

Supplementary Methods

Supplementary Table 1: Summary of cause of death.

| Cause of Death: | Control (n=36) | MDD (n=44) | $\chi^2=7.465$ | $p=0.280$ |
|-----------------|----------------|------------|----------------|-----------|
| Accidental | 1 | 2 | | |
| Cardiac arrest | 7 | 6 | | |
| Other cardiac | 10 | 6 | | |
| Suicide | 0 | 12 | | |
| Cancer | 5 | 1 | | |
| Natural | 1 | 2 | | |
| Other | 4 | 10 | | |
| Unknown | 8 | 5 | | |

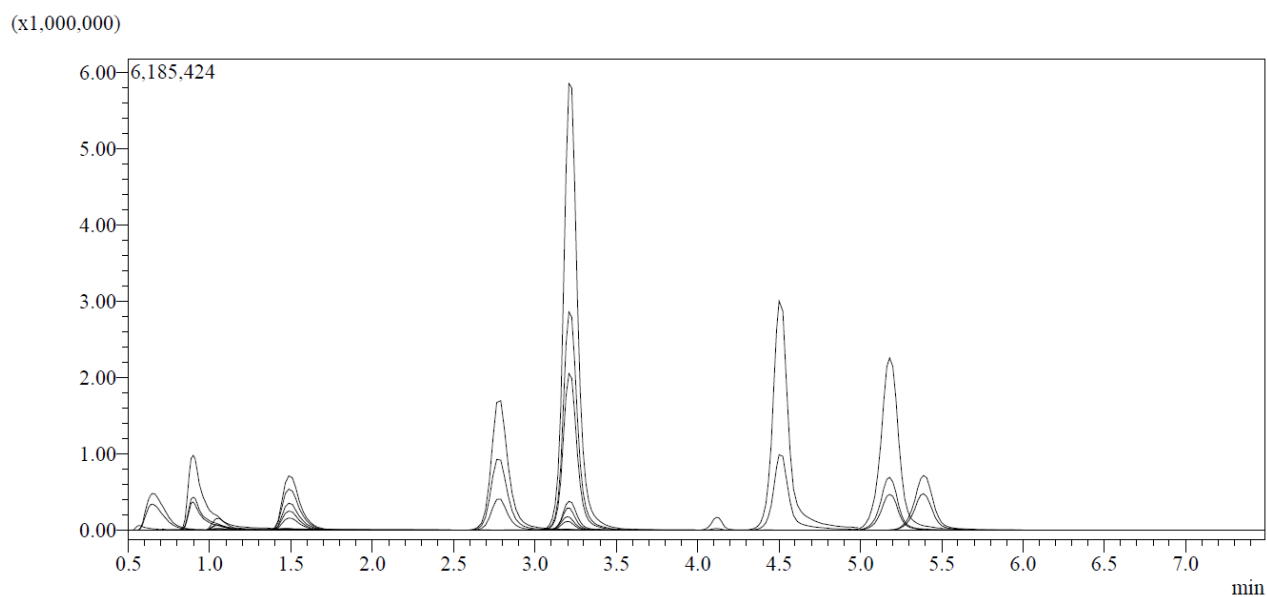
Note: Chi-square analysis excluded suicide as a cause of death.

Human ACC RNA Extraction:

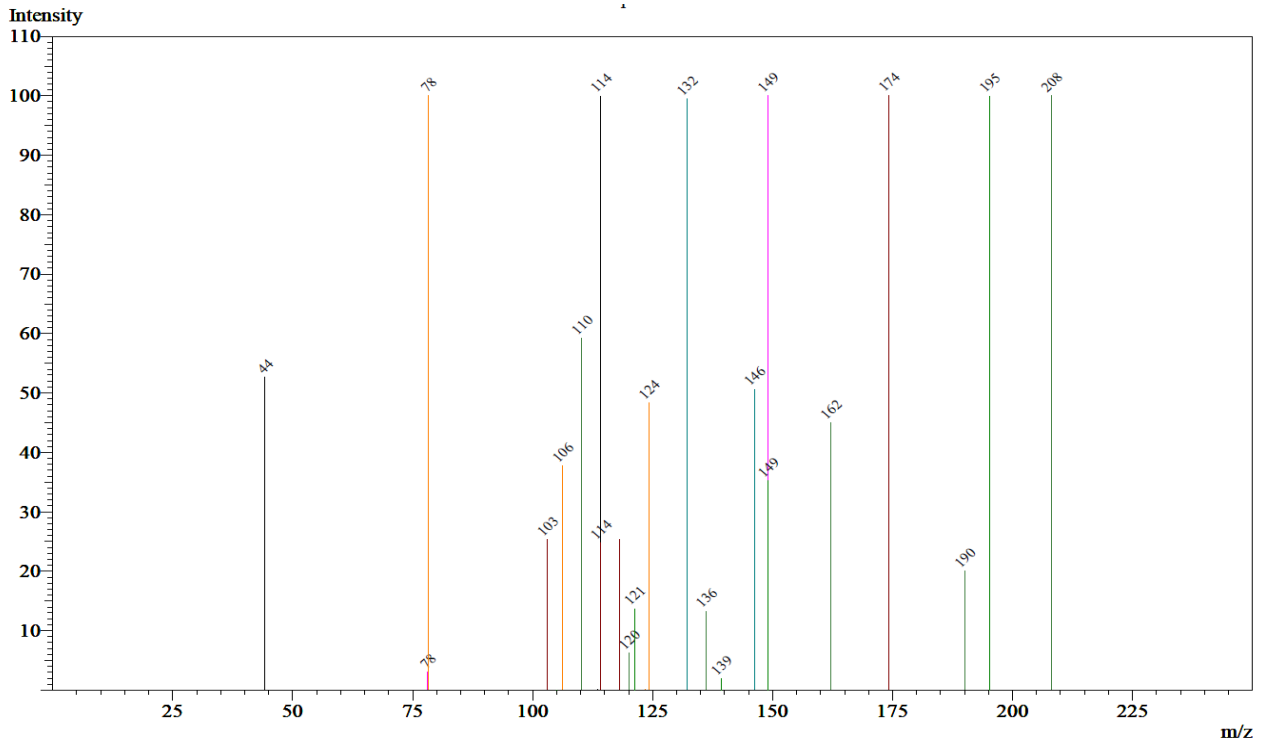
Tissue was homogenised in 800 μ l of cold TRIzol using a disposable tissue pestle (Axygen, Mount Martha, VIC, Australia) and incubated at room temperature for 5 minutes. 160 μ l of chloroform was added to the sample and then centrifuged at 12,000g for 15 minutes at 4°C. The aqueous phase was transferred to a new tube and 400 μ l of isopropanol was added, incubated for 10 minutes, followed by centrifugation at 12,000g for 10 minutes at 4°C. After removing the isopropanol, the remaining pellet was washed in 800 μ l of 70% ethanol and then centrifuged at 7500g for 5 minutes at 4°C. Ethanol was removed and samples were air-dried. The RNA was resuspended in 30 μ l RNase-free water (Sigma-Aldrich, Castle Hill, NSW, AUS).

