

# Modelling neurodegenerative disorders in mice with minimal loss – our experience with Parkinson's disease

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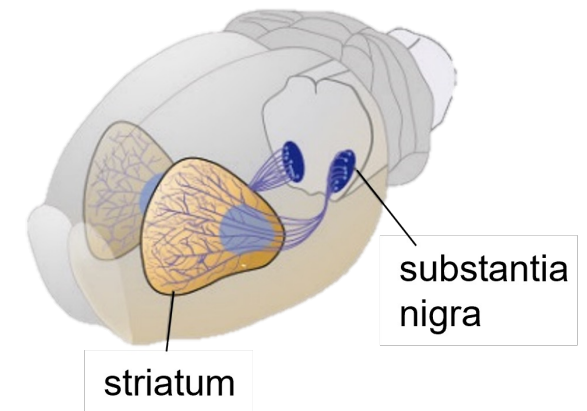
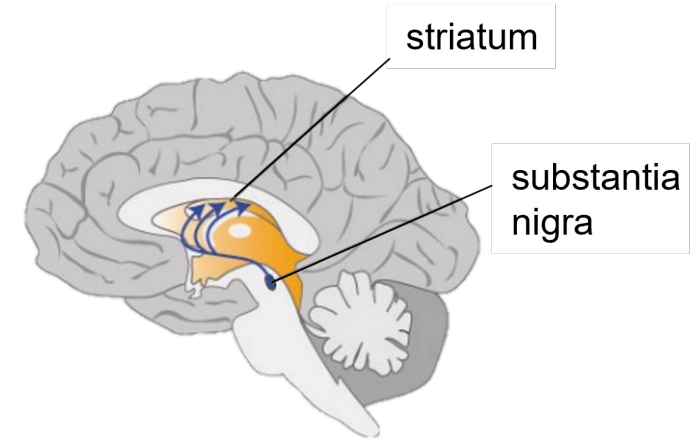
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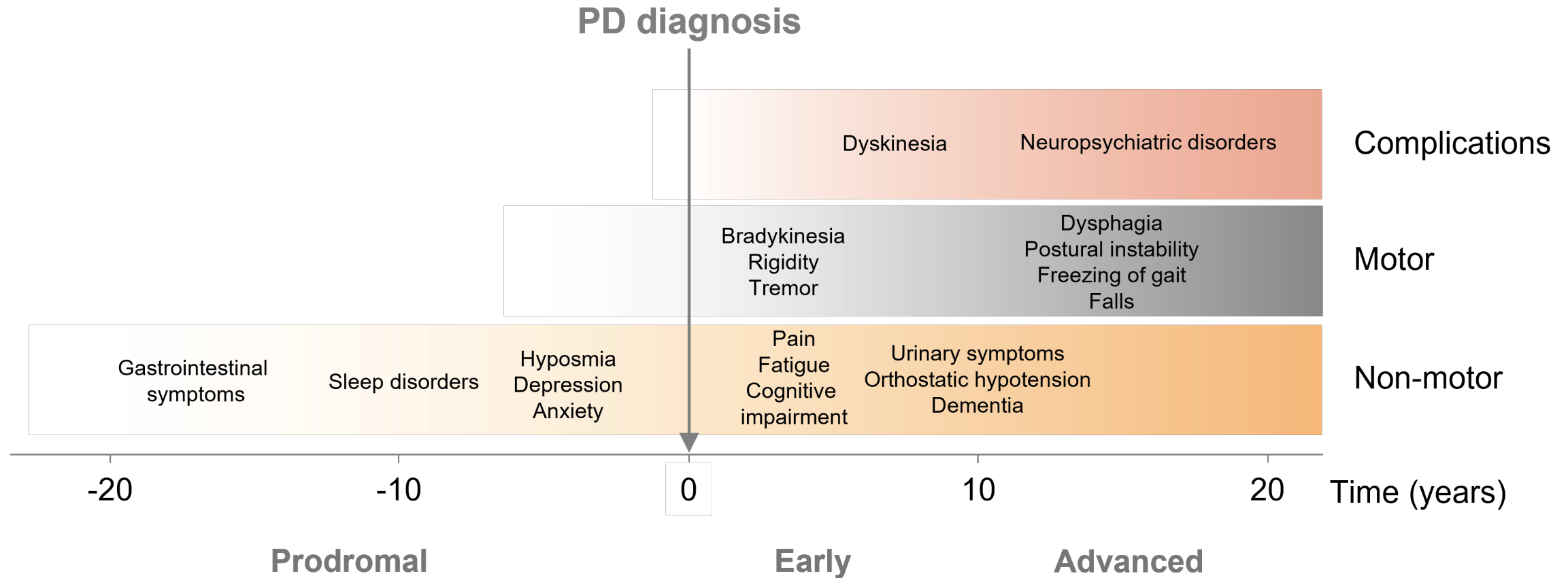
Parkinson's disease  
degenerative disorder  
nervous system that  
shaking, rigidity, slo  
what is tho

