Use of ^{18}F-ASEM PET to Determine the Availability of the α7-Nicotinic Acetylcholine Receptor in Recent-Onset Psychosis

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Limited postmortem evidence suggests a diminished availability of the α7 -nicotinic acetylcholine receptor (α7-nAChR) in the hippocampus in psychosis. **Methods:** In this cross-sectional study, we used PET with ^{18}F-ASEM (^{18}F-JHU82132; 3-(1,4-diazabicyclo[3.2.2]nonan-4-yl)-6-[^{18}F]fluorodibenzo[*b*,*d*]thiophene 5,5-dioxide), a radiotracer targeting the α7-nAChR, to compare the binding of ^{18}F-ASEM in the hippocampus of individuals who had recent-onset psychosis with that in healthy controls. **Results:** Individuals with recent-onset psychosis (nonaffective psychosis or affective psychosis), particularly those with nonaffective psychosis, showed lower hippocampal binding of ^{18}F-ASEM than healthy controls. Among patients, lower binding was associated with lower performance in 2 cognitive domains after controlling for age. **Conclusion:** Low availability of the α7-nAChR in the hippocampus may be linked to recent-onset psychosis. Further study is needed to assess its clinical relationship to neuropsychiatric symptoms.

Key Words: α7-nicotinic acetylcholine receptor; ^{18}F-ASEM; recent-onset psychosis; PET; hippocampus

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Study of postmortem tissue has suggested lower availability of the α7-nicotinic acetylcholine receptor (α7-nAChR) in the hippocampus of individuals with nonaffective psychosis (NP), such as schizophrenia, than in healthy individuals (*1*). Our group developed ^{18}F-ASEM (^{18}F-JHU82132; 3-(1,4-diazabicyclo[3.2.2]nonan-4-yl)-6-[^{18}F]fluorodibenzo[*b*,*d*]thiophene 5,5-dioxide) (*2*), a radiotracer for imaging the α7-nAChR in the living brain with PET (*3*,*4*). Here we used ^{18}F-ASEM PET to test for hypothesized low in vivo availability of the hippocampal α7-nAChR in patients who were not smokers and had recent-onset psychosis, including NP or affective psychosis (AP), and in healthy controls.

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MATERIALS AND METHODS

Human Subjects

This prospective study was approved by the Johns Hopkins Institutional Review Board and was conducted under a U.S. Food and Drug Administration Investigational New Drug application. Each nonsmoking participant provided written informed consent and completed screening and clinical assessments identical to those used in our previous work (*5*). Patients with recent-onset (within 5 y) psychosis were included if they met *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*6*), criteria for schizophrenia or schizoaffective disorder (herein grouped under NP) or for bipolar I disorder (herein referred to as AP). Eleven patients were enrolled (ages: 19–39 y, mean ± SD = 26.0 ± 6.2 y; 8 women; 8 African American, 2 white, 1 Asian; body mass index [BMI] = 28.4 ± 5.2). Five healthy controls underwent ^{18}F-ASEM PET, and we pooled their data with those of all 10 healthy individuals (<50 y old) from a previous study (*4*) (ages: 21–33 y, mean ± SD = 29.0 ± 6.9 y; 8 women; 5 African American, 9 white, 1 Asian; BMI = 23.9 ± 3.2). Exclusion criteria were identical to those published previously (*4*), except for the allowance of a psychotic disorder and monotherapy among patients (lithium or antipsychotic medication). Twenty-two participants completed neuropsychological testing.

Human Brain Imaging

Imaging data were acquired, the hippocampal volume of interest (VOI) was segmented, and PMOD v3.7 (PMOD Technologies LLC, Zurich) was used for image processing as previously described (*4*). Prepared ^{18}F-ASEM had a high radiochemical purity (>98%), and the specific activity was 2,473 ± 2,202 GBq/μmol. ^{18}F-ASEM kinetics were modeled using Logan graphical analysis with a metabolite-corrected arterial input function from 90-min dynamic data (*4*). Hippocampal total distribution volume (V_T) values were derived from images after partial-volume correction (PVC) (*7*). V_T estimates from images without PVC were secondary outcomes.

Statistics

Using SPSS Statistics v24 (IBM SPSS), we used ANOVA to test for group differences in V_T and analyses of covariance to control for potential confounding effects of age, sex, race, or BMI ($P < 0.05$).

