

Appendix 1 to Toll A, Blanco-Hinojo L, Bergé D, et al. Multidimensional predictors of negative symptoms in antipsychotic-naive first-episode psychosis. *J Psychiatry Neurosci* 2022. doi: 10.1503/jpn.210138  
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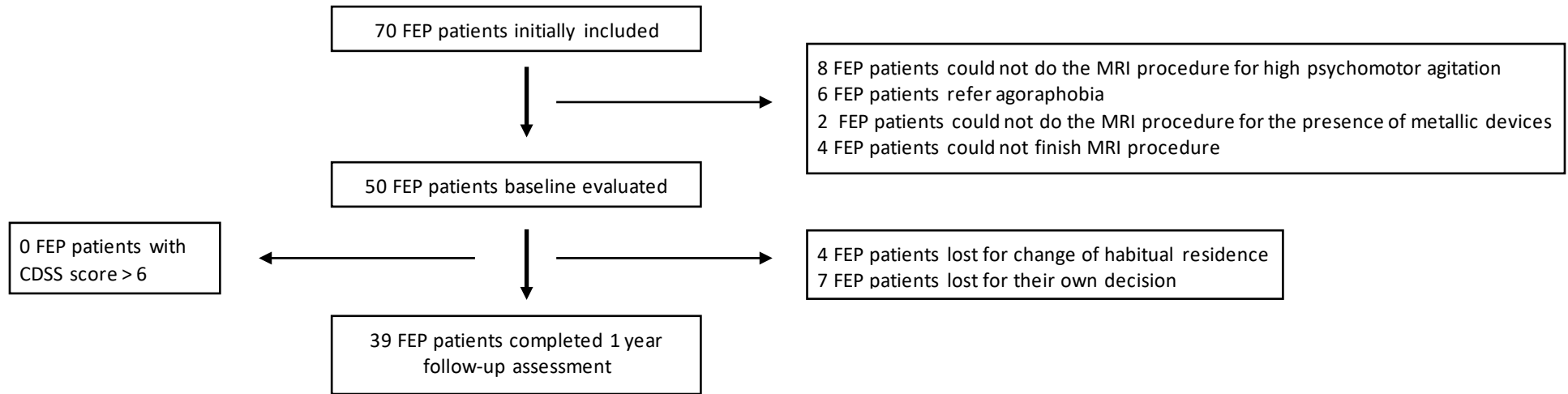
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**Supplementary Figure 1.** Study patient flowchart.



Abbreviations: FEP = First Episode Psychosis, MRI = Magnetic Resonance Imaging, CDSS = Calgary Depression Scale for Schizophrenia

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**Supplementary Table 1.** Sociodemographic, clinical and volumetric differences between FEP patients screened, evaluated at baseline and evaluated at 1 year follow - up.

	Screened (N=70)	Baseline (N=50)	1 year follow -up (N=39)	p
Age (M, IQR)	23.5 (23.68– 26.29)	26 (24 - 30.25)	24 (20 - 28)	0.985
Sex (N, %woman)	28 (40)	22 (44)	18 (47)	0.352
DUP (M, IQR)	124.74 (8 - 198)	31 (8 - 115)	59 (11 - 151)	0.152
Cannabis use (N, %users)	40 (57.2)	29 (58)	20 (51.3)	0.430
Tobacco use (M, IQR)	4.7 (0-14)	4.5 (0 - 14)	4 (0 - 14)	0.377
BDNF, baseline	39.58 (39.42)	45.27 (27.14)	48.48 (29.41)	0.945
PANSS P score, baseline	28 (6.72)	24.88 (6.74)	25.38 (6.42)	0.884
PANSS N score, baseline	21.37 (15.72)	16.86 (6.65)	17.31 (6.87)	0.882
PANSS GP score, baseline	45.56 (9.21)	43.68 (8.27)	43.85 (8.48)	0.131
PANSS T score, baseline	91.71 (18.1)	85.24 (15.76)	86.31 (15.87)	0.422
CDSS score, baseline	1.32 (2.05)	1.22 (2.02)	1.18 (2.08)	0.422
GAF score, baseline	31.42 (11.89)	29.7 (8.89)	29.23 (7.66)	0.250
Relative left hippocampus in mL		2.64 (0.27)	2.65 (0.25)	0.984
Relative right hippocampus in mL		2.78 (0.31)	2.77 (0.28)	0.982
Relative left amygdala in mL		1.01 (0.14)	1.01 (0.12)	0.179
Relative right amygdala in mL		1.14 (0.15)	1.22 (0.14)	0.392

\*All values given as means with SD, unless otherwise indicated.

