Ageing of the Somatic Motor Nervous System: 
A Nuclear and Mitochondrial Genome Perspective.

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B. Biomed. Sci. (Hons)

This thesis is submitted for the degree:
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Revised: June 2016
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Gemma M Parkinson

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- Interpretation of results (in collaboration with DW Smith)
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### Abbreviations

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<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>12S ribosomal RNA</td>
<td>12s</td>
</tr>
<tr>
<td>1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine</td>
<td>MPTP</td>
</tr>
<tr>
<td>Alzheimer’s disease</td>
<td>AS</td>
</tr>
<tr>
<td>Amyotrophic lateral sclerosis</td>
<td>ALS</td>
</tr>
<tr>
<td>Analysis of variance</td>
<td>ANOVA</td>
</tr>
<tr>
<td>Bicinchoninic acid assay</td>
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<td>Brain-derived neurotrophic factor</td>
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<td>Brown-Norway</td>
<td>BN</td>
</tr>
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<td>Carrier RNA</td>
<td>cRNA</td>
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<td>Central nervous system</td>
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<td>Cerebellum</td>
<td>CB</td>
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<td>Consensus analysis</td>
<td>ConsME</td>
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<td>Cycle threshold</td>
<td>Ct</td>
</tr>
<tr>
<td>Cytochrome B</td>
<td>CYTB</td>
</tr>
<tr>
<td>Database for Annotation, Visualisation and Integrated Discovery</td>
<td>DAVID</td>
</tr>
<tr>
<td>Diethylypyrocarbonate</td>
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<td>Differentially expressed genes</td>
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<td>Diffusion tensor imaging</td>
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<td>Dopamine</td>
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<td>Dopa-responsive dystonia</td>
<td>DRD</td>
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<tr>
<td>Dorso-lateral striatum</td>
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<td>False discovery rate</td>
<td>FDR</td>
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<td>Fischer 344</td>
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<td>Functional MRI</td>
<td>fMRI</td>
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<td>Term</td>
<td>Abbreviation</td>
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<td>----------------------------------------------</td>
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<tr>
<td>Gene significance</td>
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<td>Glial cell-derived neurotrophic factor</td>
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<td>Huntington’s disease</td>
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<td>Liver X receptor</td>
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<td>Locus Coeruleus</td>
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<td>Median spiny neurons</td>
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<tr>
<td>Messenger RNA</td>
<td>mRNA</td>
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<td>Middle</td>
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<td>Mitochondrial DNA</td>
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<td>Module membership</td>
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<td>Motor cortex</td>
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<td>Multiple Sclerosis</td>
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<td>NADH dehydrogenase subunit 1</td>
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<td>Neuromuscular junction</td>
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<td>Oxidative phosphorylation</td>
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<td>Paraformaldehyde</td>
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<td>Parkinson’s disease</td>
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<td>Phosphate buffered saline</td>
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<td>Polyethylene glycol</td>
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<td>Polymerase gamma</td>
<td>POLG</td>
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<td>Pseudo glyceraldehyde 3-phosphate dehydrogenase</td>
<td>psGAPDH</td>
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<tr>
<td>Quantitative PCR</td>
<td>qPCR</td>
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<tr>
<td>Radioimmunoprecipitation assay buffer</td>
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</tr>
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<td>Reactive nitrogen species</td>
<td>RNS</td>
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<td>Term</td>
<td>Abbreviation</td>
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<td>-------------------------------------------</td>
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<tr>
<td>Reactive oxygen species</td>
<td>ROS</td>
</tr>
<tr>
<td>Robust multi-array average</td>
<td>RMA</td>
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<tr>
<td>Sodium Chloride</td>
<td>NaCl</td>
</tr>
<tr>
<td>Sodium dodecyl sulfate</td>
<td>SDS</td>
</tr>
<tr>
<td>Somatic motor nervous system</td>
<td>SMNS</td>
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<td>Spinal cord</td>
<td>SC</td>
</tr>
<tr>
<td>Standard error of the mean</td>
<td>SEM</td>
</tr>
<tr>
<td>Substantia nigra</td>
<td>SN</td>
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<tr>
<td>Superoxide dismutase</td>
<td>SOD</td>
</tr>
<tr>
<td>Tyrosine hydroxylase</td>
<td>Th or TH</td>
</tr>
<tr>
<td>Ventral tegmental area</td>
<td>VTA</td>
</tr>
<tr>
<td>Web-based Gene Set Analysis Toolkit</td>
<td>WebGestalt</td>
</tr>
<tr>
<td>Weighted gene co-expression network analysis</td>
<td>WGCNA</td>
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<tr>
<td>Young</td>
<td>Y</td>
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Abstract

The somatic motor nervous system (SMNS) contributes to all aspects of motor function. Ageing affects most, if not all, human and animal biological systems, including the SMNS, and contributes to the decline in the quality of life of the elderly. Some of the proposed mechanisms of ageing in the brain include mitochondrial dysfunction as a result of mitochondrial DNA (mtDNA) deletion accumulation, aberrant inflammation and synaptic dysfunction. However, the mechanisms underlying the functional changes in the SMNS are not well understood. Therefore, a number of SMNS regions including the motor cortices, striatum and substantia nigra dopaminergic (SN DA) neurons, as well as the spinal cord, were examined in young and old rats to identify molecular correlates of ageing. In the SN DA neurons, an increase in mtDNA deletions was observed with age, although not to the extent reported in humans. Furthermore, there was reduced expression of genes involved in regulating dopaminergic phenotype and neuron survival; however there was no change in expression of genes associated with dopamine production and transport such as Th and Dat, unlike in humans. Both the mtDNA deletion and gene expression results suggest that rat SN DA neurons are less susceptible to age related changes than their human counterparts and thus may provide insight into potential ageing resistance mechanisms. Genomic analysis in the other SMNS regions (mentioned above) consistently revealed up-regulation of inflammatory processes including increased expression of genes in the complement and coagulation pathways with age. Furthermore, there was reduced expression of genes associated with axon growth and synaptic transmission in each region. Cholesterol and lipid synthesis pathways were also affected, particularly in the spinal cord. In depth characterisation of the spinal cord changes identified perturbed cholesterol homeostasis at the gene, protein and cholesterol species level, as well as increased inflammatory markers in the absence of gross myelin protein loss. Together, the results of these studies support a role for inflammation, synaptic dysfunction and altered white matter integrity in ageing of the SMNS.