# Parkinson's disease

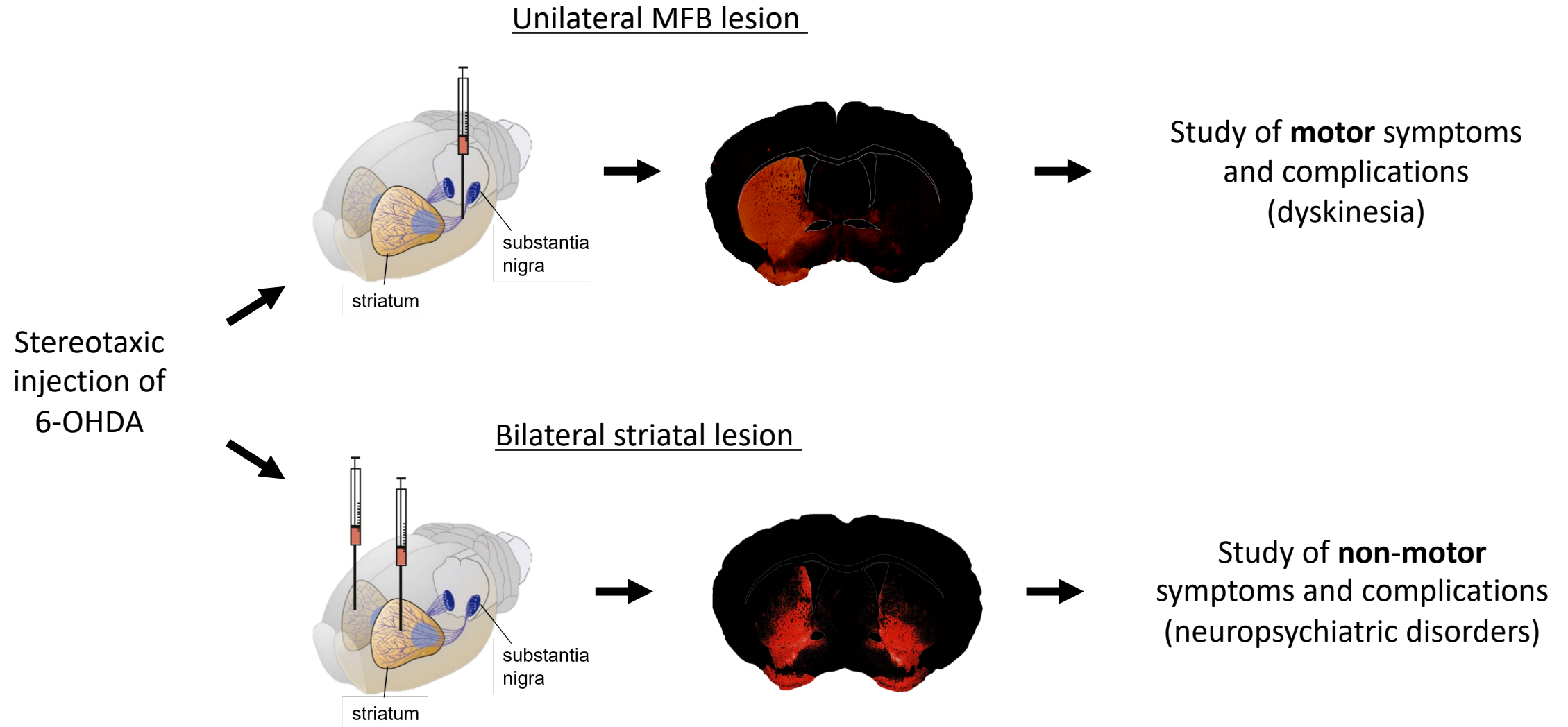
- Progressive neurodegenerative disorder (~10 million people worldwide)
- Characterized by the loss of dopaminergic neurons in the substantia nigra
- Less dopamine available in the basal ganglia
- Motor and non-motor symptoms
  - shaking, rigidity, slowness of movement
  - cognitive deficits, depression, anxiety



