

Normative modeling of brain morphometry in insomnia disorder

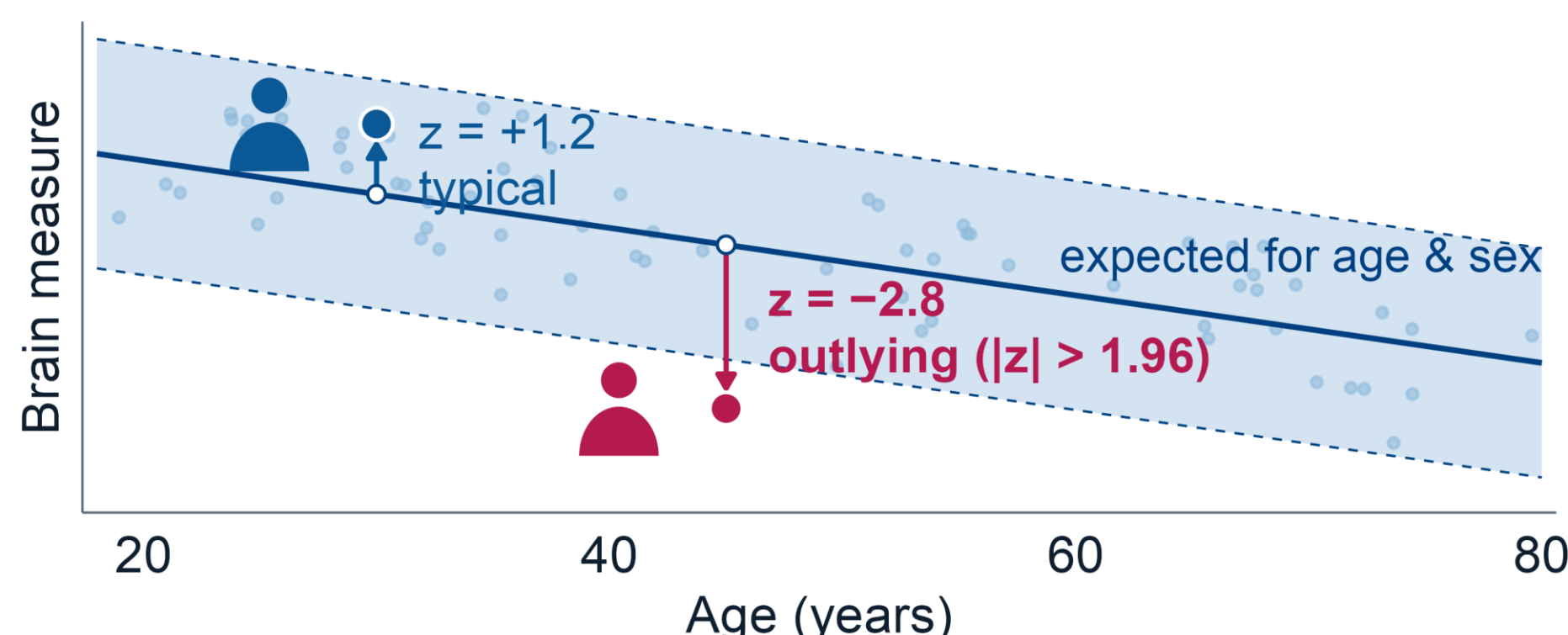
Hanwen Bi^{1,2} · Ellemarije Altena³ · Sahil Bajaj⁴ · Ji Chen^{5,6} · Bryn Evohr⁷ · Jodi Gilman^{7,8} · Hans Grabe^{9,10} · Felix Hoffstaedter^{1,2} · Neda Jahanshad¹¹ · Jolynn Jones¹² · Helmet Karim^{13,14} · Daniel Kay^{15,16} · Habibolah Khazaie¹⁷ · Yu Jin Lee¹⁸ · Xu Lei^{19,20} · Masoumeh Rostampour¹⁷ · Fateme Samea^{1,21} · Ernesto Sanz-Arigita³ · Julian Schiel²² · Kai Spiegelhalder²² · Sophia Thomopoulos¹¹ · Paul Thompson¹¹ · Antoine Weihs^{9,10} · Xiao Yao^{1,23} · Haobo Zhang^{19,20,24} · Simon Eickhoff^{1,2} · Masoud Tahmasian^{1,2,23}

