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Imaging Microglial Activation in Untreated First-Episode Psychosis: A PET Study With [^{18}F]FEPPA

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Abstract

Objective—Neuroinflammation and abnormal immune responses are increasingly implicated in the pathophysiology of schizophrenia. Previous positron emission tomography (PET) studies targeting the translocator protein 18 kDa (TSPO) have been limited by high nonspecific binding of the first-generation radioligand, low-resolution scanners, small sample sizes, and psychotic patients being on antipsychotics or not being in the first episode of their illness. The present study uses the novel second-generation TSPO PET radioligand [^{18}F]FEPPA to evaluate whether microglial activation is elevated in the dorsolateral prefrontal cortex and hippocampus of untreated patients with first-episode psychosis.

Method—Nineteen untreated patients with first-episode psychosis (14 of them antipsychotic naive) and 20 healthy volunteers underwent a high-resolution [^{18}F]FEPPA PET scan and MRI. Dynamic PET data were analyzed using the validated two-tissue compartment model with arterial plasma input function with total volume of distribution (V_T) as outcome measure. All analyses were corrected for TSPO rs6971 polymorphism (which is implicated in differential binding affinity).

Results—No significant differences were observed between patients and healthy volunteers in microglial activation, as indexed by [^{18}F]FEPPA V_T, in either the dorsolateral prefrontal cortex or the hippocampus. There were no significant correlations between [^{18}F]FEPPA V_T and duration of illness, clinical presentation, or neuropsychological measures after adjusting for multiple testing.

Conclusions—The lack of significant differences in [^{18}F]FEPPA V_T between groups suggests that microglial activation is not present in first-episode psychosis.

Microglia are a key player in the immune surveillance system of the CNS, where they act as resident macrophages and are the first responders to various types of brain insult (1). As part

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of the brain inflammatory response, microglia are transformed from a “sentry” state into an “active” state (1, 2). In this process, the microglia change their morphology from branched to globular, with a large increase in cell volume, while migrating to and engulfing the site of insult (3, 4). Activated microglia (for a review, see reference 5) express elevated levels of a protein in their mitochondria known as translocator protein 18 kDa (TSPO) (6). Because TSPO is overexpressed in response to neuroinflammation as compared with normal tissue, it represents an important imaging target for microglial activation.

Over the years, research has focused on the immune response and neuroinflammation as likely contributors to schizophrenia (7–14). Genome-wide association studies (GWAS) have reported links between schizophrenia and genetic variants in the major histocompatibility complex (MHC) genes, supporting the involvement of the immune system in the pathogenesis of schizophrenia (15, 16). Several lines of research support these GWAS findings: 1) in animal models, an induced maternal immune response (administration of synthetic viral analogue polyriboinosinic-polyribocytidillic [poly I:C] acid [17]) results in behavioral, neurochemical (18–20), and structural changes (17) in the brains of the offspring that resemble the immune alterations implicated in schizophrenia; 2) prenatal exposure to a variety of infections has been linked with an increased risk of developing schizophrenia (21–25); and 3) elevated plasma levels of proinflammatory cytokines in schizophrenia provide evidence for the involvement of peripheral inflammatory response (for a review, see reference 26). However, postmortem studies examining microglia abnormality in schizophrenia are inconclusive; increased microglia activation (27), decreased microglial activation (28), and no difference in microglial activation (29) have been reported. Given the limitations of postmortem studies, positron emission tomography (PET) with TSPO radioligands provides an opportunity to study microglial activation in schizophrenia in vivo.

To date, of five PET studies that have investigated this question in schizophrenia patients on antipsychotic treatment (30–34), three have reported results in line with increased microglial activation in schizophrenia (30–32). The first two of these (30, 31) showed increased binding potential of [^{11}C]PK11195 in schizophrenia compared with healthy volunteers in total gray matter and in the hippocampus, respectively. However, imaging studies using this early radiotracer were hindered by its recognized methodological limitations (35). Using the new generation of TSPO radiotracer [^{11}C]DAA1106, Takano et al. (33) found no difference in binding between schizophrenia patients who had received chronic treatment (N=14) and healthy volunteers (N=14), but they reported significant positive associations between tracer binding, duration of illness, and positive psychotic symptoms. Our recent study evaluating microglial activation in 18 treated patients with schizophrenia (34) using [^{18}F]FEPPA and controlling for TSPO genotype (rs6971 polymorphism) found neither a difference between groups nor any correlation between tracer binding and symptom severity, cognition, or duration of illness. While a recent study using another second-generation TSPO radioligand showed higher [^{11}C]PBR28 distribution volume ratios (DVRs—a different outcome measure reflecting change relative to another brain region) in total gray matter, frontal lobes, and temporal lobes of schizophrenia patients relative to comparison subjects (32), no significant differences were found between the groups when using the validated [^{11}C]PBR28 outcome measure total distribution volume (V_T) (36).

