Parkinsonism

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Abstract

NOTE - this document is in draft currently. If I have the discipline, I will be making additions and edits for the next few months

Parkinsonism is a category of neurological diseases characterized by common mobility symptoms. Specific diseases include Parkinson's Disease (PD), Lewy Body Dementia (LBD), Progressive Supranuclear Palsy (PSP), and Multiple System Atrophy (MSA). These diseases have complex and heterogeneous pathologies that are not well understood. Common pathology attributes for idiopathic parkinsonism include misfolded proteins leading to toxic aggregates within the central nervous system (CNS), dysfunctional mitochondria resulting in impaired energy production and oxidative stress, chronic CNS inflammation, and dysfunctional cellular machinery that would otherwise correct misfolded protein conformation. The pathologies diverge based on which types of cells are affected, which protein aggregates, and which regions of the brain these changes occur. These pathological changes are reflected in the cargo of exosomes released by affected cells, which can contain misfolded proteins, mitochondrial dysfunction markers, inflammatory mediators, and molecular indicators of impaired cellular maintenance. Since exosomes cross the blood-brain barrier and enter peripheral fluids, they offer a promising avenue for non-invasive biomarker discovery, potentially enabling earlier diagnosis and improved monitoring of disease progression in parkinsonian disorders.

Introduction

The history of Parkinsonism traces back to 1817 when James Parkinson published An Essay on the Shaking Palsy, describing the characteristic motor symptoms of what would later be called Parkinson's Disease (PD). Nearly a century later, Jean-Martin Charcot refined Parkinson's observations, distinguishing the disorder from other movement disorders and formally naming it Maladie de Parkinson. Charcot also identified degeneration of the substantia nigra as a pathological feature, an insight that would later prove essential. Around the same time, in 1900, Dejerine and Thomas described a separate disorder, now known as Multiple System Atrophy (MSA), highlighting its distinct pathology affecting both motor and autonomic functions. In 1912, Friedrich Lewy discovered intraneuronal inclusions—Lewy bodies—marking the first pathological hallmark of PD, though their role remained unclear for decades.

The mid-20th century saw a breakthrough when Arvid Carlsson identified dopamine as a critical neurotransmitter, demonstrating its depletion in PD patients. This discovery paved the way for dopamine-replacement therapy, culminating in the FDA approval of Carbidopa/Levodopa in 1975, which remains the cornerstone of PD treatment. In the 1980s, a turning point emerged when drug users exposed to MPTP developed severe Parkinsonism, revealing the vulnerability of dopaminergic neurons to environmental toxins. This event shifted research away from symptomatic treatments toward mechanistic studies, leading to the discovery that mitochondrial dysfunction, oxidative stress, and impaired protein degradation contribute to PD pathology. The 1990s solidified alpha-synuclein as a key player, with genetic mutations in SNCA linking the protein to familial PD and misfolded aggregates being identified as a major pathological feature.

Building on this, Heiko Braak proposed in 2003 that PD may originate outside the brain, with misfolded alpha-synuclein spreading from the gut or olfactory system before affecting the CNS. More recently, Filip Scheperjans and others expanded this hypothesis, implicating gut microbiota in triggering the chronic inflammation that might drive early PD pathology. These findings have reframed Parkinson's research, shifting focus from late-stage neurodegeneration to early detection and intervention.

A Broad Selection of Potential Early Detection Biomarkers

Biomarker	Category	Applicable Disorders	Source Fluid/Tissue
α-Synuclein Oligomers	Disease-specific	PD, MSA, DLB	CSF, Blood
Total α-Synuclein	Disease-associated	PD, MSA, DLB	CSF
Phosphorylated α-Synuclein	Disease-specific	PD	CSF
Neurofilament Light Chain (NfL)	Disease-associated	PD, MSA, PSP, CBD	CSF, Blood
Total Tau Protein	Disease-associated	PD, MSA, DLB, AD	CSF
Phosphorylated Tau Protein	Disease-associated	AD, DLB	CSF
Amyloid-β42	Disease-associated	AD, DLB	CSF
DJ-1 Protein	Disease-associated	PD	CSF, Blood