¹Institute of Neuroscience and Medicine, Brain and Behaviour (INM-7), Research Center Jülich, Jülich, Germany ²Institute of Systems Neuroscience, Medical Faculty and University Hospital Düsseldorf, Heinrich Heine University, Düsseldorf, Germany ³Université de Bordeaux, CNRS UMR 5287, INCIA, Bordeaux, France ⁴The University of Texas MD Anderson Cancer Center, Houston, TX, USA ⁵Center for Brain Health and Brain Technology, Global Institute of Future Technology, Shanghai Jiao Tong University, Shanghai, China ⁶School of Psychology, Shanghai Jiao Tong University, Shanghai, China ⁷Center for Addiction Medicine, Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA ⁸Department of Psychiatry, Harvard Medical School, Boston, MA, USA ⁹Department of Psychiatry and Psychotherapy, University Medicine Greifswald, Greifswald, Germany ¹⁰German Center for Neurodegenerative Diseases (DZNE), Site Rostock/Greifswald, Germany ¹¹Mark and Mary Stevens Neuroimaging and Informatics Institute, Keck School of Medicine of USC, University of Southern California, Marina del Rey, CA, USA ¹²Department of Psychiatry, University of Rochester Medical Center, Rochester, NY, USA ¹³Department of Psychiatry, University of Pittsburgh, Pittsburgh, PA, USA ¹⁴Department of Bioengineering, University of Pittsburgh, Pittsburgh, PA, USA ¹⁵Department of Psychology, Brigham Young University, Provo, UT, USA ¹⁶Neuroscience Center, Brigham Young University, Provo, UT, USA ¹⁷Sleep Disorders Research Center, Health Policy and Promotion Institute, Kermanshah University of Medical Sciences, Kermanshah, Iran ¹⁸Department of Psychiatry, Seoul National University Hospital, Seoul, South Korea ¹⁹Sleep and Neuroimaging Center, Faculty of Psychology, Southwest University, Chongqing, China ²⁰Key Laboratory of Cognition and Personality (Southwest University), Ministry of Education, Chongqing, China ²¹Clinic and Polyclinic for Child and Adolescent Psychiatry, Psychotherapy, and Psychosomatics, Medical Faculty, Leipzig University, Leipzig, Germany ²²Department of Psychiatry and Psychotherapy, Medical Centre – University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany ²³Department of Nuclear Medicine, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany ²⁴School of Psychology, Northwest Normal University, Lanzhou, China

TAKE-HOME MESSAGE Insomnia disorder is not associated with overall higher structural brain atrophy. A higher regional thickness in the right temporal pole may reflect specific cognitive and hyperarousal-related processes.

Introduction

- Structural MRI studies of insomnia disorder (ID) report inconsistent findings [1]
- Group comparisons may hide individual variability
- Normative modeling maps each person onto a reference brain chart



Schematic, illustrative data; band = central 95%

Aim

Do patients with ID deviate more from normative brain charts than healthy controls (HC)?

Methods

6 international cohorts · 5 countries

739 participants: 360 HC · 379 ID (DSM-5 / ICD-10)
mean age 40.1 ± 14.3 y · 453 female



1 FreeSurfer measures

Cortical thickness (CT) and surface area (SA) of 68 DK regions; 14 subcortical volumes (SV)

2 Site harmonization

ComBat-GAM [2] removes site effects while keeping nonlinear age effects

3 Normative model

Sex-specific CentileBrain models [3] give the expected value for age and global brain size; $z = (\text{observed} - \text{expected}) / \text{SD}$

