COGNITIVE DYSFUNCTION

Cognitive dysfunction is a common issue in Parkinson's disease (PD). Symptoms include impairments in working memory, learning, attention, cognitive flexibility, and social cognition. Cognitive dysfunction is found in 15-40% of patients, generally presenting as mild cognitive impairment at time of diagnosis and progressing to PD dementia in the decades following. The cognitive issues have been linked to dopaminergic, cholinergic, and noradrenergic circuits. Below you will find a summary of models that display cognitive dysfunction. Please note, this list is not comprehensive.

MPTP MODEL

- Description: MPTP is a toxin administered to mice that acts as a mitochondrial complex I inhibitor with high affinity for the dopamine transporter, leading to bilateral degeneration of dopaminergic neurons. There are multiple different dosing paradigms for MPTP resulting in different pathology, but sub-acute (1 administration daily for 5-7 days) and chronic (1 administration daily for 14-28 days) dosing are more often employed for cognitive phenotypes. These paradigms result in delayed nigrostriatal degeneration with accompanying aSyn pathology and neuroinflammation. Motor deficits are variable in these paradigms. The following cognitive deficits have been reported: short-term spatial learning, memory acquisition and retention, working memory, short-term social and object recognition memory, short-term inhibitory avoidance memory, contextual memory, episodic memory, and visuospatial attention (Morris water maze, novel object recognition, Barnes maze, Y-maze, T-maze, etc). Other non-motor symptoms like olfactory deficits, anxiety, depression, and GI dysfunction have also been reported.
- Recommended Use: The ability to administer MPTP through peripheral injection is a benefit of this model as it avoids the need for stereotaxic surgery. However, it is important to note that the MPTP model does not necessarily reflect the pathogenic mechanisms of PD and may fail to recapitulate changes in other pathways that are important in human disease. Note that mice and primates (including humans), but not rats, efficiently convert MPTP to its active metabolite, MPP+. Thus, rats are not recommended for use with this model and great care is imperative for the safe handling and disposal of MPTP to avoid permanent MPTP-induced parkinsonism in humans.
- Helpful Resources:
  - CRO Recommendations for the MPTP Model - Atuka, Charles River Labs, Psychogenics
  - Example MPTP Model Behavior Meta-Analysis - https://pubmed.ncbi.nlm.nih.gov/35872230/

6-OHDA MODEL

- Description: 6-OHDA is a mitochondrial complex I and IV inhibitor that is typically administered through stereotaxic injection into the rat brain via unilateral injection to the striatum, substantia nigra, or medial forebrain bundle (MFB). The route of administration affects pathology – nigral or MFB injection will result in loss of nigral dopamine neurons followed by degeneration of striatal terminals within days, whereas striatal injection results in degeneration of striatal dopamine terminals followed by loss of nigral dopamine neurons in weeks. Regardless of injected structure, robust unilateral motor deficits are present and neuroinflammation is observed. aSyn pathology, however, is not present in this model. Cognitive deficits in the 6-OHDA model include long-term spatial learning, long-term object recognition, visuospatial memory, long- and short-term working memory, attention, episodic memory, and short-term social memory (Morris water maze, novel object recognition, Barnes maze, Y-maze, T-maze, etc).
- Recommended Use: The robust degeneration and motor deficits make this an attractive model. However, it is important to note that the 6-OHDA model does not necessarily reflect the pathogenic mechanisms of PD and may fail to recapitulate changes in other pathways that are important in human disease (such as aSyn pathology). For cognitive deficits, a bilateral injection is preferred over unilateral.
- Helpful Resources:
  - CRO Recommendations for the 6-OHDA Model - Atuka, Charles River Labs, Psychogenics
  - Example 6-OHDA Model Review - https://link.springer.com/article/10.1007/BF03033565

ICON KEY

Protein Expression Level			Protein/Gene Species		Mutation	Pathology				
Endogenous Expression	Over-expression	Knockout	Human	Rodent	Mutant	Nigrostriatal Degeneration	α-Synuclein Pathology	Inflammation	Motor Impairments	Cognitive Impairments

THY1 ASYN MASLIAH "LINE 61"