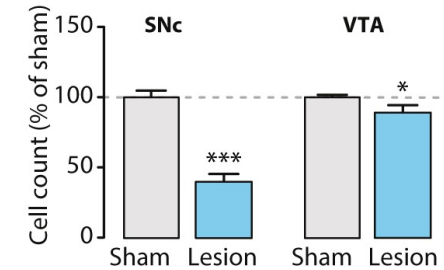
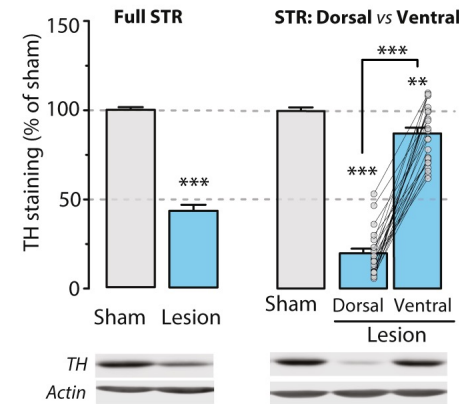
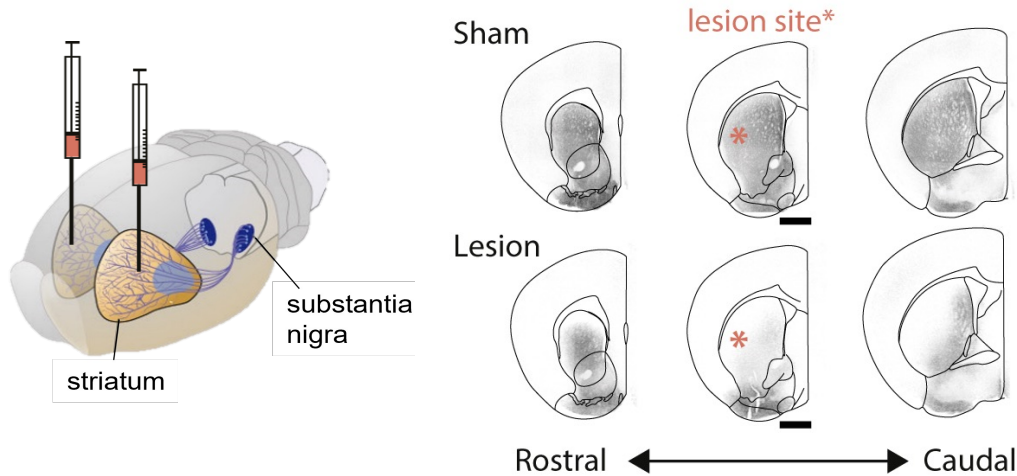
# Clinical symptoms and time course of PD progression



# The 6-hydroxydopamine mouse model of PD



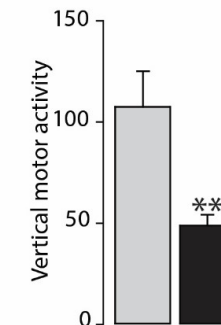
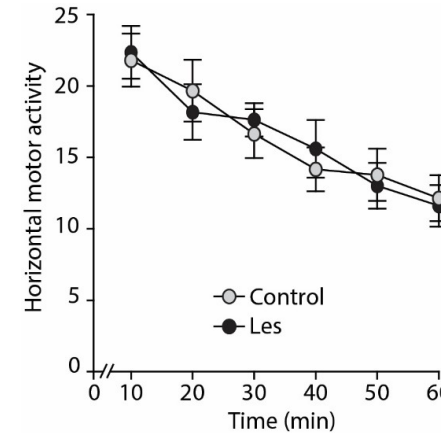
# A bilateral partial 6-OHDA mouse model of PD



