**Supplementary Material.**

**Supplementary Table 1**. Main Demographic and Clinical Characteristics of LABSP Sample (full table)

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable (continuous)** | **N** | **Mean** | **SD** |
| BDNF serum levels, ng/ml | 105 | 25.45 | 13.67 |
| Age, years | 105 | 48.85 | 10.45 |
| Education, years | 105 | 9.26 | 3.23 |
| Offspring, N | 105 | 0.34 | 0.95 |
| Age of onset, years | 105 | 21.77 | 9.30 |
| Duration of illness, months | 105 | 308.51 | 134.33 |
| Age at first treatment, years | 105 | 24.23 | 8.95 |
| Duration of untreated illness, months | 105 | 29.07 | 54.60 |
| Cigarettes smoked per day, N | 46 | 19.83 | 9.80 |
| Weight, Kg | 74 | 77.32 | 18.76 |
| Height, cm | 74 | 167.84 | 8.83 |
| BMI | 73 | 27.3 | 6.8 |
| Waist circumference, cm | 45 | 90.47 | 18.37 |
| Antipsychotics, chlorpromazine equivalents, mg/day | 103 | 378.92 | 272.03 |
| **Variable (categorical)** | N | % |
| Sex (male) | 74 | 70.5 |
| Age class |  |  |
| 18-20 | 2 | 1.9 |
| 21-25 | 38 | 36.2 |
| 26-44 | 58 | 55.2 |
| 45-65 | 7 | 6.7 |
| Marital status |  |  |
| Single | 8 | 7.6 |
| Married/Cohabiting | 10 | 9.5 |
| Divorced | 2 | 1.9 |
| Widowed | 83 | 79.0 |
| NA | 2 | 1.9 |
| Presence of offspring | 19 | 18.1 |
| Employment |  |  |
| Employed | 7 | 6.7 |
| Student | 1 | 1.0 |
| Registered disabled civilian | 95 | 90.5 |
| Unemployed | 2 | 1.9 |
| Presence of smoking | 52 | 49.5 |
| History of substance abuse | 28 | 30.8 |
| Current use of substances | 5 | 5.5 |
| Presence of family history of mental disorders | 64 | 61.0 |
| Presence of family history of schizophrenia | 31 | 29.5 |
| Presence of family history of bipolar disorder | 8 | 7.6 |
| Presence of family history of major depressive disorder | 19 | 18.1 |
| Presence of family history of anxiety disorders | 10 | 9.5 |
| Clinical course |  |  |
| Episodic with full remission | 2 | 1.9 |
| Episodic with residual symptoms | 37 | 35.2 |
| Chronic with or without periodical relapses | 65 | 61.9 |
| NA | 1 | 1 |
| Presence of hospital admissions | 93 | 88.6 |
| Diagnosis of schizophrenia (SCID-I) | 64 | 61.0 |
| Diagnosis of schizoaffective disorder (SCID-I) | 41 | 39.0 |
| Diagnosis of obsessive-compulsive disorder (SCID-I) | 5 | 4.8 |
| Diagnosis of cluster A personality disorders (SCID-II) | 2 | 1.9 |
| Diagnosis of cluster B personality disorders (SCID-II) | 2 | 1.9 |
| Diagnosis of cluster C personality disorders (SCID-II) | 2 | 1.9 |
| Diagnosis of personality disorder NOS (SCID-II) | 1 | 1.0 |
| Long-acting antipsychotic therapy | 24 | 22.9 |

Abbreviations: LABSP, longitudinal assessment of BDNF in Sardinian psychotic patients; BDNF, brain-derived neurotrophic factor; SD, standard deviation; SCID-I, Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I); SCID-II, Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II).

**Supplementary Table 2.** Interaction Effects of *BDNF* Gene Polymorphisms on the Significant Relationships Between Clinical Variables and Longitudinal BDNF Serum Levels

