

1 Context

Anorexia nervosa (AN) is a severe restrictive eating disorder marked by low BMI, fear of weight gain, and distorted body image. **Early-onset AN (EOAN)** is a subgroup with onset before 13 years of age.

At the neurobiological level:

- Both AN and EOAN show marked reductions in cortical thickness [1–2].
- Functional connectivity patterns in AN remain highly heterogeneous and often fail to replicate across studies [3]
- Early-onset AN (EO-AN, <13 years) remains largely unexplored.
- rsfMRI preprocessing methods vary widely [4], possibly contributing to inconsistent finding and underscoring the need for systematic rs-fMRI multiverse analyses.

2 Aims and hypotheses

A1. Global effect

Hypotheses:

- Lower BMI associated with reduced global connectivity
- Specific pattern associated with EOAN

A2. Acutely underweight vs partially weight restored

Hypothesis:

- Acutely underweight patients exhibit greater connectivity alterations than partially weight-restored patients.

A3. Macroscale organization

Hypothesis:

- EOAN is associated with alterations in macroscale functional gradient organization.

3 Method

Participants

- EOAN: $n = 56$ (51 F; 11.95 yo) — 42 after QC
- Controls: $n = 67$ (34 F; 10.16 yo) — 33 after QC

HALPipe multiverse rs-fMRI analytic workflow [5]

