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isolated P

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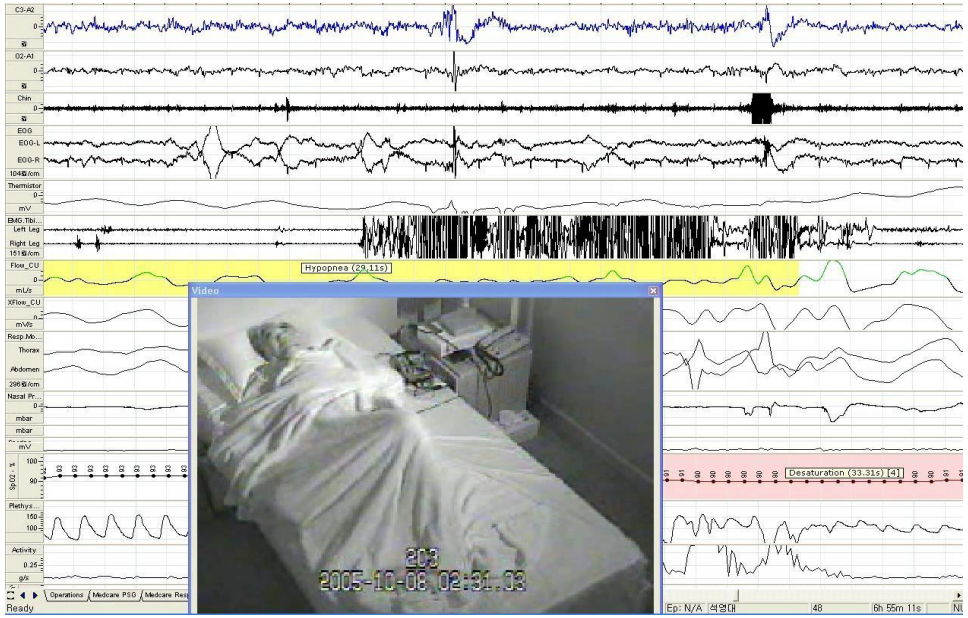
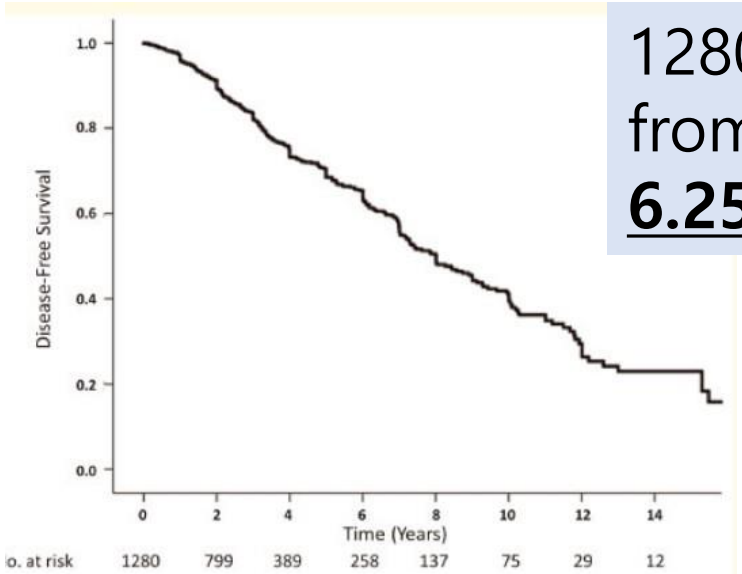
iRBD as a prodromal stage of Lewy body disease

Idiopathic REM sleep behavior disorder



Lack of atonia during rapid-eye-movement (REM) sleep resulting in dream-enacting behavior (Schenck et al. 1986)

Phenoconversion in iRBD patients



1280 patients
from 24 centers
6.25%/year

74~91% of iRBD patients convert to Lewy body disease (PD, DLB or MSA) within 15 years after onset (Postuma et al., 2019, Iranzo et al., 2014)

Biomarker for iRBD

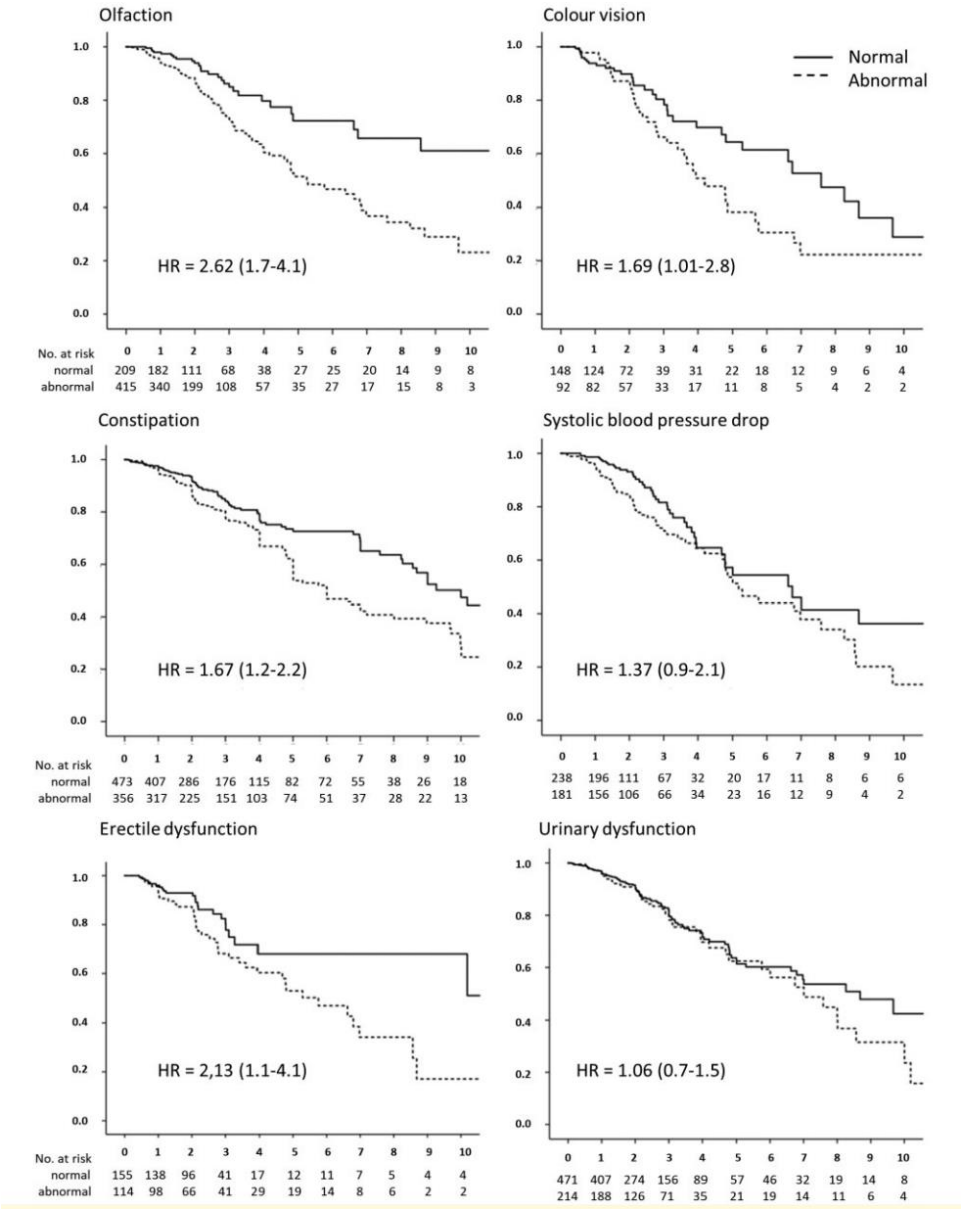
1. Reflects prodromal features (motor or non-motor) of Lewy body disease in iRBD

2. Reflects longitudinal progression of prodromal features of Lewy body disease in iRBD

3. Predicts future phenoconversion (esp. in short period) to Lewy body disease in iRBD

4. Stratification of Lewy body disease subtypes (PD vs MSA vs DLB)

Clinical biomarkers



Motor/non-motor clinical biomarkers (1280 patients from 24 centers)

