Evaluation of relationships between presence of adhesio interthalamica and cannabis use in first-episode psychosis: a magnetic resonance imaging investigation

Luciano de Menezes Sanchez[1]*
https://orcid.org/0000-0001-8722-2252
Paulo Jannuzzi Cunha[1]
https://orcid.org/0000-0002-2288-9838
Maristela S Schaufelberger[1]
https://orcid.org/0000-0002-1927-1404
Clarissa Trzesniak[3]
https://orcid.org/0000-0002-7552-9959
Fábio LS Duran[1]
https://orcid.org/0000-0002-7603-6152
Marcia Scazufca[4]
https://orcid.org/0000-0002-4545-006X
Paulo R Menezes[2]
https://orcid.org/0000-0001-6330-3314
Robin M Murray[5]
https://orcid.org/0000-0003-0829-0519
Jaime E Hallak[3]
https://orcid.org/0000-0002-8784-0189
José Alexandre S Crippa[3]
https://orcid.org/0000-0001-9520-6746
Geraldo F Busatto[1]
https://orcid.org/0000-0003-4749-4602

[1]Laboratory of Psychiatric Neuroimaging (LIM 21), Department of Psychiatry, Faculdade de Medicina FMUSP, Universidade de Sao Paulo, Sao Paulo, SP, Brazil
[2]Department of Preventive Medicine, Faculty of Medicine, University of São Paulo, São Paulo city, São Paulo, Brazil
[3]Department of Neuroscience and Behavior, School of Medicine of Ribeirão Preto, University of São Paulo, Hospital das Clinicas Ribeirão Preto, São Paulo, Brazil
[4]Department of Psychiatry, Faculty of Medicine, University of São Paulo, São Paulo city, São Paulo, Brazil
[5]Institute of Psychiatry, Psychology, and Neuroscience, King's College, London, UK

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ABSTRACT

Recent studies suggested that cannabis use influences on the emergence of psychosis by disrupting neurodevelopmental processes that occur during adolescence and early adulthood and which are reflected on brain anatomical changes detectable with MRI. However, no MRI studies have investigated whether intrauterine neurodevelopmental abnormalities also interact with later cannabis use to influence on psychosis risk. We investigated differences between first-episode psychosis (FEP) patients with history of cannabis use (FEPC+, n=28), FEP subjects without cannabis use (FEPC-, n=78) and healthy controls (n=80) in regard to the frequency of absent or short Adhesio Interthalamica (AI), a well-established marker of intrauterine neurodevelopment. The FEPC+ subgroup had a significantly lower prevalence of absent AI than FEPC- subjects, as well as a lack of a significantly shorter AI length compared to controls (as found in FEPC- subjects). These preliminary results show that psychosis subjects with cannabis use present a low rather than high frequency of absent AI, suggesting that fixed intrauterine neurodevelopmental abnormalities may not be associated with cannabis use later in life to influence on the emergence of psychosis. This is consistent with a view that multiple different etiological processes may lead to similar clinical presentations in patients with FEP.

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Keywords: Adhesio Interthalamica; Cavum Septum Pellucidum; Cannabis; First episode psychosis; Neurodevelopmental; Magnetic resonance imaging

Introduction

In his initial description of dementia praecox, Emil Kraepelin proposed this condition to be the result of adult-onset neurodegenerative processes, based on his observation of patients presenting chronic symptoms of increased severity over time [1]. Many years later, a number of research results contradicted Kraepelin´s initial view, including evidence that individuals with schizophrenia present higher rates of minor physical anomalies [2], early neuromotor development abnormalities [3], and history of gestational adverse events and perinatal complications [4]. These findings led to the reconceptualization of schizophrenia as an early-onset neurodevelopmental disorder [5]. Recently, other studies have shown that environmental variables which operate at later stages of life are also risk factors that potentially contribute to the development of schizophrenia, such as adverse life events in

Address for correspondence: Luciano de Menezes Sanchez, Centro de Medicina Nuclear, 3° andar, LIM-21/Rua Dr. Ovidio Pires de Campos, s/n, 05403-010 Sao Paulo, SP, Brazil

childhood [6], degree of urbanicity [7], and exposure to high-potency cannabis in adolescence and early adult life [8]. The complex and dynamic influences of such variables on neurodevelopment have led to the Developmental Risk Factor Model for schizophrenia, an integrative framework that aims to take into account the interplay between genetic risk, social and environmental stress factors, acting at multiples stages of neurodevelopment to influence on the emergence of psychosis [9].

