Supplement Figures

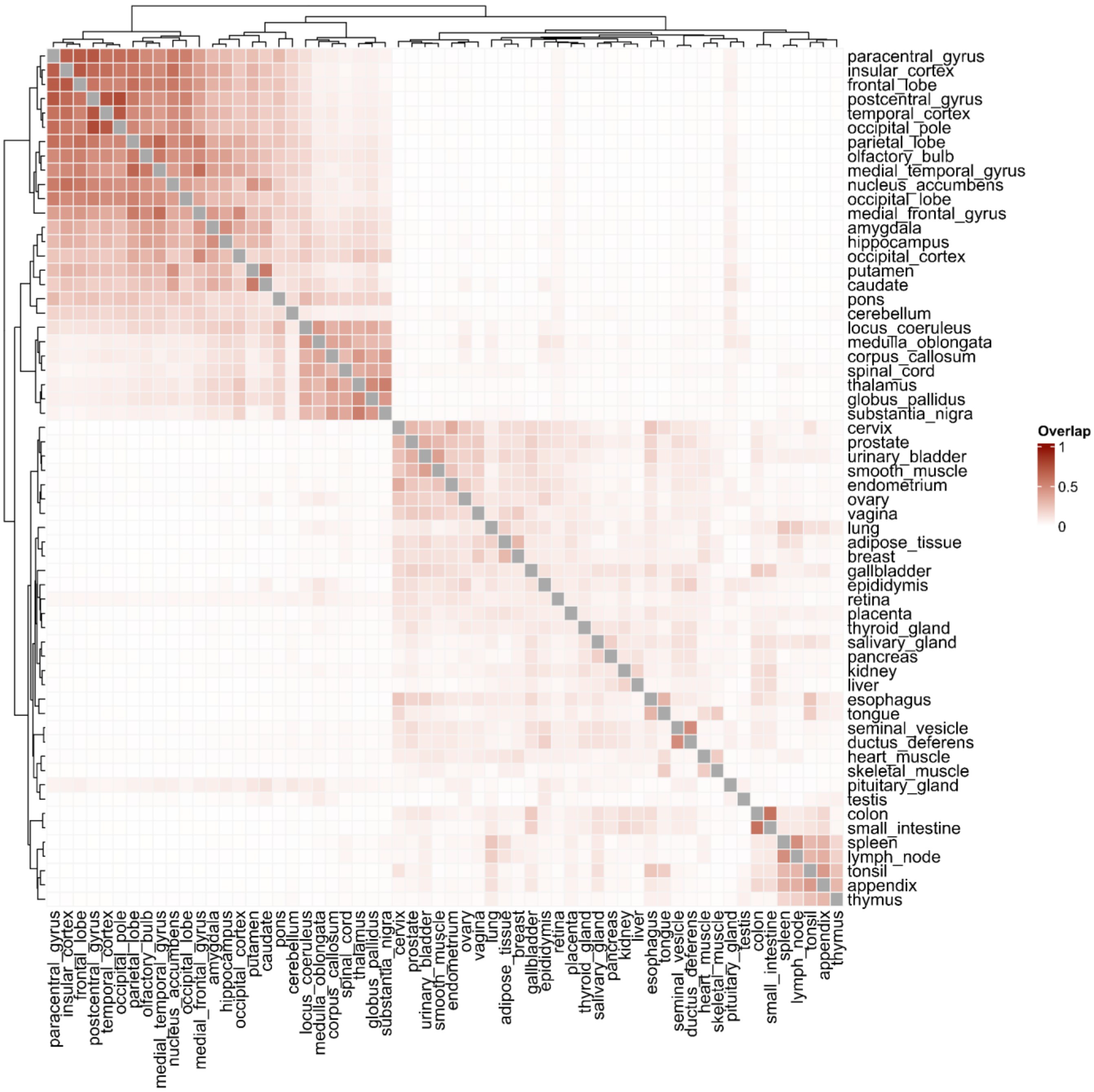


Figure S1 | Pairwise Overlap Matrix (1-Jaccard Distance) of Tissue Gene Sets
The heatmap displays the pairwise overlap between tissue gene sets, where: Dark red indicates high overlap between gene sets, pink represents moderate overlap, and white reflects low overlap. The maximum, minimum, mean, and median values of the overlap are: 77.2%, 0.07%, **7.9%** and 2.7%.

Supplement Figures

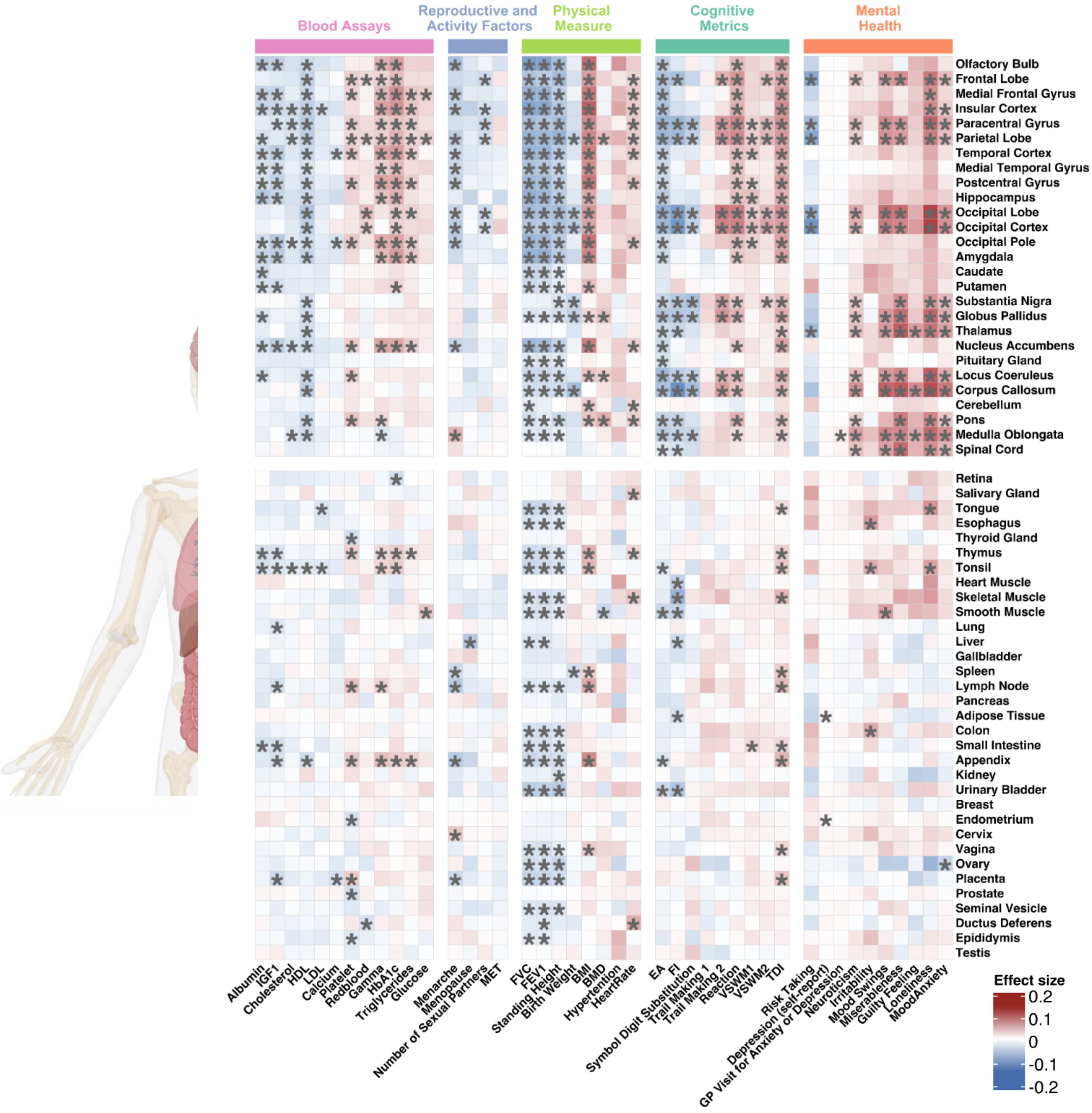


Figure S2 | Heatmap of Deletion Effect Sizes for Whole-Body Tissue across Traits

Supplement Figures

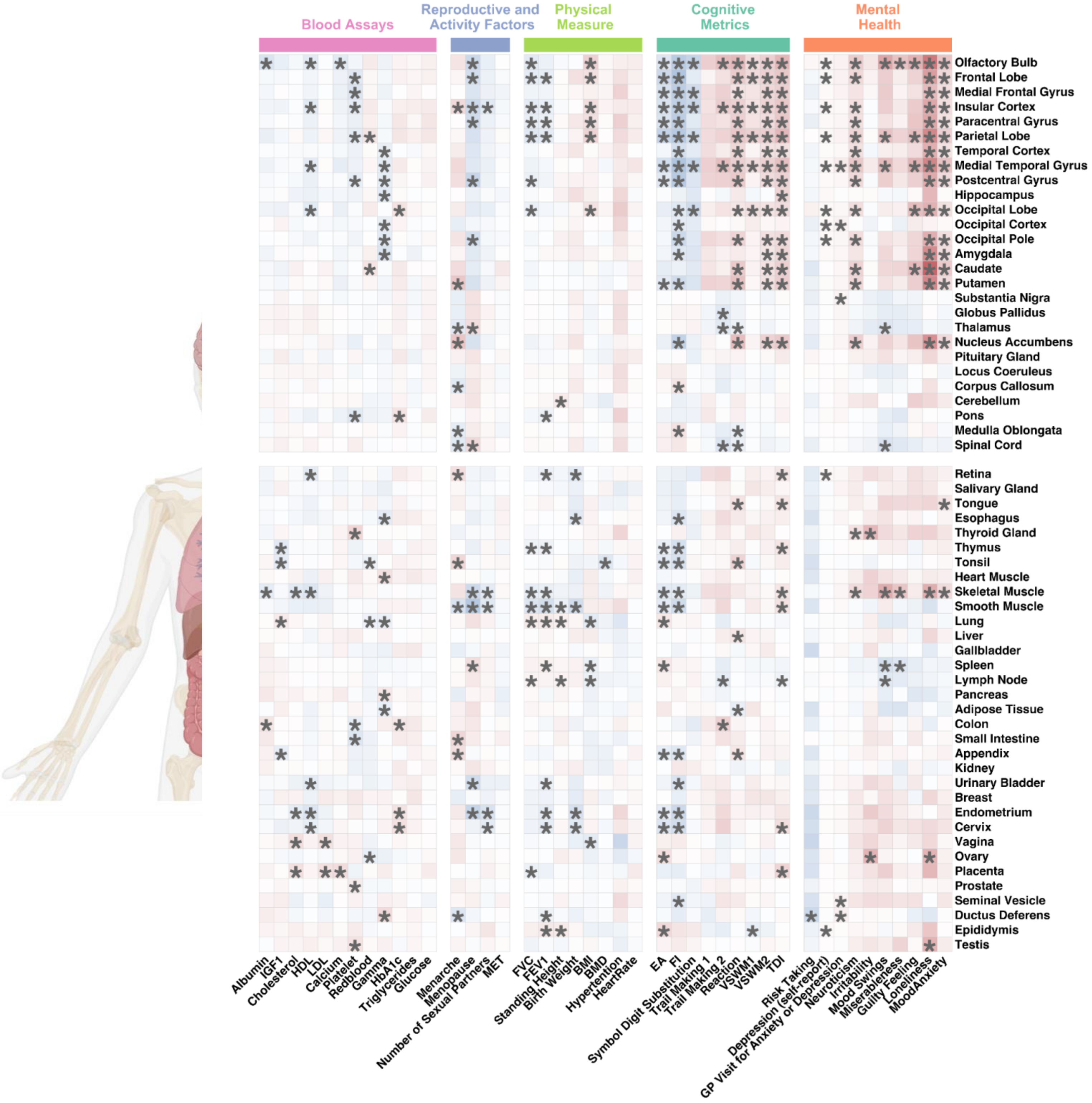


Figure S3 | Heatmap of Duplication Effect Sizes for Whole-Body Tissue across Traits

