## Supplementary materials and methods

### Assessment Measures:

Psychopathology in individuals at CHR was measured with the SIPS and the SOPS (Miller *et al.*, 2003). In the schizophrenia group, the severity of psychotic symptoms was measured with the PANSS (Kay *et al.*, 1987). Other measures used were the Global Assessment of Functioning (GAF) (Endicott *et al.*, 1976), the Zung Self-rating Anxiety Scale (SAS) (Zung, 1971) and the Social Interaction Anxiety Scale (SIAS) (Mattick and Clarke, 1998) to evaluate general anxiety and social anxiety, respectively, as well as the Recent Life Events questionnaire (RLE) (Brugha *et al.*, 1985) and the Trier Inventory of the Assessment of Chronic Stress (TICS) (Schlotz *et al.*, 2004) to assess the impact of recent stressful life events and chronic stress, respectively.

### Image acquisition and reconstruction:

**MRI acquisition.** A proton density-weighted brain MRI scan (TE=17, TR=6000, FOV=22 cm, matrix=256×256, slice thickness=2 mm, number of excitations=2) was obtained for each subject using a 1.5T Signa scanner (General Electric Medical Systems, Milwaukee, WI, USA) for 32 participants (10 HV, 9 CHR, 13 SCZ). For the remaining 9 participants, PD MRI images (TE=Min full, TR=6000, FOV=22 cm, slice thickness=2 mm, and number of acquisitions=1) were acquired using a 3T MR-750 scanner (General Electric Medical Systems). MRI images were used for the anatomical delineation of ROIs and the quantification of PET images. As we previously reported for [$^{18}$F]FEPPA (Kenk *et al.*, 2015; Suridjan *et al.*, 2015; Hafizi *et al.*, 2017), differences in MRI acquisition parameters and scanner used did not have a significant effect on [$^{11}$C]FLB457 outcome measures (data not shown).

**PET acquisition.** PET data were acquired using a high-resolution PET-CT scanner, Siemens-Biograph HiRez XVI (Siemens Molecular Imaging, Knoxville, TN, USA) which measures radioactivity in 81 brain sections with a thickness of 2.0 mm each. A custom-fitted thermoplastic mask was made for each subject and used with a head fixation system during PET acquisition to minimize head movement.

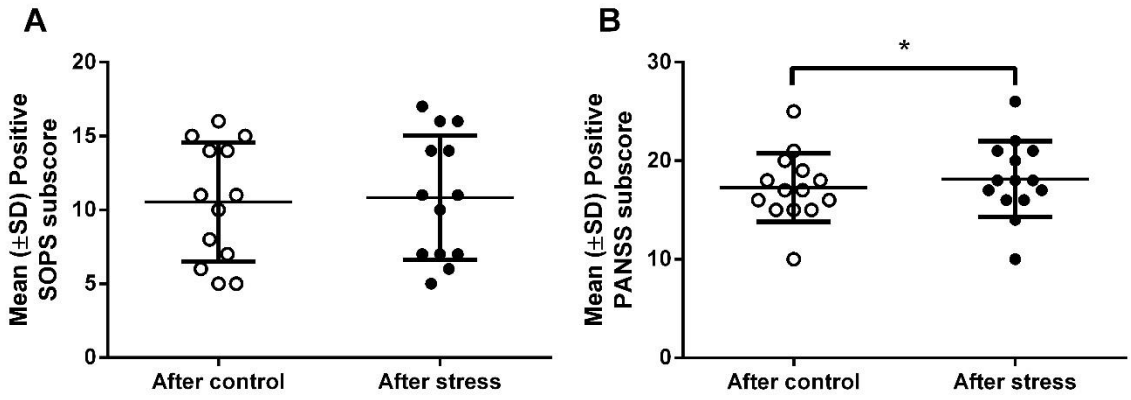
## Statistical analysis:

Demographic measures, scan parameters as well as stress and anxiety measures were examined for any group differences using independent one-way analyses of variance (ANOVAs) (for continuous variables) or Chi-square tests (for categorical variables).

