INPLASY PROTOCOL

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Conflicts of interest:
None declared.

How well do rodent models of Parkinson's disease recapitulate early non-motor phenotypes? A Systematic Review

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Review question / Objective: **The question of interest is to determine how reproducible non-motor phenotypes are amongst genetic Parkinson's disease (PD) rodent models, do these phenotypes appear with age, and how translatable these phenotypes are to the clinic. Specifically, the aim of this systematic review is to 1) identify which phenotypes present most consistently across the animal models, 2) report which phenotypes presented in an age-dependent manner, 3) investigate if animal models recapitulate most non-motor phenotypes and 4) to highlight gaps and provide future recommendations for researchers.**
Study designs to be included: **In vivo preclinical studies investigating functional outcomes between transgenic rodents and wildtypes.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 11 November 2022 and was last updated on 11 November 2022 (registration number INPLASY2022110050).

INTRODUCTION

Review question / Objective: **The question of interest is to determine how reproducible non-motor phenotypes are amongst genetic Parkinson's disease (PD) rodent models, do these phenotypes appear with age, and how translatable these phenotypes are to the clinic. Specifically, the aim of this systematic review is to 1) identify which phenotypes present most consistently across the animal models, 2) report which phenotypes presented in an age-dependent manner, 3)**

investigate if animal models recapitulate most non-motor phenotypes and 4) to highlight gaps and provide future recommendations for researchers.

Rationale: The prodromal phase of PD is characterised by many non-motor symptoms, and these have recently been posited to be predictive of later diagnosis. Genetic rodent models can develop non-motor phenotypes, providing tools to identify mechanisms underlying the early development of PD. However, the degree to which these rodent models present with similar non-motor dysfunction to the clinical condition is unknown. For these animal models to be useful in mapping risk-factors to biological pathways and disease mechanisms, they must accurately reflect clinical observations and present reliable and reproducible phenotypes.

Condition being studied: The Parkinson's disease (PD) is the fastest-growing neurological disorder and affects over 6 million people globally as reported by the Global Burden of Disease in 2016 [1,2]. The multitude of motor and non-motor symptoms associated with PD substantially affect quality of life and are poorly managed by current therapeutic approaches [3]. Unfortunately, there is no approved disease-modifying treatment for PD. One major hindrance in the development of novel treatments is the late clinical diagnosis rendering neuroprotective therapies ineffective. Current diagnosis relies on the development of hallmark motor symptoms of bradykinesia, rigidity, and tremors [4]. By the time of diagnosis, there is a 50-70% reduction in the dopaminergic cells in the substantia nigra pars compacta (SNpc) [5, 6]. This rate of cell loss remains relatively stable 27 years post-diagnosis, indicating that the most extensive neurodegenerative processes occur in the prodromal and early stages of clinical disease [7]. Given the high failure rate of disease-modifying therapies when applied from diagnosis, the field has now refocused its attention to improving early detection and developing biomarkers for tracking progression of PD.

METHODS

Search strategy: Pubmed was the primary database utilised. Search terms are: (parkinsonism OR parkinson's) AND (mouse OR rat OR rodent) AND ((olfact* OR hy-posmia) OR (circadian rhythm OR RBD OR REM OR sleep) OR (constipation OR gut OR gastrointestinal) OR (anxiety OR depression) OR (cardiovascular) OR (memory) OR (urinary). Once the primary search was complete, and the animal models were identified, a secondary search was performed. This secondary search covered each combination of animal model and phenotype (eg. A53T AND mouse model AND (olfact* OR hyposmia)).

Participant or population: Genetic rodent models of Parkinson's disease will be included, inclusive of all ages and sex.

Intervention: Not applicable.

Comparator: Not applicable.

Study designs to be included: In vivo preclinical studies investigating functional outcomes between transgenic rodents and wildtypes.

Eligibility criteria: Other eligibility criteria included using mice or rats, including appropriate controls, containing original work, and are in English.

Information sources: The main database searched was Pubmed.

Main outcome(s): The main outcomes were any outcome of behavioural tests of cognition, olfaction, anxiety/depressive-like behaviour and any (in vivo) functional outcomes of gastrointestinal function, cardiovascular and circadian rhythm and urinary function.

Additional outcome(s): Results of motor performance and cell loss within the substantia nigra (as indicated by TH+ cells) were also included as additional outcomes if they were assessed in a study included in the review. However, studies that performed only motor or cell loss were not

included in this review. Motor and cell loss were included as these represent the accepted standard of PD-like diagnosis in animal models.

Data management: Screening and data extraction were performed using the online platform, Covidence.

Quality assessment / Risk of bias analysis: SYRCLE's RoB tool for preclinical animal studies was used to perform quality assessments.

Strategy of data synthesis: The mean difference outcome for all tests of the same phenotype was scored as either 'expected deficit, no change or improvement'. This was first collated in a table for each individual study and then summarised as graphs to determine the overall consistency of the phenotype within individual models and across all models. No further analysis was performed.

Subgroup analysis: No subgroup analysis was performed.

Sensitivity analysis: Not applicable.

Language restriction: Only English manuscripts were considered for this review.

Country(ies) involved: Australia.

Keywords: Parkinson's disease; genetic rodent models; prodromal PD; non-motor PD phenotypes; systematic review.

Dissemination plans: We plan to publish this work in a journal.

Contributions of each author:

Author 1 - Tracy Zhang - TZ conceived and designed the study. TZ also carried out the literature search, collated data and created figures and tables. TZ contributed to the interpretation of the results and preparation of the original draft, and reviewing and editing of subsequent drafts.
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Author 2 - Scott Kolbe - SK conceived and designed the study. SK also contributed to the supervision of this review and to reviewing and editing of the manuscript.
Author 3 - Leah Beauchamp - LB participated in discussion of the original draft and contributed to reviewing and editing.
Author 4 - Ella Woodbridge - Assisted in the data collation and contributed to review and editing.
Author 5 - David Finkelstein - DF conceived and designed the study and contributed input to the original draft, reviewing and editing of subsequent drafts.
Author 6 - Emma Burrows - EB conceived and designed the study, interpreted the results and gave input in the original draft. EB contributed to the supervision and project administration. EB review and edited the subsequent drafts.

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