

Supplementary Figure Legends

Supplementary Figure S1. Additional evidence from Figure 2 supporting the conclusion that *N*-PPG (50 mg/kg x 9 days) induced partial normalization of HD brain transcriptomes and pathways toward WT. **A.** Pearson's linear correlation ($R_p = +0.75$, $p < 0.05$) between Log₂-fold changes (Log₂FC) in treated HD/control HT (HT/H) and control WT/HD (W/H) mean gene ratios ($n=1611$ SDE gene set, Suppl. Table S1). **B.** Normalization of set of 1611 SDE mean gene ratios with inset of heat map showing extent of normalization for three mouse brain transcripts (Th, *Drd1*, *Adora2a*) known to be dysregulated during HD disease progression and significantly downregulated in Veh treated R6/2 mice relative to Veh treated WT mice. **C.** Gene set enrichment analysis (GSEA) showing normalized enrichment scores (NES) from transcriptomes of *N*-PPG vs. vehicle treated WT mouse brains. **D.** Statistical excess of overlapping GSEA pathways (up- and down-regulated) indicating pathway normalization in *N*-PPG treated HD (R6/2) mouse brains relative toward those of WT mouse brains.

Supplementary Figure S2. Repeated weight, motor performance and survival measurements of HD R6/2 mice orally gavaged with either Veh ($n=9$) or 50 mg/kg *N*-PPG ($n=8$) for 14 days (also schematically shown in Figure 3A). **A.** No significant change in body weights during or after Veh or *N*-PPG treatments. **B.** No significant change in median 14.3 weeks of survival after Veh or *N*-PPG treatments. **C.** No significant change in metabolic cage measurement at 12 weeks of overall O₂ consumption, CO₂ production, food consumption or energy expenditure. **D.** No significant change in grip strength, rotarod coordination or hindlimb clasp measured at indicated time points during and after Veh or *N*-PPG treatments.

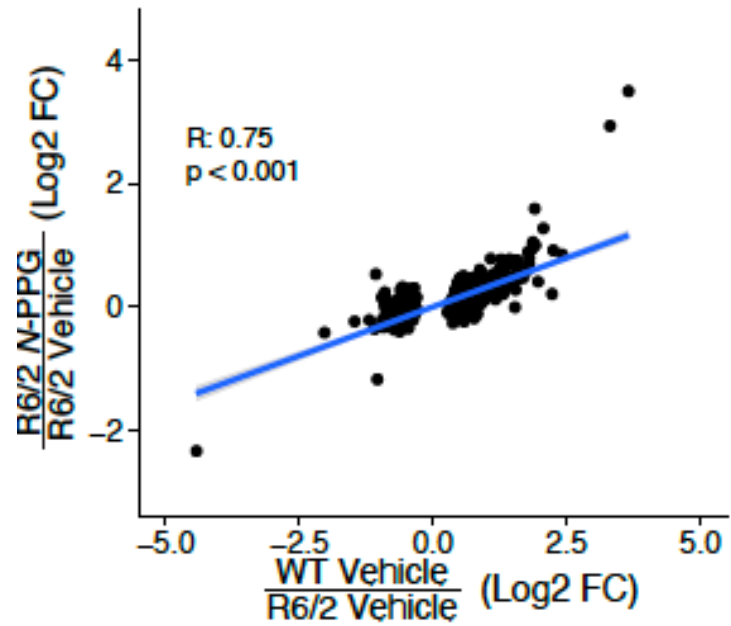
Supplementary Figure S3. Breakdown of all metabolites commonly measured in tissues (blood, brain/cerebellum, kidney) of Veh and *N*-PPG treated HD R6/2 mice, as schematically shown in Figure 3A. Of the 536 tissue analytes quantifiable by our metabolomic platform, 260 were common to all three tissue types; the 39 classified as either amino acids or amino acid-related metabolites were the subject of further analysis (Figure 3B, Suppl. Table S3).

Supplementary Figure S4. Differential metabolic cage effects on WT mice during and after *N*-PPG treatments (Veh, 100 mg/kg, or 200 mg/kg daily x 8 weeks followed by 8 weeks off all treatments), schematically shown in Figure 6A. During treatment cage measurements showed significant *N*-PPG induced increases in CO₂ production, O₂ consumption, and energy expenditure (kcal/h), which largely reversed by 8 weeks after treatment cessation.

