The Marmoset Monkey as Model for Neurological Disorders

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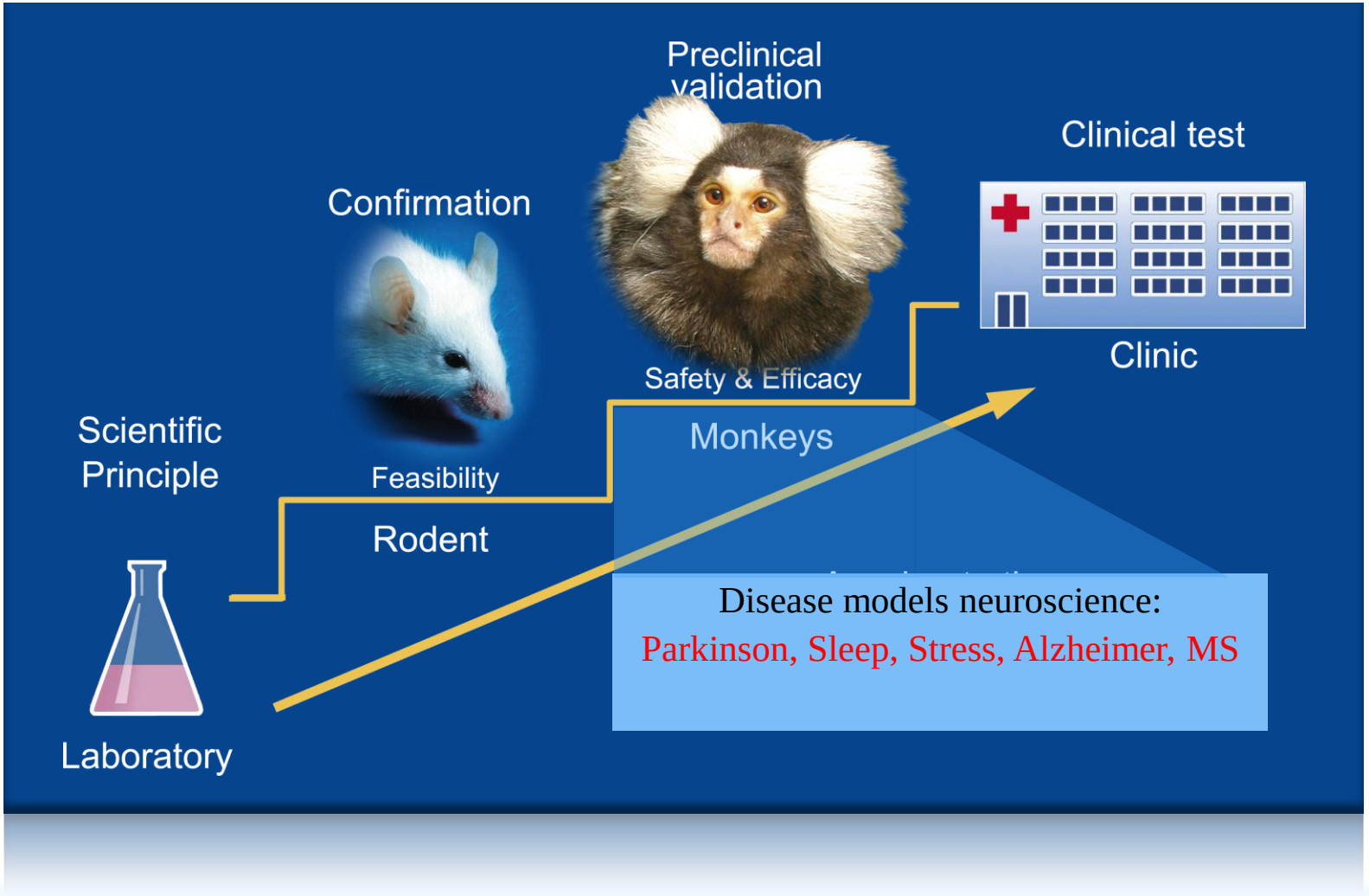
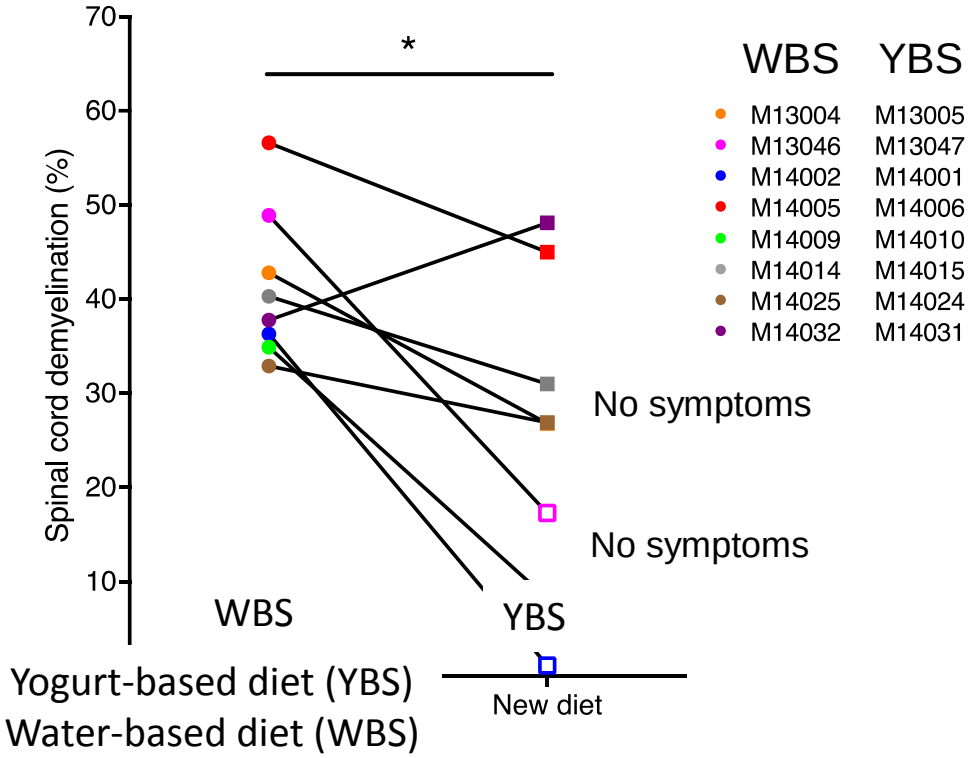
Committed to health research and alternatives