Supplementary Table 2: TaqMan gene expression codes

| Gene | Alias | Corresponding protein | Accession number |
|--------|-------|--|------------------|
| AIF1 | | Allograft inflammatory factor 1 | Hs_00741549_g1 |
| AQP4 | | Aquaporin 4 | Hs_00242342_m1 |
| CX3CR1 | | C-X3-C motif chemokine receptor 1 | Hs_01598433_m1 |
| GAPDH | | Glyceraldehyde-3-phosphate dehydrogenase | Hs_99999905_m1 |
| GFAP | | Glial fibrillary acidic protein | Hs_00909236_m1 |
| GUSB | | Glucuronidase beta | Hs_99999908_m1 |
| HAAO | 3-HAO | 3-hydroxyanthranilate 3,4-dioxygenase | Hs_00201915_m1 |
| IL6 | | Interleukin 6 | Hs_00174131_m1 |
| IL1B | | Interleukin 1 beta | Hs_01555410_m1 |
| KMO | | Kynurenine 3-monooxygenase | Hs_00175738_m1 |
| KYAT1 | | Kynurenine aminotransferase 1 | Hs_00187858_m1 |
| KYAT2 | AADAT | Kynurenine aminotransferase 2 | Hs_00212039_m1 |
| KYNU | | Kynurinase | Hs_011114099_m1 |
| QPRT | | Quinolate phosphoribosyltransferase | Hs_00204757_m1 |
| TBP | | TATA-box binding protein | Hs_00427620_m1 |



Supplementary Figure 1: Combined Total Ion Chromatogram (TIC) with all metabolites inclusive of their respective optimised MRMs at 10uM mixed Standard. X-axis represents time (sec), Y-axis represents raw intensity. Order of metabolites and their RT (sec): CRE 0.64, 3-HK 1.05, QUIN 0.56, PIC 0.88, KYN 1.49, 5HIAA 1.49, dKYN 1.48, 3HAA 2.77, TRP 3.21, dTRP 3.20, AA 4.50, dAA, 4.43, KYNA 5.18, XA 5.38.



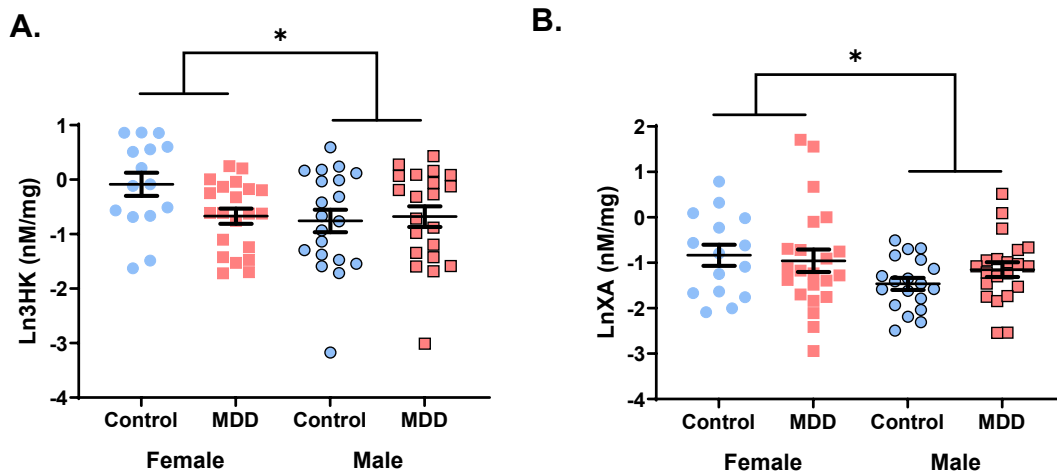
Supplementary Figure 2: Mass spectrum of all metabolites (including MRMs) from the combined method using 10uM mixed Standard. Relative abundance vs detected mass. Order of metabolites and their detected TIC mass (g/mol): CRE 113.60, 3-HK 224.70, QUIN 167.00, PIC 123.60, KYN 208.70, 5HIAA 191.70, dKYN 212.75, 3HAA 153.65, TRP 204.90, dTRP 207.75, AA 137.65, dAA, 141.65, KYNA 189.65, XA 205.65.

