Supplementary information

Sex-specific hippocampal metabolic signatures at the onset of systemic inflammation with lipopolysaccharide in the APPswe/PS1dE9 mouse model of Alzheimer's disease

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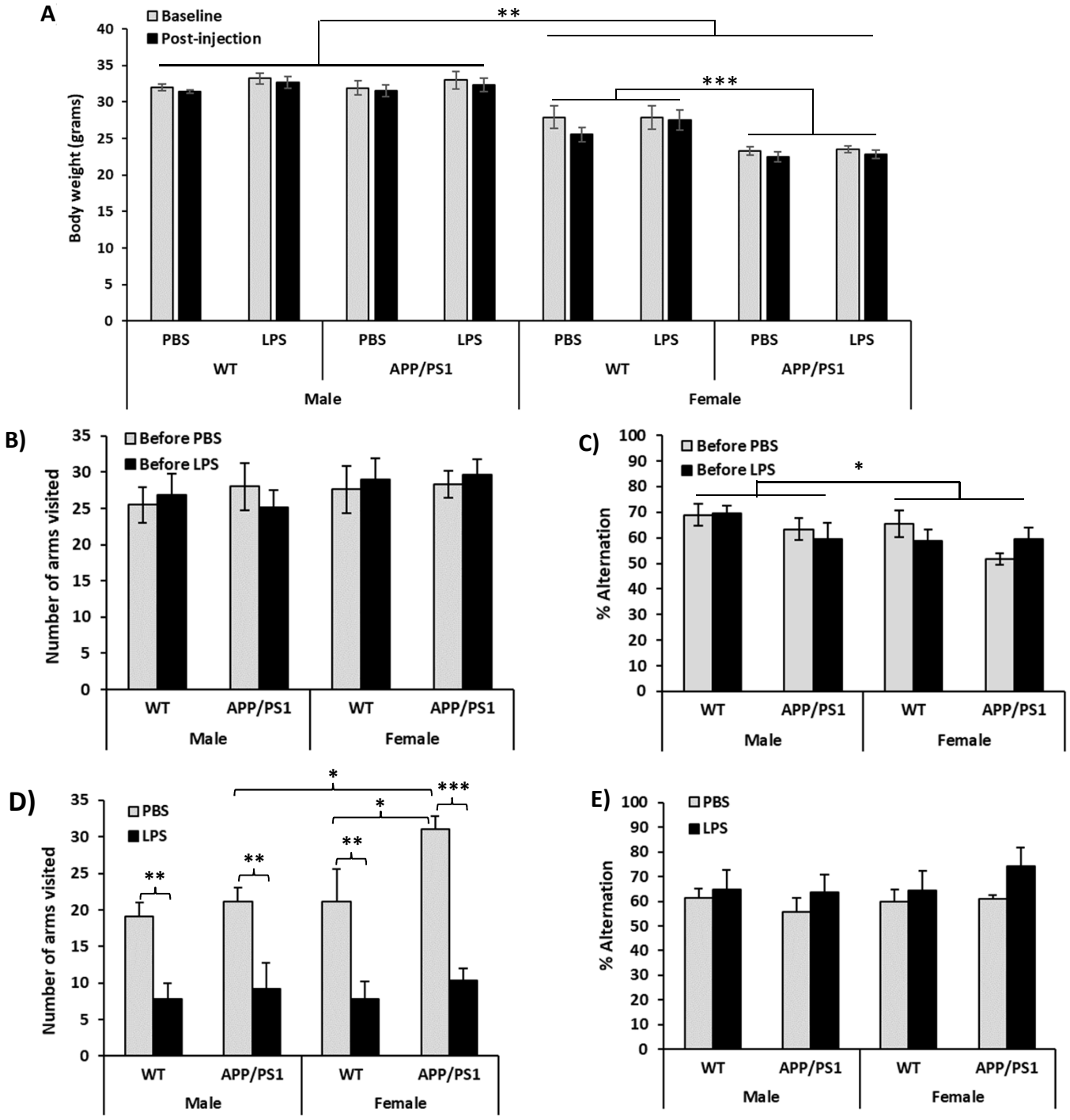

Supplementary Figure 1. Body mass (A) was recorded prior to and 4 hours after the PBS or LPS challenge. The two-way ANOVA with repeated measures revealed a significant Genotype x Sex interaction effect ($F_{(1,36)}$ = 12.22, p=0.0013). Females were overall lighter than males regardless of genotype ($F_{(1,36)}$ = 152.67, p<0.0001) but within females, the APP/PS1 mice were also lighter than their WT littermates (p<0.0001). None of the experimental groups showed significant weight loss at 4 hours following the LPS or PBS challenge. Before injection with PBS or LPS, none of the groups differed for the number of arm visits in the Y-maze (B), but females showed an overall reduction in spatial alternation performance (B; Sex effect: $F_{(1,35)}$ = 4.65, p=0.04). At 4 hours post injection, LPS-treated mice visited significantly less arms of the Y-maze than PBS-treated mice ($F_{(1,36)}$ = 65.53, p<0.0001) and but PBS-treated APP/PS1 mice were also hyperactive compared to PBS-treated APP/PS1 males and WT females (p=0.009 in both cases, C), but their spontaneous alternation performance (D) did not differ. Data are expressed as Means $\pm$ SEM. *, p<0.05; **, p<0.01; **, p<.0001

Supplementary table 1. Results of the two-way repeated measure ANOVAs on behavioral measures.

	Body weight	Food Burrowing*	Arm entries	Alternation rate
Covariate (arm entries)				$F_{(1,31)}$=0.80 p=0.38
Genotype	$F_{(1,36)}$=14.4 **p=0.0006**	$F_{(1,36)}$=0.03 p=0.86	$F_{(1,36)}$=2.12 p=0.15	$F_{(1,36)}$=0.88 p=0.36
Sex	$F_{(1,36)}$=152.67 **p<0.0001**	$F_{(1,36)}$=2.30 p=0.14	$F_{(1,36)}$=3.17 p=0.08	$F_{(1,36)}$=0.11 p=0.74
Treatment	$F_{(1,36)}$=2.30 p=0.14	$F_{(1,36)}$=22.2 **p<0.0001**	$F_{(1,36)}$=20.66 **p<0.0001**	$F_{(1,36)}$=0.41 p=0.53
Time	$F_{(1,35)}$=9.37 **p=0.004**	$F_{(1,36)}$=15.92 **p=0.003**	$F_{(1,36)}$=145.25 **p<0.0001**	$F_{(1,31)}$=0.18 p=0.68
Genotype X Sex	$F_{(1,36)}$=12.22 **p=0.0013**	$F_{(1,36)}$=1.22 p=0.28	$F_{(1,36)}$=0.59 p=0.45	$F_{(1,36)}$=1.09 p=0.30
Genotype X Treatment	$F_{(1,36)}$=0.19 p=0.67	$F_{(1,36)}$=0.20 p=0.66	$F_{(1,36)}$=0.97 p=0.33	$F_{(1,36)}$=0.85 p=0.36
Genotype X Time	$F_{(1,35)}$=0.35 p=0.56	$F_{(1,36)}$=1.62 p=0.21	$F_{(1,36)}$=3.09 p=0.09	$F_{(1,31)}$=2.98 p=0.09
Sex X Treatment	$F_{(1,36)}$=0.17 p=0.68	$F_{(1,36)}$=0.37 p=0.55	$F_{(1,36)}$=0.28 p=0.60	$F_{(1,36)}$=0.18 p=0.67
Sex X Time	$F_{(1,35)}$=1.06 p=0.31	$F_{(1,36)}$=0.06 p=0.81	$F_{(1,36)}$=0.25 p=0.62	$F_{(1,31)}$=4.25 **p=0.048**
Treatment X Time	$F_{(1,35)}$=1.02 p=0.32	$F_{(1,36)}$=9.47 **p=0.004**	$F_{(1,36)}$=58.55 **p<0.0001**	$F_{(1,31)}$=0.65 p=0.43
Genotype X Sex X Treatment	$F_{(1,36)}$=0.04 p=0.84	$F_{(1,36)}$=3.13 p=0.08	$F_{(1,36)}$=0.04 p=0.84	$F_{(1,36)}$=0.97 p=0.33
Genotype X Sex X Time	$F_{(1,35)}$=0.32 p=0.57	$F_{(1,36)}$=0.46 p=0.50	$F_{(1,36)}$=1.20 p=0.28	$F_{(1,30)}$=0.73 p=0.40
Genotype X Treatment X Time	$F_{(1,35)}$=1.05 p=0.31	$F_{(1,36)}$=0.12 p=0.73	$F_{(1,36)}$=0.24 p=0.63	$F_{(1,30)}$=0.01 p=0.91
Sex X Treatment X Time	$F_{(1,35)}$=1.29 p=0.27	$F_{(1,36)}$=0.30 p=0.59	$F_{(1,36)}$=3.79 p=0.06	$F_{(1,30)}$=0.00 p=0.95
Genotype X Sex X Treatment X Time	$F_{(1,35)}$=0.59 p=0.45	$F_{(1,36)}$=0.09 p=0.77	$F_{(1,36)}$=1.94 p=0.17	$F_{(1,30)}$=0.78 p=0.38

*: Food burrowing data were rank-transformed prior to statistical analyses.