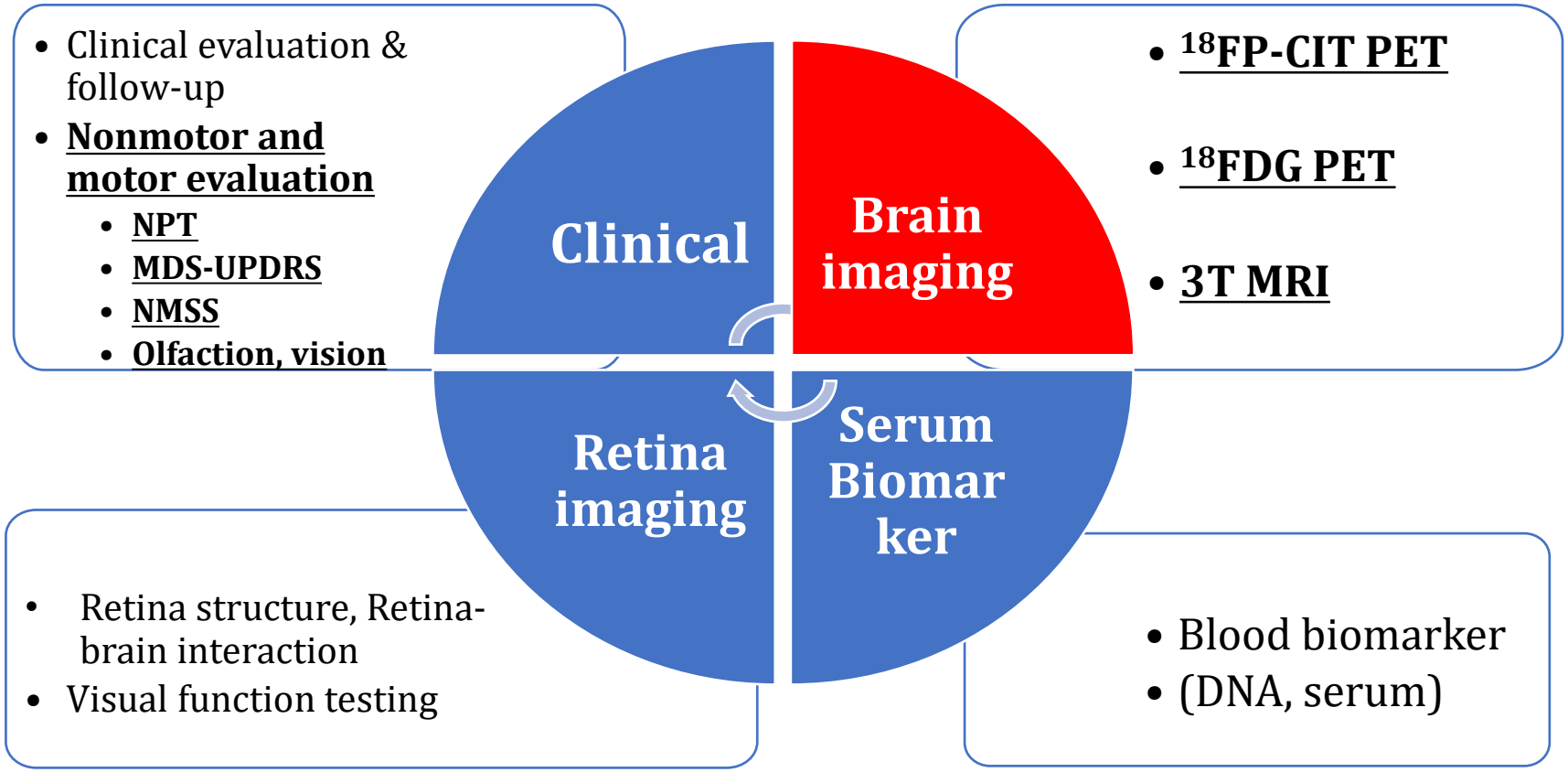
1. Hyposmia

2. Impaired color vision
3. Mild motor symtpoms
4. Mild cognitive impairment
5. Constipation
6. Erectile dysfunction

…

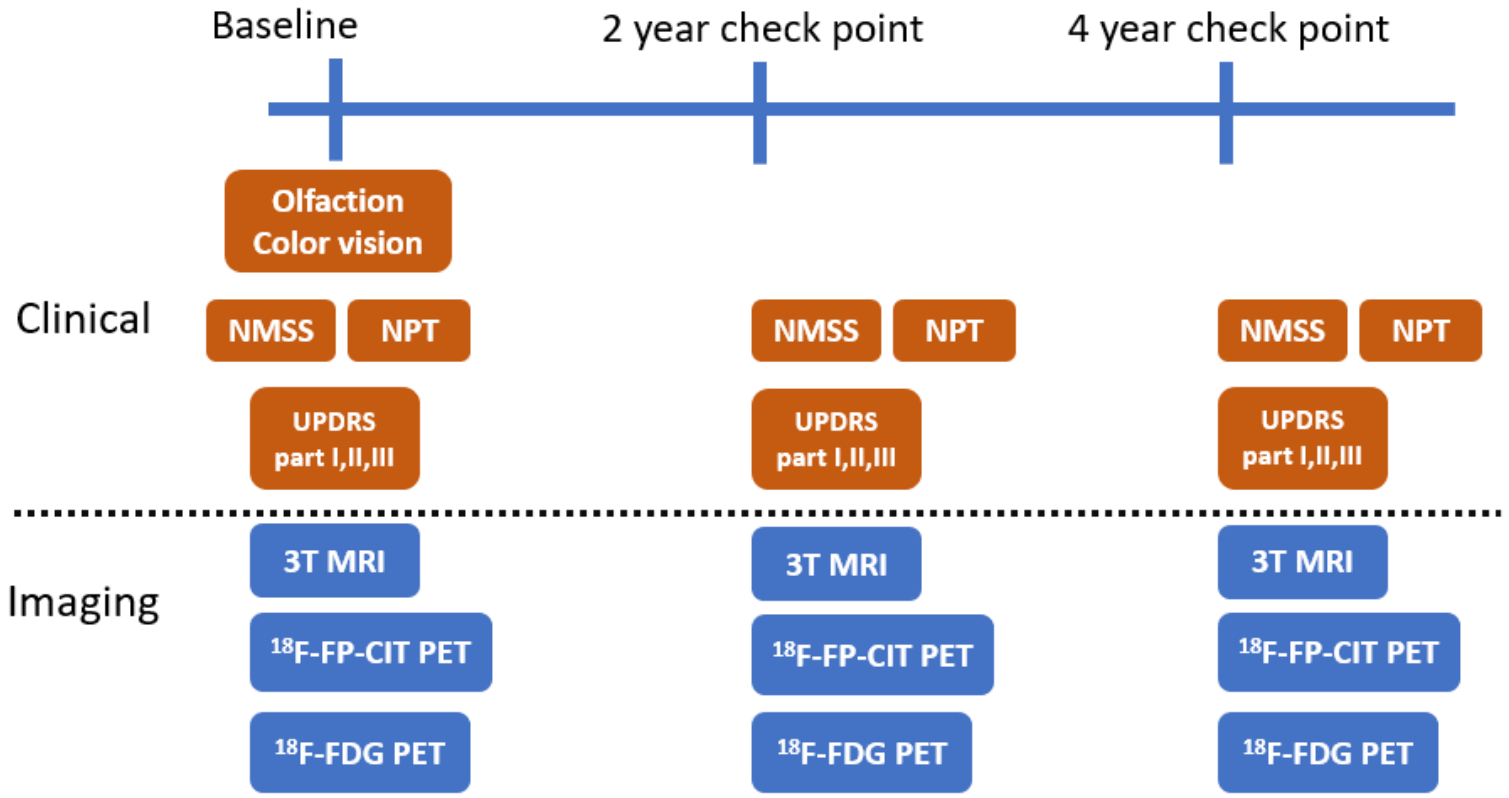
Postuma et al., 2019

SNU-BMC Prodromal parkinson progression initiative study

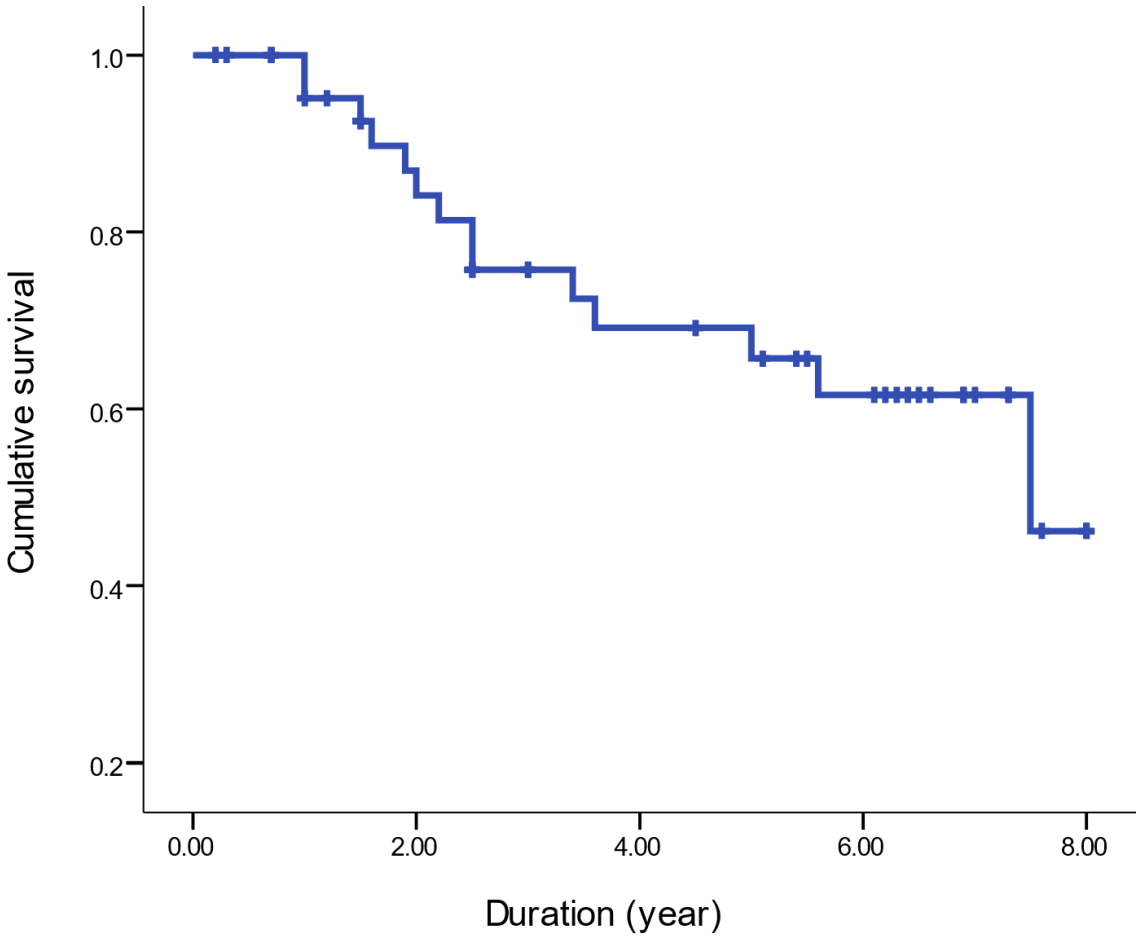


SNU-BMC Prodromal parkinson progression initiative study

- Age-matched prospective cohort from 2013.
  - Group 1 : drug-naïve early PD with **probable RBD (RBDSQ >5)**
  - Group 2 : Video PSG proven idiopathic RBD
  - Group 3 : healthy control



SNU-BMC Prodromal parkinson progression initiative study



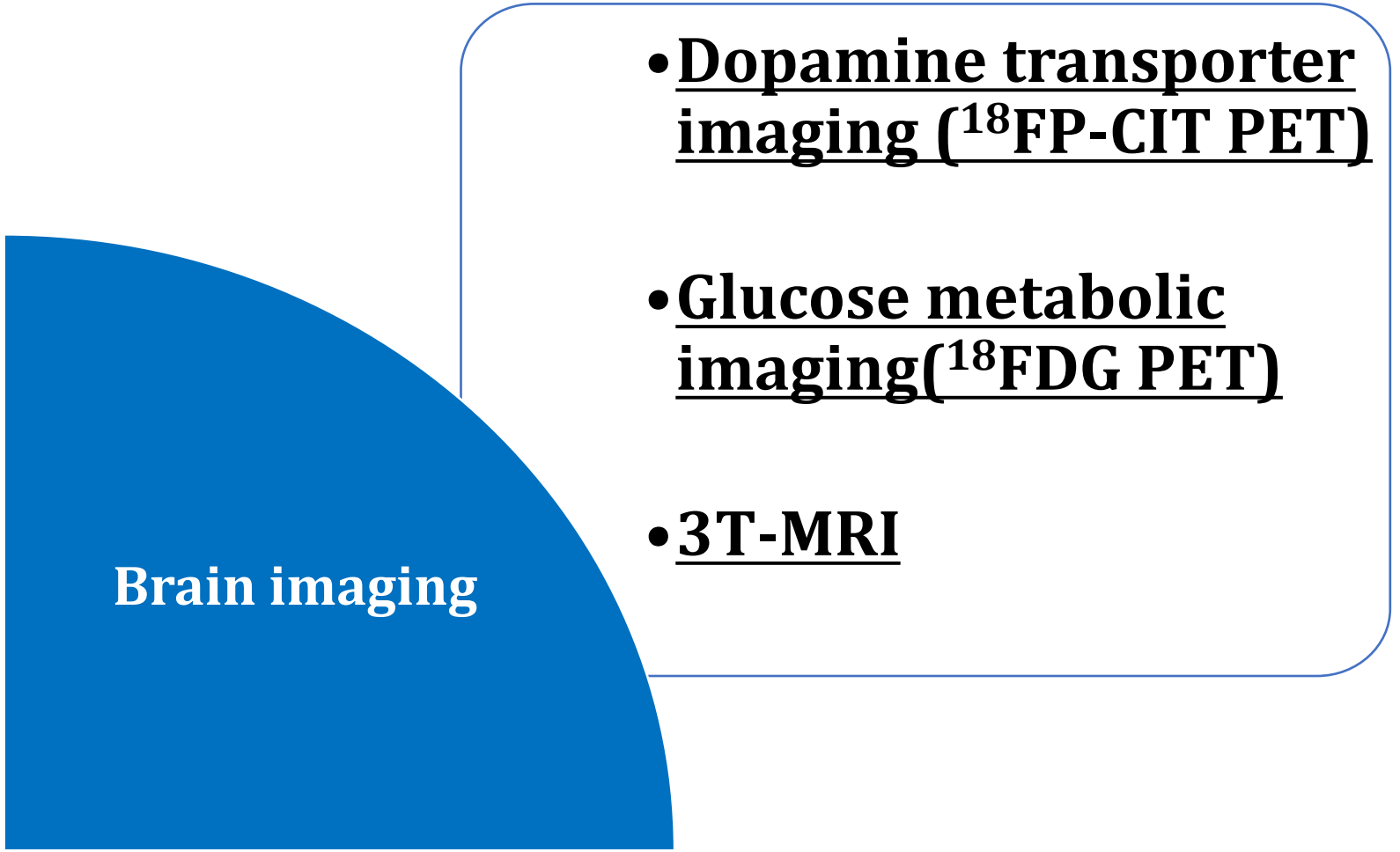
48 iRBD patients, 15 patients converted (9 PD, 1 MSA, and 5 DLB).

The mean follow-up duration was 4.23 years(maximum of 8 years)

The annual conversion rate=7.2%.

Shin et al., in revision, 2021

SNU-BMC Prodromal parkinson progression initiative study

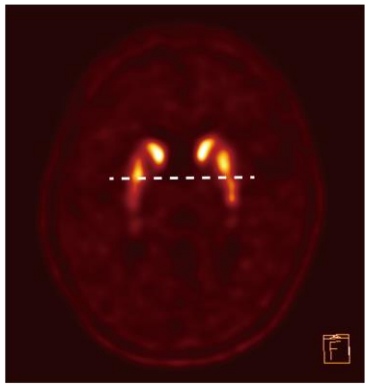


Hypothesis

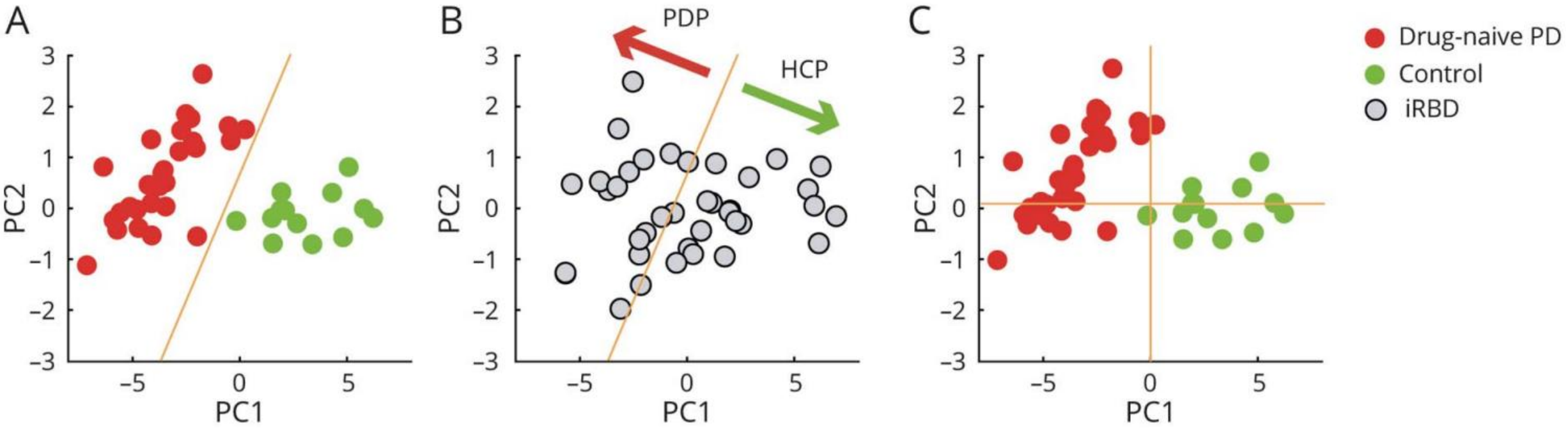
1. Dopamine binding patterns from whole striatum (using FP-CIT PET) may reflect and predict future phenoconversion.