Impact of chronic antidepressant treatment in female Sprague-Dawley rats:

Adult female Sprague-Dawley rats (12 weeks of age) were obtained from the Animal Resource Centre (Perth, Australia) and allowed to acclimate for one week. Food and water were provided ad libitum. Rats were randomly assigned to a treatment group (n=10/group): fluoxetine (10mg/kg), imipramine (10mg/kg) or vehicle (saline injection 0.9% NaCl). Treatments were administered once daily via intraperitoneal injections between 0800 and 0900 for 5 weeks. Rats were euthanized via carbon dioxide asphyxiation 24 hours after the last treatment to allow a drug washout period. The brains were immediately removed, snap frozen in liquid nitrogen, and stored at -80°C. Approval for animal experimental procedures was granted by UOW Animal Ethics (ethics number: AE14/01).

Total RNA was isolated from approximately 20 mg of frozen frontal cortex tissue using Purelink RNA Mini Kits (ThermoFisher, 12183025). Quality of the extraction was measured via Nanodrop. Complementary DNA was synthesized from 2µg total RNA using Superscript IV First-Strand Synthesis Kit and random hexamers (Life Technologies, 18091200). The mRNA expression of *Kmo* and *Kyat2*, in the rat frontal cortex was measured by reverse transcriptase-qPCR (Quant Studio 5). Quantitative real-time PCR was performed in a 20-µL final reaction volume using SensiFAST SYBR No-ROX Kit (Bioline, BIO-98020). Amplification was carried out with 40 cycles of 95 °C for 5 seconds, 60 °C for 10 seconds, and 72 °C for 10 seconds. Transcript quantities were normalized to the geometric mean of three housekeeper genes: *Ubc*, *Gusb* and *B2m*, which did not differ across the treatment groups. The 'no template control' and reverse transcriptase control did not produce a signal in any assay. All amplifications from each subject were performed in triplicate and relative quantities of expression for each gene was calculated using the comparative threshold cycle value (Ct) method, using the formula $2^{-\Delta\Delta Ct}$ (where $\Delta\Delta Ct = \Delta Ct_{\text{sample}} - \Delta Ct_{\text{reference}}$).

Supplementary Results



Supplementary Figure 3: (A) 3-hydroxykynurenine (3-HK) was significantly lower in males overall compared to females ($p=0.046$). (B) Xanthurenic acid (XA) was significantly lower in males overall compared to females ($p=0.045$). Ln=natural log; MDD=major depressive disorder. * $p < 0.05$.

Supplementary Table 3: Sex-diagnosis interaction group means for kynurenine metabolites.

| Metabolites | Control | | | | | | MDD | | | | | |
|---------------------------|---------|--------------|--------|------|--------------|--------|--------|--------------|--------|------|--------------|--------|
| | Female | | | Male | | | Female | | | Male | | |
| | n | Mean (nM/mg) | SD | n | Mean (nM/mg) | SD | n | Mean (nM/mg) | SD | n | Mean (nM/mg) | SD |
| TRP | 15 | 384.42 | 177.38 | 20 | 301.43 | 128.44 | 22 | 313.88 | 132.86 | 22 | 313.21 | 144.78 |
| LnKYN | 15 | 1.71 | 0.91 | 20 | 0.87 | 1.27 | 21 | 1.03 | 0.92 | 21 | 1.02 | 1.14 |
| LnKYNA | 15 | 1.48 | 0.81 | 20 | 0.49 | 1.23 | 22 | 0.68 | 1.39 | 21 | 0.76 | 0.81 |
| LnQUIN | 15 | 5.04 | 0.34 | 20 | 5.03 | 0.31 | 22 | 5.00 | 0.27 | 22 | 4.94 | 0.32 |
| Ln3HK | 15 | -0.09 | 0.82 | 20 | -0.76 | 0.92 | 21 | -0.67 | 0.64 | 21 | -0.68 | 0.88 |
| Ln3HAA | 14 | -2.14 | 0.89 | 19 | -2.62 | 0.77 | 18 | -2.57 | 0.63 | 18 | -2.61 | 0.71 |
| LnXA | 15 | -0.83 | 0.90 | 19 | -1.46 | 0.57 | 22 | -0.96 | 1.16 | 21 | -1.15 | 0.74 |
| LnKYN/TRP $\times 10^3$ | 15 | 2.81 | 0.85 | 20 | 2.27 | 0.90 | 21 | 2.22 | 0.93 | 22 | 2.28 | 0.91 |
| LnKYNA/QUIN $\times 10^3$ | 15 | 3.34 | 0.88 | 20 | 2.37 | 1.24 | 22 | 2.59 | 1.48 | 21 | 2.75 | 0.83 |
| LnKYNA/KYN | 15 | 6.67 | 0.39 | 20 | 6.53 | 0.39 | 21 | 6.78 | 0.47 | 21 | 6.54 | 0.36 |
| Ln3HK/KYN | 15 | 5.12 | 0.79 | 20 | 5.28 | 1.10 | 21 | 5.21 | 0.87 | 21 | 5.26 | 0.88 |
| LnQUIN/KYN | 15 | 3.33 | 0.97 | 20 | 4.16 | 1.30 | 21 | 3.95 | 0.89 | 21 | 3.90 | 1.12 |

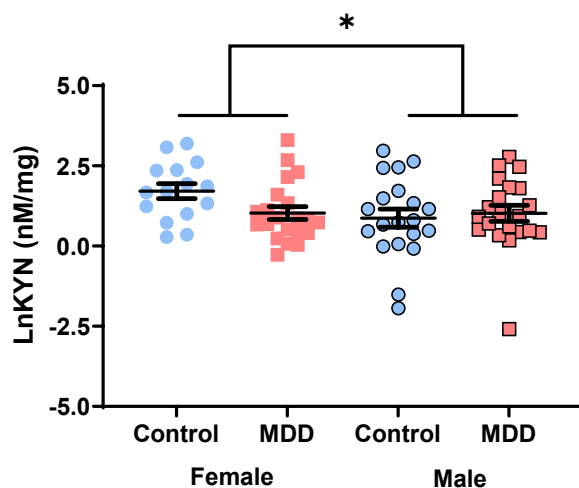
Supplementary Table 4: Main diagnosis output for kynurenine metabolites from sex*diagnosis two-way ANCOVAs.