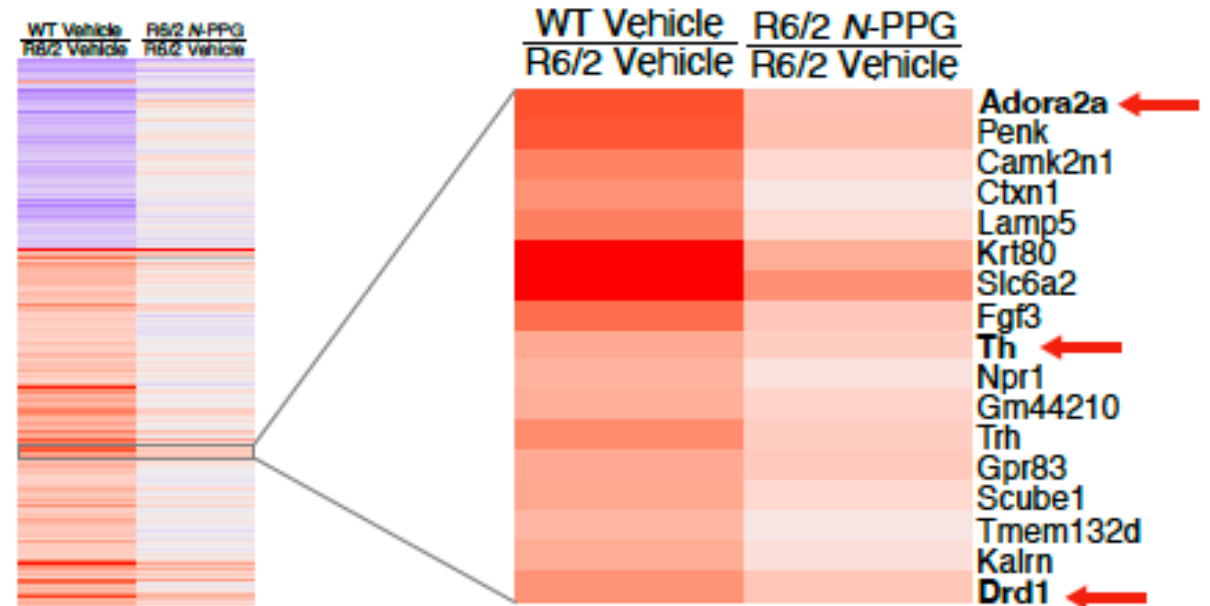
Supplementary Figure S5. Unsupervised clustering of the amino acid-related metabolites measured in blood, brain (cerebellum) and kidney tissues of WT mice collected 8 weeks after Veh or *N*-PPG (100 mg/kg) treatment, schematically shown in Figure 6A. Only the blood samples showed significant changes in proline, sarcosine and 20 other amino acid-related metabolites, suggesting a complex systemwide rebound response to the earlier *N*-PPG treatment.

