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Reduced Brain Cannabinoid Receptor Availability In Schizophrenia

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Abstract

BACKGROUND—Several lines of evidence suggest the presence of abnormalities in the endocannabinoid (eCB) system in schizophrenia (SCZ). However, there are limited *in vivo* measures of the eCB system in SCZ.

METHODS—Twenty five male SCZ subjects (SCZs), 18 antipsychotic treated [SCZ-MED] and 7 antipsychotic free [SCZ-UNMED]) were compared to 18 age- matched male healthy control subjects (HCs). Subjects underwent one Positron Emission Tomography (PET) scan each with the cannabinoid receptor-1 (CB1R) selective radiotracer [¹¹C]OMAR on the High Resolution Research Tomography (HRRT) scanner. Regional volume of distribution (V_T) values were determined using kinetic modeling of PET data as a measure of CB1R availability. Group differences in mean composite [¹¹C]OMAR V_T values were compared between SCZs and HCs. Exploratory comparisons of CB1R availability within 15 brain regions were also conducted. All analyses were covaried for age and body mass index.

RESULTS—SCZs showed significantly ($p=0.02$) lower composite [¹¹C]OMAR V_T relative to HCs (~12% difference, effect size $d=0.73$). [¹¹C]OMAR V_T was significantly (all $ps < 0.05$) lower

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in SCZs in the amygdala, caudate, posterior cingulate cortex, hippocampus, hypothalamus and insula. Composite [^{11}C]OMAR V_T was greater in HCs > SCZ-MED > SCZ-UNMED. Furthermore, composite [^{11}C]OMAR V_T was greater in HCs > SCZ smokers (n=11) > SCZ non-smokers (n=14).

CONCLUSIONS—CB1R availability is lower in males SCZs compared to HCs. Furthermore, antipsychotics and tobacco use may increase CB1R availability in this population. The findings of the study provide further evidence supporting the hypothesis that alterations in the eCB system might contribute to the pathophysiology of SCZ.

Keywords

Cannabinoid; Schizophrenia; CB1R; Antipsychotics; Smoking; OMAR

Introduction

Emerging evidence suggests the presence of abnormalities in the endocannabinoid (eCB) system in schizophrenia (i.e., the *endogenous* hypothesis). This is distinct from the better known *exogenous* hypothesis, according to which exogenous cannabinoids can induce transient schizophrenia-like effects in healthy individuals, exacerbate psychotic symptoms, trigger relapse and negatively impact the course of illness in schizophrenia (SCZ) patients, and finally, heavy exposure to exogenous cannabinoids in adolescence may contribute to the risk of later developing SCZ (1–6).

Several groups have reported elevated eCB levels in the blood or CSF of patients with SCZ (7–11). Furthermore, eCB levels are inversely correlated with psychotic symptoms, and normalize following treatment with antipsychotics (8–10) and with clinical remission (12). The results of postmortem studies have been mixed (Supplementary Table S1) with studies reporting increases, decreases or no changes in either CB1R protein or mRNA levels in SCZ (13–23). While 4/6 studies that used in vitro autoradiography reported significantly increased CB1R binding in SCZ subjects (SCZs) compared to healthy control subjects (HCs), 5/6 studies using immunodetection methods reported either a decrease or no change in CB1R density. These mixed results could be due to differences in methodologies, the regions studied, or the presence of comorbidities in the patient groups.

A related issue is the effect, if any, that antipsychotic treatment may have on the eCB system. Reports on the effects of antipsychotics on CB1R availability are mixed (24–26). Eggen et al. reported that CB1R mRNA and protein levels were significantly lower in the dorsolateral prefrontal cortex of SCZs as compared to matched HCs in a post mortem human study (17, 18, 23), but no differences between medicated (n=19) and unmedicated (n=4) SCZs (18). Uriguen et al reported reduced post mortem CB1R density in SCZs compared to HCs that was primarily noted in antipsychotic treated but not in drug free SCZs (19). In a second cohort that also included unmedicated SCZs (n=6), Eggen et al. suggested that antipsychotic treatment might blunt the decrease in CB1R immunoreactivity levels observed in SCZ (17). Others have shown in animals that treatment with haloperidol (27), risperidone (28) and clozapine (29) resulted in altered CB1R density in various brain regions.