Prior to the proposition of the above Developmental Risk Factor Model for schizophrenia, some reports suggested that patients suffering from psychotic conditions with comorbid cannabis use might present lesser neurodevelopmental abnormalities than psychosis subjects with no comorbid substance abuse [10,11]. This was based on evidence that psychosis patients with comorbid cannabis use may be less prone to present cognitive abnormalities and brain volume deficits as assessed with magnetic resonance imaging (MRI) [10–12]. Contrary to that, other recent MRI investigations have shown that cannabis use in adolescence and early adulthood is associated with abnormal patterns of cortical gyrification (possibly through disruption of normal neurodevelopment) [13], as well as with reduced cortical thickness in male subjects at high genetic risk for schizophrenia [14]. Moreover, recent epidemiological studies have shown that heavy cannabis use (but not other variables such as family history of psychosis) significantly anticipates the age of onset of psychotic disorders [15]. In the context of the conceptualization of psychotic disorders using the broad integrative model outlined above, the latter findings support a view that cannabis use during adolescence and early adulthood may influence on the emergence of psychosis by interfering with key neurodevelopmental processes that determine patterns of cortical thickness and gyrification.

The Adhesio Interthalamica (AI), also known as Massa Intermedia, is a gray matter bridge placed between the medial borders of both thalami across the third ventricle, which generally fuses *in utero* during the 13th or 14th weeks of gestation [16]. Its absence is thought to be a marker of deviant intrauterine neurodevelopment of the human brain [17], possibly associated with abnormal development of surrounding brain structures including the thalamus, third ventricle and amygdala [18,19]. There have been repeated MRI findings of absent or reduced AI in association with schizophrenia [17,20,21] as well as other neuropsychiatric disorders [22-24]. However, no previous MRI study investigated the frequency of absent AI (considered a fixed imaging marker of intrauterine neurodevelopmental disruption) in cannabis-using psychosis patients, as opposed to MRI markers that are modifiable during later stages of brain development (such as cortical gyrification and thickness) [25,26]. MRI studies measuring AI indices may be useful to investigate if antenatal neurodevelopmental abnormalities would increase susceptibility to the latter influence of cannabis use on the emergence of psychosis.

The aim of the present MRI study was to analyze qualitative and quantitative AI measures in a representative sample of first episode psychosis (FEP) subjects divided into a subgroup with history of cannabis use (FEPC+) and a subgroup without history of cannabis use (FEPC-). We wished to investigate if there would be a higher frequency of absent AI in cannabis users (thus suggesting an interaction between deviant intra-uterine neurodevelopment and latter exposure to cannabis), or a lower prevalence of absent AI in cannabis users (then suggesting a trajectory of antenatal neurodevelopmental abnormalities influencing on the latter emergence of psychosis independent of cannabis exposure). We also measured the AI length in cases in which this gray matter bridge was present, in order to evaluate its relationship with: cannabis-related variables (age of initial drug exposure and duration of use); and age of onset of psychosis, considering the previously reported association between earlier age of psychosis onset and heavy cannabis use in adolescence [15].

Methods

Participants

A sample of 106 FEP patients was drawn from an epidemiological study of the incidence of psychotic disorders in the western metropolitan area of São Paulo, Brazil [27]. Potentially eligible subjects were identified by active surveillance of mental healthcare services for that region between 2002 and 2005 and people that made contact for the first time with these services [11,27]. The present MRI study included FEP subjects aged up to 50 years with a diagnosis of psychosis (affective or nonaffective) according to DSM-IV [28] as assessed by the Structured Clinical Interview for DSM (SCID) [29], after exclusion of those with organic disorders or brain lesions identified at MRI scanning. Other inclusion and exclusion criteria are detailed elsewhere [11]. Next-door neighbors were contacted as potential controls and screened to exclude the presence of psychotic symptoms using the Psychosis Screening Questionnaire [30] or history of alcohol or cannabis use. Subjects were classified regarding lifetime use of cannabis according to data collected using the SCID; patients were classified as having a lifetime history of cannabis use when presenting a frequency of use of at least 3 times/month for at least one year, regardless of a diagnosis of abuse or dependence and regardless of other concomitant substance use [11]. In total, we evaluated 28 patients with a history of cannabis use (FEPC+), 78 patients without cannabis use (FEPC-) and 80 healthy controls (HC). Sixteen subjects with no history of cannabis use, but positive history of cocaine or alcohol abuse were excluded.