Supplement Figures

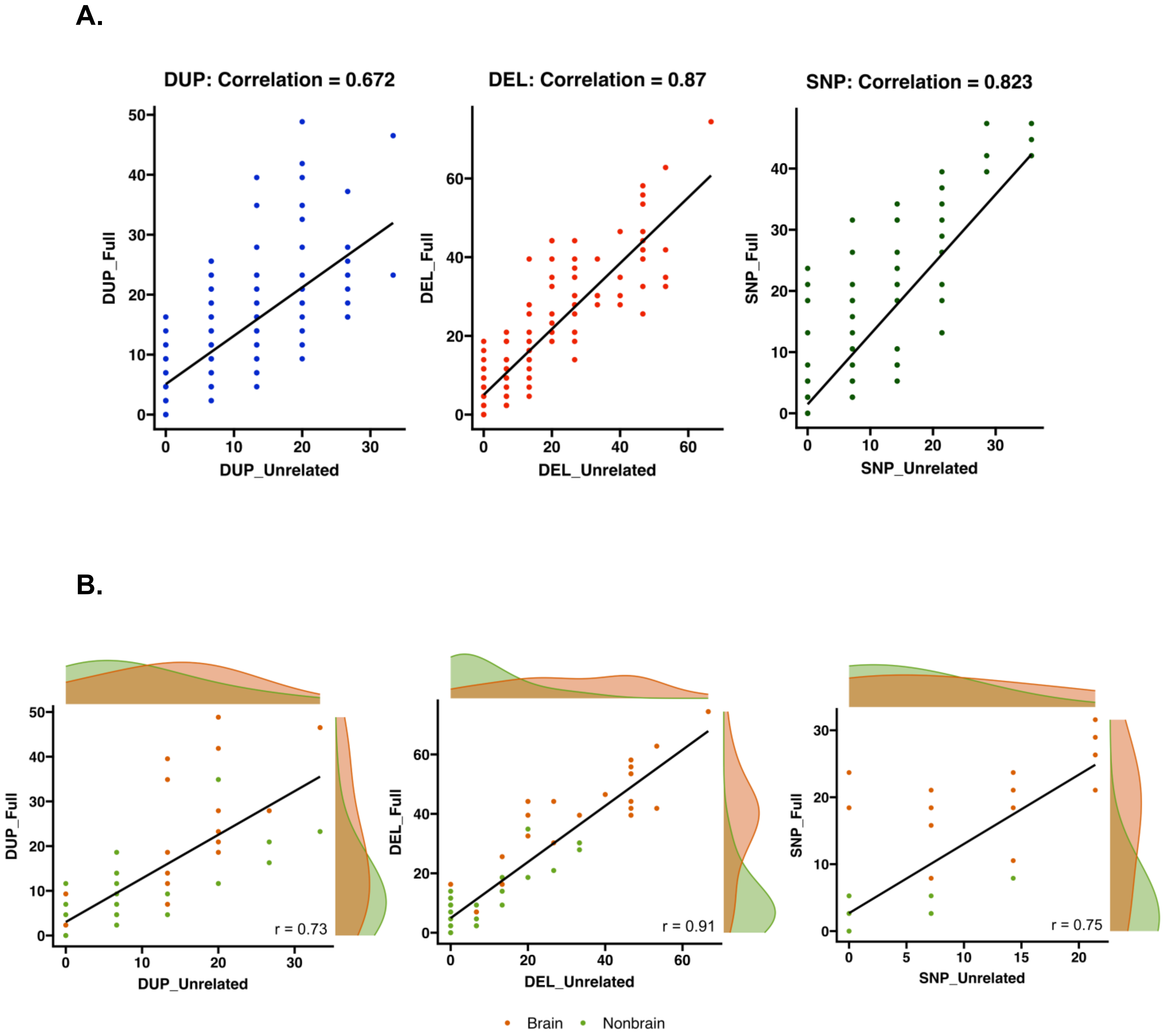


Figure S4 | Sensitivity analysis on pleiotropy computed by unrelated and all traits. X-axis & Y-axis represent the pleiotropy calculated on unrelated and all traits, respectively, using: A) All genesets (172) and B) Tissue genesets (60). For pleiotropy on unrelated traits, we recalculated pleiotropy using a subset of 15 unrelated traits that have less than **0.3** correlation with other traits. The pleiotropy estimates from this subset remained highly correlated with those from the full set, with correlations of 68% and 87% for duplications and deletions, respectively. These correlations are higher for tissue genesets, 73% and 91%, with significant separation between brain and non-brain tissue genesets.

Supplement Figures

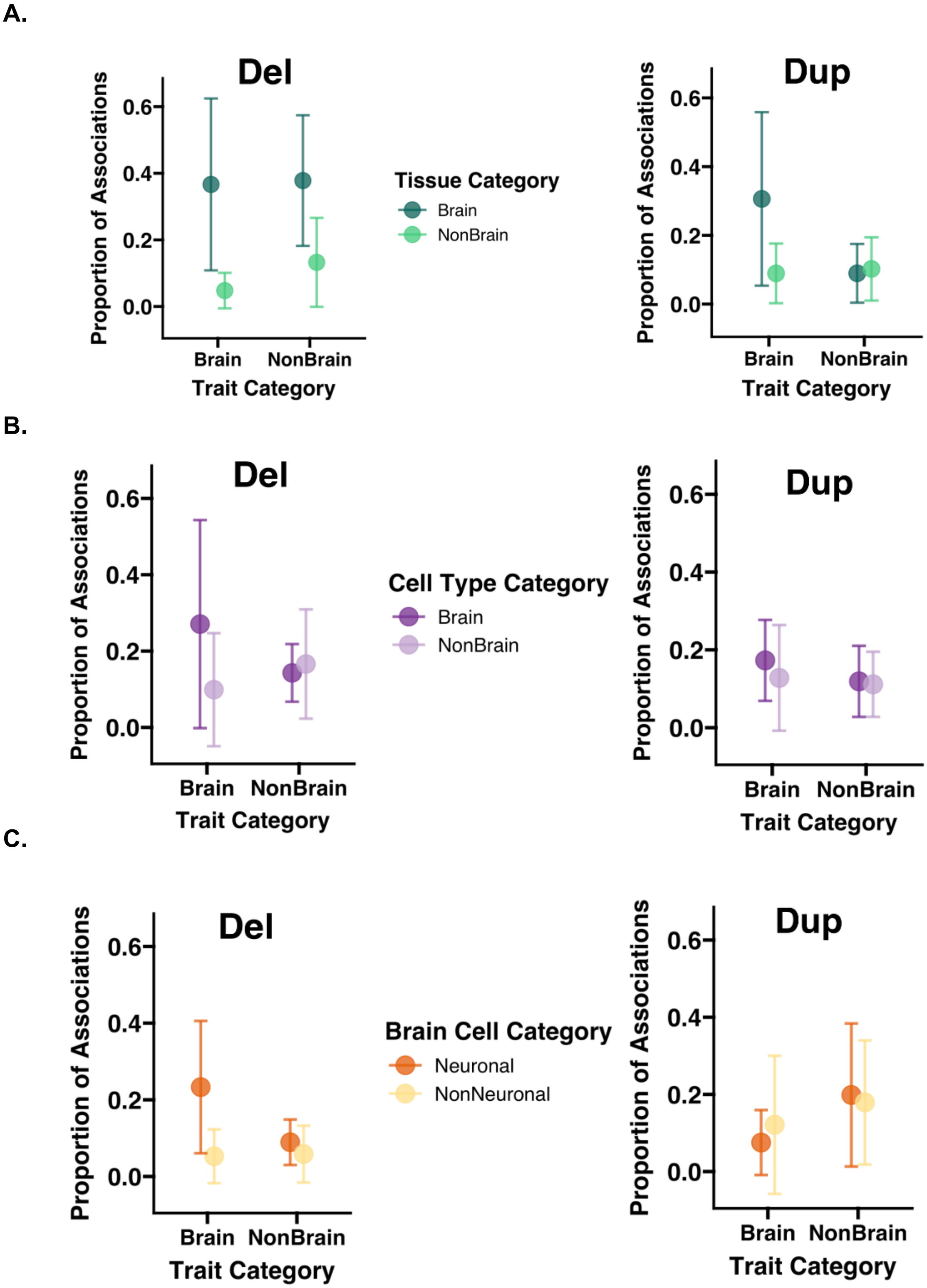
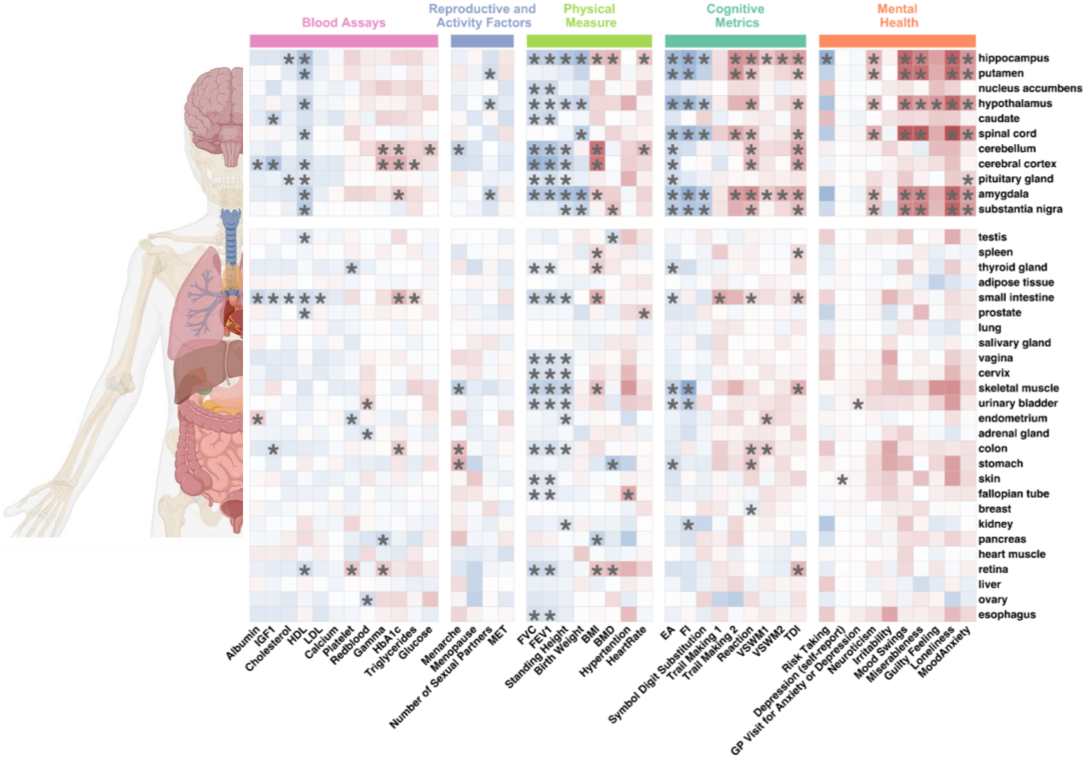


Figure S5 | Summary and Stats of Associations Proportions for Tissue (A), whole body cell type genesets (B) and whole brain cell types (C).