~60% loss of TH in the striatum and substantia nigra

## Non-motor symptoms produced by 6-OHDA

- Depression- and anxiety like behavior
- Cognitive impairment
- Circadian and sleep disturbances
- Olfactory deficits



No effect on horizontal motor activity, but mild impairment of the hindlimbs

# 6-OHDA is associated with high post-surgical mortality



Neurobiology of Disease  
Volume 16, Issue 1, June 2004, Pages 110-123



A model of L-DOPA-induced dyskinesia in 6-hydroxydopamine lesioned mice: relation to motor and cellular parameters of nigrostriatal function ☆

M. Lundblad <sup>a,\*,</sup>, B. Picconi <sup>a, b,</sup>, H. Lindgren <sup>a,</sup>, M.A. Cenci <sup>a</sup>

30-82%  
mortality



Behavioural Brain Research  
Volume 284, 1 May 2015, Pages 196-206



Research report

A partial lesion model of Parkinson's disease in mice – Characterization of a 6-OHDA-induced medial forebrain bundle lesion

Jordi Boix <sup>a,</sup>, Thomas Padel <sup>a,</sup>, Gesine Paul <sup>a, b, \*</sup>

9-20%  
mortality



Behavioural Brain Research  
Volume 230, Issue 2, 1 May 2012, Pages 309-316



Research report

Sensorimotor assessment of the unilateral 6-hydroxydopamine mouse model of Parkinson's disease

Kelly E. Glajch <sup>a, \*</sup>, Sheila M. Fleming <sup>b,</sup>, D. James Surmeier <sup>a,</sup>, Pavel Osten <sup>a, 1</sup>

15%  
mortality



Journal of Neuroscience Methods  
Volume 197, Issue 2, 30 April 2011, Pages 193-208



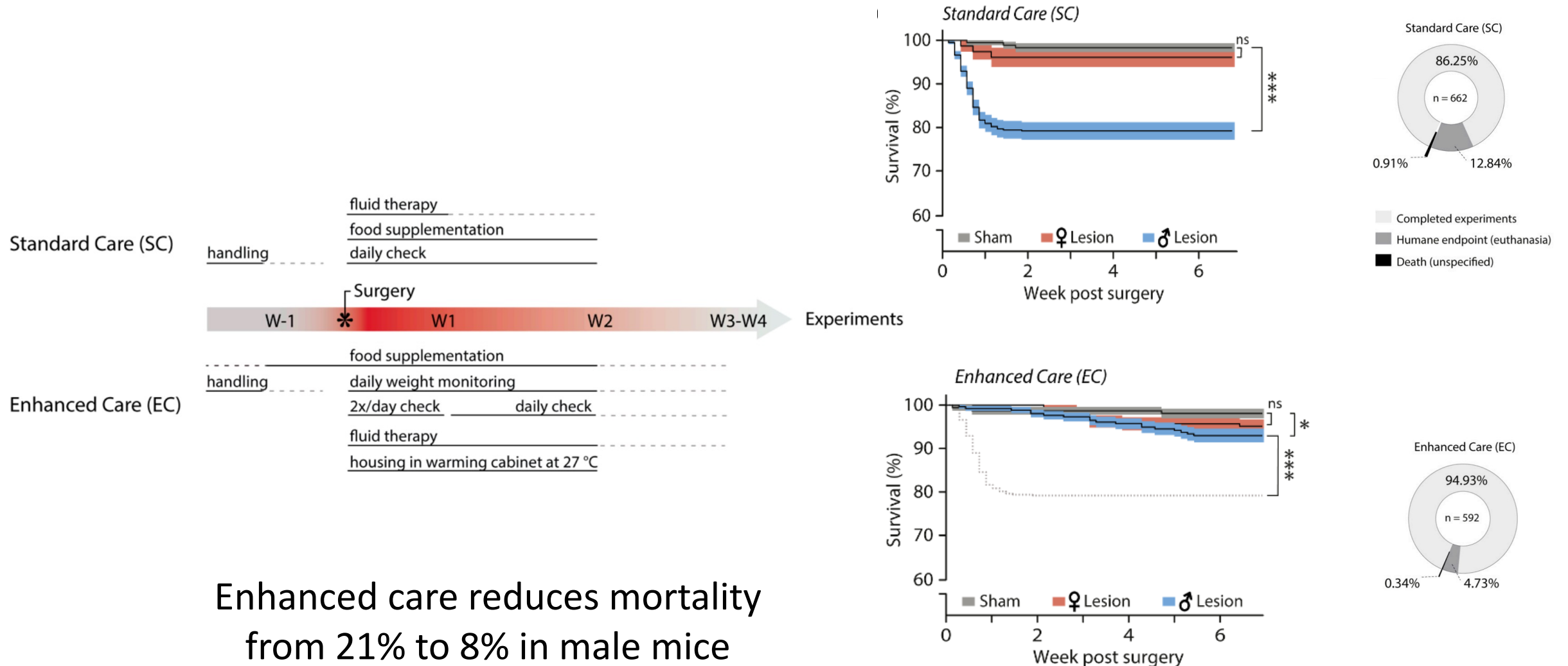
Generation of a model of L-DOPA-induced dyskinesia in two different mouse strains