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Abbreviations: N = Sample size, M = Median, IQR = Interquartile range, DUP = Duration Untreated Psychosis, BDNF = Brain derived neurotrophic factor, PANSS P = Positive and Negative Syndrome Scale positive, PANSS N = Positive and Negative Syndrome Scale negative, PANSS GP = Positive and Negative Syndrome Scale general pathology, PANSS T = Positive and Negative Syndrome Scale total, CDSS = Calgary Depression Scale for Schizophrenia, GAF = Global Assessment of Functioning, mL = milliliters.

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**Supplementary Table 2.** Sociodemographic, clinical and volumetric differences between completers and non - completers patients at baseline.

	Non-completers (N=11)	Completers (N=39)	p
Age (M, IQR)	25 (22 - 28)	24 (20 - 28)	0.172
Sex (N, %woman)	4 (38%)	18 (47%)	0.414
DUP (M, IQR)	15 (4 - 60)	59 (11 - 151)	0.441
Cannabis use (N, %users)	9 (81.8%)	20 (51.3%)	0.092
Tobacco use (M, IQR)	7 (1 - 28)	4 (0 - 14)	0.789
BDNF, baseline	33.87 (11.86)	48.48 (29.41)	0.116
PANSS P score, baseline	23.09 (7.54)	25.38 (6.42)	0.324
PANSS N score, baseline	15.27 (5.79)	17.31 (6.87)	0.375
PANSS GP score, baseline	43.09 (7.83)	43.85 (8.48)	0.792
PANSS T score, baseline	81.45 (15.46)	86.31 (15.87)	0.372
CDSS score, baseline	1.36 (1.91)	1.18 (2.08)	0.793
GAF score, baseline	31.36 (12.67)	29.23 (7.66)	0.488
Relative left hippocampus in mL	2.74 (0.35)	2.65 (0.25)	0.148
Relative right hippocampus in mL	2.83 (0.36)	2.77 (0.28)	0.361
Relative left amygdala in mL	1.08 (0.16)	1.01 (0.12)	0.221
Relative right amygdala in mL	1.24 (0.15)	1.22 (0.14)	0.122

\*All values given as means with SD, unless otherwise indicated.

