Poster number: 2811

Molecular Signatures of Cortical Thickness Alterations in Fragile X Syndrome



Rachel Bamberger[1], Simon B. Eickhoff[1,2], Juergen Dukart[1,2], Leon D. Lotter[1,2,3]

[1] Institute of Neuroscience and Medicine, Brain & Behavior (INM-7), Research Centre Jülich, Jülich, Germany | [2] Institute of Systems Neuroscience, Heinrich Heine University, Duesseldorf, Germany | [3] Max Planck School of Cognition, Leipzig, Germany

JÜLICH Forschungszentrum

Introduction

Fragile X syndrome (FrX) is a neurodevelopmental disorder caused by FMR1 gene mutation → monogenic cause for autism-spectrum-disorder (ASD)[1]

Studies report enlarged brain volumes[2] and increased cortical thickness (CT)[3]

Gap: Limited knowledge about underlying molecular processes, i.e. neurotransmitter systems

Potential solution: Colocalization analysis (spatial correlations) between MRI-derived maps and independent molecular reference maps

Aim: Link CT alterations in FrX to underlying neurobiology using colocalization analysis

Methods

OpenNeuro[4]

Sample Data
- n=12 FrX
- n=16 controls
- 18-24 years (M=21.32), all male

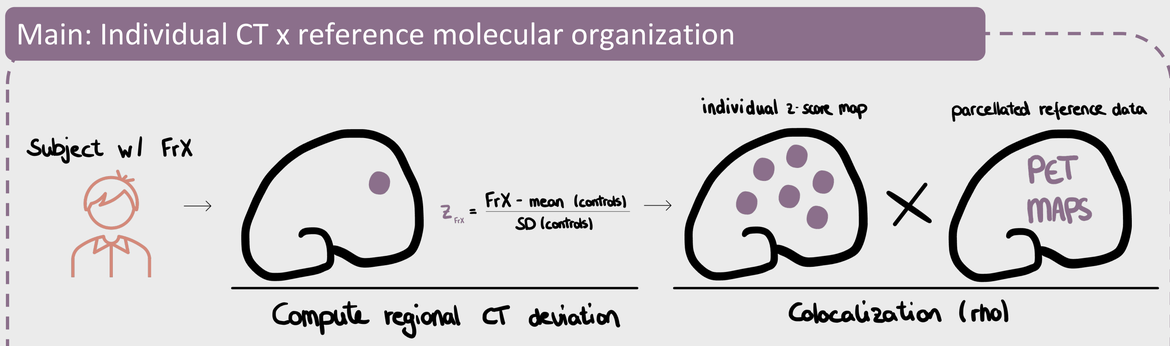
FastSurfer[5]

Preprocessing
- CT estimates
- 360 Glasser/ MMP parcellation

NiSpace[6]

Analysis Toolbox
- Spatial colocalization toolkit
- Parcellated reference data (e.g. PET maps)

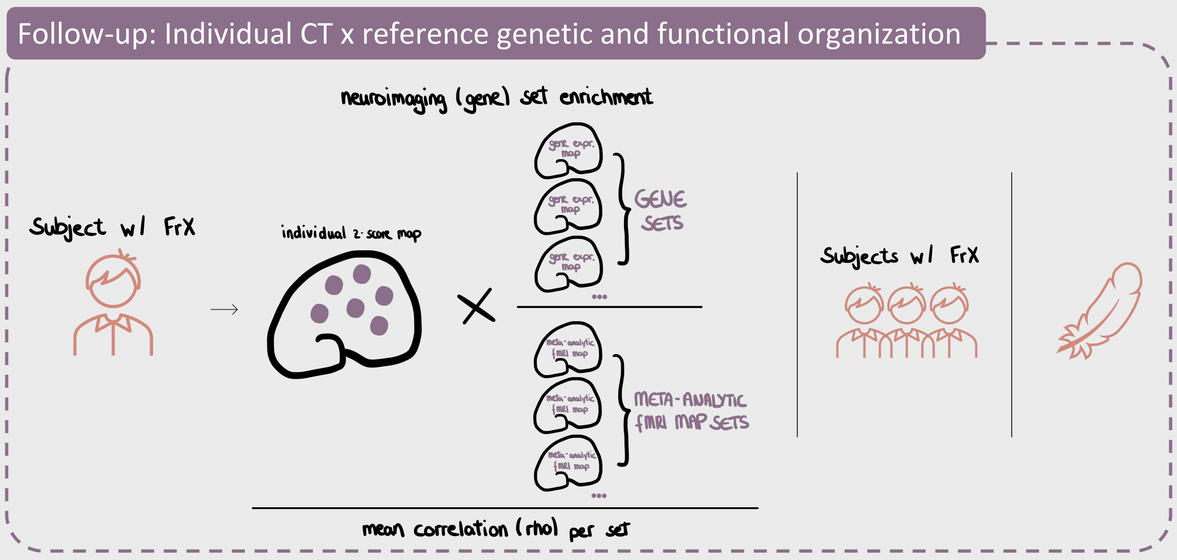
Main: Individual CT x reference molecular organization



