A Metric-Driven Framework for Dataset-Specific Preprocessing

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Context

- Resting-state fMRI (rs-fMRI) offers a scalable framework for transdiagnostic psychiatric research, as data can be aggregated across studies without the constraints imposed by task-specific paradigms. However, multisite analyses require careful harmonization of acquisition, preprocessing, and analytical procedures.
- Reproducibility remains a major challenge due to methodological heterogeneity in preprocessing and denoising strategies in rs-fMRI [1].
- Multiverse analyses have been proposed to address this issue, but interpreting results across pipelines remains difficult. Benchmarking studies suggest that no single denoising strategy is optimal across all datasets and research questions [2].

Aims

1. Establish consensus preprocessing recommendations among ENIGMA researchers.
2. Identify robust quality metrics for evaluating preprocessing pipelines in multiverse analyses.
3. Propose a scalable mini-multiverse framework for large-scale resting-state fMRI studies.

Method

Survey among ENIGMA

Google form between 2024-03 and 2024-06

28 questions on steps to harmonize including preprocessing, denoising strategies and post-processing

Resting-State fMRI preprocessing with HALFpipe (Fig. 1a)

We preprocessed 8 datasets (Table 1; n=4,892) using HALFpipe [3].

- Preprocessing included 13 different denoising strategies
- Atlas-based connectivity was extracted using a combination of atlas using cortical (Shaefer 400) [4] – subcortical (Freesurfer atlas [5]) and cerebellum (Buckner atlas [6]).

Denoising benchmarking – Wonkyconn (Fig. 1.b).

We ranked each denoising pipeline from 1-13, and then averaged the ranking based on metrics groups:

- Motion-based metrics: QC-FC & Distance dependence of QC-FC [7]
- Prediction-based metrics: Age and sex prediction
- Analytical-insight metrics: Similarity to brain network
- Percentage of degrees of freedom lost

	Participants	Cases / Controls	Age (min – max)
ABDC [a]	381	0 / 381	10-14
ABIDE1 [b]	950	461 / 489	6.47-64
BHRC [c]	580	0 / 580	5.83-14.33
CNP ds000030[d]	272	142 / 130	21-50
ds003037 [e]	44	44 / 0	18-48
ds003346 [f]	144	74 /64	18-50
HBN [g]	2,280	0 / 2,280	6-21
TCP ds005237 [h]	241	149 / 96	18-70

Table 1 – Datasets description. Number of participants, cases and controls and age range.

[a] The Adolescent Brain Cognitive Development (ABCD) Casey et al., 2018 *Dev. Cog. Neuro.*;
[b] The autism brain imaging data exchange (ABIDE1) Di Martino et al., 2014 *Mol. Psychiatry*;
[c] Brazilian high-risk cohort for mental health conditions (BHRC) Salum et al., 2025 *Inter. J. of Epidemiology*;
[d] Consortium for Neuropsychiatric Phenomics (CNP ds000030), Poldrack et al., 2016 *Scientific Data*;
[e] The Mexican dataset of rTMS for cocaine use disorder in a clinical trial (ds003037) Angeles-Valdez et al., 2022 *Scientific data*.
[f] The Mexican dataset of cocaine use disorder patients (ds003346) Garza-Villarreal et al., 2021 *Cog. Neuro. and Neuroimaging*;
[g] Healthy Brain Network (HBN) Alexander et al., 2017 Scientific data;
[h] Transdiagnostic connectome project (TCP; ds005237), Chopra et al., 2025 *Scientific data*.