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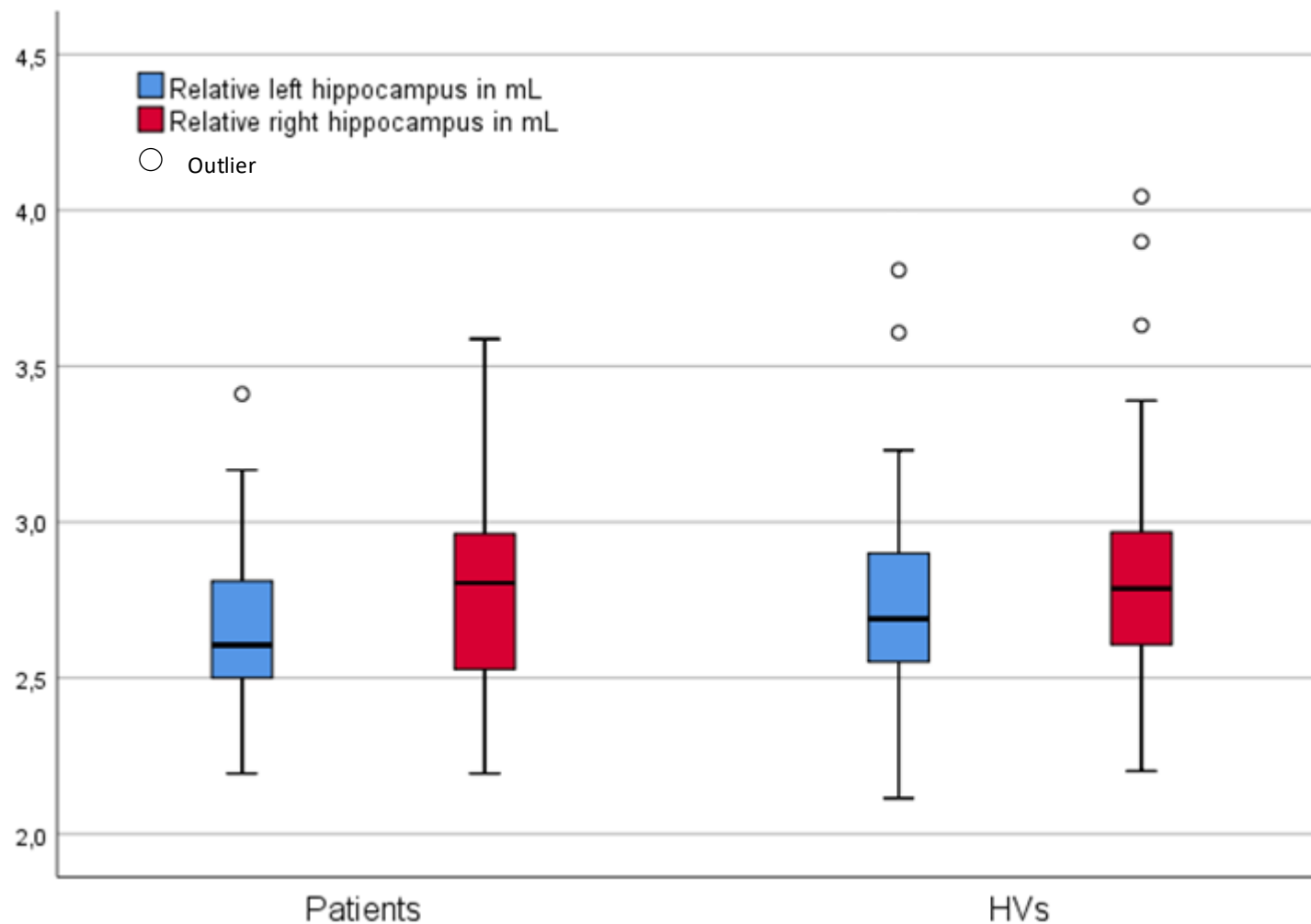
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**Supplementary Figure 2.** Relative left/right hippocampus volume (in mL) in FEP patients and HVs at baseline (box plot).

