**Supplemental** **Table 1.** KP enzyme mRNA levels in male and female healthy controls and depressed patients

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Female Controls  | Male Controls | Female Depressed  | Male Depressed | Unadjusted Statistics |
| *KAT1* | 2.26 (0.71) | 1.94 (0.77) | 1.84 (0.66)† | 1.80 (0.44) | H(3) = 9.52, *p =* 0.02  |
| *KMO* | 2.27 (0.83) | 2.04 (0.83) | 1.95 (0.82) | 1.72 (0.73) | H(3) = 8.04, *p =* 0.05 |
| *KYNU* | 0.75 (0.25) | 0.84 (0.34) | 0.63 (0.35)\* | 0.56 (0.17)\*\* | H(3) = 16.86, *p =* 0.001  |
| *IDO1* | 5.45 (4.91) | 3.27 (1.88) | 4.47 (4.24) | 3.23 (1.83) | H(3) = 2.78, *p =* 0.43 |
| *IDO2* | 1.90 (1.32) | 1.46 (0.68) | 1.17 (0.74)\* | 0.90 (0.60)\*\* | H(3) = 18.46, *p <* 0.001  |

Data are expressed as means ± SD.

*KAT1*: female controls n = 35; male controls n = 20; female depressed n= 47; male depressed n = 27.

*KMO*: female controls n = 35; male controls n = 19; female depressed n= 47; male depressed n = 26.

*KYNU*: female controls n = 33; male controls n = 19; female depressed n= 47; male depressed n = 24.

*IDO1*: female controls n = 35; male controls n = 19; female depressed n= 46; male depressed n = 24.

*IDO2*: female controls n = 34; male controls n = 19; female depressed n= 46; male depressed n = 24.

Pairwise comparisons: \*female depressed with female controls p < 0.05; †female depressed with female controls p < 0.01; \*\*male depressed with male controls p < 0.01.

|  |
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| **Supplemental Table 2**. KP enzymes in patients with unipolar and bipolar depression pre- and post-ECT |
|  | Polarity | Pre-ECT | Post-ECT | Unadjusted Statistics | Adjusted Statistics |
| *KAT*1# | Unipolar (n=56) | 1.85 (0.63) | 1.83 (0.58) | *Time: F*1,72 = 0.907, *p* = 0.344*Group:* *F*1,72 = 0.181, *p* = 0.672*Time×Group:* *F*1,72 = 0.976, *p* = 0.326 | *Time: F*1,63 = 0.006, *p* = 0.937*Group:* *F*1,63 = 0.286, *p* = 0.595*Time×Group:* *F*1,63 = 1.524, *p* = 0.222 |
|  | Bipolar (n=18) | 1.76 (0.42) | 1.94 (0.53) |
|  |  |  |  |
| *KMO#* | Unipolar (n=56) | 1.90 (0.83) | 1.99 (0.88) | *Time: F*1,71 = 1.453, *p* = 0.232*Group:* *F*1,71 = 0.005, *p* = 0.947*Time×Group:* *F*1,71 = 0.134, *p* = 0.715 | *Time: F*1,62 = 0.848, *p* = 0.361*Group:* *F*1,62 = 0.146, *p* = 0.704*Time×Group:* *F*1,62 = 0.149, *p* = 0.701 |
|  | Bipolar (n=17) | 1.78 (0.64) | 2.04 (0.99) |
|  |  |  |  |
| *KYNU* | Unipolar (n=54) | 0.62 (0.34) | 0.67 (0.31) | *Pre: U=428.50, p = 0.681**Post: U=470, p = 0.882**Unipolar: Z=861, p = 0.308**Bipolar: Z=108, p = 0.136* |  |
|  | Bipolar (n=17) | 0.55 (0.10) | 0.66 (0.24) |
|  |  |  |  |
|  |  |  |  |  |  |
| *IDO1#* | Unipolar (n=53) | 4.34 (4.02) | 3.99 (3.97) | *Time: F*1,68 = 0.199, *p* = 0.657*Group:* *F*1,68 = 0.118, *p* = 0.732*Time×Group:* *F*1,68 = 0.118, *p* = 0.732 | *Time: F*1,59 = 2.731, *p* = 0.104*Group:* *F*1,59 = 0.059, *p* = 0.809*Time×Group:* *F*1,59 = 0.236, *p* = 0.629 |
|  | Bipolar (n=17) | 3.13 (1.79) | 4.81 (7.91) |
|  |  |  |  |  |
| *IDO2* | Unipolar (n=53) | 1.09 (0.71) | 1.45 (1.18) | *Pre: U = 418, p = 0.656**Post: U = 423, p = 0.706**Unipolar: Z = 885.50, p = 0.132**Bipolar: Z = 90, p = 0.523* |
|  | Bipolar (n=17) | 1.05 (0.71) | 1.49 (1.55) |
|  | Data are presented as mean (SD).#Log10 transformed data used for statistical analysis |