Supplementary table 2. Results of the two-way repeated measure ANOVAs on plasma cytokine levels. Data were rank-transformed prior to statistical analyses.

	IL-6	TNF-α	INF-γ	IL-1β	IL-10
Genotype	$F_{(1,30)}$=0.43 p=0.51	$F_{(1,30)}$=0.21 p=0.65	$F_{(1,30)}$=0.59 p=0.45	$F_{(1,30)}$=0.05 p=0.83	$F_{(1,30)}$=0.88 p=0.35
Sex	$F_{(1,30)}$=0.76 p=0.39	$F_{(1,30)}$=1.04 p=0.31	$F_{(1,30)}$=0.41 p=0.52	$F_{(1,30)}$=0.93 p=0.34	$F_{(1,30)}$=5.07 **p=0.03**
Treatment	$F_{(1,30)}$=116.02 **p<0.0001**	$F_{(1,30)}$=7.82 **p=0.0089**	$F_{(1,30)}$=2.7 p=0.11	$F_{(1,30)}$=0.17 p=0.68	$F_{(1,30)}$=23.49 **p<0.0001**
Genotype X Sex	$F_{(1,30)}$=0.03 p=0.87	$F_{(1,30)}$=0.09 p=0.77	$F_{(1,30)}$=0.37 p=0.55	$F_{(1,30)}$=0.90 p=0.35	$F_{(1,30)}$=0.00 p=0.95
Genotype X Treatment	$F_{(1,30)}$=4.01 p=0.054	$F_{(1,30)}$=0.48 p=0.49	$F_{(1,30)}$=1.12 p=0.30	$F_{(1,30)}$=0.40 p=0.53	$F_{(1,30)}$=0.18 p=0.67
Sex X Treatment	$F_{(1,30)}$=3.13 p=0.09	$F_{(1,30)}$=2.15 p=0.15	$F_{(1,30)}$=0.98 p=0.33	$F_{(1,30)}$=0.77 p=0.38	$F_{(1,30)}$=4.54 **p=0.04**
Genotype X Sex X Treatment	$F_{(1,30)}$=3.00 p=0.09	$F_{(1,30)}$=2.69 p=0.11	$F_{(1,30)}$=0.90 p=0.35	$F_{(1,30)}$=2.26 p=0.14	$F_{(1,30)}$=1.68 p=0.20

Supplementary metabolomics results

Lack of major metabolic perturbations in the hippocampus of 4.5-month-old APP/PS1 mice

5 of the 98 selected metabolites were found to significantly discriminate between PBS-treated WT and APP/PS1 mice (Table1), albeit predominantly in females. Levels of L-beta-aspartyl-L-glutamic acid, which belongs to the family of N-acyl-alpha amino acids and derivatives which are known for their anti-inflammatory action (1), were particularly reduced in female APP/PS1 mice (Suppl. Fig. 2A), but its function and implication in AD pathology is, to the best of our knowledge, unknown. 1-Methyladenosine, an oxidized nucleoside known to be immunosuppressive on macrophage function (2) and found in elevated levels in the urine of patients with mild-to-moderate AD (3), was more abundant in the hippocampus of female APP/PS1 mice compared to their WT female littermates (Suppl. Fig. 2B).

Significant Genotype X Treatment interactions were also found for N-acetyl-(L)-arginine ($F_{(1,34)}$=12.07, p=0.001), whose levels were significantly lower in PBS-treated APP/PS1 females compared to PBS-treated WT females (Suppl. Fig. 2C), and for the hydrophobic tetrapeptide Asp-Phe-Thr-Thr ($F_{(1,34)}$=5.40, p=0.03), whose levels were significantly increased in PBS-treated APP/PS1 males compared to their PBS-treated counterparts (Suppl. Fig. 2D). Their function and potential roles in AD pathology are also, to the best of our knowledge, unknown.

Sex differences in the hippocampal metabolic profile are independent of the APP/PS1 genotype.

Forty-one metabolites with sex differences were identified revealing major changes in amino acids, carbohydrate metabolism and fatty acyls (Table 1). A few metabolites from other chemical classes and many unknown metabolites were also found in different levels between PBS-treated males and females (Table 1). Metabolic differences in the methionine and pyruvate metabolic pathways are described in the main manuscript and illustrated Fig. 5 and 6, respectively. Changes in other metabolites with previously associated with differences immune function are described below. Their potential role in brain function or implication in AD progression is presented in Suppl. Table 3.

These included reduced levels of (3R)-beta leucine (Suppl. Fig. 3), a degradation product of the anti-inflammatory amino acid L-Leucine (4), D-alanyl-D-alanine (Suppl. Fig. 3B), an anti-inflammatory antibiotic-binding protein (5), and N(pi)-methyl-L-histidine (Suppl. Fig. 3C), a metabolic product of the amino acid histidine known to be negatively associated with inflammation in obese women (6). Females also presented with an increased abundance of N-Succinyl-L-glutamate 5-semialdehyde (Suppl. Fig. 3D), a metabolite found to be elevated in the plasma of lung cancer patients harbouring a mutation in the epidermal growth factor receptor (7) that also exacerbate their pro-inflammatory status (8).

Lysine, whose dietary restriction was found to trigger pro-inflammatory changes (9), indicated the major anti-inflammatory pathway upregulated in females as seen by elevated levels in three metabolites involved in lysine biosynthesis :N6-(L-1,3-Dicarboxypropyl)-L-lysine, N2-Acetyl-L-aminoadipate and L-2-Aminoadipate (Suppl. Fig. 3E-G), and reduced levels of L-pipecolate (Suppl. Fig. 3H), a degradation product of L-lysine whose urine levels are positively associated with low grade inflammation (10). Differences in amino acid metabolism also indicative of anti-inflammatory effects in females included increased abundance of pantothenate (vitamin B5; Suppl. Fig. 3I), whose dietary intake was found to alleviate chronic low grade inflammation (11) and norepinephrinesulfate (Suppl. Fig. 3O), a metabolite of the anti-inflammatory neurotransmitter norepinephrine (12), as well as reduced levels of (Z)-4-

Hydroxyphenylacetaldehyde-oxime (Suppl. Fig. 3J), an enzyme involved in tyrosine metabolism found in increased levels in inflammatory bowel disease (13), and homoarginine (Suppl. Fig. 3K), known to be negatively associated with pro-inflammatory changes (14).

Changes in carbohydrate metabolism and fatty acyls seen in females were indicative of a pro-inflammatory status. Furthermore, isocitrate, a substrate of the tricarboxylic acid (TCA) cycle found to exert anti-inflammatory effects in a rat model of mild anemia of inflammation (15) and itaconate, a potent anti-inflammatory TCA derivative found in immune cells (16), were also less abundant in the female hippocampus (Suppl. Fig. 3M&N, respectively). Hippocampal concentrations of formyl 3-hydroxy-butanoate, a fatty ester, were also significantly lower in females (Suppl. Fig. 3L) and fatty esters are thought to be anti-inflammatory (17).

Metabolites differentially expressed in PBS- and LPS-treated mice regardless of sex and genotype.

Thirty six metabolites were altered to similar extents by LPS in all experimental groups (Table 1). The most significant changes were those affecting tryptophan and methionine metabolism, as described in the main manuscript and represented Figs. 4&5, respectively. Changes to other metabolites associated with immune status are described below and represented Suppl. Fig. 4, and the potential association of these metabolites in brain function, sex differences and/or AD progression is described in Suppl. Table 3.

These metabolic differences included increased levels of thymidine and thymine (Suppl. Fig. 4A&B), two derivatives of the anti-inflammatory nucleotide pyrimidine (18) as well as reduced levels of the inflammation signalling molecule adenosine triphosphate (ATP) (19), particularly in WT mice (Suppl. Fig. 4C) and of succinate (Suppl. Fig. 4D), a pro-inflammatory intermediate of the TCA cycle which plays a crucial role in ATP generation (20).

Pro-inflammatory metabolic changes included increased levels of N(pi)-methyl-L-histidine (Suppl. Fig. 4C), an histidine derivative positively associated with levels of pro-inflammatory markers (21), urate (Suppl. Fig. 4E) known to cause cognitive deficits through enhancing hippocampal inflammation (22), and of its downstream metabolite urea-1-carboxylate (Suppl. Fig. 4F). LPS-treated mice also had elevated hippocampal levels of L-phenylalanine (Suppl. Fig. 4G), whose circulating levels are increased in elderly people with chronic low grade inflammation (23) and prostaglandin-H2-ethanolamide (PGH2-EA) (Suppl. Fig. 4H), a precursor of prostaglandin E2 (PGE_2), which plays a major role in acute inflammation and transition to chronic inflammation (24), and is a key mediator of LPS-induced sickness (25).

Metabolites sex-dependently affected by LPS

Forty-six metabolites showed sex-dependent effects of LPS, of which twenty-one were selectively altered in males, twenty were selectively altered in females, and five showed opposite effects in the two sexes (Table 1). These changes particularly affected two metabolic pathways: pyruvate (Fig. 6) and methylglyoxal (Fig. 8). Changes in other metabolites known to be associated with immunomodulation are reported below and illustrated Suppl. Fig. 4.

Metabolic effects of LPS in males

Levels of methylimidazoleacetic acid (Sex X Treatment: $F_{(1,34)}=13.22$, $p=0.0009$, Suppl. Fig. 4J), a metabolite of the pro-inflammatory mediator histamine (26) were increased by LPS in APP/PS1 males.