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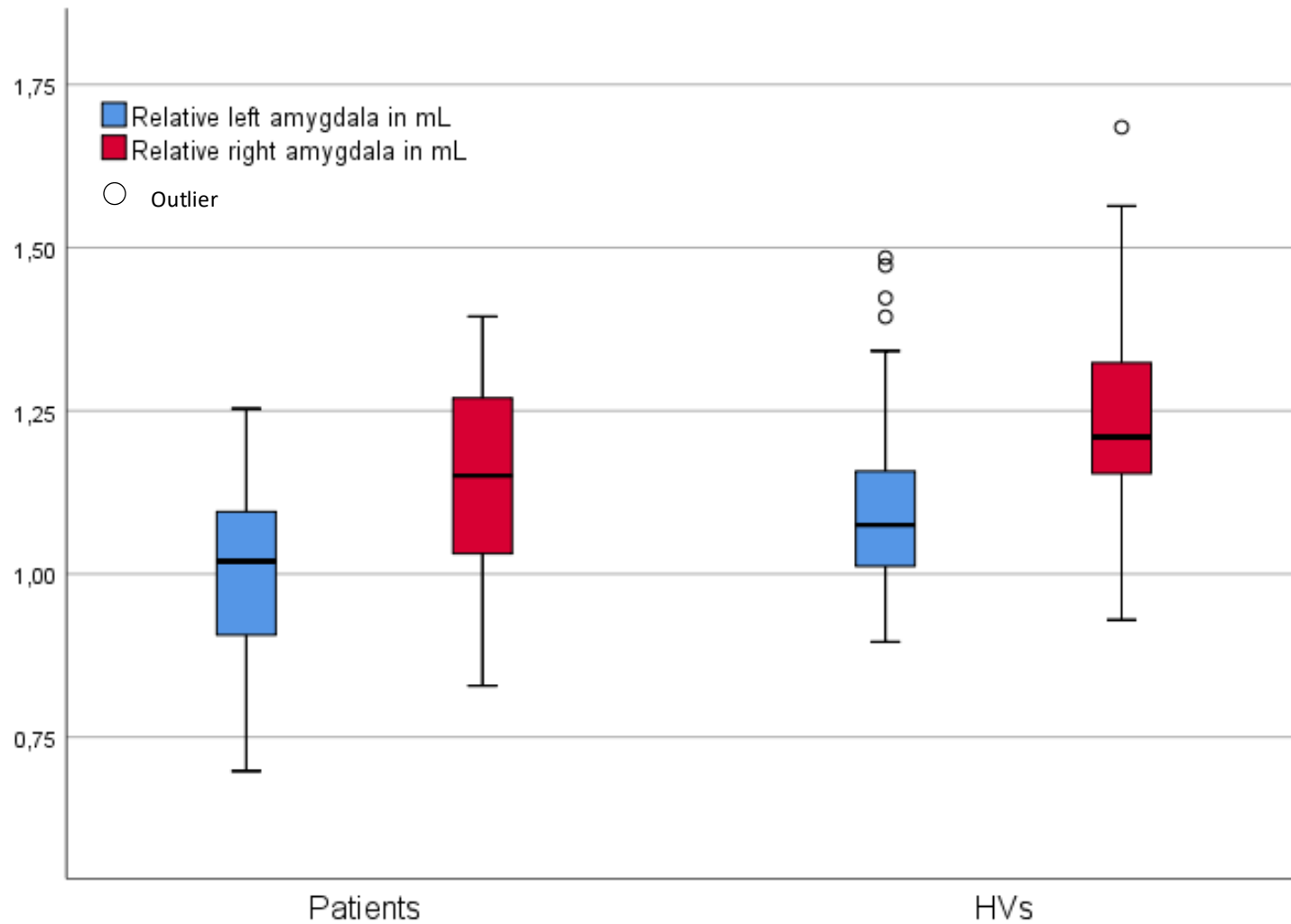
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**Supplementary Figure 3.** Relative left/right amygdala volume (in mL) in FEP patients and HVs at baseline (box plot).

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**Supplementary Table 3.** Univariate analysis: association between study variables and PANSS-N subitems at one-year follow-up.

