Combined analysis of neuroimaging and metabolomics data for Parkinson's disease

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Overview of analyses

1) Cohort overview

2) Neuroimaging data analysis (FDG and F-DOPA PET)

3) Metabolomics analysis (cross-sectional & longitudinal)

4) Machine learning analyses:
   a) FDOPA PET
   b) FDG PET
   c) FDOPA PET + metabolomics
   d) FDG PET + metabolomics
   e) ROC curves

Cohort overview

- 60 PD patients and 15 healthy age- and gender-matched controls (University Hospitals Cologne, Giessen and Marburg; Prof. C. Eggers)
- **Medication**: PD patients had been 12 hours off levodopa and 72 hours off dopamine agonists

	PD patients	Controls	P-value
N (female/male)	60 (19/41)	15 (8/7)	.14
Age	65.7 ± 9.0	65.1 ± 8.4	.831
UPDRS III	25.1 ± 9.7	2.1 ± 2.6	.000
H&Y stage	2.3 ± 0.4	-	-
BMI	26.8 ± 4.7	24.6 ± 4.1	.101

Analyses overview

- **Metabolomics**
  - Gas chromatography coupled to mass spectrometry (GC-MS)
  - Determination of metabolomic profiles for blood plasma samples:

    - Baseline: entire cohort (60 patients and 15 controls)
    - Follow-up exam after 1 year: 18 patients

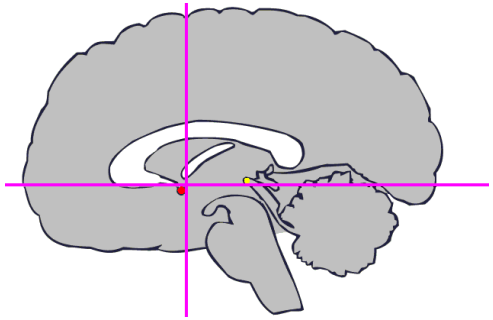
- **Neuroimaging**
  Positron emission tomography (PET):

    - 3,4-dihydroxy-6-18F-fluoro-L-phenyl-alanine (**FDOPA)**
      44 patients and 14 controls
      → How does dopamine metabolism change?

    - 2-[fluorine-18]fluoro-2-deoxy-D-glucose (**FDG)**
      51 patients and 15 controls
      → How does glucose metabolism change?

PET imaging data pre-processing

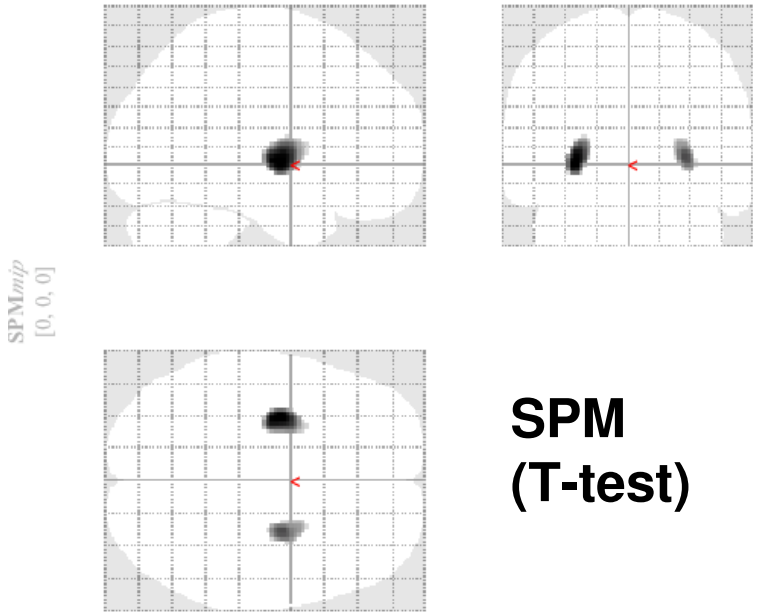
- All pre-processing steps performed in SPM12 (Matlab)
- Co-registration of each subject's averaged FDG and FDOPA images
- Centering on the anterior commissure and horizontal alignment