|  |
| --- |
|  Unadjusted Models Adjusted Models\* |
| Genetic Model | Interaction Effect | Estimated Coefficient | Z value | P value | Estimated Coefficient | Zvalue | Pvalue |
| Genotypic Effect | CGI-SCH neg \* rs7934165AGCGI-SCH neg \* rs7934165GGCGI-SCH neg \* rs6265\_Val66MetCTCGI-SCH neg \* rs6265\_Val66MetTTCGI-SCH neg \* rs11030104AGCGI-SCH neg \* rs11030104GGCGI-SCH neg\* rs1519480CTCGI-SCH neg \* rs1519480TTCGI-SCH dep \* rs7934165AGCGI-SCH dep \* rs7934165GGCGI-SCH dep \* rs6265\_Val66MetCTCGI-SCH dep \* rs6265\_Val66MetTTCGI-SCH dep \* rs11030104AGCGI-SCH dep \* rs11030104GGCGI-SCH dep \* rs1519480CTCGI-SCH dep \* rs1519480TTPANSS-FCTcr neg \* rs7934165AGPANSS-FCTcr neg \* rs7934165GGPANSS-FCTcr neg \* Val66MetCTPANSS-FCTcr neg \* Val66MetTTPANSS-FCTcr neg \* rs11030104AGPANSS-FCTcr neg \* rs11030104GGPANSS-FCTcr neg \* rs1519480CTPANSS-FCTcr neg \* rs1519480TTBACS vf \* rs7934165AGBACS vf \* rs7934165GGBACS vf \* rs6265\_Val66MetCTBACS vf \* rs6265\_Val66MetTTBACS vf \* rs11030104AGBACS vf \* rs11030104GGBACS vf \* rs1519480CTBACS vf \* rs1519480TTBACS sc \* rs7934165AGBACS sc \* rs7934165GG | -0.0196400.007011-0.002029-0.128493-0.012728-0.085754-0.318269-0.3588780.010978-0.064021-0.087187-0.195373-0.078009-0.1333190.008520-0.032705-0.0165056-0.0006924-0.009100-0.004740-0.009723-0.003059-0.360668-0.365281-0.022116-0.018360-0.0080750.0068230.003428-0.017147-0.0068660.005207-0.006509-0.000631 | -0.3210.101-0.039-1.3850.244-0.997-1.410-1.5960.200-0.973-1.812-1.756-1.615-1.4850.055-0.213-1.521-0.052-0.929-0.199-0.981-0.162-1.541-1.561-2.310-1.564-0.9900.254-0.414-0.917-0.1410.107-1.277-0.092 | 1110.831110.5530.553110.3500.3500.4510.451110.641111110.6720.6720.0830.11781111110.8061 | -0.0340350.003097-0.005331-0.120319-0.015879-0.090576-0.3192419-0.36444980.008873-0.053916-0.092358-0.217964-0.084587-0.1131670.0105572-0.0344213-0.018652-0.003033-0.010030-0.009081-0.010382-0.008865-0.3613380-0.3652496-0.020922-0.018149-0.0081880.009621-0.003259-0.026490-0.00737400.0048186-5.387e-033.117e-05 | -0.5550.045-0.102-1.267-0.305-1.057-1.417-1.6240.163-0.823-1.933-1.862-1.762-1.2360.068-0.224-1.784-0.236-1.034-0.369-1.051-0.471-1.546-1.563-2.235-1.588-1.0230.349-0.401-1.525-0.1510.099-1.0990.004 | 1111110.6260.611110.3190.3190.3910.791110.372111110.7820.7820.1020.337110.8590.509110.8151 |
| BACS sc \* rs6265\_Val66MetCTBACS sc \* rs6265\_Val66MetTTBACS sc \* rs11030104AGBACS sc \* rs11030104GGBACS sc \* rs1519480CTBACS sc \* rs1519480TT | 0.000334-0.019668-0.0028610.0058170.0150800.016632 | 0.077-2.126-0.6510.6800.2740.302 | 10.1511111 | -0.0009947-0.0183423-0.0037080.0033310.0177050.017875 | -0.228-1.656-0.8400.3600.3220.326 | 10.3771111 |
| Allelic Effect |  |  |  |  |  |  |  |
| AdditiveModel | CGI-SCH neg \* rs7934165CGI-SCH neg \* rs6265\_Val66MetCGI-SCH neg \* rs11030104CGI-SCH neg \* rs1519480CGI-SCH dep \* rs7934165CGI- SCH dep \* rs6265\_Val66Met | -0.0052690.0306080.030971-0.0605220.0291380.085461 | -0.1540.7790.837-1.2970.8862.129 | 10.8700.6560.3890.7515**0.06.** | -0.0040970.0321060.034981-0.06348400.02607470.085373 | -0.1190.8150.935-1.3640.7902.111 | 110.7140.51810.104 |
| CGI- SCH dep \* rs11030104CGI-SCH dep \* rs1519480PANSS-FCTcr neg \* rs7934165PANSS-FCTcr neg \* Val66MetPANSS-FCTcr neg \* rs11030104PANSS-FCTcr neg \* rs1519480BACS vf \* rs7934165BACS vf \* rs6265\_Val66MetBACS vf \* rs11030104BACS vf \* rs1519480BACS sc \* rs7934165BACS sc \* rs6265\_Val66MetBACS sc \* rs11030104BACS sc \* rs1519480 | 0.07134-0.0354880.0018210.0061090.005641-5.8 x 10-30.01014540.0050840.0056110.0113320.0011910.001671-1.8 x 10-50.001748 | 1.965-0.8420.2790.7440.754-0.5861.7370.6820.8081.3770.3570.448-0.0050.380 | 0.09880.80010.8590.68810.24710.9830.5051111 | 0.070881-0.03641050.0021910.0070120.006491-0.00480570.01024540.0052590.0061950.01113900.0014580.0017630.00088460.0003673 | 1.932-0.8570.3420.8550.866-0.4941.7690.7130.9001.3600.4320.4550.2490.079 | 0.137110.9490.77310.308110.6961111 |
| DominantModel | CGI-SCH neg \* rs7934165CGI-SCH neg \* rs6265\_Val66MetCGI-SCH neg \* rs11030104CGI-SCH neg \* rs1519480CGI-SCH dep \* rs7934165CGI- SCH dep \* rs6265\_Val66MetCGI- SCH dep \* rs11030104CGI-SCH dep \* rs1519480PANSS-FCTcr neg \* rs7934165PANSS-FCTcr neg \* Val66MetPANSS-FCTcr neg \* rs11030104PANSS-FCTcr neg \* rs1519480BACS vf \* rs7934165BACS vf \* rs6265\_Val66MetBACS vf \* rs11030104BACS vf \* rs1519480BACS sc \* rs7934165BACS sc \* rs6265\_Val66MetBACS sc \* rs11030104BACS sc \* rs1519480 | -0.0311150.1303290.080757-0.343123 0.059450.1611950.100181-0.017300-0.0114000.001071-0.0008102-0.3631850.004656-0.0122810.0147870.001760-0.0045340.019944-0.0074810.016066 | -0.5621.4360.969-1.5341.0901.4621.140-0.114-0.9840.045-0.044-1.5540.467-0.4570.8140.036-0.7962.235-0.9080.293 | 10.3020.6650.3440.5520.2880.50910.778110.45811110.8090.07280.7281 | -0.0401210.1166280.079297-0.3476430.0460960.1609960.084033-0.016776-0.0114390.00164270.002834-0.3637400.006152-0.0147030.0216290.001597-0.0037600.016811-0.0075800.017394 | -0.7341.2420.964-1.5550.8401.3600.946-0.111-1.0030.0670.153-1.5580.629-0.5401.3090.033-0.6461.550-0.8660.317 | 10.6422110.45110.521110.948110.569110.76210.7950.4850.7731 |
| RecessiveModel |  |  |  |  |  |  |  |
| CGI-SCH neg \* rs7934165CGI-SCH neg \* rs6265\_Val66MetCGI-SCH neg \* rs11030104CGI-SCH neg \* rs1519480CGI-SCH dep \* rs7934165CGI- SCH dep \* rs6265\_Val66MetCGI- SCH dep \* rs11030104CGI-SCH dep \* rs1519480PANSS-FCTcr neg \* rs7934165PANSS-FCTcr neg \* Val66MetPANSS-FCTcr neg \* rs11030104PANSS-FCTcr neg \* rs1519480BACS vf \* rs7934165BACS vf \* rs6265\_Val66MetBACS vf \* rs11030104BACS vf \* rs1519480BACS sc \* rs7934165BACS sc \* rs6265\_Val66MetBACS sc \* rs11030104BACS sc \* rs1519480 | -0.009513-0.019794-0.0267320.050799-0.0115260.09500-0.0869660.041953-0.011308-0.008323-0.0086750.005212-0.021399-0.007453-0.004852-0.012005-0.005358-0.000798-0.001911-0.001735 | -0.166-0.402-0.5471.034-0.222-2.049-1.9070.901-1.117-0.884-0.9270.527-2.359-0.929-0.601-1.404-1.083-0.190-0.457-0.370 | 110.9240.352 10.1210.1570.36740.79210.7610.678**0.0367**0.6750.8160.3210.55810.7951 | -0.019245-0.023853-0.0310630.0545943-0.008423-0.096152-0.0889720.044304-0.013620-0.009687-0.009798 0.0043962-0.020607-0.007586-0.005151-0.0121672-0.004580-0.001845-0.003060-0.0003604 | -0.343-0.486-0.6391.119-0.165-2.070-1.9620.948-1.414-1.039-1.0590.454-2.339-0.964-0.652-1.449-0.950-0.435-0.727-0.077 | 1110.52610.1540.1490.6870.4800.8960.8691**0.0466**0.7510.7760.4420.4100.89350.4671 |