Supplement Figures



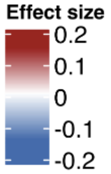


Figure S6 | Heatmap of Deletion Effect Sizes for Whole-Body Tissue (GTEx) across Traits

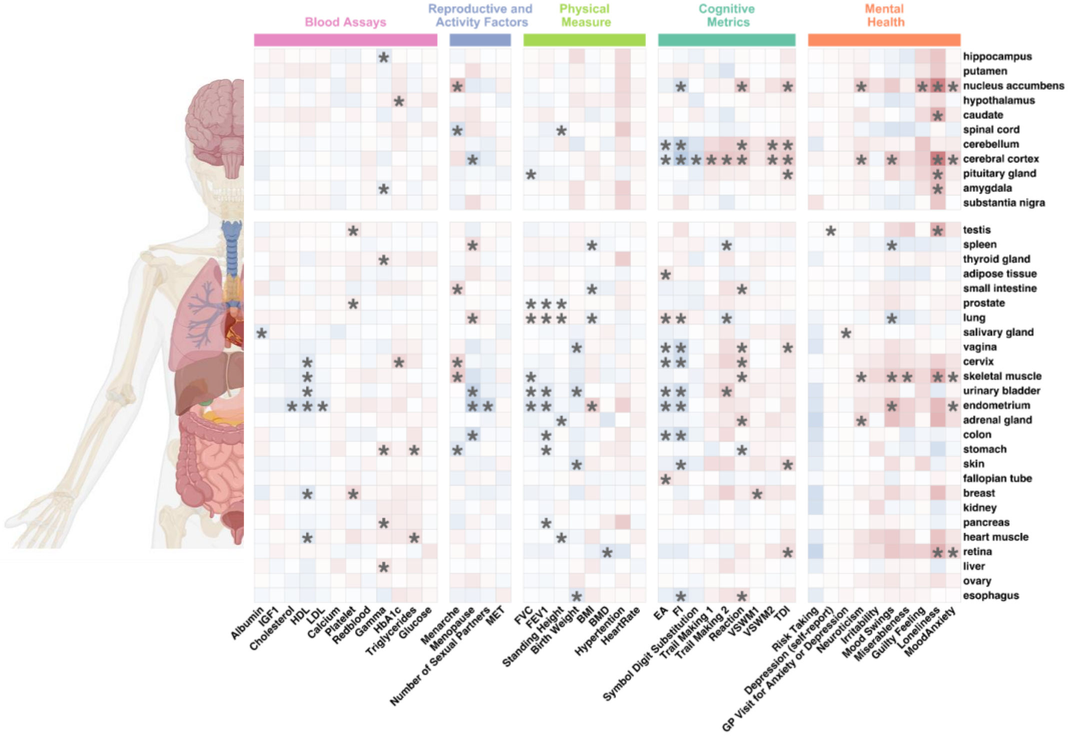


Figure S7 | Heatmap of Duplication Effect Sizes for Whole-Body Tissue (GTEx) across Traits

Supplement Figures

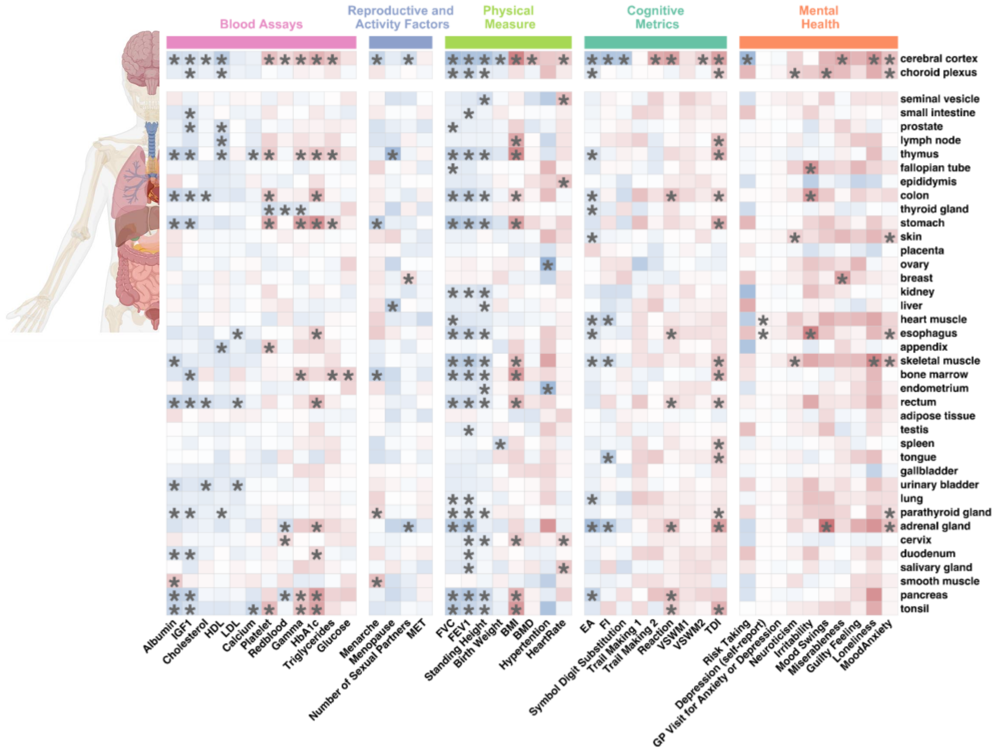


Figure S8 | Heatmap of Deletion Effect Sizes for Whole-Body Tissue (HPA) across Traits

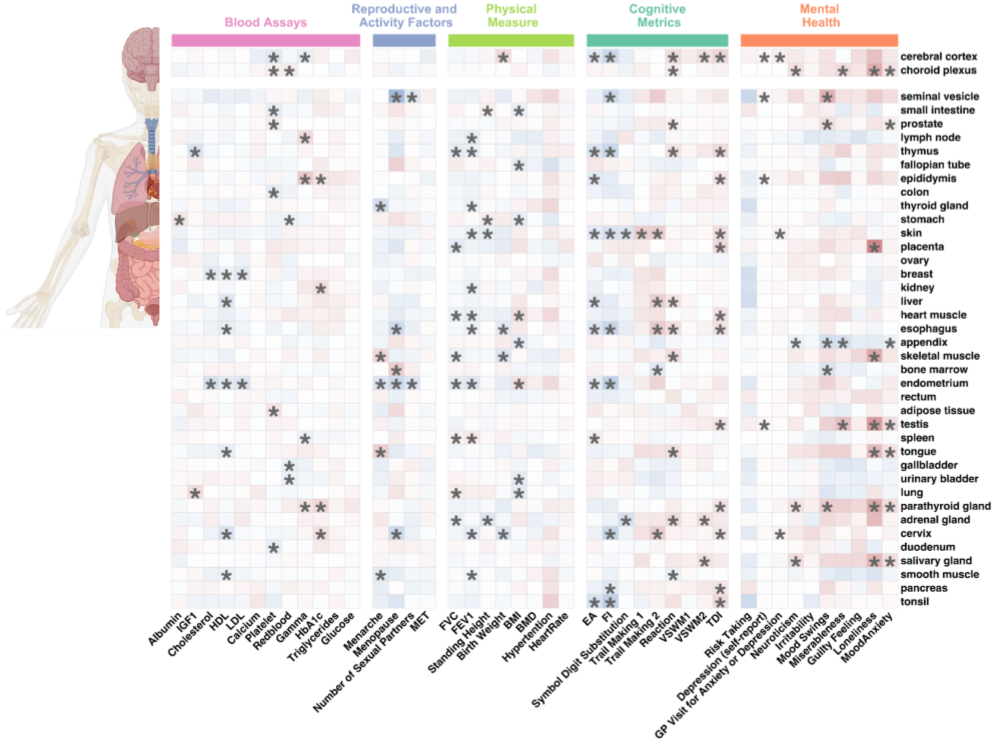


Figure S9 | Heatmap of Duplication Effect Sizes for Whole-Body Tissue (HPA) across Traits

Supplement Figures

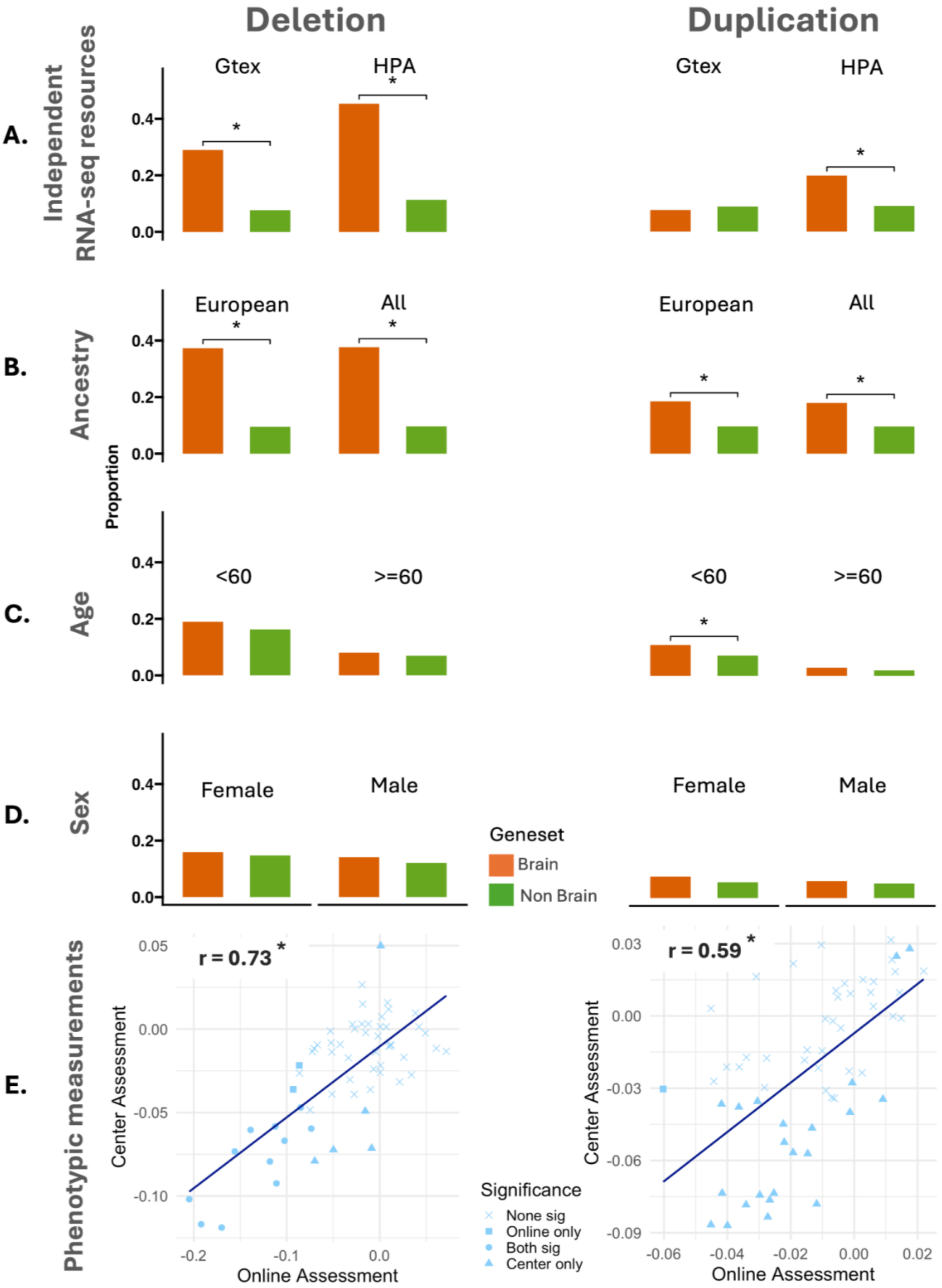


Figure S10 | Sensitivity Analysis of CNV Associations Across Brain and Non-Brain Gene Sets.

Supplement Figures

The figure presents the proportion of significant CNV-trait associations (y-axis, pleiotropy) across brain and non-brain gene sets (x-axis). Each row corresponds to a different sensitivity analysis: (A) independent RNA-seq resources (GTEx vs HPA), (B) ancestry (White vs all ancestries in UK Biobank), (C) age (<60 vs ≥60 years), (D) sex, and (E) phenotype measurement methods (Fluid Intelligence (FI) measured at assessment center, N = 217,809, vs online assessments, N = 92,106).