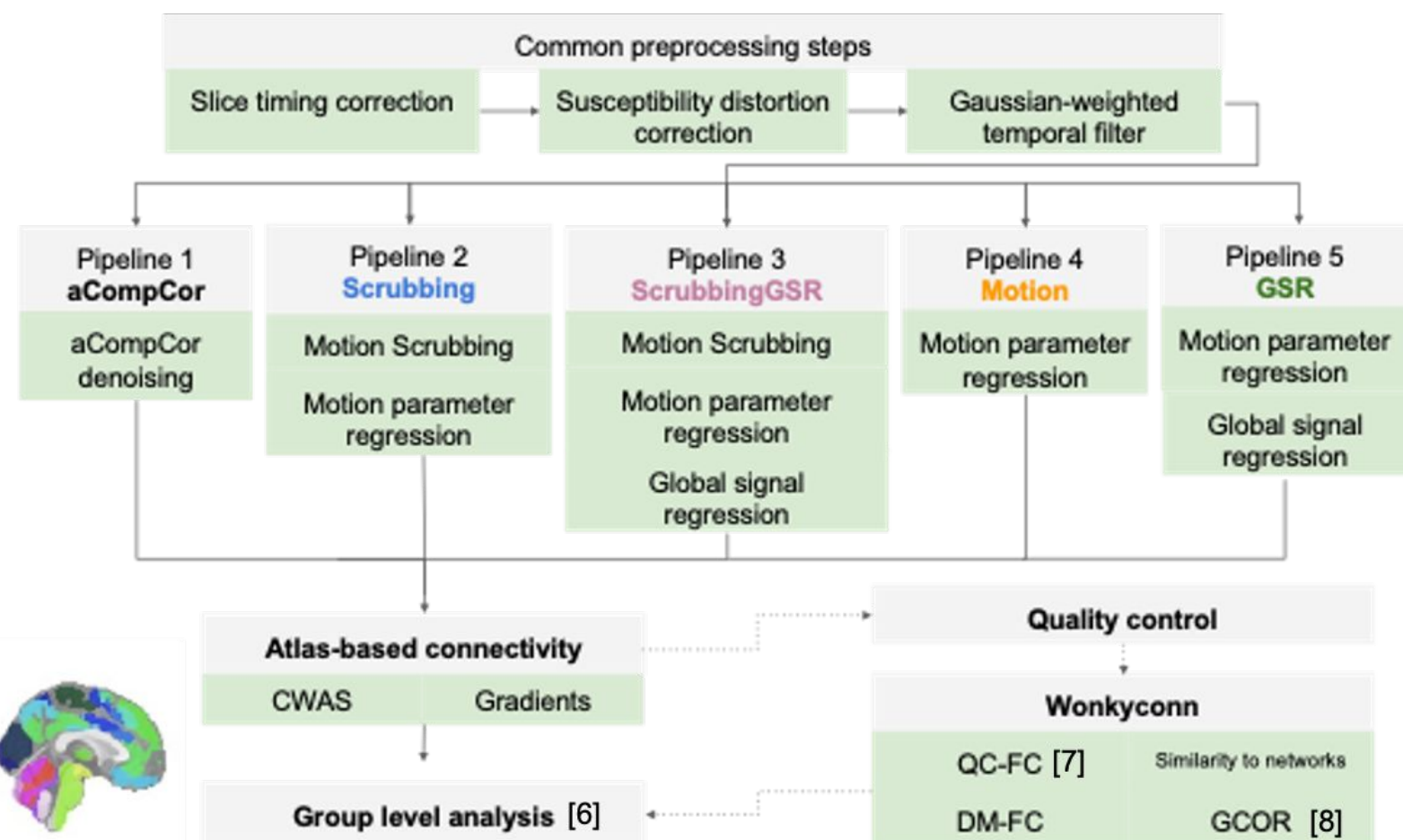


Figure 1. Analytical workflow; Atlas-based connectivity was computed using an atlas combining parcels from Schaefer2018 [9], Yeo2011 [10], Buckner [11] and Freesurfer [12].

Main analysis

- Global and network-level connectivity association with BMI-Z.
- Acute versus partially weight-restored EO-AN comparisons.
- Connectome-wide association study (CWAS) of diagnosis effects.
- Functional gradient analysis (BrainSpace).
- Multiverse sensitivity analyses across five denoising pipelines.