	N1	p	N2	p	N3	p	N4	p	N5	p	N6	p	N7	p
<b>Age</b>	-0.21 <sup>a</sup>	0.187	-0.28 <sup>a</sup>	0.067	-0.27 <sup>a</sup>	0.077	-0.32 <sup>a</sup>	<b>0.038</b>	-0.37 <sup>a</sup>	<b>0.015</b>	-0.21 <sup>a</sup>	0.179	-0.16 <sup>a</sup>	0.322
<b>Sex</b>	0.88 <sup>b</sup>	0.387	-0.33 <sup>b</sup>	0.747	-0.31 <sup>b</sup>	0.755	0.36 <sup>b</sup>	0.528	1.56 <sup>b</sup>	0.127	-0.87 <sup>b</sup>	0.392	2.96 <sup>b</sup>	<b>0.005</b>
Male (m, SD)	2.17 (1.21)		2.38 (1.44)		2.13 (1.26)		2.79 (1.72)		3.17 (1.27)		1.83 (1.34)		2.38 (1.17)	
Female (m, SD)	1.84 (1.21)		2.53 (1.61)		2.26 (1.63)		2.47 (1.51)		2.58 (1.17)		2.21 (1.51)		1.47 (0.69)	
<b>Cannabis use</b>	1.69 <sup>b</sup>	0.098	0.85 <sup>b</sup>	0.403	0.49 <sup>b</sup>	0.629	0.56 <sup>b</sup>	0.580	1.45 <sup>b</sup>	0.154	0.64 <sup>b</sup>	0.523	-0.7 <sup>b</sup>	0.480
No user (m, SD)	2.35 (1.35)		2.65 (1.42)		2.30 (1.45)		2.80 (1.58)		3.20 (1.01)		2.15 (1.42)		1.85 (0.93)	
User (m, SD)	1.74 (1.01)		2.26 (1.57)		2.09 (1.41)		2.52 (1.68)		2.65 (1.41)		1.87 (1.42)		2.09 (1.21)	
<b>Tobacco use</b>	-0.18 <sup>a</sup>	0.246	-0.05 <sup>a</sup>	0.773	-0.09 <sup>a</sup>	0.531	-0.07 <sup>a</sup>	0.663	-0.31 <sup>a</sup>	<b>0.049</b>	-0.21 <sup>a</sup>	0.185	-0.03 <sup>a</sup>	0.860
<b>DUP</b>	0.04 <sup>a</sup>	0.781	0.26 <sup>a</sup>	0.098	0.15 <sup>a</sup>	0.333	0.11 <sup>a</sup>	0.512	-0.07 <sup>a</sup>	0.656	0.11 <sup>a</sup>	0.471	0.38 <sup>a</sup>	<b>0.012</b>
<b>Chlorpromazine equivalents 1 year</b>	-0.03 <sup>a</sup>	0.861	0.11 <sup>a</sup>	0.491	0.01 <sup>a</sup>	0.984	0.06 <sup>a</sup>	0.685	-0.12 <sup>a</sup>	0.444	0.02 <sup>a</sup>	0.892	0.22 <sup>a</sup>	0.154
<b>PANSS N score, baseline</b>	0.79 <sup>a</sup>	<b>0.000</b>	0.83 <sup>a</sup>	<b>0.000</b>	0.79 <sup>a</sup>	<b>0.000</b>	0.85 <sup>a</sup>	<b>0.000</b>	0.42 <sup>a</sup>	<b>0.005</b>	0.72 <sup>a</sup>	<b>0.000</b>	0.43 <sup>a</sup>	<b>0.004</b>
<b>PANSS P score, baseline</b>	-0.15 <sup>a</sup>	0.335	-0.05 <sup>a</sup>	0.734	0.01 <sup>a</sup>	0.985	-0.02 <sup>a</sup>	0.882	0.03 <sup>a</sup>	0.863	-0.09 <sup>a</sup>	0.540	0.12 <sup>a</sup>	0.444
<b>CDSS score, baseline</b>	0.28 <sup>a</sup>	0.069	0.35 <sup>a</sup>	<b>0.020</b>	0.15 <sup>a</sup>	0.352	0.23 <sup>a</sup>	0.131	0.12 <sup>a</sup>	0.454	0.05 <sup>a</sup>	0.769	-0.07 <sup>a</sup>	0.664
<b>GAF score, baseline</b>	0.01 <sup>a</sup>	0.973	-0.05 <sup>a</sup>	0.769	-0.12 <sup>a</sup>	0.431	-0.11 <sup>a</sup>	0.481	-0.23 <sup>a</sup>	0.131	-0.18 <sup>a</sup>	0.224	-0.15 <sup>a</sup>	0.331
<b>BDNF baseline</b>	-0.06 <sup>a</sup>	0.705	-0.04 <sup>a</sup>	0.807	-0.22 <sup>a</sup>	0.152	-0.13 <sup>a</sup>	0.422	0.13 <sup>a</sup>	0.393	-0.09 <sup>a</sup>	0.541	0.05 <sup>a</sup>	0.732
<b>Relative left hippocampus</b>	0.07 <sup>a</sup>	0.659	0.19 <sup>a</sup>	0.219	0.12 <sup>a</sup>	0.430	0.13 <sup>a</sup>	0.422	-0.09 <sup>a</sup>	0.542	0.11 <sup>a</sup>	0.516	0.25 <sup>a</sup>	0.108
<b>Relative right hippocampus</b>	0.15 <sup>a</sup>	0.339	0.14 <sup>a</sup>	0.386	0.14 <sup>a</sup>	0.377	0.18 <sup>a</sup>	0.250	-0.05 <sup>a</sup>	0.764	0.07 <sup>a</sup>	0.679	0.22 <sup>a</sup>	0.159
<b>Relative left amygdala</b>	0.09 <sup>a</sup>	0.542	0.01 <sup>a</sup>	0.973	0.01 <sup>a</sup>	0.945	-0.01 <sup>a</sup>	0.984	-0.06 <sup>a</sup>	0.691	0.02 <sup>a</sup>	0.911	0.03 <sup>a</sup>	0.832
<b>Relative right amygdala</b>	0.09 <sup>a</sup>	0.587	-0.01 <sup>a</sup>	0.983	-0.02 <sup>a</sup>	0.884	-0.01 <sup>a</sup>	0.982	-0.09 <sup>a</sup>	0.531	0.09 <sup>a</sup>	0.561	-0.02 <sup>a</sup>	0.897