Suppl. Figure S1

A

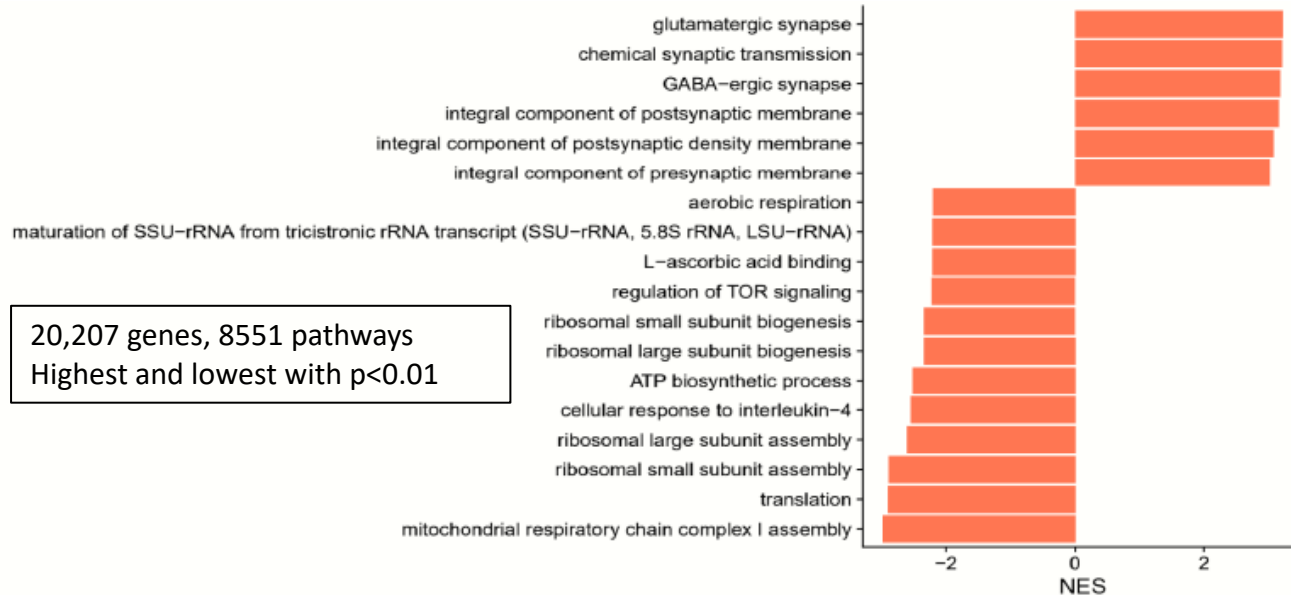


B



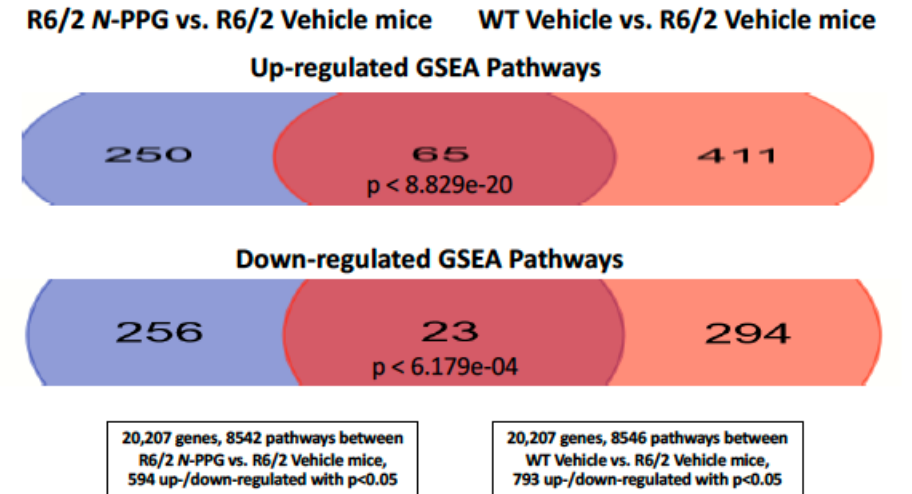
C

Brain transcriptome GSE Normalized Enrichment Scores (NES): WT N-PPG vs. WT Vehicle treated