From Laboratory to Clinic



MS Models: rhMOG induced models

Reduced spinal cord demyelination in EAE marmoset model with different diets

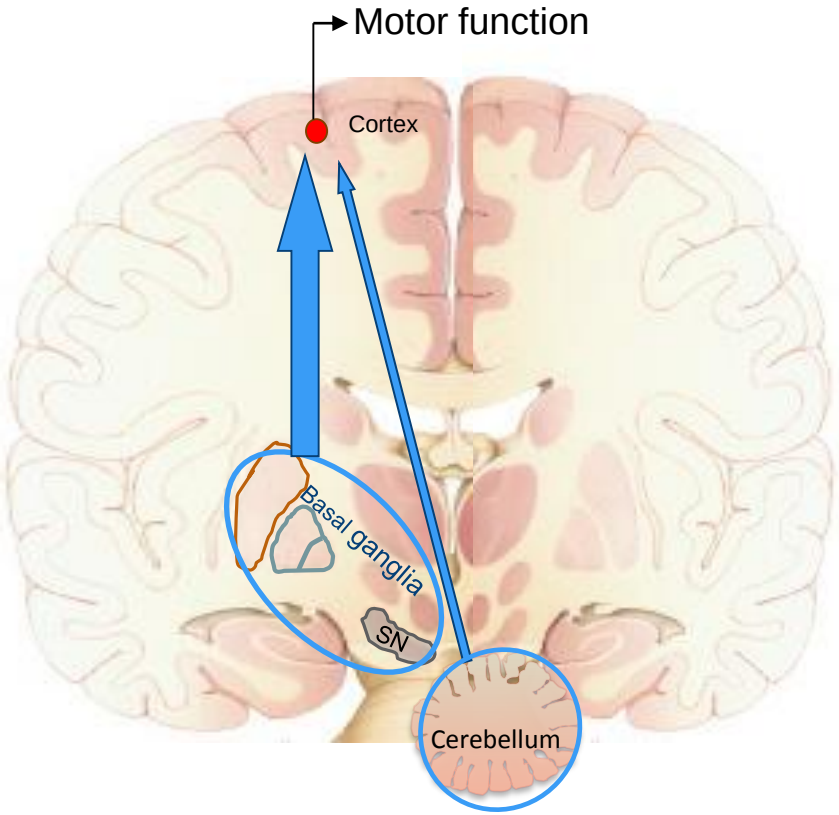


Kap YS et al, JI October 2018

Parkinson's disease (PD), a progressive disease of the CNS

Motor disorder caused by degeneration of the dopamine neurons in the substantia nigra.

Symptoms appear after already 60% of the dopamine neurons have disappeared.



Normal motor coordination

Parkinson's disease (PD), a progressive disease of the CNS

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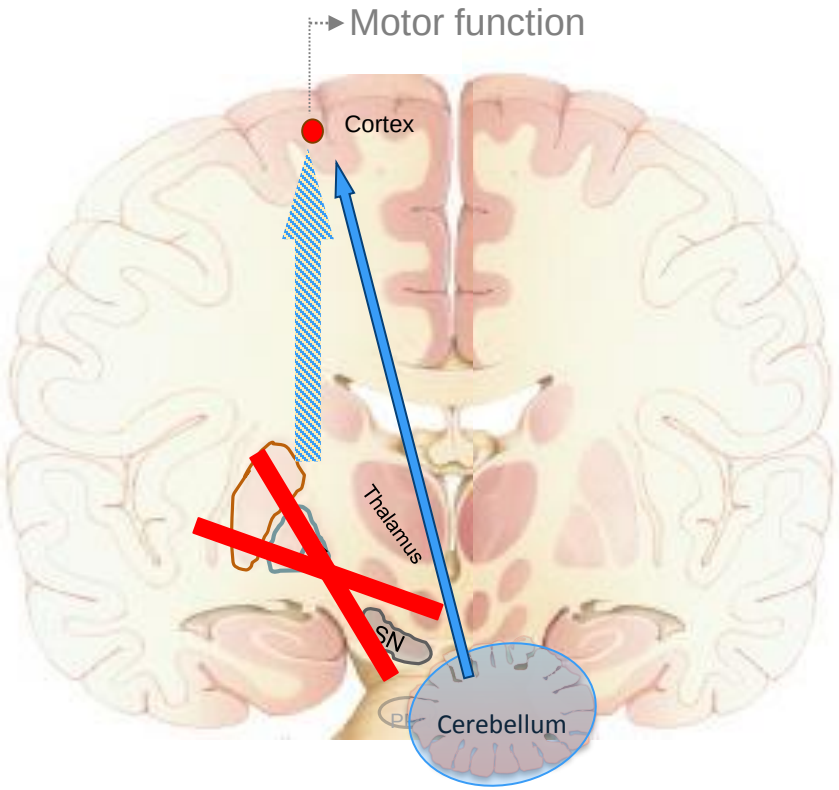