Biomarker	Category	Applicable Disorders	Source Fluid/Tissue
Lysosomal Enzymes	Disease-associated	PD, MSA	CSF
Inflammatory Cytokines (e.g., IL-6, TNF-α)	Disease-associated	PD, MSA, PSP, CBD	CSF, Blood
MicroRNAs (e.g., miR-34b/c, miR-133b)	Disease-associated	PD	Blood, CSF
PINK1/Parkin Levels	Disease-associated	PD, MSA	Blood, CSF
Complement Proteins (e.g., C3, Factor H)	Disease-associated	PD, MSA	CSF

Exosomes

Exosomes are small extracellular vesicles that play a key role in cell-to-cell communication and waste removal by transporting molecular cargo such as proteins, RNA, and lipids. Research within the last decade has focused on their potential in targeted therapy delivery, disease biomarker discovery, immune system modulation, and strategies to block their uptake to mitigate pathological processes. [Citation Needed]

Regarding neurodegenerative diseases, exosomes are being studied as potential biomarkers for early diagnosis, particularly for disorders like Parkinson's Disease and Multiple System Atrophy. [Citation Needed] These diseases have long prodromal phases, during which symptoms may be subtle or non-motor in nature, delaying diagnosis until neurodegeneration is already advanced. Since current diagnostic methods rely heavily on clinical evaluations of motor dysfunction, the identification of exosome-based biomarkers could enable earlier, more precise detection. Importantly, clinically viable biomarkers must be detectable in peripheral fluids such as blood or saliva, allowing for non-invasive testing during routine healthcare visits. This could shift the diagnostic paradigm from symptom-based assessments to proactive screening, potentially enabling earlier interventions that slow disease progression.

Importantly, exosomes can cross the blood-brain barrier (BBB) bidirectionally, [Citation Needed] allowing for the collection of CNS biomarkers in peripheral fluids and enabling potential therapeutic delivery to the brain. However, in neurodegenerative diseases, a compromised BBB may also permit the entry of exosomes carrying toxic cargo, potentially contributing to disease progression by spreading misfolded proteins, exacerbating neuroinflammation, and inducing metabolic stress. Additionally, exosomes can transport immune-modulating factors, such as cytokines or microRNA, which may further disrupt CNS homeostasis. Understanding these mechanisms is critical, as exosomes could serve as both pathological agents and therapeutic targets in neurodegenerative disease management. [Citation Needed]

Beyond their role in disease progression, exosomes also serve as natural concentrators of key biomarkers, which might otherwise be too dilute in peripheral fluids like blood or saliva for reliable detection. Furthermore, exosomes carry surface antigens reflective of their parent cells, allowing for selective isolation of disease-relevant exosomes. [Citation Needed] By isolating exosomes derived from specific cell types, such as dopaminergic neurons or oligodendrocytes, researchers can obtain enriched biomarker profiles in measurable concentrations, enhancing disease detection. This makes

exosome-based diagnostics a promising avenue for the early identification and monitoring of neurodegenerative conditions.

Exosomes Cargo and Key Biomarkers

Some text....

This manuscript is a template (aka “rootstock”) for Manubot, a tool for writing scholarly manuscripts. Use this template as a starting point for your manuscript.

The rest of this document is a full list of formatting elements/features supported by Manubot. Compare the input (`.md` files in the `/content` directory) to the output you see below.

Basic formatting

Bold text

Semi-bold text

Centered text

Right-aligned text

Italic text

Combined *italics and* ***bold***

~~Strikethrough~~

1. Ordered list item
2. Ordered list item
    a. Sub-item
    b. Sub-item
        i. Sub-sub-item
3. Ordered list item
    a. Sub-item

- List item
- List item
- List item

subscript: H_2O is a liquid

superscript: 2^{10} is 1024.

unicode superscripts^{0123456789}

unicode subscripts$_{0123456789}$

A long paragraph of text. Lorem ipsum dolor sit amet, consectetur adipiscing elit, sed do eiusmod tempor incididunt ut labore et dolore magna aliqua. Ut enim ad minim veniam, quis nostrud

exercitation ullamco laboris nisi ut aliquip ex ea commodo consequat. Duis aute irure dolor in reprehenderit in voluptate velit esse cillum dolore eu fugiat nulla pariatur. Excepteur sint occaecat cupidatat non proident, sunt in culpa qui officia deserunt mollit anim id est laborum.