Supplement Figures

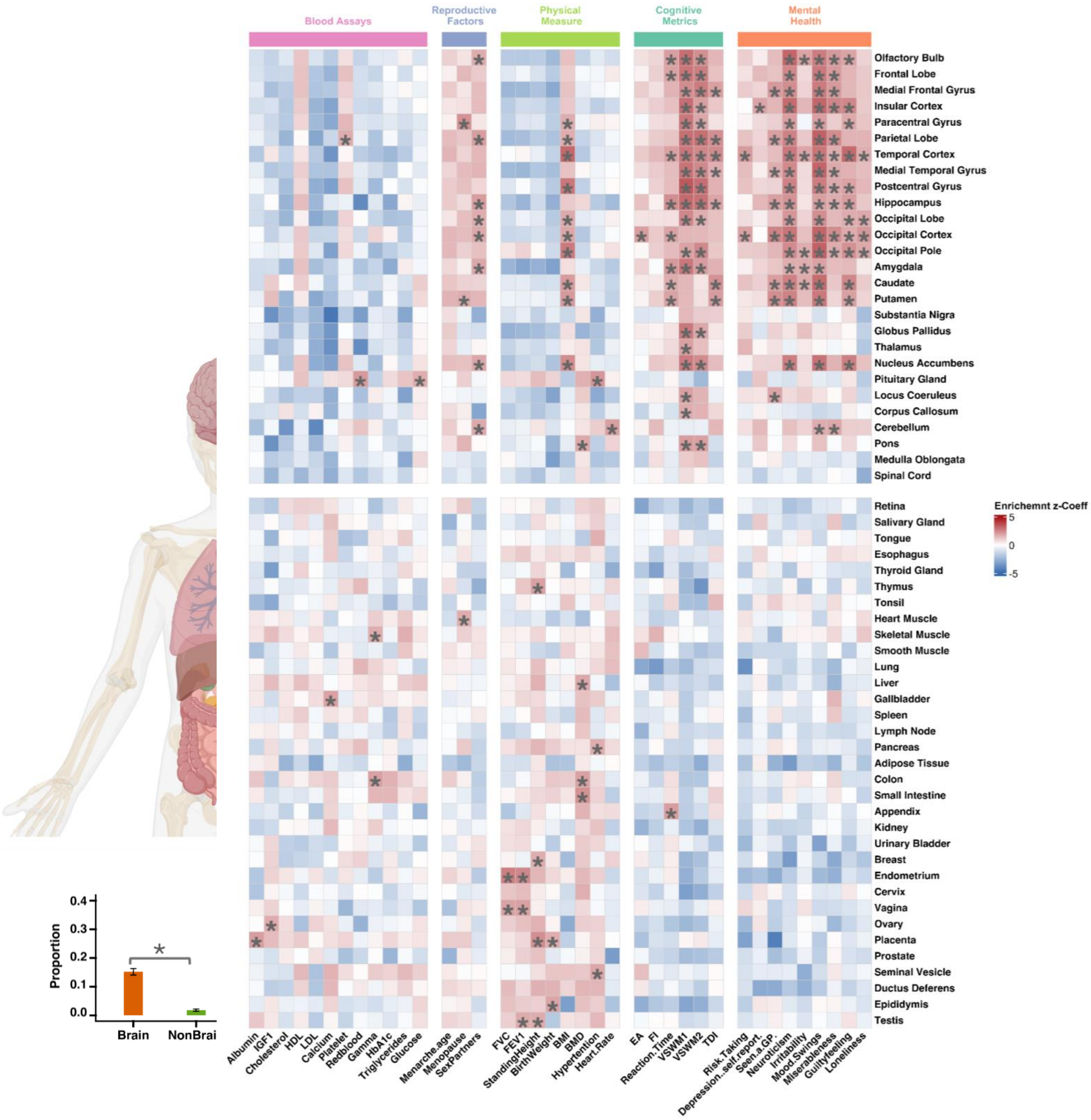


Figure S11 | Heatmap of GWAS enrichments for whole body tissues across traits using S-LDSC.

Supplement Figures

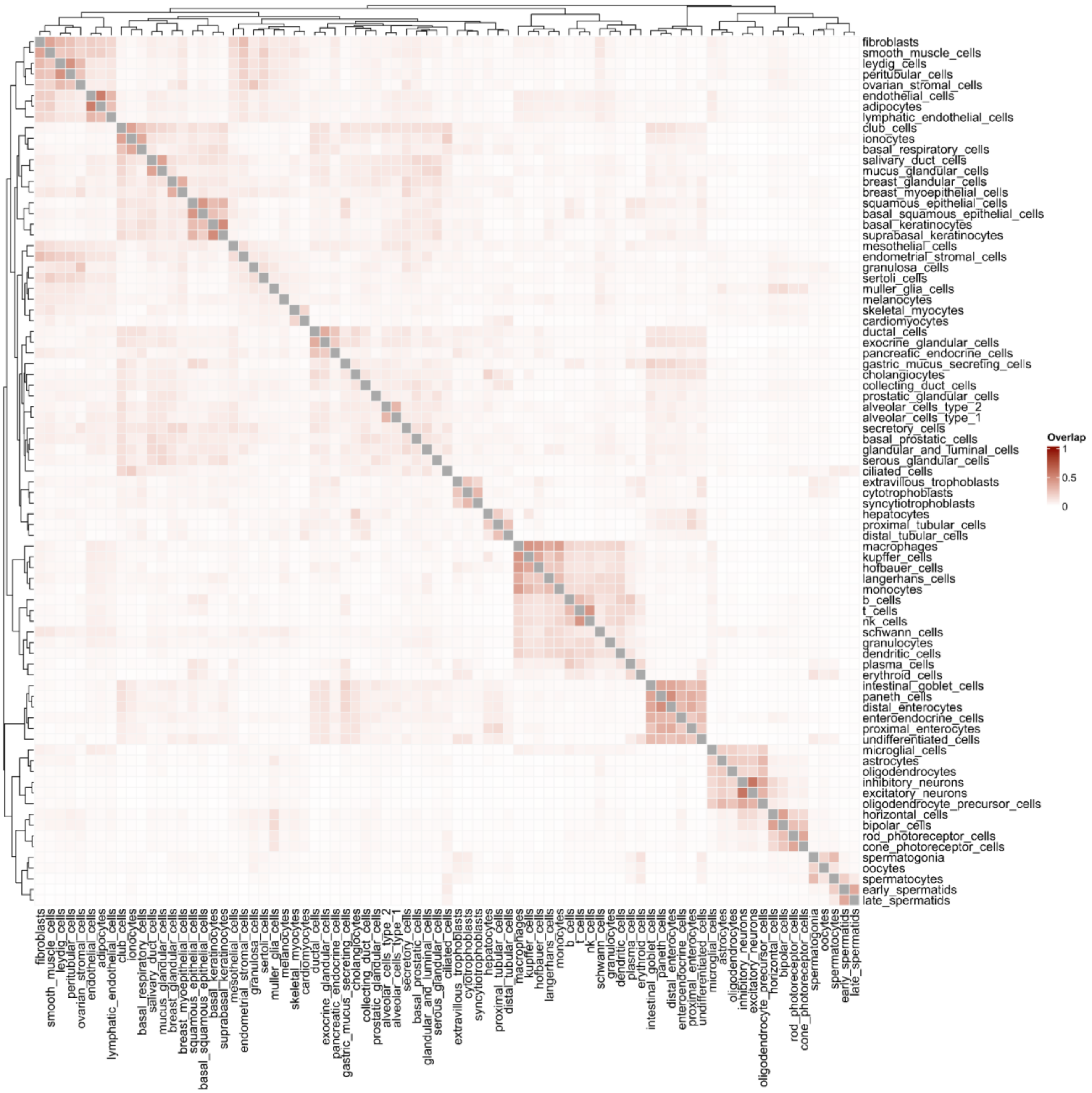


Figure S12 | Pairwise Overlap Matrix of Whole Body Gene Sets
The heatmap displays the pairwise overlap between whole body cell type gene sets. The maximum, minimum, mean, and median values of the overlap are: 58.8%, 22.9%, **4.6%** and 3.0%.

Supplement Figures

Figure S13 | Heatmap of Deletion Effect Sizes for Whole-Body Cells across Traits

Supplement Figures

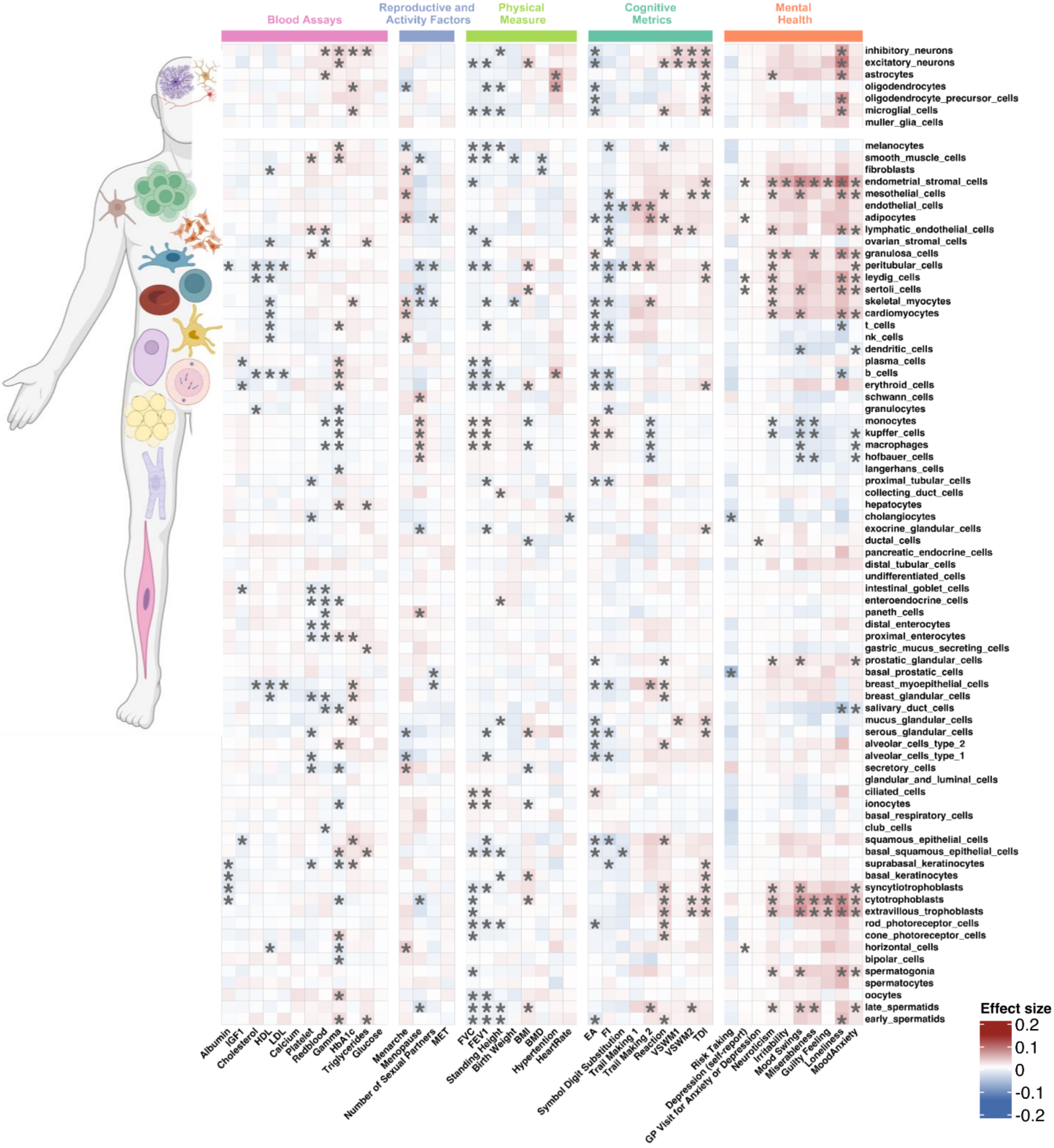


Figure S14 | Heatmap of Duplication Effect Sizes for Whole-Body Cells across Traits