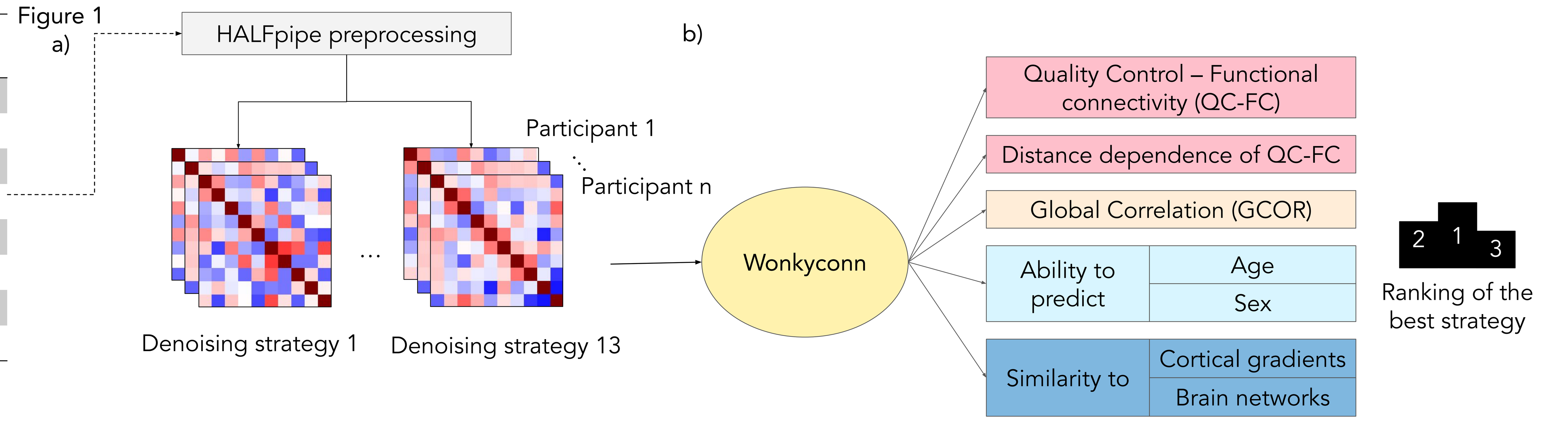
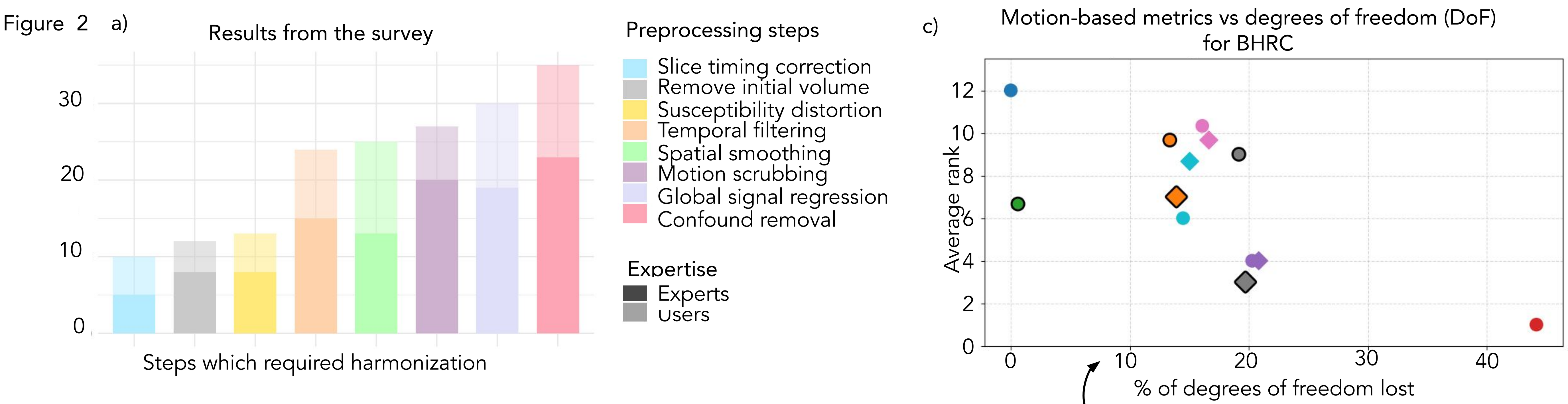


