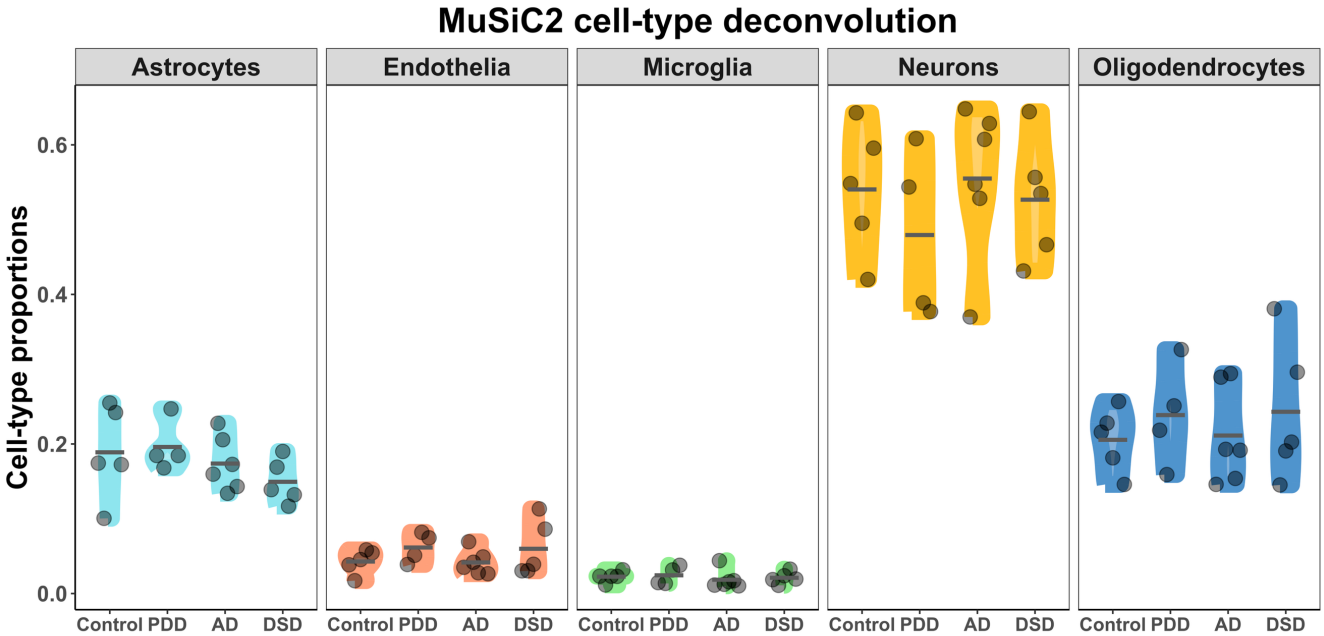
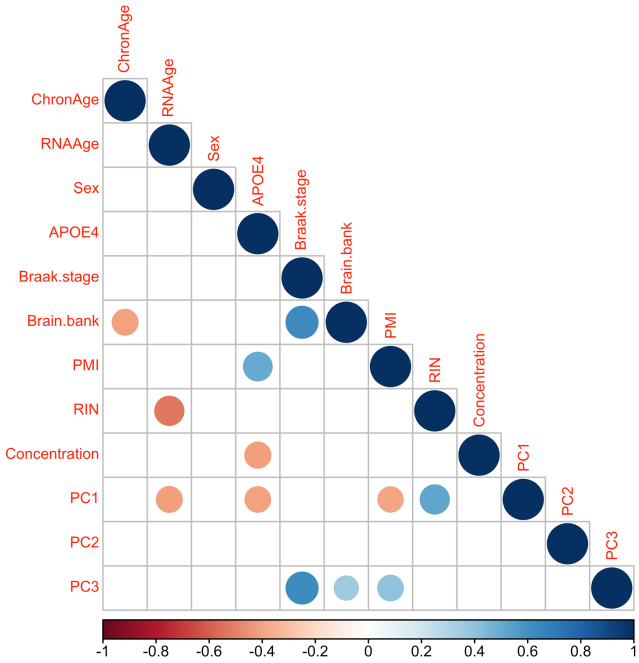
Supplementary material

Case #	Clinical diagnostic	Braak	Sex	Age	PMI	ApoE	Brain bank
No. 1	Control	*N/A*	F	73	1.50	ε3/ε3	NBB-IBB
No. 2	Control	I	F	81	2.25	ε2/ε3	NBB-IBB
No. 3	Control	*N/A*	F	81	5.53	ε3/ε3	NBB-IBB
No. 4	Control	*N/A*	F	89	2.50	ε3/ε3	NBB-IBB
No. 5	Control	*N/A*	M	78	2.00	ε3/ε3	NBB-IBB
No. 6	PDD	V	F	68	24.00	ε4/ε4	NeuroCEB
No. 7	PDD	IV	F	85	21.00	ε3/ε4	NeuroCEB
No. 8	PDD	*N/A*	F	86	3.25	ε3/ε3	NBB-IBB
No. 9	PDD	*N/A*	M	80	8.00	ε3/ε3	NBB-IBB
No. 10	AD	*N/A*	F	68	16.50	ε3/ε4	NBB-IBB