Subjects w/ FrX
- Group-level summary: average rho for FrX group
- Permutation testing (group label shuffling)
- Multiple comparison correction: effective number of tests (M_{eff})

Sensitivity analyses:
- Covariate correction for age, Euler number, intracranial volume
- Centile scores as non-parametric alternative to z-scores

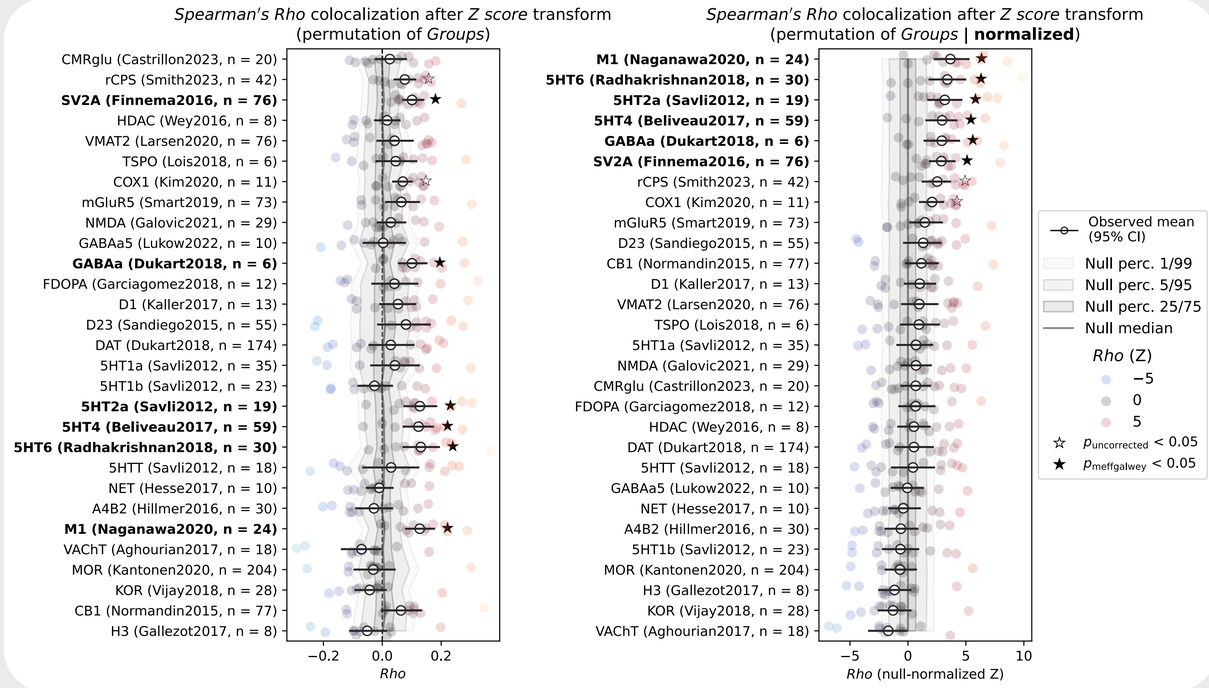
Follow-up: Individual CT x reference genetic and functional organization