2. Longitudinal change in DAT availability would reflect clinical outcome in iRBD

Distinct FP-CIT binding pattern in drug naïve PD, healthy controls and iRBD patients.

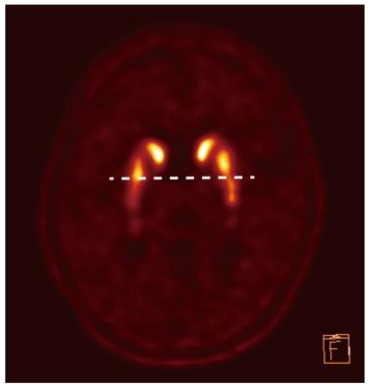


PCA analysis of whole striatal binding of FP-CIT



Shin et al., Neurology, 2020

Distinct FP-CIT binding pattern in drug naïve PD, healthy controls and iRBD patients.



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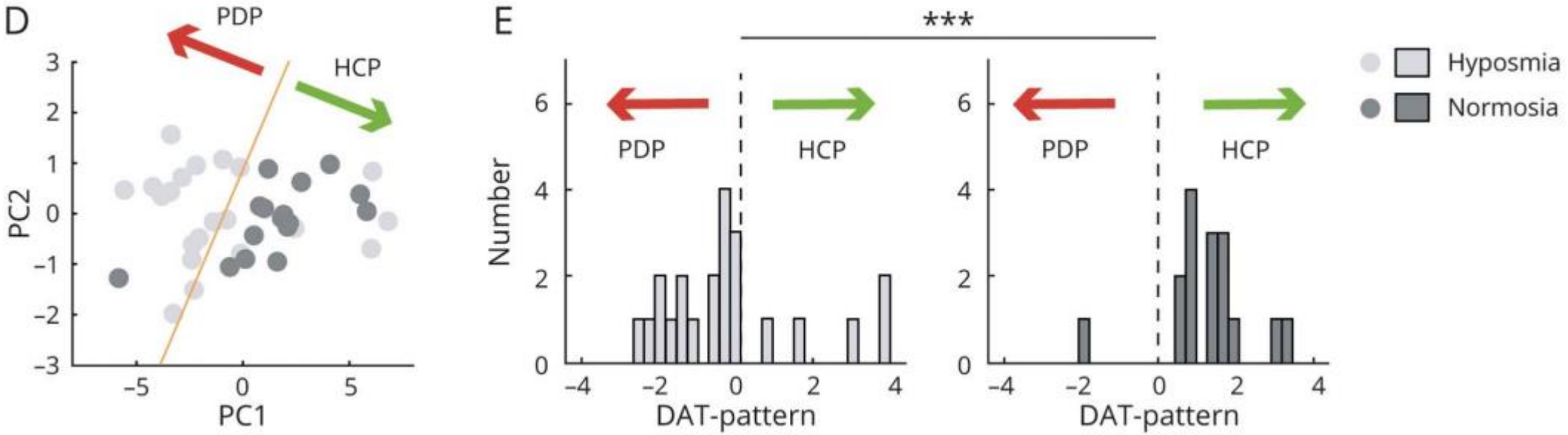
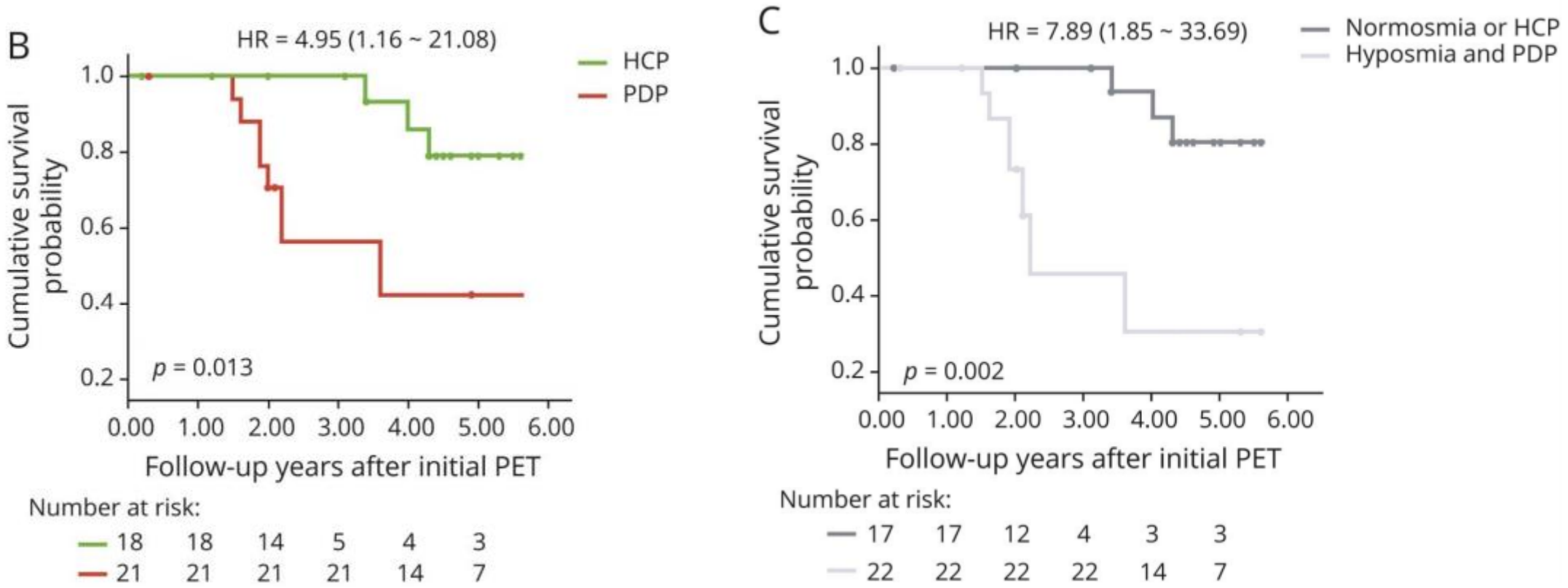


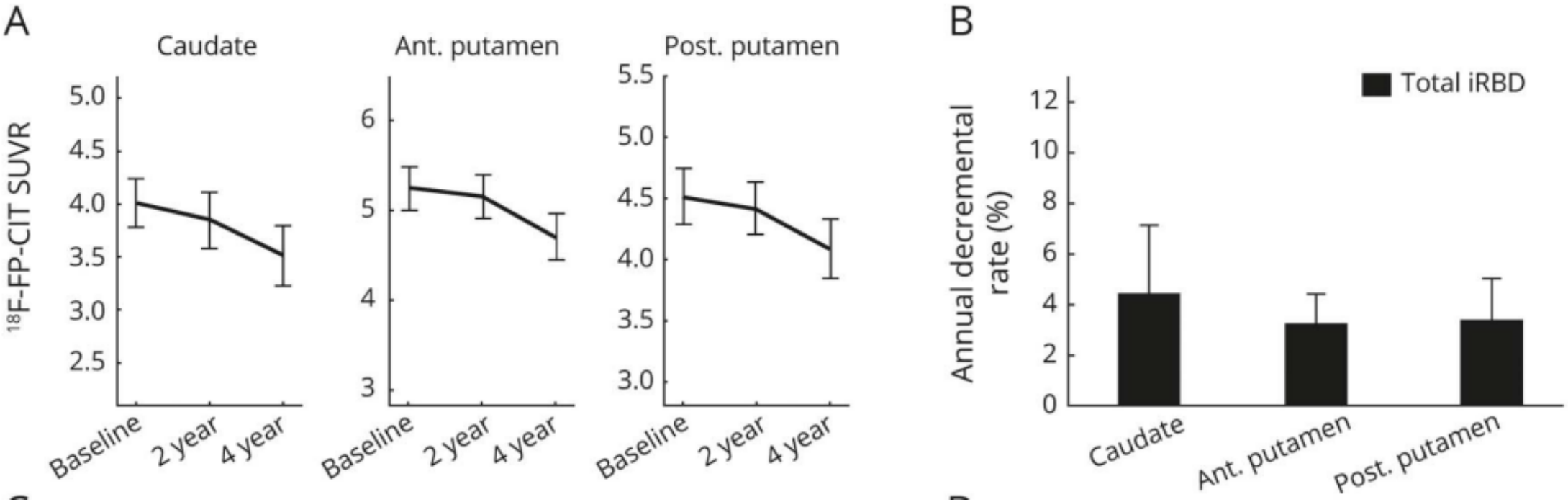
Shin et al., Neurology, 2020

Baseline PD DAT pattern predicts future phenoconversion in iRBD



Shin et al., 2020

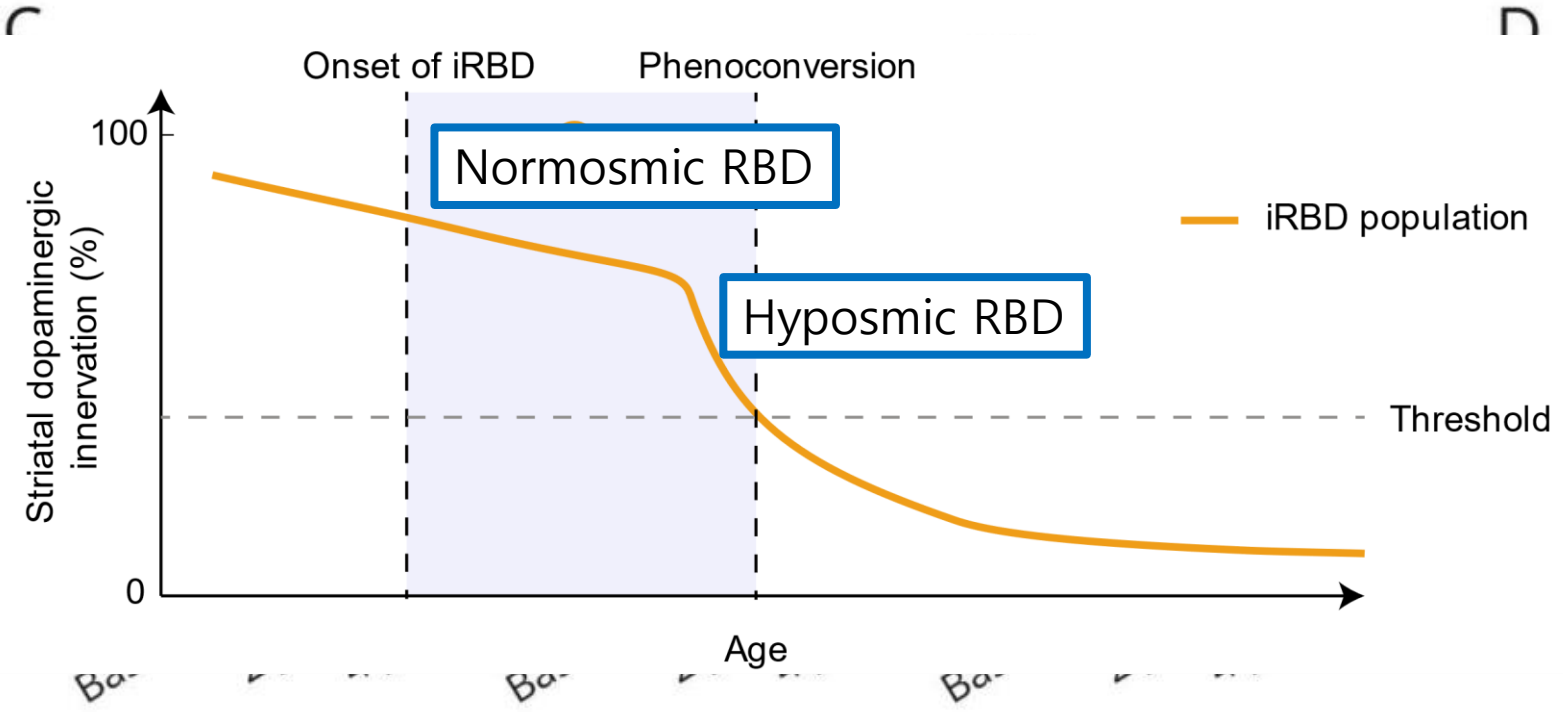
Longitudinal change of DAT binding in RBD

