**Forecasting prognostic trajectories with mismatch negativity in early psychosis**

**Supplementary Material**

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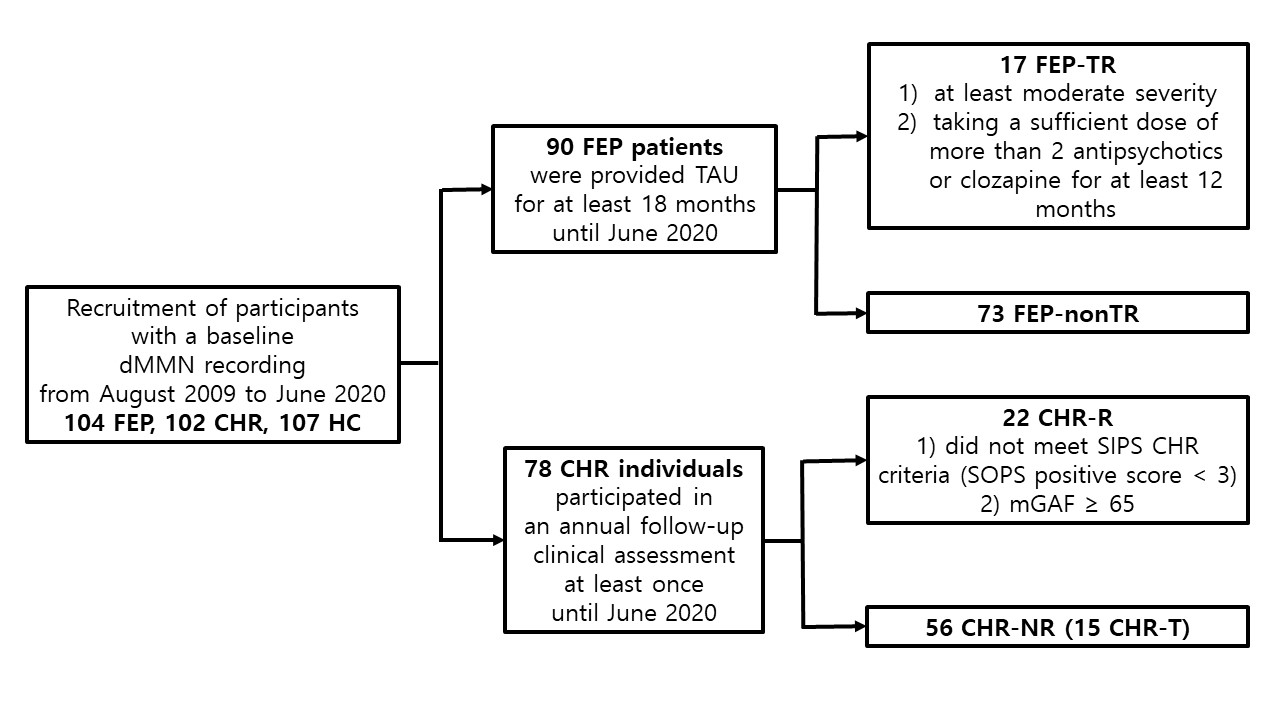
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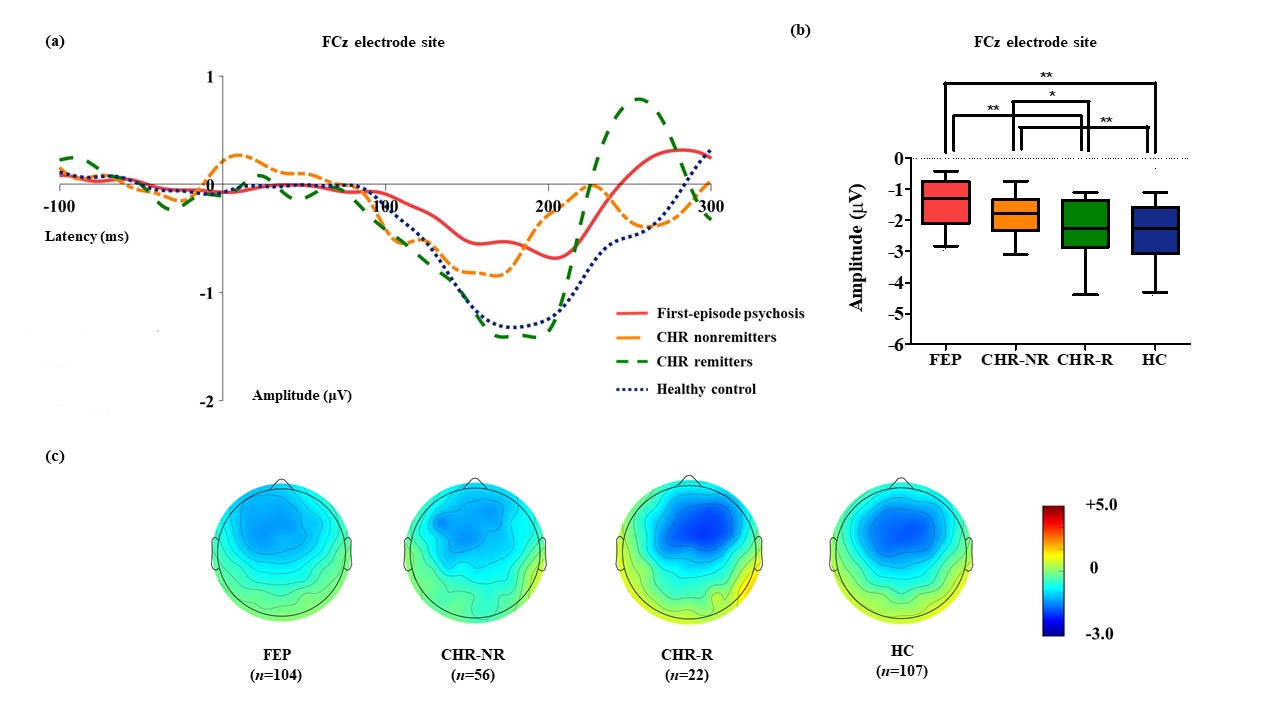
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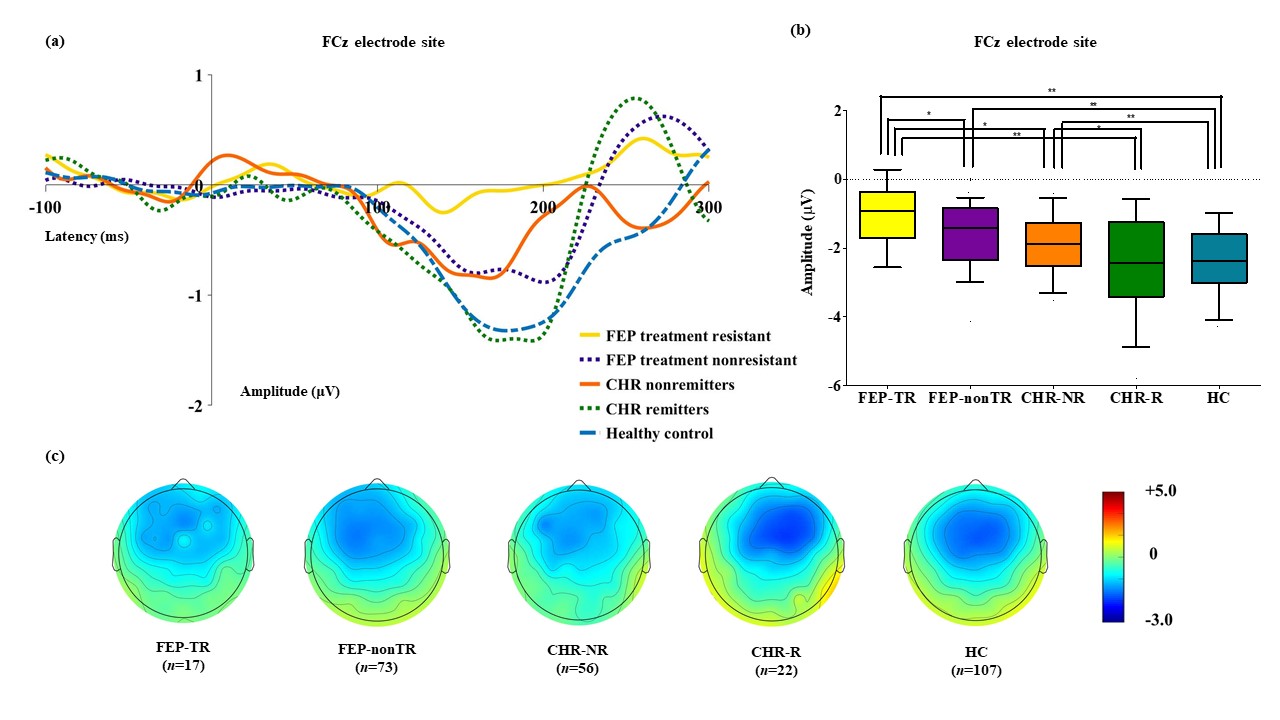
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**Figure S1.** Recruitment and clinical outcome assessment procedures. dMMN, duration deviant mismatch negativity; FEP, first-episode psychosis; CHR, clinical high risk; HC, healthy control; TAU, treatment as usual; TR, treatment resistant; nonTR, not treatment resistant; R, remitters; SIPS, Structured Interview for Prodromal Syndromes; SOPS, Scale of Prodromal Symptoms; mGAF, modified Global Assessment of Functioning; NR, nonremitters; T, transitioned to psychotic disorder.