| Metabolites | Covariate | Comparison |
|------------------------------|-----------|------------------------|
| TRP | | F(1,75)=0.797, p=0.375 |
| LnKYN | PMI | F(1,72)=0.428, p=0.515 |
| LnKYNA | | F(1,74)=1.065, p=0.306 |
| LnQUIN | Age | F(1,74)=0.481, p=0.490 |
| Ln3HK | PMI | F(1,72)=0.783, p=0.379 |
| Ln3HAA | | F(1,65)=1.296, p=0.259 |
| LnXA | | F(1,73)=0.221, p=0.639 |
| LnKYN/TRP x10 ³ | | F(1,74)=1.974, p=0.164 |
| LnKYNA/QUIN x10 ³ | | F(1,74)=0.503, p=0.481 |
| LnKYNA/KYN | | F(1,73)=0.375, p=0.542 |
| Ln3HK/KYN | | F(1,73)=0.035, p=0.851 |
| LnQUIN/KYN | | F(1,73)=0.512, p=0.477 |

Supplementary Table 5: P-values for factors included in the linear mixed effects models for the metabolite levels across sex and diagnosis with age and PMI included as covariates.

| Measures | Age | PMI | Sex | Diagnosis | Sex by Diagnosis |
|-------------|-------|--------|-------|-----------|------------------|
| LnKYNA | 0.239 | 0.156 | 0.060 | 0.603 | 0.049 |
| LnKYNA/QUIN | 0.552 | 0.337 | 0.117 | 0.693 | 0.044 |
| 3-HK | 0.450 | 0.005 | 0.050 | 0.325 | 0.117 |
| XA | 0.104 | 0.514 | 0.046 | 0.810 | 0.314 |
| TRP | 0.635 | 0.574 | 0.232 | 0.297 | 0.206 |
| LnKYN | 0.070 | 0.028 | 0.048 | 0.741 | 0.113 |
| Ln3HAA | 0.248 | 0.869 | 0.151 | 0.362 | 0.240 |
| LnKYN/TRP | 0.004 | <0.001 | 0.101 | 0.728 | 0.158 |
| LnKYNA/KYN | 0.037 | 0.414 | 0.061 | 0.935 | 0.647 |
| Ln3-HK/KYN | 0.075 | 0.603 | 0.497 | 0.818 | 0.804 |
| QUIN | 0.026 | 0.167 | 0.458 | 0.786 | 0.631 |

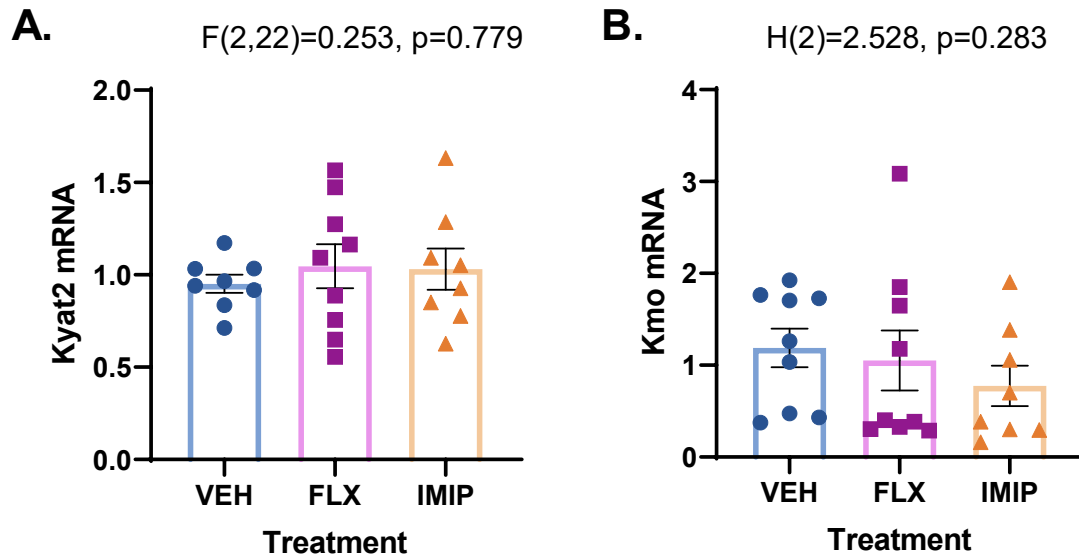
Abbreviations: KYNA: kynurenic acid; KYNA/QUIN: ratio of kynurenic acid to quinolinic acid; 3-HK: 3-hydroxykynurenine; XA: xanuthernic acid; TRP: tryptophan; KYN: kynurenine; QUIN: quinolinic acid.



Supplementary Figure 4: After controlling for age and PMI, a significant main effect of sex was observed for kynurenine ($p=0.048$). * $p<0.05$.

Supplementary Table 6: Main diagnosis output for kynurenine enzyme mRNA from sex*diagnosis two-way ANCOVAs.