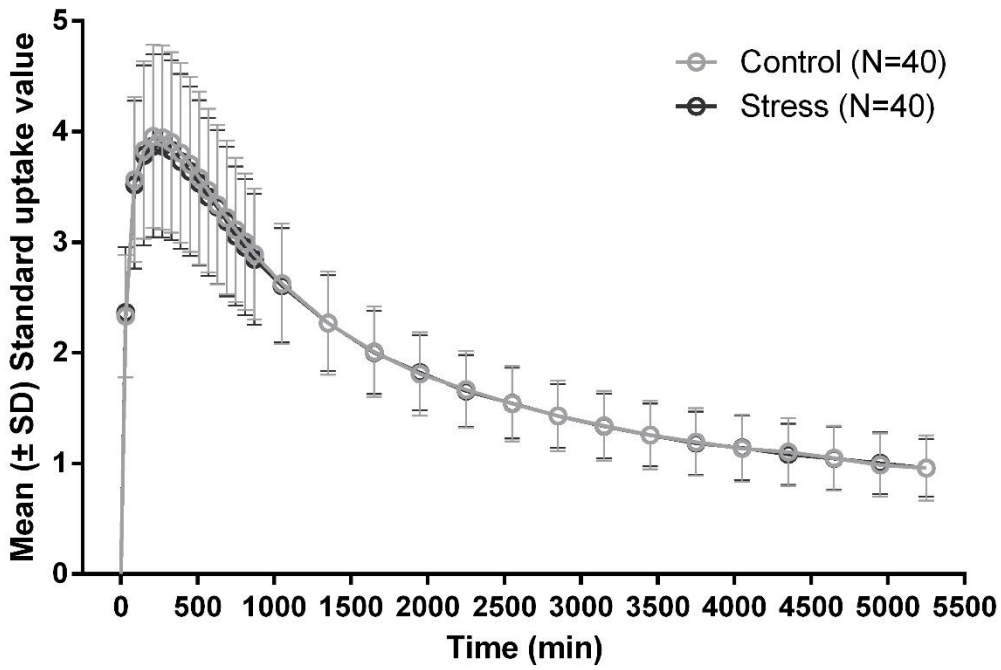
Also, one-way ANOVAs were carried out to test for differences in the salivary cortisol levels ($AUC_I$ or $\Delta AUC_I$ value as the dependent variable) or difference in $BP_{ND}$ of the control scan between groups. In addition, differences in task performance (errors in stress and control task) per group or SAQ scores per group were assessed using two-way ANOVA with repeated measures with study group as a between-subject factor. Differences in post-scan SAQ outcomes (per item), pre vs post scan positive sub-score scales (SOPS and PANSS) and task performance per task were examined using single paired t-tests.

All analyses were two-tailed with the conventional $\alpha$=0.05. To investigate differences among groups, significant ANOVAs were followed by *post hoc* analyses using Bonferroni correction.