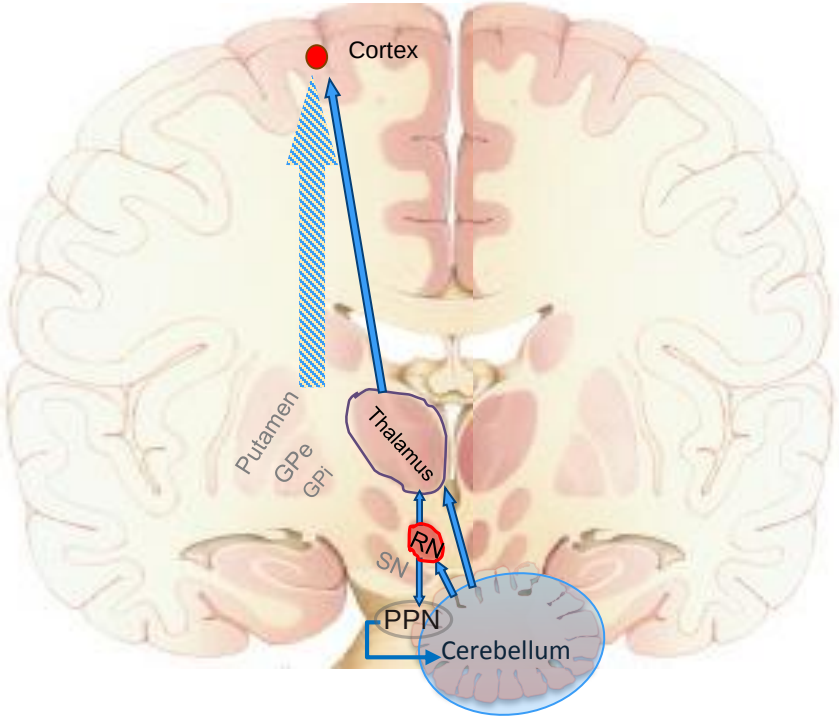
Motor disorder
caused by degeneration of dopamine neurons in the substantia nigra

Dysfunctional
Striato-thalamo-cortical
pathway

Parkinson's disease (PD), a progressive disease of the CNS

This delay is caused by compensatory pathways in the brain,
in which the red nucleus (RN) is involved.
This pathway is only active in human during the crawling period.

In rodents motor coordination is still organized by this pathway.