4 WonkyConn pipeline selection

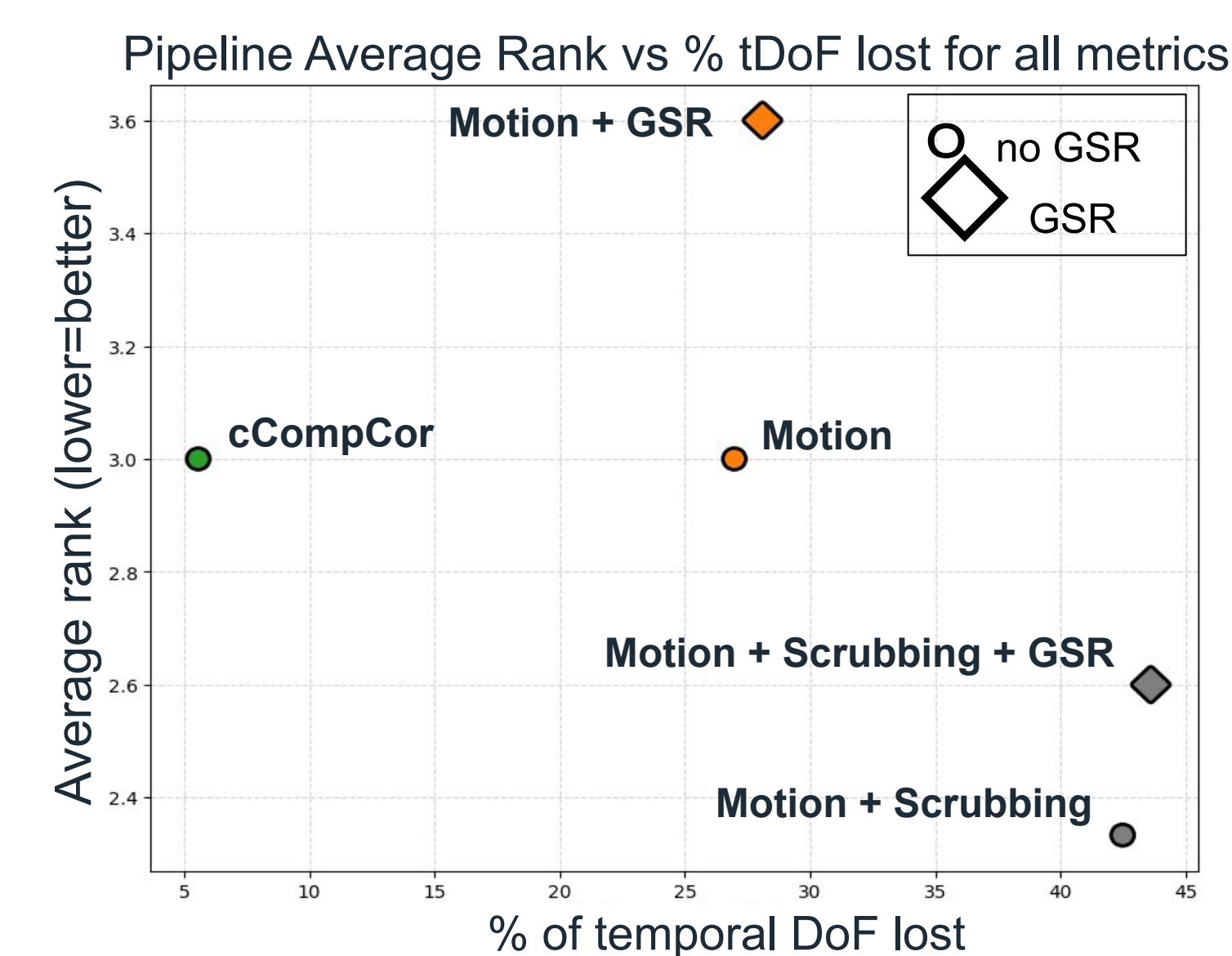


Figure 2. Mean pipeline ranking based on WonkyConn metrics

WonkyConn pipeline identified the most suitable pipelines for our dataset while accounting for percentage of temporal degrees of freedom lost. Motion parameters + scrubbing ranked best overall, but with substantial loss of degrees of freedom. cCompCor ranked third but showed the lowest loss of degrees of freedom.

5 Results

Lower BMI in EOAN is associated with lower global connectivity

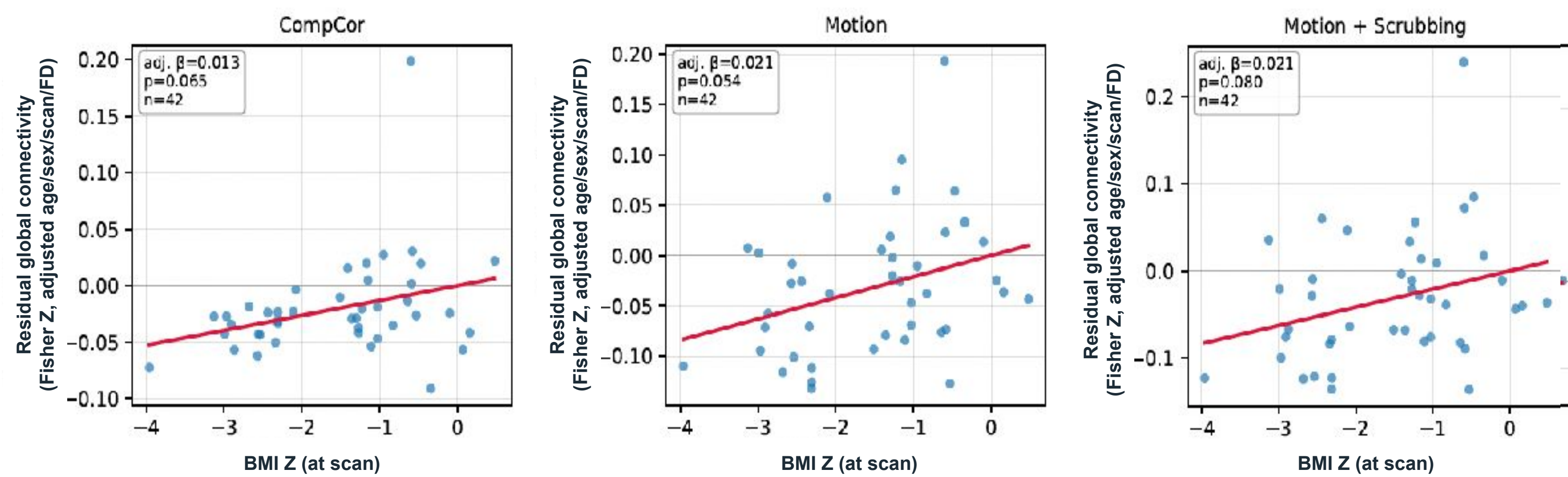


Figure 3. Global connectivity vs BMI.

Global connectivity was defined as the mean Fisher z-transformed functional connectivity and was adjusted for age, sex, scanner, and mean framewise displacement (FD). **Partial regression plots** showing residual global connectivity as a function of BMI-Z score (age- and sex-adjusted BMI z-score at the time of scanning) for each denoising pipeline. A positive association (lower BMI associated with lower global connectivity) was observed in all non-GSR pipelines.

