Brain function – neurotransmitter co-localization: Effects of aging and deviations in Parkinson's disease

Jan Kasper[1,2], Svenja Caspers[3,4], Leon D. Lotter[1,2,5], Felix Hoffstaedter[1,2], Simon B. Eickhoff[1,2], Jürgen Dukart[1,2]

[1]Institute of Systems Neuroscience, Heinrich Heine University Düsseldorf, Düsseldorf, Germany
[2]Institute of Neuroscience and Medicine (INM-7), Research Centre Jülich, Jülich, Germany
[3]Institute of Neuroscience and Medicine (INM-1), Research Centre Jülich, Jülich, Germany
[4]Institute of Anatomy I, Medical Faculty & University Hospital Düsseldorf, Heinrich Heine University Düsseldorf, Düsseldorf, Germany
[5]Max Planck School of Cognition, Leipzig, Germany

Introduction

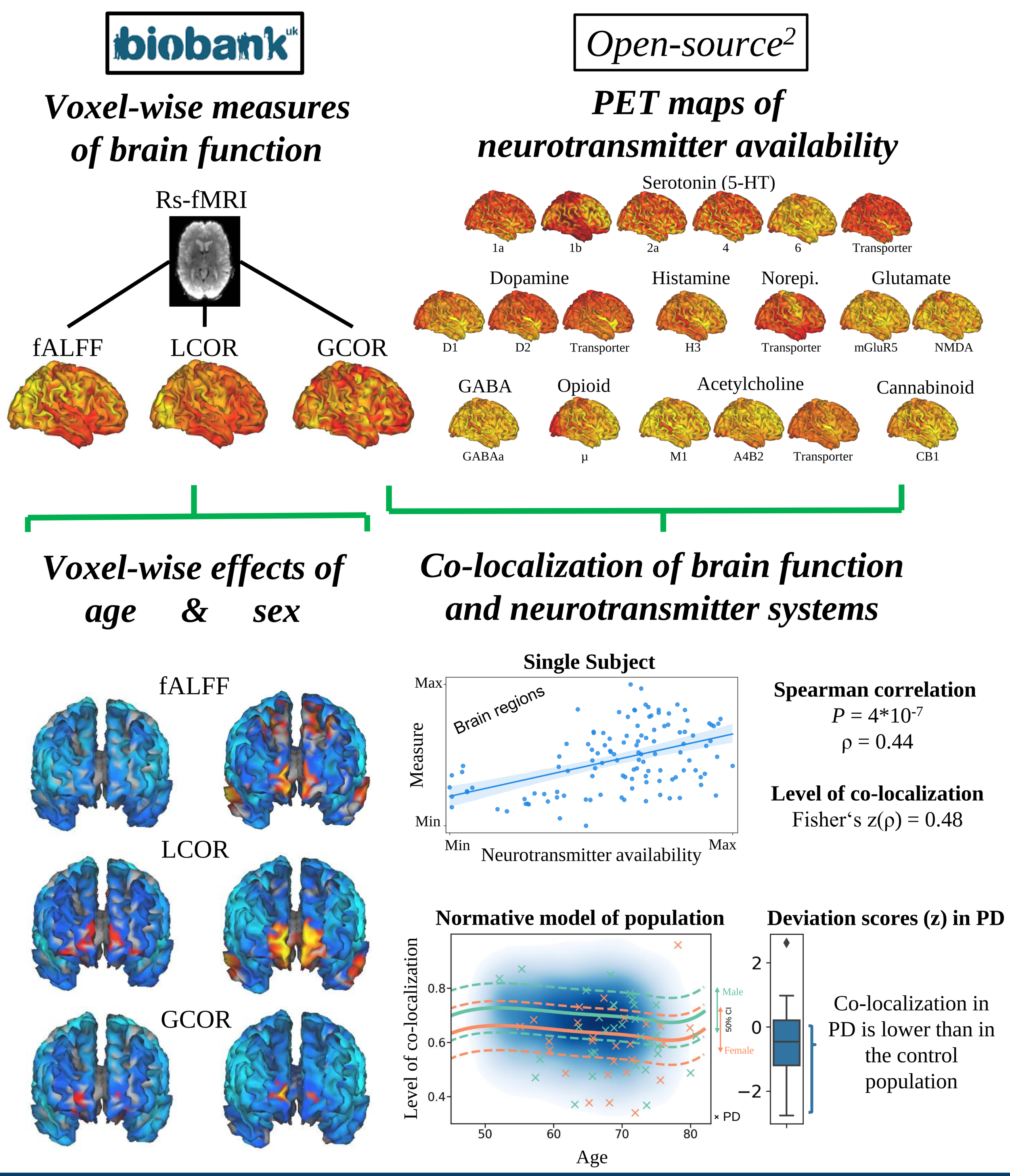
Background

- Aging is major risk factor[1] for neurodegenerative diseases (ND), like Parkinson's disease (PD), Alzheimer's disease, etc.
- Previous research on age-related brain alterations on multiple levels:
  - *Structural*, like connectivity or volumes
  - *Chemical*, like neurotransmitter (NT) systems
  - *Functional*, like local activity or synchronicity
- Sparse research on interrelationships between different levels, such as co-localizations of brain function and neurotransmitter systems
- Aging effects and deviations from normal co-localization in patients with ND may contribute to understanding the mechanisms underlying brain aging and disease-related brain pathology

Objectives

- Which neurotransmitter systems co-localize with brain function?
- **A)** Does co-localization change (sex dependent) during aging?
- **B)** Do patients with PD deviate from the normal range?
- **C)** Do aging effects and sex differences in brain function co-localize with NT systems?

Methods



Cohorts

- 26k Healthy controls (44 - 82 years; 54% F)
- 58 Patients with PD (52 - 80 years; 45% F)

Voxel-wise measures of activity & synchronicity

- Fractional amplitude of low-frequency fluctuations (fALFF) ~ *brain activity*
- Local correlation (LCOR) ~ *local synchronicity*
- Global correlation (GCOR) ~ *global synchronicity*
- Aging effects and sex differences (multiple linear regression and T-contrast) using SPM12[2]