Sherri L. Thiele <sup>a, 1, \*</sup>, Ruth Warre <sup>a, 1,</sup>, Charline S. Khademullah <sup>a,</sup>, Nusrat Fahana <sup>a,</sup>, Charlotte Lo <sup>a,</sup>, Doris Lam <sup>a,</sup>, Sheena Talwar <sup>a,</sup>, Tom H. Johnston <sup>b,</sup>, Jonathan M. Brotchie <sup>b,</sup>, Joanne E. Nash <sup>a, \*</sup>

18%  
mortality

Dehydration, Hypothermia, Aphagia/Adipsia, Urologic syndrome (males)

# Enhanced care protocol improves survival in male mice





# Perioperative health assessment and procedures

**Dehydration:** Subcutaneous or intraperitoneal fluid replacement therapy with warmed Lactated Ringer's solution, sterile saline (0.9%) or glucose (5%)

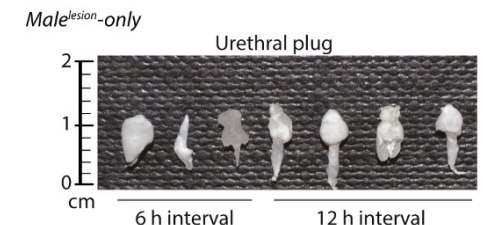
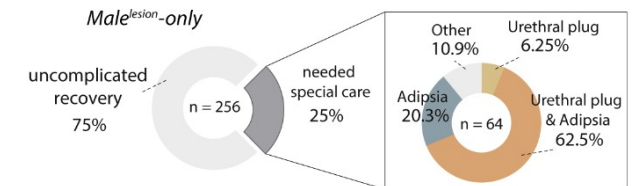
**Hypothermia:** Increase in ambient temperature of housing, cages placed in warming cabinet or on a thermal blanket, administration of warm fluids