Positron emission tomography (PET) imaging provides a means to study CB1R availability in SCZs *in vivo*. Several CB1R ligands have been developed for PET, including [¹⁸F]MK-9470, and [¹¹C]OMAR (30). In the first PET study of CB1R in SCZ, Wong et al. (2010) reported elevated [¹¹C]OMAR binding across the brain in SCZs (n= 10), all receiving antipsychotic medications (31). The mean difference was small and only significant in the pons. More recently Ceccarini et al (32) reported CB1R binding in a larger sample of SCZs on (n=51) and off (n=16) antipsychotics, and 12 cannabis naïve, age and gender-matched controls (n=12) using [¹⁸F]MK-9470 PET. Of note [¹⁸F]MK-9470 shows primarily irreversible binding, while [¹¹C]OMAR showing reversible binding, a characteristic favored for quantitative receptor imaging (33). Compared to HCs, SCZs displayed increased global gray-matter [¹⁸F]MK-9470 uptake. Volume of interest analyses revealed significant increases of [¹⁸F]MK-9470 uptake in several brain regions in SCZs. Further, cannabis or tobacco use and antipsychotic medication type did not appear to influence [¹⁸F]MK-9470 uptake.

While this study has drawn attention to the possibility of CB1R alterations in SCZ, the kinetic characteristics of [¹⁸F]MK-9470 pose challenges in quantification and furthermore, the validity of the modified standardized uptake values (mSUV) technique used has been challenged by several groups (34, 35).

In the current study, we measured CB1R availability in SCZs using the reversible ligand [¹¹C]OMAR, based on absolute quantification using arterial sampling with metabolite analysis and tracer kinetic modeling analysis that does not have the limitations associated with the mSUV method. Based on the postmortem data of Eggen et al., SCZs were hypothesized to show lower CB1R availability compared to HCs.

Methods

Approvals

This study was approved by the Yale University and VA Connecticut Healthcare System Institutional Review Boards, the Yale Magnetic Resonance Research Center, and the Yale New Haven Hospital Radiation Drug Research Committee. All subjects signed informed consent after the study was explained to them in detail.

Subjects

Male SCZs on and off antipsychotics, and age-matched (± 3 years) HCs completed a comprehensive screening process that included a psychiatric, medical, and neurological evaluation by a research physician as reported in the supplemental section.

Assessments

Positive and negative symptoms of SCZ were assessed using the Positive and Negative Syndrome Scale (PANSS)(36).

Imaging

Magnetic resonance imaging (MRI) scans were conducted before the PET scans as described in the supplemental section.

Prior to PET scanning, urine drug toxicology was repeated and IV lines and an arterial catheter were placed. PET scans were acquired as subjects rested in the HRRT scanner (207 slices, resolution better than 3 mm FWHM in 3D acquisition mode) (Siemens Medical Systems, Knoxville, TN). Procedures for PET imaging, metabolite analysis and measurement of arterial input functions were the same as those previously described (37). In addition, the fraction of plasma ^{11}C -OMAR unbound to protein (f_p) was determined by ultrafiltration.

Image Analysis

Summed PET images were registered to the subject's T1-weighted MR images, which, in turn, were registered to an MR template. Gray matter regions of interest (ROIs) were predefined on a template (Anatomical Automatic Labeling (AAL) for SPM2). This process permitted direct, automatic determination of volume of distribution (V_T) values using the MA1 method with $t^* = 30$ min (38), the preferred kinetic modeling method for [^{11}C]OMAR. V_T is the ratio at equilibrium of total tracer to that in plasma, including free, nonspecifically bound, and specifically bound tracer. Exploratory comparisons of [^{11}C]OMAR V_T levels were examined in 15 regions, some of which are implicated in the circuitry underlying the behavioral and cognitive effects of cannabinoids. The ROIs included the amygdala, globus pallidus, caudate, putamen, hippocampus, hypothalamus, cerebellum, thalamus, and cerebral cortices (insula, anterior cingulate, posterior cingulate, temporal, frontal, parietal, and occipital).

Statistical analyses

Whole brain composite [^{11}C]OMAR V_T levels were compared among diagnostic groups (SCZs vs. HCs) using analysis of covariance (ANCOVA) with age and BMI included as covariates. Composite [^{11}C]OMAR V_T values were calculated as a mean of the regional [^{11}C]OMAR V_T values using the justification and methods in Neumeister et al (2013), because regional [^{11}C]OMAR V_T values were highly correlated (r values > 0.91 in both HCs and SCZs). Group differences in regional [^{11}C]OMAR V_T values were analyzed using linear mixed models with diagnostic group (SCZs or HCs) as a between-subjects factor and region as a within-subjects factor. The interaction between group and region was modeled and age and BMI served as covariates. The best-fitting variance-covariance structure was selected based on information criteria. Additional, exploratory analyses were conducted within levels of medication and smoking. Total PANSS score was included as a covariate in all models restricted to SCZ subjects. Correlations were explored between regional CB1R availability and PANSS total and subscale scores. Given the exploratory nature of the regional analysis and correlations, results are not corrected for multiple comparisons. All tests were significant at the $\alpha=0.05$ threshold.

RESULTS

Twenty-five male SCZs, seven of whom were antipsychotic free (SCZ-UNMED), eighteen receiving antipsychotic treatment (SCZ-MED), and eighteen age-matched (± 3 years) male HCs were studied. Tables 1 and 2 show demographic and clinical characteristics of the groups. [^{11}C]OMAR injection parameters did not differ among the groups.