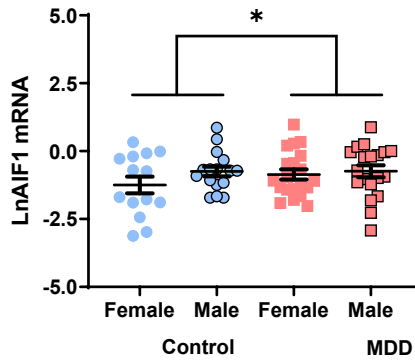
| mRNA | Covariate | Comparison |
|----------------|-----------|--------------------------|
| <i>KYAT2</i> | RIN | $F(1,63)=5.283, p=0.025$ |
| <i>LnKYAT1</i> | Age/PMI | $F(1,62)=0.008, p=0.928$ |
| <i>KYAT3</i> | Age/RIN | $F(1,63)=0.046, p=0.831$ |
| <i>KYAT4</i> | RIN | $F(1,64)=1.729, p=0.193$ |
| <i>KMO</i> | RIN | $F(1,64)=0.206, p=0.652$ |
| <i>LnKYNU</i> | Age | $F(1,62)=3.167, p=0.08$ |
| <i>LnHAAO</i> | Age/RIN | $F(1,63)=0.020, p=0.887$ |
| <i>LnQPRT</i> | Age/RIN | $F(1,63)=0.265, p=0.609$ |



Supplementary Figure 5: There were no changes in (A) *Kyat2* or (B) *Kmo* mRNAs in the frontal cortex after 5 weeks of treatment with fluoxetine (FLX) or Imipramine (IMIP) in female Sprague-Dawley rats.

Supplementary Table 7: P-values for factors included in the linear mixed effects models for the gene expression across sex and diagnosis with age, PMI and RIN included as covariates.

| Measures | age | PMI | RIN | Sex | Diagnosis | Sex by Diagnosis |
|-----------------|--------|-------|--------|-------|-----------|------------------|
| <i>KYAT2</i> | 0.262 | 0.047 | <0.001 | 0.448 | 0.016 | 0.835 |
| <i>KMO</i> | 0.042 | 0.824 | 0.020 | 0.019 | 0.911 | 0.027 |
| <i>lnIL6</i> | 0.108 | 0.201 | 0.637 | 0.206 | 0.010 | 0.711 |
| <i>lnIL1B</i> | 0.027 | 0.430 | 0.117 | 0.501 | 0.007 | 0.693 |
| <i>lnKYAT1</i> | <0.001 | 0.009 | 0.132 | 0.103 | 0.973 | 0.880 |
| <i>lnKYNU</i> | 0.003 | 0.214 | 0.604 | 0.646 | 0.051 | 0.752 |
| <i>lnHAAO</i> | 0.669 | 0.317 | <0.001 | 0.054 | 0.882 | 0.669 |
| <i>lnQPRT</i> | 0.002 | 0.893 | 0.087 | 0.092 | 0.539 | 0.147 |
| <i>lnAIF1</i> | 0.011 | 0.010 | 0.111 | 0.128 | 0.049 | 0.693 |
| <i>lnGFAP</i> | <0.001 | 0.615 | 0.002 | 0.567 | 0.673 | 0.707 |
| <i>lnAQP4</i> | 0.072 | 0.023 | 0.152 | 0.905 | 0.690 | 0.556 |
| <i>lnCX3CR1</i> | 0.313 | 0.089 | 0.474 | 0.109 | 0.492 | 0.330 |



Supplementary Figure 6: After controlling for age, PMI and RIN, a significant main effect of diagnosis was observed for *AIF1* mRNA ($p=0.049$). * $p<0.05$.

Supplementary Table 8: Summary of postmortem subject demographics in suicide subgroups.

| Variable | Control (n=36) | MDD-NS (n=27) | MDD-S (n=11) | Test statistic | p-value |
|-----------------------------|----------------|---------------|--------------|----------------|---------|
| Age at death (years) | 62.67±2.51 | 57.63±17.87 | 49.18±12.87 | H=5.631 | 0.052 |
| Postmortem interval (hours) | 17.03±0.99 | 17.55±7.47 | 23.59±9.82 | H=5.838 | 0.045 |
| RNA Integrity Number | 6.15±0.26 | 6.11±1.71 | 6.56±1.03 | F=0.371 | 0.691 |
| Sex | 20M, 16F | 11M, 16F | 7M, 5F | $\chi^2=1.691$ | 0.429 |

Values are represented as mean ± SD, unless otherwise specified. L: left; R: right; M: males; F: females

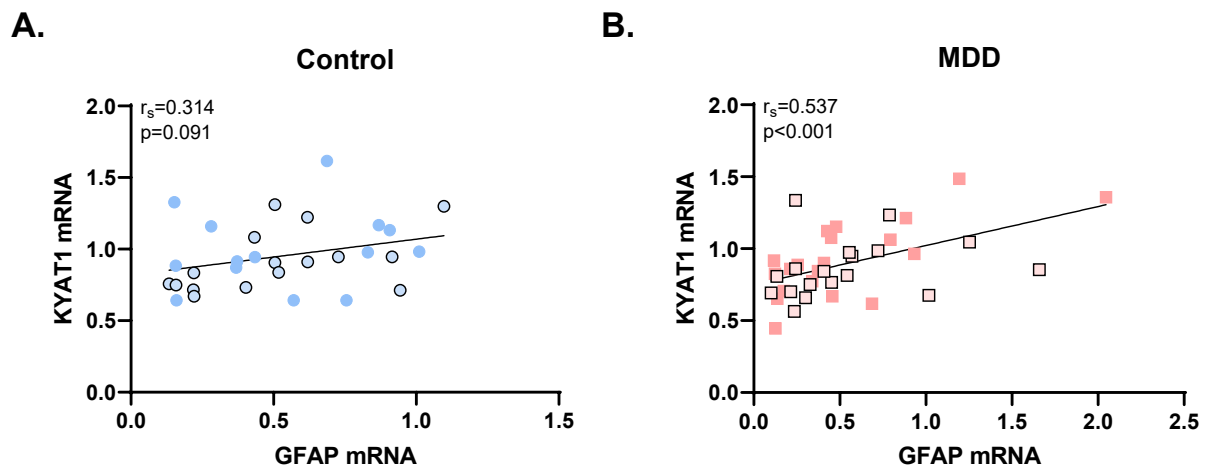
Supplementary Table 9: P-values for factors included in the linear mixed effects models for the metabolite levels across suicide subgroups with age and PMI included as covariates