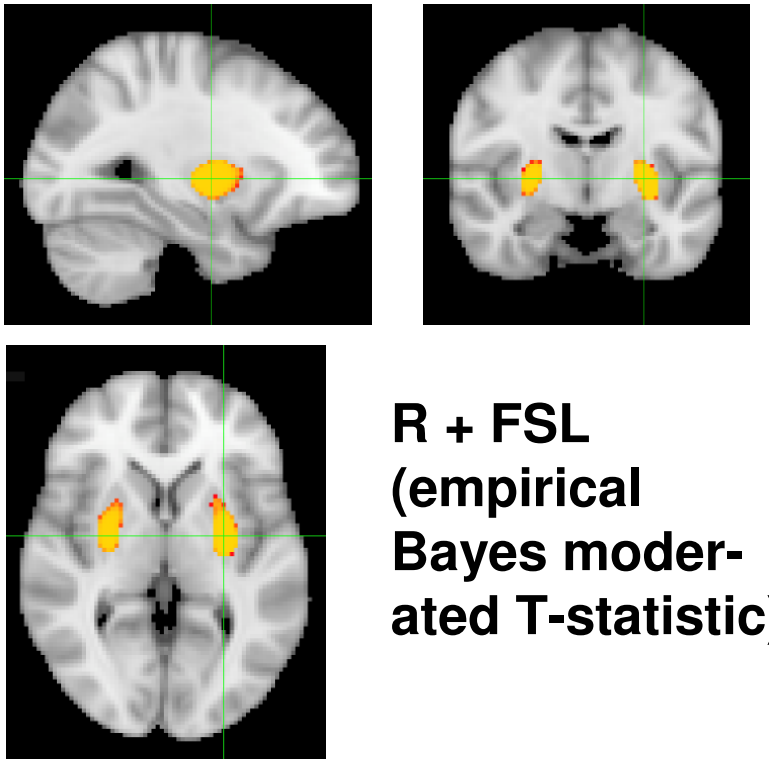
- Spatial normalization to Montreal Neurological Institute standard space (MNI152) performed using tracer-specific templates
- Spatial smoothing (Gaussian kernel, 5 mm FWHM)

FDOPA PET analyses after global mean normalization

FDOPA PET: Significant changes in putamen/striatum (FDR < 0.05)



SPM (T-test)



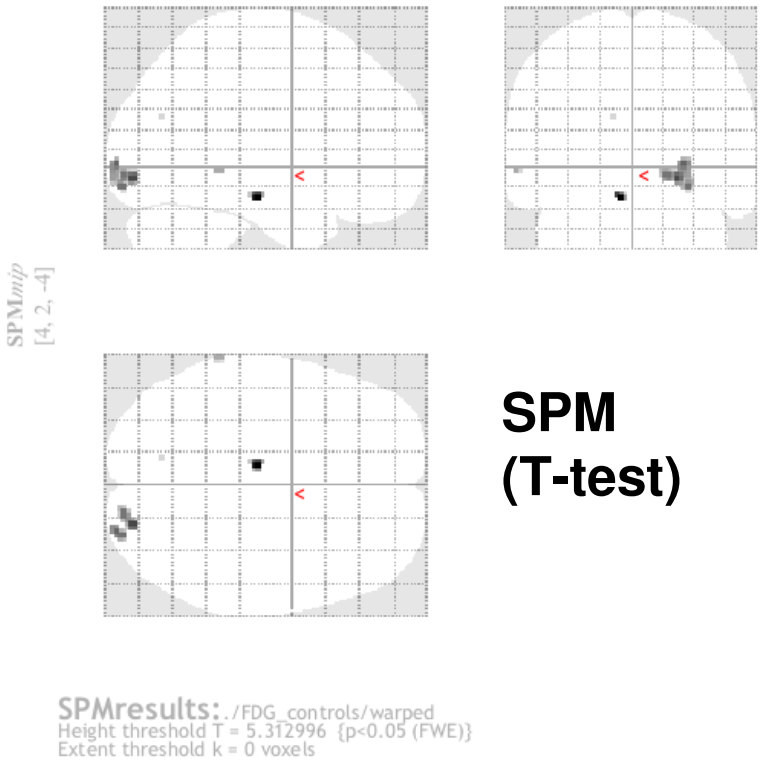
R + FSL (empirical Bayes moder-ated T-statistic)

Best FDR < 1E-3
(only 3 digits behind comma reported)