|  |
| --- |
| **Supplemental Table 3**. KP enzymes in patients with psychotic and non-psychotic depression pre- and post-ECT |
|  | Psychosis | Pre-ECT | Post-ECT | Unadjusted Statistics | Adjusted Statistics |
| *KAT1* | Yes (n=19) | 1.94 (0.60) | 1.84 (0.63) | *Pre: U* = 594, *p* = 0.376*Post: U* = 479, *p* = 0.590*Psychotic: Z* = 88, *p* = 0.778*Non-psychotic: Z* = 925, *p* = 0.194 |  |
|  | No (n=55) | 1.79 (0.58) | 1.86 (0.56) |
|  |  |  |  |
|  |  |  |  |  |  |
| *KMO#* | Yes (n=19) | 1.89 (0.80) | 2.00 (1.05) | *Time: F*1,71 = 0.635, *p* = 0.428*Group:* *F*1,71 = 0.0003, *p* = 0.985*Time×Group:* *F*1,71 = 0.277, *p* = 0.600 | *Time: F*1,62 = 0.848, *p* = 0.361*Group:* *F*1,62 = 0.034, *p* = 0.854*Time×Group:* *F*1,62 = 1.835, *p* = 0.180 |
|  | No (n=54) | 1.86 (0.80) | 2.00 (0.86) |
|  |  |  |  |
| *KYNU* | Yes (n=18) | 0.67 (0.20) | 0.65 (0.30) | *Pre: U* = 628, *p* = 0.046*Post: U* = 444.50, *p* = 0.668*Psychotic: Z* = 65, *p* = 0.372*Non-psychotic: Z* = 970, *p* = 0.024 |  |
|  | No (n=53) | 0.58 (0.32) | 0.67 (0.30) |
|  |  |  |  |
|  |  |  |  |  |  |
| *IDO1* | Yes (n=18) | 5.26 (5.09) | 4.00 (4.17) | *Pre: U* = 543, *p* = 0.314*Post: U* = 462, *p* = 0.936*Psychotic: Z* = 64, *p* = 0.349*Non-psychotic: Z* = 673, *p* = 0.884 |  |
|  | No (n=52) | 3.63 (2.92) | 4.26 (5.48) |
|  |  |  |  |  |
| *IDO2* | Yes (n=18) | 1.21 (0.93) | 1.50 (1.29) | *Pre: U* = 488, *p* = 0.788*Post: U* = 484, *p* = 0.830*Psychotic: Z* = 93, *p* = 0.744*Non-psychotic: Z* = 875, *p* = 0.090 |  |
|  | No (n=52) | 1.03 (0.61) | 1.45 (1.27) |
|  |  |  |  |
|  |  |  |  |  |  |
|  | Data are presented as mean (SD).#Log10 transformed data used for statistical analysis |