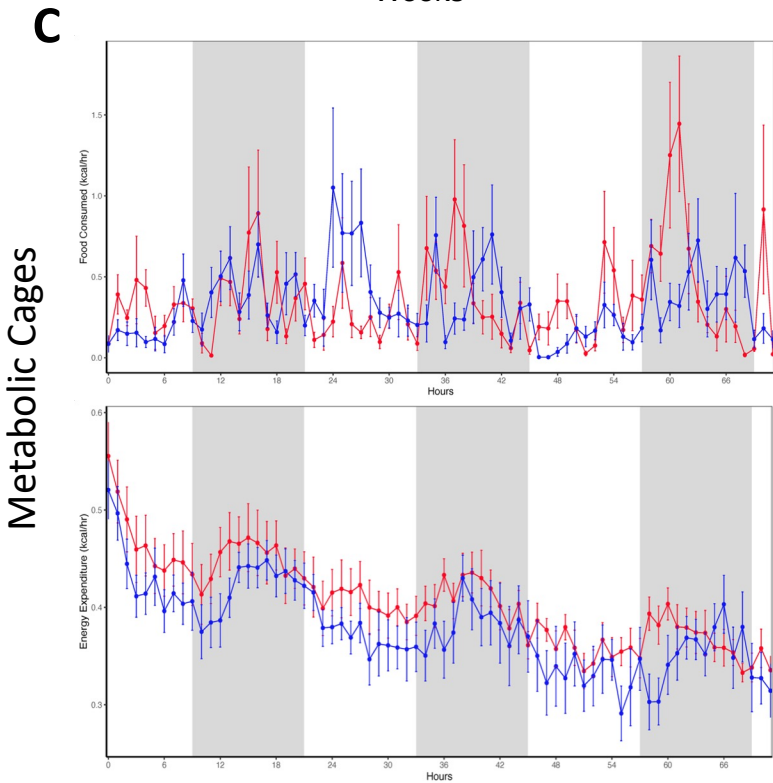
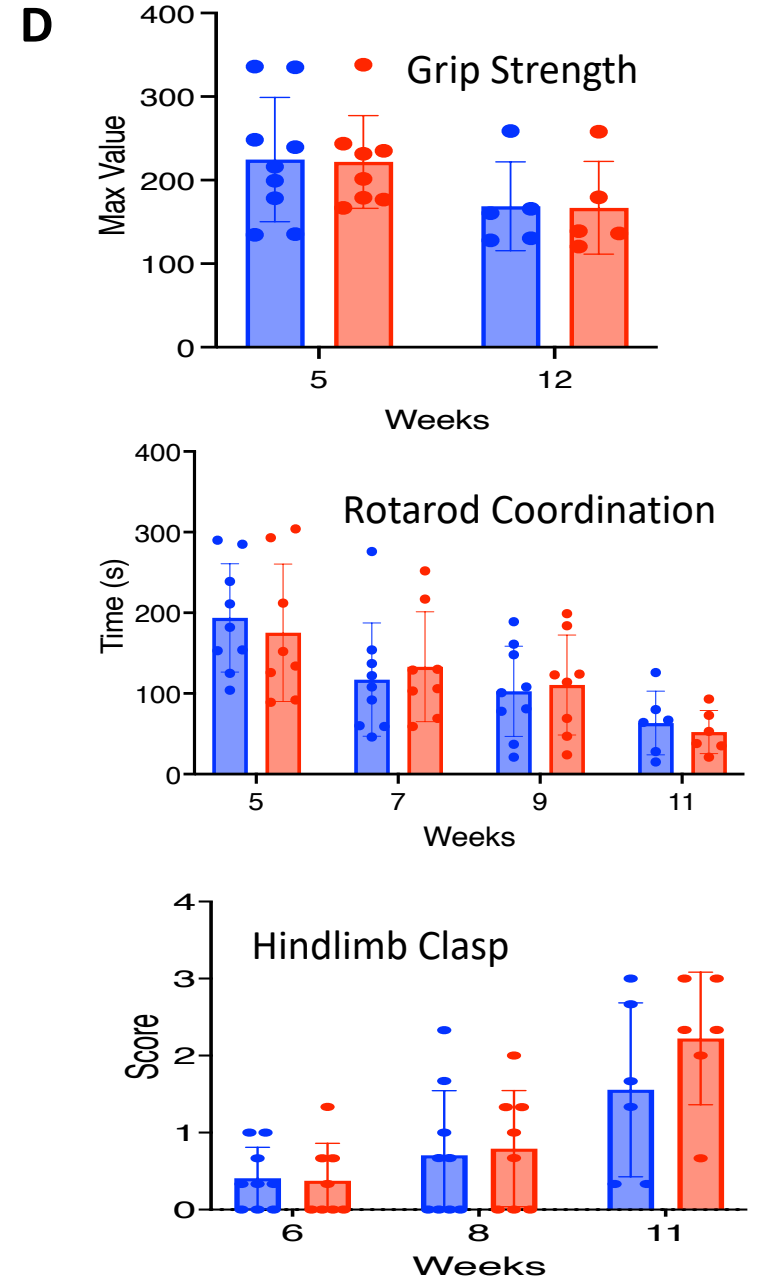
