**Supplementary material:**

Table S1: bivariate correlations of clinical variables.

Tables S2 to S7: mediation analyses PROCESS macro model 4 with parallel mediators for cognitive variables.

Tables S8 and S9: mediation analyses PROCESS macro model 4 with parallel mediators controlling premorbid IQ (for attention and verbal memory respectively).

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Table S1. Bivariate correlations.** | | | | | | | | | | | | |
| **n =157** | **DBI** | **CPZ** | **PANSS 2 yr** | **CI** | **Attention** | **Speed processing** | **Executive functions** | **Working memory** | **Verbal memory** | **Social cognition** | **FAST basal** | **FAST 2 yr** |
| **DBI** | - |  |  |  |  |  |  |  |  |  |  |  |
| **CPZ** | **.555\* .000** | - |  |  |  |  |  |  |  |  |  |  |
| **PANSS 2 yr** | -.009  .913 | **.263\***  **.001** | - |  |  |  |  |  |  |  |  |  |
| **IQ 2 yr** | -.143  .076 | **-.357**  **.000** | **-.300\***  **.000** | - |  |  |  |  |  |  |  |  |
| **Attention** | -.083  .323 | **-.241\***  **.004** | -.177  .039 | **.250**  **.003\*** | - |  |  |  |  |  |  |  |
| **Speed Processing** | .044  .590 | -.097  .231 | -.138  .101 | .050  .541 | .133  .116 | - |  |  |  |  |  |  |
| **Executive functions** | -.041  .627 | .026  .757 | -.153  .081 | .060  .480 | .010  .906 | .071  .402 | - |  |  |  |  |  |
| **Working memory** | -.198  .013 | **-.269\***  **.001** | -.171  .040 | **.481\***  **.000** | **.290\***  **.000** | -.034  .677 | -.074  .379 | - |  |  |  |  |
| **Verbal memory** | -.146  .069 | **-.305\***  **.000** | **-.426\***  **.000** | **.494\***  **.000** | **.337\***  **.000** | .014  .865 | -.081  .341 | **.383\***  **.000** | - |  |  |  |
| **Social cognition** | -.030  .731 | .041  .640 | .116  .201 | -.048  .582 | .075  .414 | -.085  .336 | .045  .647 | .120  .170 | .010  .909 | - |  |  |
| **FAST basal** | .174  .032 | **.247\***  **.002** | .158  .062 | -.134  .102 | -.096  .291 | -.013  .874 | -.139  .105 | -.132  .107 | -.197  .015 | -.068  .445 | - |  |
| **FAST 2 yr** | .125  .138 | **.336\***  **.000** | **.633\***  **.000** | **-.396\***  **.000** | **-.277\***  **.001** | -.084  .328 | -.068  .444 | **-.273\***  **.001** | **-.479\***  **.000** | .149  .120 | **.633\***  **.000** | - |

Table S1: Antipsychotic dosage, DBI score, cognitive and social functioning. r: correlation. p values under 0.0045 are statistically

significant after Bonferroni correction. \* is marked for p values under this value

DBI: Anticholingeric Drug Burden Index; CPZ scores: Chlorpromazine equivalent values; PANSS: Positive and Negative Symptom Scale; IQ: Intelligence Quotient; FAST: Functioning Assessment Short Test.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **B** | **p** | **95% CI** |
| **Outcome: Attention** | | | |
| Constant | -0.1783 | 0.2928 | -0.5124 to 0.1557 |
| CPZ | -0.001 | 0.008 | -0.0018 to -0.0003 |
| DBI | 0.1585 | 0.379 | -0.1968 to 0.5139 |
| R2 | 0.0571 |  |  |
| F (2, 128) | 3.8731 | 0.0233 |  |
| **Outcome: PANSS total score** | | | |
| Constant | 46.1592 | < 0.0001 | 40.8415 to 51.4769 |
| CPZ | 0.0214 | 0.0006 | 0.0093 to 0.0334 |
| DBI | -5.4487 | 0.0589 | -11.1062 to 0.2088 |
| R2 | 0.0875 |  |  |
| F (2, 128) | 6.1344 | 0.0029 |  |
| **Outcome: FAST score** | | | |
| Constant | -10.5388 | 0.0044 | -17.7337 to -3.3438 |
| CPZ | 0.0066 | 0.1741 | -0.003 to 0.0162 |
| DBI | 1.2708 | 0.5576 | -3.0064 to 5.548 |
| PANSS | 0.5165 | < 0.0001 | 0.3858 to 0.6471 |
| Attention | -2.4707 | 0.0203 | -4.5507 to -0.3908 |
| R2 | 0.4261 |  |  |
| F (4, 126) | 23.3804 | < 0.0001 |  |
| **Indirect effect:** | **B** | **SE** | **95% CI** |
| CPZ > Attention > FAST score | 0.0026 | 0.0015 | 0.0001 to 0.006 |
| CPZ > PANSS score > FAST score | 0.011 | 0.0033 | 0.0045 to 0.0178 |