|  |
| --- |
| **Supplemental Table 4**. KP enzymes in remitters and non-remitters pre- and post-ECT |
|  | Remitter | Pre-ECT | Post-ECT | Unadjusted Statistics | Adjusted Statistics |
| *KATI#* | Yes (n=39) | 1.74 (0.55) | 1.75 (0.52) | *Time: F*1,72 = 0.27, *p* = 0.605*Group:* *F*1,72 = 3.303, *p* = 0.073*Time×Group:* *F*1,72 = 0.011, *p* = 0.918 | *Time: F*1,62 = 0.023, *p* = 0.879*Group:* *F*1,62 = 2.14, *p* = 0.15*Time×Group:* *F*1,62 = 0.168, *p* = 0.684 |
|  | No (n=35) | 1.93 (0.62) | 1.98 (0.61) |
|  |  |  |  |
|  |  |  |  |  |  |
| *KMO#* | Yes (n=39) | 1.78 (0.74) | 2.05 (1.04) | *Time: F*1,71 = 1.255, *p* = 0.266*Group:* *F*1,71 = 0.257, *p* = 0.614*Time×Group:* *F*1,71 = 1.439, *p* = 0.234 | *Time: F*1,61 = 0.431, *p* = 0.514*Group:* *F*1,61 = 0.049, *p* = 0.825*Time×Group:* *F*1,61 = 1.073, *p* = 0.304 |
|  | No (n=34) | 1.97 (0.84) | 1.94 (0.73) |
|  |  |  |  |
| *KYNU#* | Yes (n=39) | 0.63 (0.37) | 0.65 (0.33) | *Time: F*1,69 = 4.84, *p* = 0.031*Group:* *F*1,69 = 0.150, *p* = 0.700*Time×Group:* *F*1,69 = 0.757, *p* = 0.387 | *Time: F*1,59 = 0.033, *p* = 0.855*Group:* *F*1,59 = 0.439, *p* = 0.51*Time×Group:* *F*1,59 = 1.223, *p* = 0.273 |
|  | No (n=32) | 0.57 (0.17) | 0.68 (0.25) |
|  |  |  |  |
| *IDO1#* | Yes (n=38) | 3.98 (3.86) | 4.97 (6.54) | *Time: F*1,68 = 0.747, *p* = 0.391*Group:* *F*1,68 = 0.769, *p* = 0.384*Time×Group:* *F*1,68 = 2.284, *p* = 0.135 | *Time: F*1,58 = 1.97, *p* = 0.166*Group:* *F*1,58 = 0.313, *p* = 0.578*Time×Group:* *F*1,58 = 1.222, *p* = 0.273 |
|  | No (n=32) | 4.12 (3.40) | 3.26 (2.52) |
|  |  |  |  |  |  |
| *IDO2* | Yes (n=39) | 0.99 (0.57) | 1.22 (1.10) | *Pre: U* = 642, *p* = 0.657*Post: U* = 765, *p* = 0.058*Remitter: Z* = 435.50, *p* = 0.525*Non-remitter: Z* = 0.328, *p* = 0.117 |  |
|  | No (n=31) | 1.19 (0.84) | 1.77 (1.41) |
|  |  |  |  |  |  |
|  | Data are presented as mean (SD).#Log10 transformed data used for statistical analysis |

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| **Supplemental Table 5**. KP enzymes in responders and non-responders pre- and post-ECT |
|  | Responder | Pre-ECT | Post-ECT | Unadjusted Statistics | Adjusted Statistics |
| *KATI* | Yes (n=45) | 1.77 (0.53) | 1.80 (0.55) | *Pre: U* =715*, p* = 0.489*Post: U* = 743, *p* = 0.316*Responder: Z* = 567.50, *p* = 0.572*Non-responder: Z* = 250, *p* = 0.482 |  |
|  | No (n=29) | 1.92 (0.66) | 1.94 (0.60) |
|  |  |  |  |
|  |  |  |  |  |  |
| *KMO#* | Yes (n=45) | 1.79 (0.71) | 2.06 (0.99) | *Time: F*1,71 = 0.727, *p* = 0.397*Group:* *F*1,71 = 0.046, *p* = 0.831*Time×Group:* *F*1,71 = 1.926, *p* = 0.170 | *Time: F*1,61 = 0.254, *p* = 0.616*Group:* *F*1,61 = 0.019, *p* = 0.891*Time×Group:* *F*1,61 = 2.747, *p* = 0.103 |
|  | No (n=28) | 1.99 (0.91) | 1.90 (0.74) |
|  |  |  |  |
| *KYNU#* | Yes (n=45) | 0.63 (0.35) | 0.68 (0.34) | *Time: F*1,69 = 4.58, *p* = 0.036*Group:* *F*1,69 = 0.141, *p* = 0.708*Time×Group:* *F*1,69 = 0.146, *p* = 0.703 | *Time: F*1,59 = 0.002, *p* = 0.963*Group:* *F*1,59 = 0.010, *p* = 0.921*Time×Group:* *F*1,59 = 0.000007, *p* = 0.984 |
|  | No (n=26) | 0.56 (0.17) | 0.65 (0.21) |
|  |  |  |  |
| *IDO1#* | Yes (n=44) | 3.94 (3.77) | 4.57 (6.18) | *Time: F*1,68 = 0.853, *p* = 0.359*Group:* *F*1,68 = 0.047, *p* = 0.830*Time×Group:* *F*1,68 = 0.725, *p* = 0.398 | *Time: F*1,58 = 2.16, *p* = 0.147*Group:* *F*1,58 = 0.349, *p* = 0.557*Time×Group:* *F*1,58 = 0.451, *p* = 0.505 |
|  | No (n=26) | 4.22 (3.46) | 3.55 (2.61) |
|  |  |  |  |  |  |
| *IDO2* | Yes (n=45) | 1.03 (0.62) | 1.30 (1.19) | *Pre: U* = 569*, p* = 0.936*Post: U* = 681*, p* = 0.146*Responder: Z =* 581.50*, p =* 0.470*Non-remitter: Z =* 222*, p =* 0.109 |  |
|  | No (n=25) | 1.16 (0.84) | 1.75 (1.38) |
|  |  |  |  |
|  | Data are presented as mean (SD).#Log10 transformed data used for statistical analysis |