Recent studies with new-generation PET radioligands targeting TSPO report significant intersubject variability in binding. On the basis of analyses performed in brain tissue and platelets, three distinct levels of binding affinity have been noted, with participants grouped as high-affinity binders, low-affinity binders, and mixed-affinity binders (37–39). A polymorphism in exon 4 of the TSPO gene (rs6971) has been implicated in this differential binding affinity (40), suggesting that rs6971 gene polymorphism needs to be considered in the quantification of second-generation TSPO radioligands, including [^{18}F]FEPPA (41). Using this methodology, recent PET studies in Alzheimer's disease and major depressive episode using [^{18}F]FEPPA have demonstrated the ability of this radiotracer to quantify microglia activation in humans (42, 43).

In the present study, we used the validated [^{18}F]FEPPA V_T to examine microglial activation in untreated patients in first-episode psychosis with either minimal (less than 4 weeks) or no lifetime exposure to antipsychotics. We explored the association between microglial activation and severity of psychopathology as well as neuropsychological deficits, given reported positive associations between microglial activation and severity of symptoms in schizophrenia (32, 33). We also explored DVRs as a pseudo-reference region method—in this case, the ratio of [^{18}F]FEPPA V_T in the region of interest to V_T in cerebellum, gray matter, or whole brain (44).

METHOD

Subjects

Twenty-three untreated patients with psychosis and 20 matched healthy volunteers were initially enrolled and scanned in this study. In the patient group, two who were low-affinity binders and two whose PET images were of insufficient quality were excluded, leaving 19 patients for analysis. All patients were either antipsychotic free with less than 4 weeks of lifetime cumulative exposure (N=5) or antipsychotic naive (N=14). Fourteen of the healthy volunteers were included in our previous cohort (34); the patient populations do not overlap between the studies.

To be eligible for the study, first-episode psychosis patients had to have a diagnosis of schizophreniform disorder, delusional disorder, schizophrenia, or psychosis not otherwise specified, as determined with the Structured Clinical Interview for DSM-IV Axis I Disorders (45), and no concurrent axis I disorders, such as major depressive disorder, which has been shown to be associated with microglial activation (42). Healthy volunteers with any history of psychiatric illness or first-degree relatives with a major mental disorder were excluded. Exclusion criteria for all subjects included a current diagnosis of substance dependence or abuse, pregnancy or current breastfeeding, clinically significant medical illness, and the presence of metal implants precluding MRI.

In the patient group, neurocognitive performance was assessed using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (46). The clinical status of psychosis was assessed with the Positive and Negative Syndrome Scale (PANSS) (47), the Calgary Depression Scale, the Snaith-Hamilton Pleasure Scale, the Scale for the Assessment of Negative Symptoms (SANS), the Global Assessment of Functioning Scale (GAF), and

the Apathy Evaluation Scale. Assessments are referenced in the data supplement that accompanies the online edition of this article.

The study was approved by the Research Ethics Board at the Centre for Addiction and Mental Health and the University of Toronto. All participants provided written informed consent after receiving a description of all study procedures.

PET and MRI Data Acquisition and Analysis

Details for PET and MRI data acquisition have been described elsewhere and are summarized below and in the online data supplement. All PET scans were performed using a high-resolution research tomography scanner (Siemens Molecular Imaging, Knoxville, Tenn.) for 125 minutes following an intravenous bolus injection of [^{18}F]FEPPA (mean=182.94 MBq, SD=13.08). Arterial blood samples were collected both automatically (with an automatic blood sampling system: model PBS-101, Veenstra Instruments, Joure, the Netherlands) and manually to measure radioactivity in blood and determine the relative proportion of radiolabeled metabolites. The dispersion-and metabolite-corrected plasma input function was generated as previously described (41).