Other metabolic changes found in LPS-treated males include increased levels of norepinephrinesulfate (Sex X Treatment: $F_{(1,34)}$=6.64, p=0.01, Suppl. Fig. 3O), a metabolite of the anti-inflammatory neurotransmitter norepinephrine (12), choline (Sex X Treatment: $F_{(1,34)}$=19.89, p<0.0001, Suppl. Fig. 4K), a precursor of acetylcholine and agonist of α7 nicotinic receptors expressed in neurons and macrophages with established anti-inflammatory effects (27, 28), found to dose-dependently inhibit LPS-induced TNFa production by macrophages (29), L-rhamnose (Sex X Treatment: $F_{(1,34)}$=7.25, p=0.01, Suppl. Fig. 4L), previously shown able to inhibit pro-inflammatory cytokines production (30), and hypoxantine (Sex X Treatment: $F_{(1,34)}$=10.06, p=0.003, Suppl. Fig. 4M), whose levels are negatively correlated with the severity of mucosal inflammation (31).

Metabolic effects of LPS in females

6-Phospho-D-gluconate (Suppl. Fig. 4N), an intermediate of the pentose phosphate pathway known to trigger pro-inflammatory cytokines secretion in LPS-activated macrophages (32), was less abundant in LPS-treated females

Pro-inflammatory metabolic changes found in LPS-treated females include reduced levels of N2-Succinyl-L-ornithine (Sex X Treatment: $F_{(1,34)}$=6.25, p=0.02, Suppl. Fig. 4N), a degradation product of the anti-inflammatory amino acid arginine (33), and, in WT LPS-treated females, and homoarginine (Suppl. Fig. 3K), known to be negatively associated with pro-inflammatory changes (14).

Metabolites showing opposite pattern in LPS-treated males and females

Two of the five metabolites that showed opposite effects of LPS in males and females, S-Adenosy-L-homocysteine Fig. 4E) and N-Succinyl-L-glutamate 5-semialdehyde (Suppl. Fig. 3D), have been reported to be associated with increased inflammation. They both were found more abundant in male hippocampi but less abundant in female hippocampi 4 hours after LPS administration.

Suppl. Table 3. Physiological role of metabolites from known metabolic pathways differently expressed between PBS-treated WT and APP/PS1 mice, PBS-treated males and females and in response to LPS.

Putative metabolite	Metabolic Pathway	Physiological role in the brain	Implication in sex differences in brain function	Implication in Alzheimer's disease (AD)	Implication in immune status
Amino acid metabolism					
(3R)-beta-Leucine	Valine, leucine and isoleucine degradation	Degradation product of L-Leucine which is produced by muscle protein catabolism and serves as a donor for brain glutamate synthesis by astrocytes and cerebral protein synthesis (34).	Not known	Increased serum levels of l-leucine in AD patients and in the 3xTg mouse model of AD (35). L-leucine up-regulates tau phosphorylation in 3xTg mice (35).	L- leucine reduces inflammation and increases repair after muscle injury in rats (4).
Choline	Glycine, serine and threonine metabolism	Precursor for the cerebral synthesis of acetylcholine, a neurotransmitter essential for cognitive function, and phospholipid phosphatidylcholine, a major constituent of biological membranes in neurons and glial cells (36, 37).	Higher choline concentrations in the hippocampus of cognitively intact elderly females (38).	Loss of cholinergic function in AD is associated with memory decline (39). Dietary intake of choline improves cognitive function in AD patients and mouse models (37).	Agonist of α7 nicotinic receptors expressed on macrophages, supresses LPS-induced TNFa production by macrophages (29).
L-cystathionine	Glycine, serine and threonine metabolism Methionine metabolism	Intermediate in the transsulfuration pathway which decreases neurotoxic homocysteine concentrations (40) Mediates the conversion of homocysteine into cysteine (Fig. 5).	Not known	Increased levels in the temporal cortex of post-mortem AD brains (41).	Inhibits the expression of the pro-inflammatory cytokine MCP-1 in macrophages *in vitro* (42).
L-methionine	Methionine metabolism	Key role in epigenetic regulation in the brain through conversion into homocysteine via S-adenosyl-L-methionine (43).	No differences in mouse brain concentrations (44).	Decreased levels in the temporal cortex of post-mortem AD brains (41). Elevated CSF levels in MCI and AD (45). Excess dietary methionine induces cognitive and neurological hallmarks of AD in mice (46).	Excess dietary methionine induces astrocyte and microglia activation in the hippocampus (46). Induces pro-inflammatory activation in macrophages in vitro (47).
L-methionine S-oxide	Methionine metabolism	Toxic oxidation product of methionine (48).	Not known	Increased production triggers Aβ aggregation (49).	Inhibition reduces TNFa and IL1β secretion in LPS-stimulated microglia (50).
S-adenosyl-L-homocysteine	Methionine metabolism	Biosynthetic precursor of homocysteine (Fig. 5) which is neurotoxic and pro-inflammatory in microglia (51). Formed by demethylation of S-adenosyl-L-methionine.	No differences in mouse brain concentrations (44).	Increased levels in the post-mortem AD brain are associated with cognitive dysfunction and neurological hallmarks of AD (52). Increase Aβ formation in BV-2 microglial cells (53).	Induces pro-inflammatory activation in endothelial cells in vitro (54).
O-succinyl-L-homoserine	Methionine metabolism	Mediates the conversion of homocysteine into cystathionine (Fig. 5).	Not known	Not known	Not known

S-adenosyl-L-methionine	Methionine metabolism Arginine and proline metabolism	Main donor of methyl groups for DNA methylation in the brain (43). Dietary supplementation improves cognitive abilities in mice (55).	No differences in mouse brain concentrations (44).	Decreased levels in the post-mortem AD brain (56) and CSF of AD patients (57).	Inhibits TNFa production and enhances IL-6 and IL-10 secretion in LPS-stimulated human macrophages and/or murine monocytes (58, 59).
5'-methylthioadenosine	Methionine metabolism Arginine and proline metabolism	Neuro-protective and anti-inflammatory derivative of methionine.	Not known	Increased CSF levels in MCI impaired patients (60).	Reduces brain damage; inhibits INFg and TNFa production and enhances IL-10 production in animal models of neuroinflammation (61).
N-carbamoylsarcosine	Arginine and proline metabolism	Not known	Not known	Not known	Not known
N-succinyl-L-glutamate 5-semialdehyde	Arginine and proline metabolism	Not known	Not known	Not known	Elevated in plasma from lung cancer patients harbouring a genetic mutation (7) which increases their susceptibility to inflammation (8).
Urea-1-carboxylate	Arginine and proline metabolism	Not known	Not known	Not known	Not known
Homoarginine	Arginine and proline metabolism	Precursor of the free radical nitric oxide. Unclear role in healthy brain function (62).	Not known	Not known	Reduced plasma levels associated with increased C-reactive protein levels in chronic kidney disease patients (14).
L-aspartate	Arginine and proline metabolism Lysine biosynthesis	Excitatory amino acid and selective glutamatergic NMDA receptor agonist (63).	Not known	Not known	No known
N6-(L-1,3-Dicarboxypropyl)-L-lysine	Lysine biosynthesis	Not known	Not known	Not known	Not known
N2-acetyl-L-aminoadipate	Lysine biosynthesis	Not known	Not known	Not known	Not known
L-2-aminoadipate	Lysine degradation	Intermediate in lysine degradation. Antagonises excitatory NMDA receptors and reduces kynurenine levels in the hippocampus (64).	Not known	Increased plasma levels in MCI and AD patients (65).	Produced by peritoneal cells in response to acute inflammation (66). Inhibits kynurenine production by astrocytes (64).
L-pipecolate	Lysine degradation Alkaloid biosynthesis I	Major degradation product of lysine in the murine brain (67).	Not known	Reduced CSF levels in MCI, but not AD, patients (60).	Urine levels are positively associated with low grade inflammation in healthy individuals (10).
(Z)-4-hydroxyphenylacetaldehyde-oxime	Tyrosine metabolism	Not known	Not known	Not known	Increased gut levels in inflammatory bowel disease (13).
[FA hydroxy,oxo(7:0/2:0)]	Tyrosine metabolism	Not known	Not known	Not known	Not known