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| **Supplemental Table 6**. KP enzymes in female and male patients with depression pre- and post-ECT |
|  | Sex | Pre-ECT | Post-ECT | Unadjusted Statistics | Adjusted Statistics† |
| *KAT1* | Female (n=47) | 1.84 (0.66) | 1.94 (0.56) | *Time: F*1,72 = 0.003, *p* = 0.955*Group:* *F*1,72 = 1.323, *p* = 0.254*Time×Group:* *F*1,72 = 1.299, *p* = 0.258 | *Time: F*1,63 = 0.007, *p* = 0.933*Group:* *F*1,63 = 1.656, *p* = 0.203*Time×Group:* *F*1,63 = 0.790, *p* = 0.377 |
|  | Male (n=27) | 1.80 (0.44) | 1.72 (0.54) |
|  |  |  |  |
| *KMO#* | Female (n=47) | 1.95 (0.82) | 2.20 (0.97) | *Time: F*1,71 = 0.556, *p* = 0.458*Group:* *F*1,71 = 5.986, *p* = 0.017*Time×Group:* *F*1,71 = 2.068, *p* = 0.155 | *Time: F*1,62 = 0.848, *p* = 0.361*Group:* *F*1,62 = 4.907, *p* = 0.030*Time×Group:* *F*1,62 = 0.928, *p* = 0.339 |
|  | Male (n=26) | 1.72 (0.73) | 1.64 (0.65) |
|  |  |  |  |
| *KYNU* | Female (n=47) | 0.63 (0.35) | 0.72 (0.34) | *Pre: U=490.50, p = 0.372**Post: U=410, p = 0.061**Female: Z=693, p = 0.172**Male: Z=171, p = 0.548* |  |
|  | Male (n=24) | 0.56 (0.17) | 0.57 (0.15) |
|  |  |  |  |
|  |  |  |  |  |  |
| *IDO1#z* | Female (n=46) | 4.47 (4.24) | 4.43 (5.77) | *Pre: U=489, p = 0.436**Post: U=528, p = 0.767**Female: Z=461, p = 0.385**Male: Z=156, p = 0.864* |  |
|  | Male (n=24) | 3.23 (1.83) | 3.73 (3.76) |
|  |  |  |  |  |
| *IDO2* | Female (n=46) | 1.17 (0.74) | 1.63 (1.46) | *Pre: U = 428, p = 0.125**Post: U = 475, p = 0.341**Female: Z = 638, p = 0.287**Male: Z = 195, p = 0.199* |
|  | Male (n=24) | 0.90 (0.60) | 1.14 (0.70) |
|  | Data are presented as mean (SD).#Log10 transformed data used for statistical analysis†Adjusted for age, BMI, smoking, education, baseline HAM-D24, electrode placement, polarity, psychosis. |