Image processing and calculation of total distribution volumes (V_T)

Time-activity curves were extracted for the dorsolateral prefrontal cortex, the hippocampus, the medial prefrontal cortex, the temporal cortex, total gray matter, and whole brain using a validated in-house imaging pipeline (the ROMI software program) (48). All regions of interests were delineated using proton density MRI in each participant (48). The kinetic parameters of [^{18}F]FEPPA were derived from the time-activity curves using the two-tissue compartment model and plasma input function to obtain the V_T for each region of interest, a method that has been validated for [^{18}F]FEPPA quantification and has been described elsewhere (34, 49). PET images were also corrected for partial volume effect using the approach described by Müller-Gärtner et al. (50); the results are presented in the online data supplement (see Figure S1).

Estimation of [^{18}F]FEPPA pseudo-reference-region distribution volume ratio (DVR)

For exploratory purposes, we investigated the difference between the groups using DVR as an outcome measure. DVR is defined as regional V_T normalized by V_T in the cerebellum, gray matter, or whole brain ($DVR=V_{T\_region}/V_{T\_k}$, where k represents cerebellum, gray matter, or whole brain). This method has been used in other TSPO PET studies (32, 51) and is suggested to reduce variability in the data (51).

Voxel-based PET image analysis

Parametric images of [^{18}F]FEPPA V_T were generated using the Logan graphical analysis method to examine voxel-wise group differences of V_T. More details are provided in the data supplement.

rs6971 Polymorphism Genotyping

Participants were categorized on the basis of the TSPO rs6971 as high-affinity (C/C), mixed-affinity (C/T), and low-affinity (T/T) binders, as described elsewhere (40, 41). Details of the genotyping procedures are provided in the data supplement.

Statistical Analysis

Demographic measures were examined for any group differences using independent-sample t tests for continuous variables and chi-square tests for categorical variables. Multivariate analysis of variance (MANOVA), with regional V_T values and DVRs as the dependent variables, group (patients, healthy volunteers) as the independent variable, and the TSPO genotype (rs6971) as a covariate, were carried out to test for differences in [^{18}F]FEPPA V_T and DVR values between clinical groups. Partial correlations were used to examine the association between [^{18}F]FEPPA V_T and DVR values and a number of clinical variables, including the duration of untreated psychosis, duration of illness, age at illness onset, number of acute crises, clinical presentation, and neuropsychological measures (controlling for the effects of TSPO rs6971 polymorphism). All statistical analyses were performed using SPSS, version 22.0 (IBM, Armonk, N.Y.), with p values <0.05 considered significant. Bonferroni correction was used to correct for multiple comparisons in regions we set out to test (i.e., the dorsolateral prefrontal cortex and hippocampus only). We also report, for descriptive purposes, differences in the medial prefrontal cortex, the temporal cortex, total gray matter, and whole brain, with $V_T$and DVR data.

RESULTS

Participant Characteristics and Injection Parameters

Participants' demographic and clinical characteristics are presented in Table 1. Among the 19 psychotic subjects, 14 were antipsychotic naive, and 15 were within 5 years of the first episode of their illness at the time of scanning. Except for amount injected, which was significantly higher in the first-episode psychosis group ($F=7.43$, $p=0.01$), PET radiotracer injection parameters did not differ between the patient and healthy groups.

Group Differences in [^{18}F]FEPPA V_T

After controlling for the rs6971 polymorphism, no significant effect of group (healthy volunteers versus patients) was observed on [^{18}F]FEPPA V_T values (Figure 1). The lack of a group effect was observed after controlling for age and/or tobacco use and also with the correction for partial volume effects (see Figure S1 in the data supplement). The results were consistent with other exploratory regions of interest and remained so after excluding the four patients with more than 5 years since their first episode (see the Supplemental Results section and Table S1 in the data supplement).

Exploratory Analysis of DVRs With Cerebellum, Whole Brain, or Gray Matter as Denominator

First, there was no significant group effect on [^{18}F]FEPPA V_T in the cerebellum, whole brain, or gray matter before or after correction for partial volume effects (see Tables S2–S4 in the data supplement).

We found no significant effect of clinical group with any of the DVR methods used. While not statistically significant, higher DVR values were observed in healthy volunteers in the hippocampus and dorsolateral prefrontal cortex using all the DVR methods. Results obtained before and after correction for partial volume effect and also for other regions of interest are reported in Tables S2–S4 in the data supplement.