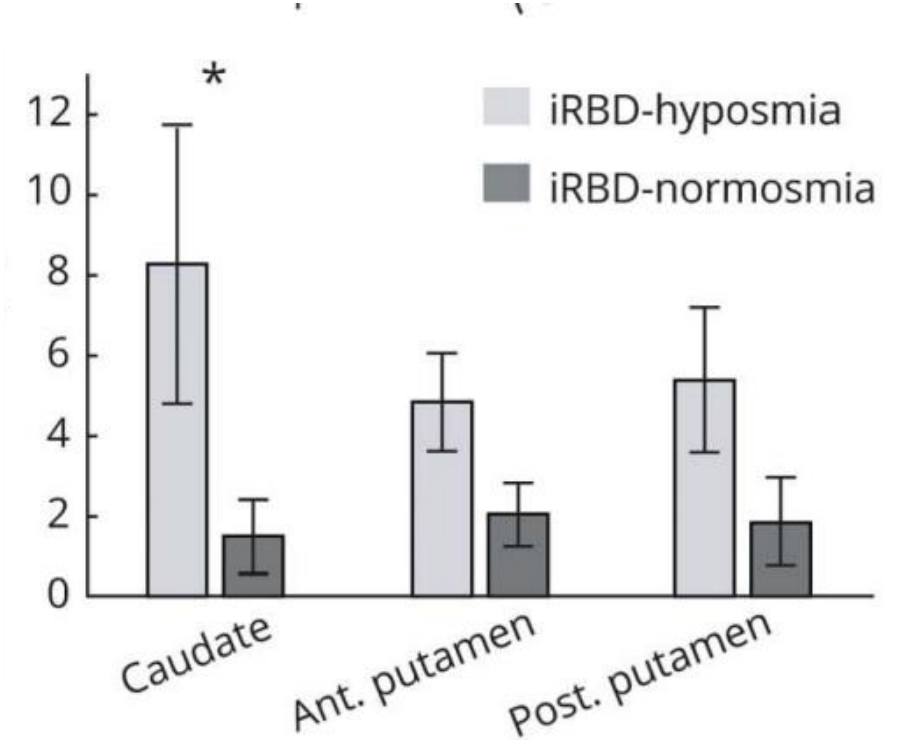


Annual decremental rate = 4.4%, 3.3%, and 3.4% in the caudate, anterior putamen, and posterior putamen

Shin et al., 2020

Longitudinal change of DAT binding in RBD





iRBD hyposmia has similar annual decremental rate of DAT binding compared to early PD (4% to 8.9% in the putamen and 3.5% to 4.4% in the caudate, Morrish et al., Hilker et al.)

iRBD-normosia has similar rate to healthy control (Iranzo et al., 2011)

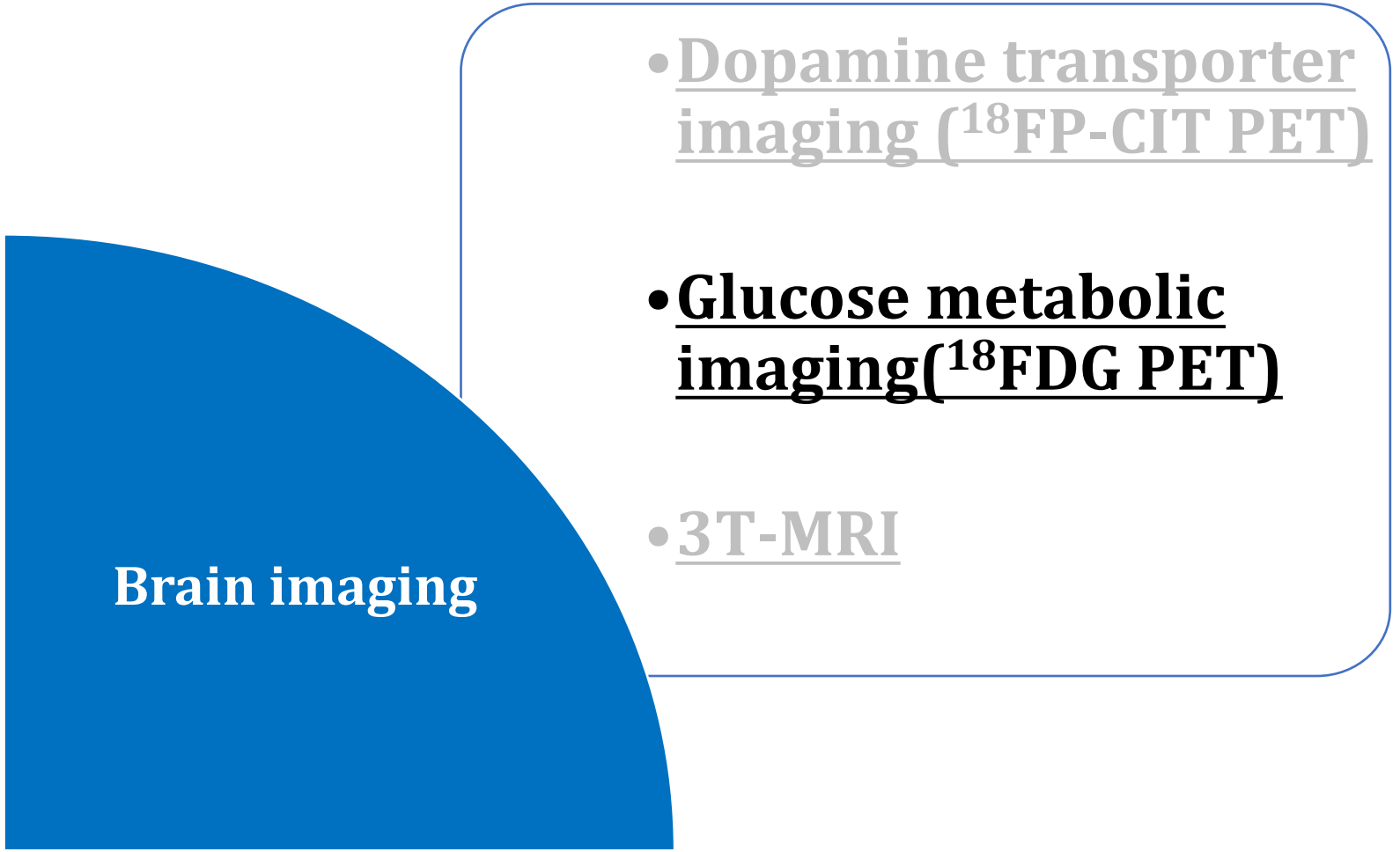
Shin et al., 2020

Conclusion_DAT imaging

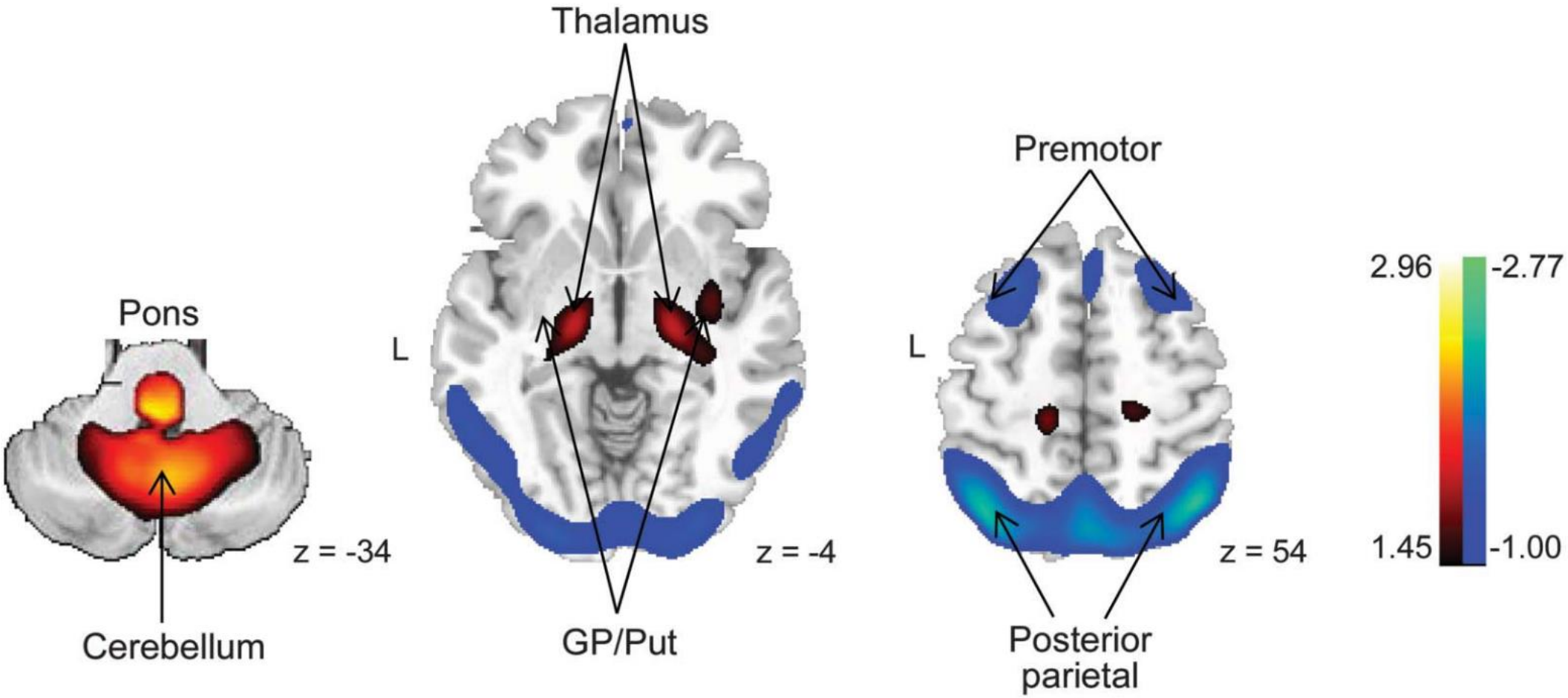
DAT-pattern as a biomarker in iRBD

- 1. Reflects degeneration in the prodromal stage of PD
- 2. Correlates with prodromal biomarkers
- 3. Significantly predict future pheonconversion
- 4. Lowest sample size for simulated neuro protective trials (using DAT-pattern as outcome)

Metabolic functional imaging as a biomarker in iRBD



PD related pattern (PD-RP)



Correlates with motor scores (UPDRS part III)
and DAT binding in PD

Eidelberg, 2007, 2014
Holtbernd and Gagnon, 2014

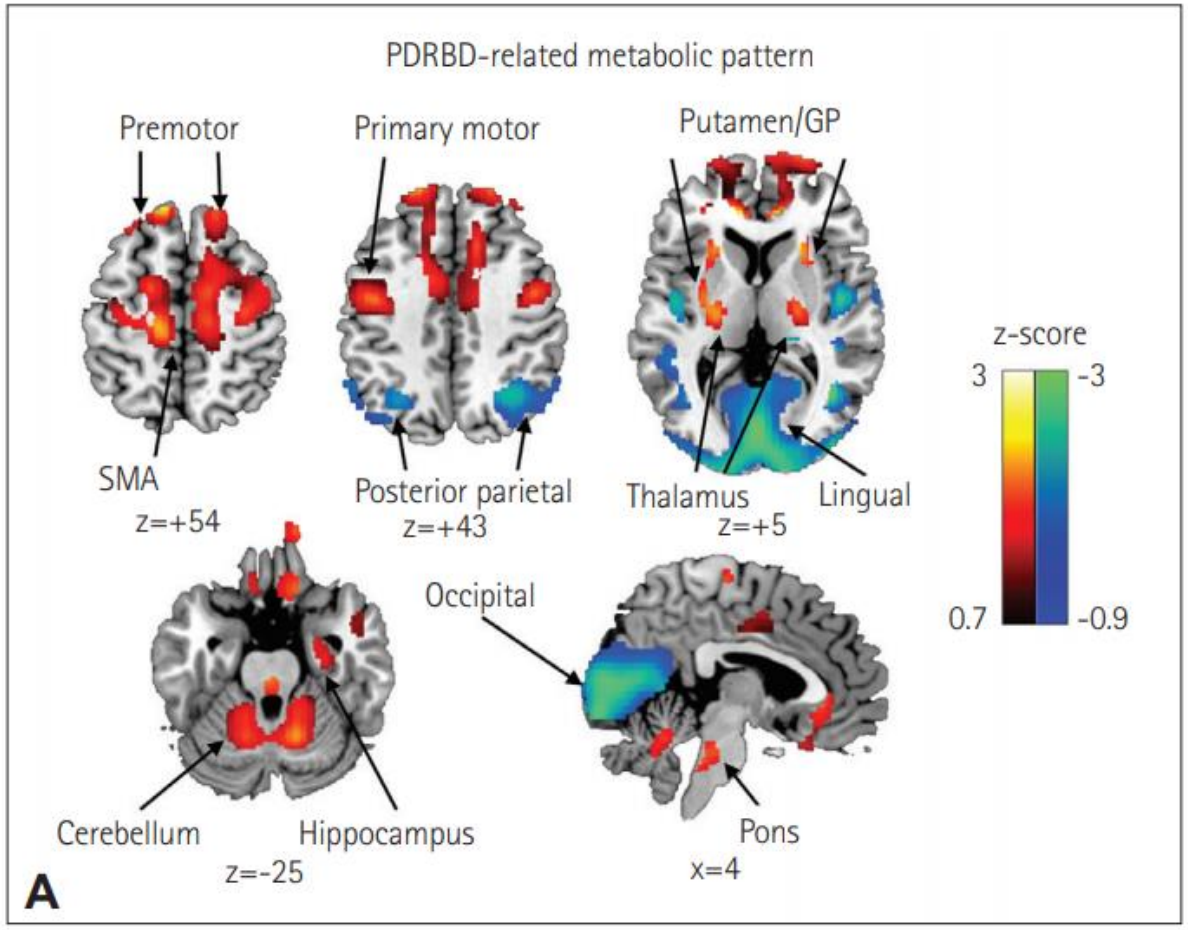
PD-RP

PD-RP and RBD	PD-RP was derived from PD patients regardless of RBD as a prodromal symptom
PD without RBD	- Prevalence of RBD is about 50% in PD patients - RBD may first appear during any stages of PD - Different clinical characteristics in PDRBD vs PD without RBD