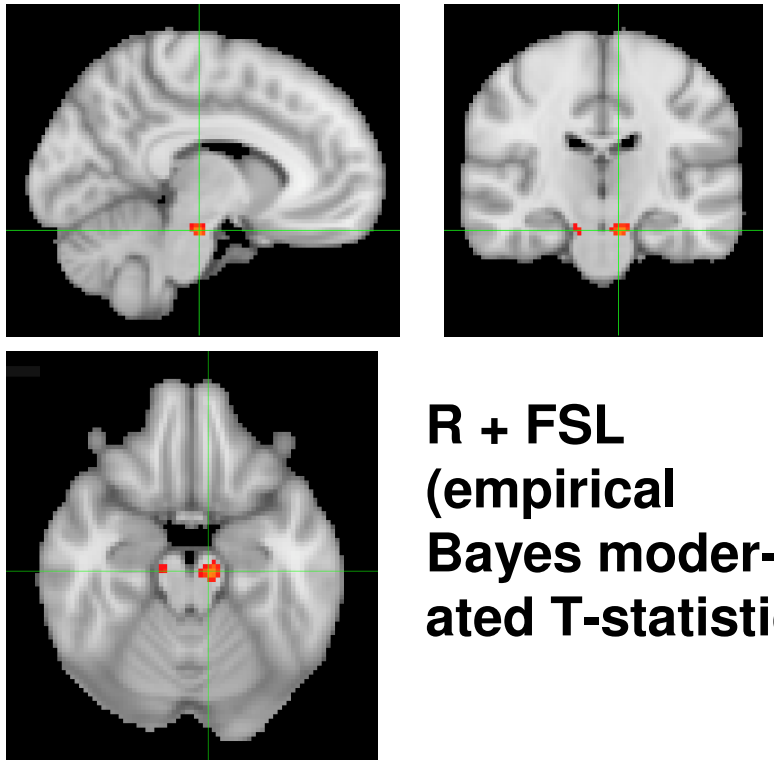
Best FDR < 1.18E-5

FDG PET analyses after global mean normalization

FDG PET: Significant changes in lower midbrain (FDR < 0.05)



SPM (T-test)