**Figure S2.** (a) Grand-averaged duration deviant mismatch negativity (dMMN) waveforms across first-episode psychosis (FEP) patients, nonremitted individuals at clinical high risk (CHR-NR) for psychosis, remitted CHR subjects (CHR-R), and healthy controls (HCs) at the FCz electrode site. (b) dMMN amplitude across the groups at the FCz electrode site. Analysis of covariance with age as a covariate showed that dMMN amplitudes were significantly different across FEP patients, CHR-NR subjects, CHR-R subjects, and HCs (F = 14.435, p < 0.001). A *post hoc* simple contrast test revealed that dMMN amplitudes were similarly impaired in FEP patients and CHR-NR subjects compared to CHR-R subjects and HCs (FEP vs CHR-NR, p = 0.164; FEP vs CHR-R, p = 0.004; CHR-R vs HC, p = 0.441). Horizontal lines in groups indicate means, and vertical lines indicate 95% confidence intervals. \* indicates statistical significance at p < 0.05. \*\* indicates statistical significance at p < 0.005. (c) Two-dimensional topographic maps of dMMN in FEP patients, CHR-NR subjects, CHR-R subjects, and HCs. The colored bar with numbers indicates the dMMN amplitude (μV).



**Figure S3.** (a) Grand-averaged duration-deviant mismatch negativity (dMMN) waveforms across treatment-resistant first-episode psychosis (FEP-TR) patients, treatment-nonresistant FEP patients (FEP-nonTR), nonremitted individuals at clinical high risk (CHR-NR) for psychosis, remitted CHR subjects (CHR-R), and healthy controls (HCs) at the FCz electrode site. (b) dMMN amplitude across the groups at the FCz electrode site. Analysis of covariance with age as a covariate showed that dMMN amplitudes were significantly different across FEP-TR patients, FEP-nonTR patients, CHR-NR subjects, CHR-R subjects, and HCs (F = 10.169, p < 0.001). A *post hoc* simple contrast test revealed that dMMN amplitudes were smallest in FEP-TR patients (FEP-TR vs FEP-nonTR, p = 0.029; FEP-TR vs CHR-NR, p = 0.020; FEP-TR vs CHR-R, p = 0.001; FEP-TR vs HC, p < 0.001), intermediate in FEP-nonTR patients and CHR-NR subjects (FEP-nonTR vs CHR-NR, p = 0.718; FEP-nonTR vs CHR-R, p = 0.043; FEP-nonTR vs HC, p < 0.001), and largest in CHR-R subjects and HCs (CHR-R vs HC, p = 0.431). Horizontal lines in groups indicate means, and vertical lines indicate 95% confidence intervals. \* indicates statistical significance at p < 0.05. \*\* indicates statistical significance at p < 0.005. (c) Two-dimensional topographic maps of dMMN in FEP-TR patients, FEP-nonTR patients, CHR-NR subjects, CHR-R subjects, and HCs. The colored bar with numbers indicates the dMMN amplitude (μV).