4-hydroxy-2-oxo-Heptanedioic acid					
L-phenylalanine	Phenylalanine, tyrosine and tryptophan biosynthesis	Dietary precursor of catecholamines. Accumulation in the brain due to impaired degradation causes brain damage and mental retardation (68).	Not known	Increased circulating levels correlate with inflammation in a subgroup of AD patients (69).	Increased circulating levels in elderly people with chronic low grade inflammation (23).
L-tryptophan	Phenylalanine, tyrosine and tryptophan biosynthesis Tryptophan metabolism	Dietary precursor of serotonin and vitamin B3 (nicotinic acid). Improves mood and cognition by enhancing serotoninergic neurotransmission (70) and nicotinamide pathway (71)	Women are more susceptible to episodic memory impairment caused by acute tryptophan depletion (72). Lower plasma tryptophan levels in females associated with reduced serotonin synthesis rate throughout the brain (73).	Reduced CSF levels in MCI, but not AD, patients (60). Reduced serotoninergic neurotransmission associated with the development of cognitive symptoms in AD (74). Upregulation of kynurenine pathway associated with neurological hallmarks of AD (75).	Increases inflammation via stimulation of the kynurenine pathway (76). Serotoninergic neurotransmission thought to protect against neuroinflammation (77).
5-hydroxyindoleacetate	Tryptophan metabolism	End metabolite of the serotonin pathway of tryptophan metabolism (Fig. 6).	See L-tryptophan	Elevated CSF levels in MCI and AD (45).	See L-tryptophan
Pantothenate	beta-Alanine metabolism Pantothenate and CoA biosynthesis	Vitamin B5. Substrate for the biosynthesis of coenzyme A which contributes to the structure and function of brain cells *via* its role in the synthesis and oxidation of fatty acids (71).	Not known	Dietary intake positively associated with cerebral Aβ burden in MCI patients (78).	Dietary intake lower systemic inflammation (C-reactive protein levels) in healthy adults over 40 (11).
D-alanyl-D-alanine	D-Alanine metabolism Peptidoglycan biosynthesis	Not known	Not known	Not known	Anti-inflammatory antibiotic-binding protein (5).
Glutathione disulphide (GSSG)	Glutamate metabolism Glutathione metabolism	Toxic oxidation product of the anti-oxidant glutathione produced and exported by astrocytes in the brain (79).	No sex differences in brain tissue content with aging in mice despite the most pronounced decline in glutathione concentrations seen in males (80).	Higher activity of glutathione reductase activity, which catalyses the reduction of GSSG disulphide in glutathione, in the temporal cortex of AD patients (81), but unaltered GSSG contents (82).	Increased circulating levels during acute systemic inflammation in the rats (83).
Methylimidazoleacetic acid	Histidine metabolism	Main metabolite of histamine, a neuromodulator, also involved in cognition, wakefulness and anxiety and motivated behaviours (84, 85).	Not known	Degeneration of histaminergic nerve fibres in AD (86).	Histamine is produced by immune cells in the brain, induces pro-inflammatory microglial activation but inhibits LPS-induced microglial activation (87).
N(pi)-methyl-L-histidine	Histidine metabolism	Derivative of histidine, a precursor of brain histamine (85).	Not known	Not known	Serum histidine levels are negatively associated with systemic inflammation (C-reactive protein levels) in obese women (6).
Hypotaurine	Taurine and	Intermediate in the synthesis of	Not known	Not known	Suppresses inflammatory and

	hypotaurine metabolism	taurine from the methionine derivative cysteine (Fig. 5) in neurons, astrocytes and microglia (88, 89).			neuropathic pain (90).
Carbohydrate metabolism					
Succinate	Citrate cycle (TCA cycle) Glyoxylate and dicarboxylate metabolism	Support brain energy metabolism by promoting ATP generation in mitochondria (91). Ameliorates metabolic deficits of glial cells with mitochondrial dysfunction (92).	Not known	Reduced whole brain content from 9 months of age in an APP/PS1 mouse model (93).	Pro-inflammatory mediator in macrophages mediating LPS-induced IL-1β production (20, 94).
Isocitrate	Citrate cycle (TCA cycle) Glyoxylate and dicarboxylate metabolism	Not known	Not known	Increased CSF levels in a transgenic rat model of tauopathy (95).	Anti-inflammatory in rat model of anaemia of inflammation (15). Microglial deficiency in isocitrate dehydrogenase, the enzyme that catalyses oxidative decarboxylation of isocitrate, suppresses LP-induced pro-inflammatory cytokine production (TNFa, IL-6, IL-1β) (96).
(S)-malate	Citrate cycle (TCA cycle) Pyruvate metabolism Glyoxylate and dicarboxylate metabolism	Metabolite of the KREBS cycle which promotes mitochondrial ATP generation and can be recycled into pyruvate (97).	Not known	Not known	Produced by pro-inflammatory activation of macrophages (98).
(D)-lactate	Pyruvate metabolism	Produced by methylglyoxal metabolism. Excess levels can cause encephalopathy (99).	Sex differences in D-lactate metabolism may contribute to reduced association between microbiota and neurological symptoms in females (100).	Methylglyoxal can cause Aβ aggregation (101) and its neurotoxicity is associated with AD (102).	Methylglyoxal is pro-inflammatory and activates glial cells in the brain (103).
(D)-S-lactoylglutathione	Pyruvate metabolism	Intermediate in the formation of D-lactate from methylglyoxal.	Not known	Not known	Not known
Phosphoenolpyruvate	Citrate cycle (TCA cycle) Pyruvate metabolism Glycolysis / Gluconeogenesis	Intermediate in glycolysis and gluconeogenesis.	Not known	Not known	Systemic LPS increases brain levels of phosphoenolpyruvate carboxykinase (104), which catalyses the conversion of oxaloacetate to phosphoenolpyruvate in gluconeogenesis and has anti-inflammatory effects on LPS-induced circulating pro-inflammatory cytokines levels (104) and macrophages phenotype

					(105).
Pyruvate	Citrate cycle (TCA cycle) Glycolysis / Gluconeogenesis	Intermediate metabolite of glucose with potent antioxidant and anti-inflammatory properties (106).	Sex differences in pyruvate metabolism associated with reduced oxidative stress and damage in females (107, 108).	Improves cognitive performance in mouse models of AD without affecting tau or Aβ pathology (109, 110).	Ethyl derivatives of pyruvate alleviate pro-inflammatory changes in the brain (111, 112).
D-glyceraldehyde 3-phosphate	Glycolysis / Gluconeogenesis	Intermediate in glycolysis and gluconeogenesis.	Not known	Not known	Not known
3-phospho-D-glycerate	Glycolysis /Gluconeogenesis Glyoxylate and dicarboxylate metabolism	Conversion of 3-phospho-D-glycerate to phosphohydroxypyruvate by the enzyme 3-phosphoglycerate dehydrogenase (3PGDH) is the first step in serine production. Deficiency in 3PGDH causes brain atrophy, seizures and psychomotor retardation (113).	Not known	Not known	3PGDH is an astrocytic enzyme that catalases the production of serine by neurons and glia (114) and is anti-inflammatory in fibroblasts (115).
2-phosphoglycolate	Glyoxolate and dicatboxylate metabolism	Possible indicator of damage and repair of DNA ends (116).	Not known	Decreased expression and activity in AD brain of phosphoglucomutase 1 (PGM1) the glycolytic enzyme that catalyses the conversion of 3-phosphoglycerate to 2-phosphoglycerate (117).	Not known
3-oxalomalate	Glyoxolate and dicatboxylate metabolism	Not known	Not known	Not known	Antioxidant in LPS-activated macrophages (118).
L-rhamnose	Fructose and mannose metabolism	Not known	Not known	Not known	Inhibits pro-inflammatory cytokines production in macrophages (119).
D-sorbitol	Fructose and mannose metabolism	Intermediate in the production of fructose from glucose in the brain (120).	Not known	Elevated levels in the post-mortem AD brain (121).	Anti-inflammatory properties in resident cells from articular cartilage (122).
6-phospho-D-gluconate	Pentose phosphate pathway	Regulatory control of brain metabolism (123).	Not known	Increased activity of the pentose phosphate pathway associated with increased pro-oxidant activity in the post mortem AD brain (124)	Triggers pro-inflammatory cytokines secretion in LPS-activated macrophages (32).
Propanoyl phosphate	Propanoate metabolism C5-Branched dibasic acid metabolism	Not known	Not known	Not known	Not known
Itaconate	C5-Branched dibasic acid metabolism Citrate cycle (TCA cycle)	Endogenous antibiotic in the brain (125).	Not known	Not known	Anti-inflammatory metabolite found in macrophages (16) and produced by microglia (125).

Methyloxaloacetate	C5-Branched dibasic acid metabolism	Not known	Not known	Not known	Not known
Nucleotide metabolism					
Hypoxanthine	Purine metabolism	Endogenous ligand of benzodiazepine-binding sites in the brain (126).	Not known	Increased brain concentration in a transgenic rat model of tauopathy (95). Elevated CSF levels in MCI patients (45).	Hypoxanthine is anti-inflammatory and depleted in LPS-stimulated macrophages (127).
Urate	Purine metabolism	Neuroprotective and antioxidant at physiological levels (128).	Reduced brain tissue contents in women (129).	Increased CSF contents in AD (130). Trends towards reduced levels in the post-mortem AD brain (129).	High uric acid diet causes cognitive deficits by inducing hippocampal neuroinflammation (22). Suppresses LPS-induced pro-inflammatory microglial activation in vitro (131).
N6-(1,2-Dicarboxyethyl)-AMP	Purine metabolism	Not known	Not known	Not known	Not known
Orotate	Pyrimidine metabolism	Not known	Not known	Not known	Not known
Thymidine	Pyrimidine metabolism	Not known	Not known	Not known	Not known
Thymine	Pyrimidine metabolism	Not known	Not known	Not known	Not known
5,6-dihydrouracil	Pyrimidine metabolism Beta-Alanine metabolism Pantothenate and CoA biosynthesis	Not known	Not known	Not known	Not known
Lipid metabolism and Fatty acyls					
Octadecanoic acid (18:0 stearic acid)	Fatty acids biosynthesis Biosynthesis of unsaturated fatty acids	Needed for the synthesis of membranes of neurons and astrocytes during brain development (132).	No sex differences in mouse brain content with normal diet (133).	Induces tau phosphorylation in cultured neurons and astrocytes (134). Triggers secretion of Aβ peptide (135). Reduced levels in the post-mortem AD brain (136).	Accumulates primarily in astrocytes (137) where it triggers the release of TNFα and IL-6 (138).
Hexadecanoic acid (16:0 palmitic acid)	Biosynthesis of unsaturated fatty acids	Dietary administration, which enters the brain, improves cognitive and motor function (139).	No sex differences in mouse brain content with normal diet (133).	Induces tau phosphorylation and amyloid processing in cultured neurons and astrocytes (134, 135, 140). Increased levels in the post-mortem AD brain (136).	Triggers astrocytic release of TNFα and IL-6 in vitro (138). Impairs the protective migratory and phagocytic activities of microglia in both males and females (141).