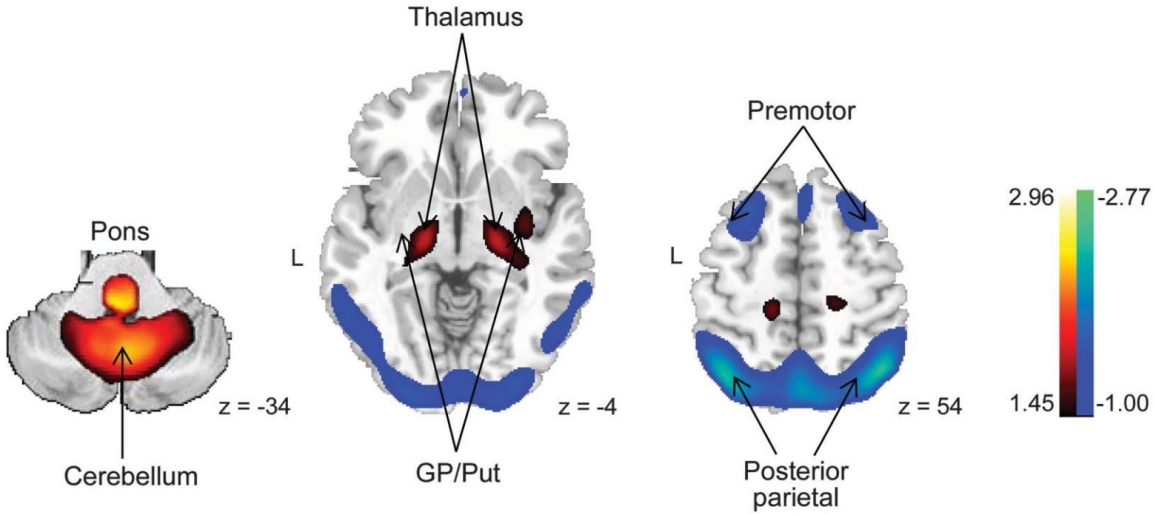
PD-RP may not fully reflect specific metabolic change related to progression from iRBD to Lewy body disease.

dnPDRBD-RP

Metabolic pattern from drug naïve PD patients with prolonged RBD before parkinsonism



Metabolic pattern from PD patients



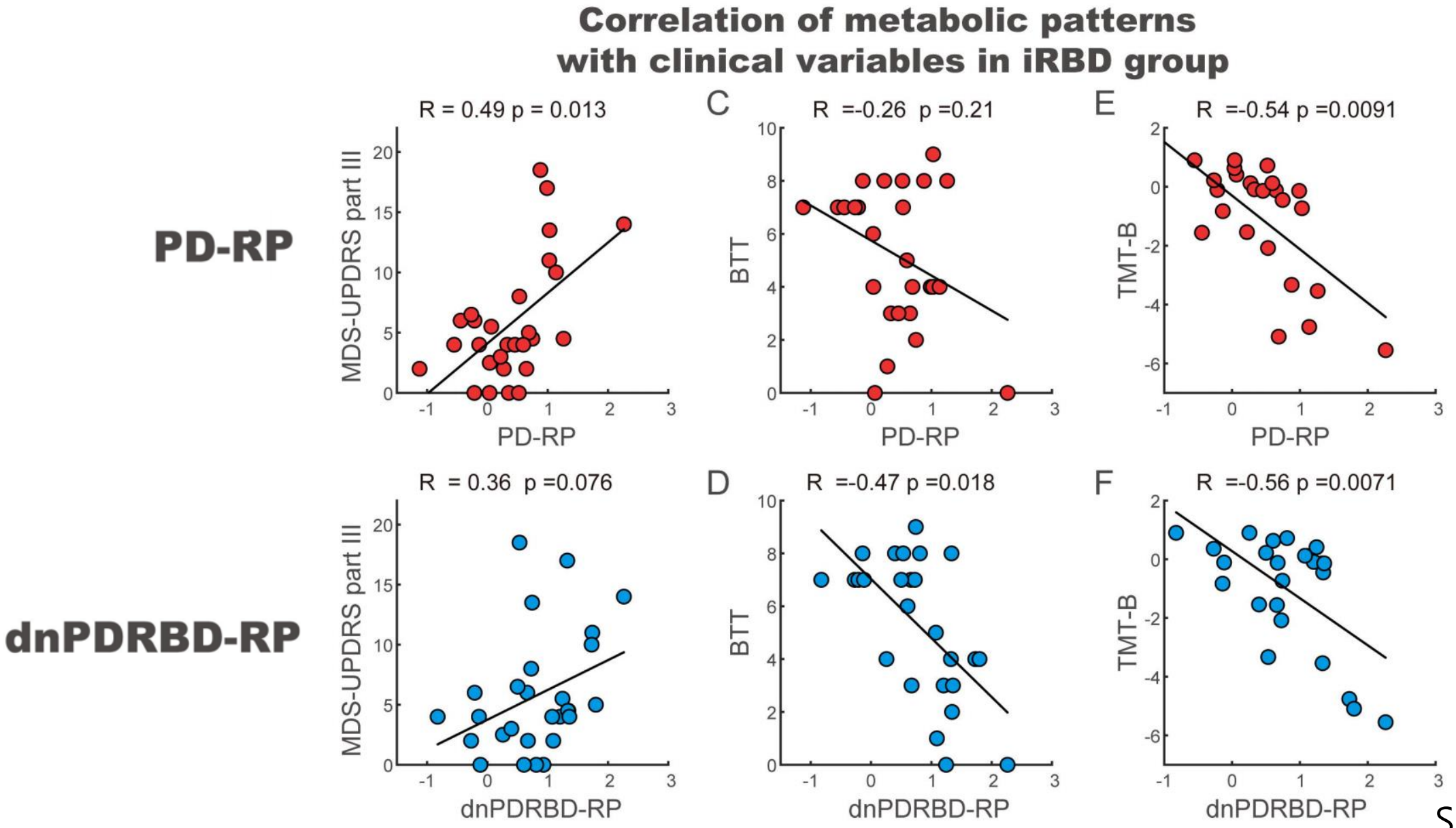
Yoon, 2019

Hypothesis

1. Metabolic patterns from dnPDRBD may better reflect prodromal biomarkers than PD-RP

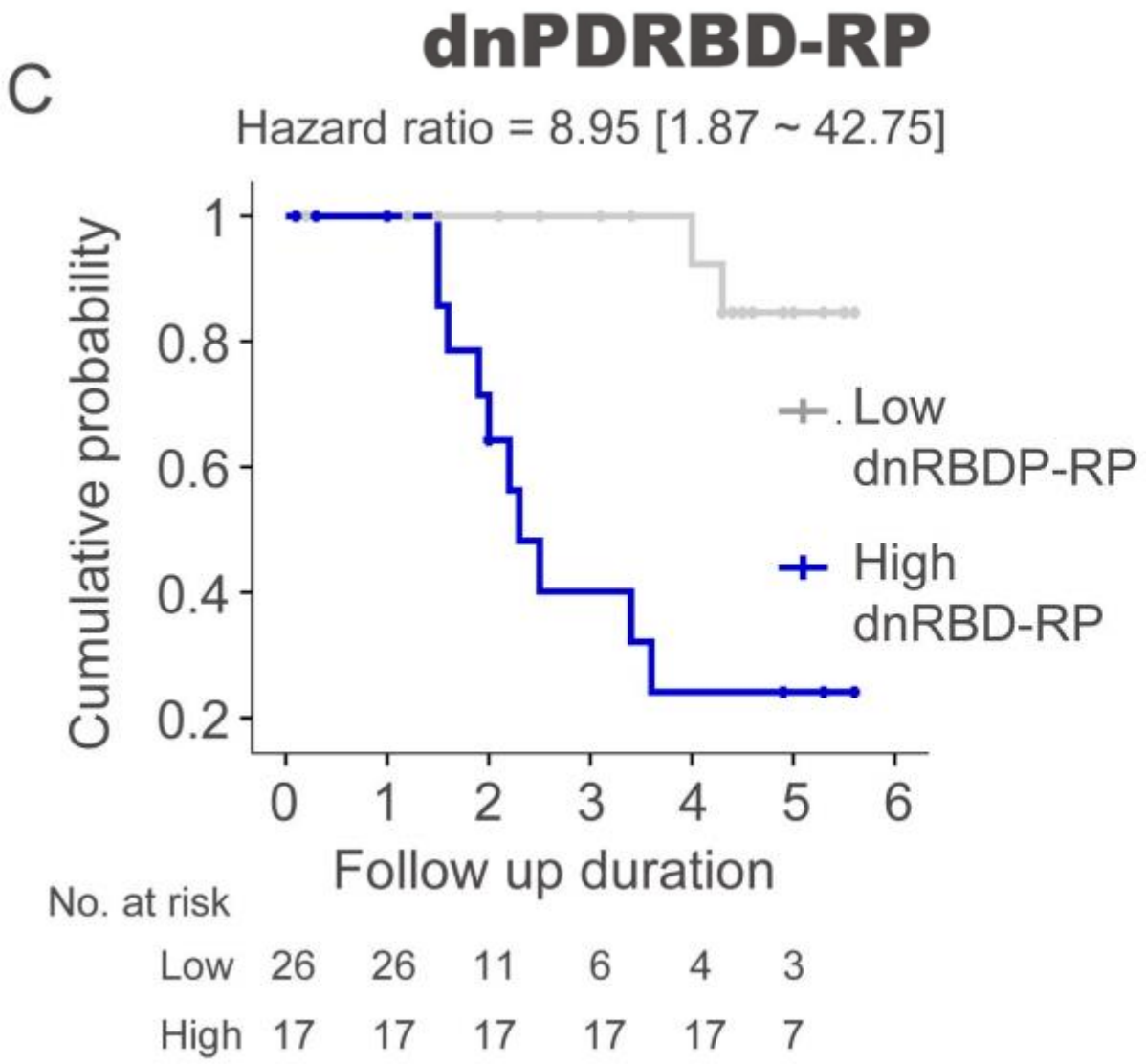
2. Metabolic patterns from dnPDRBD may better predict future phenoconversion than PD-RP