**Table S1.** Demographic and clinical characteristics of patients with first-episode psychosis (FEP) who were and were not treatment resistant (FEP-TR and FEP-nonTR).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | FEP-TR | FEP-nonTR | Statistical analysisa | |
| Characteristics | (n = 17) | (n = 73) | χ2 or Z | P |
| Sex (male/female) | 8/9 | 29/44 | 0.306 | 0.580 |
| Handedness (right/left) | 15/2 | 69/4 | 0.875 | 0.349 |
| Age (years) | 23.2 ± 4.5 | 23.6 ± 5.2 | -0.201 | 0.840 |
| IQ | 96.8 ± 18.3 | 101.6 ± 13.5 | -1.516 | 0.129 |
| Education (years) | 14.2 ± 3.9 | 13.9 ± 2.3 | -0.404 | 0.686 |
| DOI (months) | 10.6 ± 5.9 | 6.9 ± 5.1 | -2.377 | 0.017\* |
| DUP (months) | 5.7 ± 5.4 | 4.0 ± 4.2 | -0.745 | 0.457 |
| *Baseline characteristics* |  |  |  |  |
| PANSS at baseline |  |  |  |  |
| Positive symptoms | 16.9 ± 5.0 | 14.5 ± 5.4 | -1.751 | 0.080 |
| Negative symptoms | 16.5 ± 6.3 | 16.1 ± 5.9 | -0.341 | 0.733 |
| General symptoms | 29.9 ± 9.2 | 31.7 ± 8.5 | -0.671 | 0.502 |
| mGAF at baseline | 46.8 ± 16.0 | 51.7 ± 12.7 | -1.181 | 0.237 |
| Medication use at baselineb |  |  |  |  |
| Antipsychotics | 17 (100.0) | 65 (89.0) | 2.045 | 0.153 |
| Antidepressants | 3 (17.6) | 8 (11.0) | 0.575 | 0.448 |
| Mood stabilizers | 2 (11.8) | 7 (9.6) | 1.540 | 0.215 |
| Anxiolytics | 11 (64.7) | 41 (56.2) | 0.412 | 0.521 |
| Antipsychotics dose at baselinec | 20.0 ± 12.1 | 11.4 ± 8.4 | -2.884 | 0.004\*\* |
| Diagnosis at baselined |  |  |  |  |
| Schizophrenia   /schizophreniform disorder | 16 (94.1) | 66 (90.4) | 0.234 | 0.629 |
| Schizoaffective disorder | 1 (5.9) | 7 (9.6) |
| *Follow-up characteristics* |  |  |  |  |
| Follow-up duration (months) | 39.4 ± 32.7 | 46.1 ± 34.2 | -0.734 | 0.465 |
| Medication use at last follow-upe |  |  |  |  |
| Clozapine | 10 (58.8) | 0 (0.0) | 48.309 | <0.001\*\* |
| Multiple antipsychotics | 12 (70.6) | 21 (28.8) | 10.385 | 0.001\*\* |
| Antipsychotics | 17 (100.0) | 70 (95.9) | 0.723 | 0.395 |
| Antipsychotics dose at last follow-upf | 24.0 ± 11.1 | 11.6 ± 8.6 | -4.095 | <0.001\*\* |