Figure 1. a) Preprocessing workflow implemented in HALFpipe [5] and the 13 denoising pipelines evaluated in this study. Atlas-based connectivity matrices are extracted at the individual level (connectomes shown are random examples of 10 × 10 connectivity matrices for illustration purposes only). b) Overview of the Wonkyconn pipeline, using atlas-based connectivity matrices as input and generating multiple evaluation metrics. Motion-related metrics (red) include QC–FC and QC–FC distance dependence; prediction metrics (light blue) include age and sex prediction accuracy; analytical-insight metrics (dark blue) include similarity to canonical brain networks and gradient similarity. The percentage of degrees of freedom lost was also quantified for each pipeline.

Results



Aim 1

- Confound removal, GSR, and motion scrubbing were identified as the highest-priority targets for harmonization

Aim 2

- Pipeline performance varied considerably across datasets and metrics.
- The Everything pipeline ranked highest for motion metrics but resulted in the greatest loss of DoF.

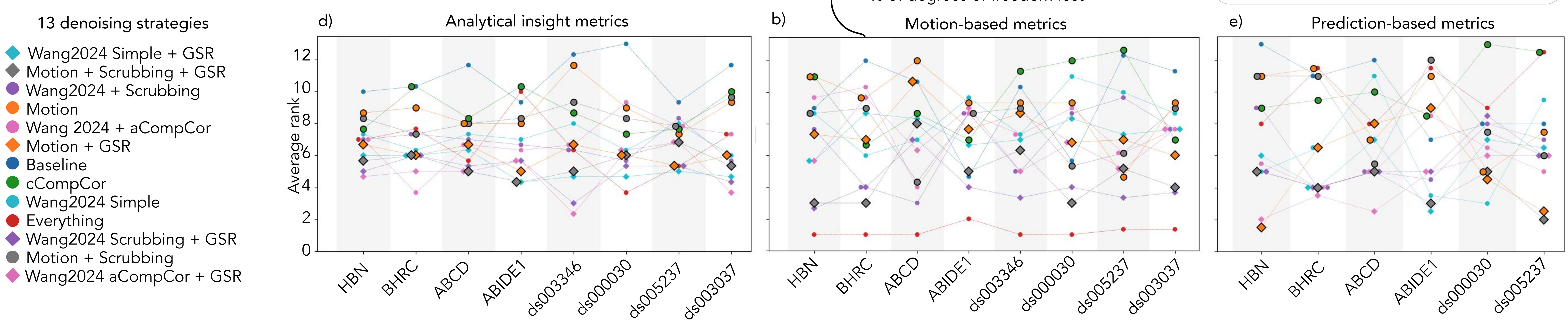


Figure 2. (a) Survey responses to the question, "Which preprocessing steps require harmonization?" Colors indicate preprocessing steps; darker shades represent self-identified experts, and lighter shades represent self-identified users. (b,d,e) Mean ranking (y-axis) of each pipeline across datasets (x-axis) for motion-based metrics (b), analytical insight metrics (d), and prediction metrics (available only for datasets with n > 100). Pipelines outlined in black are those recommended in Figure 3. (c) Example from the Brazilian High Risk Cohort (BHRC) dataset showing average pipeline ranking as a function of the percentage of degrees of freedom (DoF) lost. Abbreviations. Wang2024: pipelines from Wang et al. 2024 [9]; GSR: Global signal regression; motion: motion parameters, motion derivatives and their quadratic terms, Simple: motion parameters, white matter and cerebrospinal fluid.