No. 11	AD	*N/A*	F	70	16.50	ε4/ε4	NBB-IBB
No. 12	AD	IV	F	72	6.17	ε4/ε4	NBB-IBB
No. 13	AD	*N/A*	M	62	1.75	ε3/ε4	NBB-IBB
No. 14	AD	*N/A*	M	73	10.25	ε2/ε4	NBB-IBB
No. 15	AD	VI	M	90	28.00	ε3/ε4	NeuroCEB
No. 16	DSD	VI	F	56	28.50	ε3/ε4	KCL
No. 17	DSD	*N/A*	F	64	8.00	ε3/ε3	Cambridge
No. 18	DSD	VI	M	52	7.00	ε3/ε3	Cambridge
No. 19	DSD	VI	M	55	11.00	ε3/ε3	Cambridge
No. 20	DSD	V	M	67	3.00	ε3/ε3	Cambridge

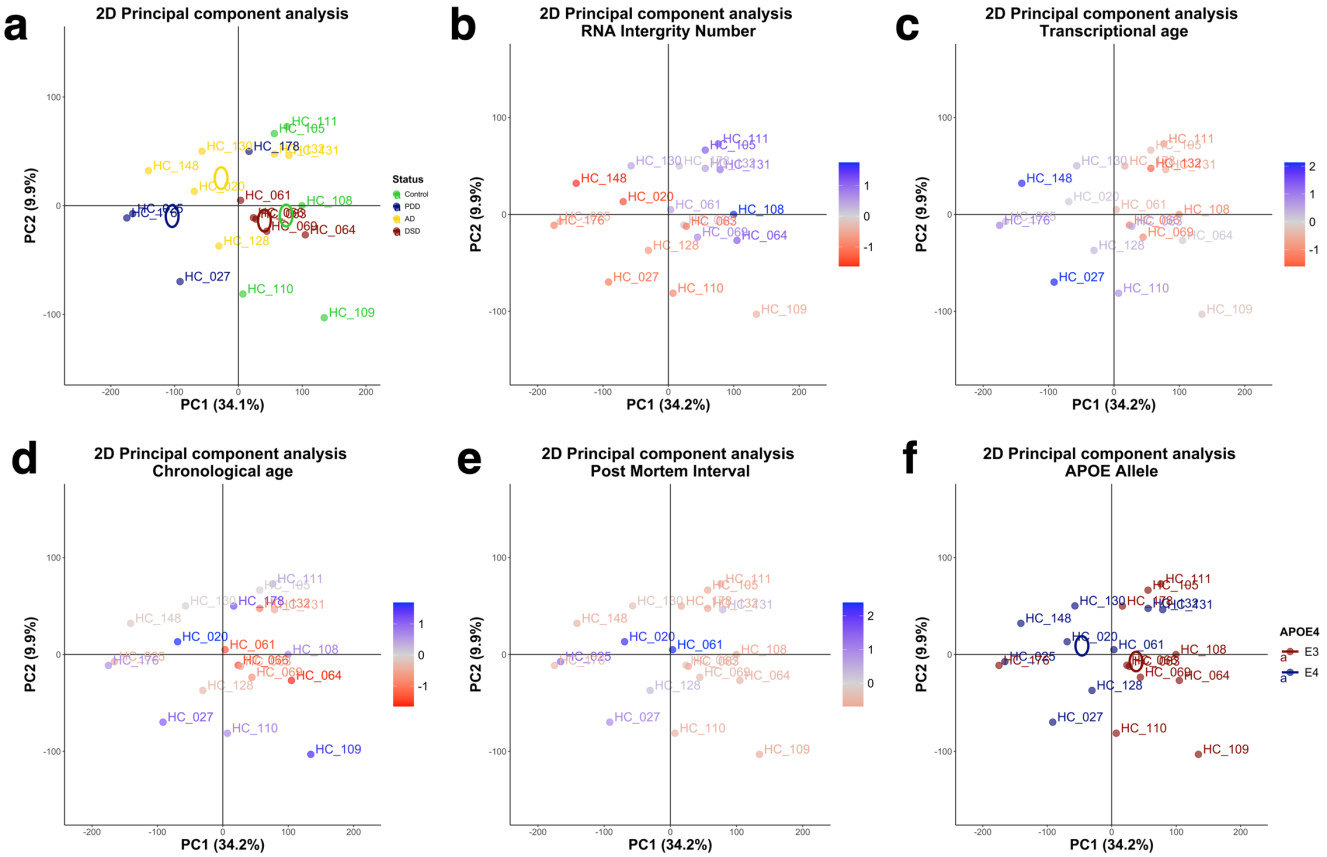
Supplementary Table S1 | Demographics of the post-mortem human hippocampal tissues used in the study.