Putting each sentence on its own line has numerous benefits with regard to editing and version control.

Line break without starting a new paragraph by putting
two spaces at end of line.

Document organization

Document section headings:

Heading 1

Heading 2

Heading 3

Heading 4

Heading 5

Heading 6

A heading centered on its own printed page

Horizontal rule:

`Heading 1`'s are recommended to be reserved for the title of the manuscript.

`Heading 2`'s are recommended for broad sections such as *Abstract*, *Methods*, *Conclusion*, etc.

`Heading 3`'s and `Heading 4`'s are recommended for sub-sections.

Links

Bare URL link: https://manubot.org

Long link with lots of words and stuff and junk and bleep and blah and stuff and other stuff and more stuff yeah

Link with text

Link with hover text

Link by reference

Citations

Citation by DOI [1].

Citation by PubMed Central ID [2].

Citation by PubMed ID [3].

Citation by Wikidata ID [4].

Citation by ISBN [5].

Citation by URL [6].

Citation by alias [7].

Multiple citations can be put inside the same set of brackets [1,5,7]. Manubot plugins provide easier, more convenient visualization of and navigation between citations [2,3,7,8].

Citation tags (i.e. aliases) can be defined in their own paragraphs using Markdown's reference link syntax:

Referencing figures, tables, equations

Figure 1

Figure 2

Figure 3

Figure 4

Table 1

Equation 1

Equation 2

Quotes and code

> Quoted text

> Quoted block of text
>
> Two roads diverged in a wood, and I—
> I took the one less traveled by,
> And that has made all the difference.

Code `in the middle` of normal text, aka `inline code`.

Code block with Python syntax highlighting:

```
from manubot.cite.doi import expand_short_doi

def test_expand_short_doi():
    doi = expand_short_doi("10/c3bp")
    # a string too long to fit within page:
    assert doi == "10.25313/2524-2695-2018-3-vliyanie-enhansera-copia-i-
        insulyatora-gypsy-na-sintez-ernk-modifikatsii-hromatina-i-
        svyazyvanie-insulyatornyh-belkov-vtransfetsirovannyh-geneticheskih-
        konstruktsiyah"
```

Code block with no syntax highlighting:

```
Exporting HTML manuscript
Exporting DOCX manuscript
Exporting PDF manuscript
```

Figures

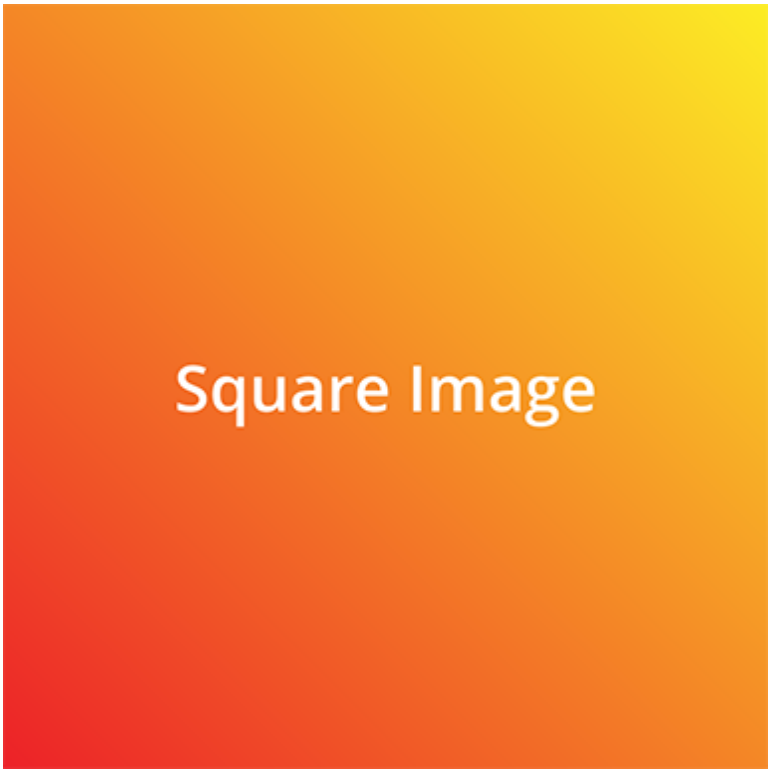

Figure 1: A square image at actual size and with a bottom caption. Loaded from the latest version of image on GitHub.