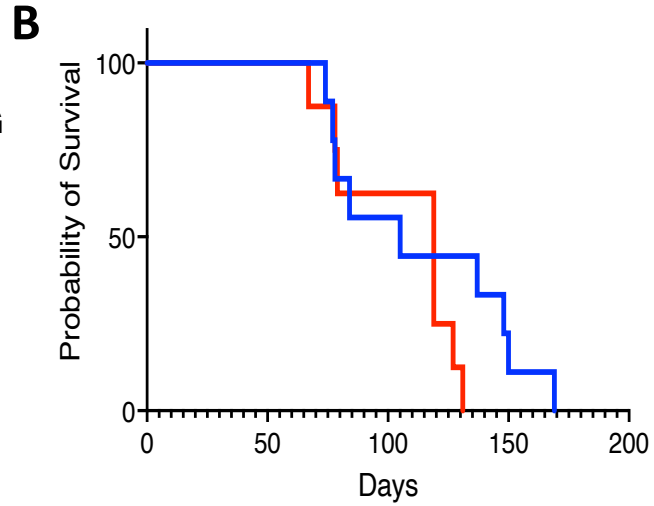
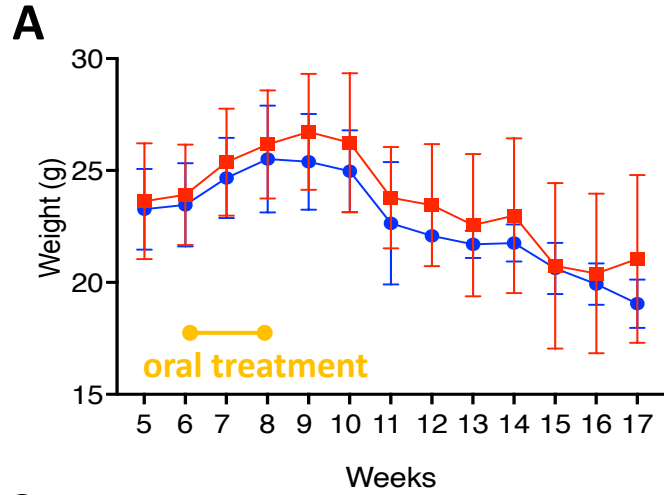