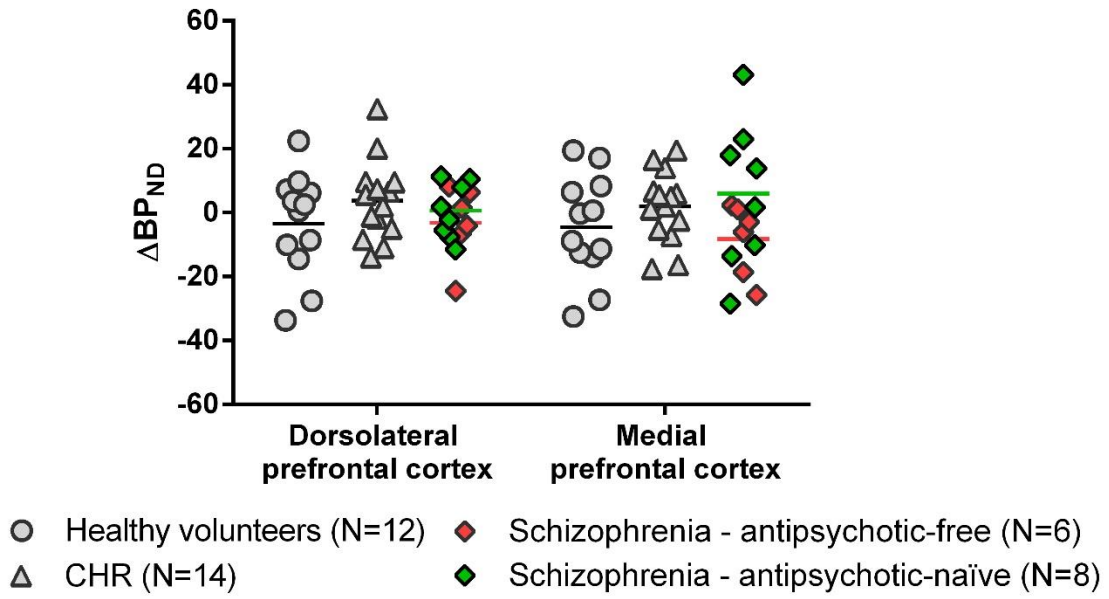
## Supplementary results




**Supplementary Figure 1. (Attenuated) Positive symptoms in response to the stress task in clinical high risk (CHR; N=13) and schizophrenia (N=14).** Graphs represent score of the positive subscale from the scale of psychosis-risk symptoms (SOPS) for CHR (A) and the positive and negative syndrome scale (PANSS) for schizophrenia (B) after control and stress task. SOPS score for one participant was not available. * $p \leq 0.05$.



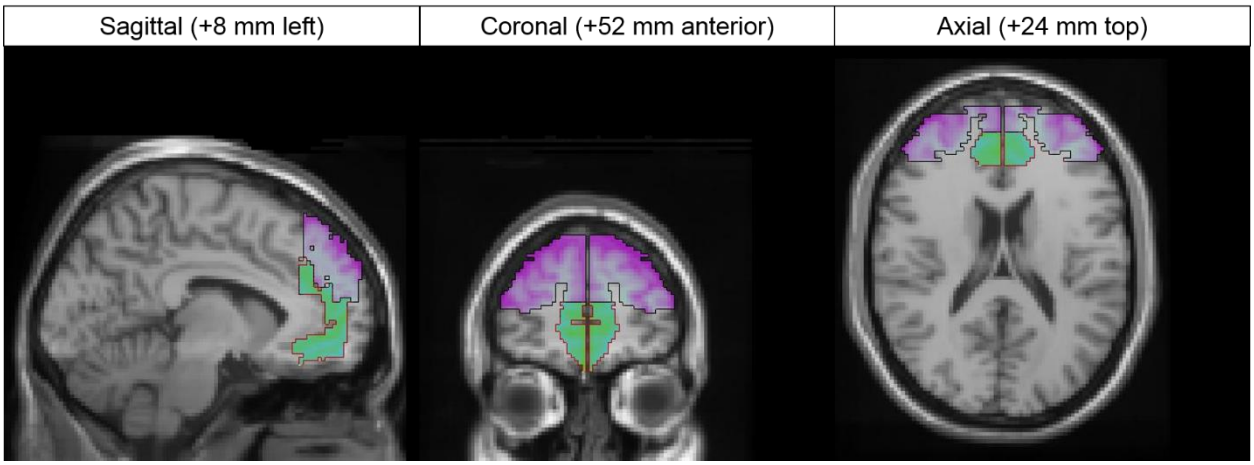

**Supplementary Figure 2. [$^{11}$C]FLB457 time activity curves of the cerebellum expressed as standard uptake values (SUVs) for control and stress task.**




**Supplementary Figure 3. Change in binding potential ($\Delta BP_{ND}$) in healthy volunteers, clinical high risk (CHR) and schizophrenia being antipsychotic-free or antipsychotic-naïve.**

Lines represent mean.


