Quantifying Sex-Related Brain Variation: Brain-Based Sex Scores and Clinical Heterogeneity in Schizophrenia

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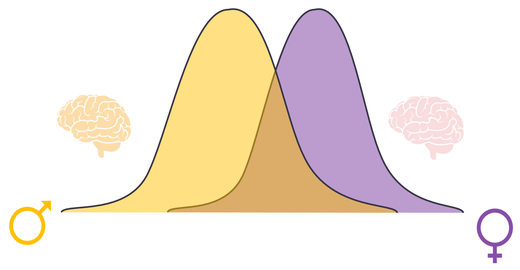
Introduction

- ✓ Sex differences in schizophrenia are well-documented in terms of age of onset, symptoms, and treatment response (Ochoa et al., 2012; Riecher-Rössler et al., 2018).
- ✓ Sex is often treated as a covariate rather than a primary variable of interest.
- ✓ "**Sex-scores**" have been proposed to quantify the "maleness/femaleness" of multiple traits, as a complement to biological sex (Vosberg et al., 2021).
- ✓ Sex differences have been detected in the brain showing a considerably overlap between the two sexes (Joel et al. 2015) (Figure 1).

OBJECTIVE

To compute brain sex-scores in patients with schizophrenia and examine their associations with schizophrenia symptoms.



Brain sex-scores
Quantitative values of biological sex based on brain features

Figure 1. Representation of the continuum and overlap of brain features between males and females

Methodology

SAMPLES

Table 1. Independent sample used to derive sex weights for the computation of sex-scores

Sample A Healthy individuals		
Sex	n	Age (SD)
Males	215	49.9 (4.81)
Females	211	46.5 (4.85)

Table 2. Sample in which sex-scores were computed

Sample B Schizophrenia Patients		
Sex	n	Age (SD)
Males	173	38.95 (11.88)
Females	64	41.57 (11.08)

T1w MRI — Each individual underwent T1w MRI

34 Desikan Killiany (DK) regions — Cortical Thickness (CT), Surface Area (SA) extracted for each DK region

1 In **Sample A** (Table 1), linear regressions were performed for each DK region considering age as covariate and sex as factor for cortical thickness (CT) and surface area (SA).

Sample A CT ~ Age + Sex → CT $\beta_{Sex\text{-}SAMPLE\ A}$

Sample A SA ~ Age + Sex → SA $\beta_{Sex\text{-}SAMPLE\ A}$

2 Sex betas ($\beta_{Sex\text{-}SAMPLE\ A}$) of each linear regression were multiplied for the values of CT/SA from individuals in **Sample B** (Table 2), summed up and normalized to obtain a CT sex-score or SA sex-score ranging from 0 (max maleness) and 1 (max femaleness) for each individual.

CT Sex-score = $\sum$ CT Sample B* CT $\beta_{Sex\text{-}SAMPLE\ A}$

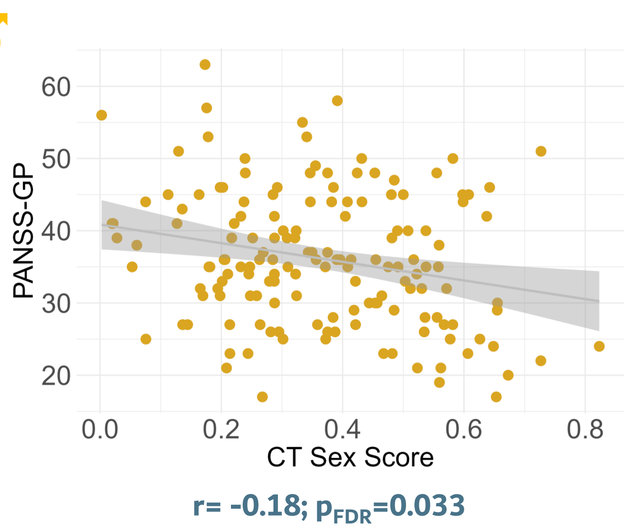
SA Sex-score = $\sum$ SA Sample B* SA $\beta_{Sex\text{-}SAMPLE\ A}$

3 The correlations between SA/CT sex-scores and Positive and Negative Syndrome Scale (PANSS) were tested within each sex group.