RESULTS

Among the patients with recent-onset psychosis, 5 had NP (schizophrenia ($n = 3$) and schizoaffective disorder ($n = 2$)) and 6 had AP (Table 1). The 15 healthy controls did not differ from the

11 patients with recent-onset psychosis (AP and NP) or from either independent patient group (AP or NP) in hippocampal volume ratio (hippocampal volume normalized to total intracerebral volume) before or after controlling for age.

In the patients with recent-onset psychosis, the injected dose was 527 ± 15 MBq and the injected mass was 0.1 ± 0.1 μg. In the controls, the injected dose was 521 ± 33 MBq and the injected mass was 0.2 ± 0.2 μg. The metabolism of ^{18}F-ASEM was moderately fast in each group (patients or controls) and did not differ between groups at any time point. The mean parent fractions at 10, 30, and 90 min after injection were 70% ± 6%, 44% ± 10%, and 16% ± 5%, respectively, in the patients, and 72% ± 9%, 44% ± 13%, and 18% ± 9%, respectively, in the controls.

Significant group effects on the hippocampal V_T were found using 3 groups (controls, patients with AP, and patients with NP) or 2 groups (controls and all patients [i.e., those with AP and those with NP]) (all P values were ≤0.001), even after controlling for age (each $P = 0.001$). Patients with recent-onset psychosis (AP and NP) had lower V_T (15.97 ± 2.50) than healthy controls (19.55 ± 2.49) ($P = 0.001$), although V_T in the AP group alone (17.57 ± 2.24) did not differ from that in healthy controls. V_T was lower in patients with NP (14.05 ± 0.89) than in healthy controls ($P < 0.001$) or patients with AP ($P = 0.04$) (Fig. 1A) and remained lower in patients with NP than in healthy controls after controlling for each covariate (all P values were ≤0.002). Controlling for BMI or race did not change the lower V_T in patients with NP than in those with AP (all P values were 0.01), but significance was lost after controlling for age. In all patients, V_T was positively correlated with performance in processing speed or verbal memory after controlling for age (Table 2)]. V_T estimates from images without PVC did not change these results and produced parametric images that supported group differences outside the hippocampus (Fig. 1B).

TABLE 1
Clinical Characteristics for Participant Groups

Characteristic	Healthy controls ($n = 15$)*	AP group ($n = 6$)*	NP group ($n = 5$)*	P†
Age	26.0 y (3.3 y)	29.0 y (6.9 y)	22.0 y (2.3 y)‡	0.04
Sex (men)§	7 (47)	0 (0)‡	3 (60)	0.08
Race§			‡	0.14
African American	5 (33)	4 (66)	4 (80)	
White	9 (60)	2 (33)	0 (0)	
Asian	1 (7)		1 (20)	
Body mass index	23.9 (3.2)‖	28.1 (5.6)	28.9 (5.1)	0.04
Years of psychosis		3.1 (1.5)	2.2 (1.3)	0.33
Not medicated§		3 (50)	3 (60)	1.00
Antipsychotic drug use§		0 (0)	2 (40)	0.18
Lithium use§		3 (50)	0 (0)	0.18
SAPS or SANS				
Negative symptoms		0.7 (1.2)	11.8 (5.8)	0.001
Positive symptoms		1.7 (3.2)	2.8 (4.1)	0.62
Disorganized symptoms		0.7 (1.6)	0.6 (1.3)	0.94
Calgary Depression Scale score	0.5 (2.1)	2.2 (3.5)	3.0 (3.7)	0.19
Neurocognitive domains¶				
Processing speed	121.3 (9.0)‖	113.8 (10.3)	94.7 (14.1)‡	0.001
Attention and working memory	111.7 (9.1)‖	97.5 (11.9)	76.0 (11.0)‡,#	<0.001
Verbal memory	108.8 (11.6)	110.0 (7.1)	82.5 (12.7)‡,#	0.001
Visuospatial memory	119.6 (7.4)‖	105.5 (13.0)	96.5 (18.6)‡	0.004
Ideational fluency	110.1 (11.6)‖	107.3 (6.2)	88.7 (7.2)‡,#	0.002
Executive function	104.4 (5.2)‖	104.5 (5.4)	80.5 (8.2)‡,#	<0.001

*Data are presented as mean, with SD in parentheses, unless otherwise indicated.
†P values were determined with 1-way ANOVA, χ-square test, or Fisher exact test, as appropriate.
‡$P < 0.05$ versus controls.
§Data are presented as number of participants, with percentage in parentheses.
‖$P < 0.05$ versus all patients (AP + NP).
¶Sample sizes for neurocognitive testing were as follows: healthy controls ($n = 12$), patients with recent onset of AP ($n = 5$), and patients with recent onset of NP ($n = 5$). One participant with AP had wrist injury that precluded computation of processing speed. Standardized scores were averaged across tests to compute domain-specific factor scores.
#$P < 0.05$ versus AP.
SAPS = Scale for the Assessment of Positive Symptoms; SANS = Scale for the Assessment of Negative Symptoms.