Reference datasets

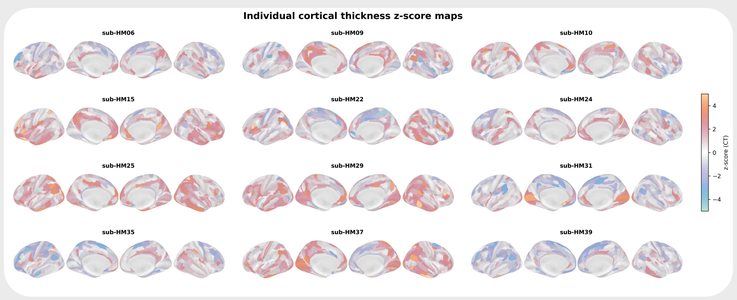
Datasets integrated in NiSpace *(see Poster Nr. 0341)*
- **PET**: 29 unique tracer maps (neurotransmitter receptors & transporters)
- **Gene sets**: *MAGICC*[7] – *SynGO*[8] synaptic functions (166 sets x 9270 genes)
- **Meta-analytic fMRI maps**: *Neurosynth*[9] – *'Cognitive Functions'* (10 sets x 101 terms)

Results

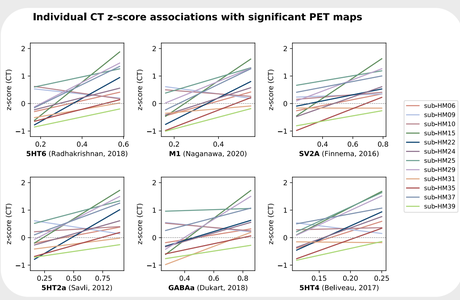


Group-level: higher CT in FrX is spatially associated with high normative cholinergic, serotonergic, GABAergic and synaptic (SV2A) density distributions – cf. neurotransmitter dysregulation in FrX animal models[10,11]

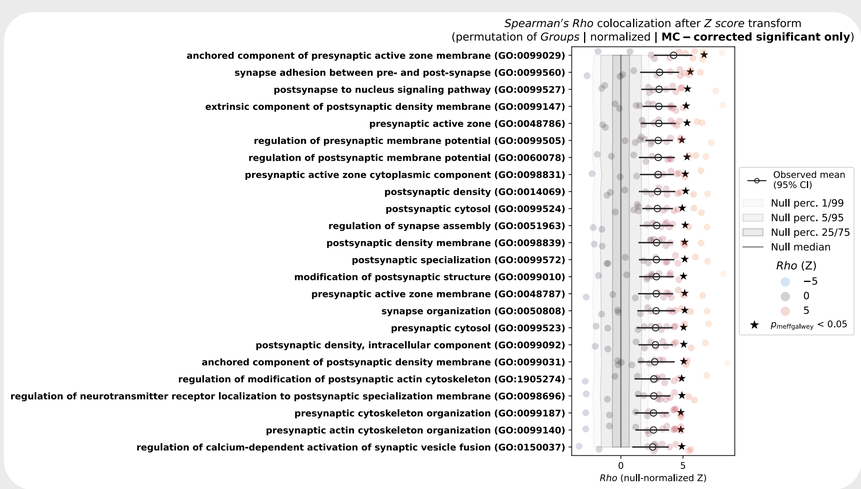
Subject-level: highly homogeneous SV2A effect – cf. role of fragile X mental retardation protein (FMRP) in synaptic formation and pruning[12] and synaptic vesicle regulation[13]



Similar deviation patterns: pronounced alterations in prefrontal (dorsolateral, orbitofrontal), temporo-parietal, occipital regions