CB1R availability in SCZ vs. HC (Figures 1 and 2)

Composite brain [^{11}C]OMAR V_T values were $\sim 12\%$ lower in SCZs relative to HCs ($F(1,39) = 5.56$, $p = .02$; effect size (d) = 0.73). In the exploratory analysis including region as a factor, significant group ($F(1,39) = 4.51$, $p = .04$), region ($F(14,574) = 82.4$, $p < .0001$) and group \times region interaction ($F(14,574) = 1.72$, $p = .05$) effects were observed. Post hoc analyses revealed that SCZs had significantly lower [^{11}C]OMAR V_T values compared to HCs in the amygdala, caudate, posterior cingulate cortex, hippocampus, hypothalamus and insula (all $p < 0.05$) with a trend level ($0.05 < p < 0.1$) in the anterior cingulate, frontal, occipital and parietal cortices, pallidum, putamen and thalamus.

Effects of antipsychotic medication on CB1R availability: CB1R availability in SCZ-UNMED vs. SCZ-MED vs. HCs (Figure 3)

There was a main effect of group ($F(2,38) = 3.16$, $p = .05$) such that composite brain [^{11}C]OMAR V_T was HCs $>$ SCZ-MED $>$ SCZ-UNMED (effect size (d) = 0.40). In the exploratory analysis including region as a factor, the region ($F(14,38) = 55.92$, $p < .0001$) and group \times region interaction ($F(28,38) = 2.98$, $p = .001$) effects were significant, and there was no main group effect ($F(2,38) = 2.01$, $p = 0.14$). Post hoc analyses revealed significantly lower [^{11}C]OMAR V_T (all $p < 0.05$) in SCZ-UNMED compared to HCs in the amygdala, caudate, posterior cingulate cortex, and pallidum with trend level ($0.05 < p < 0.1$) differences in the hippocampus, hypothalamus, insula, putamen and thalamus. [^{11}C]OMAR V_T was significantly ($p = 0.02$) lower in SCZ-MED compared to HCs only in the posterior cingulate cortex with trend ($0.05 < p < 0.1$) level differences in the caudate and hypothalamus. There were no significant differences between SCZ-UNMED and SCZ-MED. Finally, there were no significant correlations between antipsychotic dose (in risperidone equivalents) and [^{11}C]OMAR V_T in any brain region.

Effect of tobacco smoking on CB1R availability in SCZ: CB1R availability in non-smoker SCZs (n=14) vs. smoker SCZs (n=11) vs. HCs (n=18) (Figure 4)

There was a significant main effect of group ($F(2,38) = 4.37$, $p = .02$) such that composite brain [^{11}C]OMAR V_T was HCs $>$ smoker SCZs $>$ non-smoker SCZs. In the exploratory analysis including region as a factor, the region ($F(14,38) = 84.15$, $p < .0001$) and group \times region interaction ($F(28,38) = 3.44$, $p = .0002$) effects were significant and there were trend level ($F(2,38) = 2.51$, $p = 0.09$) group differences. Post hoc analyses revealed significantly lower [^{11}C]OMAR V_T (all $p < 0.05$) in non-smoker SCZs compared to HCs in the amygdala, caudate, hippocampus, hypothalamus, insula, putamen, pallidum and frontal, parietal, occipital and posterior cingulate cortices, and trend level ($0.05 < p < 0.1$) differences in the cerebellum and anterior cingulate and temporal cortices. In contrast, there were no significant differences in [^{11}C]OMAR V_T between smoker-SCZs and HCs. Finally,

[¹¹C]OMAR V_T was significantly (all $p < 0.05$) lower in non-smoker SCZs vs. smoker SCZs in the parietal and occipital cortices with trend level differences ($0.05 < p < 0.1$) in the cerebellum and frontal and temporal cortices. There was no significant correlation between Fagerstrom Test for Nicotine Dependence scores and composite or regional [¹¹C]OMAR V_T .

Free fraction corrected results—There was no significant difference ($p = 0.1$) in the plasma free fraction (f_p) between HCs and SCZs. Nevertheless, for completeness, f_p -corrected results are presented in supplementary Table S2 – the results were no different.

Effect of unequal partial volume loss on results—Due to the high resolution of the HRRT PET scanner used in this study, partial volume effects tend to be smaller than those found on conventional PET scanners. However, to address the possibility that the group differences may be driven by partial volume effects, further analyses were conducted.