Sociodemographic data, clinical measures and ethical aspects

Sociodemographic data were directly collected from case-notes and participant/family interviews. Psychotic symptoms were evaluated with the Positive and Negative Syndrome Scale (PANSS) [31], while information on substance use, psychosis diagnoses, drug treatment, illness duration and duration of untreated psychosis were evaluated using the SCID [29]. The local Institutional Review Board (IRB) approved the protocol and we obtained written informed consent from all participants.

MRI data and brain markers

Neuroimaging data were acquired using two 1.5 T MRI GE Signa scanners (General Electric, Milwaukee Wisconsin, USA) with the same acquisition protocols [11]. The presence of AI and its length were rated blindly by an experienced researcher (CMFT). The AI was considered present when seen in two or more contiguous coronal slices and in three or more 0.86 mm axial slices [32]. The AI length was calculated by multiplying the number of consecutive coronal slices presenting AI by 1.5 mm. This method was described by Crippa [32], and all measures were assessed for reliability by inter-rater (CMFT e JASC) and intra-rater (CMFT) intraclass correlation coefficients (ICCs), based on measurements of 30 randomly selected subjects. For all measures, ICCs were equal or higher than 0.91.

Statistical analysis

Normality of data was assessed for continuous sociodemographic, clinical and biomarkers data using the Shapiro–Wilk test. Between-group comparisons among the three subgroups (FEPC+, FEPC- and HC) were carried out with the Welch Two Sample t-test for normally distributed continuous variables, and the Kruskal-Wallis

rank sum test for variables that were not normally distributed. For the between-group comparison of mean AI length, subjects without AI were excluded [21]. Categorical variables were compared between subgroups using the Pearson's Chi-square test, except for the comparison of AI presence between the FEPC+ and FEPC- or FEPC+ and HC subgroups; in those two analyses, because of the small number of cases in the FEPC+ subgroup, we used the Corrected Pearson's Chi-square test [33], following the implementation suggested by Busing [34].

Significant associations between cannabis use variables (age of onset and duration of use) and AI length were analyzed in the FEPC+ subgroup with the Pearson Correlation test for normally distributed variables or Spearman's rank correlation rho test for non-normally distributed variables. Finally, in order to investigate the association between AI variables and age of psychosis onset taking into account the potential influence of cannabis use, a forced-entry multiple linear regression model was applied using age of onset of psychosis as dependent variable, and lifetime cannabis use, AI length and AI presence as potential predictors.

The statistical significance for all tests was set at $p < .05$. All statistical analyses were performed using the software R statistics, version 3.5.0.

Results

Clinical and demographic characteristics

The FEPC+ subgroup was younger and more frequently male (see Table 1). There were no differences in symptom severity (PANSS total score) or treatment history (use of antipsychotics) between the two patient subgroups. Also, there were no differences in the number of days with untreated psychosis and duration of psychosis between the two subgroups (Table 1). The age of onset of psychosis was earlier in the FEPC+ subgroup in relation to the FEP C- subgroup (p=0.002). In the FEPC+ subgroup, the average age of onset of cannabis use was 15.9 years (sd = 3.10), and the average duration of cannabis use in years was 6.54 (sd = 4.90, Table 1).

Neuroimaging markers

Between-group comparisons of adhesio interthalamica (AI)

The FEPC+ subgroup had a higher prevalence (96.43%) of AI when directly compared with the FEPC- subgroup (80.77%, p=0.046). No differences were found regarding to the presence of AI in either of the two FEP subgroups in comparison with HC (Table 2).

The AI length was significantly lower in the FEPC- subgroup compared to HC (p=0.003) (Table 1). There were no significant differences between the two FEP subgroups (p=0.776) or between the FEPC+ subgroup and controls (p=0.449) regarding this quantitative AI measure (Table 1).

Intra-group correlation analyses (FEPC+)

No significant correlations were found between AI length and variables associated with cannabis use: age of onset (r_S = -0.140, p = 0.474) or duration of use (r_S = -0.220, p = 0.260) (Figure 1).

Multiple Linear Regression (FEP)

A significant model was found (F(3,102)= 3.564, p=0.016, R-squared=0.094) (Table 3) including lifetime use of cannabis as

Table 1. Sociodemographic, clinical and neuroimaging variables in First Episode Psychosis subjects with cannabis use (FEP C+), First Episode Psychosis without cannabis use (FEP C-) and Healthy Controls (HC).