Abbreviations: IQ, intelligence quotient; DOI, duration of illness; DUP, duration of untreated psychosis; PANSS, Positive and Negative Syndrome Scale; mGAF, Modified Global Assessment of Functioning.

a Mann-Whitney U test, χ2 analysis or Fisher's exact test for categorical data.

b Number (percentage) of FEP patients who were prescribed each medication at baseline.

c Mean daily olanzapine equivalent dose prescribed at baseline.

d Number (percentage) of FEP patients who met each diagnosis at baseline when assessed with the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Axis I Disorders (SCID-I).

e Number (percentage) of FEP patients who were prescribed each medication at last follow-up.

f Mean olanzapine equivalent dose prescribed at the last follow-up.

Data are presented as the mean ± standard deviation.

\*, statistical significance at p < 0.05.

\*\*, statistical significance at p < 0.005.

**Table S2.** Demographic and clinical characteristics of subjects at clinical high risk (CHR) for psychosis who did and did not remit and those who did and did not transition to psychotic disorder (CHR-T and CHR-NT).

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | CHR remitters | CHR nonremitters | Statistical analysisa | | CHR-T | CHR-NT | Statistical analysisb | |
| Characteristics | (n = 22) | (n = 56) | χ2 or T | P | (n = 15) | (n = 63) | χ2 or Z | P |
| Sex (male/female) | 16/6 | 40/16 | 0.013 | 0.909 | 9/6 | 47/16 | 1.276 | 0.259 |
| Handedness (right/left) | 22/0 | 52/4 | 1.656 | 0.198 | 13/2 | 61/2 | 2.570 | 0.109 |
| Age (years) | 19.9 ± 3.1 | 20.5 ± 3.8 | -0.643 | 0.522 | 21.2 ± 4.6 | 20.1 ± 3.3 | -0.564 | 0.573 |
| IQ | 105.8 ± 14.6 | 104.3 ± 12.0 | 0.474 | 0.637 | 105.5 ± 11.2 | 104.5 ± 13.1 | -0.152 | 0.879 |
| Education (years) | 12.5 ± 1.4 | 12.6 ± 1.8 | -0.244 | 0.808 | 12.7 ± 2.0 | 12.5 ± 1.7 | -0.085 | 0.932 |
| DUPP (months) | 19.5 ± 22.9 | 17.4 ± 16.4 | 0.455 | 0.651 | 17.5 ± 16.4 | 18.1 ± 18.9 | -0.527 | 0.598 |
| Prodromal syndromesc |  |  |  |  |  |  |  |  |
| APS | 18 (81.8) | 46 (82.1) | 0.001 | 0.973 | 12 (80.0) | 52 (82.5) | 0.053 | 0.818 |
| BIPS | 1 (4.5) | 1 (1.8) | 0.482 | 0.488 | 1 (6.7) | 1 (1.6) | 1.251 | 0.263 |
| GRD | 3 (13.6) | 15 (26.8) | 1.538 | 0.215 | 4 (26.7) | 14 (22.2) | 0.135 | 0.713 |
| *Baseline characteristics* |  |  |  |  |  |  |  |  |
| SOPS at baseline |  |  |  |  |  |  |  |  |
| Positive symptoms | 9.3 ± 3.6 | 9.8 ± 3.8 | -0.476 | 0.636 | 11.5 ± 3.7 | 9.2 ± 3.6 | -2.018 | 0.044\* |
| Negative symptoms | 13.3 ± 7.1 | 14.3 ± 6.5 | -0.612 | 0.542 | 13.7 ± 6.2 | 14.1 ± 6.8 | -0.318 | 0.751 |