Co-localization analyses

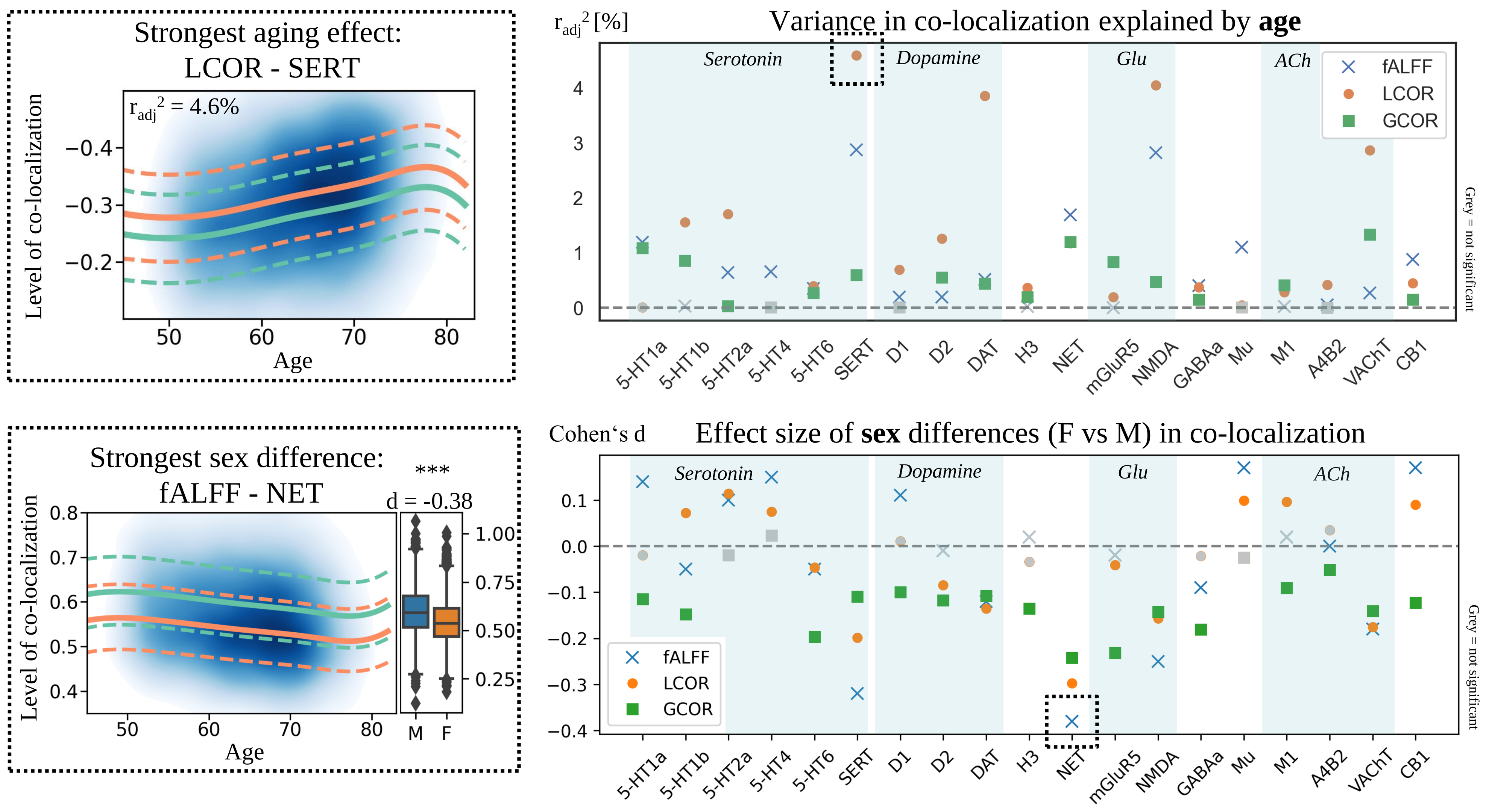
- Individual Spearman correlation between brain function and 19 NT systems (*co-localizations*) using JuSpace[3] ➔ Fisher's z(Spearman ρ)
- Aging effects (linear regression) and sex differences (t-tests) in Fisher's z(Spearman ρ)
- Normative modeling of co-localizations using PCNtoolkit[4]