| Measures | Age | PMI | Suicide |
|------------|-------|-------|---------|
| KYNA | 0.353 | 0.229 | 0.105 |
| KYNA/QUIN | 0.688 | 0.451 | 0.412 |
| 3-HK | 0.709 | 0.051 | 0.157 |
| XA | 0.143 | 0.928 | 0.547 |
| TRP | 0.299 | 0.558 | 0.297 |
| KYN | 0.452 | 0.091 | 0.623 |
| Ln3HAA | 0.299 | 0.948 | 0.506 |
| LnKYN/TRP | 0.015 | 0.005 | 0.673 |
| LnKYNA/KYN | 0.034 | 0.276 | 0.355 |
| Ln3-HK/KYN | 0.032 | 0.684 | 0.518 |
| QUIN | 0.027 | 0.198 | 0.921 |

Abbreviations: KYNA: kynurenic acid; KYNA/QUIN: ratio of kynurenic acid to quinolinic acid; 3-HK: 3-hydroxykynurenine; XA: xanthurenic acid; TRP: tryptophan; KYN: kynurenine; QUIN: quinolinic acid.

Supplementary Table 10: P-values for factors included in the linear mixed effects models for the gene expression across suicide subgroups with age, PMI and RIN included as covariates.

| Measures | Age | PMI | RIN | Suicide |
|-----------------|--------|-------|--------|---------|
| <i>KYAT2</i> | 0.560 | 0.148 | <0.001 | 0.021 |
| <i>KMO</i> | 0.133 | 0.814 | 0.037 | 0.970 |
| <i>LnIL6</i> | 0.769 | 0.160 | 0.563 | 0.191 |
| <i>LnIL1B</i> | 0.133 | 0.297 | 0.740 | 0.061 |
| <i>KYAT1</i> | <0.001 | 0.030 | 0.134 | 0.931 |
| <i>LnKYNU</i> | 0.008 | 0.144 | 0.699 | 0.212 |
| <i>LnHAAO</i> | 0.702 | 0.817 | <0.001 | 0.945 |
| <i>LnQPRT</i> | 0.012 | 0.855 | 0.101 | 0.634 |
| <i>LnAIF1</i> | 0.027 | 0.089 | 0.165 | 0.191 |
| <i>LnGFAP</i> | <0.001 | 0.447 | <0.001 | 0.331 |
| <i>LnAQP4</i> | 0.069 | 0.029 | 0.108 | 0.762 |
| <i>LnCX3CR1</i> | 0.350 | 0.311 | 0.668 | 0.863 |



Supplementary Figure 7: (A) There was no significant correlation between *KYAT1* and *GFAP* mRNAs in controls ($p=0.091$). (B) In major depressive disorder (MDD) there was a strong positive correlation between *KYAT1* and *GFAP* mRNAs ($r_s=0.537$ $p<0.001$). Males are represented by the outlined shapes.

Supplementary Table 11a: Metabolite-metabolite correlations and correlations between metabolites and pro-inflammatory cytokines in control subjects.

| Control | | KYNA | TRP | QUIN | KYN | 3HK | 3HAA | XA | <i>IL1B</i> |
|-------------|-------|------------------|------------------|--------|------------------|------------------|----------------|--------|----------------|
| TRP | r_s | 0.422* | | | | | | | |
| | Sig. | 0.011 | | | | | | | |
| QUIN | r_s | 0.085 | 0.230 | | | | | | |
| | Sig. | 0.628 | 0.184 | | | | | | |
| KYN | r_s | 0.926** | 0.398* | 0.045 | | | | | |
| | Sig. | <0.001 | 0.018 | 0.797 | | | | | |
| 3HK | r_s | 0.596** | 0.672** | 0.320 | 0.544** | | | | |
| | Sig. | <0.001 | <0.001 | 0.061 | <0.001 | | | | |
| 3HAA | r_s | 0.564** | 0.366* | 0.131 | 0.599** | 0.552** | | | |
| | Sig. | <0.001 | 0.036 | 0.469 | <0.001 | <0.001 | | | |
| XA | r_s | 0.594** | 0.683** | -0.017 | 0.496** | 0.806** | 0.483** | | |
| | Sig. | <0.001 | <0.001 | 0.925 | 0.002 | <0.001 | 0.004 | | |
| <i>IL1B</i> | r_s | 0.002 | -0.175 | -0.017 | 0.235 | -0.075 | 0.282 | -0.174 | |
| | Sig. | 0.992 | 0.356 | 0.930 | 0.212 | 0.695 | 0.146 | 0.358 | |
| <i>IL6</i> | r_s | 0.576** | -0.032 | 0.118 | 0.757** | 0.210 | 0.358 | 0.027 | 0.538** |
| | Sig. | 0.001 | 0.871 | 0.543 | <0.001 | 0.275 | 0.067 | 0.889 | 0.003 |

Abbreviations: KYNA: kynurenic acid; TRP: tryptophan; QUIN: quinolinic acid; KYN: kynurenine; 3HK: 3-hydroxykynurenine; 3HAA: 3-hydroxyanthranilic acid; XA: xanthurenic acid; *IL1B*: interleukin 1 beta; *IL6*: interleukin 6. * $p < 0.05$, ** $p < 0.01$.