Table S2 Completely standardized indirect effects of X (dopaminergic load measured as CPZ) on Y (FAST total score) in model 4 with two parallel mediators (attention) and one covariate (anticholinergic load measured as DBI). OLS estimates for direct effects, bootstrap results for indirect effects, using 10,000 bootstraps and a bias-corrected method. Probe interactions for moderation and conditioning were made if p < 0.01 due to multiple comparisons.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **B** | **p** | **95% CI** |
| **Outcome: Speed processing** | | | |
| Constant | -0.2401 | 0.0403 | -0.4693 to-0.0108 |
| CPZ | -0.0004 | 0.1036 | -0.0009 to 0.0001 |
| DBI | 0.2122 | 0.1091 | -0.048 to 0.4724 |
| R2 | 0.0248 |  |  |
| F (2, 133) | 1.6994 | 0.1886 |  |
| **Outcome: PANSS total score** | | | |
| Constant | 47.1716 | < 0.0001 | 41.6061 to 52.647 |
| CPZ | 0.0221 | 0.0006 | 0.0098 to 0.0345 |
| DBI | -6.0617 | 0.0558 | -12.2758 to 0.1523 |
| R2 | 0.0859 |  |  |
| F (2, 133) | 6.2489 | 0.0025 |  |
| **Outcome: FAST score** | | | |
| Constant | -10.5943 | 0.0036 | -17.6677 to -3.5209 |
| CPZ | 0.0092 | 0.0549 | -0.0002 to 0.0196 |
| DBI | 1.0167 | 0.6619 | -3.5728 to 5.6061 |
| PANSS | 0.5268 | < 0.0001 | 0.4011 to 0.6525 |
| Speed Processing | -0.8795 | 0.5631 | -3.8803 to 2.1213 |
| R2 | 0.4284 |  |  |
| F (4, 131) | 24.5439 | < 0.0001 |  |
| **Indirect effect:** | **B** | **SE** | **95% CI** |
| CPZ > Attention > FAST score | 0.0004 | 0.0007 | -0.0006 to 0.0021 |
| CPZ > PANSS score > FAST score | 0.0117 | 0.0034 | 0.0052 to 0.0189 |

Table S3 Completely standardized indirect effects of X (dopaminergic load measured as CPZ) on Y (FAST total score) in model 4 with two parallel mediators (speed processing) and one covariate (anticholinergic load measured as DBI). OLS estimates for direct effects, bootstrap results for indirect effects, using 10,000 bootstraps and a bias-corrected method. Probe interactions for moderation and conditioning were made if p < 0.01 due to multiple comparisons.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **B** | **p** | **95% CI** |
| **Outcome: Executive functions** | | | |
| Constant | -0.0028 | 0.9625 | -0.1215 to 0.01158 |
| CPZ | 0.0001 | 0.5134 | -0.0002 to 0.0004 |
| DBI | -0.0643 | 0.3076 | -0.1886 to 0.06 |
| R2 | 0.0085 |  |  |
| F (2, 125) | 0.5333 | 0.588 |  |
| **Outcome: PANSS total score** | | | |
| Constant | 45.5659 | < 0.0001 | 40.1969 to 50.9349 |
| CPZ | 0.0203 | 0.0013 | 0.0081 to 0.0325 |
| DBI | -4.5225 | 0.114 | -10.1466 to 1.1016 |
| R2 | 0.0804 |  |  |
| F (2, 125) | 5.4634 | 0.0053 |  |
| **Outcome: FAST score** | | | |
| Constant | -10.416 | 0.0056 | -17.7228 to -3.1092 |
| CPZ | 0.0071 | 0.1432 | -0.0024 to 0.0167 |
| DBI | 1.6579 | 0.4449 | -2.624 to 5.9399 |
| PANSS | 0.5229 | < 0.0001 | 0.389 to 0.6568 |
| Executive functions | 0.1414 | 0.9632 | -5.9181 to 6.201 |
| R2 | 0.3933 |  |  |
| F (4, 123 ) | 19.9328 | < 0.0001 |  |
| **Indirect effect:** | **B** | **SE** | **95% CI** |
| CPZ > Executive functions > FAST score | < 0.0001 | 0.0004 | -0.0008 to 0.0007 |
| CPZ > PANSS score > FAST score | 0.0106 | 0.0036 | 0.0041 to 0.0184 |