Parkinson's disease analyses

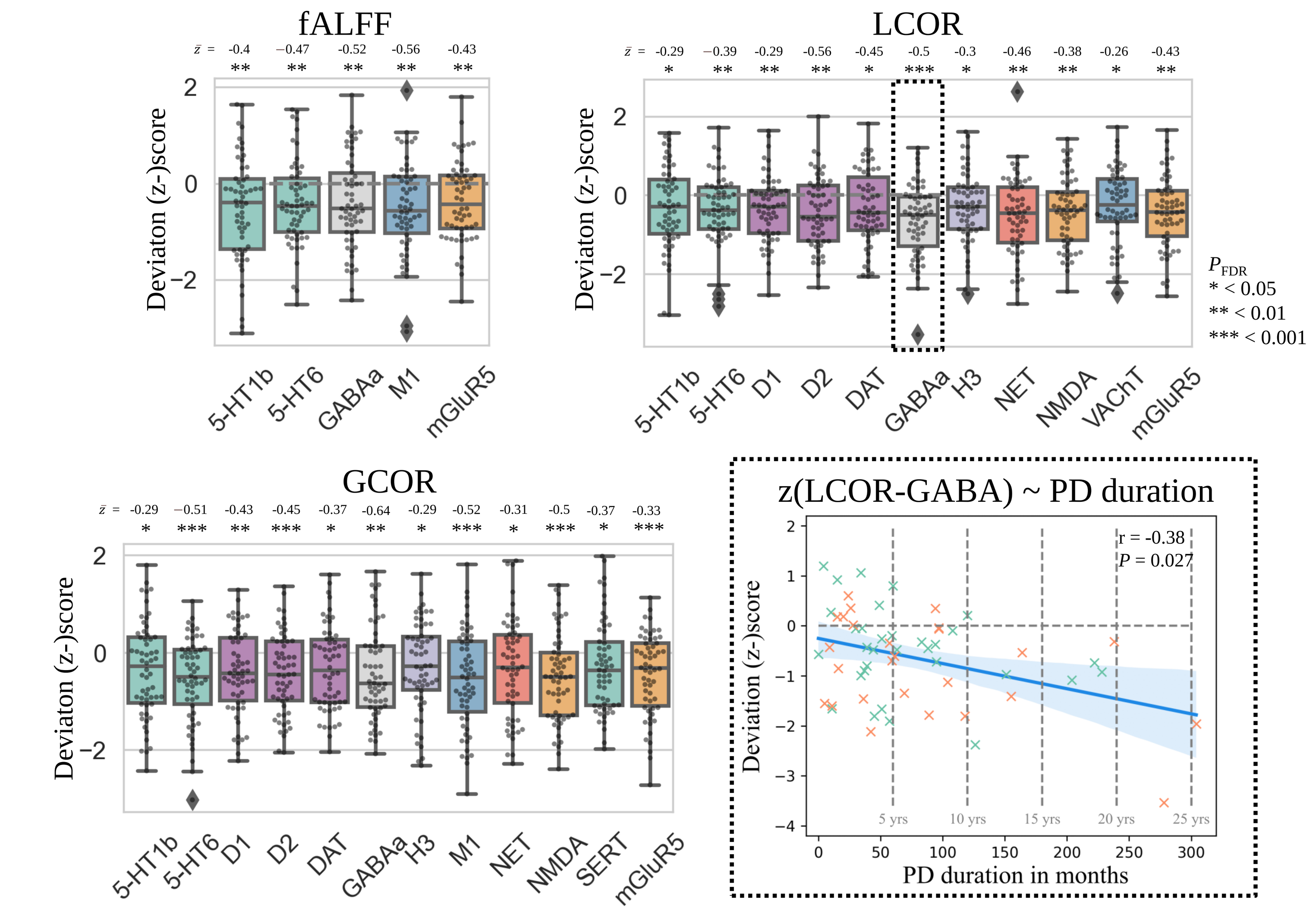
- Identify NT systems regarding which PD deviate significantly (t-test on z-scores) from the norm