Voxel-Based Analyses

Congruent with results of the region-of-interest analyses, we did not find any group differences using the region-of-interest independent voxel-based analysis, confirming the lack of difference in [^{18}F]FEPPA V_T between groups (see Figure S2 in the data supplement).

Correlation Between [^{18}F]FEPPA V_T and Duration of Illness, Symptom Severity, Clinical Presentation, and Neuropsychological Measures

There were no significant correlations between [^{18}F]FEPPA V_T (before and after partial volume error correction) and age at illness onset, number of psychotic episodes, duration of illness, anhedonia as measured by the Snaith-Hamilton Pleasure Scale, general functioning as measured by the GAF, and apathy as measured by the Apathy Evaluation Scale. Interestingly, RBANS total score was significantly associated with [^{18}F]FEPPA V_T in the hippocampus ($r=0.50$, $p=0.04$; with partial volume effect correction, $r=0.51$, $p=0.04$), such that higher [^{18}F]FEPPA V_T in the hippocampus was associated with better overall cognitive performance (Figure 2). Follow-up analysis revealed a significant contribution of the RBANS attention subscale ($r=0.49$, $p=0.05$). Moreover, we found a negative association between [^{18}F]FEPPA V_T in the hippocampus and SANS attention subscore both with and without partial volume correction ($r=-0.48$, $p=0.04$) (see Tables S5–S9 in the data supplement). After excluding the four patients with more than 5 years since diagnosis, we found a significant negative correlation between PANSS general psychopathology subscore and [^{18}F]FEPPA V_T in gray matter before and after correction for partial volume effects (see Table S10 in the data supplement), such that higher [^{18}F]FEPPA V_T was associated with lower PANSS general psychopathology subscore. None of these correlations survived Bonferroni correction.

DISCUSSION

To the best of our knowledge, this is the first PET study to evaluate microglial activation using a second-generation TSPO radioligand in untreated, mostly antipsychotic-naive patients in first-episode psychosis.

Early PET studies using [^{11}C]PK11195 reported increased tracer binding in the hippocampus of patients with schizophrenia (30) and in the total gray matter of patients with

recent-onset schizophrenia (31). Based on previous reports (27, 30) and a postmortem study using second-generation [^{3}H]PBR28 (27), we expected significantly higher [^{18}F]FEPPA binding in the hippocampus and dorsolateral prefrontal cortex of patients with first-episode psychosis compared with healthy volunteers. In the present study, despite the use of a second-generation TSPO radioligand and scanning all untreated (mostly antipsychotic naive) first-episode patients in a high-resolution research tomography scanner, we observed no significant differences in [^{18}F]FEPPA binding between groups. While not statistically significant, [^{18}F]FEPPA uptake was higher in the healthy group than in the patient group in the hippocampus (13.4% higher) and the dorsolateral prefrontal cortex (6% higher). Additionally, we explored [^{18}F]FEPPA binding in the medial prefrontal cortex, the temporal cortex, total gray matter, and whole brain and obtained similar results. Nevertheless, our results are in line with other investigations using second-generation TSPO ligands, such as a study that found no differences in [^{11}C]DAA1106 binding in chronic schizophrenia patients (33) and our previous study using [^{18}F]FEPPA in patients with schizophrenia who had received chronic treatment (34). The present study therefore confirms these findings in a larger sample and in untreated, mostly first-episode patients.

While V_T is the gold standard to quantify [^{18}F]FEPPA binding (49), because there is no reference region available, DVR has been proposed as an alternative measure (44). Thus, we also present regional DVR values showing no significant differences between the patient and healthy groups. This finding is inconsistent with the recent study (32) using the second-generation TSPO radioligand [^{11}C]PBR28, which showed higher microglial activation indexed as DVRs in total gray matter and the frontal and temporal lobes of schizophrenia patients compared with healthy volunteers. It should be noted that, using the gold-standard two-tissue compartment model with [^{11}C]PBR28V_T as the outcome measure, the authors of that study did not find any significant difference between schizophrenia patients and healthy volunteers, in line with the present findings and with other studies using second-generation radioligands (33, 34).