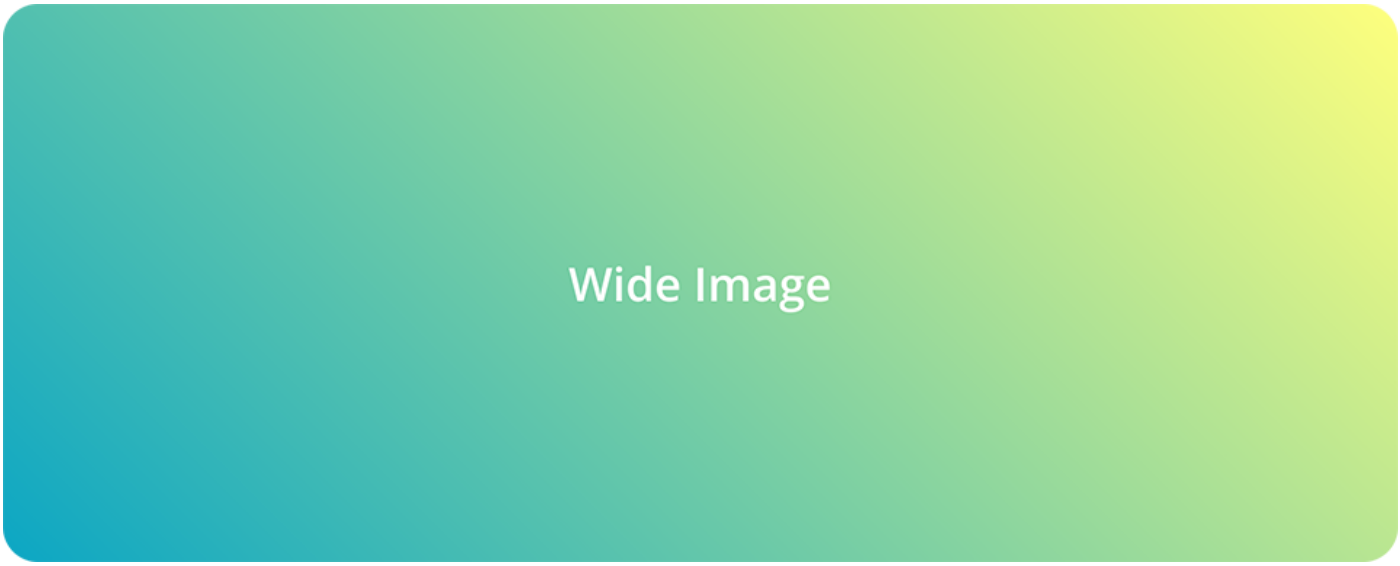

Figure 2: An image too wide to fit within page at full size. Loaded from a specific (hashed) version of the image on GitHub.

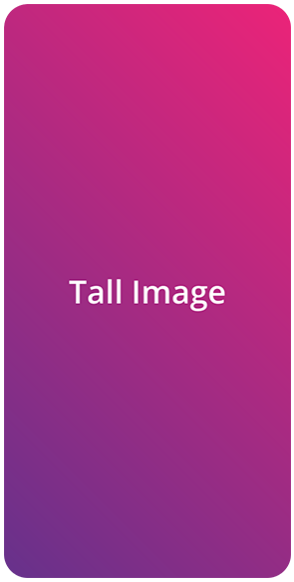

Figure 3: A tall image with a specified height. Loaded from a specific (hashed) version of the image on GitHub.

Figure 4: A vector `.svg` image loaded from GitHub. The parameter `sanitize=true` is necessary to properly load SVGs hosted via GitHub URLs. White background specified to serve as a backdrop for transparent sections of the image. Note that if you want to export to Word (`.docx`), you need to download the image and reference it locally (e.g. `content/images/vector.svg`) instead of using a URL.

Tables

Table 1: A table with a top caption and specified relative column widths.

Bowling Scores	**Jane**	**John**	**Alice**	**Bob**
Game 1	150	187	210	105
Game 2	98	202	197	102
Game 3	123	180	238	134

Table 2: A table too wide to fit within page.