| Disorganization | 4.3 ± 2.6 | 4.6 ± 3.1 | -0.390 | 0.698 | 5.0 ± 2.2 | 4.4 ± 3.1 | -1.164 | 0.244 |
| General symptoms | 7.0 ± 3.8 | 7.3 ± 4.1 | -0.281 | 0.779 | 7.5 ± 4.7 | 7.1 ± 3.9 | -0.419 | 0.675 |
| mGAF at baseline | 50.3 ± 9.5 | 52.0 ± 9.0 | -0.769 | 0.444 | 52.2 ± 9.6 | 51.4 ± 9.0 | -0.337 | 0.736 |
| Medication use at baselined |  |  |  |  |  |  |  |  |
| Antipsychotics | 3 (13.6) | 7 (12.5) | 0.018 | 0.893 | 3 (20.0) | 7 (11.1) | 0.856 | 0.355 |
| Antidepressants | 4 (18.2) | 17 (30.4) | 1.190 | 0.275 | 4 (26.7) | 17 (30.0) | 0.001 | 0.980 |
| Mood stabilizers | 1 (4.5) | 1 (1.8) | 0.482 | 0.488 | 1 (6.7) | 1 (1.6) | 1.251 | 0.263 |
| Anxiolytics | 5 (22.7) | 17 (30.4) | 0.454 | 0.500 | 6 (40.0) | 16 (15.9) | 1.276 | 0.259 |
| *Follow-up characteristics* |  |  |  |  |  |  |  |  |
| Follow-up duration (months) | 46.0 ± 36.5 | 30.1 ± 27.9 | 1.843 | 0.075 | 41.7 ± 37.4 | 32.9 ± 29.5 | -0.767 | 0.443 |
| SOPS positive symptoms | 2.0 ± 2.0 | 9.1 ± 6.3 | -7.202 | <0.001\*\* | - | - | - | - |
| mGAF | 72.8 ± 6.2 | 56.9 ± 11.6 | 7.627 | <0.001\*\* | - | - | - | - |
| Medication use during follow-upe |  |  |  |  |  |  |  |  |
| Antipsychotics | 14 (63.6) | 48 (85.7) | 3.032 | 0.082 | - | - | - | - |
| Antidepressants | 15 (68.2) | 29 (51.8) | 2.180 | 0.140 | - | - | - | - |
| Mood stabilizers | 11 (50.0) | 30 (53.6) | 0.029 | 0.866 | - | - | - | - |
| Anxiolytics | 8 (36.4) | 28 (50.0) | 1.001 | 0.317 | - | - | - | - |
| Antipsychotic dosef | 2.1 ± 2.2 | 5.3 ± 4.8 | -3.910 | <0.001\*\* | - | - | - | - |

Abbreviations: IQ, intelligence quotient; DUPP, duration of untreated prodromal psychosis; APS, attenuated positive symptom; BIPS, brief intermittent psychotic symptom; GRD, genetic risk and deterioration; SOPS, Scale of Prodromal Symptoms; mGAF, modified Global Assessment of Functioning.

a Independent t-test or Welch's t-test if the variances were not equal; χ2 analysis or Fisher's exact test for categorical data.

b Mann-Whitney U test; χ2 analysis or Fisher's exact test for categorical data.

c Prodromal syndromes for APS, BIPS, and GRD are not mutually exclusive according to the SIPS criteria.

d Number (percentage) of CHR subjects who were prescribed each medication at baseline.

e Number (percentage) of CHR subjects who were prescribed each medication during the follow-up period.

f Mean daily olanzapine equivalent dose prescribed during the follow-up period.

Data are presented as the mean ± standard deviation.

\*, statistical significance at p < 0.05.

\*\*, statistical significance at p < 0.005.