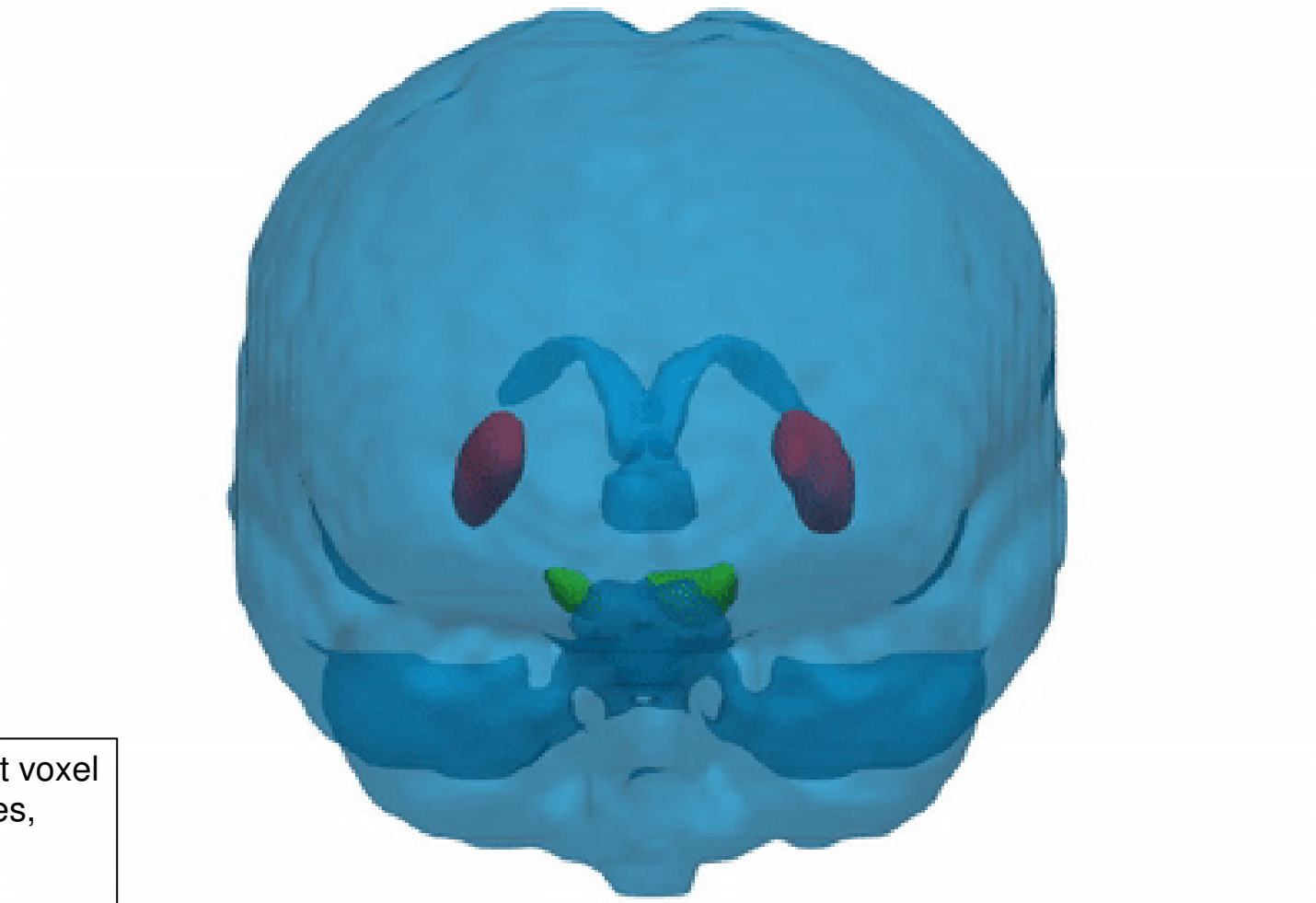


R + FSL (empirical Bayes moder-ated T-statistic)

Best FDR = 0.026 (FWE < 1E-3)