Abbreviations: AD = Alzheimer's disease; DSD = Down syndrome dementia; PDD = Parkinson's disease dementia; ApoE = ApoE genotype; PMI = post-mortem interval (in hours); Braak = Braak tau stage; M = male; F = female; N/A = not available data; NBB-IBB = Neurobiobank of the Institute Born-Bunge; NeuroCEB = National Brain Bank Neuro-CEB; KCL = King's College London Brain Bank; Cambridge = Cambridge Brain Bank.



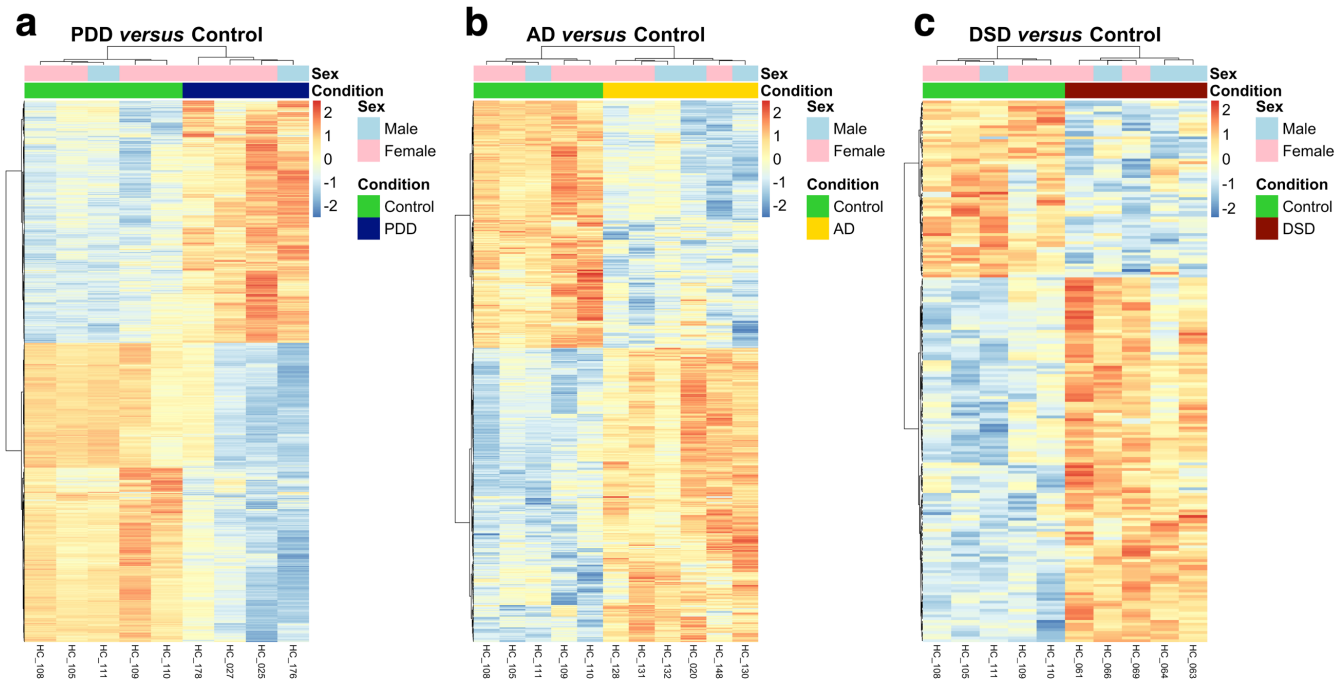
Supplementary Fig. S1 | Violin plot for astrocytes, endothelia, microglia, neurons and oligodendrocytes cell-type deconvolution.