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| **Supplemental Table 7.** Correlations between *IDO2* and HAM-D24 scores |
|  | Baseline *IDO2* & Baseline HAM-D24 | Baseline *IDO2* & ΔHAM-D24  | Δ*IDO2* & ΔHAM-D24 |
| *Polarity* |  |  |  |
| Unipolar (*n* = 52) | *ρ* = -0.212, *p* = 0.127 | *ρ* =0.143, *p* = 0.311 | *ρ* = 0.014, *p* = 0.924  |
| Bipolar (*n* = 17) | *r* = -0.275, *p* = 0.286 | *r* = 0.117, *p* = 0.654 | *ρ* = -0.264, *p* = 0.306 |
| *Psychosis* |  |  |  |
| Yes (*n* = 18) | *ρ* = -0.584, ***p* = 0.011** | *ρ* = 0.458, *p* = 0.187 | *ρ* = -0.346, *p* = 0.160 |
| No (*n* = 51) | *ρ* = -0.074*, p* = 0.603 | *ρ* = 0.064, *p* = 0.657 | *ρ* = 0.055, *p* = 0.699 |
| *Response* |  |  |  |
| Yes (*n* = 45) | *ρ* = -0.107, *p* = 0.485 | *ρ* = 0.144, *p* = 0.346  | *ρ* = -0.317, *p* = 0.034  |
| No (*n* = 24) | *ρ* = -0.349, *p* = 0.088 | *ρ* = 0.099, *p* = 0.647 | *r* = -0.257, *p* = 0.226 |
| *Remission* |  |  |  |
| Yes (*n* = 39) | *ρ* = -0.062, *p* = 0.709 | *r* = 0.113, *p* = 0.495 | *ρ* = -0.254, *p* = 0.118 |
| No (*n* = 30) | *ρ* = -0.417, ***p* = 0.020** | *ρ* = 0.078, *p* = 0.684 | *r* =  *ρ* = -0.225, *p* = 0.232  |
| Abbreviations: HAM-D24, Hamilton depression rating scale, 24-item version; ΔHAM-D24, change in Hamilton depression rating scale, 24-item version score. |

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|  **Supplemental Table 8.** Correlations between *KATI* and HAM-D24 scores |
|  | Baseline *KATI* & Baseline HAM-D24 | Baseline *KATI* & ΔHAM-D24  | Δ*KATI* & ΔHAM-D24 |
| *Polarity* |  |  |  |
| Unipolar (*n* = 55) | *ρ* = -0.044, *p* = 0.747 | *r =* 0.095, *p* = 0.492 | *r =* 0.035, *p* = 0.798  |
| Bipolar (*n* = 18) | *r* = 0.478, *p* = 0.045 | *r* = -0.013, *p* = 0.960 | *r* = -0.195, *p* = 0.439 |
| *Psychosis* |  |  |  |
| Yes (*n* = 19) | *r* = 0.006, *p* = 0.982 | *r* = 0.442, *p* = 0.058 | *r* = -0.362, *p* = 0.127 |
| No (*n* = 54) | *ρ* = 0.010*, p* = 0.944 | *ρ* = -0.054, *p* = 0.699 | *r* = 0.160, *p* = 0.248 |
| *Response* |  |  |  |
| Yes (*n* = 45) | *ρ* = 0.228, *p* = 0.131 | *ρ* = -0.163, *p* = 0.284  | *ρ* = -0.119, *p* = 0.435  |
| No (*n* = 28) | *ρ* = -0.224, *p* = 0.242 | *ρ* = 0.091, *p* = 0.646 | *r* = 0.077, *p* = 0.697 |
| *Remission* |  |  |  |
| Yes (*n* = 39) | *ρ* = 0.260, *p* = 0.110 | *r* = -0.103, *p* = 0.531 | *r* = -0.015, *p* = 0.926 |
| No (*n* = 34) | *r* = -0.191, *p* = 0.271 | *r* = 0.039, *p* = 0.827 | *ρ* = 0.041, *p* = 0.819 |
| Abbreviations: HAM-D24, Hamilton depression rating scale, 24-item version; ΔHAM-D24, change in Hamilton depression rating scale, 24-item version score. |