Icosatrienoic acid 20:3	Biosynthesis of unsaturated fatty acids	Increased brain levels associated with reduced brain growth in developing rats fed with an essential fatty acid deficient diet (142). Intermediate in the synthesis of Arachidonic acid.	Not known	Not known	Not known
[FA (20:4)] 5Z,8Z,11Z,14Z-eicosatetraenoic acid (20:4 Arachidonic acid)	Fatty Acids and Conjugates	Contributes in brain growth and function in combination with other fatty acids (143).	No sex differences in mouse brain content with normal diet (133).	Triggers secretion of Aβ peptide (135). Reduced levels in the post-mortem AD brain (136, 144).	Precursor of potent pro-inflammatory eicosanoids (e.g. prostaglandins) in astrocytes (145). Does not trigger pro-inflammatory cytokine release in astrocytes (138).
PGH2-EA	Eicosanoids	Metabolite of the endocannabinoid anandamide known to modulate the brain reward system (146)	Not known	Increases the neurotoxicity of Aβ peptide (147).	Precursor of prostaglandin E2 which mediates LPS-induced sickness (148).
Formyl 3-hydroxy-butanoate	Fatty esters	Not known	Not known	Not known	Not known
sn-glycerol 3-phosphate	Glycerolipid metabolism Glycerophospholipid metabolism	Intermediate in the glycolysis metabolic pathway. Increased biosynthesis in the hippocampus during long-term potentiation (149).	Not known	Not known	Not known
sn-glycero-3-Phosphoethanolamine	Glycerophospholipid metabolism Ether lipid metabolism	Not known.	Not known	Not known	Not known
Energy Metabolism					
ATP	Oxidative phosphorylation Purine metabolism	Main cellular source of energy in the brain, which can improve cognitive function (150).	Greater ATP production in female mitochondria in the rodent brain (107)	Decreased brain contents in a transgenic rat model of tauopathy (95) and mouse model of amyloidosis (151).	Pro-inflammatory signalling molecule in the brain via increased synthesis of prostaglandin E2 (19). Produced by microglia and astrocytes, leading to microglial activation and chemotactic factor for microglia towards tissue injury (152, 153)
D-fructose 1,6-bisphosphate	Carbon fixation	Neuroprotective high energy glycolytic intermediate (154).	Not known	Not known	Anti-inflammatory in pain models (155)
D-sedoheptulose 1,7-bisphosphate	Carbon fixation	Not known	Not known	Not known	Not known
Metabolism of Cofactors and Vitamins					
Iminoglycine	Thiamine metabolism	Not known	Not known	Not known	Not known

N1-methyl-2-pyridone-5-carboxamide	Nicotinate and nicotinamide metabolism	Toxic end metabolite of the tryptophan-nicotinamide pathway (156)	Not known	Not known	Elevated circulating levels associated with systemic inflammation (157).
Peptides					
Gamma glutamylglutamic acid	Peptide	Not known	Not known	Not known	Not known
L-beta-aspartyl-L-glutamicacid	Peptide	Not known	Not known	Not known	Belongs to the family of N-acyl-alpha amino acids and derivatives which are known for their anti-inflammatory action (1)
Asp-Ser-His	Basic peptide	Not known	Not known	Not known	Not known
Asn-Met-Met-Asn	Hydrophobic peptide	Not known	Not known	Not known	Not known
Asp-Phe-Thr-Thr	Hydrophobic peptide	Not known	Not known	Not known	Not known
Asn-Asn-Asn	Polar peptide	Not known	Not known	Not known	Not known
Biosynthesis of Polyketides and nonribosomal Peptides					
Narbomycin	Biosynthesis of 12-, 14- and 16-membered macrolides	Not known	Not known	Not known	Not known
13-dihydrocarminomycin	Biosynthesis of type II polyketide products	Not known	Not known	Not known	Not known
Biosynthesis of Secondary metabolites					
Dihydroclavaminic acid C8H12N2O4	Clavulanic acid biosynthesis	Not known	Not known	Not known	Not known
Not known					
γ-aminobutyramide C4H10N2O	Not known	Not known	Not known	Not known	Not known
1-deoxy-D-altro-heptulose 7-phosphate	Not known	Not known	Not known	Not known	Not known
1-methyladenosine	Not known			Increased urinary levels in patients with mild-to-moderate Alzheimer's disease (3).	Immunosuppressive on macrophage function (2).
3, 5-tetradecadiencarnitine	Not known	Not known	Not known	Not known	Not known
3-methylphosphoenol-pyruvate	Not known	Not known	Not known	Not known	Not known
6-methyltetrahydropterin	Not known	Not known	Not known	Not known	Not known

Athamantin	Not known	Not known	Not known	Not known	Not known
Camptothecin	Not known	Not known	Not known	Not known	Not known
Dimethyl citraconate	Not known	Not known	Not known	Not known	Not known
DL-2-sulfoctanoicacid	Not known	Not known	Not known	Not known	Not known
Elaidiccarnitine	Not known	Not known	Not known	Not known	Not known
Glutarylcarnitine	Not known	Not known	Not known	Not known	Not known
Glycerophosphoglycerol	Not known	Not known	Not known	Not known	Not known
Linoelaidylcarnitine	Not known	Not known	Not known	Not known	Not known
N-acetyl-(L)-arginine	Not known	Not known	Not known	Not known	Not known
NG,NG-dimethyl-L-arginine	Not known	Not known	Not known	Not known	Not known
Nocardicin C	Not known	Not known	Not known	Not known	Not known
Nonulose 9-phosphate	Not known	Not known	Not known	Not known	Not known
Norepinephrinesulfate	Not known	Not known	Not known	Not known	Not known
Orotidine	Not known	Not known	Not known	Not known	Not known
Tetradecanoylcarnitine	Not known	Not known	Not known	Not known	Not known
GDP-3,6-dideoxy-D-galactose	Not known	Not known	Not known	Not known	Not known
N-hydroxyvaline	Linamarin biosynthesis	Not known	Not known	Not known	Not known