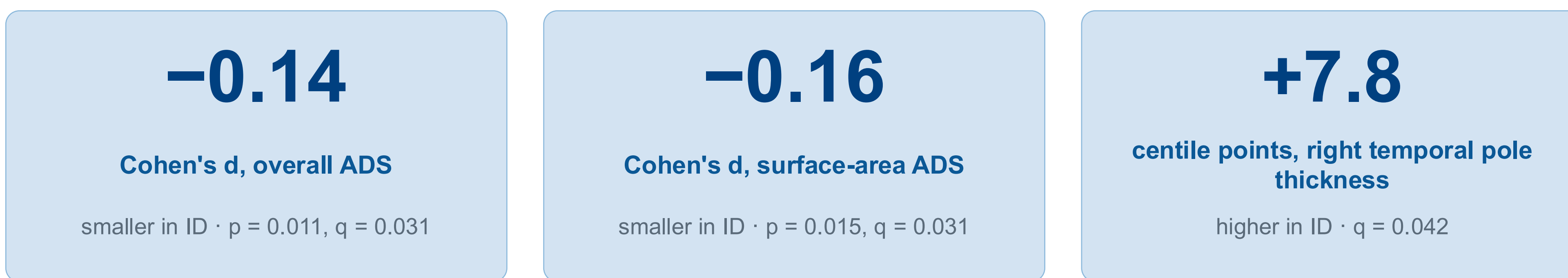
4 Deviation scores

Outlying: $|z| > 1.96$ (outside the central 95%). Average deviation score (ADS) = mean $|z|$ per measure and overall [4]

5 Statistics

ADS: Wilcoxon test and Cohen's d. Regional centiles: Kruskal–Wallis test. FDR (Benjamini–Hochberg) within each test family. Sensitivity: earliest Boston scan per person (N = 693)

Results



ADS = average deviation score (mean $|z|$ across regions) · d = Cohen's d effect size · q = FDR-corrected p · HC = healthy controls · ID = insomnia disorder

Lower overall and surface-area deviations in ID

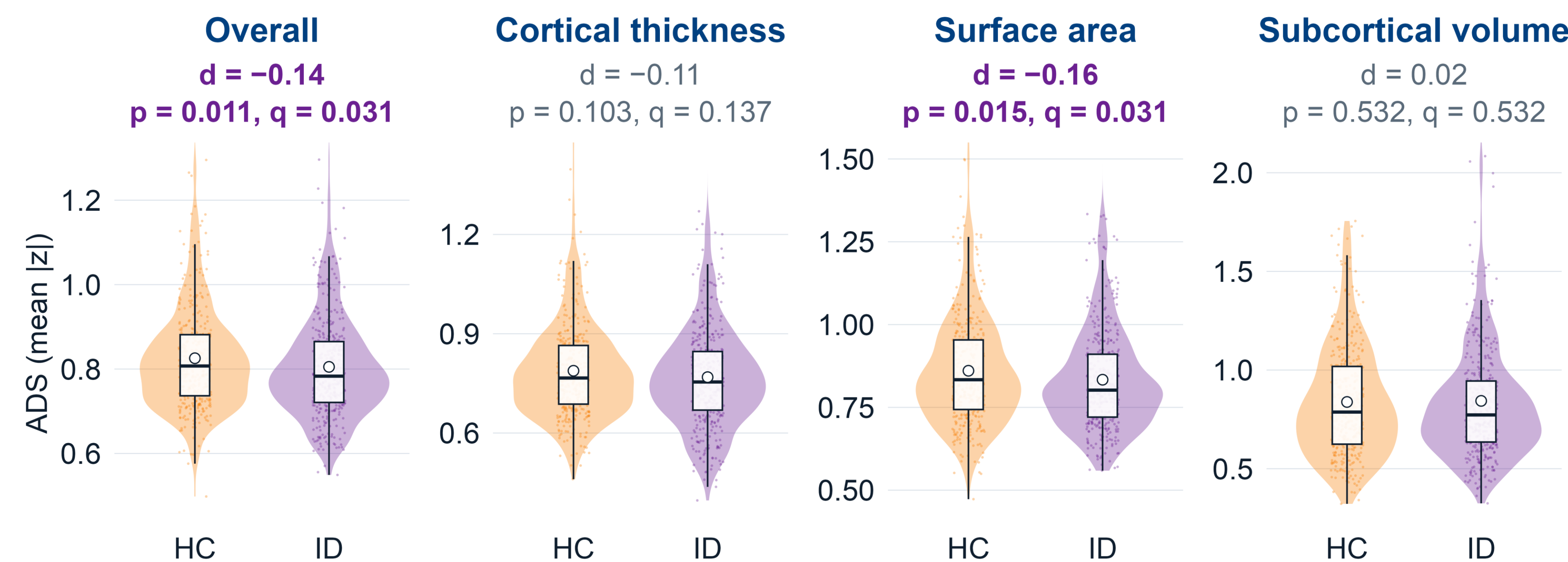


Fig. 1 ADS per participant; Wilcoxon tests, q = FDR across the four ADS. ≥ 1 outlying region: 99.4% HC vs 99.2% ID.