- Correlation of deviation with disease duration

Results

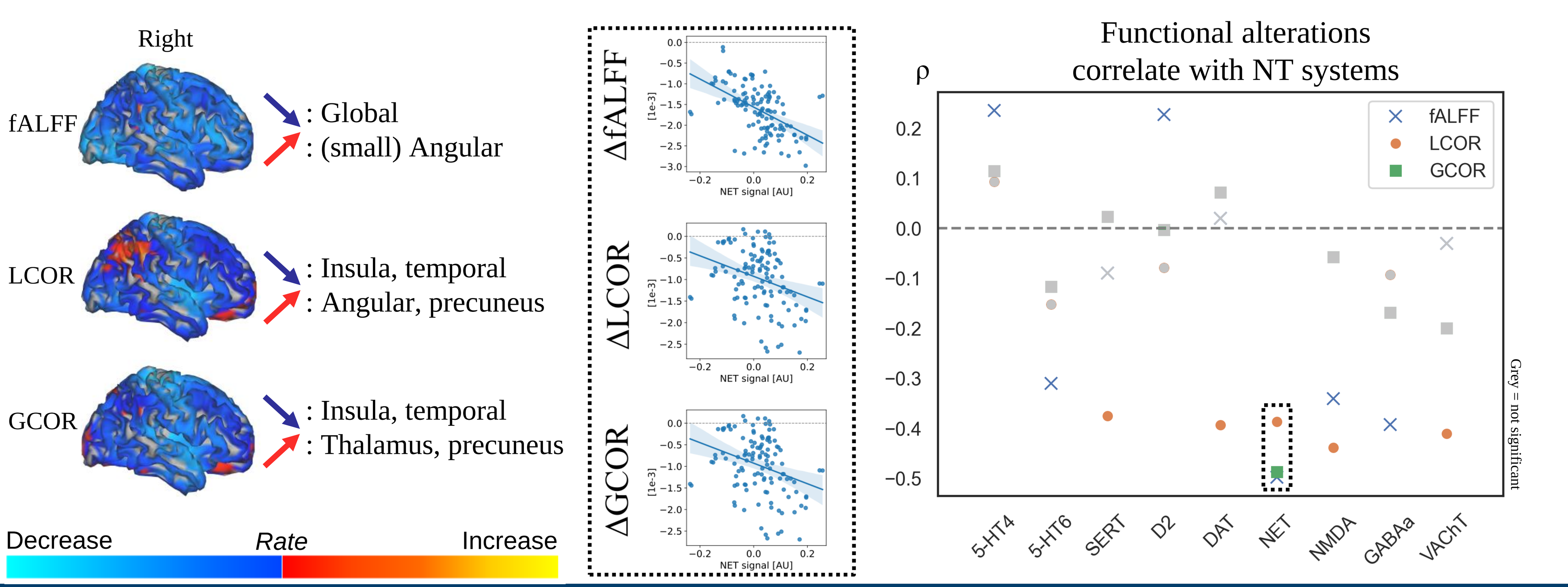
A) Aging effects and sex differences in co-localization