The cell-type composition was inferred with the MuSiC2 algorithm for the bulk RNA-sequencing data from non-demented (Control), Parkinson´s disease with dementia (PDD), Alzheimer´s disease (AD) and Down syndrome with dementia (DSD) cases. For each cell-type, the solid line represents the average proportions across samples, which was inferred through bulk data deconvolution with the single-cell RNA-sequencing dataset obtained from Darmanis *et al.*, 2015. No single cell-type significantly differed between groups. Statistical significance was tested using the one-way ANOVA followed by the Tukey´s HSD *post hoc* test.



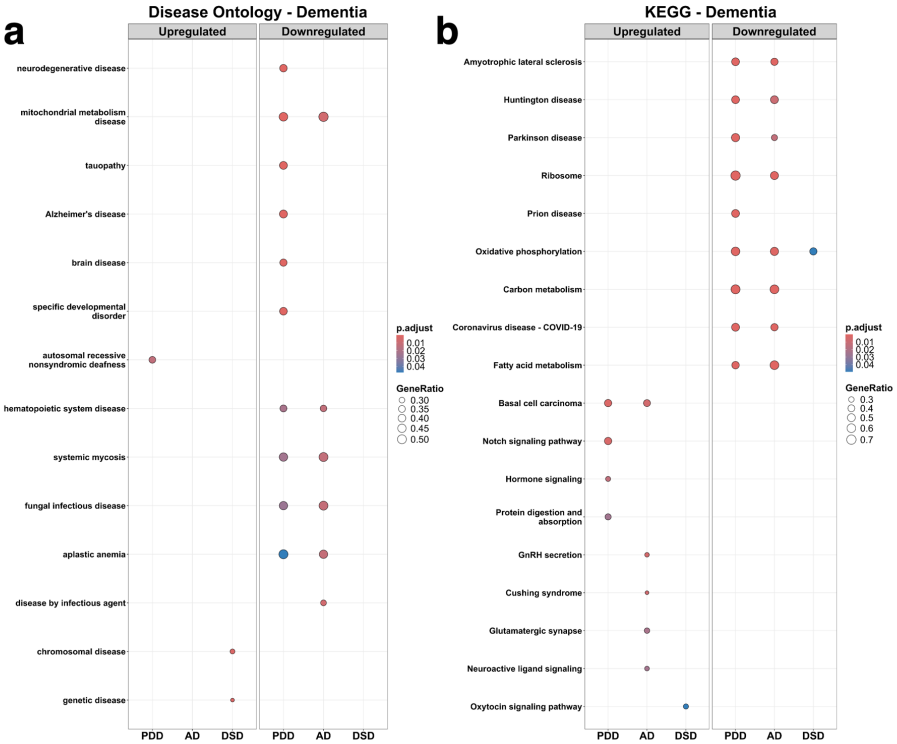
Supplementary Fig. S2 | Kendall´s Tau correlation between potential sources of biological variation and the first three principal components.