D

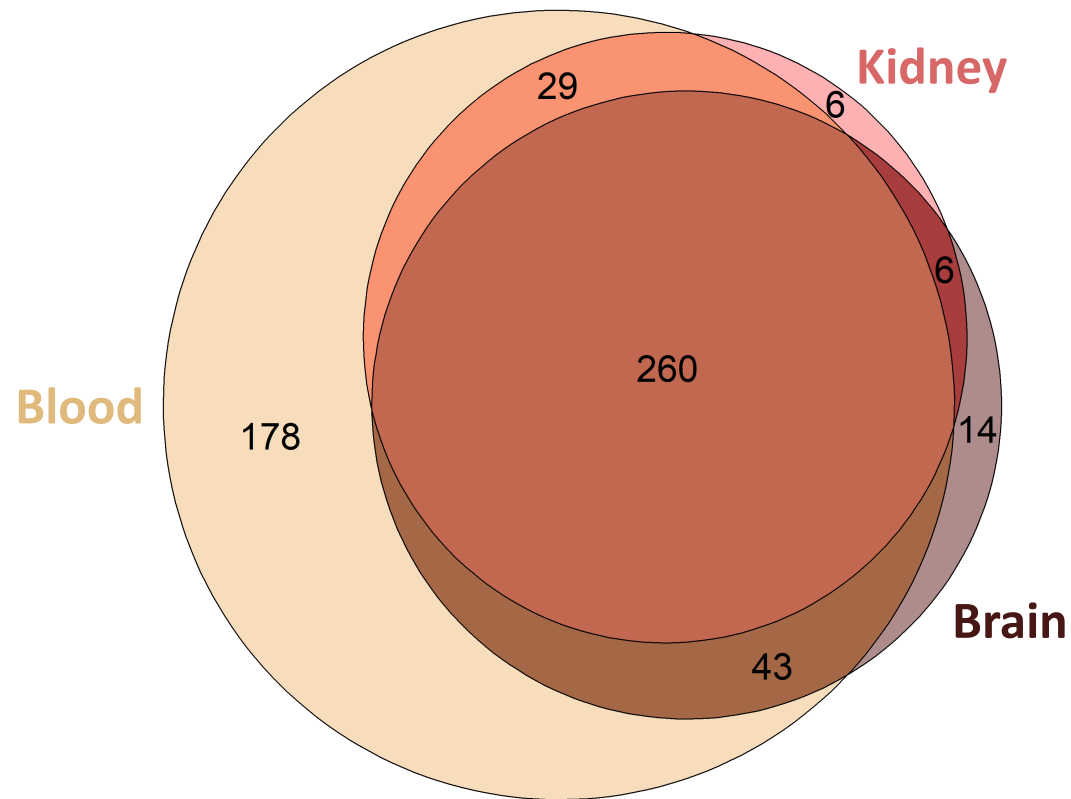
Excess overlap of brain transcriptome GSEA pathways between R6/2 N-PPG vs. R6/2 Vehicle and WT Vehicle vs. R6/2 Vehicle mice