Variablesa	FEP C+ (n = 28)	FEP C- (n = 78)	HC (n = 80)	Statistics (p)		
				FEP C+ vs. FEP C-.	FEP C+ vs. HC	FEP C- vs. HC
Demographic and Clinical Variables						
Age, years	24.14 (6.51)	29.29 (8.65)	30.4 (8.30)	0.014b	0.002b	0.003b
Sex (Male/Female), n	21/7	31/47	41/39	0.003b	0.012b	0.006b
Psychosis, age of onset	23 (6.60)	28.6 (8.60)	-	0.002b	-	-
Total days of psychosis	419.42 (524.54)	237.83 (260.08)	-	0.088b	-	-
Days of untreated psychosis	273.35 (510.04)	121.12 (247.96)	-	0.139b	-	-
Use of Antipsychotics (AP), n	15 (53.57%)	48 (61.53%)	-	0.460b	-	-
AP exposure, days	121 (122)	105 (112)	-	0.630b	-	-
PANSS, total score	45.6 (12.70)	44.9 (11)	-	0.780b	-	-
Cannabis use, age of onset	15.9 (3.10)	-	-	-	-	-
Cannabis use, duration of use	6.54 (4.90)	-	-	-	-	-
Neuroimaging Variable						
AI Length, mm	20.28 (6.38)	19.88 (5.16)	21.93 (5.51)	0.776b	0.449f	0.003f

notes: PANSS (Positive and Negative Syndrome Scale); AI (adhesio interthalamica) a. Continuous variables are expressed by their means (standard deviation) and discrete variables are expressed by absolute numbers (percentage); b. Welch Two Sample t-test; c. Kruskal-Wallis rank sum test ; p<.05 are highlighted in bold.

Table 2. Comparison of AI prevalence among the First Episode Psychosis subjects with cannabis use (FEP C+), First Episode Psychosis without cannabis use (FEP C-) and Healthy Controls (HC).

Groups	AI present	AI absent	χ2 (df)	Phi	p
FEPC+ FEPC-	1 (3.57%) 15 (19.23%)	27 (96.43%) 63 (80.77%)	3.979 (1)	0.192	0.046a
FEPC+ HC	1 (3.57%) 9 (11.25%)	27 (96,43%) 71 (88.75%)	1.469 (1)	0.116	0.225a
FEPC- HC	15 (19.23%) 9 (11.25%)	63 (80.77%) 71 (88.75%)	1.959 (1)	0.112	0.161b

notes: a. Corrected Pearson's Chi-squared test; b. Pearson's Chi-squared test; p<.05 are highlighted in bold.

Table 3. Forced-Entry Multiple Linear Regression model of the lifetime cannabis use, AI presence and AI length vs. Age of onset of psychosis in the FEP group

Variables	Coefficient (β)	Std. Error	t	95% CI	p
Age of onset of psychosis (Dependent Variable)					
Intercept	19.180	4.132	4.641	10.98 - 27.37	<0.000
Lifetime cannabis use	5.363	1.849	2.900	1.69 - 9.03	0.004
AI presence	0.684	3.885	0.176	-7.02 - 8.39	0.860
AI length	-0.113	0.158	-0.715	-0.42 - 0.20	0.476

note: Multiple R-squared: 0.094, Adjusted R-squared: 0.068; F-statistic: 3.564 on 3 and 102 DF, p-value: 0.016; p<.05 are highlighted in bold.