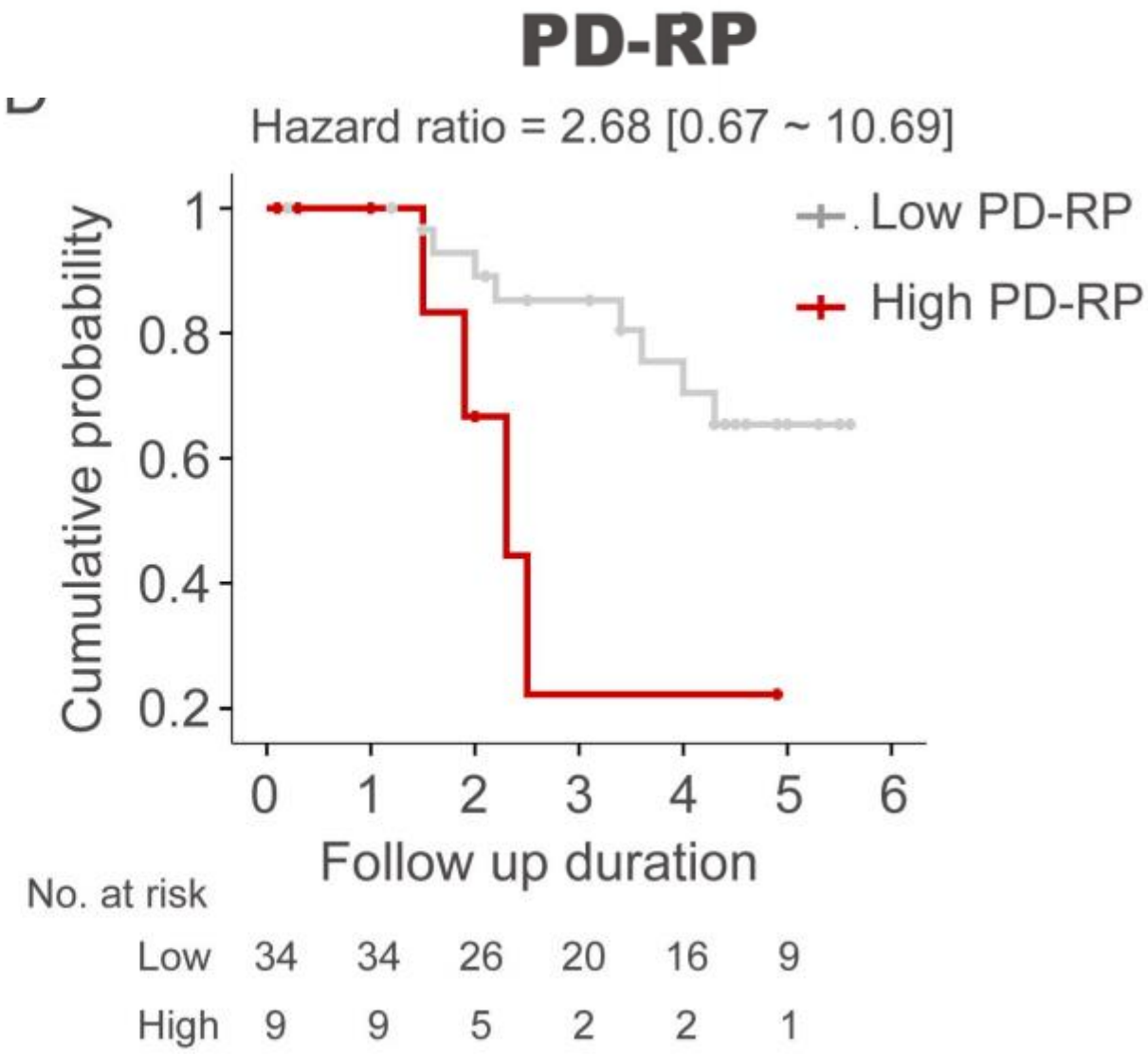
dnPDRBD-RP and PD-RP in iRBD



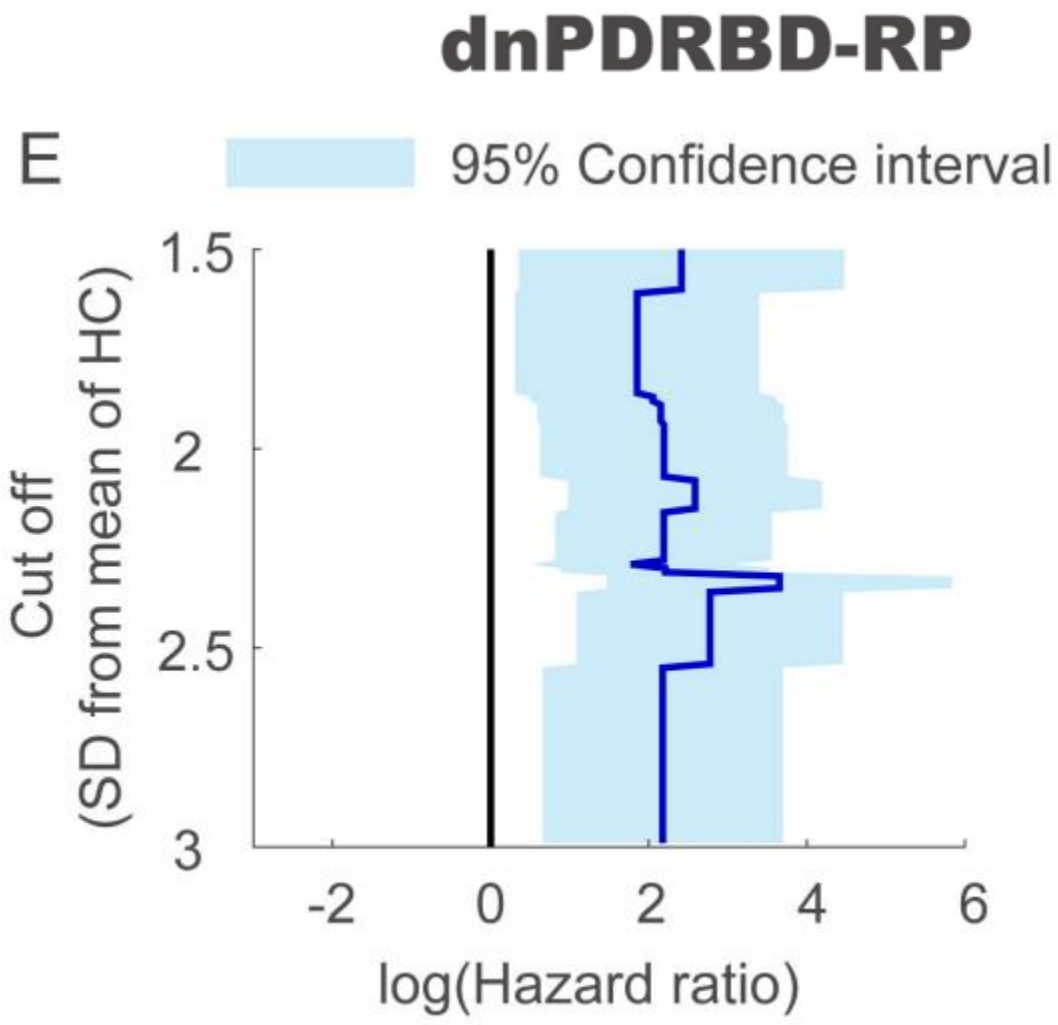
Shin et al., 2021

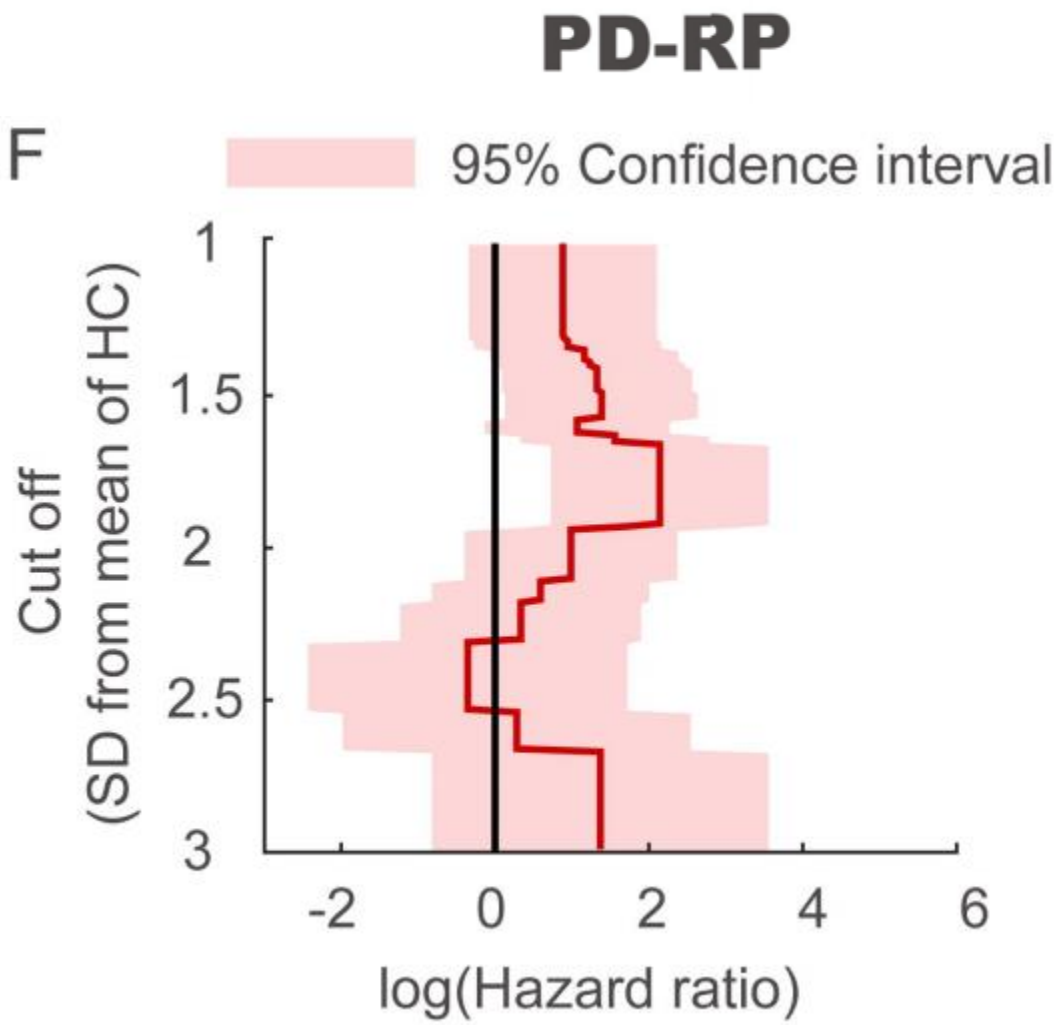
Predictability of future phenoconversion (2 std from HC)





Predictability of future phenoconversion



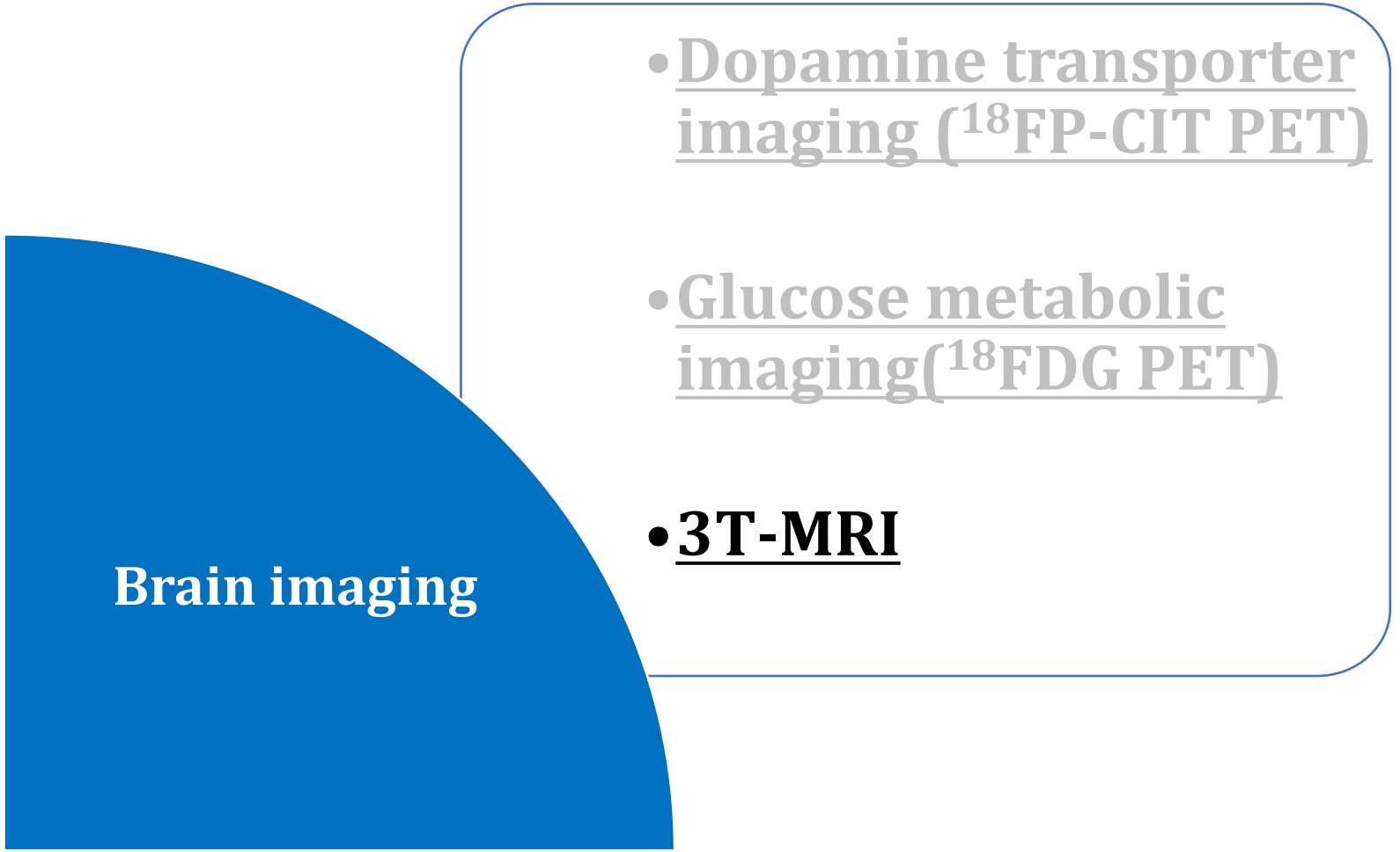


Conclusion

dnPDRBD-RP as a biomarker in iRBD

- Reflects metabolic alteration in the prodromal stage of PD (both PD-RP and iRBD-RP)
- Correlates with prodromal biomarkers (e.g. olfaction)
- Significantly predict future phenoconversion
- Individual application