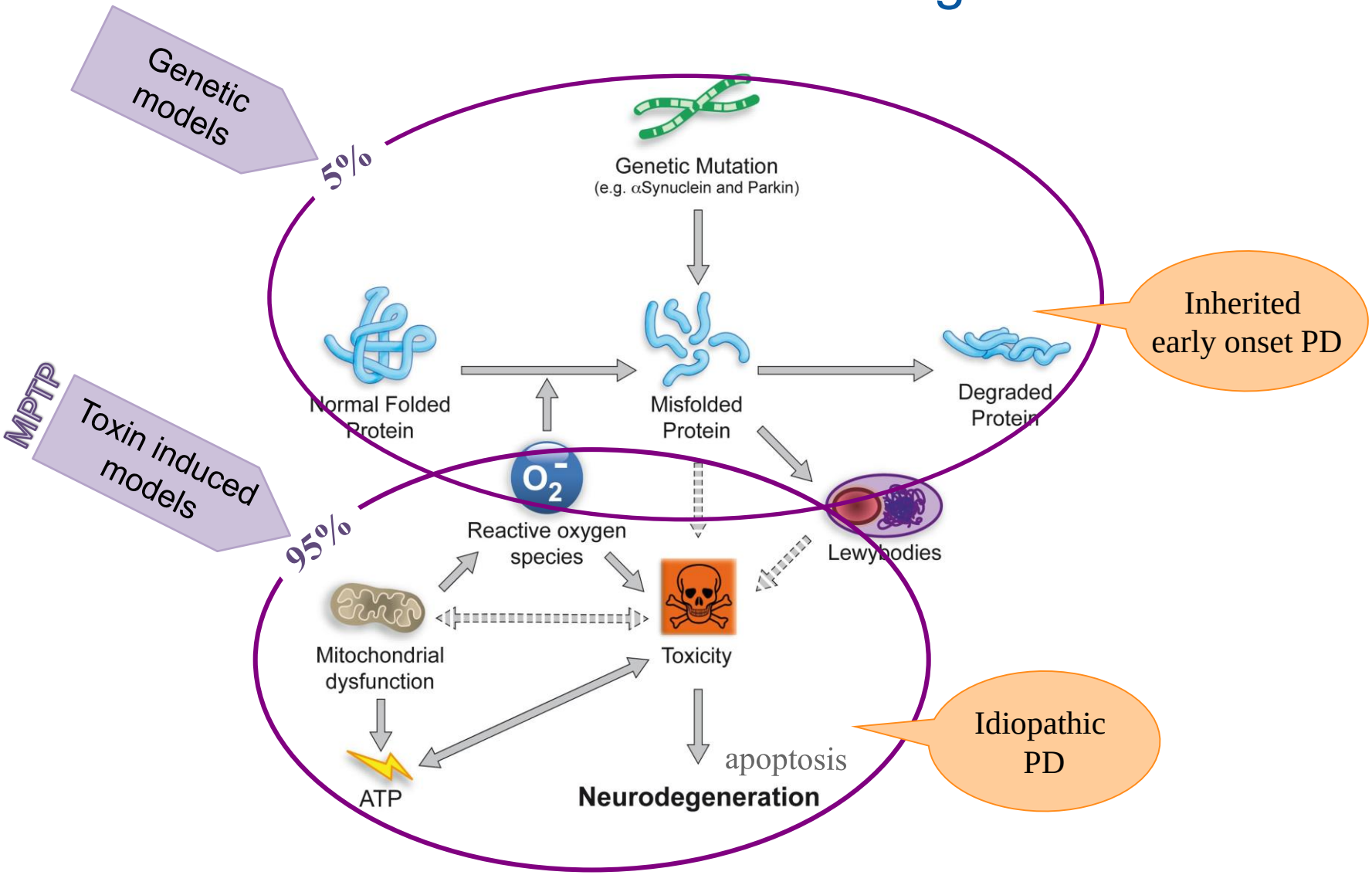


Pre-symptomatic compensatory mechanism

Cerebello-rubro-thalamo-cortical pathway

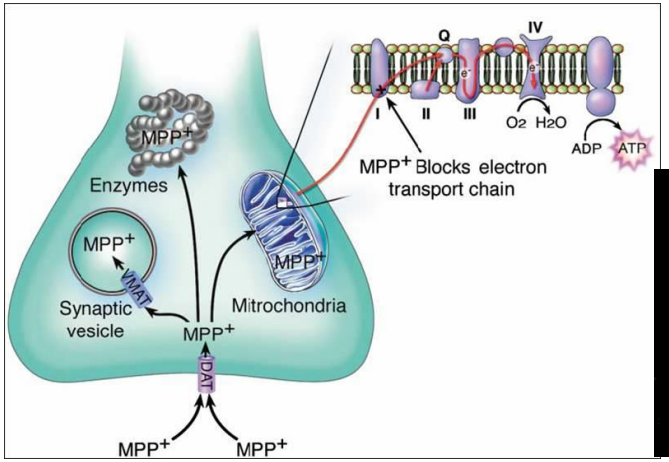
Appel-Cresswell, et al. (2010)
Curr. Opin. Neurol. **23(4)**, 407-12

Parkinson's disease: Pathogenesis

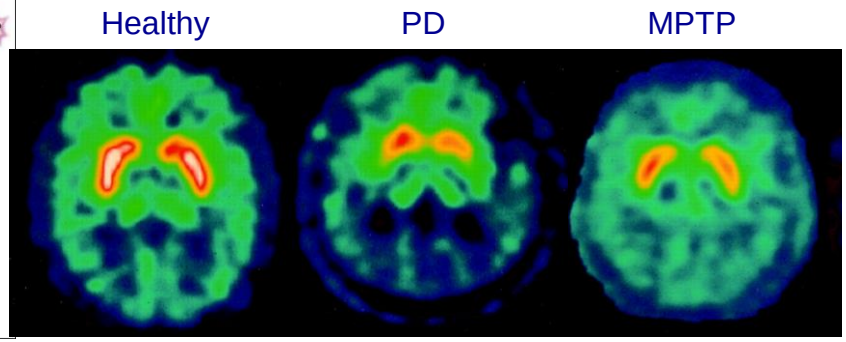


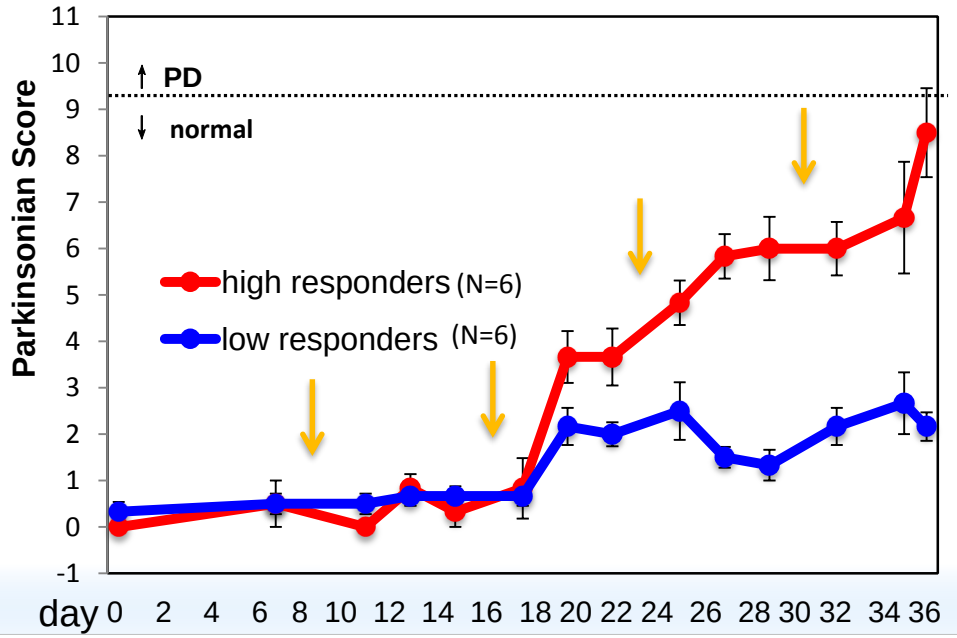
MPTP PD model

byproduct in the synthesis of heroin



Clearly linked to a form of human parkinsonism: indistinguishable from idiopathic PD





Red nucleus size	
High	96 ± 5%
Low	127 ± 9%

In PD patients the RN is increased by 32%.