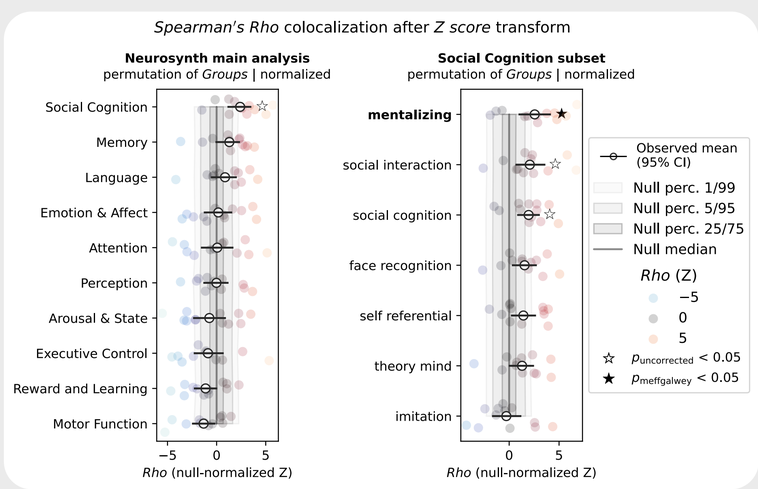


Intra-individual effects: colocalization direction consistent across all 6 PET maps



Individual CT x reference genetic organization

- Effects across pre- and postsynaptic structure and signaling (postsynaptic dominance)
- Conceptual overlap with ASD-associated genes[14] at gene ontology level (e.g. synapse, synaptic vesicle, neurotransmitter transport)



Individual CT x reference functional organization

- CT alterations colocalise with regions consistently activated in social-cognitive processes, especially mentalizing
- Aligns with known social cognition and theory-of-mind deficits in FrX[15]

Largely stable results regarding direction and strength of effects for all reference datasets

Conclusion

- Spatial colocalization analysis links CT alterations in FrX to molecular and functional reference data across PET, transcriptomic, and meta-analytic fMRI maps
- Results align with known FrX molecular and behavioural phenotype
- Validation studies are needed to confirm reliability and interpretability of results

MRI-based colocalization analysis shows promise for exploring neurobiological mechanisms in neurodevelopmental disorders

References: **(1)** Protic et al., 2022, *Int J Mol Sci*. https://doi.org/10.3390/ijms23041935 | **(2)** Payne et al., 2025, *Mol Psychiatry*. https://doi.org/10.1038/s41380-024-02863-4 | **(3)** Meguid et al., 2012, Brain Cogn. https://doi.org/10.1016/j.bandc.2011.09.005 | **(4)** Schmidt et al., 2023, OpenNeuro. https://doi.org/10.18112/openneuro.ds004654.v1.0.1 | **(5)** Reuter et al., 2025, Zenodo. https://doi.org/10.5281/zenodo.14894486 | **(6)** Lotter & Dukart, 2024, Zenodo. https://doi.org/10.5281/zenodo.12514622 | **(7)** Hawrylycz et al., 2012, Nature. https://doi.org/10.1038/nature11405 | **(8)** Koopmans et al., 2019, Neuron. https://doi.org/10.1016/j.neuron.2019.05.002 | **(9)** Yarkoni et al., 2011, Nat Methods. https://doi.org/10.1038/nmeth.1635 | **(10)** Davidovic et al., 2011, Genome Res. https://doi.org/10.1101/gr.116764.110 | **(11)** Du et al., 2026, Sci Rep. https://doi.org/10.1038/s41598-025-34492-4 | **(12)** Swanger & Bassell, 2011, Curr Opin Genet Dev. https://doi.org/10.1016/j.gde.2011.04.002 | **(13)** Broek et al., 2016, Mol Autism. https://doi.org/10.1186/s13229-016-0080-1 | **(14)** Voineagu et al., 2011, Nature. https://doi.org/10.1038/nature10110 | **(15)** Hiralal et al., 2026, J Neuropsychol. https://doi.org/10.1111/jnp.70048 | Header image AI-generated (ChatGPT, OpenAI)

Corresponding Author

Rachel Bamberger

r.bamberger@fz-juelich.de

Poster PDF