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Abbreviations: N1 = Blunted Affect, N2 = Emotional Withdrawal, N3 = Poor Rapport, N4 = Passive Social Withdrawal, N5 = Difficulty in Abstract Thinking, N6 = Lack of spontaneity, N7 = Stereotyped Thinking, m = mean, SD = Standard deviation, PANSS-N = Positive and Negative Syndrome Scale negative, GAF = Global Assessment of Functioning, PNS = Persistent negative symptoms, DUP = Duration untreated psychosis, PANSS-P = Positive and Negative Syndrome Scale positive, CDSS = Calgary Depression Scale for Schizophrenia, BDNF = Brain derived neurotrophic factor. <sup>a</sup> Pearson Correlation, <sup>b</sup> t Student test

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**Supplementary Table 4.** Robust regression of predictors of PANSS negative at 1 year follow - up.

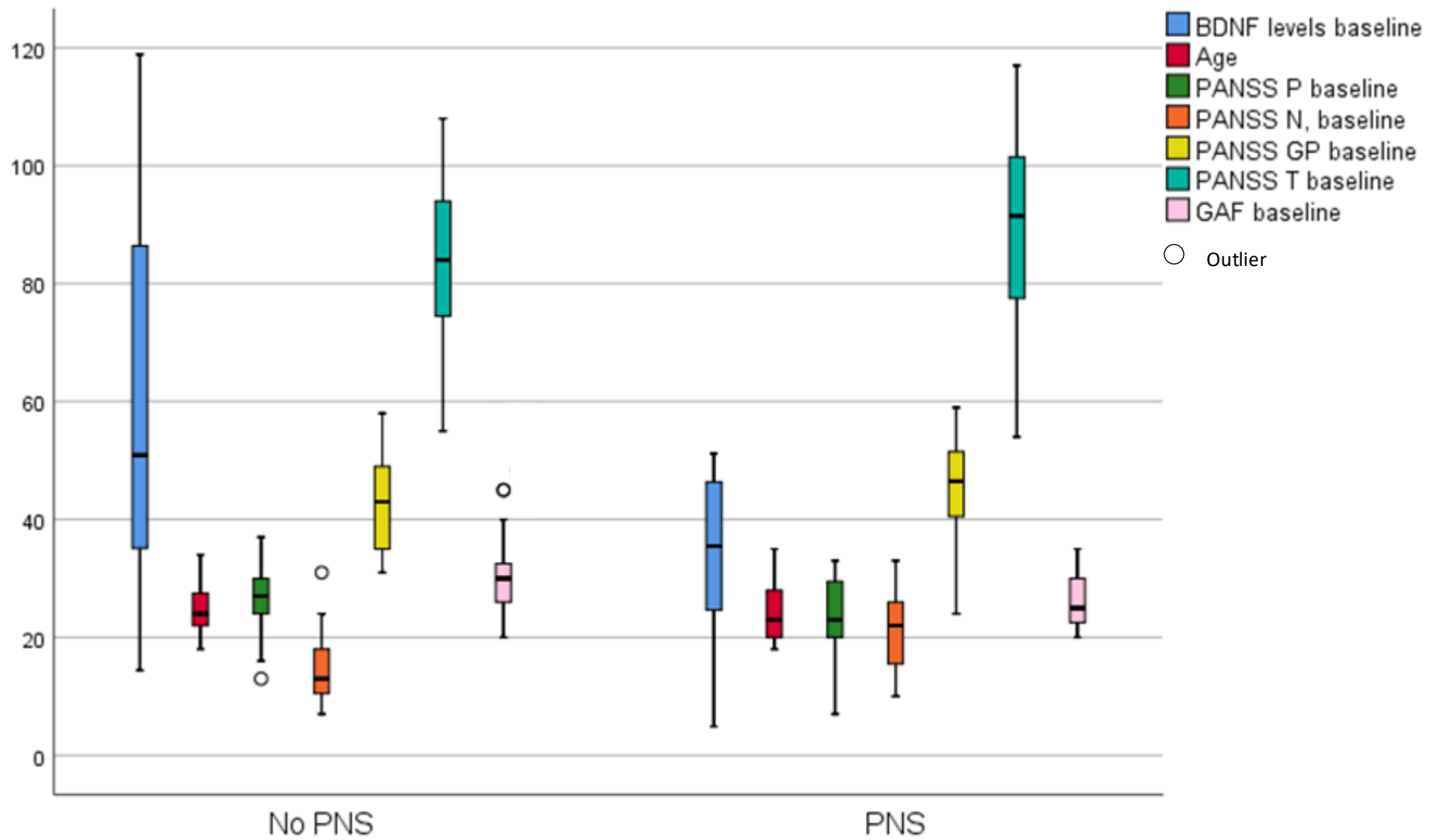
Predictor	$\beta$	95% CI	p
PANSS N score, baseline	0.34	0.11; 0.58	<b>0.006</b>
BDNF at baseline	-0.07	-0.13; -0.01	<b>0.015</b>
Relative left amygdala volume in mL	-0.01	-0.02; -0.00	<b>0.003</b>