	Digits 1-33	**Digits 34-66**	**Digits 67-99**	**Ref.**
pi	3.14159265358979323 846264338327950	28841971693993751 0582097494459230	78164062862089986 2803482534211706	`piday.org`
e	2.71828182845904523 536028747135266	24977572470936999 5957496696762772	40766303535475945 7138217852516642	`nasa.gov`

Table 3: A table with merged cells using the `attributes` plugin.

	Colors	
Size	**Text Color**	**Background Color**
big	blue	orange
small	black	white

Equations

A LaTeX equation:

$$\int_0^\infty e^{-x^2} dx = \frac{\sqrt{\pi}}{2} \tag{1}$$

An equation too long to fit within page:

$$\begin{aligned} x = a + b + c + d + e + f + g + h + i + j + k + l + m + n + o + p + q + r + s + t \\ + u + v + w + x + y + z + 1 + 2 + 3 + 4 + 5 + 6 + 7 + 8 + 9 \end{aligned} \tag{2}$$

Special

⚠ **WARNING** *The following features are only supported and intended for* `.html` *and* `.pdf` *exports. Journals are not likely to support them, and they may not display correctly when converted to other formats such as* `.docx`*.*

LINK STYLED AS A BUTTON

Adding arbitrary HTML attributes to an element using Pandoc's attribute syntax:

Manubot Manubot Manubot Manubot Manubot. Manubot Manubot Manubot Manubot. Manubot Manubot Manubot. Manubot Manubot. Manubot.

Adding arbitrary HTML attributes to an element with the Manubot `attributes` plugin (more flexible than Pandoc's method in terms of which elements you can add attributes to):

Manubot Manubot Manubot Manubot Manubot. Manubot Manubot Manubot Manubot. Manubot Manubot Manubot. Manubot Manubot. Manubot.

Available background colors for text, images, code, banners, etc:

`white` `lightgrey` `grey` `darkgrey` `black` `lightred` `lightyellow` `lightgreen` `lightblue` `lightpurple` `red` `orange` `yellow` `green` `blue` `purple`

Using the Font Awesome icon set:

✔ ? ★ 🔔 ⊗ ⋯

Light Grey Banner
useful for *general information* - manubot.org

Blue Banner
useful for *important information* - manubot.org

Light Red Banner
useful for *warnings* - manubot.org

References

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   Daniel S Himmelstein, Ariel Rodriguez Romero, Jacob G Levernier, Thomas Anthony Munro, Stephen Reid McLaughlin, Bastian Greshake Tzovaras, Casey S Greene
   eLife (2018-03-01) https://doi.org/ckcj
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2. **Reproducibility of computational workflows is automated using continuous analysis**
   Brett K Beaulieu-Jones, Casey S Greene
   Nature biotechnology (2017-04) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6103790/
   DOI: 10.1038/nbt.3780 · PMID: 28288103 · PMCID: PMC6103790

3. **Bitcoin for the biological literature.**
   Douglas Heaven
   Nature (2019-02) https://www.ncbi.nlm.nih.gov/pubmed/30718888
   DOI: 10.1038/d41586-019-00447-9 · PMID: 30718888

4. **Plan S: Accelerating the transition to full and immediate Open Access to scientific publications**
   cOAlition S
   (2018-09-04) https://www.wikidata.org/wiki/Q56458321

5. **Open access**
   Peter Suber
   MIT Press (2012)
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6. **Open collaborative writing with Manubot**
   Daniel S Himmelstein, Vincent Rubinetti, David R Slochower, Dongbo Hu, Venkat S Malladi, Casey S Greene, Anthony Gitter
   Manubot (2020-05-25) https://greenelab.github.io/meta-review/

7. **Opportunities and obstacles for deep learning in biology and medicine**
   Travers Ching, Daniel S Himmelstein, Brett K Beaulieu-Jones, Alexandr A Kalinin, Brian T Do, Gregory P Way, Enrico Ferrero, Paul-Michael Agapow, Michael Zietz, Michael M Hoffman, … Casey S Greene
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   Daniel S Himmelstein, Vincent Rubinetti, David R Slochower, Dongbo Hu, Venkat S Malladi, Casey S Greene, Anthony Gitter
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   DOI: 10.1371/journal.pcbi.1007128 · PMID: 31233491 · PMCID: PMC6611653