**Table S3.** Demographic and clinical characteristics of patients with first-episode psychosis (FEP) who were or were not assessed for treatment resistance (FEP-A and FEP-NA).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | FEP-A | FEP-NA | Statistical analysisa | |
| Characteristics | (n = 90) | (n = 14) | χ2 or Z | P |
| Sex (male/female) | 37/53 | 4/10 | 0.798 | 0.372 |
| Handedness (right/left) | 84/6 | 13/1 | 0.004 | 0.947 |
| Age (years) | 23.5 ± 5.0 | 22.6 ± 3.0 | -0.573 | 0.567 |
| IQ | 100.7 ± 14.5 | 97.3 ± 15.6 | -0.777 | 0.437 |
| Education (years) | 13.9 ± 2.7 | 14.4 ± 2.1 | -0.992 | 0.321 |
| DOI (months) | 7.6 ± 5.4 | 12.0 ± 9.7 | -1.417 | 0.156 |
| DUP (months) | 4.3 ± 4.5 | 6.5 ± 5.8 | -1.685 | 0.092 |
| PANSS |  |  |  |  |
| Positive symptoms | 14.9 ± 5.3 | 16.8 ± 6.4 | -0.926 | 0.355 |
| Negative symptoms | 16.1 ± 6.0 | 15.7 ± 6.8 | -0.386 | 0.699 |
| General symptoms | 31.4 ± 8.6 | 34.6 ± 11.7 | -0.724 | 0.469 |
| mGAF | 50.7 ± 13.4 | 50.8 ± 10.9 | -0.014 | 0.989 |
| Medication useb |  |  |  |  |
| Antipsychotics | 82 (91.1) | 13 (92.9) | 0.047 | 0.829 |
| Antidepressants | 11 (12.2) | 1 (7.1) | 0.306 | 0.580 |
| Mood stabilizers | 5 (5.6) | 5 (35.7) | 12.680 | <0.001\*\* |
| Anxiolytics | 52 (57.8) | 9 (64.3) | 0.212 | 0.646 |

Abbreviations: IQ, intelligence quotient; DOI, duration of illness; DUP, duration of untreated psychosis; PANSS, Positive and Negative Syndrome Scale; mGAF, modified Global Assessment of Functioning.

a Mann-Whitney U test; χ2 analysis or Fisher's exact test for categorical data.

b Number (percentage) of FEP patients who were prescribed each medication at baseline.

Data are presented as the mean ± standard deviation.

\*\*, statistical significance at p < 0.005.

**Table S4.** Demographic and clinical characteristics of subjects at clinical high risk (CHR) for psychosis who did and did not participate in the follow-up assessment (CHR-F and CHR-NF).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | CHR-F | CHR-NF | Statistical analysisa | |
| Characteristics | (n = 78) | (n = 24) | χ2 or T | P |
| Sex (male/female) | 56/22 | 19/5 | 0.512 | 0.474 |
| Handedness (right/left) | 74/4 | 23/1 | 0.036 | 0.849 |
| Age (years) | 20.3 ± 3.6 | 20.0 ± 4.0 | 0.376 | 0.708 |
| IQ | 104.7 ± 12.7 | 108.8 ± 15.0 | -1.318 | 0.191 |
| Education (years) | 12.6 ± 1.7 | 12.3 ± 2.1 | 0.765 | 0.446 |
| DUPP (months) | 17.9 ± 18.3 | 17.3 ± 16.3 | 0.166 | 0.868 |
| SOPS |  |  |  |  |
| Positive symptoms | 9.6 ± 3.7 | 10.2 ± 3.2 | -0.667 | 0.506 |
| Negative symptoms | 14.0 ± 6.7 | 13.2 ± 6.8 | 0.541 | 0.589 |
| Disorganization | 4.5 ± 2.9 | 3.5 ± 2.9 | 1.445 | 0.152 |
| General symptoms | 7.2 ± 4.0 | 6.0 ± 3.4 | 1.377 | 0.171 |
| mGAF | 51.5 ± 9.0 | 58.9 ± 9.3 | -3.442 | 0.001\*\* |
| Medication useb |  |  |  |  |
| Antipsychotics | 10 (12.8) | 4 (16.7) | 0.229 | 0.632 |
| Antidepressants | 21 (26.9) | 4 (16.7) | 1.043 | 0.307 |
| Mood stabilizers | 2 (2.6) | 1 (4.2) | 0.165 | 0.684 |
| Anxiolytics | 22 (28.2) | 4 (16.7) | 1.287 | 0.257 |