Supplement Figures

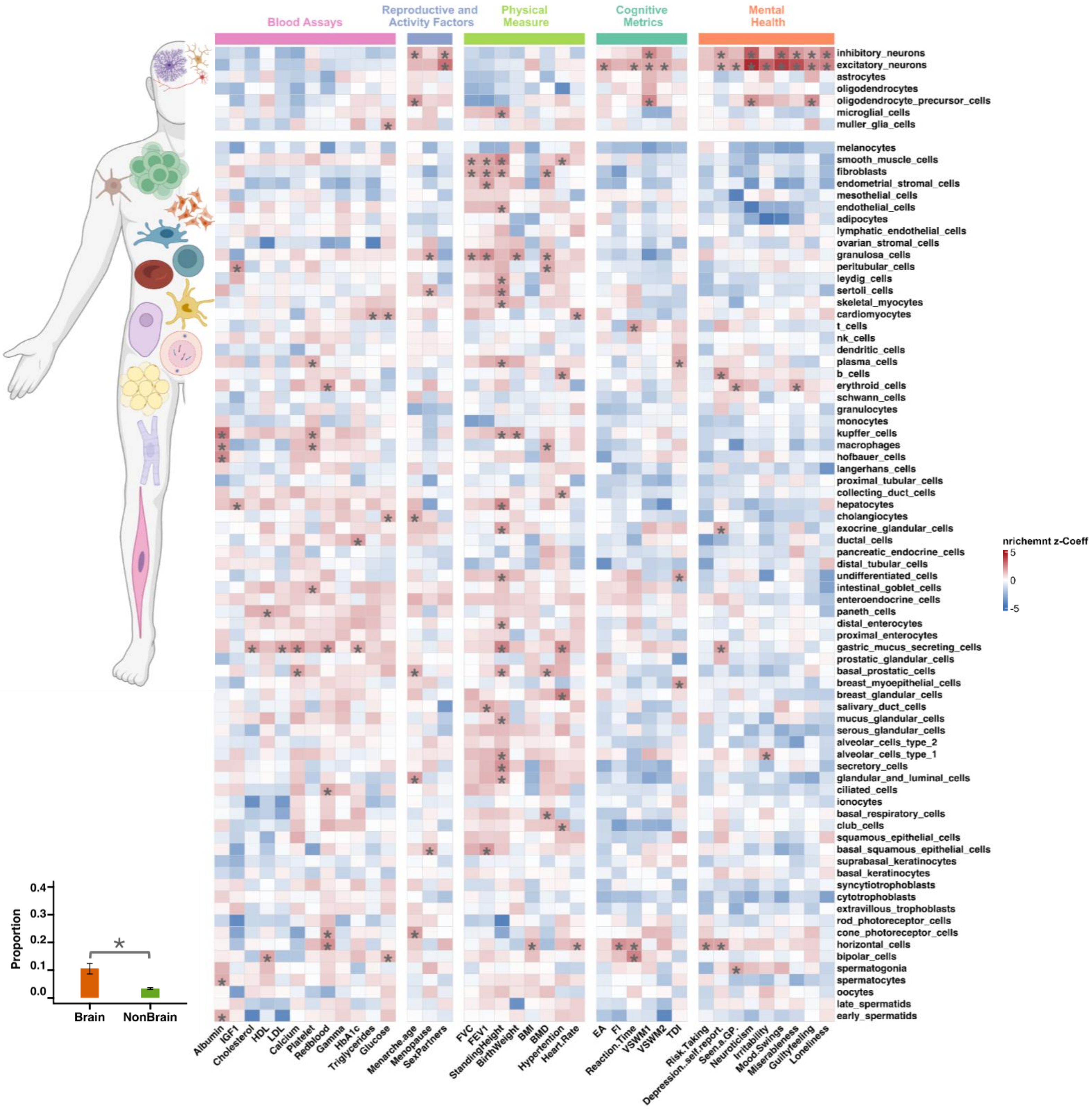


Figure S15 | Heatmap of GWAS enrichments for whole body cell types across traits using S-LDSC.

Supplement Figures

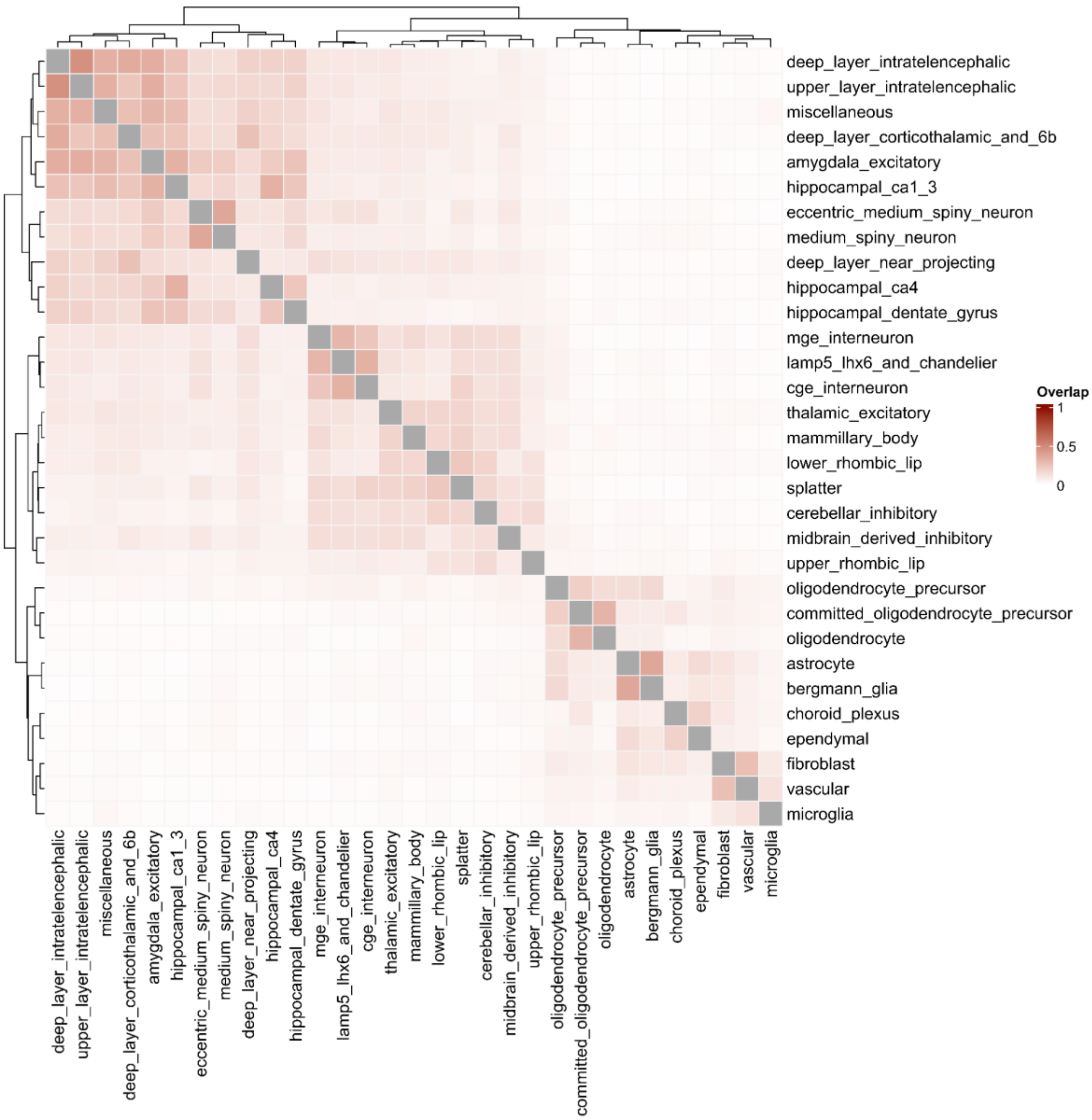


Figure S16 | Pairwise Overlap Matrix of Whole Brain Cell Gene Sets
The heatmap displays the pairwise overlap between whole brain gene sets. The maximum, minimum, mean, and median values of the overlap are: 46.7%, 0.98%, **7.5%** and 4.9%.

Supplement Figures

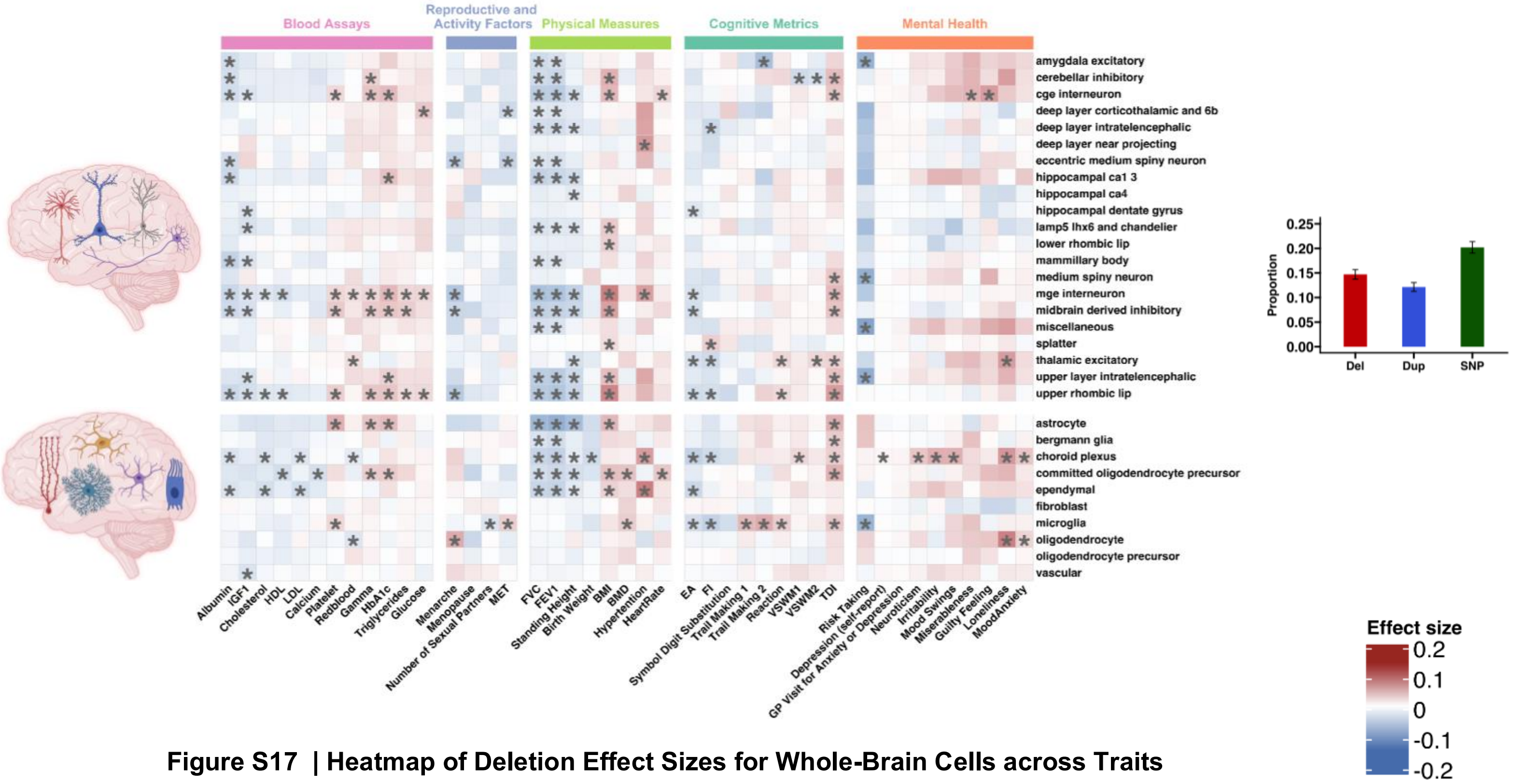


Figure S17 | Heatmap of Deletion Effect Sizes for Whole-Brain Cells across Traits