**Supplementary Figure 4. Changes in (attenuated) positive symptoms between positron emission tomography (PET) scans in clinical high risk (CHR; N=13) and schizophrenia (N=14).** Graphs represent score of the positive subscale from the scale of psychosis-risk symptoms (SOPS) for CHR (A) and the positive and negative syndrome scale (PANSS) for schizophrenia (B) before and after control and stress task. SOPS score for one participant was not available. Before PET scan SOPS score changed by -0.75% between conditions (control vs stress). After PET scan SOPS score changed by 2.94% between conditions (control vs stress). Before PET scan PANSS score changed by -0.40% between conditions (control vs stress). After PET scan PANSS score changed by 4.92% between conditions (control vs stress). * $p \leq 0.05$.




**Supplementary Figure 5. Location of regions of interest (ROIs) used in the study.** Template used for the delineation of the dorsolateral prefrontal cortex (dlPFC, purple) and medial prefrontal cortex (mPFC, green). ROIs are overlaid on the magnetic resonance image of a single subject in the MNI space. The distances are calculated in respect of the anterior commissure location. The template was previously described (Matthews *et al.*, 2014) and is applied into the individual brain using ROMI (Rusjan *et al.*, 2006), as described in the methods section.

## Supplementary references


Brugha T, Bebbington P, Tennant C, Hurry J. The List of Threatening Experiences: a subset of 12 life event categories with considerable long-term contextual threat. Psychol Med 1985; 15(1): 189-94.

Endicott J, Spitzer RL, Fleiss JL, Cohen J. The global assessment scale. A procedure for measuring overall severity of psychiatric disturbance. Arch Gen Psychiatry 1976; 33(6): 766-71.

Hafizi S, Tseng HH, Rao N, Selvanathan T, Kenk M, Bazinet RP, *et al.* Imaging microglial activation in untreated first-episode psychosis: A PET study with [18F]FEPPA. The American journal of psychiatry 2017; 174(2): 118-24.

Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 1987; 13(2): 261-76.

Kenk M, Selvanathan T, Rao N, Suridjan I, Rusjan P, Remington G, *et al.* Imaging neuroinflammation in gray and white matter in schizophrenia: An in-vivo PET study with [18F]-FEPPA. Schizophr Bull 2015; 41(1): 85-93.

Matthews BA, Kish SJ, Xu X, Boileau I, Rusjan PM, Wilson AA, *et al.* Greater monoamine oxidase a binding in alcohol dependence. Biological psychiatry 2014; 75(10): 756-64.

Mattick RP, Clarke JC. Development and validation of measures of social phobia scrutiny fear and social interaction anxiety. Behav Res Ther 1998; 36(4): 455-70.

Miller TJ, McGlashan TH, Rosen JL, Cadenhead K, Cannon T, Ventura J, *et al.* Prodromal assessment with the structured interview for prodromal syndromes and the scale of prodromal

symptoms: predictive validity, interrater reliability, and training to reliability. Schizophr Bull 2003; 29(4): 703-15.

Rusjan P, Mamo D, Ginovart N, Hussey D, Vitcu I, Yasuno F, *et al.* An automated method for the extraction of regional data from PET images. Psychiatry research 2006; 147(1): 79-89.

Schlotz W, Hellhammer J, Schulz P, Stone AA. Perceived work overload and chronic worrying predict weekend-weekday differences in the cortisol awakening response. Psychosom Med 2004; 66(2): 207-14.

Suridjan I, Pollock B, Verhoeff N, Voineskos A, Chow T, Rusjan P, *et al.* In-vivo imaging of grey and white matter neuroinflammation in Alzheimer's disease: a positron emission tomography study with a novel radioligand,[18F]-FEPPA. Molecular psychiatry 2015; 20(12): 1579–87.

Zung WW. A rating instrument for anxiety disorders. Psychosomatics 1971; 12(6): 371-9.