The variability of V_T in this study, as with other second-generation TSPO ligands, was relatively high even after controlling for the effect of rs6971 polymorphism on binding affinity. However, sample size calculations using the present data suggest that to detect group effects (i.e., higher microglial activation in healthy volunteers than in first-episode patients) in the dorsolateral prefrontal cortex (the observed effect size was 0.22) or the hippocampus (the observed effect was 0.42), we would need 316 or 89 subjects per group, respectively, for a significance level of 0.05 (two-tailed) and 80% power in each brain region.

In patients with first-episode psychosis, we found a trend toward positive correlation between [^{18}F]FEPPA V_T in the hippocampus and RBANS total score, suggesting that higher microglial activation in the hippocampus is associated with better cognitive function. Similar trends were present when exploring associations between [^{18}F]FEPPA V_T and clinical measures in first-episode psychosis. Although this may be explained by multiple beneficial roles that microglia play in the CNS (52), further studies will clarify the link between psychopathology and neuroinflammation in psychosis.

The results of this study should be interpreted with several limitations in mind. First, a significantly larger amount of [^{18}F]FEPPA was administered to the patient group, on average, than to the healthy group. However, this did not affect our results, as there were no differences between groups in the specific activity or the mass injected. Moreover, we did not find any significant correlations between the amount injected and binding of the radiotracer in any of the regions of interest. Second, studies have shown that microglia are not the only cells that express TSPO, and thus it is possible that a portion of the signal of [^{18}F]FEPPA binding comes from astrocytes (53). Nevertheless, this would not have affected the overall conclusions of our study. TSPO is under neurohormonal control, and there are suggestions that other factors, such as stress and anxiety, can affect TSPO expression (54, 55). Since these factors are commonly seen in psychotic patients, they should be taken into consideration in future studies. We explored a subsample of patients (N=5) for whom a stress scale was available and found a positive association between the state subscale of the State-Trait Anxiety Inventory and [^{18}F]FEPPA binding in the hippocampus (r=0.978, p=0.022) (see Figure S3 in the data supplement). Third, some research groups have reported differences in the arterial input function between schizophrenia patients and comparison subjects (32). While the robust outcome measure V_T is inherently designed to be unbiased under such circumstances, using repeated-measures mixed-model analysis, we empirically compared the arterial input function between patients and healthy volunteers at four different time intervals (0–30 minutes, 30–60 minutes, 60–90 minutes, and 90–120 minutes of the PET scan) and found no group differences. Finally, in neurochemical brain imaging studies, relatively small sample sizes constantly represent a potential limitation; however, to our knowledge, this is the largest PET study to date investigating microglial activation in first-episode psychosis, particularly in mostly antipsychoticnaive patients. While similar sample sizes were sufficient to test a difference between patients with Alzheimer's disease and patients with major depressive episode compared with healthy volunteers using the same radioligand (42, 43), it is possible that microglial activation may have a smaller magnitude in first-episode psychosis and would thus necessitate a larger sample size (as described above).