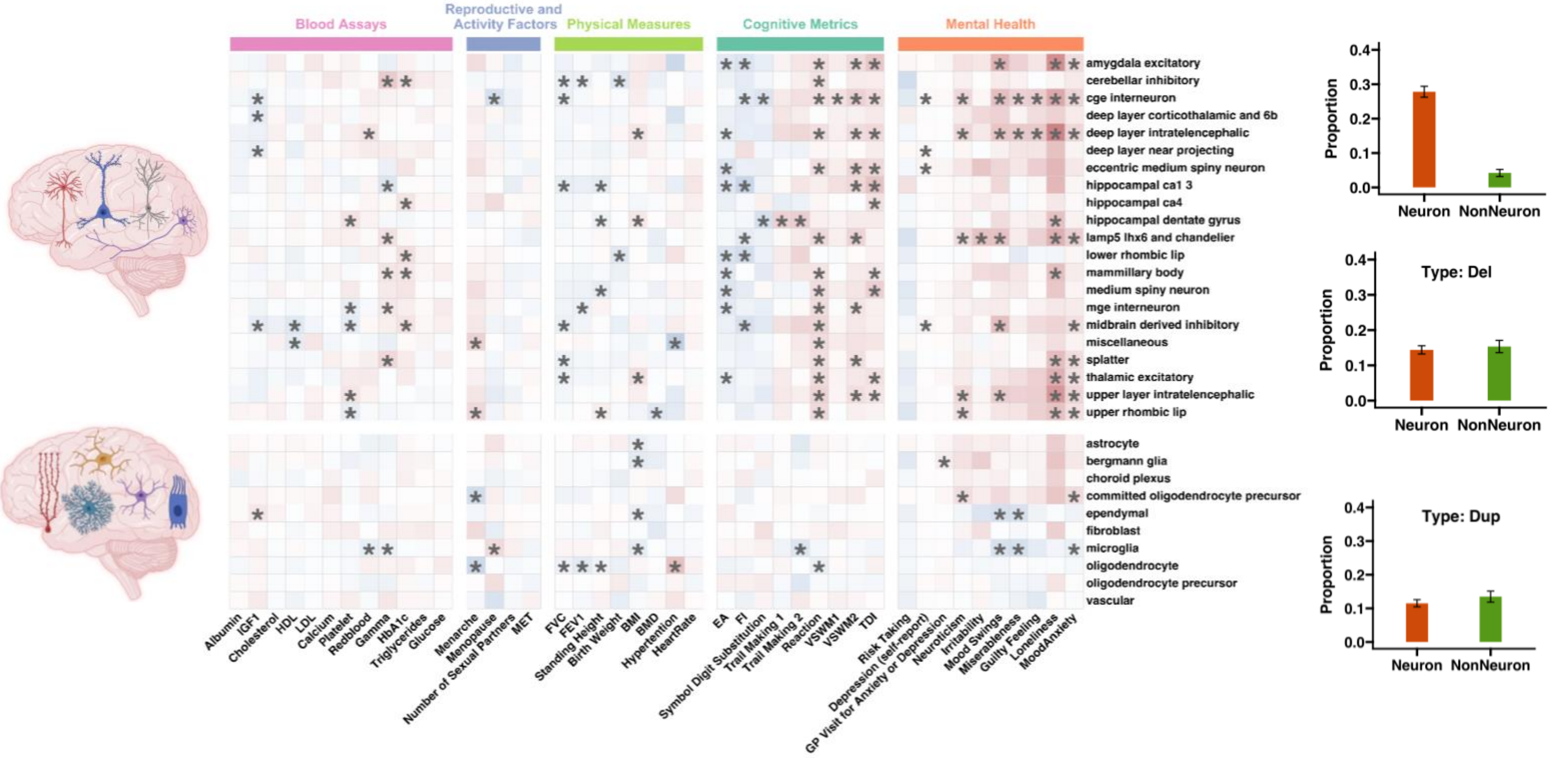


Figure S18 | Heatmap of Duplication Effect Sizes for Whole-Brain Cells across Traits

Supplement Figures

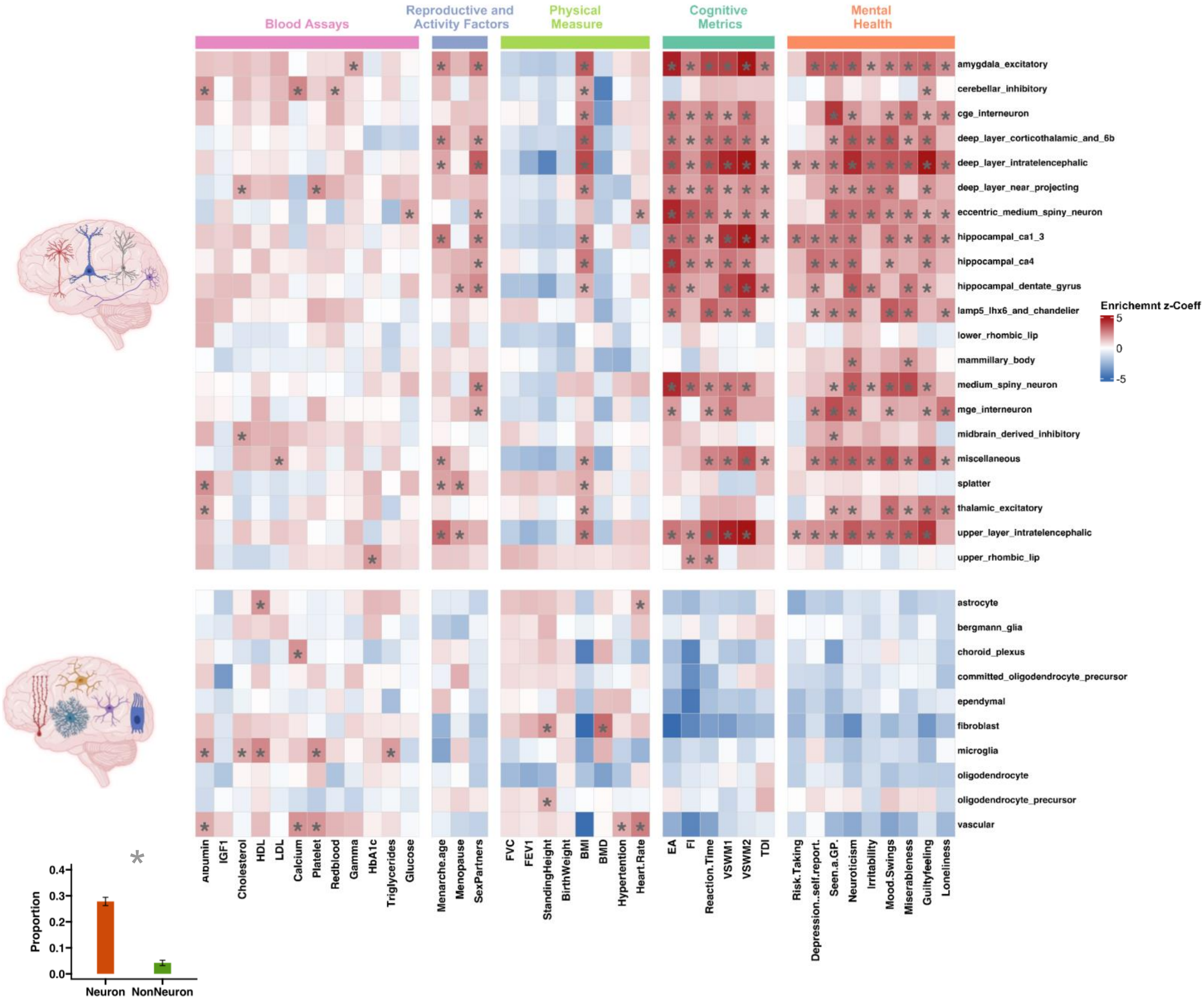


Figure S19 | Heatmap of GWAS enrichments for whole brain cell types across traits using S-LDSC.

Supplement Figures

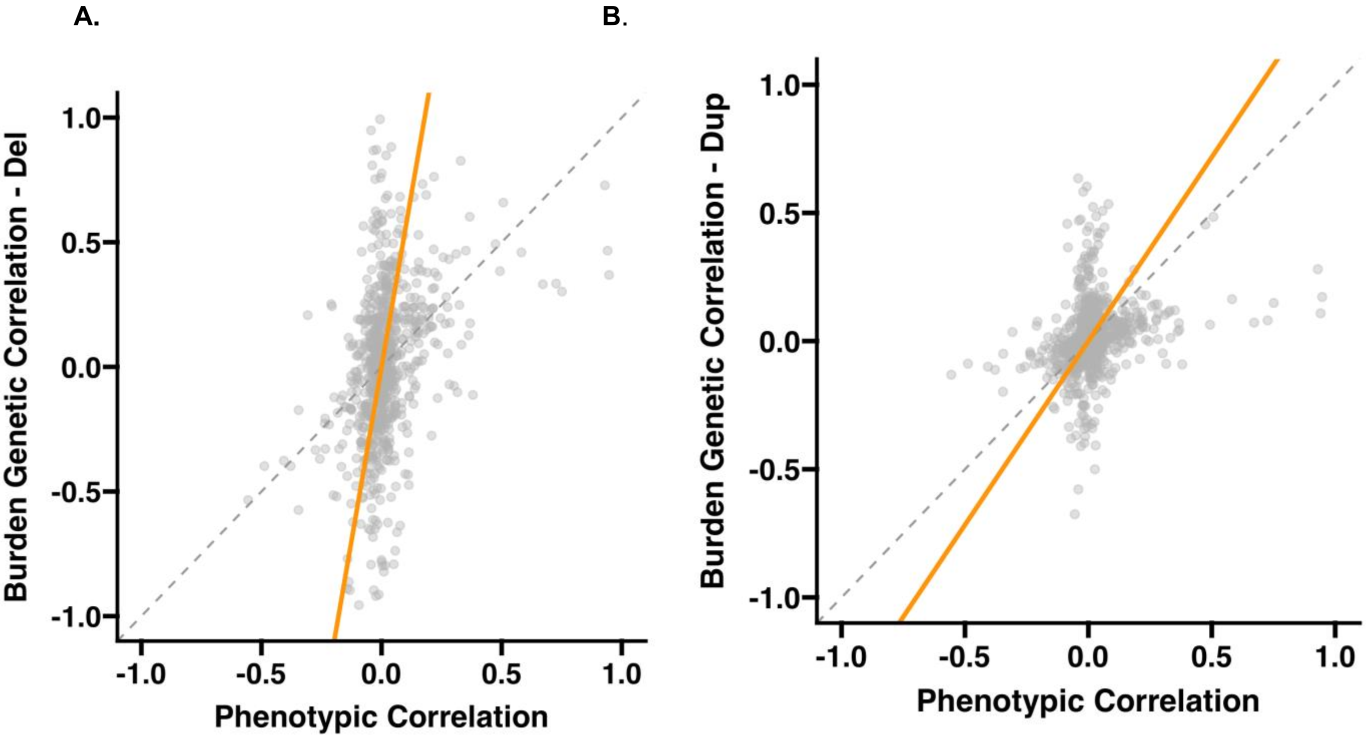


Figure S20 | Comparison between Deletion and Duplication burden, with phenotypic correlations (A & B)