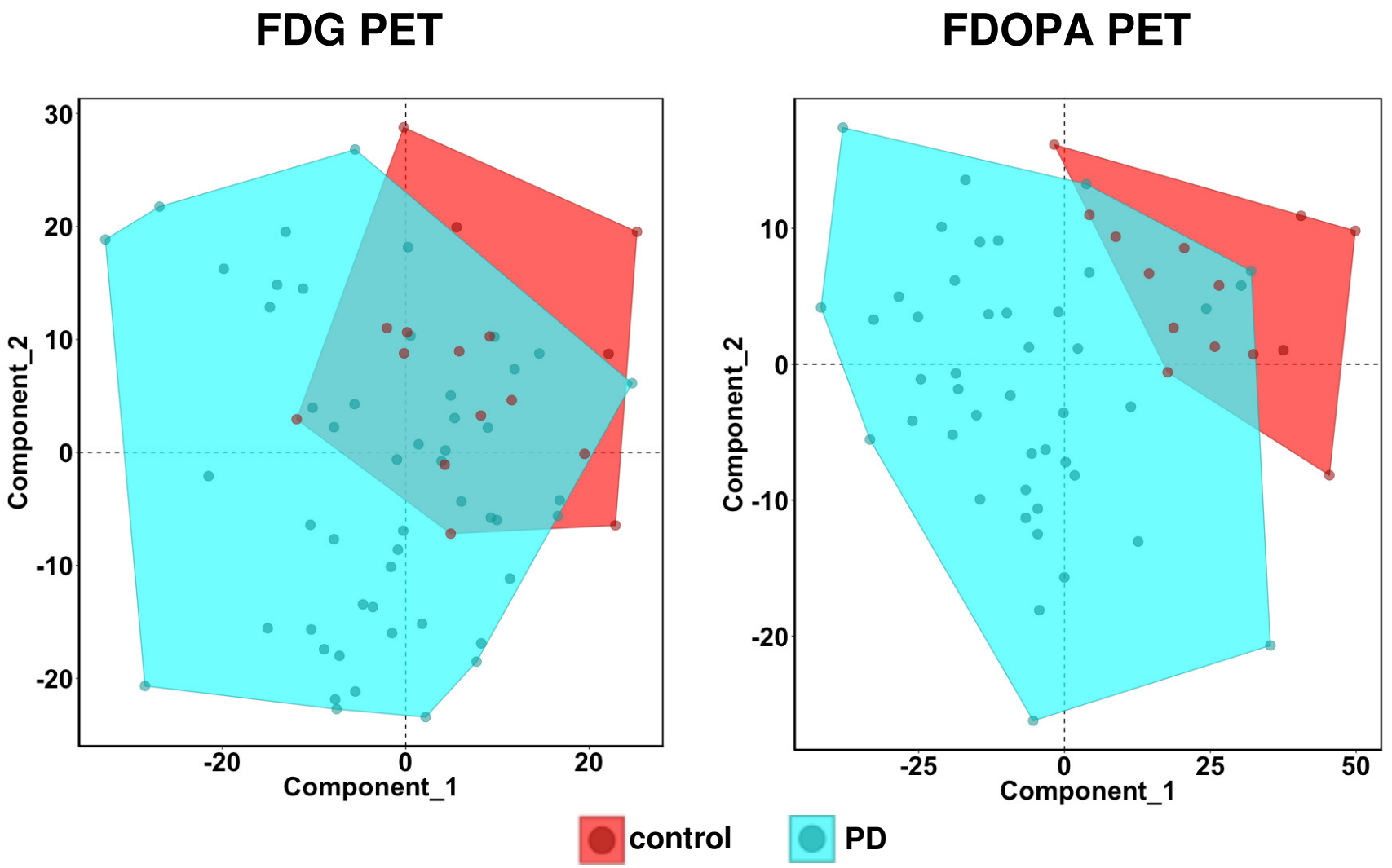
Best FDR = 0.009

FDOPA PET – Visualization of significant clusters



Most significant voxel clusters (eBayes, FDR < 0.05):
- FDOPA
- FDG

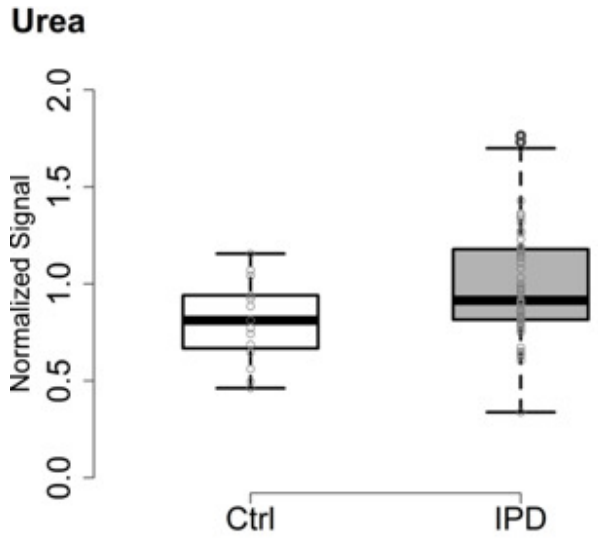
Partial Least Squares Discriminant Analysis



Metabolomics analyses (Baseline)

- 1 unknown metabolite (RI 1446) with higher abundance in PD (FDR < 0.05)
- Urea = top-ranked known metabolite → marker of oxidative stress (but FDR > 0.05, see box plot)

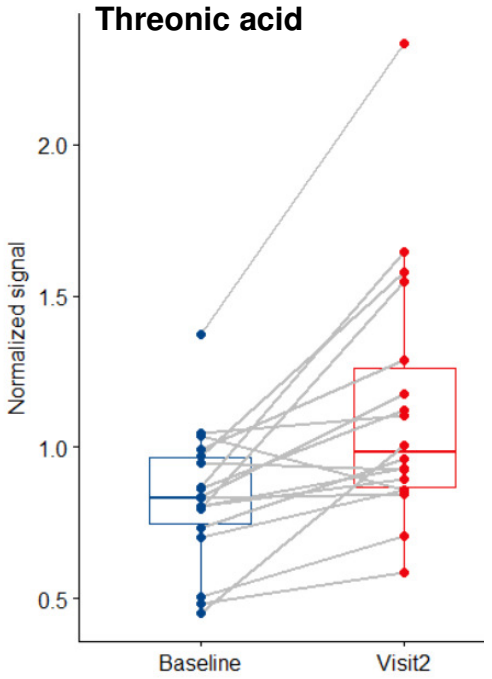
Metabolite	Fold-change	P-value	FDR
RI 1446 (unknown)	1.270	0.001	0.039
Urea	1.262	0.005	0.140
RI 1050 (unknown)	1.324	0.006	0.140
Hexadecanoic acid	1.256	0.030	0.371
Dodecanoic acid	1.403	0.033	0.371



Metabolomics analyses (Longitudinal: Visit 2 vs. Visit 1)

- Threonic and glycolic acid are top-ranked, but FDR > 0.05
- Most top-ranked metabolites tend to have higher abundance in PD