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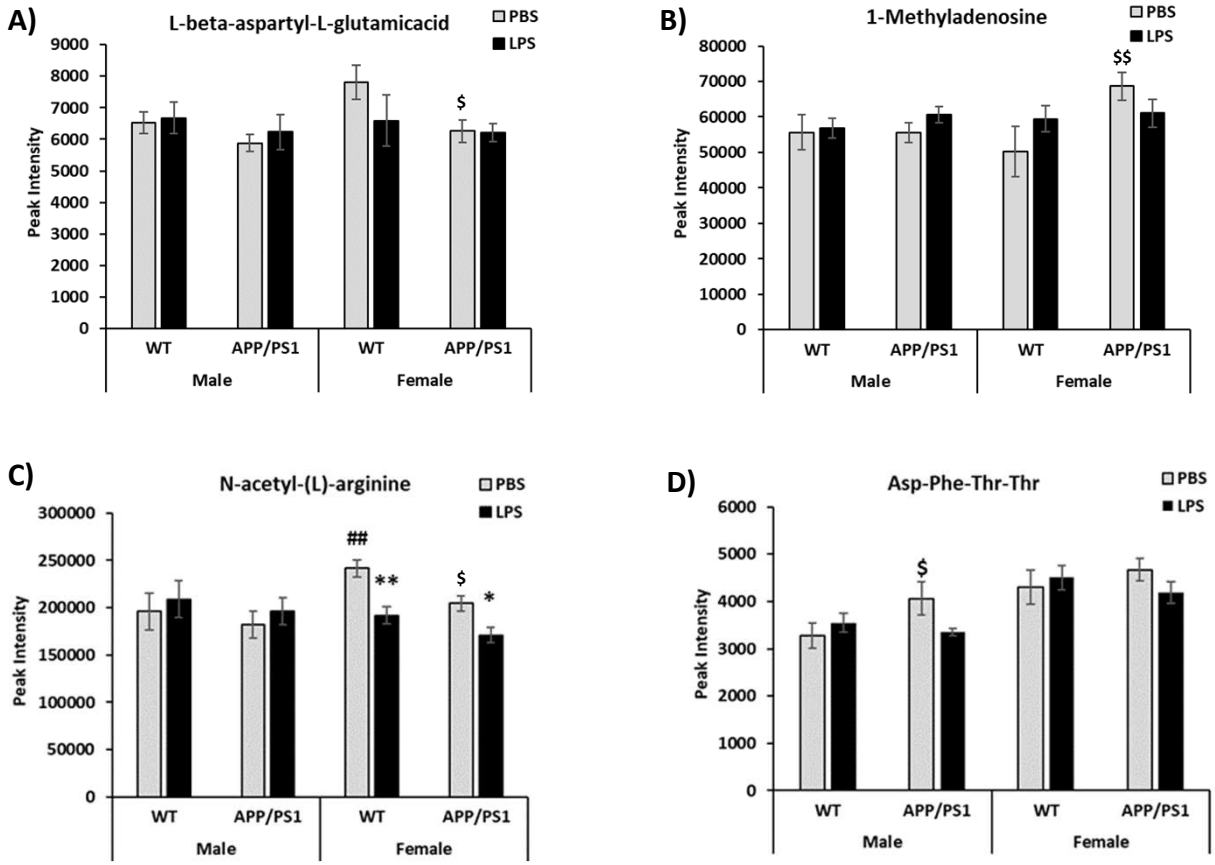
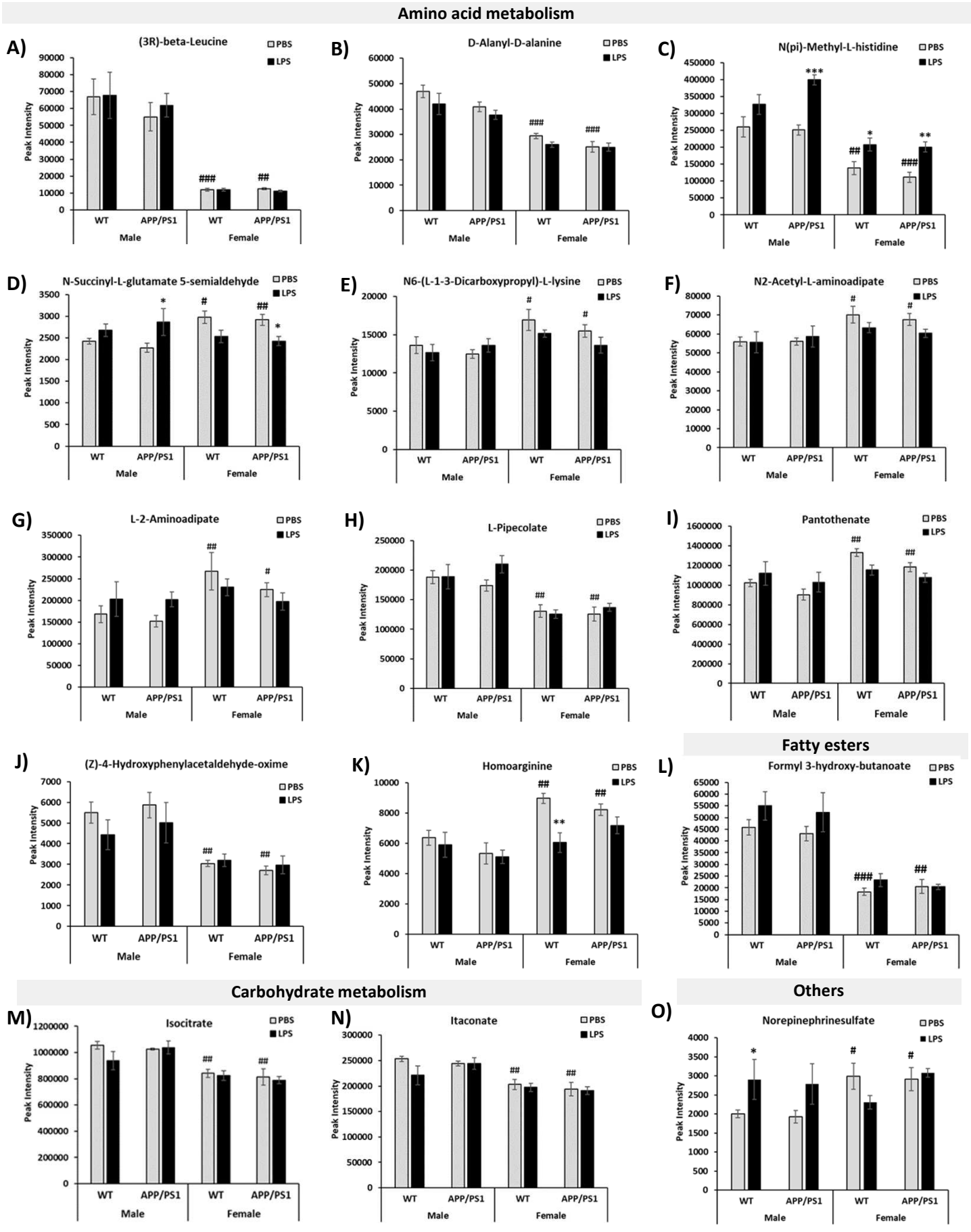
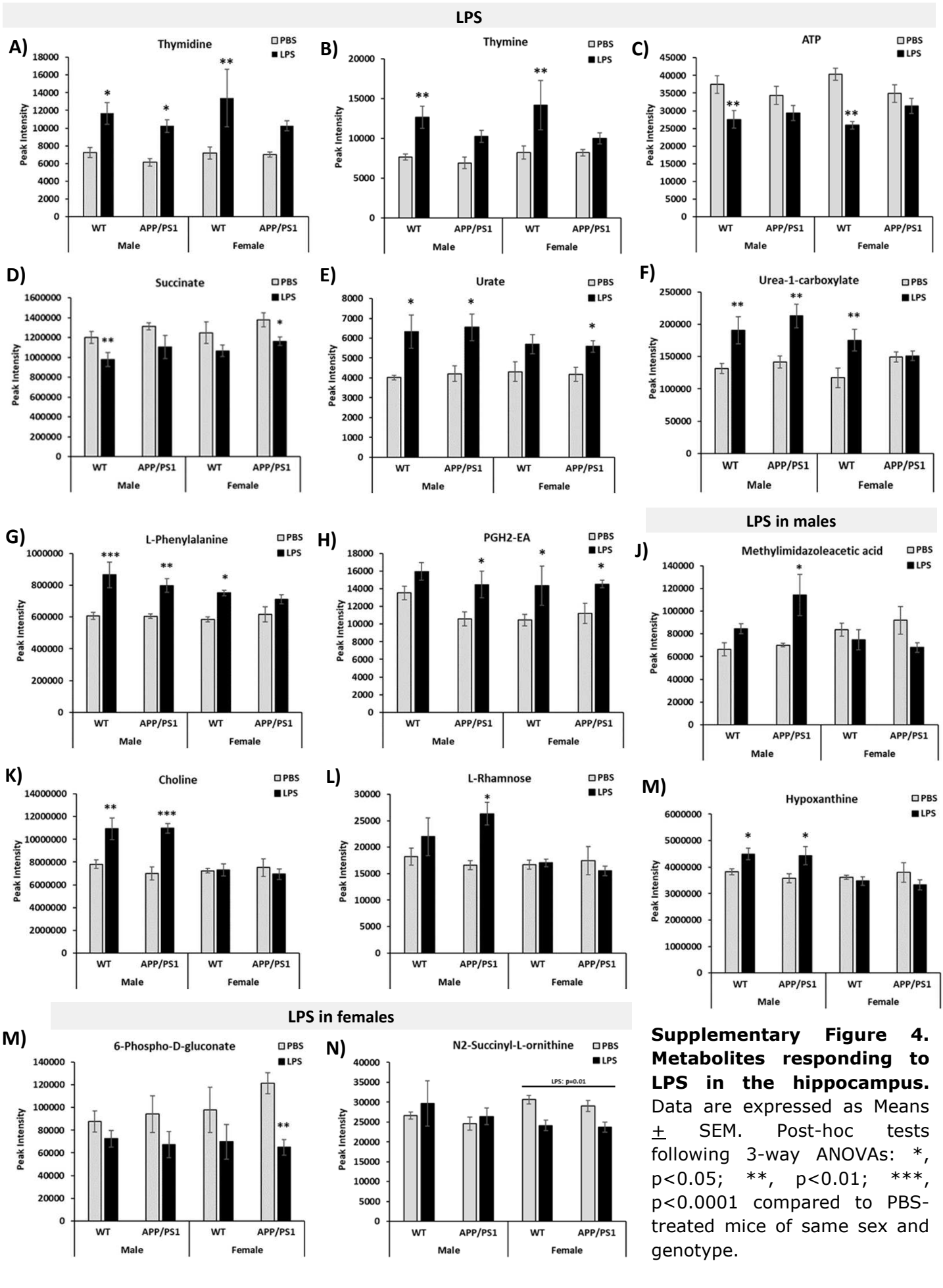


Supplementary. Fig. 2. Metabolites affected in APP/PS1 mice in the absence of immune stimulation. Levels of L-beta-aspartyl-L-glutamic acid, were particularly reduced in female APP/PS1 mice (A). B) 1-Methyladenosine, was more abundant in the hippocampus of female APP/PS1 mice compared to their WT female littermates (B). Significant Genotype X Treatment interactions were also found for N-acetyl-(L)-arginine ($F_{(1,34)}$=12.07, p=0.001), whose levels were significantly lower in PBS-treated APP/PS1 females compared to PBS-treated WT females (C), and for the hydrophobic tetrapeptide Asp-Phe-Thr-Thr ($F_{(1,34)}$=5.40, p=0.03), whose levels were significantly increased in PBS-treated APP/PS1 males compared to their PBS-treated counterparts (D). Data are expressed as Means $\pm$ SEM. Pairwise comparisons following 3-way ANOVAs: $^{\$}$, p<0.05; $^{\$\$}$, p<0.01 compared to WT PBS-treated (same sex); $^{\#\#}$, p<0.01 compared to PBS-treated males (same genotype); *, p<0.05; **, p<0.01 compared to PBS-treated mice of same sex and genotype.