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| **Supplemental Table 9.**  Correlations between KYNU and HAM-D24 scores |
|  | Baseline *KYNU* & Baseline HAM-D24 | Baseline *KYNU* & ΔHAM-D24  | Δ*KYNU* & ΔHAM-D24 |
| *Polarity* |  |  |  |
| Unipolar (*n* = 53) | *ρ* = 0.084, *p* = 0.544 | *ρ* = *-*0.167, *p* = 0.233 | *ρ* = 0.240, *p* = 0.084  |
| Bipolar (*n* = 17) | *ρ* = -0.041, *p* = 0.875 | *ρ* = -0.273, *p* = 0.289 | *r* = -0.416, *p* = 0.097 |
| *Psychosis* |  |  |  |
| Yes (*n* = 18) | *r* = 0.367, *p* = 0.135 | *r* = -0.472, *p* = 0.048 | *ρ* = -0.017, *p* = 0.906 |
| No (*n* = 52) | *ρ* = -0.168*, p* = 0.229 | *ρ* = -0.025, *p* = 0.861 | *r* = 0.232, *p* = 0.354 |
| *Response* |  |  |  |
| Yes (*n* = 45) | *ρ* = 0.036, *p* = 0.816 | *ρ* = -0.109, *p* = 0.476  | *ρ* = -0.032, *p* = 0.836  |
| No (*n* = 25) | *r* = 0.121, *p* = 0.557 | *r* = -0.253, *p* = 0.222 | *r* = 0.435, *p* = 0.030 |
| *Remission* |  |  |  |
| Yes (*n* = 39) | *ρ* = 0.013, *p* = 0.936 | *ρ* = -0.121, *p* = 0.464 | *r* = 0.003, *p* = 0.986 |
| No (*n* = 31) | *r* = 0.173, *p* = 0.345 | *r* = -0.306, *p* = 0.094 | *ρ* = 0.165, *p* = 0.376 |
|  |  |  |  |
| Abbreviations: HAM-D24, Hamilton depression rating scale, 24-item version; ΔHAM-D24, change in Hamilton depression rating scale, 24-item version score. |