Widespread underconnectivity pattern associated with EO-AN

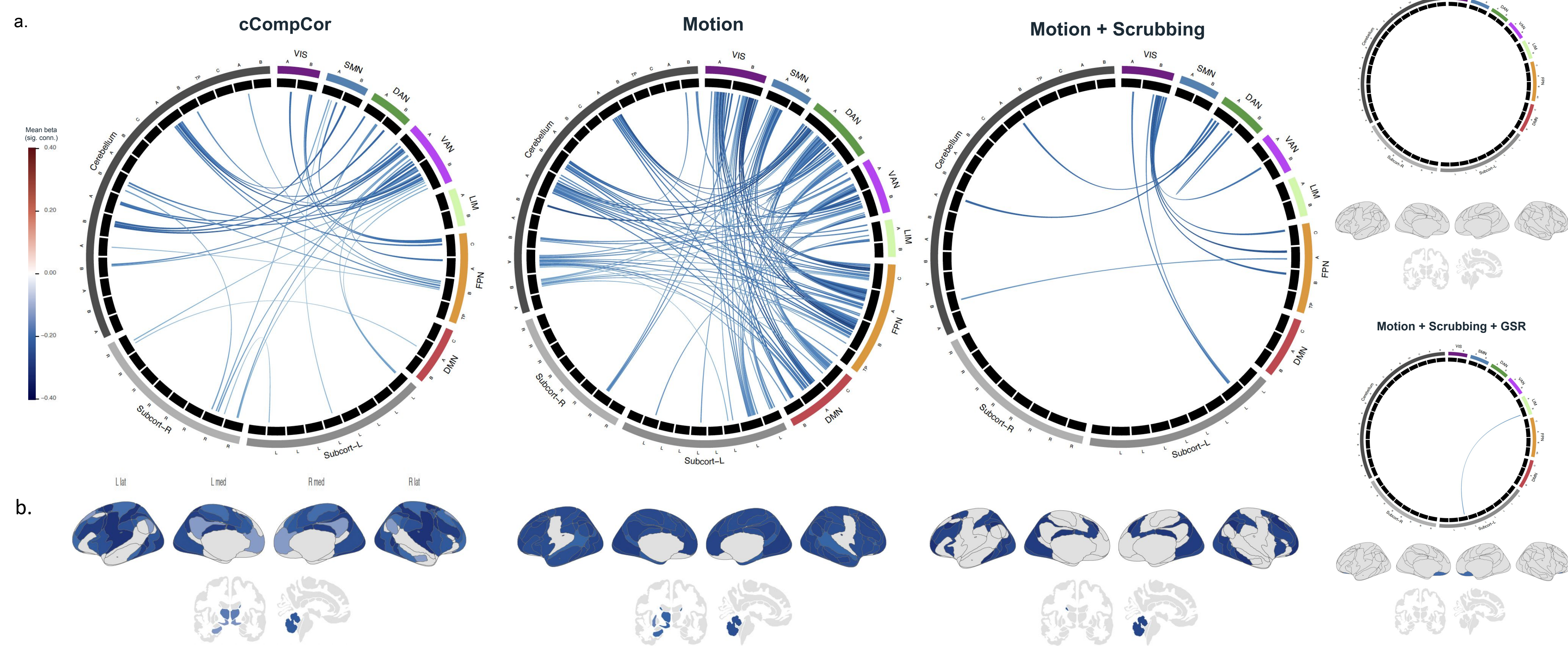
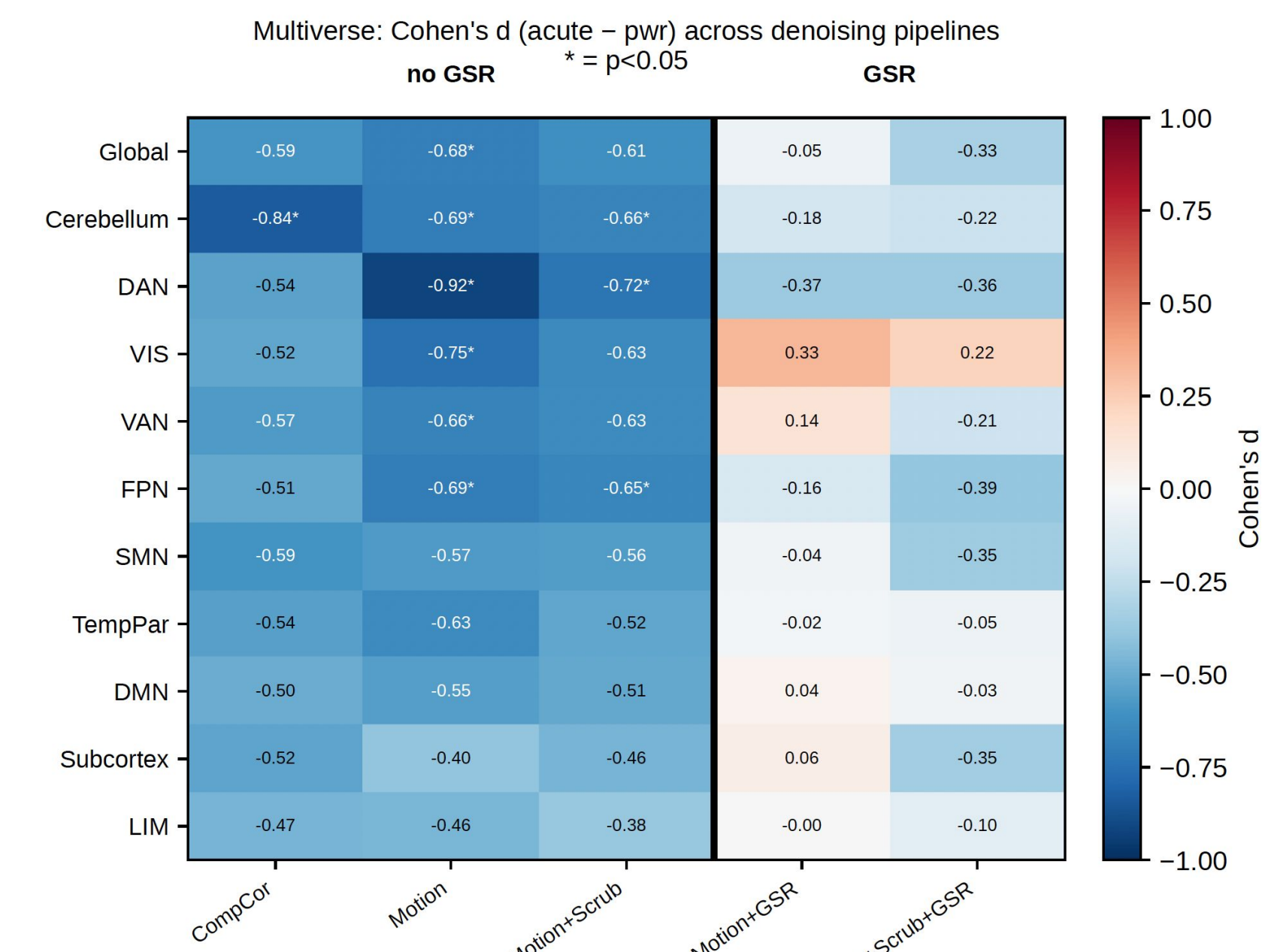