Supplement Figures

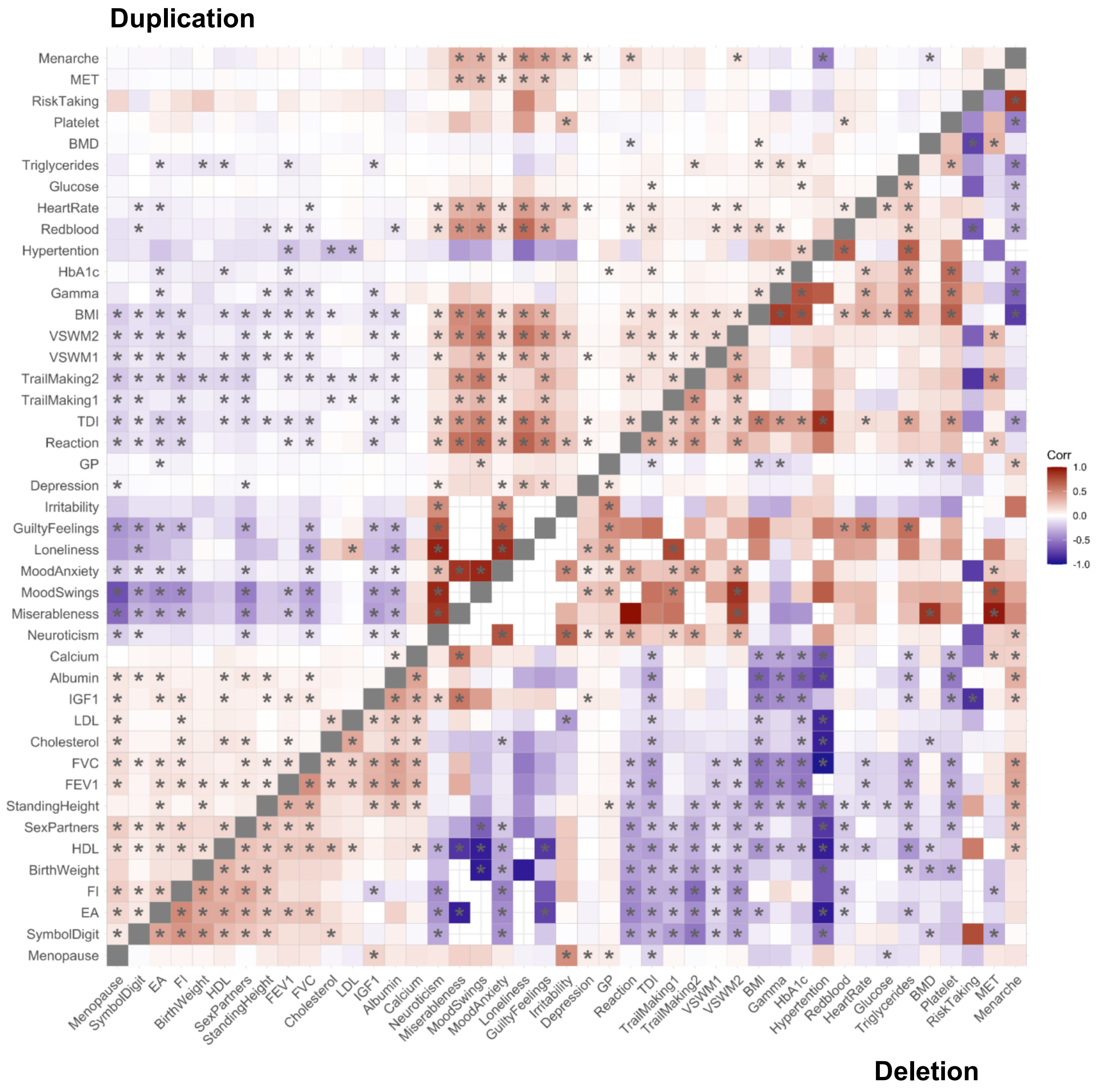


Figure S21 | Pairwise CNV Burden Genetic Correlations across 43 traits A combined heatmap of genetic correlations, showing functional burden genetic correlations for deletions and duplications in the lower and upper triangle matrices, respectively, with significant correlations marked by asterisks (FDR p-Jaccard).

Supplement Figures

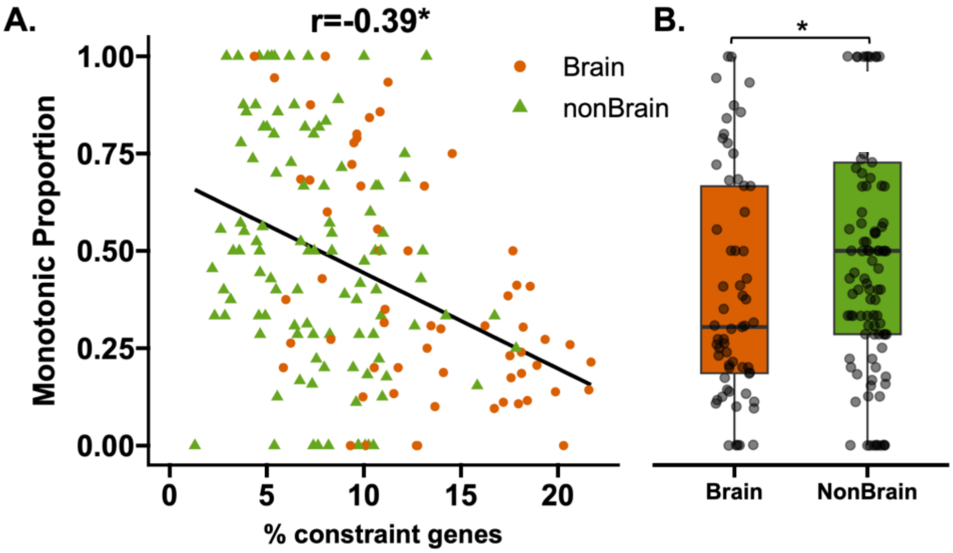


Figure S22 | Gene dosage responses at genesets' level

A) Correlation between the fraction of constraint genes (LOEUF top-decile) within a gene set and the proportion of monotonic gene dosage responses for that gene set (r=-0.39, p-Jaccard=1e-3). The proportions of monotonic responses are calculated across all traits, and using the total number of responses that are FDR-significant (for either deletions, duplications, or both). Each data point is a gene set. Y-axis: the proportion of monotonic responses within the gene set; X-axis: the percentage of top decile LOEUF genes within the gene set. **B)** Box plots show the distribution of monotonic proportions for Brain and Non-Brain gene sets. Each point represents a gene set, and asterisks (*) indicate statistically significant (Wilcox Ranksum) differences between groups.

Supplement Figures

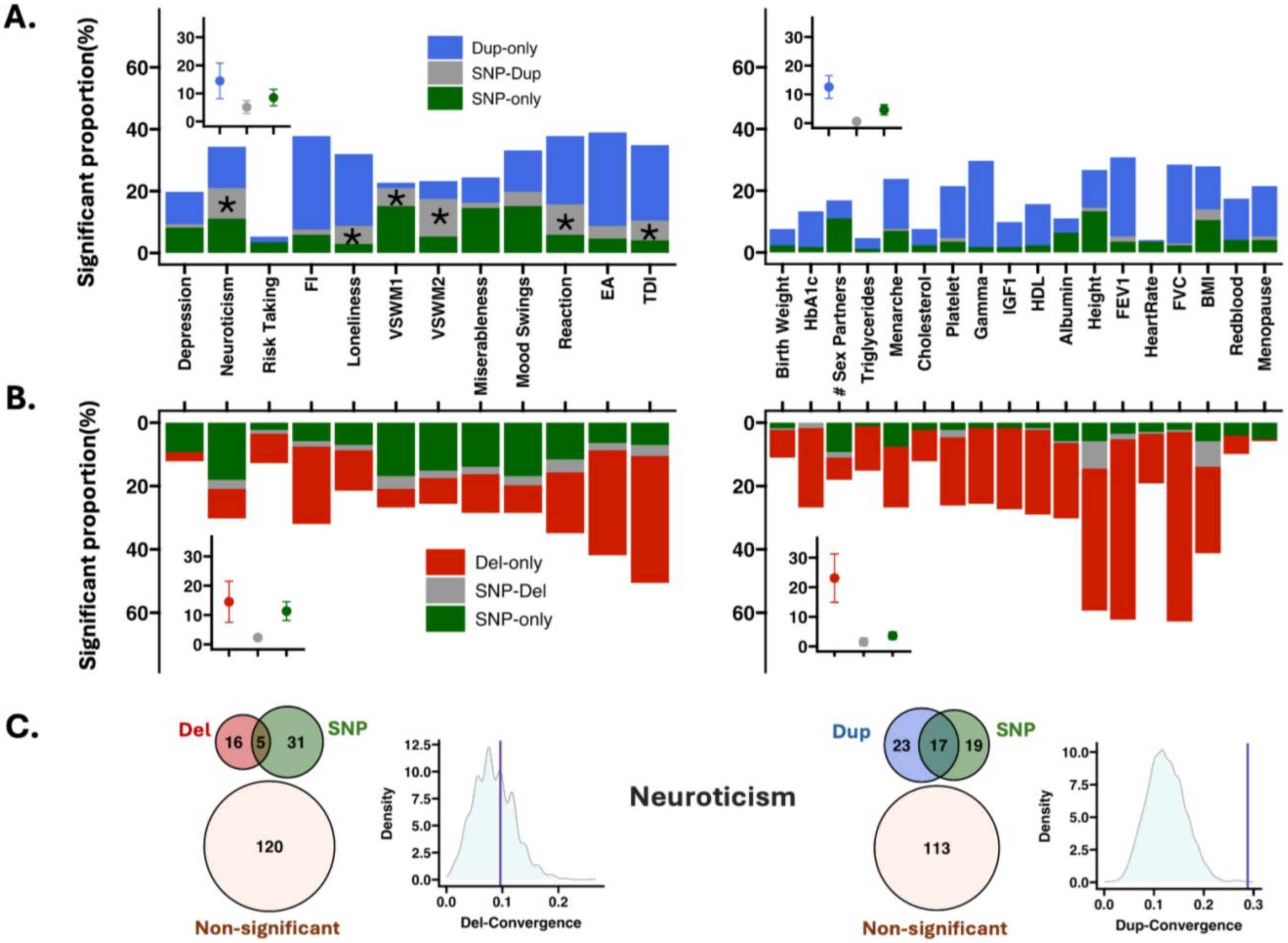


Figure S23 | Functional overlap between common variants and CNVs.

A) The stack bar plot represents the proportion of functional genes set overlapping between common variants and duplications for each trait. Overlapping functional gene sets (enriched in common variant and CNV signal) are gray, and non-overlapping functional gene sets are represented in blue (associations only significant for duplications or deletions). Stars represent significant functional overlap (FDR permutation p-value < 0.05). Y-axis: proportion of associated gene sets. X-axis: Brain and non-brain traits. The inserts represent the average convergence (between common variants and duplications) and average duplication-specific associations across traits.

The same information on functional convergence is shown in **(B)** between deletions and common variants (SNPs). **C)** illustrates the example of the functional overlap between SNPs and CNVs for Neuroticism using a Venn diagram. The density plot represents the null distribution of overlap significance (1000 permutations), with the observed overlap shown by the purple vertical line.