Supplementary Table 11b: Metabolite-metabolite correlations and correlations between metabolites and pro-inflammatory cytokines in major depressive disorder.

| MDD | | KYNA | TRP | QUIN | KYN | 3HK | 3HAA | XA | <i>IL1B</i> |
|-------------|-------|------------------|---------------|-------|------------------|------------------|---------------|--------|------------------|
| TRP | r_s | 0.365* | | | | | | | |
| | Sig. | 0.015 | | | | | | | |
| QUIN | r_s | 0.024 | -0.206 | | | | | | |
| | Sig. | 0.879 | 0.179 | | | | | | |
| KYN | r_s | 0.827** | 0.178 | 0.259 | | | | | |
| | Sig. | <0.001 | 0.252 | 0.093 | | | | | |
| 3HK | r_s | 0.689** | 0.208 | 0.176 | 0.530** | | | | |
| | Sig. | <0.001 | 0.187 | 0.266 | <0.001 | | | | |
| 3HAA | r_s | 0.345* | 0.032 | 0.139 | 0.534** | 0.117 | | | |
| | Sig. | 0.040 | 0.853 | 0.420 | <0.001 | 0.503 | | | |
| XA | r_s | 0.537** | 0.348* | 0.001 | 0.261 | 0.567** | -0.134 | | |
| | Sig. | <0.001 | 0.022 | 0.997 | 0.095 | <0.001 | 0.435 | | |
| <i>IL1B</i> | r_s | 0.086 | -0.285 | 0.096 | 0.382* | 0.055 | 0.388* | -0.006 | |
| | Sig. | 0.603 | 0.079 | 0.56 | 0.018 | 0.748 | 0.028 | 0.972 | |
| <i>IL6</i> | r_s | 0.001 | -0.202 | 0.173 | 0.209 | -0.005 | 0.33 | 0.154 | 0.699** |
| | Sig. | 0.993 | 0.225 | 0.300 | 0.215 | 0.977 | 0.07 | 0.363 | <0.001 |

Abbreviations: KYNA: kynurenic acid; TRP: tryptophan; QUIN: quinolinic acid; KYN: kynurenine; 3HK: 3-hydroxykynurenine; 3HAA: 3-hydroxyanthranilic acid; XA: xanthurenic acid; *IL1B*: interleukin 1 beta; *IL6*: interleukin 6. * $p < 0.05$, ** $p < 0.01$.

Supplementary Table 12a: Correlations between the KYNA/KYN ratio and the gene expression of KAT enzymes.

| Diagnosis | Gene | | KYNA/KYN |
|-----------|--------------|-------|----------------|
| Control | <i>KYAT1</i> | r_s | -0.081 |
| | | p | 0.670 |
| | <i>KYAT2</i> | r_s | 0.382* |
| | | p | 0.037 |
| MDD | <i>KYAT1</i> | r_s | -0.393* |
| | | p | 0.016 |
| | <i>KYAT2</i> | r_s | 0.041 |
| | | p | 0.807 |

*Correlation is significant at the 0.05 level.

Supplementary Table 12b: Correlations between the 3HK/KYN ratio and gene expression of the KMO enzyme.

| Diagnosis | Gene | | 3HK/KYN |
|-----------|------------|-------|---------|
| Control | <i>KMO</i> | r_s | 0.274 |
| | | p | 0.142 |
| MDD | <i>KMO</i> | r_s | 0.180 |
| | | p | 0.285 |

Supplementary Table 12c: Correlations between the KYNA/KYN ratio and gene expression of the KAT enzymes across the suicide subgroups.

| Suicide subgroup | Gene | | KYNA/KYN |
|------------------|--------------|-------|----------------|
| Control | <i>KYAT1</i> | r_s | -0.1091 |
| | | p | 0.600 |
| | <i>KYAT2</i> | r_s | 0.390* |
| | | p | 0.037 |
| MDD-NS | <i>KYAT1</i> | r_s | -0.509* |
| | | p | 0.016 |
| | <i>KYAT2</i> | r_s | -0.281 |
| | | p | 0.206 |
| MDD-S | <i>KYAT1</i> | r_s | -0.067 |
| | | p | 0.865 |
| | <i>KYAT2</i> | r_s | 0.800** |
| | | p | 0.010 |

* Correlation is significant at the 0.05 level;

**Correlation is significant at the 0.01 level.

Supplementary Table 12d: Correlations between the 3HK/KYN ratio and gene expression of the KMO enzyme.