Supplementary Table S3 lists the results for ROI volume and V_T where the AAL regions were masked to only include gray matter. Cortical regions were analyzed because segmentations of gray and white matters were considered reliable only in these regions. SCZs had slightly lower ROI volumes compared to HCs, with a mean group difference of 4.33% (SD= 1.93). In comparison, group difference in [¹¹C]OMAR V_T calculated after grey matter masking was much larger, with a mean of 17.93% decrease in SCZs (SD= 3.88). Thus, the magnitude of difference in [¹¹C]OMAR V_T between SCZs and HCs cannot be explained by ROI volume difference between the two groups.

Relationship between symptom levels and cannabis exposure with CB1R availability

Overall, there were no group differences in PANSS Total or any PANSS subscale scores between SCZ-UNMED and SCZ-MED. Among SCZ patients, there was a positive association ($r = 0.41 - 0.48$) observed between PANSS general and total scores and CB1R availability in the hippocampus, hypothalamus and thalamus (all $p < 0.05$) respectively. There were no significant correlations between cannabis use and [¹¹C]OMAR V_T .

Discussion

Male SCZs have reduced CB1R availability as compared to male HCs. The magnitude of the reduction was medium (effect size $d = \sim 0.73$) and the pattern of reduction was global rather than localized. Reduced [¹¹C]OMAR V_T in SCZs relative to HCs is most likely driven by the diagnosis of SCZ rather than other factors. That differences in CB1R availability between HCs and SCZ-UNMED were larger than those between HCs and SCZ-MED suggests that antipsychotic treatment is not likely an explanation for the observed differences between SCZs and HCs. Similarly, that differences in CB1R availability between SCZ non-smokers and HCs were larger than those between SCZ smokers and HCs suggest that tobacco use is unlikely to explain differences between SCZs and HCs. Finally, since the groups studied had minimal and similar exposure to cannabis, it is further unlikely that the group differences can be explained by cannabis exposure.

The outcome measure used in this study was V_T , which includes specific binding and non-displaceable binding (free + non-specific). We have interpreted the global differences seen here as being lower specific CB1R availability in SCZs compared to HCs. However, it is possible that some or all of the difference can be attributed to non-displaceable binding. Blocking studies are generally used to assess the magnitude of specific binding. In nonhuman primates (NHP), rimonabant was able to block more than half of the signal in the regions with high specific binding (³⁹). We had previously assessed the level of nonspecific binding in NHP using low specific activity injections of OMAR (⁴⁰) and found that the nondisplaceable volume of distribution (V_{ND}) represented 40–50% of the V_T values in high-binding regions. However, to the best of our knowledge, human blocking studies have not been performed with [¹¹C]OMAR due to the lack of available blocking drug, and thus the portion of non-specific binding in human brain regions remains unknown.

The global pattern of reduced CB1R availability in SCZs is in contrast to the patterns observed in cannabis dependence where the reduction in CB1R availability is greater in cortical compared to subcortical regions (^{41–45}). Furthermore, the findings of *reduced* CB1R availability in SCZ are in contrast to the findings of studies with the same ligand ([¹¹C]OMAR) and methodology that showed *increased* CB1R availability in PTSD (⁴⁶) and in alcohol dependence (⁴⁷). This suggests that our findings are not merely a nonspecific consequence of chronic neuropsychiatric illness but are specific to SCZ.

The reductions in CB1R availability in chronic SCZ observed in our study may have several interpretations. Decreased or increased eCB levels are associated with up or downregulation of CB1R, respectively. For example, Neumeister et al. reported that low anandamide levels were associated with increased CB1R in PTSD (⁴⁶). Thus, our findings of lower CB1R availability in SCZs are consistent with the findings of elevated CSF eCB levels in SCZ (^{7–11}). Whether elevated eCB levels drive the reduction in CB1R availability or vice versa remains unknown. Furthermore, while elevated eCB levels reportedly normalize with symptom resolution (^{7–11}), whether the same occurs with CB1R availability is not known.

The relationship between CB1R availability and symptoms remains unclear. While Ceccarini et al. observed that CB1R binding was negatively correlated to negative symptoms and depression, we found modest positive relationships between symptoms (PANSS total scores) and regional CB1R availability. However, our findings should be interpreted with caution given that they were not adjusted for multiple comparisons.

It is tempting to speculate how the eCB hypothesis supported by our observations of reduced CB1R availability in SCZ interacts with the exogenous cannabinoid hypothesis. According to the latter, early and heavy exposure to cannabis increases the risk for SCZ reviewed by (⁴⁸). Also, exposure to cannabis results in CB1R downregulation (^{41–45}). Hence, CB1R may be reduced de novo and/or secondary to cannabis exposure, thus incorporating both the endogenous and exogenous hypotheses under one overarching hypothesis. Furthermore, and admittedly speculative, if those at risk for SCZ have reduced CB1R to begin with, and if reduced CB1R availability contributes to the pathophysiology of SCZ, then heavy and early exposure to cannabis might further enhance the risk for the development of the illness.