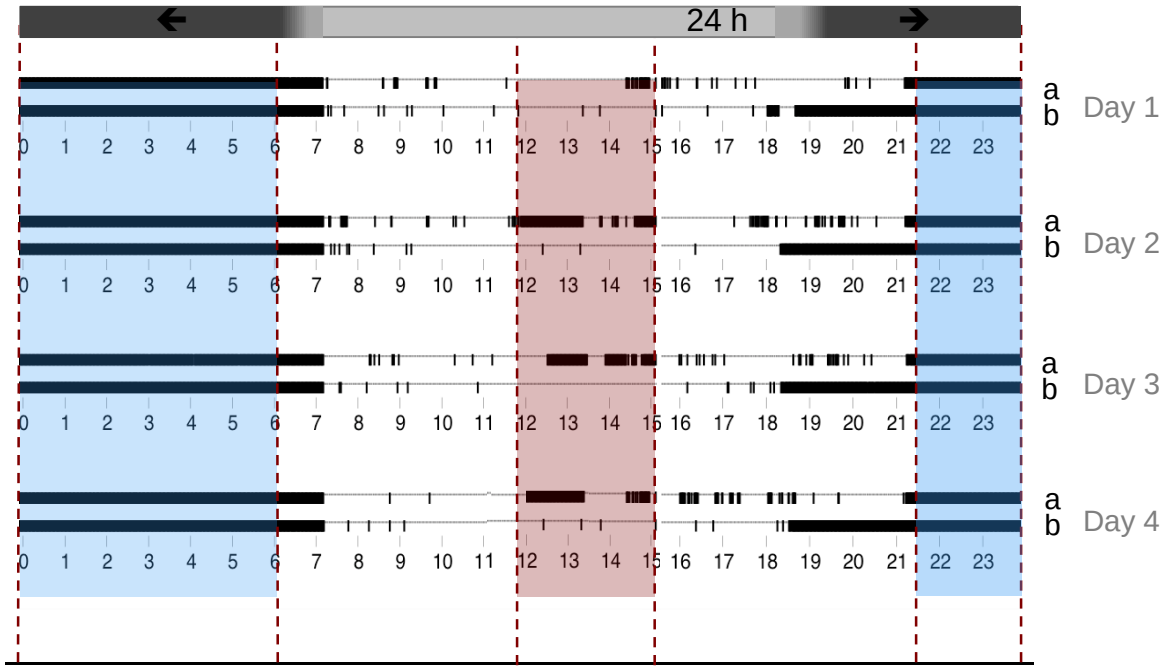
This suggests increased activity to compensate for the dysfunctional striato-thalamo-cortical pathway.

Colpan & Slavin 2010 *Parkins. Relat Disord.*

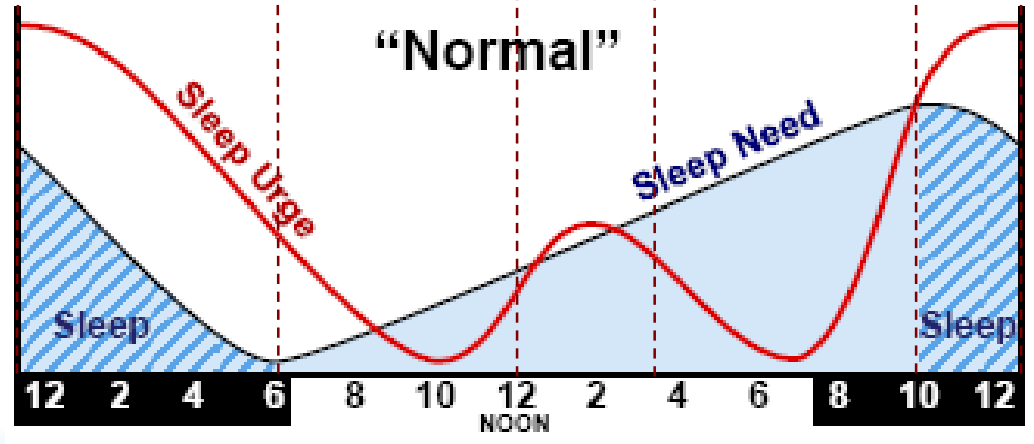
Sleep & Circadian rhythm: marker for prodromal stage of neurological disorders