Suppl. Figure S2



Suppl. Figure S3



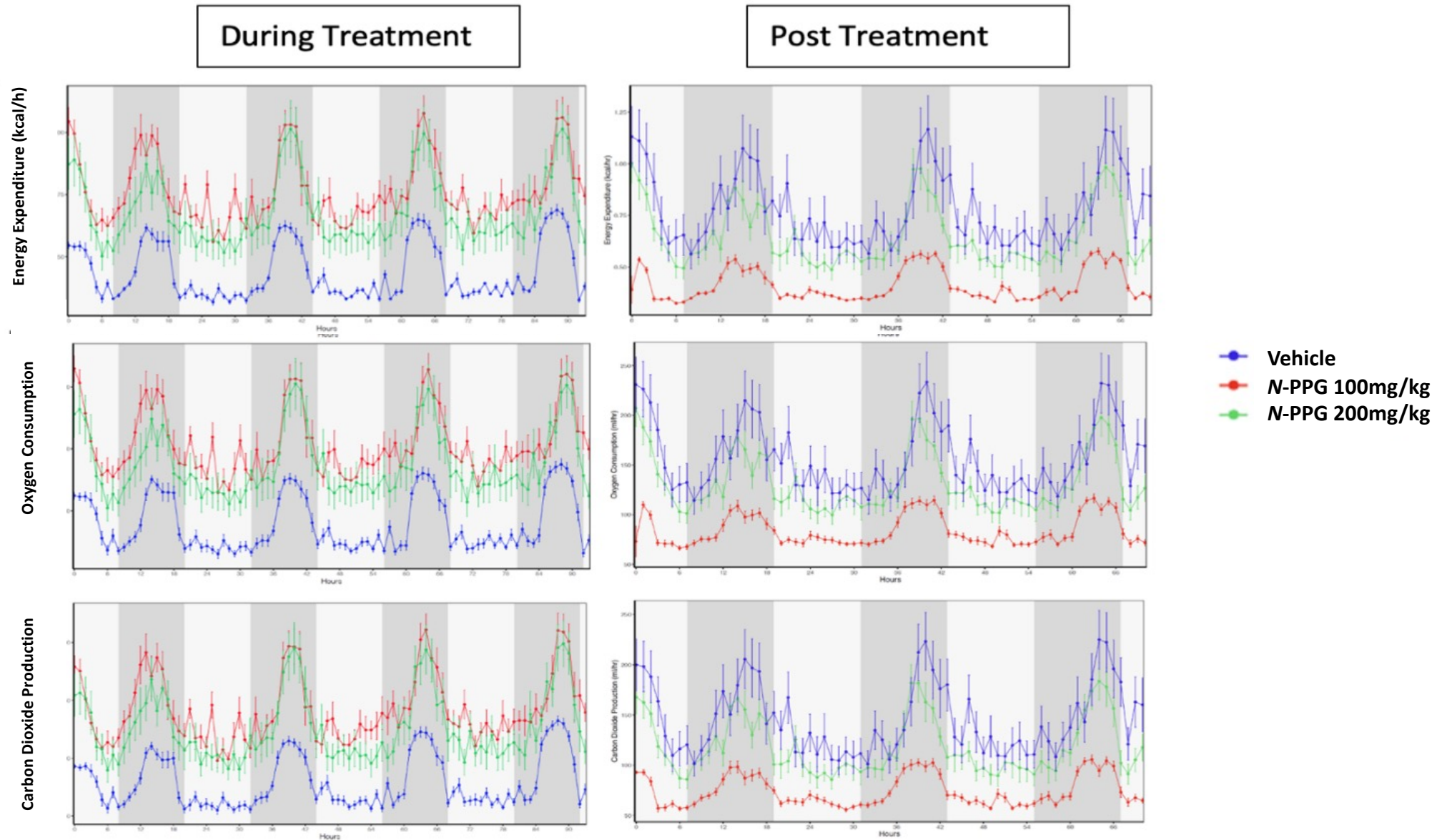
260 common to blood, brain and kidney

Class	Number of metabolites
Acylcarnitines	37
Alkaloids	1
Aminoacids	20
Aminoacids Related	19
Bile Acids	1
Biogenic Amines	6
Carboxylic Acids	1
Ceramides	14
Cholesterol Esters	2
Diacylglycerols	6
Fatty Acids	3
Glycerophospholipids	81
Glycosylceramides	11
Indoles Derivatives	1
Nucleobases Related	2
Sphingolipids	14
Sugars	1
Triacylglycerols	39
Vitamins & Cofactors	1

39 common to blood, brain and kidney

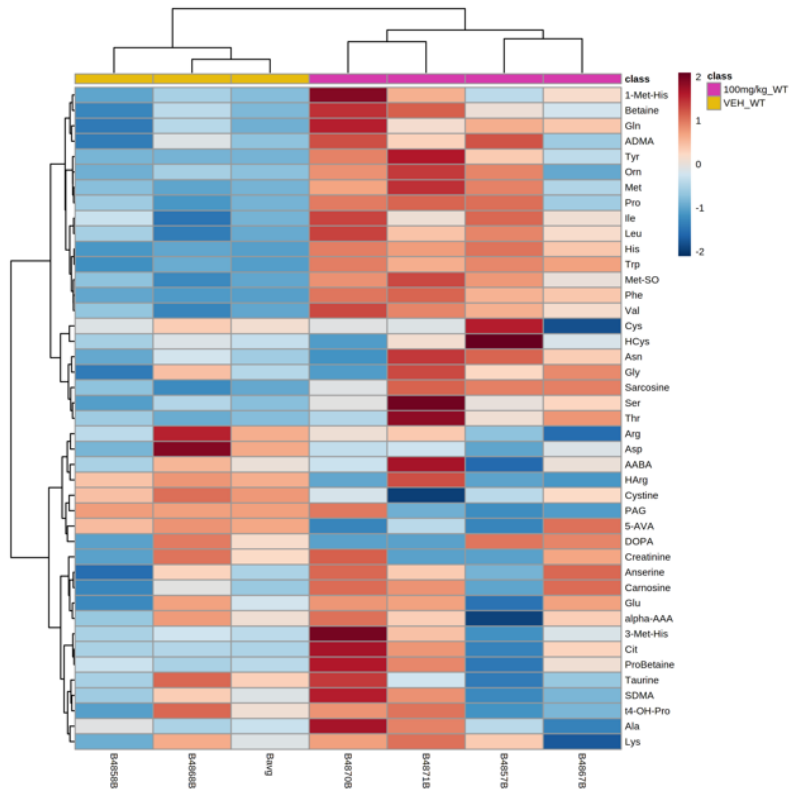
Amino acids (20)	Amino acid-related (19)
Ala	1-Met-His
Arg	3-Met-His
Asn	5-AVA
Asp	AABA
Cys	ADMA
Gln	alpha-AAA
Glu	Anserine
Gly	Betaine
His	Carnosine
Ile	Cit
Leu	Creatinine
Lys	Cystine
Met	HArg
Phe	HCys
Pro	Orn
Ser	ProBetaine
Thr	SDMA
Trp	t4-OH-Pro
Tyr	Taurine
Val	