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| **Supplemental Table 10.** Correlation data used to generate Figure 1. |
| KP metabolite correlations with other KP metabolites |
| ***Healthy control cohort*** | **Correlation coefficient (ρ)** | **P value** |
| TRP & KYN | 0.422 | 0.016 |
| TRP & 3-HK | 0.504 | 0.003 |
| TRP & KYNA | 0.561 | 0.001 |
| TRP & XA | 0.492 | 0.004 |
| TRP & 3-HAA | 0.556 | 0.001 |
| TRP & PIC | 0.518 | 0.002 |
| 3-HK & KYN | 0.744 | 0.000001 |
| KYN & KYNA | 0.702 | 0.000007 |
| KYN & 3-HAA | 0.691 | 0.000012 |
| KYN & PIC | 0.455 | 0.009 |
| KYN & QUIN | 0.766 | 3.32 × 10-7 |
| 3-HK & KYNA | 0.746 | 9.46 ×10-7 |
| 3-HK & XA | 0.709 | 0.000006 |
| 3-HK & 3-HAA | 0.771 | 2.47 × 10-7 |
| 3-HK & PIC | 0.653 | 0.00005 |
| 3-HK & QUIN | 0.655 | 0.000047 |
| KYNA & XA | 0.752 | 6.94 × 10-7 |
| KYNA & 3-HAA | 0.618 | 0.00016 |
| KYNA & PIC | 0.612 | 0.000199 |
| KYNA & QUIN | 0.49 | 0.004 |
| XA & 3-HAA | 0.689 | 0.000013 |
| XA & PIC | 0.769 | 2.77 × 10-7 |
| XA & QUIN | 0.407 | 0.021 |
| 3-HAA & PIC | 0.571 | 0.001 |
| 3-HAA & QUIN | 0.645 | 0.000066 |
| PIC & QUIN | 0.405 | 0.022 |
|  |  |  |
| ***Depressed pre-ECT cohort*** | **ρ** | **P value** |
| TRP & KYN | 0.513 | 0.000011 |
| TRP & KYNA | 0.314 | 0.011 |
| TRP & XA | 0.458 | 0.000123 |
| TRP & 3-HAA | 0.544 | 0.000003 |
| TRP & PIC | 0.283 | 0.022 |
| KYN & 3-HK | 0.696 | 1.23 × 10-10 |
| KYN & KYNA | 0.609 | 7.27 × 10-8 |
| KYN & XA | 0.57 | 7.31 × 10-7 |
| KYN & 3-HAA | 0.663 | 1.78 × 10-9 |
| KYN & PIC | 0.265 | 0.033 |
| KYN & QUIN | 0.79 | 5.38 × 10-15 |
| 3-HK & KYNA | 0.437 | 0.00027 |
| 3-HK & XA | 0.381 | 0.002 |
| 3-HK & 3-HAA | 0.419 | 0.001 |
| 3-HK & QUIN | 0.574 | 5.91 × 10-7 |
| KYNA & XA | 0.779 | 2.07 × 10-14 |
| KYNA & 3-HAA | 0.697 | 1.11 × 10-10 |
| KYNA & PIC | 0.567 | 8.61 × 10-7 |
| KYNA & QUIN | 0.41 | 0.001 |
| XA & 3-HAA | 0.819 | 7.60 × 10-17 |
| XA & PIC | 0.576 | 5.18 × 10-7 |
| XA & QUIN | 0.39 | 0.001 |
| 3-HAA & PIC | 0.585 | 3.05 × 10-7 |
| 3-HAA & QUIN | 0.474 | 0.000067 |
|  |  |  |
| ***Depressed post-ECT cohort*** | **ρ** | **P value** |
| TRP & KYN | 0.332 | 0.010 |
| TRP & KYNA | 0.381 | 0.003 |
| TRP & XA | 0.497 | 0.000062 |
| TRP & HAA | 0.432 | 0.001 |
| TRP & PIC | 0.367 | 0.004 |
| KYN & 3-HK | 0.692 | 1.29 × 10-9 |
| KYN & KYNA | 0.683 | 2.56 × 10-9 |
| KYN & XA | 0.483 | 0.00011 |
| KYN & 3-HAA | 0.6 | 5.21 × 10-7 |
| KYN & PIC | 0.261 | 0.046 |
| KYN & QUIN | 0.855 | 6.65 × 10-18 |
| 3-HK & KYNA | 0.589 | 9.14 × 10-7 |
| 3-HK & XA | 0.477 | 0.000134 |
| 3-HK & 3-HAA | 0.593 | 7.39 × 10-7 |
| 3-HK & PIC | 0.273 | 0.037 |
| 3-HK & QUIN | 0.718 | 1.59 × 10-10 |
| KYNA & XA | 0.711 | 2.75 × 10-10 |
| KYNA & 3-HAA | 0.669 | 6.74 × 10-9 |
| KYNA & PIC | 0.481 | 0.00012 |
| KYNA & QUIN | 0.576 | 0.000002 |
| XA & 3-HAA | 0.779 | 3.90 × 10-13 |
| XA & PIC | 0.512 | 0.000034 |
| XA & QUIN | 0.466 | 0.0002 |
| 3-HAA & PIC | 0.57 | 0.000002 |
| 3-HAA & QUIN | 0.609 | 3.01 × 10-7 |
|  |  |  |
| KP enzyme mRNA expression correlations with other KP enzymes |
| ***Healthy control cohort*** | **ρ** | **P value** |
| *KMO* & *KYNU* | 0.533 | 0.000048 |
| *IDO1* & *IDO2* | 0.481 | 0.000266 |
|  |  |  |