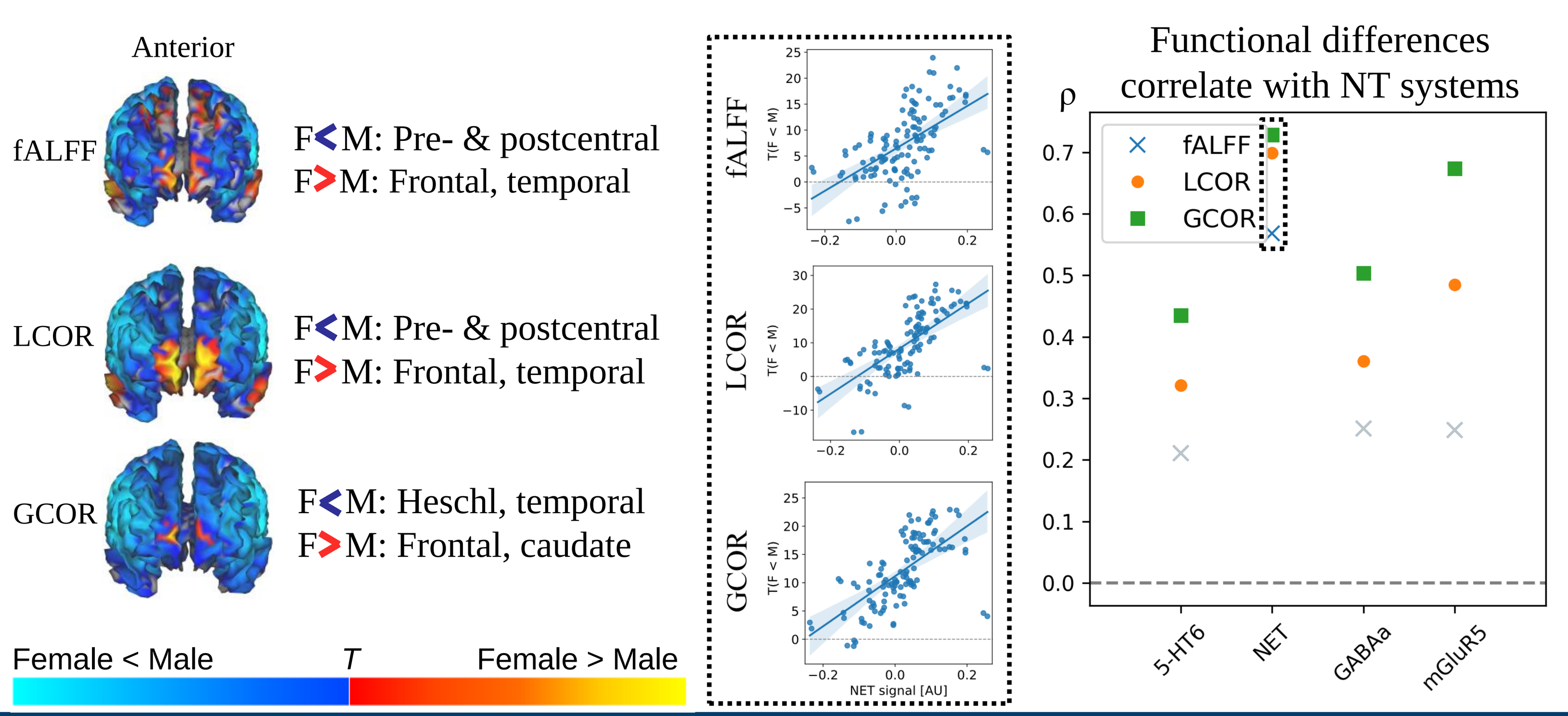
B) Deviations in Parkinson's disease



C1) Aging effects on brain function co-localize with NT systems



C2) Sex differences in brain function co-localize with NT systems



Discussion

- Both aging and sex differences have strong effects on brain function – neurotransmitter co-localizations. Taking them into is crucial for deriving appropriate deviation scores
- NET rich regions may be particularly vulerable to brain function changes during aging. NET is involved in cognitive functions known to be impaired in the elderly, including working memory, cognitive control, and neuronal plasticity[5]
- Effects of aging and sex differences on local brain activity and synchronicity are similar but more widespread than in previous studies[6-9]
- Deviations from normal co-localization levels were found for neurotransmitter whose availability was reported to be altered in PD[10-26]. We found evidence for potentially impaired NT systems (5-HT4, 5-HT6, D1, and μ) in PD for which deviations from normal levels had either not previously been found or had not yet been investigated[27-30]

Limitations

- Limited generalizability due to *healthy controls bias*[31] in the UK-Biobank: Participant are socioeconomically advantaged, drink less alcohol, and smoke less than a nationally representative cohort
- PD duration is only proxy for disease staging
- PET maps of healthy subjects are proxy for true distribution of NT systems. Unfortunately, there is little longitudinal PET data from healthy subjects