Marmoset

Telemetric 24-h
home cage activity

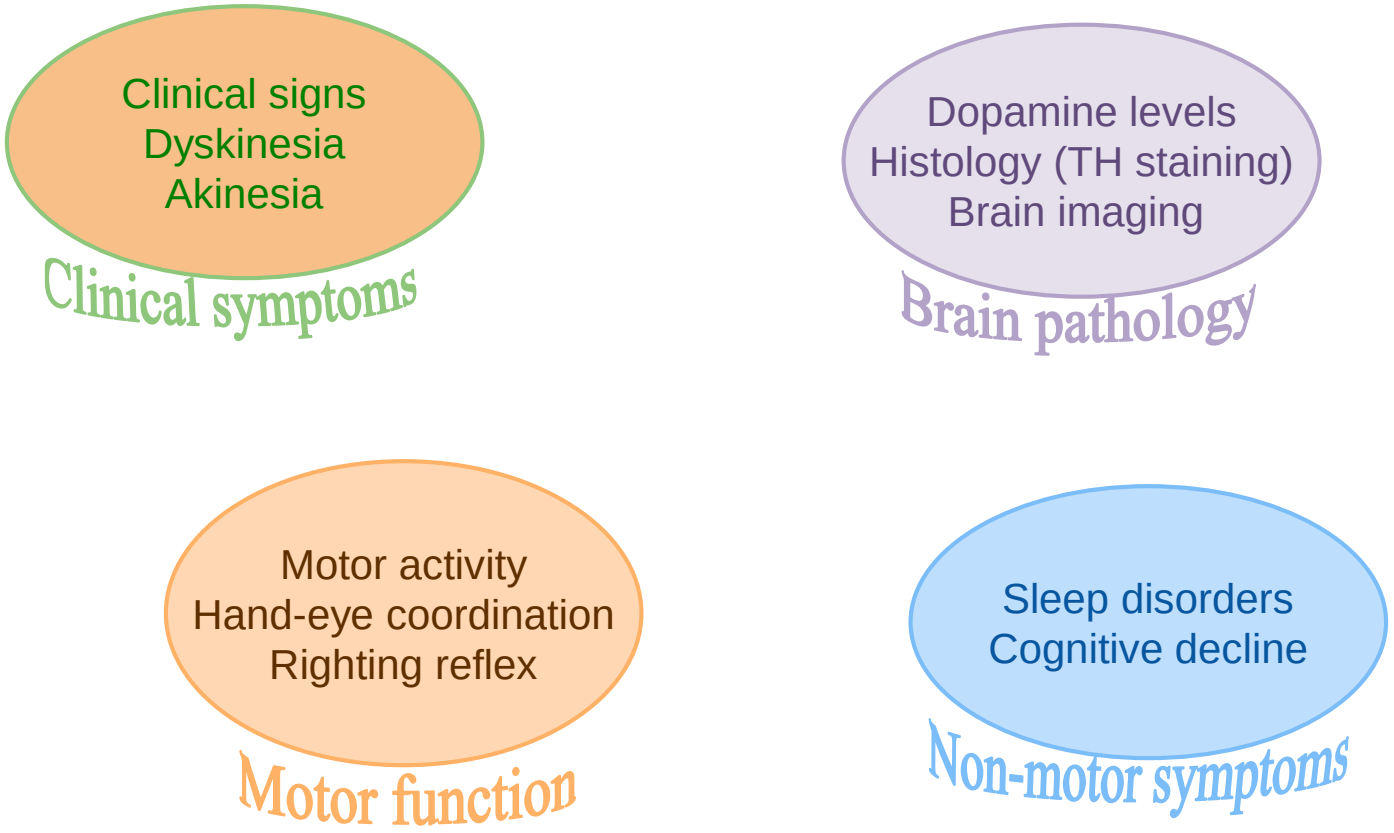


Human



Test Methods

Non-invasive behavioral test, telemetric neurophysiology and post-mortem assays to quantify effects of the disease progression and of a therapeutic intervention