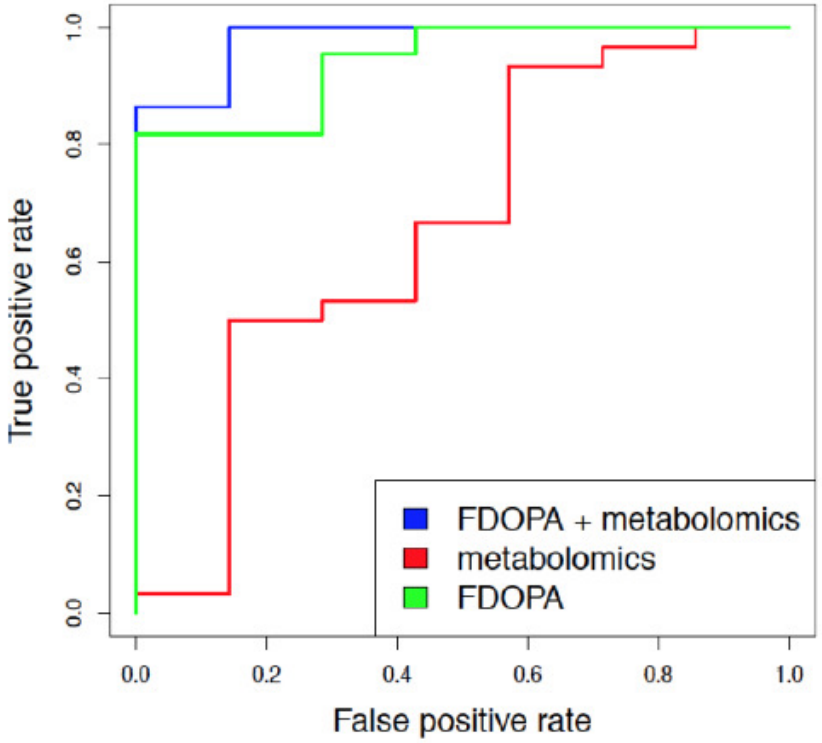
Metabolite	FC	*P*	FDR
Threonic acid	1.353	0.001	0.059
Glycolic acid	1.258	0.002	0.059
Iminodiacetic acid	1.154	0.007	0.140
Glycerol	0.642	0.008	0.140
Succinic acid	1.161	0.029	0.317
Mannose	1.148	0.030	0.317
Glyceric acid	1.229	0.031	0.317
Citric acid	1.144	0.046	0.375
RI 1708	0.876	0.048	0.375



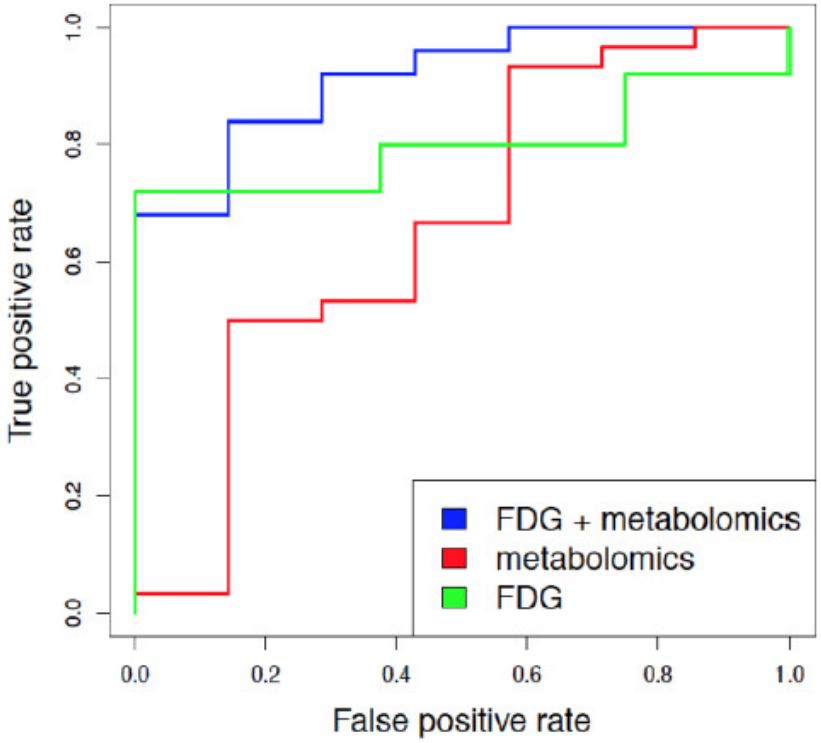
Machine Learning (SVM) – ROC Curve Analyses

Combine attributes from **FDOPA** and **FDG** PET data with **metabolomics data** for the same samples to create integrated machine learning models

ROC curves (FDOPA)



ROC curves (FDG)



Summary

- **PET analyses**: Significant changes in both FDOPA (putamen/striatum) and FDG (midbrain) analysis

- **Metabolomics analyses**: Few significant changes; top-ranked metabolites tend to have associations with oxidative stress and mitochondrial dysfunction

- **Integrated machine learning**: Combination of standardized PET + metabolomics features tends to provide higher predictive performance than PET or metabolomics only

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