[1]: Hou et al., 2019: Ageing as a risk factor for neurodegenerative disease; DOI: 10.1038/s41582-019-0244-7
[2]: Hansen et al., 2022: Mapping neurotransmitter systems to the structural and functional organization of the human neocortex; DOI: 10.1038/s41593-022-01186-3
[3]: Dukart et al., 2021:JuSpace: A tool for spatial correlation analyses of magnetic resonance imaging data with nuclear imaging derived neurotransmitter maps; DOI: 10.1002/hbm.25244
[4]: Rutherford et al., 2022: The normative modeling framework for computational psychiatry; DOI: 10.1038/s41596-022-00696-5
[5]: Lee & Kim, 2022: Normal Aging Induces Changes in the Brain and Neurodegeneration Progress: Review of the Structural, Biochemical, Metabolic, Cellular, and Molecular Changes; DOI:10.3389/fnagi.2022.931536
[6]: Hu et al., 2014: Changes in cerebral morphometry and amplitude of low-frequency fluctuations of BOLD signals during healthy aging: correlation with inhibitory control. DOI:10.1007/s00429-013-0548-0
[7]: Vieira et al., 2020: Evidence of regional associations between age-related inter-individual differences in resting-state functional connectivity and cortical thinning revealed through a multi-level analysis. DOI:10.1016/j.neuroimage.2020.116662
[8]: Wu et al., 2007: Normal aging decreases regional homogeneity of the motor areas in the resting state. DOI:10.1016/j.neulet.2007.06.057
[9]: Bernier et al., 2017: Spatial distribution of resting-state BOLD regional homogeneity as a predictor of brain glucose uptake: A study in healthy aging. DOI:10.1016/j.neuroimage.2017.01.055
[10]: Kaasinen et al., 2021: Dopamine Receptors in Parkinson's Disease: A Meta-Analysis of Imaging Studies. DOI:10.1002/mds.28632
[11]: Kaasinen et al., 2000: Extrastriatal dopamine D2 and D3 receptors in early and advanced Parkinson's disease. DOI: 10.1212/WNL.54.7.1482
[12]: Seeman et al., 1990: Dopamine receptors and transporters in Parkinson's disease and schizophrenia. DOI: 10.1096/fasebj.4.10.2197154
[13]: Politis et al., 2008: Evidence of dopamine dysfunction in the hypothalamus of patients with Parkinson's disease: An in vivo 11C-raclopride PET study. DOI: 10.1016/j.expneurol.2008.07.021
[14]: Takashima et al., 2022: In vivo Illustration of Altered Dopaminergic and GABAergic Systems in Early Parkinson's Disease. DOI: 10.3389/fneur.2022.880407
[15]: Yao et al., 2020: Positron emission computed tomography/single photon emission computed tomography in Parkinson disease. DOI: 10.1097/CM9.0000000000000836
[16]: Huot et al., 2011: The serotonergic system in Parkinson's disease. DOI: 10.1016/j.pneurobio.2011.08.004
[17]: Melse et al., 2014: Changes in 5-HT2A Receptor Expression in Untreated, de novo Patients with Parkinson's Disease. DOI: 10.3233/JPD-130300
[18]: Varrone et al., 2014: Positron emission tomography imaging of 5-hydroxytryptamine1B receptors in Parkinson's disease. DOI: 10.1016/j.neurobiolaging.2013.08.025
[19]: Kang et al., 2019: 18F-FPEB PET/CT Shows mGluR5 Upregulation in Parkinson's Disease: mGluR5 and DaT in PD. DOI: 10.1111/jon.12563
[20]: Zhang et al., 2019: Roles of Glutamate Receptors in Parkinson's Disease. DOI: 10.3390/ijms20184391
[21]: Sharma et al., 2021: Histamine H3 and H4 receptors modulate Parkinson's disease induced brain pathology. Neuroprotective effects of nanowired BF-2649 and clobenpropit with anti-histamine-antibody therapy. DOI: 10.1016/bs.pbr.2021.06.003
[22]: Meyer et al., 2014: Radioligand imaging of α4β2* nicotinic acetylcholine receptors in Alzheimer's disease and Parkinson's disease.
[23]: Asahina et al., 1998: Brain muscarinic receptors in progressive supranuclear palsy and Parkinson's disease: a positron emission tomographic study. DOI: 10.1136/jnnp.65.2.155
[24]: Van der Zee et al., 2022: Altered Cholinergic Innervation in De Novo Parkinson's Disease with and Without Cognitive Impairment. DOI: 10.1002/mds.28913
[25]: Nahimi et al., 2018: Molecular Imaging of the Noradrenergic System in Idiopathic Parkinson's Disease. DOI: 10.1016/bs.irn.2018.07.028
[26]: Brumberg et al., 2019: PET imaging of noradrenaline transporters in Parkinson's disease: focus on scan time. DOI: 10.1007/s12149-018-1305-5
[27]: Miguelez et al., 2014: Interaction between the 5-HT system and the basal ganglia: functional implication and therapeutic perspective in Parkinson's disease. DOI: 10.3389/fncir.2014.00021
[28]: Niccolini et al., 2014: Dopamine receptor mapping with PET imaging in Parkinson's disease. DOI: 10.1007/s00415-014-7302-2
[29]: Shinotoh et al., 1993: Dopamine D1 receptors in Parkinson's disease and striatonigral degeneration: a positron emission tomography study. DOI: 10.1136/jnnp.56.5.467
[30]: Thobois et al., 2018: Molecular Imaging of Opioid System in Idiopathic Parkinson's Disease. DOI: 10.1016/bs.irn.2018.07.029
[31]: Fry et al., 2017: Comparison of Sociodemographic and Health-Related Characteristics of UK Biobank Participants With Those of the General Population; DOI: 10.1093/aje/kwx246

Acknowledgments: Thanks a lot to my colleagues and tutors: Svenja Caspers (INM-1), Leon D. Lotter (INM-7), Felix Hoffstaedter (INM-7), Simon Eickhoff (INM-7), Jürgen Dukart (INM-7) + Team of INM-7 for their support in organization and data management!