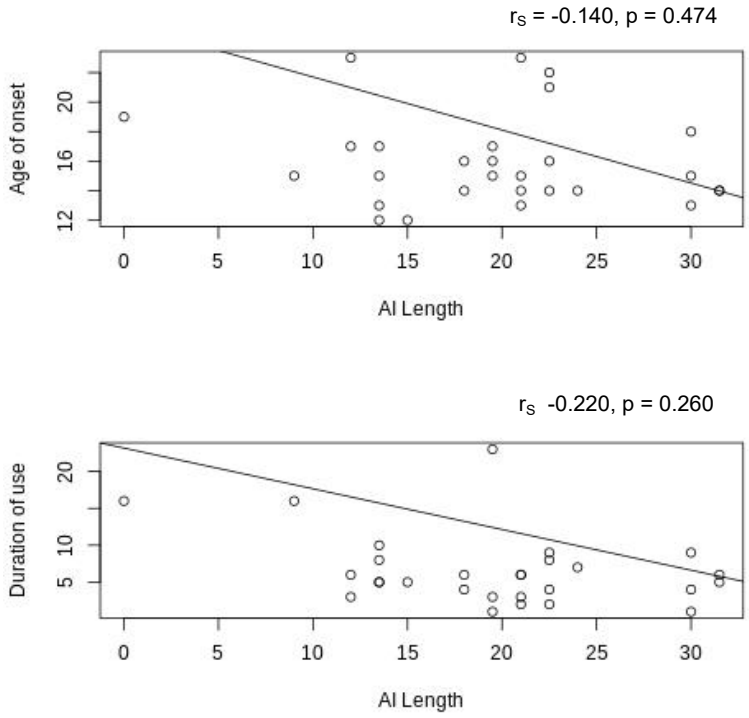

Figure 1. Scatterplot of FEPC+ Correlations (Spearman's rank correlation rho)

the only significant predictor of age of onset of psychosis (p=0.004). Age of onset of psychosis was not significantly predicted by AI presence (p=0.860) or AI Length (p=0.476), nor by interactions between AI variables and cannabis use (Table 3).

Discussion

Several previous studies and meta-analyses have reported an increased frequency of absent AI in psychosis patients, and established absent AI as a reliable marker of early, antenatal neurodevelopmental alterations associated with psychosis [17,20,21,24]. To the best of our knowledge, this is the first study to compare indices of absent or reduced AI between cannabis using (FEPC+) and non-using (FEPC-) subgroups of FEP patients. We found that FEP patients with a history of cannabis use (FEPC+) had a significantly lower prevalence of absent AI than those without cannabis use (FEPC-), as well as a lack of a significantly shorter AI length compared to controls (as found in the FEPC- subgroup). Additionally, we found no significant correlations between AI length and either age of onset of cannabis use or duration of drug use in the FEPC+ subgroup. Taken together, these results suggest that fixed intrauterine neurodevelopmental abnormalities (of which absent AI is considered a marker) may not interact with cannabis use later in life to influence on the emergence of psychosis. This reinforces a view that different etiological processes may lead to similar clinical presentations in patients with FEP, with antenatal neurodevelopmental abnormalities possibly increasing risk of psychosis in some cases through a trajectory that is independent of later environmental influences such as cannabis use.

Previous studies have shown that multiple factors may independently impact on the age of onset of psychotic symptoms, including cannabis use [15] and events related to early neurodevelopmental processes such as obstetric complications [35]. The results of our multiple regression analysis indicated lifetime cannabis use as the only significant predictor of age of psychosis onset. The lack of any relationship between AI indices and age of psychosis onset is consistent with the results of previous studies [20,36] except for one [24], and it should be noted that none of such studies controlled results for cannabis use. We tested the significance of a forced-entry multiple linear regression model, and found no significant interactions between history of cannabis use and either reduced AI length or absent AI in predicting an earlier age of onset of psychotic symptoms. This might be taken to further suggest that cannabis use does not significantly interact with the presence of fixed markers of aberrant intrauterine neurodevelopment to influence on the emergence of psychosis.

Neurodevelopmental processes are complex and unfold in multiple ways during many years after childbirth [37]. Recent MRI studies have introduced evidence suggesting that cannabis use may influence on the emergence of psychosis by interfering with processes of brain maturation that evolve during adolescence and early adulthood [13,14]. As we did find an association between

cannabis use and an earlier age of psychosis onset, our pattern of neuroimaging results hint at a possible dichotomy whereby cannabis use would influence on the emergence of psychosis by interacting predominantly with neurodevelopmental processes that occur during adolescence and early adulthood [38], while not interacting significantly with neurodevelopmental abnormalities originated *in utero*.

History of antipsychotic use, intensity and duration of psychotic symptoms were all similar among the FEPC- and FEPC+ subgroups; it is therefore unlikely that the between-group AI differences reported herein would have been significantly influenced by such variables. There was a higher prevalence of male gender in the FEPC+ subgroup relative to the FEPC- subgroup; however, this would be expected to increase the prevalence of absent AI in the FEPC+ subgroup, given the known greater frequency of such finding in the overall male population [39,40]. Since we found the opposite in the FEPC+ subgroup, the hypothesis of no interaction between cannabis use and abnormal intrauterine neurodevelopment is further corroborated.