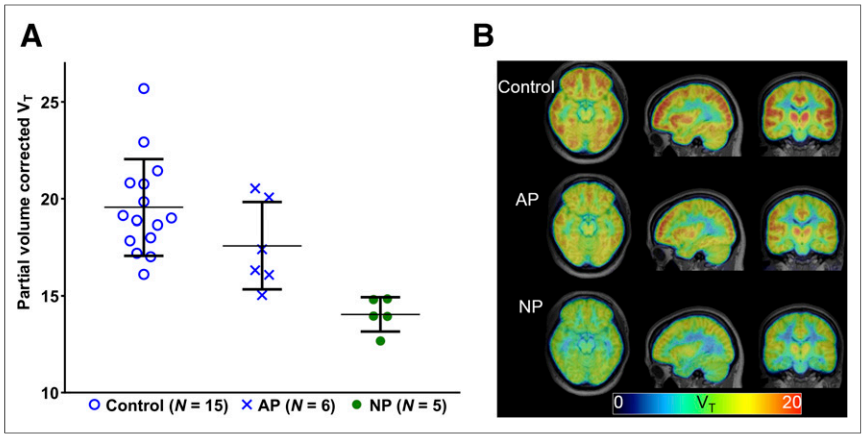

FIGURE 1. Comparison of ^{18}F-ASEM V_T values from nonsmoking participants who were grouped as healthy controls (n = 15), patients with recent-onset AP (n = 6), and patients with recent-onset NP (n = 5). (A) Scatterplot of ^{18}F-ASEM V_T values in hippocampus from healthy controls, patients with AP, and patients with NP. V_T was estimated from images that were corrected for partial-volume effects, and mean and SD are shown (lines). (B) Mean parametric ^{18}F-ASEM V_T images derived from PET data that were not corrected for partial-volume effects from the study population of 15 controls (top), 6 patients with AP (middle), and 5 patients with NP (bottom). These data suggested group differences in binding outside hippocampus as well. Images are displayed in groups of 3 views (from left to right: axial, sagittal, and coronal), and V_T is reported in mL·cm^{-3}.

DISCUSSION

The results of the present study are consistent with lower hippocampal availability of the α7-nAChR in nonsmoking individuals with recent-onset psychosis, particularly those with NP, than in healthy controls and its association with cognitive deficits after controlling for age. We focused on the hippocampus; however, visual inspection of parametric images of V_T derived from PET data without PVC (Fig. 1B) suggested that α7-nAChR availability may be lower across the brains of patients with recent-onset psychosis, particularly those with NP, than in healthy controls.

TABLE 2
Correlation of Factor Scores in Processing Speed and Verbal Memory with ^{18}F-ASEM V_T in Hippocampus of Patients with Recent-Onset Psychosis*

Neuropsychological domain	Partial correlation coefficient (r)
Processing speed	0.73†
Attention and working memory	0.62
Verbal memory	0.75†
Visual memory	0.63
Ideational fluency	0.67
Executive functioning	0.53

*After controlling for effect of age. Of 11 patients who underwent ^{18}F-ASEM PET, 10 patients (5 with NP and 5 with AP) completed the neuropsychological battery because it was added after the first patient participant. Factor scores were generated as averages of standardized scores from tests within each of 6 cognitive domains. Hippocampal ^{18}F-ASEM V_T values were estimated using data from images that were corrected for partial-volume effects.

†$P < 0.05$.

The young age of those with NP relative to those with AP must be noted as a potential limitation, as we found a positive relationship between ^{18}F-ASEM binding and healthy aging (*4*), but we found no change in the results when we controlled for age. The patients had higher a BMI than the healthy controls, but there was no difference between the BMI of patients with NP and the BMI of those with AP, and we found no change in the results after controlling for BMI. The patients were predominantly women and not medicated, and the effects of clinical variables, including psychotropic medication use, on ^{18}F-ASEM binding must be further evaluated. Nevertheless, ^{18}F-ASEM PET is a promising tool for studying the clinical importance of low α7-nAChR availability in recent-onset psychosis.

CONCLUSION

Low availability of the α7-nAChR in the hippocampus may be linked to recent-onset psychosis. Further study is needed to assess its clinical relationship to neuropsychiatric symptoms.

DISCLOSURE

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