CB1R activation serves to inhibit the release of other neurotransmitters e.g., gamma-aminobutyric acid (GABA), dopamine and glutamate (49), that have been implicated in the pathophysiology of SCZ. Therefore, one possible consequence of reduced CB1R may be the unregulated release of neurotransmitters relevant to psychosis. Alternatively, as suggested by Eggan et al (17), it is conceivable that reduced CB1R may be a compensatory response to abnormalities in other neurotransmitter systems. While the current study does not allow us to determine the consequences of a reduction in CB1R availability, similar small reductions in CB1R availability in cannabis dependence are associated with functional consequences (50–53).

Effects of Antipsychotic treatment on CB1R availability in SCZ

CB1R availability was greater in HC > SCZ-MED > SCZ-UNMED suggestive of a “restorative” effect of antipsychotics on CB1R availability in SCZs. While the preclinical literature on the effects of antipsychotics on CB1R availability are mixed (24–26), our results are consistent with data demonstrating regional increase in CB1R binding associated with treatment with haloperidol (27) and risperidone (28).

Furthermore, our finding of higher CB1R availability in SCZ-MED vs. SCZ-UNMED which may be interpreted as a “normalization” of CB1R availability with antipsychotic treatment, is also consistent with the findings of Leweke et al that elevated CSF eCB levels in acutely ill SCZs “normalized” with antipsychotic treatment (7–11). Future studies with larger samples of medicated and unmedicated SCZs will be necessary to determine the effects, if any, of antipsychotics in general and the effects of specific antipsychotics on CB1R availability.

Effects of Tobacco Smoking on CB1R availability in SCZ

CB1R availability was greater in HC > SCZ smokers > SCZ non-smokers suggesting that tobacco smoking may increase CB1R availability in SCZs. Several lines of evidence suggest interplay between CB1R and nicotinic acetyl cholinergic receptor (nAChR) systems. Rodent studies suggest that intact CB1R is required for the rewarding effects of nicotine and CB1R antagonists have shown some efficacy in treating tobacco dependence (54–56). A recent PET study in rats failed to show an effect of subchronic (2 weeks) nicotine treatment on the binding of the CB1R ligand [¹⁸F]MK-9470 (57). However, the authors reported an increase in CB1R only in the cerebellum, a finding that would be consistent with the findings of the current study. Nicotine does not appear to have a direct effect on CB1R but exposure to nicotine may alter eCB levels (58, 59) and elevated eCBs in turn can alter CB1R binding capacity by enhancing affinity (acutely) and increasing receptor density (chronically) (60). Thus, it is conceivable that chronic tobacco smoking is associated with increased CB1R availability as was observed in our study. Since this study did not include smokers *without* SCZ, it is not clear whether this effect of smoking is limited to SCZ or more generalizable. Finally, it is important to note that the effects of tobacco use in SCZs may have been confounded by medication status given that there were more tobacco users in the medicated group.

Implications for Cannabis Use in SCZ

Cannabis is one of the most commonly used drugs by SCZ patients⁽⁶¹⁾. Whether reduced CB1R has any implications on the risk of cannabis or other drug/alcohol use by this population is not known but warrants further study. Given the large CB1R reserve⁽⁶²⁾, only a small number of receptors need to be activated to produce psychoactive effects of cannabinoids so it is unlikely that reduced CB1R should have any bearing on the amount of cannabis required to produce effects.

Comparison to extant findings

Our findings are consistent with some but not other postmortem literature on CB1R in SCZ^(13_22) (supplementary table S1). For example, Uriguen et al and Eggan et al., reported reduced CB1R mRNA and immunocytochemical receptor protein expression in SCZ^(17_19). Our findings are at variance with the *in vivo* findings of Wong et al and Ceccarini et al., who showed *increased* CB1R availability in SCZ compared to HCs^(31, 32). This may be related to differences in the sample size and characteristics, and/or PET methodology.

Partly due to its high binding affinity, the kinetics of [¹⁸F]MK-9470, used in Ceccarini et al., are very slow, which presents difficulties in quantifying the uptake and binding using conventional tracer kinetic modeling methods. Due to its nearly irreversible uptake, reliable measurements of V_T cannot be obtained. There is consensus in the neuroreceptor imaging community that reversible-binding tracers provide more meaningful and reliable data⁽³³⁾. The outcome measure used by Ceccarini et al. was a mSUV value, where tracer uptake is normalized by injected dose and an adjusted subject weight. The mSUV approach assumed no group differences in peripheral tracer clearance or metabolism among the groups studied. Factors such as tobacco smoking status, level of smoking, cannabis use status, antipsychotic treatment or diagnosis of SCZ could theoretically impact peripheral metabolism. While SUV measurements can still potentially be useful to demonstrate large differences in receptor binding, e.g., those obtained from a receptor occupancy study⁽⁶³⁾, smaller between-group differences can easily be confounded by the lack of absolute measurements. As acknowledged by Ceccarini et al. and others there are limitations to the validity of the mSUV technique^(34, 35). Given the range of demographic factors in these populations (gender, BMI, smoking, drug-status), we feel that reliable results can only be obtained by measuring the arterial input functions in all subjects, so that the final outcome measure (V_T) is no longer affected by tracer availability, which is controlled by peripheral tracer metabolism and clearance from the body. In contrast to Ceccarini et al., we conducted kinetic analysis of [¹¹C]OMAR data using metabolite-corrected arterial input functions in all subjects.