Table S4 Completely standardized indirect effects of X (dopaminergic load measured as CPZ) on Y (FAST total score) in model 4 with two parallel mediators (executive functions) and one covariate (anticholinergic load measured as DBI). OLS estimates for direct effects, bootstrap results for indirect effects, using 10,000 bootstraps and a bias-corrected method. Probe interactions for moderation and conditioning were made if p < 0.01 due to multiple comparisons.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **B** | **p** | **95% CI** |
| **Outcome: Working memory** | | | |
| Constant | -0.4381 | 0.002 | -0.7129 to -0.1633 |
| CPZ | -0.0007 | 0.0259 | -0.0013 to -0.0001 |
| DBI | -0.0642 | 0.6623 | -0.354 to 0.2257 |
| R2 | 0.0599 |  |  |
| F (2, 136) | 4.3302 | 0.015 |  |
| **Outcome: PANSS total score** | | | |
| Constant | 49.9316 | < 0.0001 | 41.5834 to 52.2798 |
| CPZ | 0.0211 | 0.0006 | 0.0092 to 0.0329 |
| DBI | -5.5742 | 0.0528 | -11.2159 to 0.0675 |
| R2 | 0.0836 |  |  |
| F (2, 136) | 6.2036 | 0.0026 |  |
| **Outcome: FAST score** | | | |
| Constant | -11.4512 | 0.0014 | -18.3998 to -4.5026 |
| CPZ | 0.0079 | 0.0863 | -0.0011 to 0.0170 |
| DBI | 0.7170 | 0.7329 | -3.4294 to to 4.8634 |
| PANSS | 0.536 | < 0.0001 | 0.4024 to 0.6496 |
| Working memory | -2.5014 | 0.0416 | -4.9067 to -0.0961 |
| R2 | 0.4425 |  |  |
| F (4, 134) | 26.5854 | < 0.0001 |  |
| **Indirect effect:** | **B** | **SE** | **95% CI** |
| CPZ > Working memory > FAST score | 0.0017 | 0.0013 | -0.0004 to 0.0046 |
| CPZ > PANSS score > FAST score | 0.0111 | 0.0032 | 0.05 to 0.0177 |

Table S5 Completely standardized indirect effects of X (dopaminergic load measured as CPZ) on Y (FAST total score) in model 4 with two parallel mediators (working memory) and one covariate (anticholinergic load measured as DBI). OLS estimates for direct effects, bootstrap results for indirect effects, using 10,000 bootstraps and a bias-corrected method. Probe interactions for moderation and conditioning were made if p < 0.01 due to multiple comparisons.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **B** | **p** | **95% CI** |
| **Outcome: Verbal memory** | | | |
| Constant | -1.0219 | 0.0001 | -1.5246 to -0.5192 |
| CPZ | -0.002 | 0.0005 | -0.0031 to -0.0009 |
| DBI | 0.1644 | 0.5401 | -0.3649 to 0.6936 |
| R2 | 0.0982 |  |  |
| F (2, 136) | 7.4011 | 0.0009 |  |
| **Outcome: PANSS total score** | | | |
| Constant | 46.9757 | < 0.0001 | 41.5972 to 52.3543 |
| CPZ | 0.0222 | 0.0003 | 0.0103 to 0.0342 |
| DBI | -5.9505 | 0.0396 | -11.6127 to -0.2883 |
| R2 | 0.0914 |  |  |
| F (2, 136) | 6.84 | 0.0015 |  |
| **Outcome: FAST score** | | | |
| Constant | -9.9526 | 0.0046 | -16.779 to -3.1262 |
| CPZ | 0.0069 | 0.1318 | -0.0021 to 0.0159 |
| DBI | 0.7683 | 0.7088 | -3.2913 to 4.8279 |
| PANSS | 0.4692 | < 0.0001 | 0.341 to 0.5974 |
| Verbal memory | -2.2215 | 0.0017 | -3.5935 to -0.8495 |
| R2 | 0.4731 |  |  |
| F (4, 134) | 30.0830 | < 0.0001 |  |
| **Indirect effect:** | **B** | **SE** | **95% CI** |
| CPZ > Verbal memory > FAST score | 0.0045 | 0.0021 | 0.0011 to 0.0091 |
| CPZ > PANSS score > FAST score | 0.0104 | 0.0031 | 0.0049 to 0.0172 |