**Aphagia/Adipsia:** Easy access to palatable food supplementation, hydration complemented with glucose solution

**Penile Prolapse (Paraphimosis):** Lubrication and placement of soft bedding to decrease swelling, hydration support

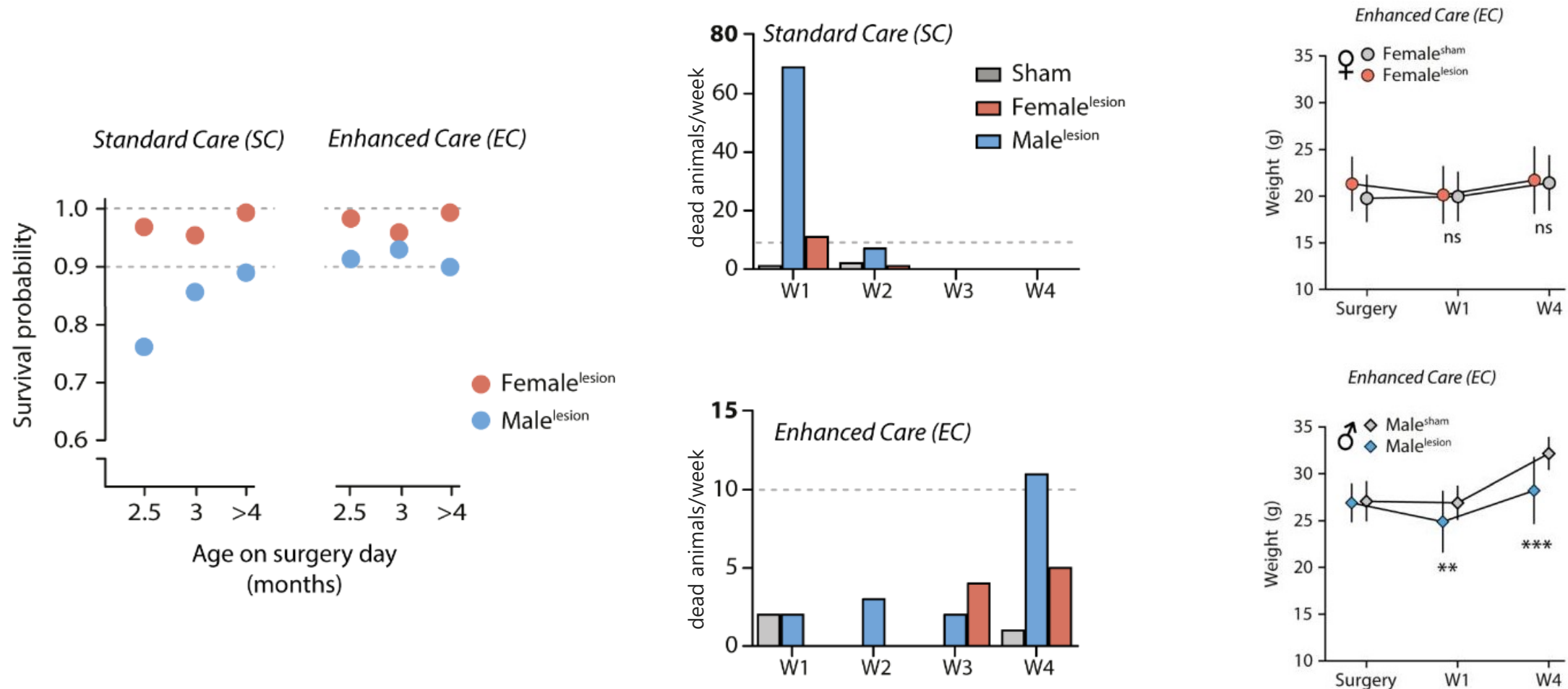
**Urethral Obstruction:** Removal of plug with lubrication and local analgesics or short anesthesia

**Pain or Distress:** Administration of buprenorphine and consideration of euthanasia based on humane endpoints





# Age and weight are predictors of survival in male mice



# Conclusions

- Survival rates of male and female mice differ significantly, with a much higher mortality among males
- An enhanced care protocol nearly eliminates mortality
- A standardized protocol improves reproducibility between research groups
- The bilateral model can be employed to study multiple non-motor symptoms



biomedicines



Article

## **A Guide to the Generation of a 6-Hydroxydopamine Mouse Model of Parkinson's Disease for the Study of Non-Motor Symptoms**

Débora Masini <sup>1,2</sup> , Carina Plewnia <sup>1</sup>, Maëlle Bertho <sup>1,2</sup>, Nicolas Scalbert <sup>1</sup>, Vittorio Caggiano <sup>1</sup>   
and Gilberto Fisone <sup>1,\*</sup>

Thank you  
for your  
attention!

