Cell loss in the motor and cingulate cortex correlates with symptomatology in Huntington’s disease
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The extent of cell loss in two different regions of the cerebral cortex varies greatly between HD patients depending on whether the main symptoms they present are in the motor domain, behavioural domain, or both.

Background
The symptoms of Huntington’s disease (HD) vary markedly between individuals. Some patients show pronounced motor symptoms but only mild behavioural and/or cognitive disturbances. Others present severe mood problems and cognitive impairments but minimal movement abnormalities, while others are affected in all three domains to a similar extent. The cause of this variation is unknown.

Tippett et al. (Brain 2007, 130: 206-21) have shown previously that mood dysfunction correlates with gamma-aminobutyric acid (GABA) receptor and cell loss in the striatum. However, in recent years, a number of studies have shown that atrophy of the whole brain and thinning of the cerebral cortex occur in premanifest and manifest HD, demonstrating that HD pathology extends beyond the striatum. The present study aimed to examine whether or not the symptom variability in HD can be related to different patterns of neurodegeneration in the cerebral cortex.

Methods
The study was double-blinded and used unbiased stereological cell counting methods to quantify cell loss in the primary motor cortex and anterior cingulate cortex in the post mortem brains of 12 HD patients and 15 control subjects. The primary motor cortex is involved in the control of movements, whilst the anterior cingulate cortex plays a role in the regulation of emotions and mood.

Detailed information of motor and behavioural symptoms was collected retrospectively from family members and from reviewing clinical records. HD patients were classified into three groups depending on whether their dominant symptoms were in the motor domain, behavioural domain, or both domains.

Results
The total average number of neurones in both primary motor cortex and anterior cingulate cortex was significantly reduced in HD patients compared to control subjects. Surprisingly, the extent of cell loss varied greatly between individuals, ranging from 0 to 51% in the motor cortex and from 0 to 65% in the cingulate cortex. Some brains that showed major cell loss in the motor cortex had minimal cell loss in the cingulate cortex, whereas other brains showed the opposite trend.

The pattern of cell loss clearly correlated with the symptom phenotype (see figure). Brains from individuals with predominantly motor symptoms showed major cell loss in the motor cortex with no significant cell loss in the cingulate cortex. By contrast, brains from patients in whom mood was primarily affected showed extensive cell loss in the cingulate cortex, with no significant cell loss in the motor cortex. Brains from individuals with mixed motor and mood symptoms showed considerable cell loss in both the motor and cingulate cortices. In each of the affected regions, the neurones that remained showed marked pathological changes in morphology. There was no correlation between CAG repeat number and cell loss from either region.

Conclusions
The heterogeneous pattern of cell loss in the motor and cingulate cortices correlates with the variability of motor and mood symptoms presented in each case. The authors concluded that the HD mutation produces variable topographical patterns of cortical neurodegeneration that contribute to specific symptoms.