Transcriptional changes in Parkinson's disease white matter: an underappreciated player in disease progression

James D. Mills[1], J.J. Anink[1], A.M. Iyer[2], D.F. Swaab[3], E. Aronica[1]

[1]*Amsterdam UMC, University of Amsterdam, Amsterdam Neuroscience, Department of (Neuro)Pathology, Amsterdam, Netherlands*
[2]*Department of Internal Medicine, Erasmus Medicine Center, Rotterdam, Netherlands*
[3]*Netherlands Institute for Neuroscience, an Institute of the Royal Netherlands Academy of Arts and Sciences, Amsterdam, Netherlands*

Introduction

- Parkinson's disease (PD) is an irreversible, progressive, complex, neurodegenerative disease.
- The most obvious observable result of PD pathogenesis is the loss of neurons in the grey matter (GM), it is possible that white matter (WM) abnormalities may precede changes in GM.
- Non-coding RNAs (ncRNAs) refer to RNA molecules that are transcribed but not translated to protein.
- The majority of ncRNAs have not been functionally explored.
- There have only been a limited number of whole transcriptome studies in PD and these have failed to explore all classes of ncRNAs, and none have explored WM.

1. Greater transcriptional changes in WM than in GM at PD Braak stage 4

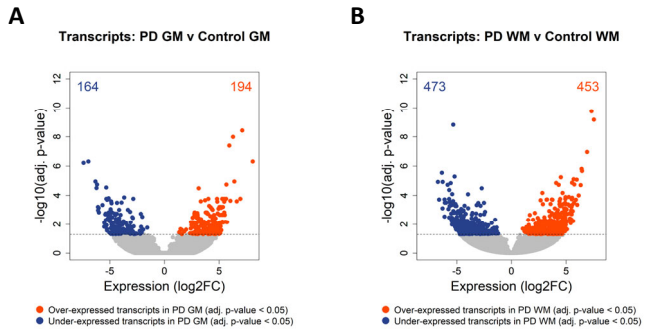

Figure 1. Differentially expressed transcripts in the GM and WM from the middle frontal gyrus of the PD brain (Braak stage 4). **A.** In the GM there were 194 over-expressed and 164 under-expressed transcripts when PD brain tissue was compared to control brain tissue. **B.** In the WM there were 453 over-expressed and 473 under-expressed transcripts when PD brain tissue was compared to control brain tissue. Significance defined as a Benjamini-Hochberg corrected p-value < 0.05.

2. Largest class of differentially expressed transcripts were novel RNAs

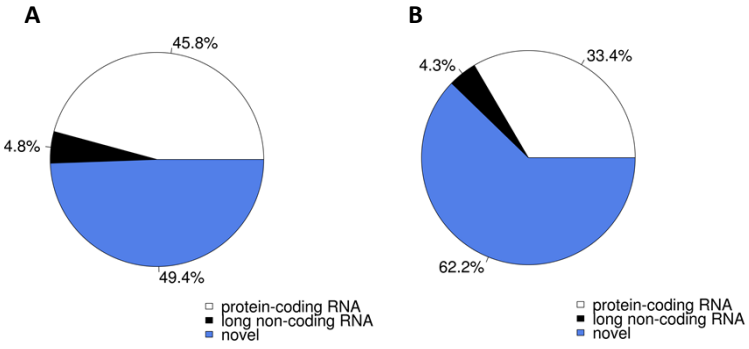

Figure 2. Biotypes of differentially expressed transcripts when PD (Braak stage 4) brain tissue was compared to control tissue. **A.** In GM 45.8% of the differentially expressed transcripts were protein-coding RNAs, 4.8% were long non-coding RNAs (lncRNAs) and 49.4% were novel RNAs of unknown biotype. **B.** In WM 33.4% of the differentially expressed transcripts were protein-coding RNAs, 4.3% were lncRNAs and 62.2% were novel RNAs of unknown biotype. The novel RNAs await further investigation but can currently be classed as putative lncRNAs.

Acknowledgements

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Aim

To investigate transcripitonal changes in both the GM and WM of PD patients during disease progression.

Methods

Post-mortem brain tissue from the middle frontal gyrus of 10 controls and 20 PD patients (10 Braak stage 4, 10 Braak stage 5/6) was separated into GM and WM. Selection of the middle frontal gyrus, a region of the brain affected in the later stages of PD (Braak stage 5 and 6), allowed for the determination of the underlying molecular changes driving the progression of PD pathology. RNA-Seq coupled with ribosomal depletion was carried out on all samples and allowed for the detection of all lncRNAs and protein-coding RNAs. Data analysis was carried out using a variety of different bioinformatic tools.

3. Gross transcriptional changes in both GM and WM at PD Braak stage 5/6

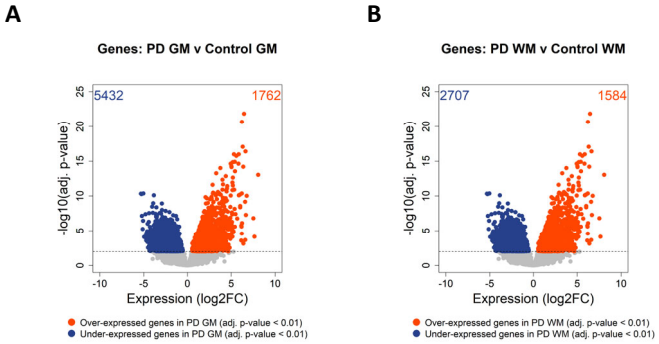

Figure 3. Differentially expressed transcripts in the GM and WM from the middle frontal gyrus of the Parkinson's disease brain (Braak stage 5/6). **A.** In the GM there were 1762 over-expressed and 5432 under-expressed genes when PD brain tissue was compared to control brain tissue. **B.** In the WM there were 1584 over-expressed and 2707 under-expressed genes when PD brain tissue was compared to control brain tissue. Significance defined as a Benjamini-Hochberg corrected p-value < 0.01.

4. Alterations in WM were distinct from those in GM

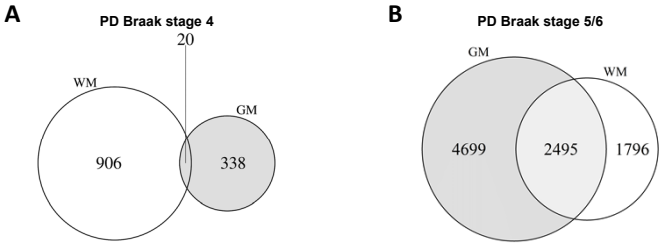

Figure 4. Overlap of the differentially expressed transcripts when PD GM was compared to control GM and when PD WM was compared to control WM. **A.** PD Braak stage 4: 20 transcripts that had altered expression patterns in both GM and WM. **B.** PD Braak stage5/6: 2495 genes had altered expression pattern in both GM and WM. Hypergeometric testing revealed that tissue type changes were more distinct in PD Braak stage 4 (p-value < 2.2e-16)

Conclusions

- Putative long non-coding RNAs represent a novel class of transcripts that may play a crucial role in PD pathogenesis.
- Early stage transcriptomic changes in PD are greater in WM and distinct from GM.
- Alterations in WM may precede those in GM and contribute to the progression of PD.