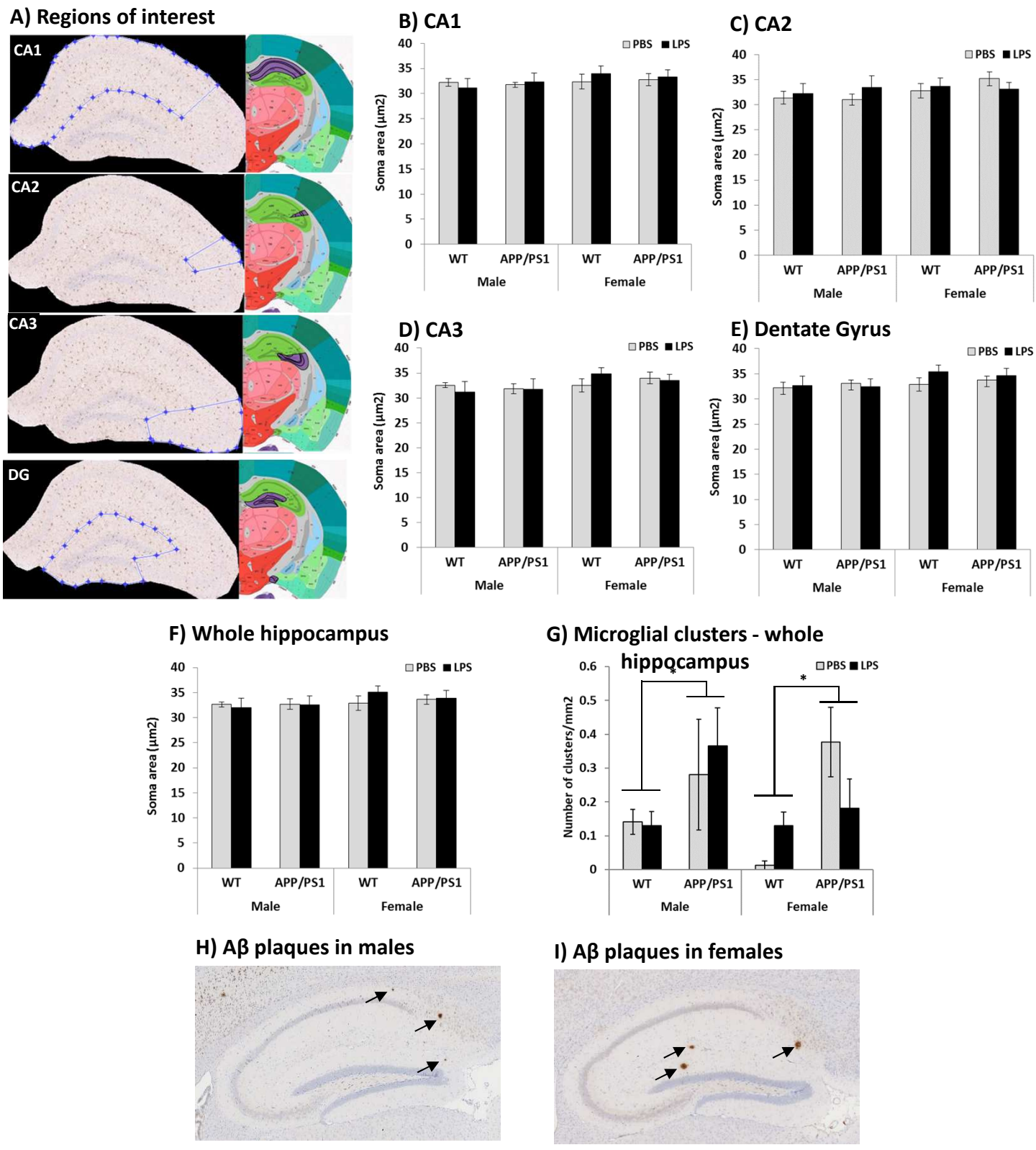
Supplementary Figure 3. Metabolites with sex differences in the hippocampus. Data are expressed as Means ± SEM. Post-hoc tests following 3-way ANOVAs: #, p<0.05, ##, p<0.01 compared to PBS-treated males (same genotype); **, p<0.01; ***, p<0.0001 compared to PBS-treated mice of same sex and genotype.



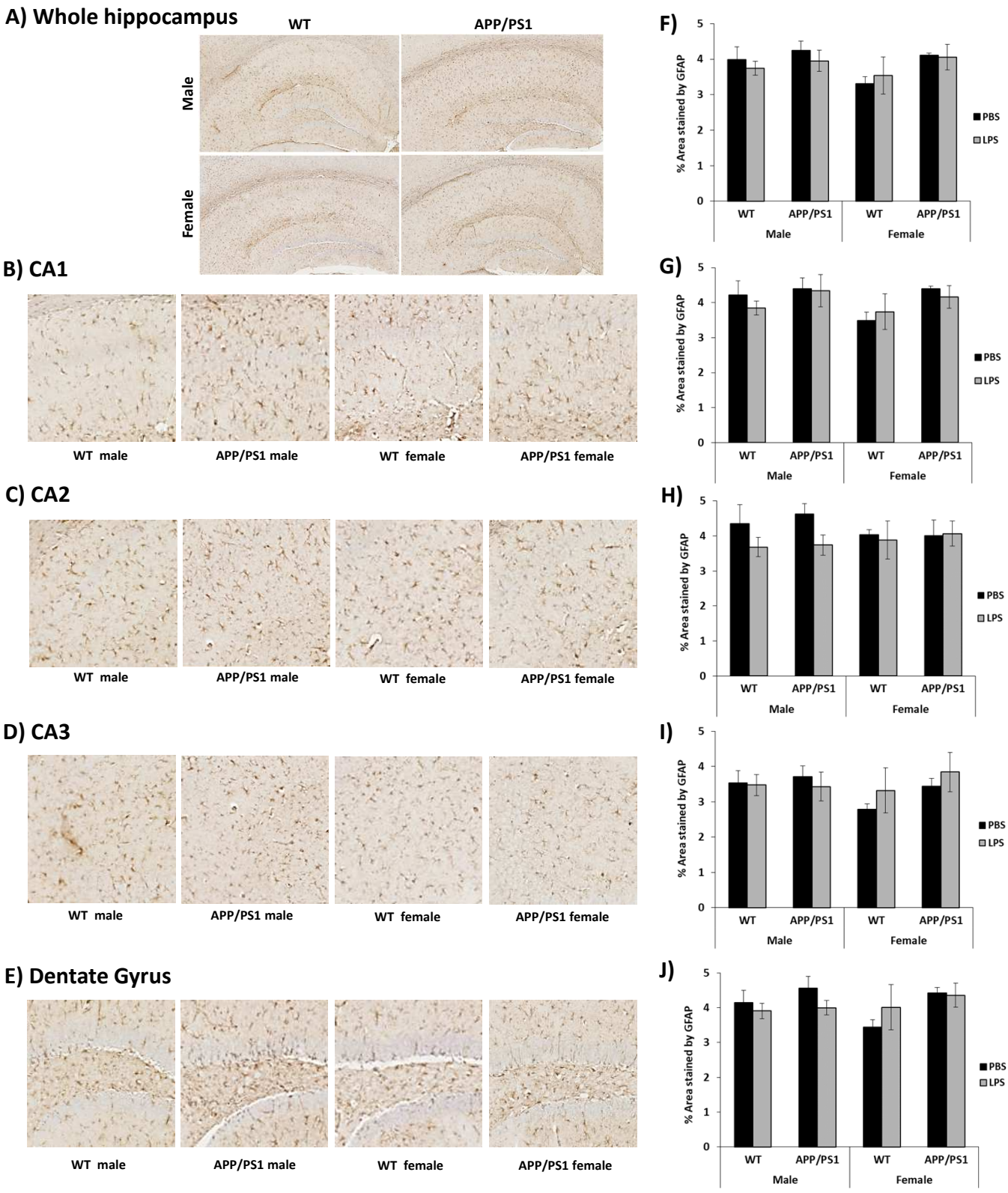
Supplementary Figure 4. Metabolites responding to LPS in the hippocampus. Data are expressed as Means ± SEM. Post-hoc tests following 3-way ANOVAs: *, $p<0.05$; **, $p<0.01$; ***, $p<0.0001$ compared to PBS-treated mice of same sex and genotype.

Supplementary table 3. Results of the two-way repeated measure ANOVAs on glial measures.