Higher right temporal pole thickness centiles in ID

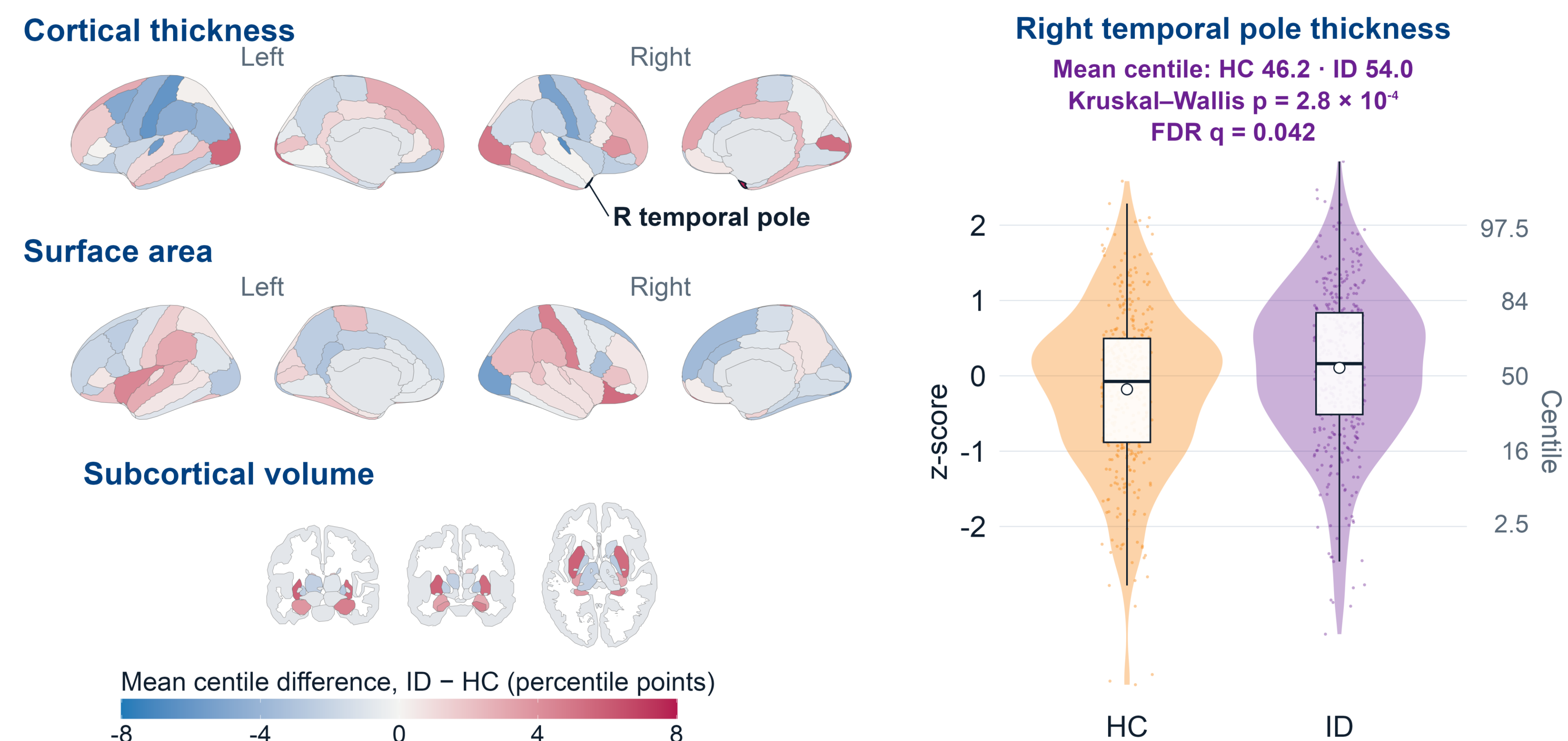


Fig. 2 Left: mean centile difference, ID – HC (outlined: FDR q < 0.05). Right: same region as z-scores; Kruskal–Wallis test.

Conclusion

- Across 6 cohorts in 5 countries, ID was not linked to greater brain deviations
- Overall and surface-area deviations were slightly smaller in ID than in HC
- Right temporal pole thickness centiles were higher in ID
- Normative modeling can characterize individual brain variation in sleep disorders