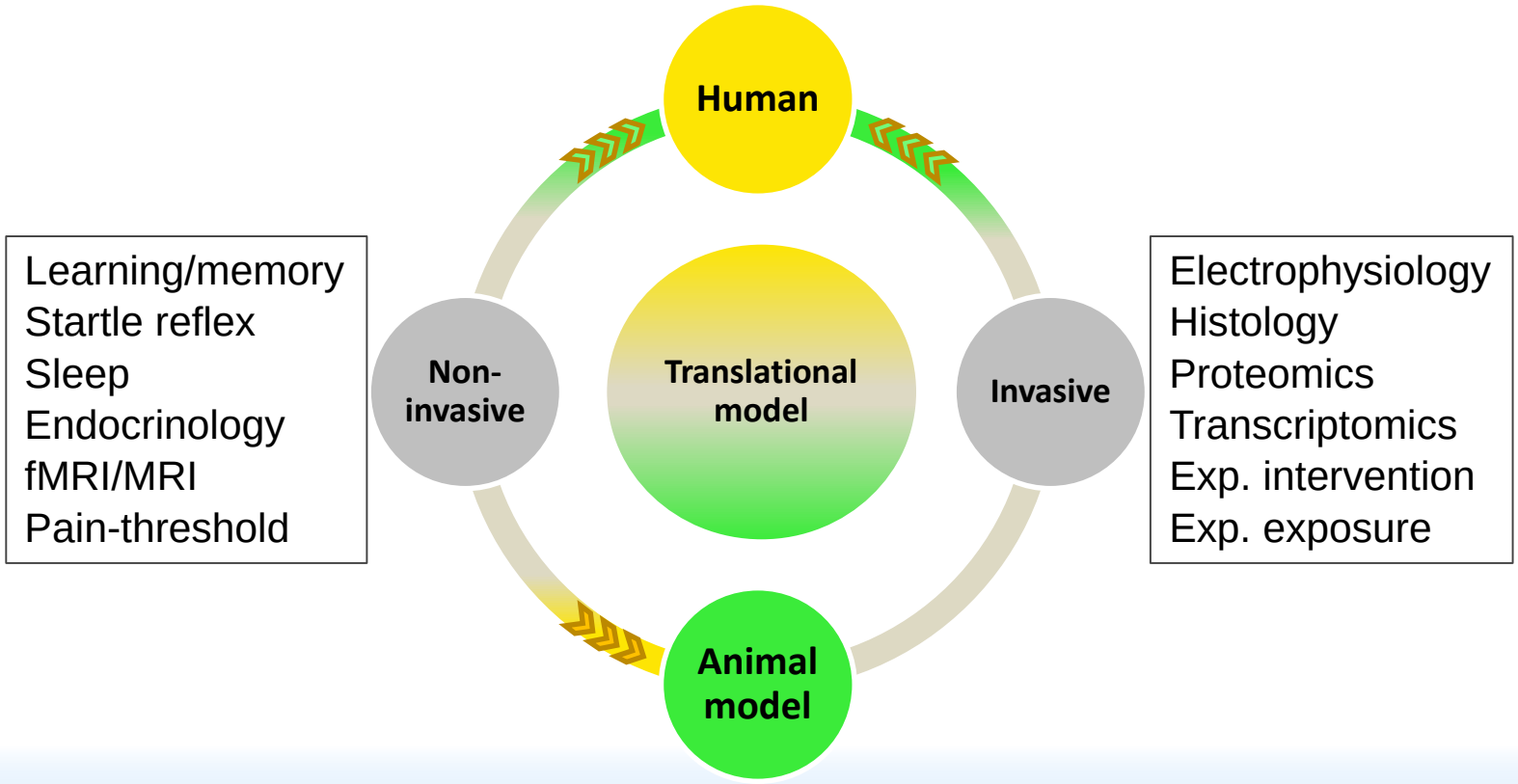


Stress related emotional memory

Retrospective studies in humans are difficult to perform and

most studies fail to control for stress event, limiting the results of these studies.

⇒ Controlled animal research is needed that optimally uses cross-species characteristics by integration of the mechanistic disturbance with symptoms, which can be applied to animals and humans alike.



Why the marmoset monkey for stress research

Anatomical

- The structural plasticity in the amygdala in the marmoset is in line with other non-human primates and humans (Marlatt et al., 2011).
- The evolutionary anatomical and functional organization of the prefrontal cortex is well conserved in primate species including the marmoset monkey.

Behavioural and hormonal

- Monkeys are diurnal and the sleep stages are similar to those in humans;
  Rodents have a fragmented sleep during the day.
- Sleep affects hormones involved in the circadian rhythm, such as cortisol.
  In human and marmoset cortisol increases in the morning, in rodents in the evening.
- In contrast to this fluctuation, melatonin levels in all species increase in the evening, which is related to sleepiness in humans and monkeys and to wakefulness in rodents.

Marmoset for stress research

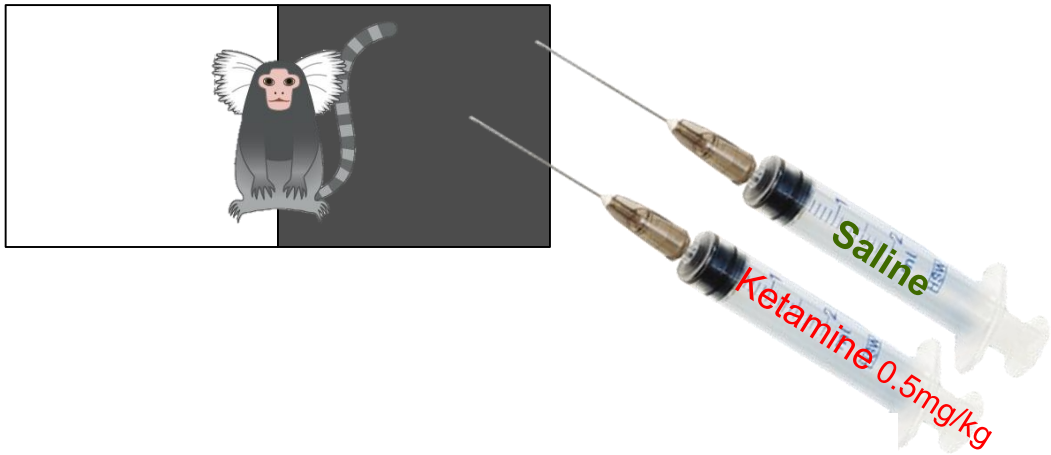
Week 1
Consolidation

Physical stress paradigms makes use of the classical conditioning procedure:

- it relates an aversive stimulus to an environment factor
- (shock-context with situational memories)
- Such as the passive avoidance test

The time of stress exposure is known and the time of treatment can be well defined.

Week 2
Re-consolidation



Amyloid-beta model for AD in the marmoset

Amyloidosis is inducible in the marmoset and activated by inflammation

Marmosets spontaneously develop Aβ aggregates during aging with a distribution and chemical composition similar to those found in human

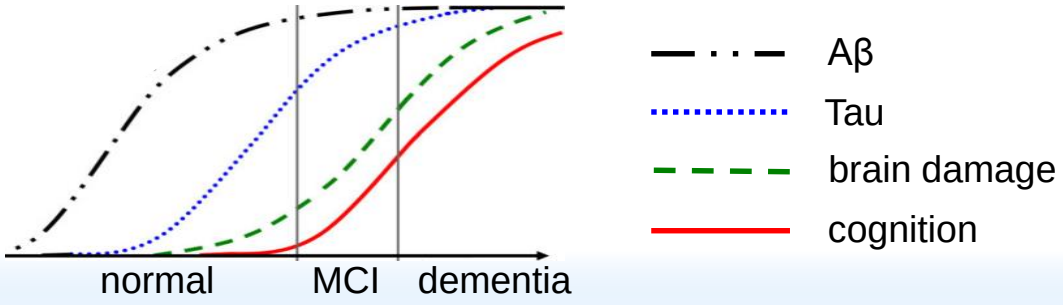
β-amyloidosis is a transmissible process from patients to primates and the addition accelerate the process of amyloidosis in primates

(*Baker et al. 1993; Maclean et al.2000; Ridley et al.2006; Geula et al.2002*).

High levels of IL-1β, IL-6 & TNF-α are found in brains of PD and AD patients.

Anti-inflammatory medication reduces the risk of AD.