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Katharina Eriksson



**KI-NIH PhD program**



# Perioperative health assessment and procedures

| Type   | Identification  | Treatment  | Reference |
|--|---|--|-----------|
| <b>General Health</b>                          | Appearance and activity pattern of the animal in home cage including interaction with environment, cage mates and nest building.  | Further hands-on examination.  | [54]      |
| <b>Body Condition</b>                          | Visual assessment of body shape and hands-on examination by passing the fingers over sacroiliac bones.  | Assess body condition score and further examine with attention to humane endpoints.  | [55]      |
| <b>Pain or Distress</b>                        | Mouse shows reluctance to move, failure to groom and unkempt appearance of fur coat, lack of appetite and thin body condition, loss of nest-building behavior, in some cases vocalization. Determined by mouse facial expression orbital tightening (squinting), nose bulging, cheek bulging, drawing of the ears back behind the head. | Administration of buprenorphine and consideration of euthanasia based on humane endpoints.   | [56,57]   |
| <b>Dehydration</b>                             | Weak appearance with recessed eyes and fuzzy fur. Skin turgor is reduced and pinched skin over the back remains tented.   | Subcutaneous or intraperitoneal fluid replacement therapy with warmed Lactated Ringer's solution, sterile saline (0.9%) or glucose (5%). | [47]      |
| <b>Hypothermia</b>                             | Animals are cool at touch and have a body temperature lower than 36.5 °C.   | Increase in ambient temperature of housing, cages placed in warming cabinet or on a thermal blanket, administration of warm fluids.      | [58]      |
| <b>Aphagia and Adipsia</b>                     | Measurement of food and water consumption. Body weight monitoring.  | Easy access to palatable food supplementation, hydration complemented with glucose solution.   | [59,60]   |
| <b>Penile Prolapse (Paraphimosis) *</b>        | Swollen, distended and reddened penis.  | Lubrication and placement of soft bedding to decrease swelling, hydration support.   | [49,54]   |
| <b>Urethral Obstruction (urethral plugs) *</b> | Firm, cream-colored proteinaceous material observed at tip of penis.  | Remove plug with lubrication and local analgesics or short anesthesia.   | [61,62]   |

\* urologic syndrome [63].

# Motor and non-motor behavioral profile

|           | Domain                   | Test   | Phenotype  | Pharmacological Intervention   | References |
|-----------|--------------------------|--|--|--|------------|
| Motor     | Spontaneous locomotion   | Open field   | No effect  | -  | [40,41]    |
|           |                          | Novel home cage  | No effect  | -  | [21]       |
|           | Vertical activity        | Cylinder   | Reduced rearing  | -  | [21]       |
|           | Gait pattern             | Treadmill (ventral plane videography)                                    | Impaired hindlimb gait dynamics  | -  | [40]       |
| Affective | Depression               | Porsolt forced swim  | Increased immobility   | L-DOPA =<br>Pramipexole +<br>Reboxetine +<br>Rapamycin +                   | [40,41]    |
|           |                          | Tail suspension  | Increased immobility   | -  | [40]       |
|           | Anxiety                  | Open field center zone   | Center avoidance (thigmotaxis)   | Rapamycin +  | [40,41]    |
|           |                          | Elevated plus maze   | Reduced exploration of open arms   | L-DOPA =<br>Pramipexole +<br>Reboxetine +<br>Thioperamide =<br>Rapamycin + | [39–41]    |
|           |                          | Light-dark box   | Increased latency to enter the bright chamber                                  | Thioperamide =   | [39]       |
| Cognitive | Novelty detection        | Novel object recognition   | Deficit in long-term recognition memory  | L-DOPA +<br>Pramipexole =<br>Thioperamide +<br>Rapamycin +                 | [21,39,41] |
| Circadian | Circadian activity       | Circadian activity rhythm in social environment                          | Reduced activity during the active period of the 24 h cycle                    | Thioperamide +   | [39]       |
|           |                          | Endogenous activity cycle in social environment during constant darkness | Disruption of the endogenous circadian rhythm (activity pattern fragmentation) | -  | [39]       |
| Olfactory | Olfactory discrimination | Olfactory habituation/dishabituation                                     | Deficit of olfactory discrimination  | -  | [40]       |

+ indicate recovery; = lack of effect; - not investigated.