In conclusion, we found no evidence of increased microglial activation as indexed with [^{18}F]FEPPA binding in the dorsolateral prefrontal cortex and hippocampus in patients with first-episode psychosis compared with healthy volunteers. The lack of significant between-group differences in [^{18}F]FEPPA V_T suggests that microglial activation is not present in first-episode psychosis. Neuroinflammatory processes may take place earlier in the course of schizophrenia, such as during the clinical high-risk state of psychosis, or may be present only in a subpopulation of patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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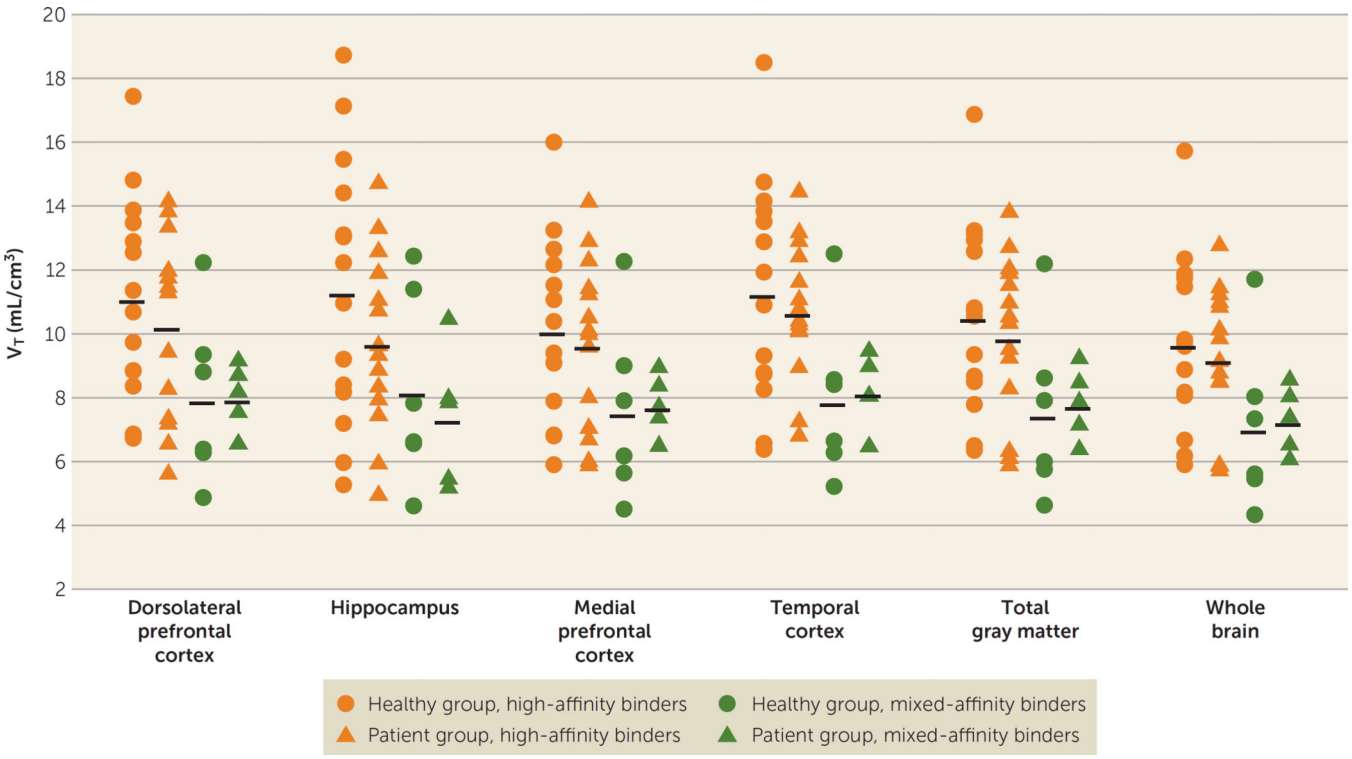

FIGURE 1. Total Distribution Volume (V_T) of [^{18}F]FEPPA in Patients With First-Episode Psychosis and Healthy Volunteers Across Different Regions of Interesta

[a]Horizontal black lines represent mean values.