| ***Depressed pre-ECT cohort*** | **ρ** | **P value** |
| *KMO* & *KYNU* | 0.457 | 0.000145 |
| *KMO* & *KAT1* | 0.295 | 0.011 |
| *IDO1* & *IDO2* | 0.300 | 0.012 |
| *IDO1* & *KMO* | 0.477 | 0.000029 |
| *IDO1* & *KAT1* | 0.288 | 0.015 |
| *IDO2* & *KAT1* | 0.328 | 0.006 |
| ***Depressed post-ECT cohort*** | **ρ** | **P value** |
| *KMO* & *KYNU* | 0.595 | 4.582 × 10-8 |
| *KMO* & *KAT1* | 0.317 | 0.006 |
| *IDO1* & *IDO2* | 0.311 | 0.009 |
| *IDO2* & *KAT1* | 0.270 | 0.024 |
|  |  |  |
| KP enzyme mRNA expression correlations with KP metabolites |
| ***Healthy control cohort*** | **ρ** | **P value** |
| *IDO1* & KYN/TRP | 0.382 | 0.031 |
| *KMO* & 3-HK | 0.402 | 0.023 |
| *KMO* & PIC | 0.350 | 0.049 |
| *KAT1* & PIC | 0.372 | 0.036 |
|  |  |  |
| ***Depressed pre-ECT cohort*** | **ρ** | **P value** |
| *IDO1* & KYNA/KYN | -0.324 | 0.010 |
| *IDO1* & KYNA/QUIN | -0.368 | 0.003 |
| *KYNU* & TRP  | -0.250 | 0.045 |
| *KYNU* & KYN | -0.258 | 0.038 |
| *KYNA* & KAT1 | -0.265 | 0.033 |
| *KAT1* & KYNA/KYN | -0.305 | 0.013 |
|  |  |  |
| ***Depressed post-ECT cohort*** | **ρ** | **P value** |
| *IDO1* & KYNA/KYN | -0.323 | 0.014 |
| *IDO1* & KYNA/QUIN | -0.381 | 0.003 |
| *IDO2* & KYNA/KYN | -0.326 | 0.013 |
| *IDO2* & KYNA/QUIN | -0.265 | 0.046 |
|  |  |  |
| KP enzyme mRNA expression correlations with markers of stress and inflammation |
| ***Healthy control cohort*** | **ρ** | **P value** |
| *KMO* & *IL-6*  | 0.327 | 0.017 |
| *KAT1* & *IL-6* | 0.296 | 0.03 |
| *IDO2* & *GILZ*\* | 0.376 | 0.006 |
| *IDO2* & *NR3C1* | 0.318 | 0.02 |
| *KYNU* & *FKBP5*\* | -0.306 | 0.027 |
| *KAT1* & *FKBP5*\* | 0.273 | 0.044 |
| *KAT1* & *NR3C1* | 0.559 | 0.000009 |
|  |  |  |
| ***Depressed pre-ECT cohort*** | **ρ** | **P value** |
| *IDO1* & *IL-6* | 0.312 | 0.009 |
| *IDO2* & *IL-6* | 0.294 | 0.014 |
| *KMO* & *IL-6* | 0.511 | 0.000004 |
| *KAT1* & *IL-6* | 0.327 | 0.005 |
| *IDO1* & *NR3C1* | 0.279 | 0.019 |
| *IDO2* & *NR3C1* | 0.347 | 0.003 |
| *KMO* & *NR3C1* | 0.275 | 0.018 |
| *KAT1* & *NR3C1* | 0.492 | 0.000009 |
|  |  |  |
| ***Depressed post-ECT cohort*** | **ρ** | **P value** |
| IDO2 & *NR3C1* | 0.315 | 0.008 |
| *KYNU* & *GILZ*\* | 0.305 | 0.01 |
| *KAT1* & *GILZ*\* | 0.238 | 0.042 |
| *KAT1* & *NR3C1* | 0.473 | 0.000021 |
| *KMO* & *IL-6* | 0.509 | 0.000005 |
| \*Denotes a correlation that was not included in Figure 1 in order to improve the clarity of the schematic. |

**Supplementary Table 11.** KP enzyme DNA methylation levels in individuals with a history of depression compared to individuals without a history of depression

|  |
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|  |
| **Probe ID** | **Gene annotation from GREAT (distance from TSS)** | **Mean DNA methylation Differences (%)** | **Adjusted P value †** |
| cg13263723 | KYNU (-330445), LRP1B (-415480) | -1% | 0.027 |
| cg21542308 | IDO2 (+61305), C8orf4 (-157208) | 2% | 0.009 |
| cg08465774 | IDO1 (+429) | 0% | 0.822 |
| cg00606312 | KMO (+183) | 0% | 0.206 |
| TSS: Transcriptional start site; † adjusted for history of an inflammatory disorder, age, Sex, anti-depressant use, chip and estimated blood cell composition |
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