Supplementary On-Line Data: Detailed Methods

General VBM Analysis

For each section, the same linear regression model was used to assess differences between the groups. Voxel intensity (V) was modeled as a function of group, controlling for age and TIV (an index of head size) by including them as covariates. TIV was measured as previously described.[1] This model is shown in equation 1, where the contrasts of interest are the 1-tailed *t* tests between the estimates of the group parameters, $\beta_1 > \beta_3$ (ie, where the controls had more volume than the early HD group):

1) $V = \beta_1$ Control + β_2 PM + β_3 HD + β_4 age + β_5 TIV + $\mu + \varepsilon$,

where μ is a constant, ε is error, HD is early HD subjects, and PM, premanifest.

Unless otherwise stated, statistical parametric maps were corrected for multiple comparisons by using random field theory to control FWE $P < .05$.

Adjusting for "Brain" Size

Three models were fitted, according to the following equations:

2) $V = \beta_1$ Control + β_2 PM + β_3 HD + β_4 age + β_5 TIV + $\mu + \varepsilon$

3) $V = \beta_1$ Control + β_2 PM + β_3 HD + β_4 age + $\mu + \varepsilon$

4) $V = \beta_1$ Control + β_2 PM + β_3 HD + β_4 age + β_5 TIV + β_6 GM volume + $\mu + \varepsilon$.

Equation 2 adjusts for head size (TIV) and is the standard model used elsewhere in this article. Equation 3 does not adjust for head size, and equation 4 includes total GM volume as an additional covariate. For each model, the contrast of interest was $\beta_1 > \beta_3$ (ie, regions in which controls had more GM than early HD subjects).

Subgroup Analysis

Three models were fitted, according to the following equations:

5) $V = \beta_1$ Control + β_2 low motor scores + β_3 age + β_4 TIV + $\mu + \varepsilon$

6) $V = \beta_1$ Control + β_2 high motor scores + β_3 age + β_4 TIV + $\mu + \varepsilon$

7) $V = \beta_1$ low motor scores + β_2 high motor scores + β_3 age + β_4 TIV + $\mu + \varepsilon$.

The contrast of interest in equations 5-7 is the 1-tailed *t* test between the estimates of the group parameters, $\beta_1 > \beta_2$, so in the first model, this shows regions in which the low motor group has less GM than controls; in the second model, regions in which the high motor group has less GM than controls; and in the third model, regions in which the high motor group has less GM than the low motor group.

General Methods

Models were fitted and parameters estimated (described in the relevant sections) at all voxels within an explicit mask that excluded any voxels for which >10% of the images had a value of <0.1. This "majority masking" was preferred to the default "absolute" mask option in SPM, which would exclude any voxels for which 1 or more images had a value of less than 0.1 and thus perhaps be unduly influenced by a single poorly registered or highly atrophied scan.[2] All maps were displayed as overlays on a smoothed version of the template used for normalization; for DARTEL, this was the template produced by the DARTEL "make template" routine.

References

1. Whitwell JL, Crum WR, Watt HC, et al. **Normalization of cerebral volumes by use of intracranial volume: implications for longitudinal quantitative MR imaging.** *AJNR Am J Neuroradiol.* 2001;22:1483–89
2. Ridgway GR, Omar R, Ourselin S, et al. **Issues with threshold masking in voxel-based morphometry of atrophied brains.** *Neuroimage* 2009;44:99–111. Epub 2008 Sep 20