Table S6 Completely standardized indirect effects of X (dopaminergic load measured as CPZ) on Y (FAST total score) in model 4 with two parallel mediators (verbal memory) and one covariate (anticholinergic load measured as DBI). OLS estimates for direct effects, bootstrap results for indirect effects, using 10,000 bootstraps and a bias-corrected method. Probe interactions for moderation and conditioning were made if p < 0.01 due to multiple comparisons.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **B** | **p** | **95% CI** |
| **Outcome: Social cognition** | | | |
| Constant | -0.6483 | 0.0011 | -1.0316 to -0.2651 |
| CPZ | 0.0004 | 0.3816 | -0.0005 to 0.0012 |
| DBI | -0.313 | 0.1453 | -0.7358 to 0.1098 |
| R2 | 0.0184 |  |  |
| F (2, 115) | 1.0783 | 0.3436 |  |
| **Outcome: PANSS total score** | | | |
| Constant | 46.4659 | < 0.0001 | 40.6827 to 52.2491 |
| CPZ | 0.0219 | 0.0008 | 0.0093 to 0.0345 |
| DBI | -5.3113 | 0.1019 | -11.6920 to 1.0694 |
| R2 | 0.0935 |  |  |
| F (2, 115) | 5.9314 | 0.0035 |  |
| **Outcome: FAST score** | | | |
| Constant | -10.1726 | 0.0146 | -18.2968 to -2.0485 |
| CPZ | 0.0067 | 0.1918 | -0.0034 to 0.0168 |
| DBI | 1.6211 | 0.5176 | -3.3272 to 6.5694 |
| PANSS | 0.5434 | < 0.0001 | 0.4021 to 0.6844 |
| Social cognition | 1.0252 | 0.3424 | -1.1052 to 3.1557 |
| R2 | 0.4131 |  |  |
| F (4, 113) | 19.8821 | < 0.0001 |  |
| **Indirect effect:** | **B** | **SE** | **95% CI** |
| CPZ > Social cognition > FAST score | 0.0004 | 0.0008 | -0.0008 to 0.0023 |
| CPZ > PANSS score > FAST score | 0.0119 | 0.0035 | 0.0054 to 0.0193 |

Table S7 Completely standardized indirect effects of X (dopaminergic load measured as CPZ) on Y (FAST total score) in model 4 with two parallel mediators (social cognition) and one covariate (anticholinergic load measured as DBI). OLS estimates for direct effects, bootstrap results for indirect effects, using 10,000 bootstraps and a bias-corrected method. Probe interactions for moderation and conditioning were made if p < 0.01 due to multiple comparisons.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **B** | **p** | **95% CI** |
| **Outcome: Attention** | | | |
| Constant | -0.9853 | 0.0949 | -2.144 to 0.1734 |
| CPZ | -0.0009 | 0.0324 | -0.0017 to -0.0001 |
| DBI | -4.7894 | 0.1017 | -10.5374 to 0.9586 |
| Premorbid IQ | -0.1145 | 0.2255 | -0.3006 to 0.0715 |
| R2 | 0.0722 |  |  |
| F (3, 127) | 3.2936 | 0.0228 |  |
| **Outcome: PANSS total score** | | | |
| Constant | 57.0597 | < 0.0001 | 38.5717 to 75.5476 |
| CPZ | 0.0191 | 0.0033 | 0.0064 to 0.0317 |
| DBI | -4.7894 | 0.1017 | -10.5374 to 0.9586 |
| Premorbid IQ | -0.1145 | 0.2255 | -0.3006 to 0.0715 |
| R2 | 0.098 |  |  |
| F (3, 127) | 4.5995 | 0.0043 |  |
| **Outcome: FAST score** | | | |
| Constant | 2.5235 | 0.7493 | -13.0706 to 18.1176 |
| CPZ | 0.0045 | 0.3652 | -0.0053 to 0.0142 |
| DBI | 1.9236 | 0.3768 | -2.3689 to 6.2162 |
| Premorbid IQ | -0.1310 | 0.0647 | -0.2702 to 0.0081 |
| PANSS | 0.5045 | < 0.0001 | 0.3745 to 0.6346 |
| Attention | -2.2399 | 0.0346 | -4.3145 to -0.1654 |
| R2 | 0.4416 |  |  |
| F (5, 125) | 19.7692 | < 0.0001 |  |
| **Indirect effect:** | **B** | **SE** | **95% CI** |
| CPZ > Attention > FAST score | 0.0019 | 0.0013 | -0.0001 to 0.0047 |
| CPZ > PANSS score > FAST score | 0.0096 | 0.0034 | 0.0032 to 0.0165 |