Circle sizes are proportional to the correlation coefficient, while the colors indicate positive (blue) and negative (red) coefficients. Non-significant pairwise correlations (p-value > 0.05) are not presented in the figure.



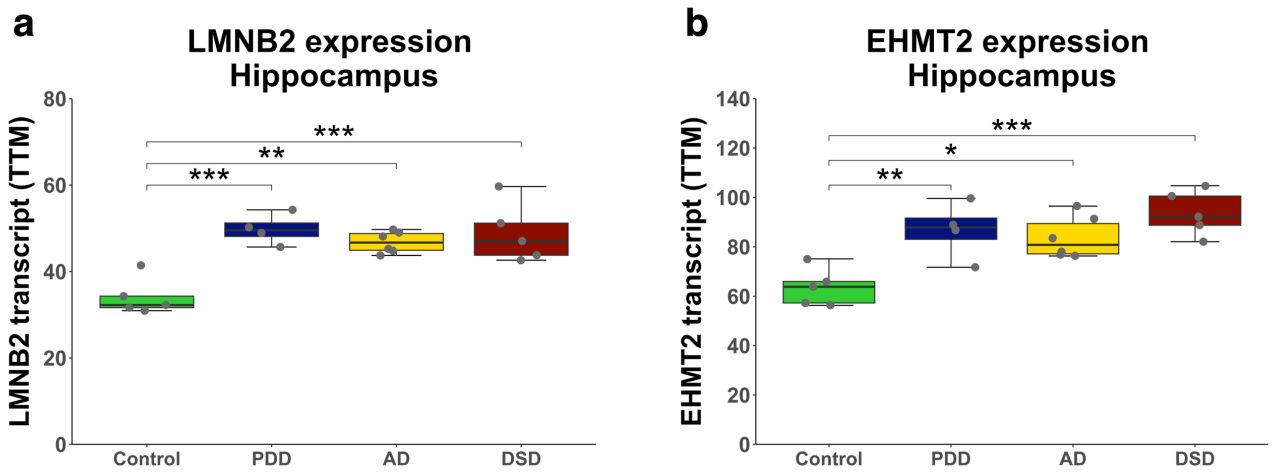
Supplementary Fig. S3 | Two-dimensional principal component analysis cluster plots of the RNA-sequencing dataset.
The distribution of **a** the sample groups by their status, **b** RNA integrity number, **c** transcriptional age (RNAAge), **d** chronological age, **e** post-mortem interval, and **f** APOE status.



Supplementary Fig. S4 | Heatmaps of differentially expressed genes (DEGs).
a Heatmap showing the DEGs between Parkinson´s disease dementia (PDD) and non-demented cases (Control). **b** Heatmap showing the DEGs between Alzheimer´s disease (AD) and Control. **c** Heatmap showing the DEGs between Down syndrome dementia (DSD) and Control. Red lines indicate upregulated genes, whereas blue lines represent downregulated genes.



Supplementary Fig. S5 | Disease Ontology (DO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis for the samples of Parkinson´s disease dementia (PDD), Alzheimer´s disease (AD) and Down syndrome dementia (DSD).
a DO terms that were significantly enriched for PDD, AD and DSD individuals. **b** KEGG terms that were significantly enriched for PDD, AD and DSD individuals. In each plot, dot size indicates the number of genes in that gene set by ratio (GeneRatio) and dot color reflects statistical significance based on FDR-adjusted p-values (p.adjust).



Supplementary Fig. S6 | Hub gene expression in the normalized count matrix with the Trimmed Mean of M-values (TMM) method. **a** Normalized LMNB2 expression levels in the hippocampus obtained from the count matrix for the samples of non-demented controls (Control), Parkinson´s disease dementia (PDD), Alzheimer´s disease (AD) and Down syndrome dementia (DSD). **b** Normalized EHMT2 expression levels in the hippocampus obtained from the count matrix for Control, PDD, AD and DSD samples. Statistical significance was tested using the one-way ANOVA followed by the Tukey´s HSD *post hoc* test, which was presented with * p-value ≤ 0.05; ** p-value ≤ 0.01; *** p-value ≤ 0.001.