- Positive (P)
- Negative (N)
- General Psychopathology (GP)

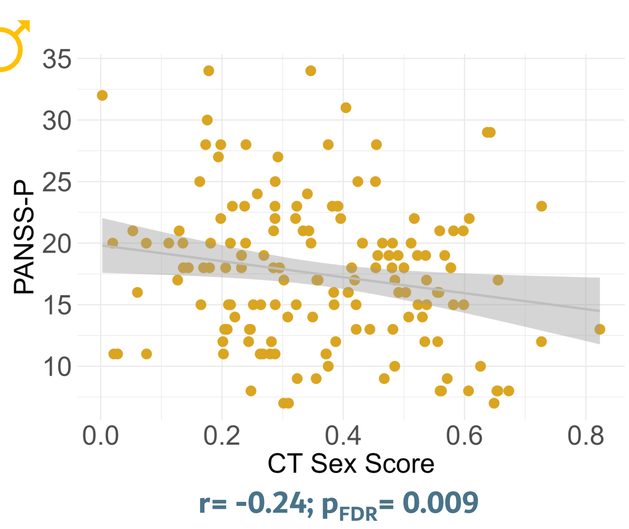
Results

Correlation: CT Sex-score and PANSS-GP



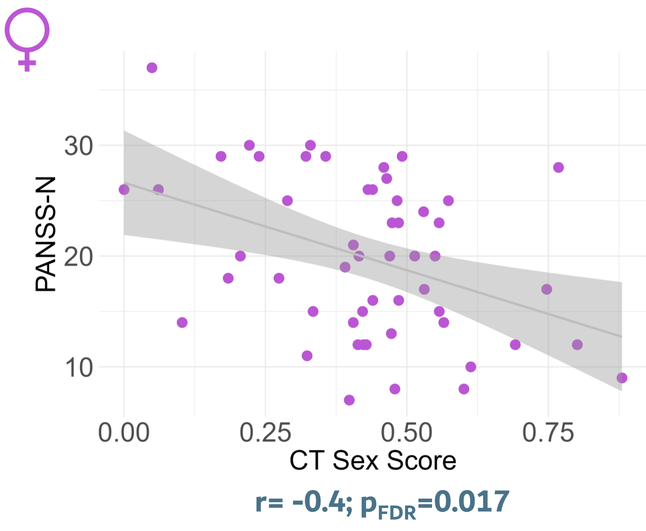
r= -0.18; p_{FDR}=0.033

Correlation: CT Sex-score and PANSS-P



r= -0.24; p_{FDR}= 0.009

Correlation: CT Sex-score and PANSS-N



r= -0.4; p_{FDR}=0.017

No significant correlations between SA Sex-scores and PANSS were detected

Conclusions

Independently of chromosomal sex, our findings suggest that lower CT sex-scores (associated with greater maleness) are related to more severe symptoms.

Our results highlight the importance of considering sex-related variability in a quantitative manner, beyond its binary consideration.

Sex-scores emerge as a useful tool to study sex- and gender-related variability in the neurobiology and clinical expression of schizophrenia.

References Joel et al. *Proc Natl Acad Sci USA.*2015;112(50):15468-73, DOI: 10.1073/pnas.1509654112;. 2015 Ochoa et al.*Schizophr Res Treat.*2012:916198, DOI: 10.1155/2012/916198; Riecher-Rössler et al. *Arch Womens Ment Health.* 2018;21(6):627–48, DOI: 10.1007/s00737-018-0847-9; Vosberg et al. *Nature Human Behaviour .* 2021; 5(2): 265–272. DOI: 0.1038/s41562-020-00968-8.

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