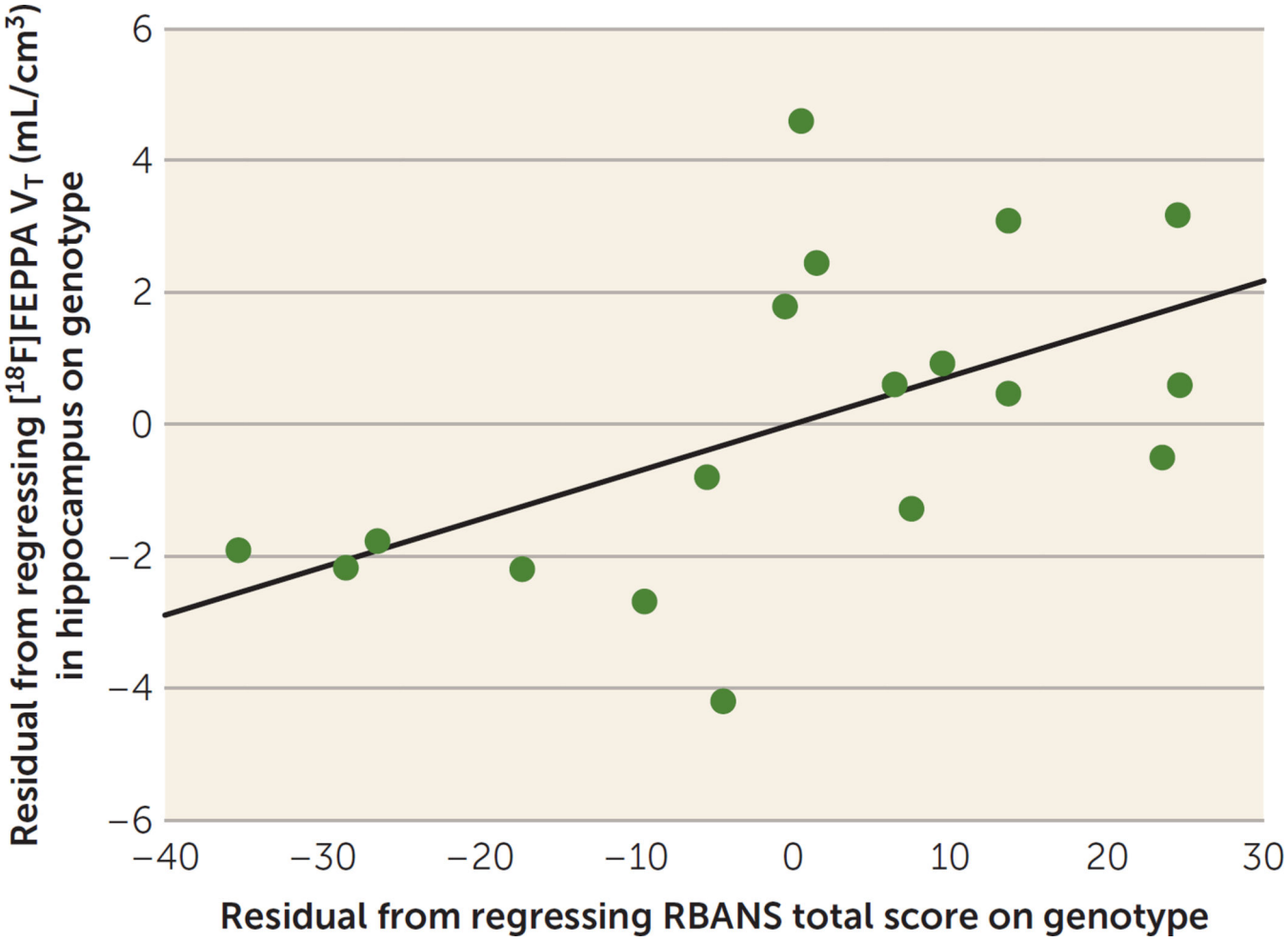

FIGURE 2. Relationship Between [^{18}F]FEPPA V_T in Hippocampus and RBANS Total Score in First-Episode Psychosis

TABLE 1

Participants' Demographic and Clinical Characteristics and Radioligand Injection Parameters in a Positron Emission Tomography (PET) Study of Microglial Activation in Schizophrenia

Measure	Healthy Volunteers (N=20)		First-Episode Psychosis Patients (N=19)	
	N	%	N	%
Male	9	45.0	12	63.2
Genotype[a]				
High-affinity binder	14	70.0	14	73.7
Mixed-affinity binder	6	30.0	5	26.3
	Mean	SD	Mean	SD
Age (years)	27.75	8.77	27.53	6.7
PET measures ([^{18}F]FEPPA)				
Amount injected[b] (mCi)	4.80	0.35	5.09	0.20
Specific activity (mCi/μmol)	4659.7	4130.2	2859.4	2797.2
Mass injected (μg)	0.93	0.95	1.02	0.50
Age at illness onset (years)			24.0	8.0
Number of episodes			1.4	1.2
Duration of illness (months)			33.6	40.1
Calgary Depression Scale[c]			3.7	3.3
Apathy Evaluation Scale			34.3	10.2
Snaith-Hamilton Pleasure Scale			2.1	3.2
Positive and Negative Syndrome Scale				
Total score			68.6	13.0
Positive score			19.2	3.8
Negative score			16.1	6.1
General psychopathology score			33.4	7.3
Repeatable Battery for the Assessment of Neuropsychological Status[c]				
Total score			80.9	17.2
Immediate memory score			83.2	20.0
Visuospatial memory score			83.9	16.8
Language score			82.0	20.9
Attention score			88.4	22.3
Delayed memory score			85.4	18.6

[a] Two patients with the low-affinity binder genotype were excluded from the analyses.

[b] Significant difference between groups (p=0.010).

[c] One schizophrenia patient declined the Calgary Depression Scale and the Repeatable Battery for the Assessment of Neuropsychological Status.