Effects of α-synuclein levels on cerebral synaptic function: Validation of a novel PET radioligand for the early diagnosis of Parkinson's disease

Tarragon E[1], Ferrara A[2], Tirelli E[2], Bahri M.A[1], Plenevaux A[1], Garraux G[1]

[1]Centre de Recherches du Cyclotron & GIGA-neurosciences, Université de Liège

[2]Dépt. de Psychologie: cognition et comportament, Université de Liège

INTRODUCTION

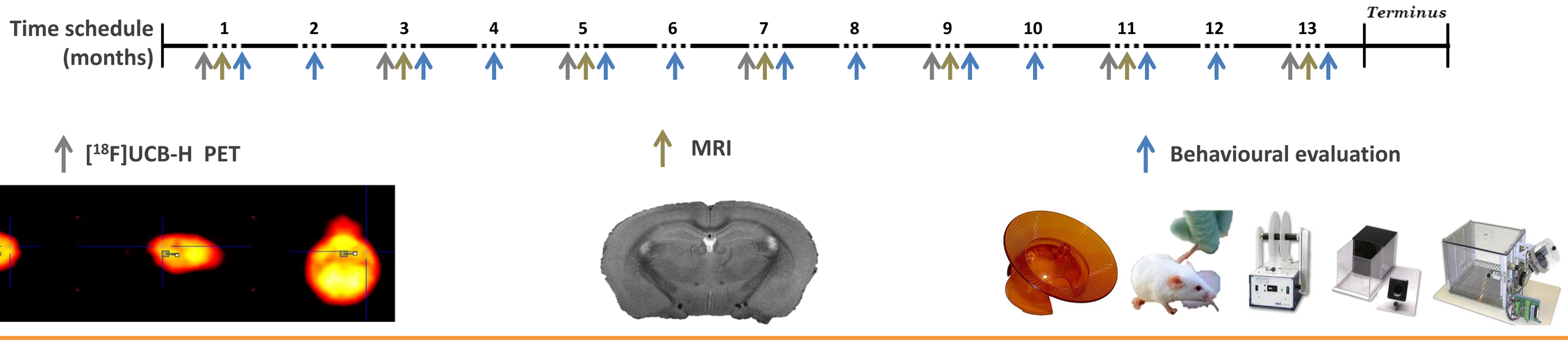
In Parkinson's disease, converging evidence supports a pathogenic role for excessive α–synuclein accumulation in synaptic terminals that may propagate back to the soma of vulnerable nerve cells such as neurons in the *substantia nigra pars compacta*. The resulting loss of dopaminergic terminals in the *striatum* can be demonstrated in vivo using [^{18}F]-Dopa-PET (positron emission tomography). However, there's currently no validated biomarker of the progressive synaptic dysfunction in other vulnerable areas such as the cerebral cortex.

Therefore, the goal of this longitudinal study is to test the hypothesis that the loss of synaptic terminals in a mouse model of excessive α–synuclein accumulation can be demonstrated *in vivo* before the occurrence of behavioural disturbances using **[^{18}F]UCB-H** , a new PET biomarker. We will also test if this new imaging modality is sensitive enough to study the effect of a disease modifying therapy such as chronic physical exercise.

METHODS & EXPERIMENTAL DESIGN

- **MicroPET** scan will be used every 2 months for the in vivo quantification of **[^{18}F]UCB-H** brain uptake in
  - 16 wild-type (WT)
  - 16 transgenic (Tg) mice overexpressing **human α–syn under the mThy1 promotor,**
- Physical activity will be monitored and registered every other month for further correlations
  - Running wheel *ad libitum*
  - Running wheel blocked
- Data will be validated against *post-mortem* analyses after the last PET study.

Mice \ Treatment	[18F]UCB-H brain uptake	Effect of Chronic physical exercise on synaptic plasticity: Running wheel ad libitum	Effect of Chronic physical exercise on synaptic plasticity: Running wheel blocked
Wild type	*N = 16*	*N = 8*	*N = 8*
mThy1	*N = 16*	*N = 8*	*N = 8*



PREDICTIONS

1. We predict decreased tracer uptake over time in the basal ganglia and cerebral cortex in Tg mice as compared with WT animals.
2. We predict a relationship between **[^{18}F]UCB-H** uptake levels in basal ganglia and cerebral cortex and progressive alterations in both motor and cognitive functions, respectively.
3. We also expect that chronic exercise will slow down both motor and cognitive disturbances, as well as the rate of **[^{18}F]UCB-H** brain uptake decreases.

CONCLUSION

If **[^{18}F]UCB-H** PET proves to be a valid biomarker for the early detection of α–synuclein accumulation in the pre-clinical model of PD, the methods will tested on human clinical populations.

ACKNOWLEDGEMENTS & SPONSORS

This research was supported by the Université de Liège and the UE within the MSCA-COFOUND BeIPD project framework. Alain Plenevaux is Research Director of the FRS-FNRS Belgium.