Abbreviations: CI = Confidence interval, PANSS-N = Positive and Negative Syndrome Scale negative, BDNF = Brain derived neurotrophic factor, mL = milliliters,

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**Supplementary Figure 4.** Clinical variables and BDNF levels at baseline in FEP patients with and without PNS (box plot).

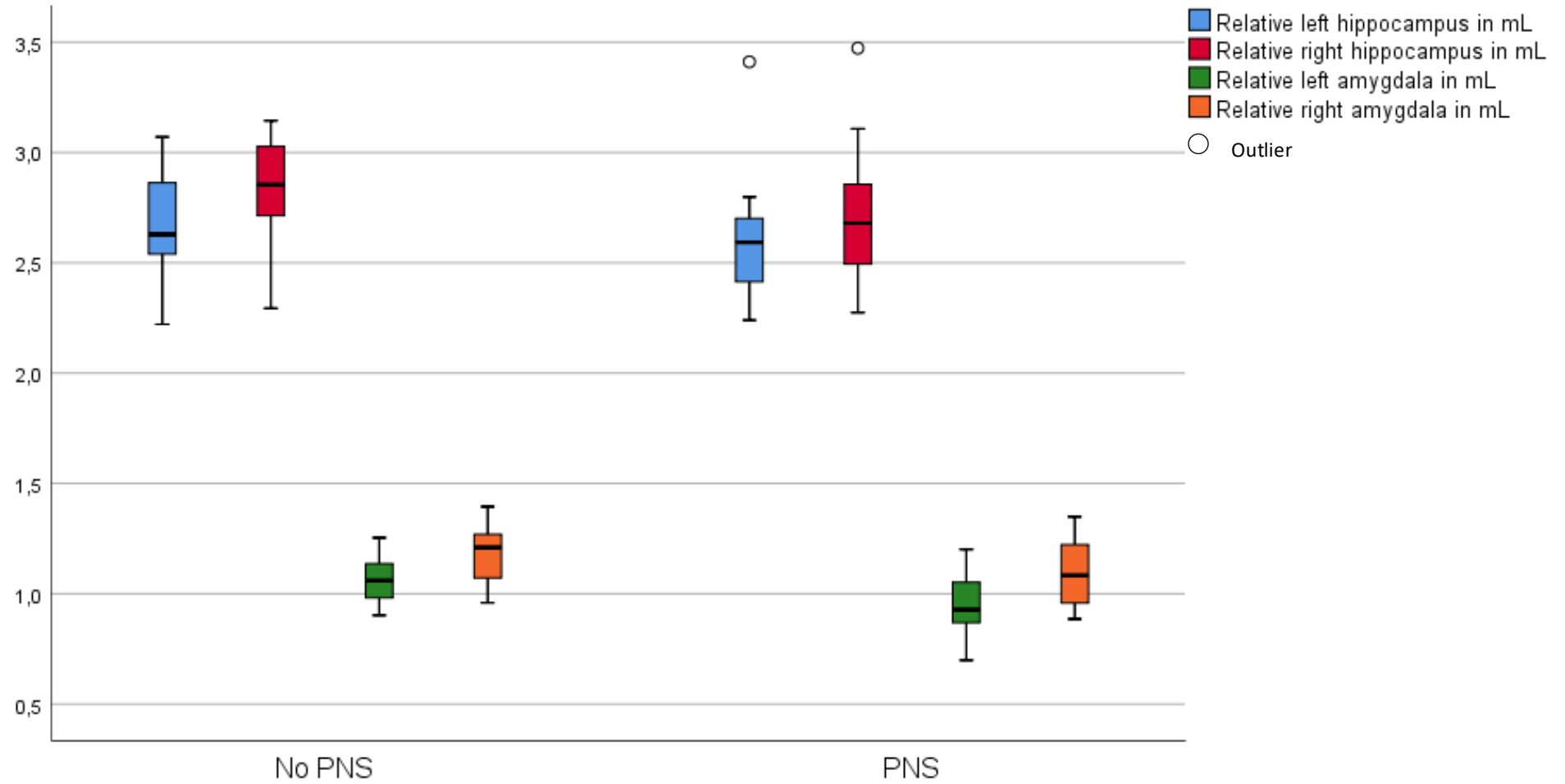


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**Supplementary Figure 5.** Relative left/right hippocampus and amygdala volume (in mL) in FEP patients with and without PNS (box plot).

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**Supplementary Table 5.** Multivariate analysis of predictors of Persistent Negative Symptoms (PNS) at one-year follow-up with chlorpromazine equivalents.

Predictor	aOR (95% CI)	p
Relative left amygdala volume in mL	0.99 (0.98; 0.99)	<b>0.012</b>
BDNF at baseline	0.92 (0.87; 0.98)	<b>0.012</b>
Chlorpromazine equivalents 1 year	0.99 (0.99; 1.1)	0.333