Discussion

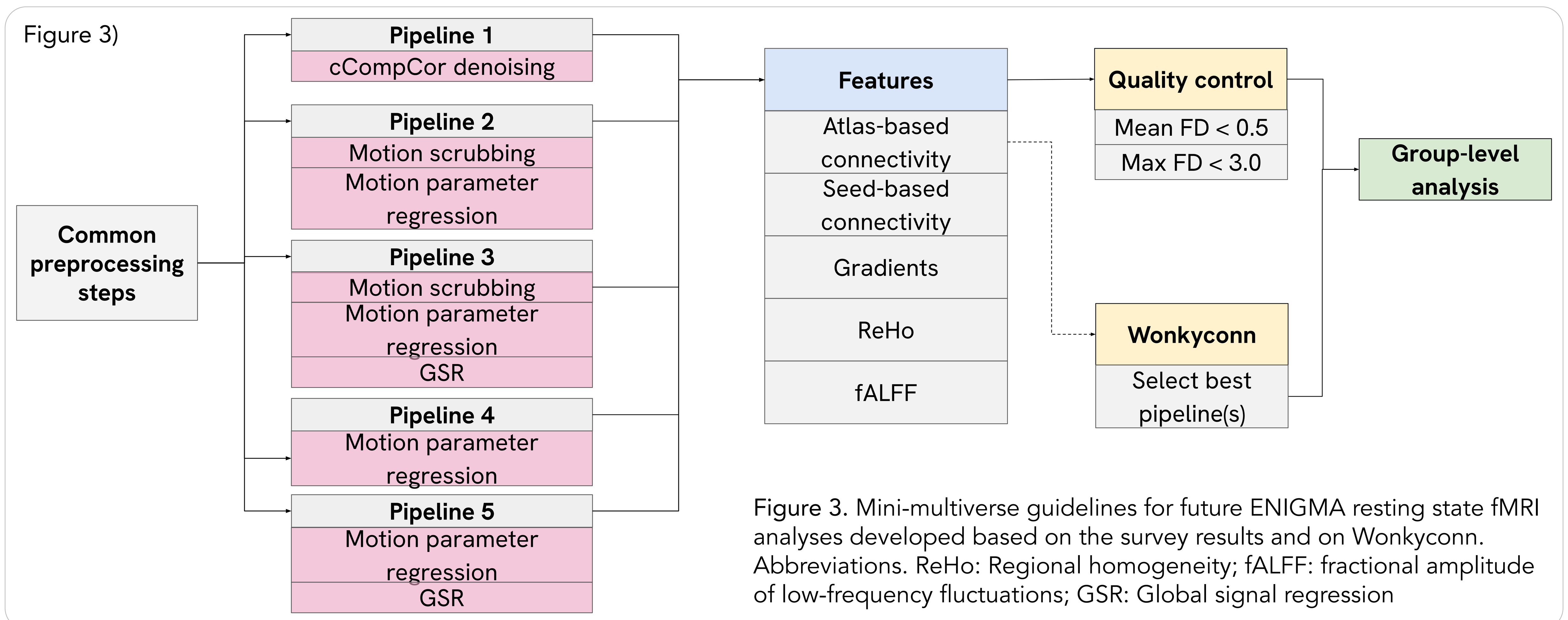


Figure 3. Mini-multiverse guidelines for future ENIGMA resting state fMRI analyses developed based on the survey results and on Wonkyconn. Abbreviations. ReHo: Regional homogeneity; fALFF: fractional amplitude of low-frequency fluctuations; GSR: Global signal regression

Aim 3

We propose a harmonized framework for ENIGMA resting-state fMRI analyses, combining community consensus, expert recommendations, and quantitative benchmarks for pipeline selection.

This framework is designed to improve comparability and reproducibility across studies, enabling large-scale transdiagnostic and lifespan investigations of brain function (Figure 3).

References

1. Botvinik-Nezer et al., 2020
2. Ciric et al., 2017
3. Waller et al., 2022
4. Schaefer et al., 2018
5. Fischl et al., 2002
6. Buckner et al., 2011
7. Wang et al., 2024

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