Suppl. Figure S4

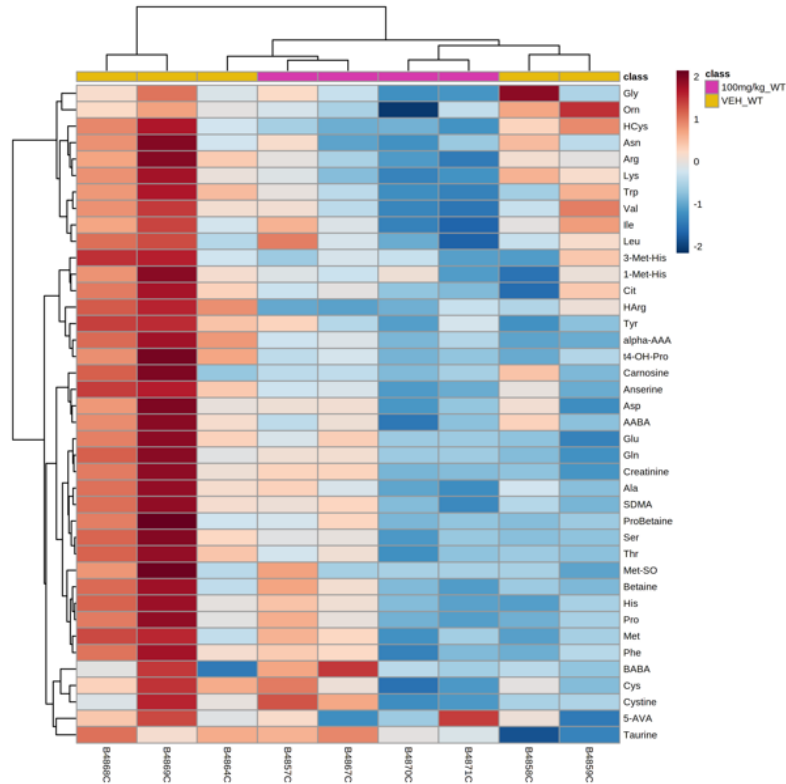


Suppl. Figure S5

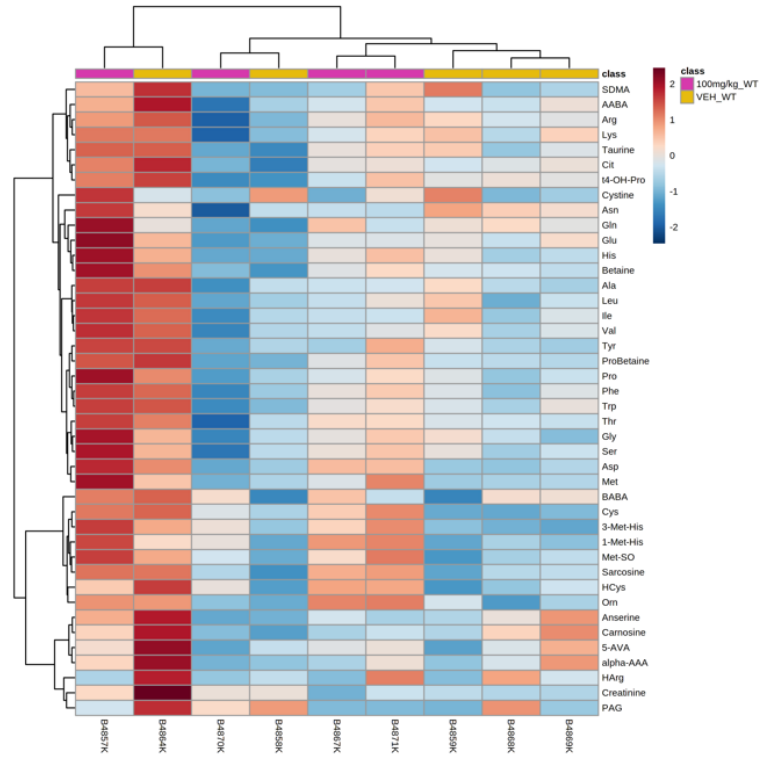
Blood



Brain/cerebellum



Kidney



100 mg/kg _ WT
VEH _ WT