	% area stained by Iba1	Number of cells/mm²	Microglial soma area	% area stained by GFAP
Whole hippocampus				
Genotype	$F_{(1,35)}$=0.96; p=0.33	$F_{(1,35)}$=0.43; p=0.51	$F_{(1,35)}$=0.00; p=0.95	$F_{(1,33)}$=3.81; p=0.059
Sex	$F_{(1,35)}$=0.80; p=0.38	$F_{(1,35)}$=3.28; p=0.08	$F_{(1,35)}$=2.16; p=0.15	$F_{(1,33)}$=1.02; p=0.32
Treatment	$F_{(1,35)}$=2.26; p=0.14	$F_{(1,35)}$=1.39; p=0.24	$F_{(1,35)}$=0.20; p=0.66	$F_{(1,33)}$=0.16; p=0.69
Genotype X Sex	**$F_{(1,35)}$=4.14; p=0.049**	$F_{(1,35)}$=3.01; p=0.09	$F_{(1,35)}$=0.20; p=0.75	$F_{(1,33)}$=0.87; p=0.36
Genotype X Treatment	$F_{(1,35)}$=0.65; p=0.42	$F_{(1,35)}$=0.22; p=0.64	$F_{(1,35)}$=0.10; p=0.70	$F_{(1,33)}$=0.13; p=0.72
Sex X Treatment	$F_{(1,35)}$=0.71; p=0.40	$F_{(1,35)}$=0.23; p=0.64	$F_{(1,35)}$=0.75; p=0.39	$F_{(1,33)}$=0.66; p=0.42
Genotype X Sex X Treatment	$F_{(1,35)}$=0.98; p=0.33	$F_{(1,35)}$=1.75; p=0.19	$F_{(1,35)}$=0.42; p=0.52	$F_{(1,33)}$=0.06; p=0.80
CA1				
Genotype	$F_{(1,35)}$=1.08; p=0.31	$F_{(1,35)}$=0.07; p=0.79	$F_{(1,35)}$=0.02; p=0.90	$F_{(1,33)}$=4.13; p=0.0503
Sex	$F_{(1,35)}$=1.45; p=0.24	$F_{(1,35)}$=3.21; p=0.08	$F_{(1,35)}$=1.60; p=0.21	$F_{(1,33)}$=1.03; p=0.32
Treatment	$F_{(1,35)}$=3.30; p=0.08	$F_{(1,35)}$=0.19; p=0.66	$F_{(1,35)}$=0.15; p=0.70	$F_{(1,33)}$=0.16; p=0.69
Genotype X Sex	$F_{(1,35)}$=3.56; p=0.07	$F_{(1,35)}$=1.95; p=0.17	$F_{(1,35)}$=0.06; p=0.80	$F_{(1,33)}$=0.43; p=0.52
Genotype X Treatment	$F_{(1,35)}$=0.51; p=0.48	$F_{(1,35)}$=0.13; p=0.72	$F_{(1,35)}$=0.03; p=0.86	$F_{(1,33)}$=0.03; p=0.85
Sex X Treatment	$F_{(1,35)}$=1.15; p=0.29	$F_{(1,35)}$=0.50; p=0.48	$F_{(1,35)}$=0.42; p=0.52	$F_{(1,33)}$=0.20; p=0.66
Genotype X Sex X Treatment	$F_{(1,35)}$=0.89; p=0.35	$F_{(1,35)}$=1.76; p=0.19	$F_{(1,35)}$=0.52; p=0.48	$F_{(1,33)}$=0.68; p=0.42
CA2				
Genotype	$F_{(1,35)}$=0.82; p=0.37	$F_{(1,34)}$=0.45; p=0.51	$F_{(1,34)}$=0.34; p=0.56	$F_{(1,32)}$=0.18; p=0.67
Sex	$F_{(1,35)}$=0.73; p=0.40	$F_{(1,34)}$=0.66; p=0.42	$F_{(1,34)}$=2.01; p=0.16	$F_{(1,32)}$=0.13; p=0.72
Treatment	$F_{(1,35)}$=1.29; p=0.26	$F_{(1,34)}$=1.00; p=0.32	$F_{(1,34)}$=0.22; p=0.64	$F_{(1,32)}$=1.93; p=0.17
Genotype X Sex	**$F_{(1,35)}$=4.24; p=0.047**	$F_{(1,34)}$=2.26; p=0.14	$F_{(1,34)}$=0.04; p=0.84	$F_{(1,32)}$=0.03; p=0.87
Genotype X Treatment	$F_{(1,35)}$=0.02; p=0.90	$F_{(1,34)}$=0.10; p=0.75	$F_{(1,34)}$=0.09; p=0.77	$F_{(1,32)}$=0.00; p=0.99
Sex X Treatment	$F_{(1,35)}$=0.11; p=0.74	$F_{(1,34)}$=0.61; p=0.44	$F_{(1,34)}$=0.93; p=0.34	$F_{(1,32)}$=1.54; p=0.22
Genotype X Sex X Treatment	$F_{(1,35)}$=0.29; p=0.59	$F_{(1,34)}$=0.03; p=0.85	$F_{(1,34)}$=0.95; p=0.33	$F_{(1,32)}$=0.13; p=0.71
CA3				
Genotype	$F_{(1,36)}$=2.50; p=0.12	$F_{(1,36)}$=1.79; p=0.19	$F_{(1,36)}$=0.00; p=0.99	$F_{(1,33)}$=1.21; p=0.28
Sex	$F_{(1,36)}$=0.97; p=0.33	$F_{(1,36)}$=1.55; p=0.22	$F_{(1,36)}$=3.62; p=0.06	$F_{(1,33)}$=0.41; p=0.53
Treatment	$F_{(1,36)}$=1.77; p=0.19	$F_{(1,36)}$=3.08; p=0.09	$F_{(1,36)}$=0.01; p=0.93	$F_{(1,33)}$=0.24; p=0.63
Genotype X Sex	**$F_{(1,36)}$=7.37; p=0.01**	$F_{(1,36)}$=3.04; p=0.09	$F_{(1,36)}$=0.00; p=0.96	$F_{(1,33)}$=0.76; p=0.39
Genotype X Treatment	$F_{(1,36)}$=0.56; p=0.46	$F_{(1,36)}$=0.59; p=0.45	$F_{(1,36)}$=0.16; p=0.69	$F_{(1,33)}$=0.09; p=0.76
Sex X Treatment	$F_{(1,36)}$=0.98; p=0.33	$F_{(1,36)}$=0.03; p=0.85	$F_{(1,36)}$=0.68; p=0.41	$F_{(1,33)}$=1.15; p=0.29
Genotype X Sex X Treatment	$F_{(1,36)}$=0.47; p=0.49	$F_{(1,36)}$=0.05; p=0.82	$F_{(1,36)}$=1.08; p=0.30	$F_{(1,33)}$=0.01; p=0.93
Dentate Gyrus				
Genotype	$F_{(1,36)}$=1.33; p=0.26	$F_{(1,36)}$=0.17; p=0.68	$F_{(1,36)}$=0.04; p=0.83	$F_{(1,33)}$=3.43; p=0.07
Sex	$F_{(1,36)}$=0.82; p=0.37	$F_{(1,36)}$=3.69; p=0.06	$F_{(1,36)}$=2.82; p=0.10	$F_{(1,33)}$=0.15; p=0.70
Treatment	$F_{(1,36)}$=3.15; p=0.08	$F_{(1,36)}$=0.00; p=0.99	$F_{(1,36)}$=0.75; p=0.39	$F_{(1,33)}$=0.09; p=0.77
Genotype X Sex	$F_{(1,36)}$=2.81; p=0.10	**$F_{(1,36)}$=5.02; p=0.03**	$F_{(1,36)}$=0.01; p=0.92	$F_{(1,33)}$=0.68; p=0.41
Genotype X Treatment	$F_{(1,36)}$=0.14; p=0.71	$F_{(1,36)}$=0.45; p=0.50	$F_{(1,36)}$=0.50; p=0.48	$F_{(1,33)}$=0.94; p=0.34
Sex X Treatment	$F_{(1,36)}$=0.51; p=0.48	$F_{(1,36)}$=0.11; p=0.74	$F_{(1,36)}$=0.96; p=0.34	$F_{(1,33)}$=1.75; p=0.19
Genotype X Sex X Treatment	$F_{(1,36)}$=0.83; p=0.36	$F_{(1,36)}$=1.17; p=0.29	$F_{(1,36)}$=0.02; p=0.90	$F_{(1,33)}$=0.10; p=0.76



Supplementary Figure 5. Microglial soma size a morphometric marker of microglial activation was measured using Iba1 immunostaining at 4 hours after the PBS or LPS challenge. Illustration of the regions of interests used for microglia and astrocytes segmentation, delineated using a custom made Matlab tool. No differences were found in the whole hippocampus (B), CA1(C), CA2 (D), CA3 (E) or Dentate Gyrus (F) subfields. The number of microglial clusters was elevated in APP/PS1 mice ($F_{(1,35)}$=10.05, p=0.003; G), which displayed relatively few plaques (white arrows) at 4.5 months of age (H, I). *, p<0.05. Data are expressed as Means ± SEM.



Supplementary Figure 6. The area occupied by astrocytes was quantified using GFAP immunostaining 4 hours after the PBS or LPS challenge. Representative image of GFAP positive astrocytes in the whole hippocampus (A), CA1(B), CA2 (C), CA3 (D) or Dentate Gyrus (E) subfields. No differences were found between any of the experimental conditions in these regions of interests: whole hippocampus (F), CA1(G), CA2 (H), CA3 (I) or Dentate Gyrus (J). Data are expressed as Means $\pm$ SEM.