

Conclusions

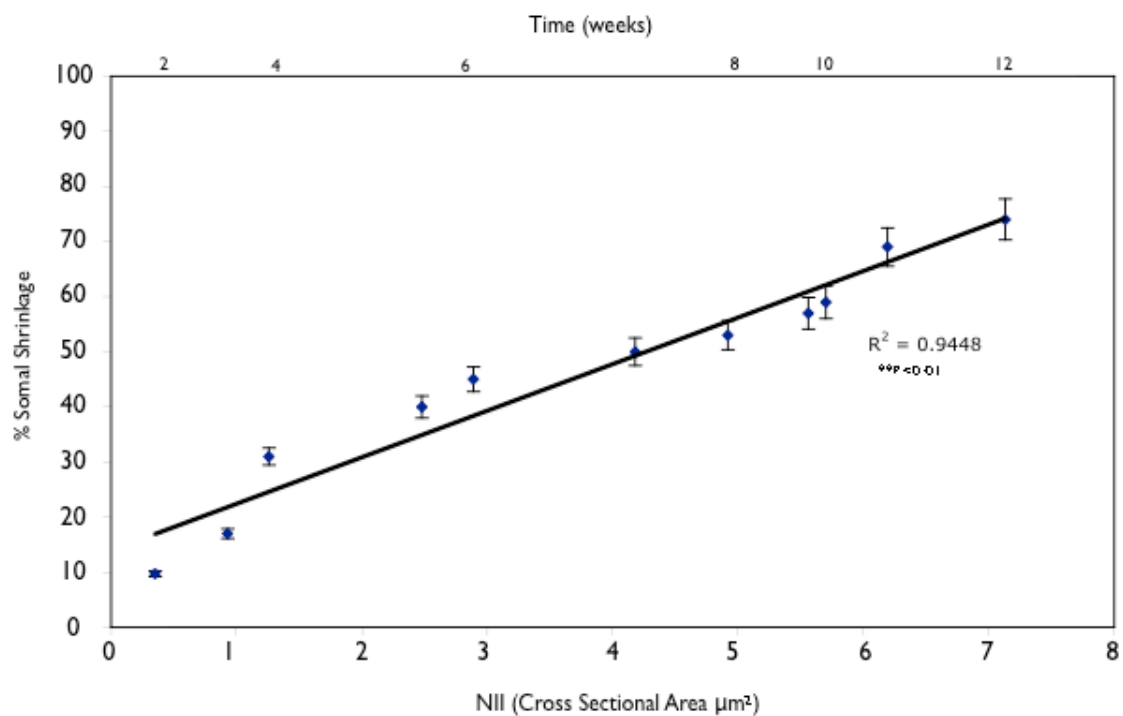
Chapter 10.

10.1. Conclusions drawn from this study

In conclusion I have presented a novel and innovative theory for the pathogenesis of HD and the other poly Q diseases. This theory appears to integrate remarkably well with published literature and incorporate all the new observations presented in this thesis. Indeed the formation and growth of the NII is highly correlative with the atrophy of the affected neuron (see [Figure 10.1 and 10.2](#)). It is the more remarkable that these features namely NII growth and somal atrophy and death encompass the full pathological process as well as firmly establishing the nuclear pathology with these changes.

However there did appear to be a strong correlation between the somal area and the inclusion area, and it became increasingly apparent that as the neuron shrank the inclusion grew, a particularly significant finding in the R6/2 model. To give an idea of the significance of this correlation; when it is considered that the increased size of the inclusion does not have any correlation to the presence of cell death, a relationship which is widely believed to be causative in HD.

Figure 10.2: Graph showing the correlation between somal atrophy and the growth of the inclusion over time in the R6/2 model. This correlation has been shown to be highly significant with the Student's t-test where $p > 0.01$.



From the correlation in the figure on the previous page it can be seen that the increase in size of the inclusion does in fact appear to be exerting an effect on the somal area of the host neuron namely that of atrophy, the mechanism or reasoning behind this may be a disruption of any of the many metabolic processes going on within the neuron. In the literature only a handful of papers can be found which report the formation of a proteinaceous pathological inclusion and accompanying neuronal atrophy, these are; in HD (Klivenyi *et al.* 2003), Pick's disease (Gleckman *et al.* 1999) and ALS (Kihira *et al.* 1991). However none of these studies correlates the two events or speculate that they may be in fact consequential to each other. The majority of studies correlate areas of atrophy in regions of brain and presence of inclusions but fail to investigate these in much depth at the level of individual neurons, there may be a mention of cell death but there are no definite correlates. This problem highlights the predicament of neuropathological studies such as these which utilise *post mortem* tissue. However increasingly it is more convenient to employ imaging techniques applied to gross neuroanatomical structures so the majority of studies fail to consider the cellular milieu of the brain.

My proposed model appears to embrace many of the observations I have reported in the R6/2, R6/1 and HD80 knock in mouse models. However a major disparity exists with the changes observed in the HD94 model. These mice exhibit many features that are not found in many of the HD mouse models which may be due to the complex nature of the genetic rearrangements, in these mice, since these differences are not found in the HD.

Another surprising difference between all HD models and the human disease they attempt to mimic is the massive neuronal cell death seen in the human brain. This again is not easily incorporated into the new theory. It is now quite well recognised by investigators working with mouse models that cell death is quite difficult to induce in these murine models, perhaps due to a species specific, and currently unexplained reason.

10.2. Future Studies

The purpose of any theory is to stimulate new investigations into novel avenues of research. Further studies of the mechanisms of dendritic spine to nuclear signalling, the mTOR pathway and the phenomenon of 'neuronal cachexia' will I believe greatly advance our understanding of the as yet unrealised basic mechanisms of poly Q diseases.

Currently avenues being investigated as a result of this thesis are the molecular and structural nature of autophagic DCD seen in mouse models of neurodegenerative disorders including those studied here. Further investigation into the identity of proteasomal components present in the clastosome and aggresome structures aggregated within dying neurons are required, in order to elucidate the purpose of their formation and the process employed. The underlying basis for the location of these structures additionally poses more intriguing questions. What is becoming increasingly apparent is that the neuronal nuclear changes and those taking place at the periphery are interdependent but consequential to each other and in the diseased state this becomes highly significant.

In the completion of this thesis some of the original questions have been answered but many more new ones now await explanation!