Figure 4. a. The EO-AN vs TD connectivity difference is widespread. Edge-level case-control effect (β , $FDR < 0.05$) on the Yeo2011Combined atlas (51 nodes: 17 cortical Yeo + 17 subcortical [FreeSurfer] + 17 cerebellar [Buckner]). (a) Chord diagram - 51 regions (black cells) grouped by the outer coloured arc into 10 blocks (7 cortical Yeo networks + Subcortical-L + Subcortical-R + Cerebellum); links coloured by β (blue = $AN < TD$). (b) Cortical, subcortical and cerebellar surface/score map of the same effect.



The global reduction is dependent to weight status: acute < partially weight restored patients

Figure 5. Acutely underweight EO-AN patients (BMI percentile < 3; $n = 17$) were compared with partially weight-restored (pwr) patients ($n = 25$). Effect sizes are shown as adjusted Cohen's d (acute - pwr), controlling for age, sex, scanner, and mean FD. In the non-GSR pipelines, a homogeneous negative shift was observed across all networks (acute < pwr), with a global effect size of approximately $d = -0.6$ (median across non-GSR pipelines: $d = -0.59$).

Reduced connectivity amplitude with preserved macroscale gradients

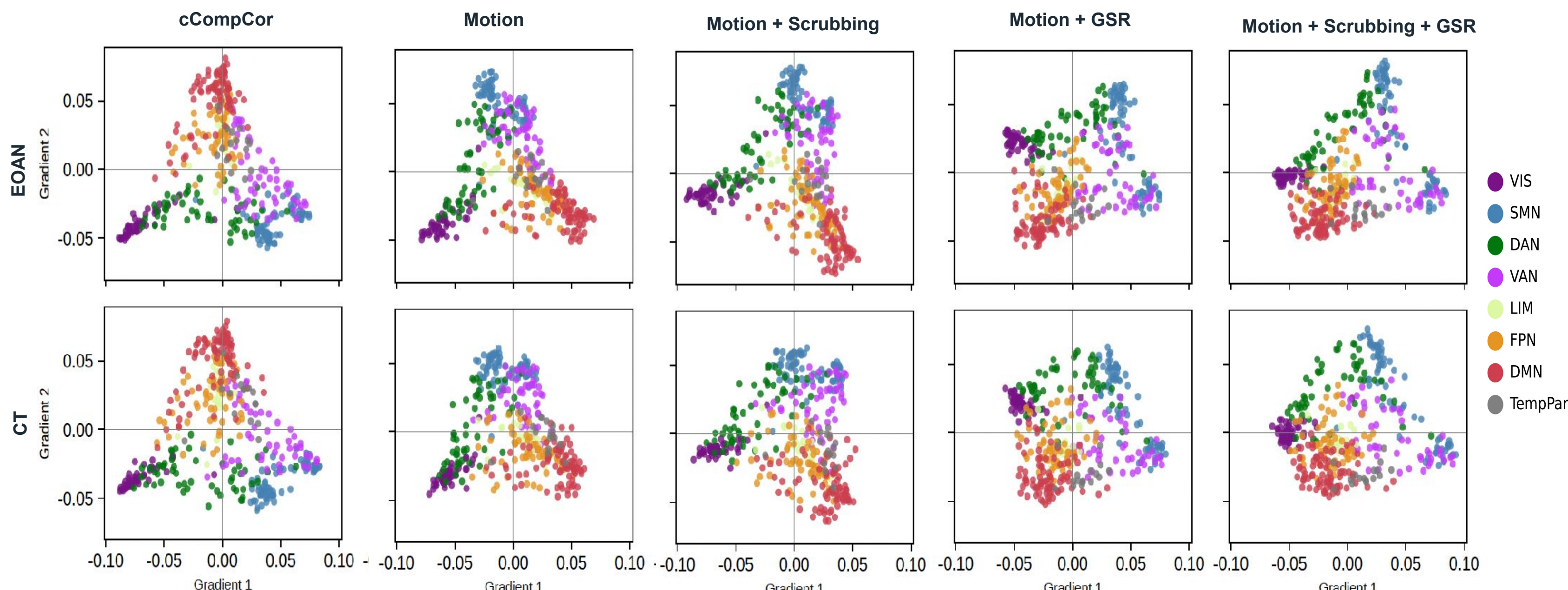


Figure 6. Amplitude reduction with preserved macroscale gradients. Connectome gradients (Gradient 1 $\times$ Gradient 2) derived from diffusion-map embedding are highly preserved and largely overlapping between EO-AN and TD participants across all denoising pipelines, indicating maintenance of the canonical macroscale functional organisation despite reduced overall connectivity.

6 Discussion

H1. Global hypoconnectivity

- Global reduction of connectivity associated with low BMI
- Widespread underconnectivity pattern associated with EOAN

H2. Weight status dependence: acute < partially weight restored

- Acutely underweight patients show stronger global hypoconnectivity than partially weight restored (BMI > 3p), again global-signal-dependents, Cross-sectionally compatible with recovery after weight restoration (longitudinal needed)

H.3 Preserved gradients

- Preserved macroscale gradients.

References & Acknowledgements

- Walton et al. 2022, Biol Psychiatry
- Moreau et al. 2025, Nat. Ment. Health
- Chen et al. 2024, BMC Med Imaging
- Botvinik-Nezer et al. 2020, Nature
- Waller et al. 2022, Hum Brain Mapp
- Jenkinson et al. 2012, Neuroimage
- Wang et al. 2024, PLoS Comput Biol
- Saad et al. 2013, Brain Connect
- Schaefer et al. 2018, Cereb Cortex
- Yeo et al. 2011, J Neurophysiol
- Buckner et al. 2011, J Neurophysiol
- Fischl et al. 2002, Neuron

Acknowledgements. We thank the Bourse de la Montagne scholarship, the Fondation CHU Sainte-Justine and the Paris Pasteur Institute for supporting this project.