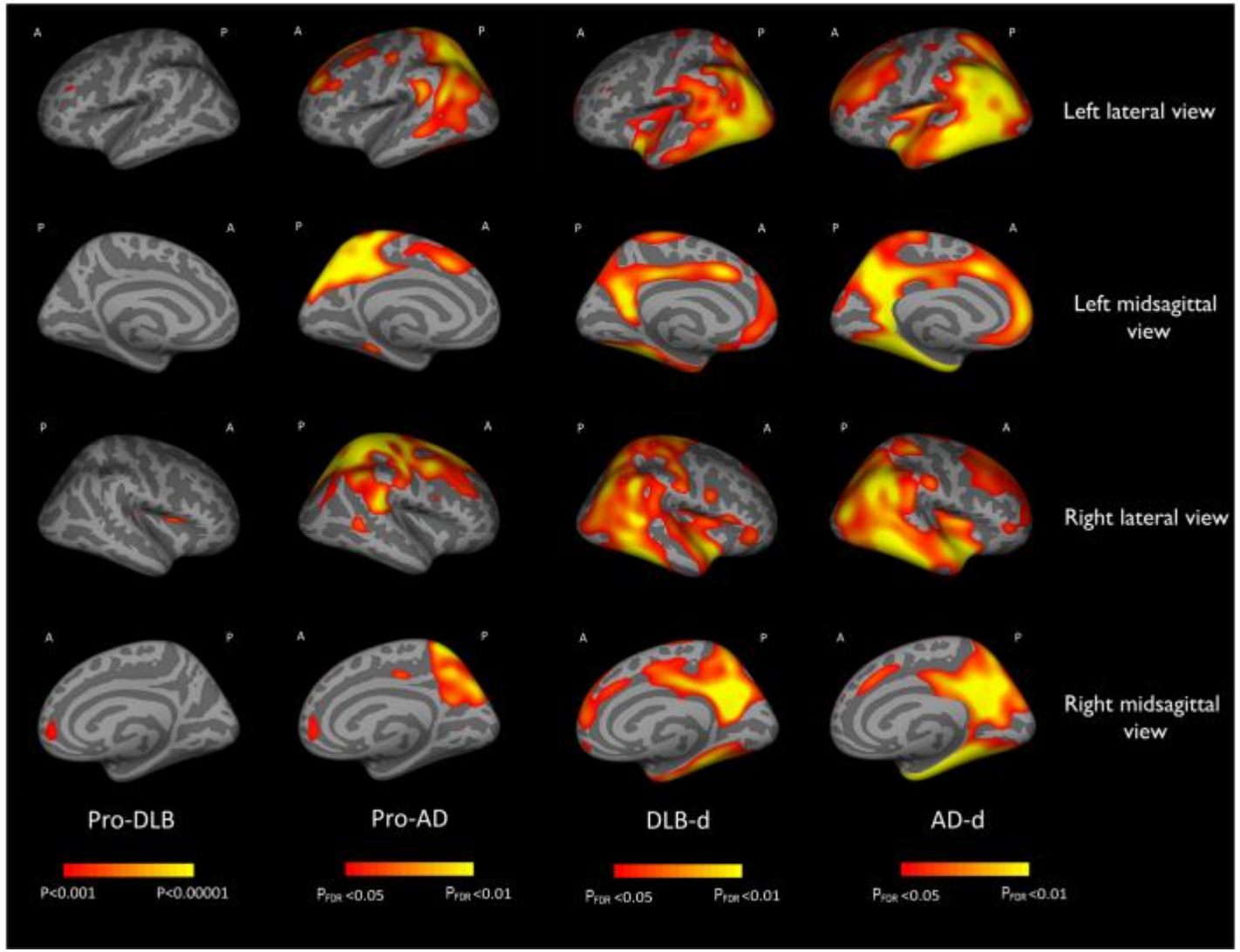
SNU-BMC Prodromal parkinson progression initiative study



Background

1. PD and DLB is a major waypoint in the progression of iRBD patient
2. Clinical and pathological characteristics of PD and DLB are distinct, even in prodromal state
3. Biomarkers that can easily and reliably predict subtype-specific pheonconversion have not been established.

DLB patients show diffuse cortical thinning compared to controls



Blanc et al., Plos One 2015

Hypothesis

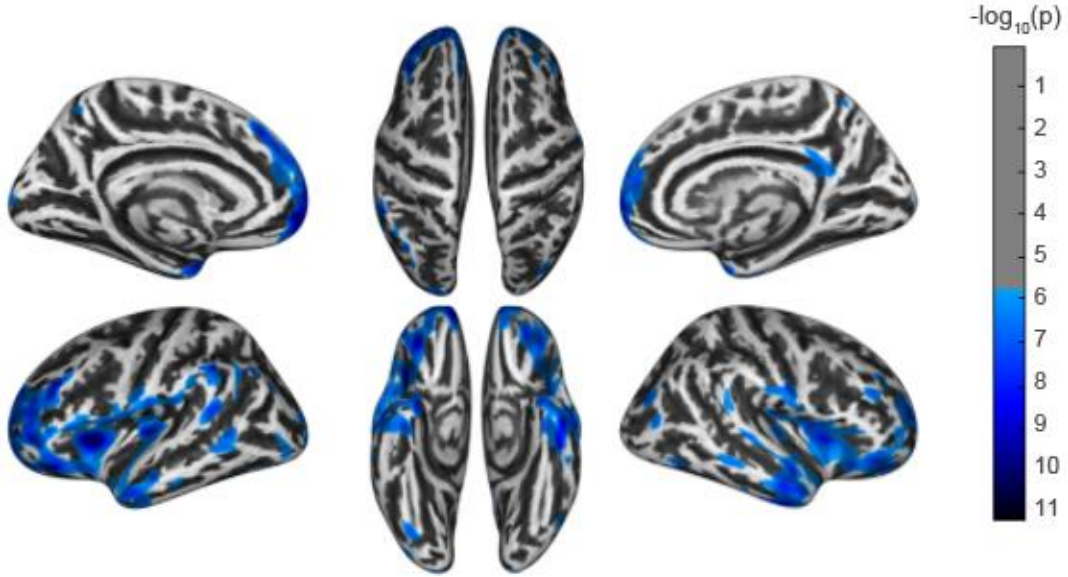
1. Cortical thickness pattern derived from DLB-HC would reflect prodromal cortical thickness pattern in future DLB converters

2. Baseline cortical thickness pattern might differentiate future DLB and PD converters.

Cortical thickness in DLB (vs HC)

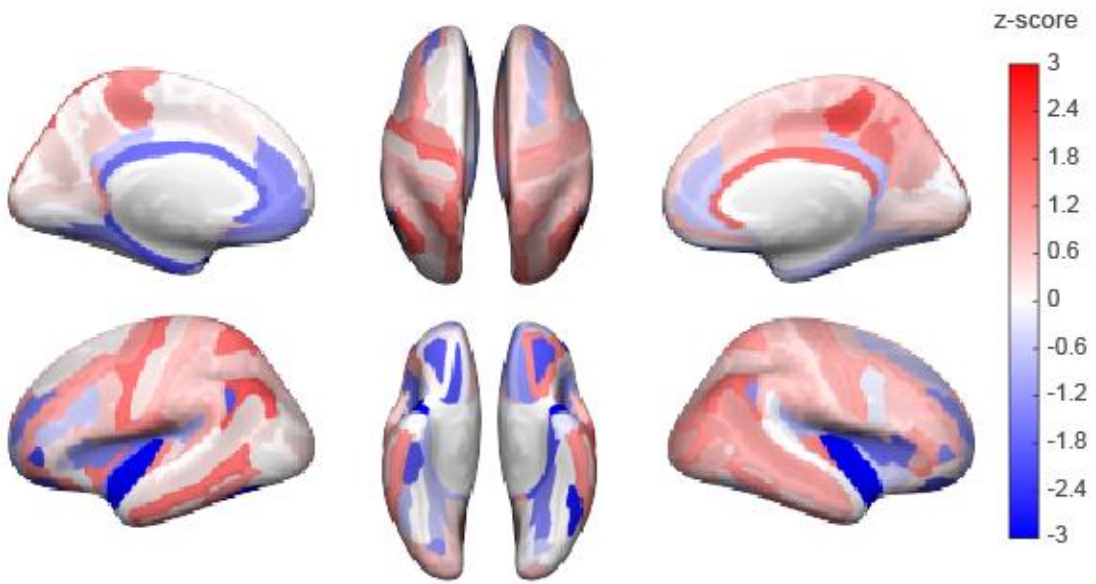
A

Cortical thickness difference between age-matced HC and DLB (HC > DLB)



B

DLB-related cortical thickness pattern (DLB-pattern)

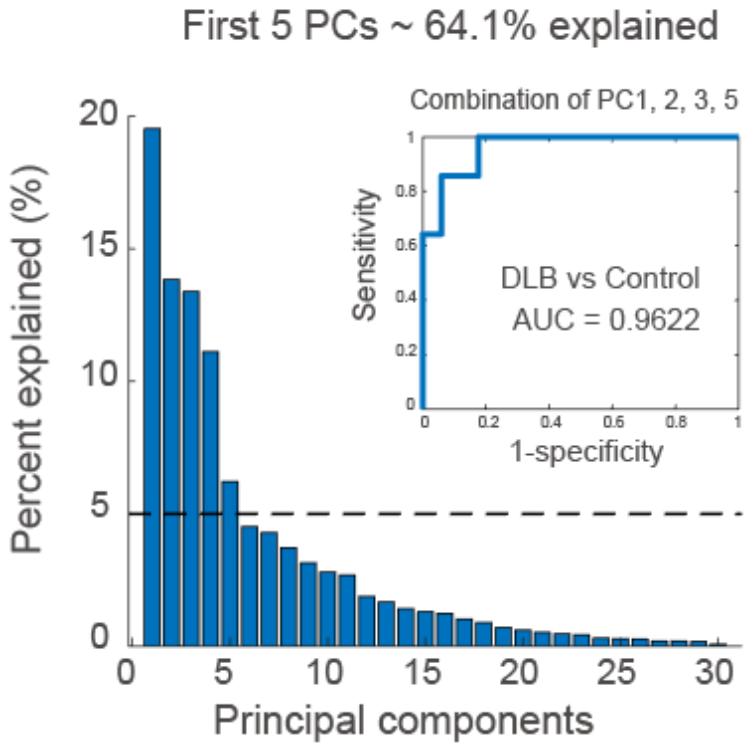


Negative association with medial temporal, anterior temporal, orbitofrontal, insula cortices and positive association with and precentral and inferior parietal cortices (absolute z score > 1.5, Figure 1B).

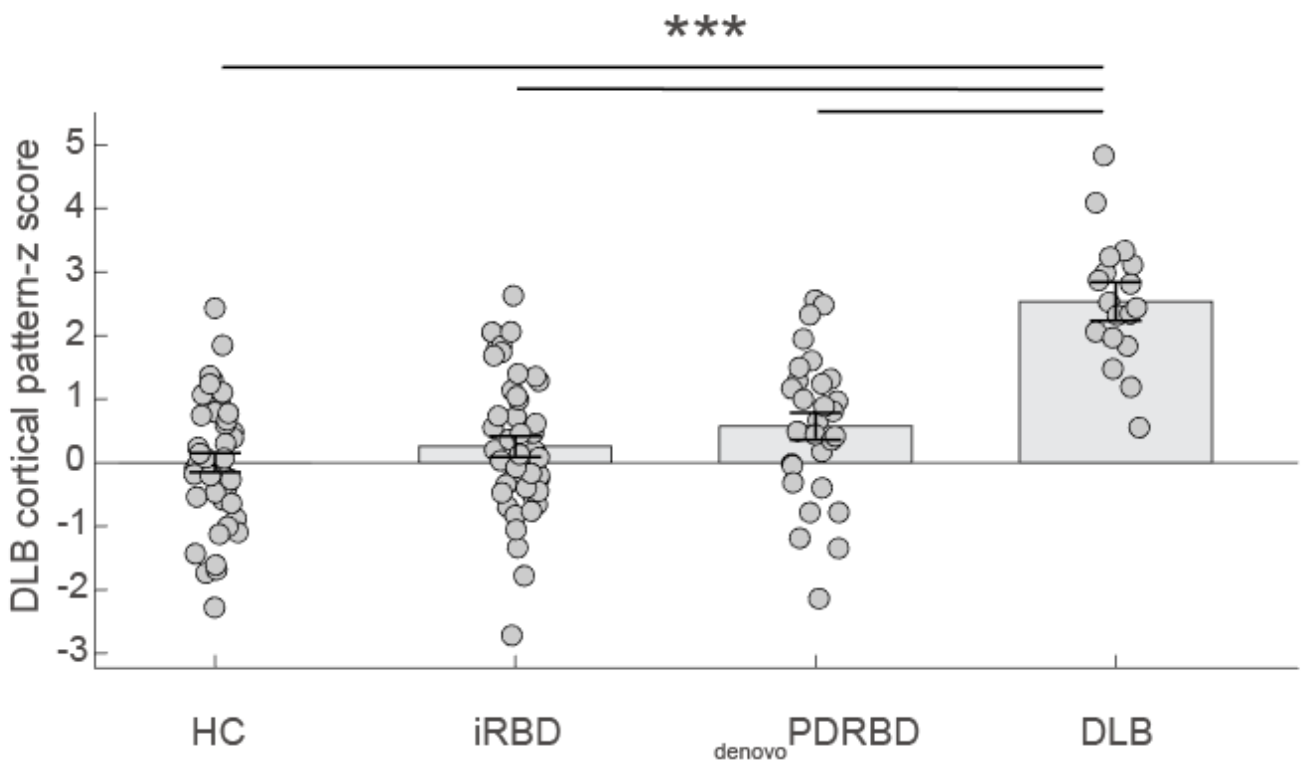
Shin et al., in revision

Cortical thickness in DLB (vs HC)