Using [¹¹C]OMAR, the same tracer as the one used in our study, Wong et al. reported a small *increase* in CB1R availability significant only in the pons, in a small sample (n=10) of SCZs all of whom were receiving antipsychotic medications⁽³¹⁾. The latter is important to consider given our findings suggesting that antipsychotic treatment may increase CB1R availability.

Further, relative to our sample, the chronic SCZs studied by both Wong et al. and Ceccarini et al. were less symptomatic. The mean PANSS total scores in our sample was 73.9 vs. 52.3 in Ceccarini et al's sample (group means ranged from 45–59), while the sample of Wong et al. had mean BPRS scores of 34.1, suggesting that our sample consisted of more symptomatic chronic SCZs. Psychotic symptoms are inversely correlated with eCB levels and tend to normalize following treatment with antipsychotics (8–10) and with clinical remission (12). Furthermore, eCB levels are related to CB1R availability. Thus, it is conceivable that the higher CB1R availability observed by Wong et al. and Ceccarini et al. may reflect the lower symptoms levels in their study samples.

Conclusions and future directions

This is the first report, to our knowledge, of *reduced* CB1R availability in males with SCZ. Antipsychotic and tobacco use may affect CB1R availability in this population. These findings provide further evidence supporting the hypothesis that alterations in the eCB system might contribute to the pathophysiology of SCZ.

In light of published data from our center showing higher CB1R availability in women (64), it will be important to study females with SCZ. Attention and memory are well known to be acutely impaired by cannabinoids (65, 66) and to be impaired in SCZ (67–69). Furthermore, SCZ patients are more sensitive to the cognitive impairing effects of cannabinoids (70). Similarly, cannabinoids can induce a range of acute SCZ-relevant behavioral outcomes, and SCZ patients are more sensitive to the psychosis-inducing effects of cannabinoids (66). Thus, future studies that are adequately powered will be necessary to establish the relationship between CB1R availability and cognitive outcomes, core symptoms in SCZ, stage of illness and eCB levels.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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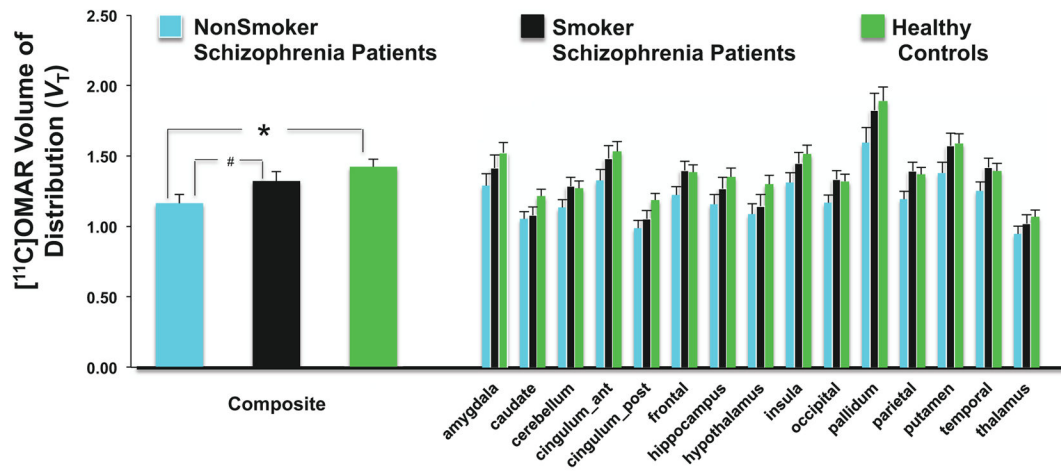


Figure 1. Grand Averaged CB1R availability in Schizophrenia Patients vs. Healthy Controls

Top row: HC averaged (n=21) of the distribution volume (V_T ; Innis et al., 2007) images computed using the multilinear analysis (MA1; Ichise et al., 2002)

Middle row: SCZ averaged (n=25) of the distribution volume (V_T ; Innis et al., 2007) images computed using the multilinear analysis (MA1; Ichise et al., 2002)