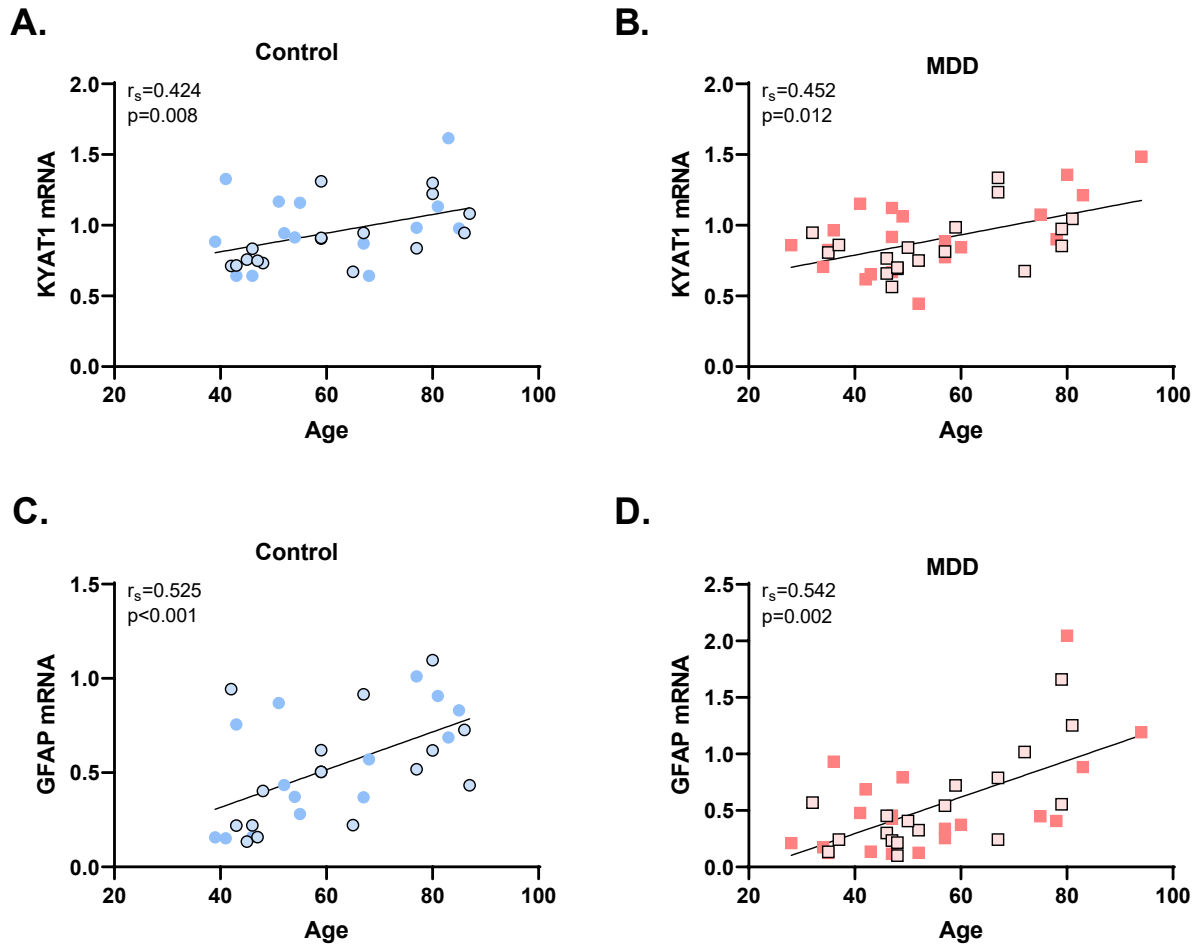
| Suicide subgroup | Gene | | 3HK/KYN |
|------------------|------------|-------|---------|
| Control | <i>KMO</i> | r_s | 0.273 |
| | | p | 0.144 |
| MDD-NS | <i>KMO</i> | r_s | 0.261 |
| | | p | 0.218 |
| MDD-S | <i>KMO</i> | r_s | -0.119 |
| | | p | 0.779 |

* Correlation is significant at the 0.05 level; **

Correlation is significant at the 0.01 level.

Supplementary Table 13: Spearman's correlations between age and kynurenine pathway metabolites, genes and relevant glial/inflammatory markers.

| Measure | | Age | |
|---------|-------|----------------|------------------|
| | | Control | MDD |
| KYNA | r_s | 0.262 | 0.222 |
| | Sig. | 0.140 | 0.152 |
| TRP | r_s | -0.135 | -0.070 |
| | Sig. | 0.439 | 0.652 |
| QUIN | r_s | -0.078 | 0.575** |
| | Sig. | 0.664 | <0.001 |
| KYN | r_s | 0.208 | 0.313* |
| | Sig. | 0.246 | 0.044 |
| 3HK | r_s | -0.186 | 0.134 |
| | Sig. | 0.284 | 0.398 |
| 3-HAA | r_s | -0.135 | 0.320 |
| | Sig. | 0.478 | 0.065 |
| XA | r_s | -0.279 | -0.142 |
| | Sig. | 0.122 | 0.362 |
| KYAT1 | r_s | 0.452* | 0.424** |
| | Sig. | 0.012 | 0.008 |
| KYAT2 | r_s | 0.041 | -0.086 |
| | Sig. | 0.828 | 0.604 |
| KMO | r_s | -0.224 | -0.308 |
| | Sig. | 0.234 | 0.056 |
| KYNU | r_s | 0.371* | 0.389* |
| | Sig. | 0.047 | 0.016 |
| HAAO | r_s | 0.367* | -0.077 |
| | Sig. | 0.046 | 0.646 |
| QPRT | r_s | 0.482** | 0.210 |
| | Sig. | 0.007 | 0.200 |
| AIF1 | r_s | 0.313 | 0.198 |
| | Sig. | 0.093 | 0.228 |
| GFAP | r_s | 0.542** | 0.525** |
| | Sig. | 0.002 | <0.001 |
| IL1B | r_s | 0.348 | 0.284 |
| | Sig. | 0.06 | 0.084 |
| IL6 | r_s | 0.385* | 0.140 |
| | Sig. | 0.048 | 0.417 |
| CX3CR1 | r_s | 0.087 | 0.063 |
| | Sig. | 0.647 | 0.704 |
| AQP4 | r_s | 0.305 | 0.188 |
| | Sig. | 0.101 | 0.251 |



Supplementary Figure 8: (A) There was a significant positive correlation between *KYAT1* mRNA and age in controls ($r_s=0.424$, $p=0.008$) (B) and in MDD ($r_s=0.452$, $p=0.012$). (C) There was a significant positive correlation between *GFAP* mRNA and age in controls ($r_s=0.525$, $p<0.001$) (D) and in MDD ($r_s=0.542$, $p=0.002$). Males are represented by the outlined shapes.