- NSAIDs in Rheumatoid arthritis patients: lower incidence of AD (Dinkel, K. et al. (2004) PNAS).
- Ibuprofen suppresses plaque pathology in an AD mouse model (Lim GP et al , J Neurosci. 2000).

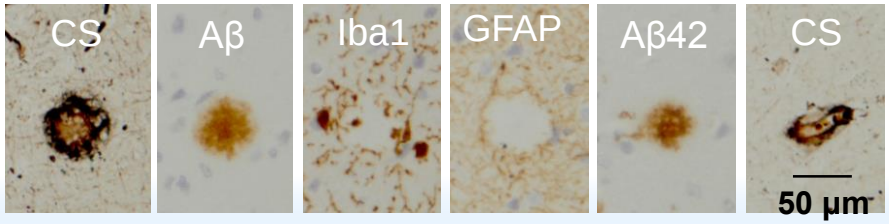


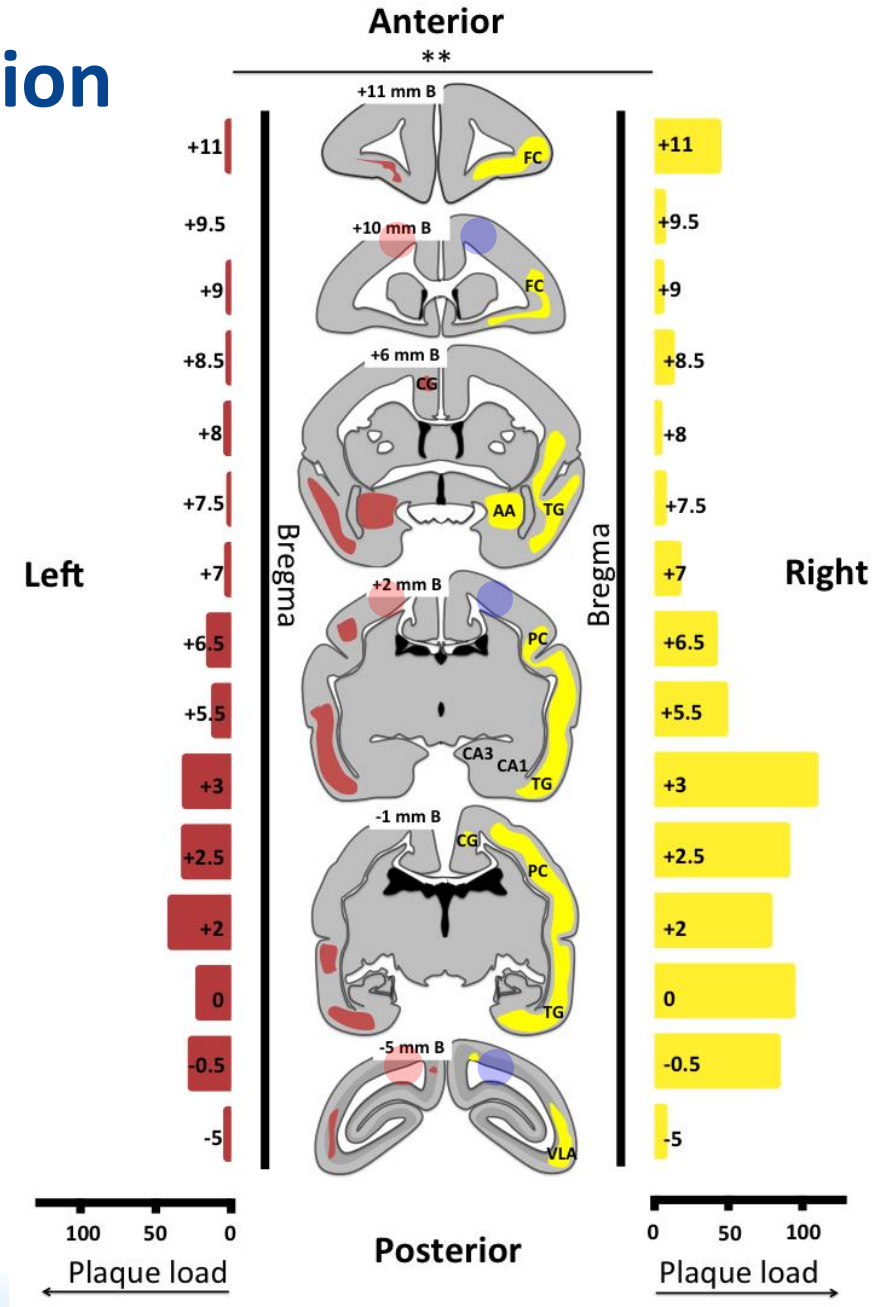
Induction

IS	Substance injected
1	LPS/PBS
2	LPS/PBS
3	LPS/PBS
4	human Aβ + LPS/PBS
5	artificial Aβ + LPS/PBS
6	artificial Aβ + LPS/PBS

2/3 of the LPS+Aβ injected marmosets developped plaque progression.

None of de PBS+Aβ injected marmosets showed any plaques in a 5-month period.





Conclusions

Brain Related Disorders can be Induced or appears Spontaneously in the Marmoset monkey.

- ✓ MPTP model for Parkinson; A-beta model for Alzheimer; stress model
- ✓ Similarity of circadian rhythm and sleep architecture between marmosets and human

Non-invasive (behavioural) Test Methods are Available.

- ✓ Activity, motor function, cognition, clinical signs
- ✓ Telemetry gives the opportunity to measure EEG in free moving animals preventing stress caused by immobilization due to wires
- ✓ Disease progression or the effect of a treatment can be followed during a long period of time in the same animal strengthen the 3-Rs policy