Table S8. Post hoc analyses controlling premorbid IQ as covariate. Completely standardized indirect effects of X (dopaminergic load measured as CPZ) on Y (FAST total score) in model 4 with two parallel mediators (Verbal Memory) and two covariates (anticholinergic load measured as DBI and premorbid IQ). OLS estimates for direct effects, bootstrap results for indirect effects, using 10,000 bootstraps and a bias-corrected method. Probe interactions for moderation and conditioning were made if p < 0.01 due to multiple comparisons.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **B** | **p** | **95% CI** |
| **Outcome: Verbal memory** | | | |
| Constant | -4.7208 | < 0.0001 | -6.3022 to -3.1394 |
| CPZ | -0.0012 | 0.029 | -0.0023 to -0.0001 |
| DBI | -0.0559 | 0.825 | -0.5544 to 0.4427 |
| Premorbid IQ | 0.039 | < 0.0001 | 0.0231 to 0.0549 |
| R2 | 0.2315 |  |  |
| F (2, 136) | 13.5581 | < 0.0001 |  |
| **Outcome: PANSS total score** | | | |
| Constant | 61.2052 | < 0.0001 | 43.0524 to 79.3579 |
| CPZ | 0,192 | 0.0027 | 0.0068 to 0.0316 |
| DBI | -5.1033 | 0.0801 | -10.8262 to 0.6196 |
| Premorbid IQ | -0.15 | 0.1071 | -0.333 to 0.0329 |
| R2 | 0.1088 |  |  |
| F (3, 135) | 5.4919 | 0.0014 |  |
| **Outcome: FAST score** | | | |
| Constant | -1.0376 | 0.8945 | -16.4785 to 14.4033 |
| CPZ | 0.0057 | 0.2174 | -0.034 to 0.0149 |
| DBI | 1.2218 | 0.5577 | -2.8896 to 5.3333 |
| Premorbid IQ | -0.0903 | 0.2054 | -0.2307 to 0.0501 |
| PANSS | 0.4692 | < 0.0001 | 0.3412 to 0.5971 |
| Verbal memory | -1.8791 | 0.0126 | -3.3479 to 0.4104 |
| R2 | 0.4795 |  |  |
| F (5, 133) | 24.5015 | < 0.0001 |  |
| **Indirect effect:** | **B** | **SE** | **95% CI** |
| CPZ > Verbal memory > FAST score | 0.009 | 0.03 | 0.033 to 0.0151 |
| CPZ > PANSS score > FAST score | 0.0023 | 0.014 | 0.0001 to 0.0157 |

Table S9. Post hoc analyses controlling premorbid IQ as covariate. Completely standardized indirect effects of X (dopaminergic load measured as CPZ) on Y (FAST total score) in model 4 with two parallel mediators (Verbal Memory) and two covariates (anticholinergic load measured as DBI and premorbid IQ). OLS estimates for direct effects, bootstrap results for indirect effects, using 10,000 bootstraps and a bias-corrected method. Probe interactions for moderation and conditioning were made if p < 0.01 due to multiple comparisons.