Bottom row: Aligned T1 MR image for anatomical reference

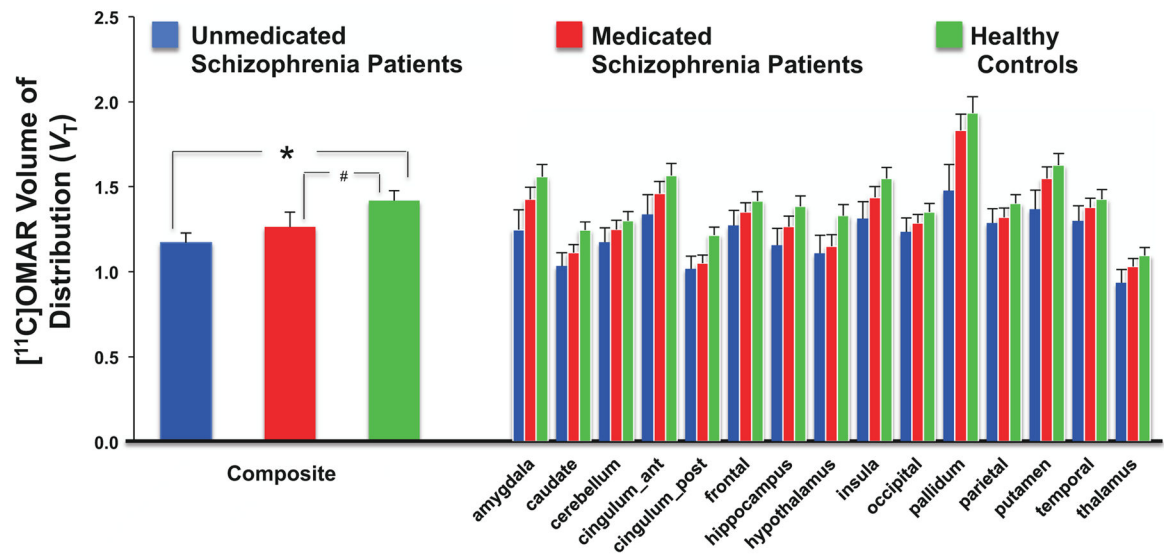


Figure 2. CB1R availability in Schizophrenia Patients vs. Healthy Controls

The figure shows the mean and standard error bars of [11C]OMAR Volume of Distribution (V_T).

Significant differences ($p < 0.05$) between groups are indicated with *.

Trend differences ($p < 0.06-0.1$) between groups are indicated with #.

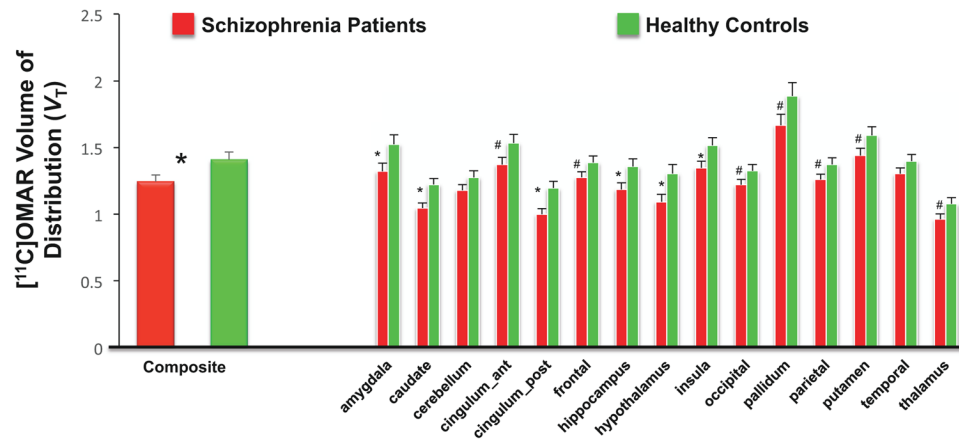


Figure 3. Effects of Antipsychotic Treatment on CB1R availability

The figure shows the mean and standard error bars of [^{11}C]OMAR Volume of Distribution (V_T).

See text for statistically significant differences between 3 groups. * $p = 0.025$. # $p = 0.07$.