Abbreviations: CGI-SCH, Clinical Global Impression Scale for Schizophrenia; BACS, Brief Assessment of Cognitive in Schizophrenia; PANSS-FCTcr, consensus five-factor model of Positive and Negative Syndrome Scale

Holm–Bonferroni corrections were used to adjust P values for multiple comparisons between models

\*Adjusted for age and sex

**Supplementary Table 3.** Interaction Effects of Duration of Illness and Duration of Untreated Psychosis on Longitudinal BDNF Serum Levels

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Estimated Coefficient | Std. Error | Z value | P value |
| Time | -1.055 x 10-2 | 9.744 x 10-2 | -0.108 | 0.914 |
| Illness duration | 4.612 x 10-4 | 3.280 x 10-4 | 1.406 | 0.160 |
| Time:Illness duration | -9.663 x 10-6 | 2.873 x 10-4 | -0.034 | 0.973 |
| Time | -1.414 x 10-2 | 4.404 x 10-3 | -3.210 | **0.0013** |
| Duration of untreated psychosis | 1.062 x 10-3 | 2.041 x 10-3 | 0.520 | 0.603 |
| Time: Duration of untreated psychosis | -8.072 x 10-5 | 1.653 x 10-4 | -0.428 | 0.669 |

**Supplementary Figures**

**Supplementary Figure 1** The receiver operating characteristic (ROC) curve for binary classification



**Supplementary Figure 2** Raw BDNF levels at each wave of assessment with 95% confidence intervals (CI)



**Supplementary Figure 3** Log-transformed BDNF levels at each wave of assessment with 95% confidence intervals (CI)