It is relevant to mention that the sample size of the FEPC+ subgroup in our study is smaller when compared with some previous investigations (sample sizes of psychosis patients from multiple published AI studies have ranged from 26 to 192) [17]. Nonetheless, the frequency of cannabis users in our study is consistent with the prevalence of patients with cannabis use reported in previous epidemiological cohorts of FEP patients [8] Moreover, our sample size was sufficient to demonstrate a significant difference between FEP subgroups in regard to the frequency of absent AI, the antenatal neurodevelopmental marker most consistently associated with psychosis [17,20,21,24]. When considering only the previous studies that compared AI measures across subgroups of psychosis patients, sample sizes were comparable to the size of the FEP subgroups evaluated herein [36,41]. Given the practical difficulties in recruiting large samples at a single site, future investigations pooling together MRI data from different single-site studies may be needed to afford effect sizes of greater magnitude. The ENIGMA Consortium provides recent examples of such international multi-site endeavors [42].

A number of considerations should be made regarding to the MRI methods employed herein. First, we combined data acquired using two different MRI scanners. However, equipment and acquisition protocols were identical, and we previously reported results of a reliability analysis for brain volume measurements showing high ICCs for the right and left thalamus, neocortical regions, medial temporal cortex and total brain volume [43]. Second, several recent MRI studies of schizophrenia have used equipment of higher field strength (3.0T) compared to the 1.5T scanners used in the present study [17], but only one 3.0T study to date evaluated AI measurements in psychosis patients [44]. Third, a number of other 1.5T MRI studies have calculated AI indices using data acquired in slices of 1.0mm or thinner compared to our 1.5mm slice thickness protocol [20,24,32]. In general, it is considered that thinner and contiguous slices are the "gold-standard" method to afford estimates of AI measures with superior accuracy. The use of thicker slides might occasionally miss a narrow connection between the thalami and overestimate the prevalence of absent AI [17]. However, to our knowledge, no study directly compared AI measurements on the same samples evaluated repeatedly using slice thickness of 1.5mm or thinner, in order to investigate whether there differences in the prevalence of absent AI across distinct standardized rating protocols. One meta-analysis performed a sensitivity analysis excluding studies with slice thickness > 1.0mm and found no difference in the results [17]. Future multi-centric studies pooling raw MRI data acquired with diverse protocols and analyzed using different standardized AI rating methods may be needed to provide sensitivity information for multiple AI measuring protocols.

A few other limitations of the current study must also be acknowledged. First, the cross-sectional design limits the interpretation of causality implicating cannabis use on variations in AI length; due to the limited number of FEPC+ subjects who underwent a second MRI assessment [21], we refrained from investigating differences between FEPC+ and FEPC- in regard to AI changes over time. Second, only retrospective information was used to ascertain patterns of cannabis consumption, with no confirmation of use by toxicological tests. Third, the FEP sample was dichotomized into subjects with and without lifetime cannabis use, and this prevented us from investigating how a less or more frequent cannabis use might be associated with our quantitative AI variable. Finally, we did not have objective information about the estimated THC/cannabidiol ratios and other cannabinoids present in the cannabis that the FEPC+ subjects used.

On the other hand, there are two strengths of the study that should, in our view, be highlighted. First, the groups were drawn from participants of an epidemiological study [27] including next-door neighbors as controls, with subjects being more representative of the overall population than those recruited for MRI studies typically carried out in tertiary hospitals. Second, we used a well-established quantitative method for the evaluation of AI, thus improving reliability and sensitivity and reducing the variability inherent to using only qualitative ranking methods to ascertain the presence or absence of AI [17,44].

To conclude, the preliminary results of the current study show that psychosis subjects with cannabis present a low rather than high frequency of absent AI, suggesting that fixed intrauterine neurodevelopmental abnormalities may not be associated with cannabis use later in life to influence on the emergence of psychosis. This is consistent with a view that multiple different etiological processes may lead to similar clinical presentations in patients with FEP. Future MRI studies involving larger samples of psychosis patients with and without cannabis use and acquiring prospective follow-up data are warranted to further investigate the interplay between cannabis use and the several types of neuroanatomic variations related to neurodevelopmental processes which may unfold during different periods of life.

Future MRI studies involving larger samples of psychosis patients with and without cannabis use and acquiring prospective follow-up data are warranted to further investigate the interplay between cannabis use and the several types of neuroanatomic variations related to neurodevelopmental processes which may unfold during different periods of life.

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