- Description: This transgenic mouse model overexpresses human wildtype aSyn under the Thy1 promotor. The model displays robust aSyn pathology, primarily in the cortex and limbic system. Loss of dopaminergic terminals in the striatum and inflammation occur at late timepoints but the line does not develop loss of substantia nigra neurons. Motor deficits are pronounced and begin in the first few months of life, progressing as the mouse ages. Cognitive deficits begin at 4-6 months with recognition and spatial memory (Y-maze, novel object recognition, etc) and continue with impairments in emotional learning, social cognition, and fear conditioning at 7-8 months. The model also exhibits other non-motor impairments in olfaction, sleep, and GI dysfunction.
- Recommended Use: Pathology in this model is driven by high levels of aSyn overexpression (~1.5-3.5 fold). The model is recommended for researchers who want a transgenic mouse to study synuclein pathology and resulting nonmotor and motor deficits (although the motor deficits are not driven by nigral degeneration). The model is not ideal for those who want fast timelines.
- Helpful Resources:
  - Model information at Alzforum and JPND
  - CRO Recommendations – Psychogenics, QPS Austria
  - Commercial Availability – Not available. A similar line is available at JAX (#17682) but does not display the phenotypes of Line 61.

"M83" HUMAN A53T ASYN MOUSE

- Description: This transgenic mouse model overexpresses human A53T mutant aSyn under the prion promotor. Homozygous mice display robust aSyn pathology and motor dysfunction (paralysis). However, the dopaminergic neurons of the substantia nigra do not display aSyn pathology and do not degenerate. Therefore, motor dysfunction is thought to be caused by aSyn pathology in the spinal cord. Homozygous M83 mice display cognitive impairments in spatial and working memory (Morris water maze, Y-maze, Barnes maze) at 6 months of age
- Recommended Use: Pathology in homozygous mice is driven by high levels of aSyn overexpression (~4.5-fold in cortex and 28-fold in spinal cord). The model is recommended for researchers who want a transgenic mouse to study synuclein pathology and motor deficits (although the deficits are not driven by nigral cell loss). It is important to consider that the A53T aSyn mutation is very rare and does not model idiopathic PD.
- Helpful Resources:
  - Model information at JPND
  - Commercial Availability – this line is available at JAX (#004479)

LEE G2-3 Prp-A53T *SNCA* MOUSE

- Description: This line displays overexpression of human A53T aSyn in brain and peripheral tissues. Motor deficits appear around 8-10 months of age and culminate in paralysis, but this is due to motor neuron loss rather than loss of dopamine neurons in the substantia nigra. When motor symptoms appear, robust astrogliosis and aSyn pathology are observed in the midbrain, brainstem, and spinal cord. Constipation and aSyn pathology in the colon are present at 3 months of age, prior to motor dysfunction and brain pathology. Cognitive impairments in spatial memory have also been reported in the line starting at 6 months of age (Morris water maze and Barnes maze).
- Recommended Use: Pathology in this model is driven by high levels of aSyn overexpression. As this model does not display nigrostriatal degeneration, it should not be used to evaluate that system.
- Helpful Resources:
  - Summary of Line Phenotypes – JPND Model Summary
  - Commercial Availability – This model is available at JAX (JAX #006823).

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GBA1 D409V KI MOUSE

- Description: The D409V mutation is not a PD-linked mutation but was chosen for use in a rodent model because it results in substantial reduction of GCase activity. In this model, a D409V point mutation in the mouse *Gba1* gene leads to dramatic reduction in GCase activity and accumulation of GlcSph (but not GlcCer) substrates. There are two different *GBA1* D409V KI mouse lines in the field. The nigrostriatal system remains intact in both lines and motor deficits are not observed. Differences exist in GCase express and extent of hippocampal pathology:
  - Grabowski Line - In the homozygous line GCase activity is reduced 75% with GlcSph increase ~4-fold in brain. Homozygous mice display robust aSyn pathology and inflammation in the hippocampus at 6 months of age with impairments in recognition and fear memory (novel object recognition and fear conditioning).
  - MJFF Line - In this homozygous line, brain GCase activity is reduced 90% and brain GlcSph increases ~12-fold. Hippocampal pathology (increased aSyn and inflammation) is observed at 12 months of age in heterozygous mice with corresponding impairments in spatial and working memory (Morris water maze, Y-maze).
- Recommended Use: This model is recommended for researchers who are interested in a model with constitutive, substantial GCase activity reduction. It is a useful model for studying the hippocampal/memory-associated changes resulting from decreased GCase activity. It is not suited for studies into nigrostriatal pathology.
- Helpful Resources:
  - Commercial Availability
    - The Grabowski line is not commercially available. The MJFF line is available at JAX (JAX #019106).
  - Characterization of the Grabowski line: https://pubmed.ncbi.nlm.nih.gov/21730160/
  - Hippocampal evaluation of the MJFF line: https://pubmed.ncbi.nlm.nih.gov/31299418/

ICON KEY

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