% uncertainty interval of [0.684, 0.771]) and impairment increased at a rate of 0.121 [0.109, 0.133] points per year. Vertical pursuit at onset was more impaired than horizontal by 0.130 [0.104, 0.158] points, but had no difference in impairment over time [-0.000, 0.012].

For horizontal saccade latency, at onset the expected score was 1.194 points (95% uncertainty interval of [1.141, 1.248]) and impairment increased at a rate of 0.117 [0.104, 0.130] points per year. Vertical saccade latency at onset was more impaired than horizontal by 0.014 [-0.014, 0.042] which was not statistically significant, and had no difference in impairment over time by [-0.003, 0.010].

For horizontal saccade velocity, at onset the expected score was 0.998 points (95% uncertainty interval of [0.949, 1.038]) and impairment increased at a rate of 0.133 [0.119, 0.147] points per year. Vertical velocity at onset was more impaired than horizontal by 0.072 [0.038, 0.105] points, but had no difference in impairment over time [-0.002, 0.013].

Conclusion:

This study is the largest ever analysis of eye movement dysfunction in HD patients, providing high quality evidence regarding eye movement symptom progression in early HD. The findings from this study suggest that vertical eye movements are more affected in Huntington disease for both smooth pursuit and for saccade velocity (although the rate of progression is the same), which is consistent with preexisting findings. However, there was no statistical difference between horizontal and vertical saccade latency.

Moving forward, there is going to be increased need for suitable markers for HD progression and response to therapy, and eye movements may provide this opportunity.