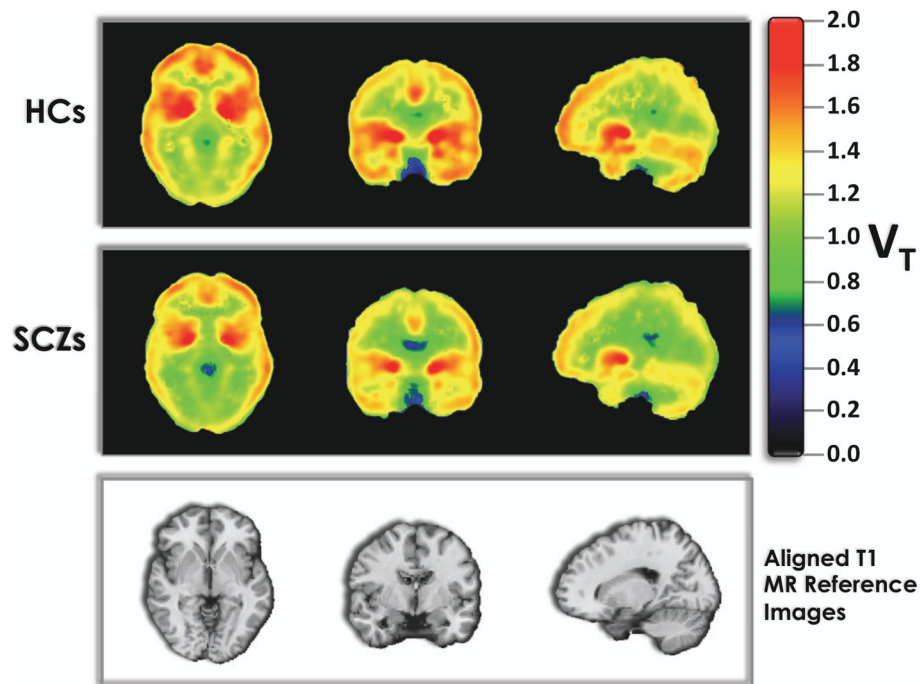


Figure 4. Effects of Tobacco Smoking on CB1R availability

The figure shows the mean and standard error bars of [^{11}C]OMAR Volume of Distribution (V_T).

See text for statistically significant differences between 3 groups. * $p = 0.006$. # $p = 0.096$.

Table 1

All Subject Demographics

Variable	Schizophrenia (n=25)		Controls (n=18)		Statistics p-value
	Mean or n	SD or %	Mean or n	SD or %	
Age (Years)	34.7	11.3	28.7	8.1	0.060
Education (years)	13.2	1.5	15.4	2.4	0.001*
BMI	30.7	5.1	26.9	5.3	0.020*
NART	109.4	8.5	113.6	7	0.096
FTND	2	2.6	-	-	-
Injected Activity [mCi]	14.09	3.65	15.68	2.87	0.14
Injected Mass [μ g]	3.67	3.22	3.62	3.22	0.95
Specific Activity [mCi/nmol]	3.85	3.57	5.35	4.58	0.23
Free Fraction (f_p)	0.001	0.0004	0.001	0.0004	0.16
Antipsychotic Treatment (No/Yes)	7/18	28/72	-	-	0.001*
Tobacco Smoker (No/Yes)	14/11	56/44	18/0	100/0	0.410
Race (White/AA/Other)	15/9/1	60/36/4	14/4/0	78/22/0	
Ethnicity (Non-Hispanic/Hispanic)	21/4	84/16	14/4	78/22	
Lifetime DSM-IV Cannabis Use Disorder	0	0	0	0	

BMI: Body Mass Index; NART = National Adult Reading Test; BMI = Body Mass Index; FTND = Fagerstrom Tobacco Test for Nicotine Dependence; AA= African American

Table 2

Schizophrenia Subjects Demographics

Variable	Medicated (n=18)		Unmedicated (n=7)		Statistics p-value
	Mean or n	SD or %	Mean or n	SD or %	
Age (years)	35.7	10.9	32.3	12.9	0.515
Education (years)	13.1	1.5	13.3	1.5	0.805
BMI	30.7	4.1	30.7	7.6	0.994
NART	108.4	8.1	111.9	9.6	0.377
FTND	2.2	2.7	1.4	2.4	0.527
Injected Activity [mCi]	13.64	3.96	15.18	2.71	0.36
Injected Mass [µg]	3.84	3.29	3.25	3.23	0.69
Specific Activity [mCi/nmol]	3.40	2.78	5.01	5.17	0.32
Free Fraction (<i>f_p</i>)	0.001	0.0004	0.001	0.004	0.26
Duration since antipsychotic exposure (months)	N.A	-	27*	24	
Tobacco Smoker (No/Yes)	9/9	50/50	5/2	71/29	0.4
Race (White/AA/Other)	11/6/1	61/33/6	4/3/0	57/43/0	
Ethnicity (Non-Hispanic/Hispanic)	16/2	89/11	5/2	71/29	
Lifetime Cannabis Exposure** (No/Yes)	5/12	29/71	2/4	33/66	1
Recent Cannabis exposure (No/Yes)	17/1	94.5/0.05	7/0	100/0	0.5

Medicated = receiving antipsychotic treatment; Unmedicated = not receiving antipsychotic treatment;

NART = National Adult Reading Test; BMI = Body Mass Index; FTND = Fagerstrom Tobacco Test for Nicotine Dependence; AA = African American

* Range (2 months – 60 months); One patient was antipsychotic naïve.

** Lifetime cannabis use data are missing in 2 SCZs (neither subject met criteria for any lifetime cannabis use disorder).