\*  $r^2$  Nagelkerke = 0.554

Abbreviations: aOR = adjusted odds ratio, CI = Confidence interval, BDNF = Brain derived neurotrophic factor,  $r^2$  = determination coefficient.

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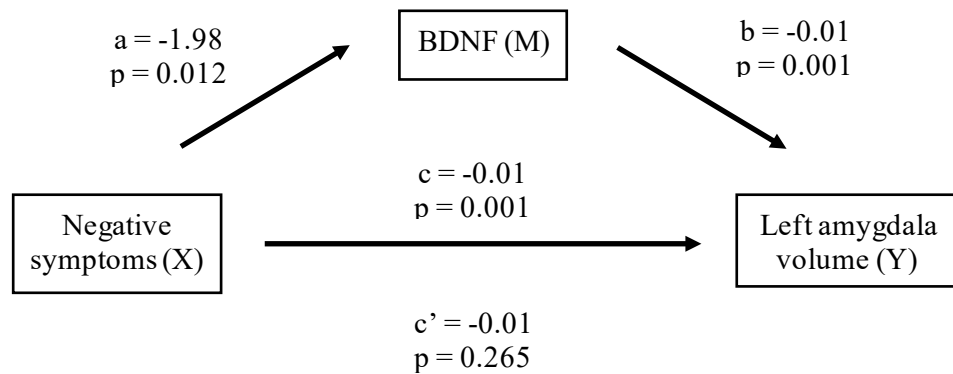
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**Supplementary Figure 6.** Mediation analysis between negative symptoms at 1 year - follow up, BDNF at baseline and relative left amygdala volume at baseline in FEP patients.



Negative symptoms → BDNF → Left amygdala volume  
 Indirect effect  
 $B = 0.01, SE = 0.01, 95\% CI (-0.01, 0.01)$

Abbreviations: X = dependent variable, M = mediation variable, Y = independent variable, CI = Confidence interval, SE = standard error, BDNF = Brain derived neurotrophic factor, B = regression coefficient, a = X-M regression coefficient; b = M-Y regression coefficient; C = X-Y regression coefficient, c' = X-M-Y regression coefficient