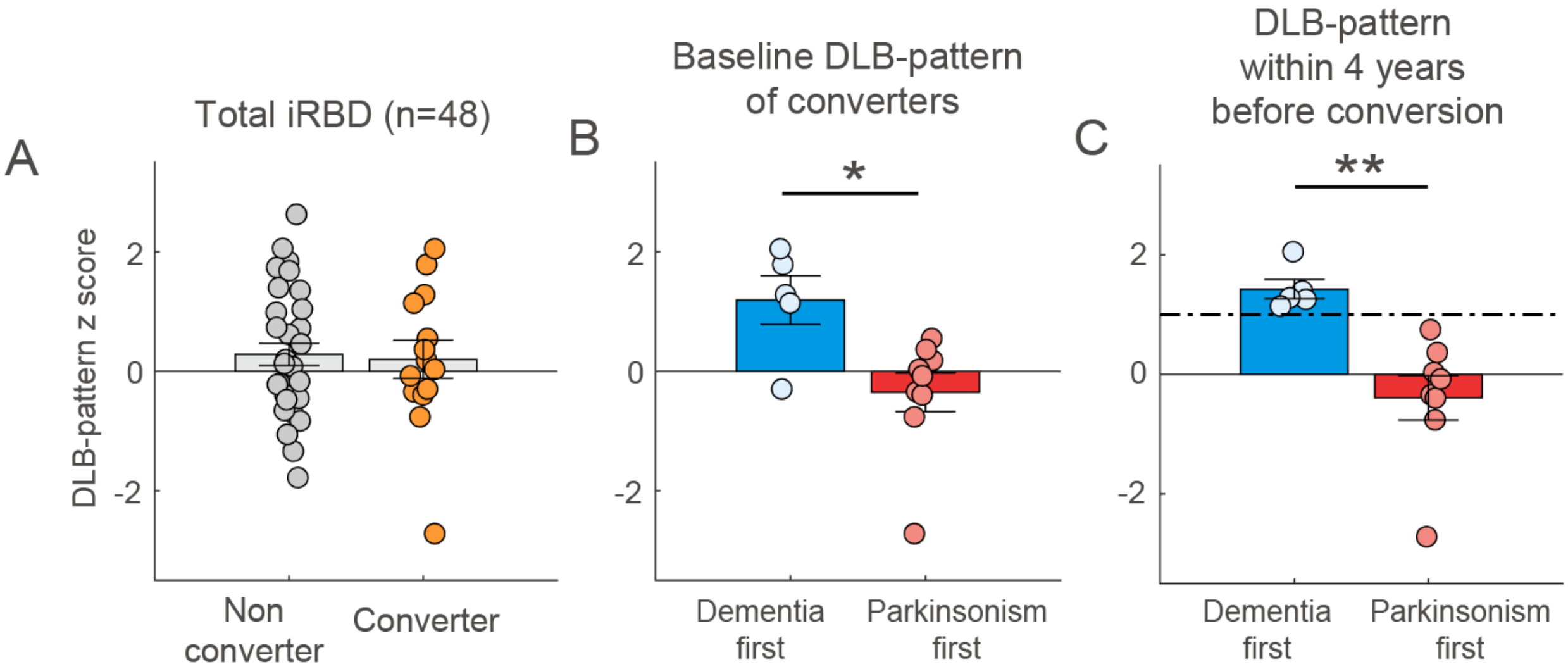
C



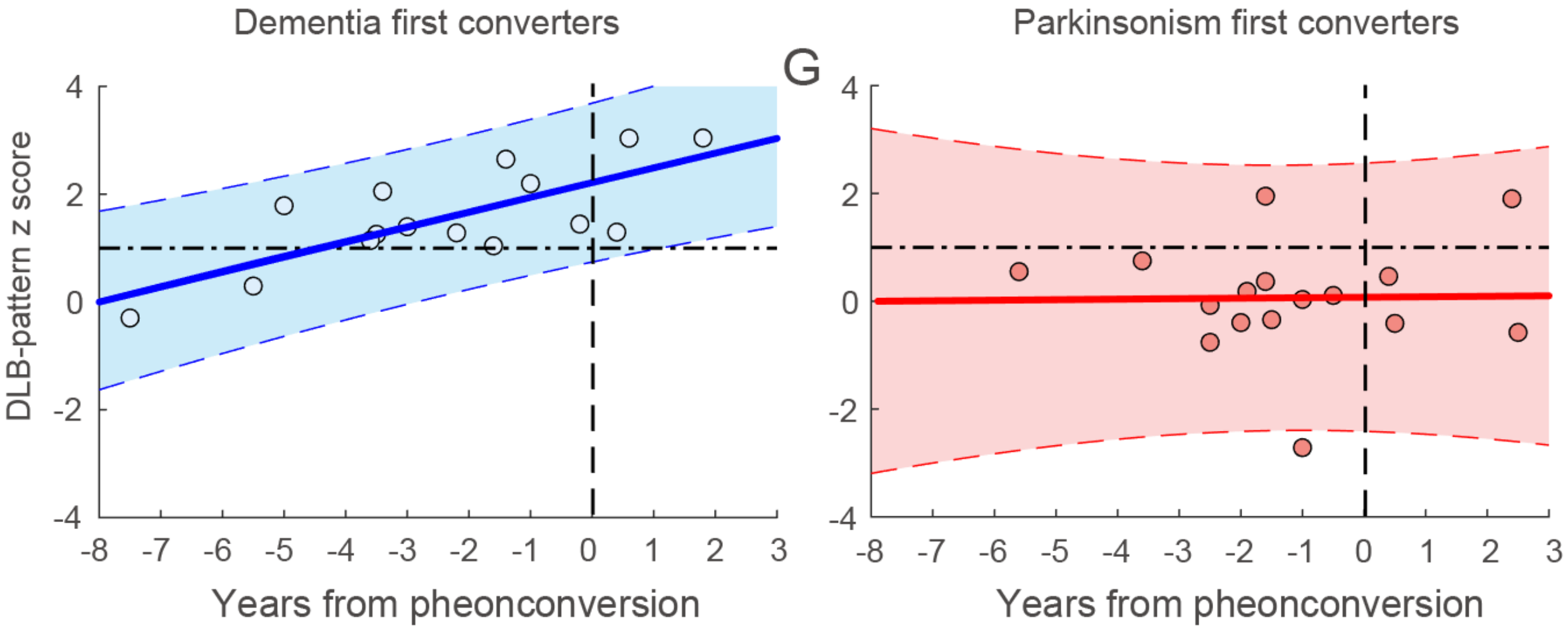
D



DLB cortical thickness pattern and phenoconversion



Longitudinal progression of DLB-cortical pattern



Differentiation of dementia-first vs parkinsonism –first conversion in iRBD

Dementia-first vs Motor-first conversion among converters	Overall discriminative prediction			Prediction of conversion within 4 years		
	Sensitivity	Specificity	Diagnostic accuracy	Sensitivity	Specificity	Diagnostic accuracy
^{18}F-FDG-PET (PDRBD-RP)	60 (3/5)	0 (0/7)	25 (3/12)	80 (4/5)	0 (0/7)	33.3 (4/12)
^{18}F-FP-CIT PET (DAT pattern)	40 (2/5)	0 (0/9)	14.3 (2/14)	18.2 (2/5)	11.1 (1/9)	21.4 (3/14)
MRI (DLB-pattern)	**80 (4/5)**	**100 (9/9)**	**92.9 (13/14)**	**100 (5/5)**	**100 (9/9)**	**100 (14/14)**
PDRBD-RP + DAT pattern	40 (2/5)	0 (0/7)	16.6 (2/12)	22.2 (2/5)	14.3 (1/7)	25(3/12)
PDRBD-RP + DLB-pattern	**60 (3/5)**	**100 (7/7)**	**83.3 (10/12)**	**80 (4/5)**	**100 (7/7)**	**91.7 (11/12)**
DAT pattern + DLB-pattern	**40 (2/5)**	**100 (9/9)**	**78.6 (11/14)**	**40 (2/5)**	**100 (9/9)**	**78.6 (11/14)**
MCI	80 (4/5)	33.3 (3/9)	50 (7/14)	80 (4/5)	33.3 (3/9)	50 (7/14)

Conclusion

DLB-cortical thickness pattern as a biomarker in iRBD

- Higher in future dementia-first converters
- Excellent sensitivity and specificity differentiating dementia-first converters from parkinsonism-first converters
- Do not predict overall pheonconversion

Combination of clinical and imaging biomarkers

Predict overall pheonconversion

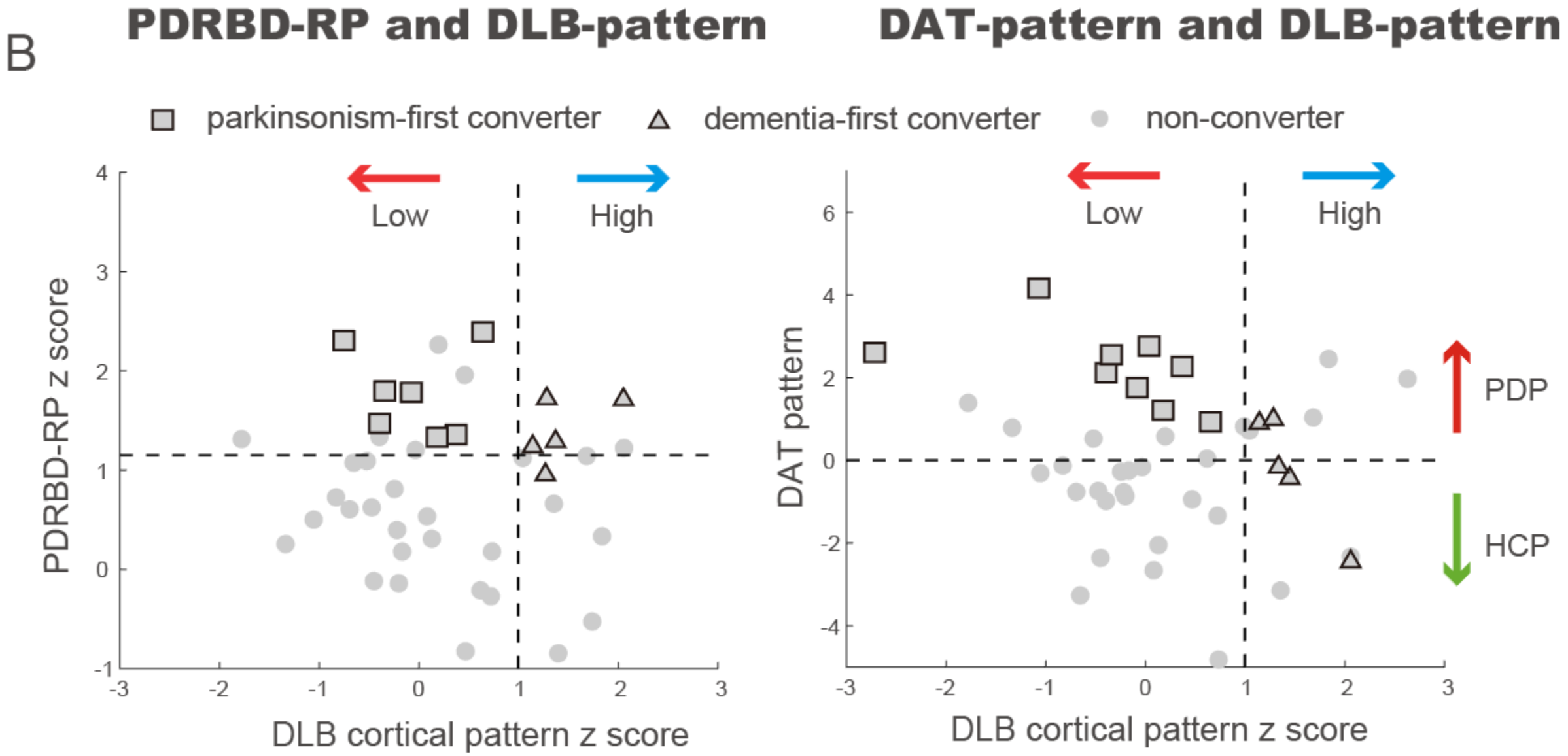
Differentiation of disease subtype

dnPDRBD-RP
(FDG-PET)

DAT-pattern
(FP-CIT PET)

DLB-cortical thickness pattern
(MRI)

Multimodal imaging in iRBD



Conclusion

1. Combining **multimodal imaging** markers shows a **synergistic** power in predicting disease-subtype specific phenoconversion in iRBD

2. The multimodal imaging marker would be an efficient tool for stratification and measuring outcome of **neuroprotective clinical trials in iRBD**