Abbreviations, BMI: body mass index; Del: deletion; Dup: duplication; EA: educational attainment; FI: fluid intelligence; SNP: single nucleotide polymorphism; TDI: townsend deprivation index;

Supplement Figures

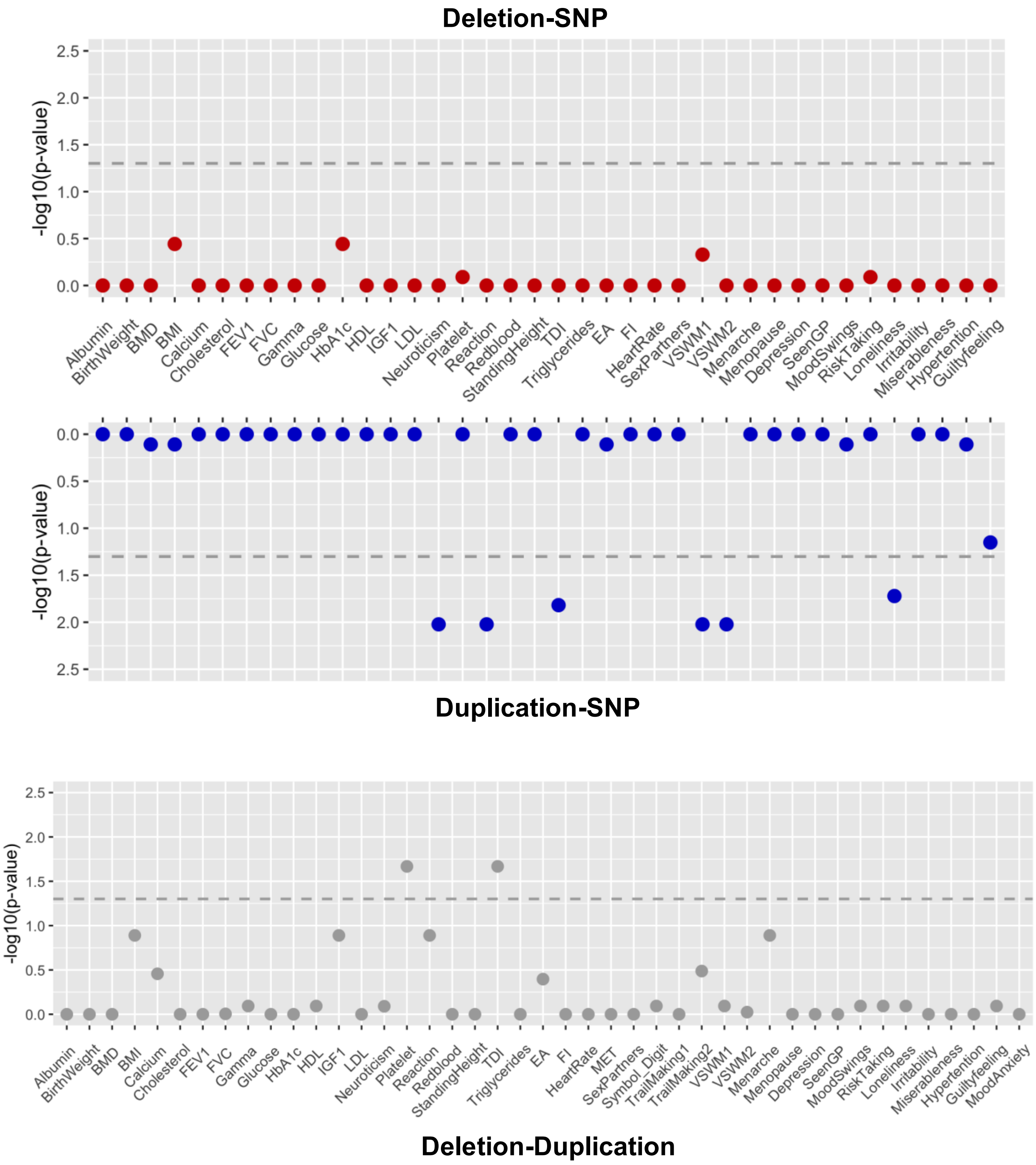


Figure S24 | Permutation test P-Values (1000 nulls) for functional overlap between CNV associations and GWAS enrichments, and Deletion and Duplication.

Supplement Figures

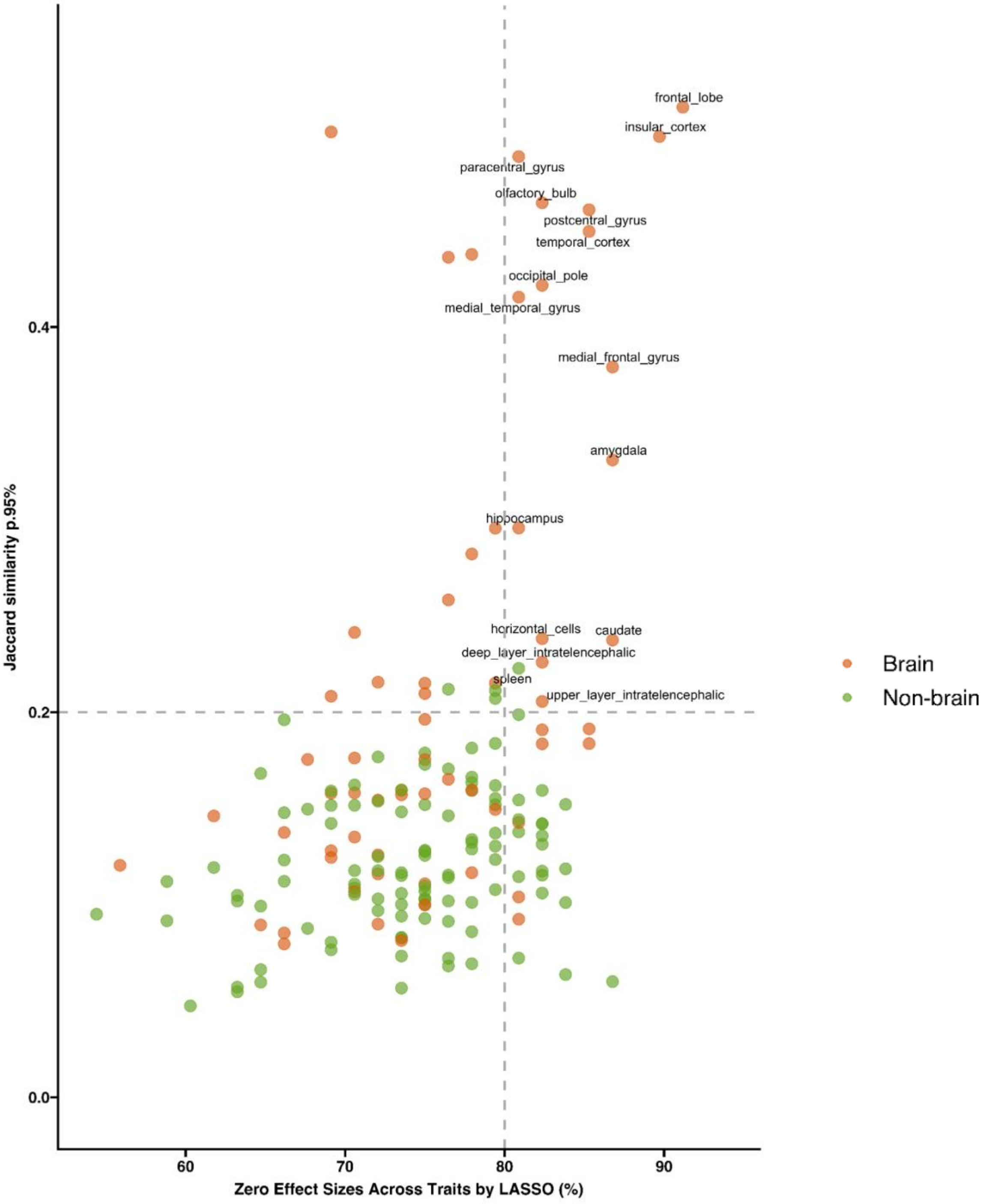
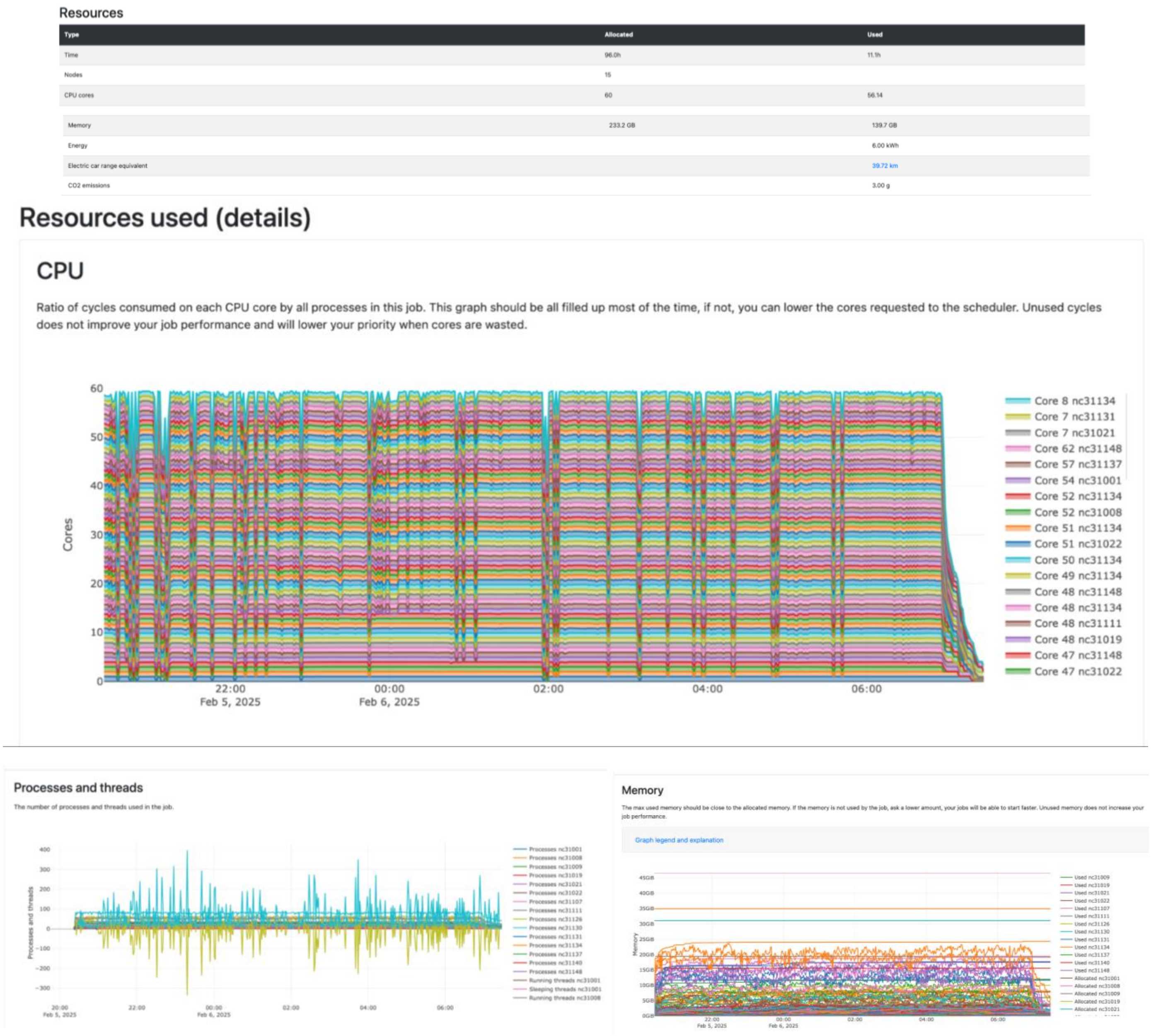


Figure S25 | Scatterplot of geneset Jaccard similarity (95th percentile) vs geneset zero effect sizes across traits excluded by LASSO (%). Genesets with Jaccard similarity > 0.2 and > 80% zero effect sizes across traits were excluded. In total, 16 gene sets were removed from the genetic correlation analysis.

Supplement Figures



Resources

Type	Allocated	Used
Time	96.0h	11.1h
Nodes	15	
CPU cores	60	56.14
Memory	233.2 GB	139.7 GB
Energy		6.00 kWh
Electric car range equivalent		39.72 km
CO2 emissions		3.00 g

Resources used (details)

CPU

Ratio of cycles consumed on each CPU core by all processes in this job. This graph should be all filled up most of the time, if not, you can lower the cores requested to the scheduler. Unused cycles does not improve your job performance and will lower your priority when cores are wasted.

Processes and threads

The number of processes and threads used in the job.

Memory

The max used memory should be close to the allocated memory. If the memory is not used by the job, ask a lower amount, your jobs will be able to start faster. Unused memory does not increase your job performance.

Graph legend and explanation

Figure S26 | Performance of FunBurd Running in Parallel for Constraint Nulls Genesets and traits (4,300 Jobs).

This hybrid computation was executed in parallel across 100 constraint-based null gene sets and 43 trait combinations. Within each run, the Funburd function utilized multithreading to evaluate 20 levels of constraint percentages ranging from 5% to 100%. In total, the computation involved 43 traits × 100 constraint nulls × 20 constraint levels × 2 CNV types (deletions and duplications), resulting in 172,000 individual Funburd executions. *Statistics of the performance of hybrid jobs derived from Compute Canada.*