Abbreviations: IQ, intelligence quotient; DUPP, duration of untreated prodromal psychosis; SOPS, Scale of Prodromal Symptoms; mGAF, modified Global Assessment of Functioning.

a Independent t-test or Welch's t-test if the variances were not equal, χ2 analysis or Fisher's exact test for categorical data.

b Number (percentage) of CHR subjects who were prescribed each medication at baseline.

Data are given as the mean ± standard deviation.

\*\*, statistical significance at p < 0.005.

**Table S5.** Mismatch negativity (MMN) characteristics of subjects at clinical high risk (CHR) for psychosis who did and did not transition to psychotic disorder (CHR-T and CHR-NT).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | CHR-T | CHR-NT | Statistical analysisa | |
|  | (n = 15) | (n = 63) | Z | P |
| *Peak amplitudes (μV)* |  |  |  |  |
| FCz electrode site | -2.1 ± 0.8 | -1.9 ± 1.0 | -1.084 | 0.278 |
| *Peak latencies (ms)* |  |  |  |  |
| FCz electrode site | 184.6 ± 33.8 | 191.1 ± 29.8 | -0.488 | 0.625 |
| Number of epochs for  deviant stimuli | 184.9 ± 33.6 | 194.6 ± 23.6 | -0.761 | 0.447 |

a Mann-Whitney U test.

Data are presented as the mean ± standard deviation.

**Table S6.** Mismatch negativity (MMN) characteristics of patients with first-episode psychosis (FEP) who were and were not assessed for treatment resistance (FEP-A and FEP-NA).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | FEP-A | FEP-NA | Statistical analysisa | |
|  | (n = 90) | (n = 14) | Z | P |
| *Peak amplitudes (μV)* |  |  |  |  |
| FCz electrode site | -1.6 ± 1.1 | -1.1 ± 0.6 | -1.514 | 0.130 |
| *Peak latencies (ms)* |  |  |  |  |
| FCz electrode site | 178.4 ± 30.2 | 227.4 ± 21.6 | -4.801 | <0.001\*\* |
| Number of epochs for  deviant stimuli | 192.7 ± 25.9 | 192.3 ± 24.6 | -0.500 | 0.617 |

a Mann-Whitney U test.

Data are presented as the mean ± standard deviation.

\*\*, statistical significance at p < 0.005.

**Table S7.** Mismatch negativity (MMN) characteristics of subjects at clinical high risk (CHR) for psychosis who did and did not participate in the follow-up assessment (CHR-F and CHR-NF).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | CHR-F | CHR-NF | Statistical analysisa | |
|  | (n = 78) | (n = 24) | T | P |
| *Peak amplitudes (μV)* |  |  |  |  |
| FCz electrode site | -2.0 ± 1.0 | -2.2 ± 1.1 | 1.065 | 0.290 |
| *Peak latencies (ms)* |  |  |  |  |
| FCz electrode site | 189.9 ± 30.5 | 199.5 ± 27.5 | -1.386 | 0.169 |
| Number of epochs for  deviant stimuli | 192.7 ± 25.9 | 192.3 ± 24.6 | 0.060 | 0.952 |

a Independent t-test or Welch's t-test if the variances were not equal.

Data are presented as the mean ± standard deviation.