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Associations between adolescent cannabis use and brain structure in psychosis

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ABSTRACT

Associations between cannabis use and psychotic disorders suggest that cannabis may be a contributory risk factor in the neurobiology of psychosis. In this study, we examined brain structure characteristics, total and regional gray matter density (GMD), using Voxel Based Morphometry, in psychotic individuals, stratified by history of cannabis use (total $n = 109$). We also contrasted GMD estimates in individual diagnostic groups (schizophrenia/bipolar I disorder) with and without history of adolescent cannabis use (ACU). Individuals with psychosis as a whole, both with and without history of ACU, had lower total and regional GMD, compared to healthy controls. ACU was associated with attenuated GMD reductions, compared to non-users, especially in the schizophrenia cases, who showed robust GMD reductions in fronto-temporal and parietal cortex, as well as subcortical regions. Notably, total and regional GMD estimates in individuals with psychosis and ACU were not different from controls with no ACU. These data indicate that the history of ACU in psychotic individuals is associated with attenuated GMD abnormalities. Future investigations targeting potential unique etiological and risk factors associated with psychosis in individuals with ACU may help in understanding of the neurobiology of psychotic disorders and novel treatment options for these individuals.

1. Introduction

According to the UNO World Drug Report, about 3.8 percent of the global population used cannabis in the past year, roughly the same proportion as in the last decade (United Nations Office on Drugs and Crime, World Drug Report 2017), making cannabis among the most frequently used illicit drugs in the world. In the US, the prevalence of cannabis use is on the rise and has reached 13.5% of the population (United Nations Office on Drugs and Crime, World Drug Report 2017). Cannabis use disorders are a common comorbidity for schizophrenia and related psychotic disorders, with a recent meta-analysis estimating current cannabis use at 16%, and lifetime cannabis use at 27%, with higher rates in males and in first episode schizophrenia individuals (Koskinen et al., 2010). Cross-sectional and longitudinal studies show a consistent relationship between cannabis use and psychotic disorders (Gage et al., 2016). Cannabis use prior to onset of psychosis (Semple et al., 2005) is associated with earlier onset of illness (Tosato et al., 2013). In addition, onset of cannabis use at younger ages (Large et al., 2011) and the frequent use of more potent strains of cannabis are associated with higher risk of developing psychosis (Di Forti et al., 2014). This temporal and dose response relationship between cannabis use and psychosis (Kraan et al., 2016) suggests that cannabis can be a contributory risk factor in the neurobiology of psychotic disorders. This clinical observation can also be found in basic neuroscience studies showing that the adolescent brain responds differently to cannabis use than the adult brain, making it susceptible to cannabis use and resulting in lasting effects on brain circuitry and morphology (Grigorenko et al., 2002; Kittler et al., 2000; Quinn et al., 2008; Realini et al., 2011; Rubino and Parolaro, 2016; Rubino et al., 2009).

An unexpected and intriguing observation is that premorbid cannabis use in schizophrenia is associated with better cognitive function, compared to individuals with schizophrenia without history of cannabis use (Hanna et al., 2016; Schnell et al., 2012; Yucel et al., 2012), though some studies have not supported this observation (Ringen et al., 2010). Schnell et al., (2012) have found less severe cognitive impairments and

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Table 1
Substance use characteristics of the study sample.

a. Substance use characteristics in the Psychosis Groups

	HC-NonACU *(n = 32)*	HC-ACU *(n = 14)*	PSY-NonACU *(n = 35)*	PSY-ACU *(n = 28)*	Statistical test**
Lifetime substance use disorder diagnosis					
Cannabis use–Age of first use	21.11 (17–35)	15.57 (14–17)	17.83 (15–20)	14.48 (5–17)	$F_{(3,60)} = 13.79$, $p < 0.001$
Cannabis use–Age of last use	21.00 (10–37)	24.90 (16–31)	41.67 (27–55)	36.60 (15–55)	$F_{(3,29)} = 0.52$, NS
Cannabis use–Amount of use					$\chi^2_{(6)} = 107.27$, $p < 0.001$
Less than 5 times over lifetime	100%	0%	100%	0%	
5–50 times over lifetime	0%	25%	0%	4%	
More than 50 times over lifetime	0%	75%	0%	96%	
Cannabis abuse	0%	7%	0%	4%	$\chi^2_{(3)} = 3.91$, NS
Cannabis dependence	0%	14%	0%	32%	$\chi^2_{(3)} = 22.8$, $p = 0.001$
Other substance Abuse/Dependence*	6%	43%	26%	89%	$\chi^2_{(3)} = 47.07$, $p < 0.001$

b. Substance use characteristics in the Diagnosis Groups

	HC-NonACU *(n = 32)*	HC-ACU *(n = 14)*	BP-NonACU *(n = 12)*	BP-ACU *(n = 7)*	SZ-NonACU *(n = 23)*	SZ-ACU *(n = 21)*	Statistical test*
Lifetime substance use disorder diagnosis							
Cannabis use–Age of first use	21.11 (17–35)	15.57 (14–17)	18.67 (18–20)	12.64 (5–17)	17.56 (15–20)	15.10 (12–17)	$F_{(5,58)} = 9.26$, $p < 0.001$
Cannabis use–Age of last use	21.00 (10–37)	24.90 (16–31)	n\a	32.50 (32–43)	41.67 (27–55)	37.23 (15–55)	$F_{(5,27)} = 0.48$, NS
Cannabis use–Amount of use							$\chi^2_{(10)} = 108.09$, $p < 0.001$
Less than 5 times over lifetime	100%	0%	100%	0%	100%	0%	
5–50 times over lifetime	0%	25%	0%	14%	0%	0%	
More than 50 times over lifetime	0%	75%	0%	86%	0%	100%	
Cannabis abuse	0%	7%	0%	0%	0%	5%	$\chi^2_{(5)} = 4.57$, NS
Cannabis dependence	0%	14%	0%	29%	0%	33%	$\chi^2_{(5)} = 22.93$, $p < 0.001$
Other substance abuse/ Dependence*	6%	43%	33%	86%	22%	90%	$\chi^2_{(5)} = 47.57$, $p < 0.001$

***Other Substance Abuse/Dependence diagnoses included Alcohol, Cocaine, and Amphetamine use disorders.**

****Post hoc pairwise comparisons (Tukey HSD or chi square, as appropriate);** only statistically significant ($p < 0.05$) differences are reported:

a. Psychosis Groups:

Cannabis use – Age of first use: HC-NonACU > HC-ACU ($p < 0.001$), PSY-NonACU ($p < 0.05$); PSY-ACU ($p < 0.001$); PSY-NonACU > PSY-ACU ($p < 0.01$).

Cannabis use – Amount of use: There was a higher proportion of heavy users among HC-ACU compared to HC-NonACU ($\chi^2_{(2)} = 44.0$, $p < 0.001$) and PSY-NonACU ($\chi^2_{(2)} = 46.0$, $p < 0.001$); and among PSY-ACU compared to HC-NonACU ($\chi^2_{(2)} = 56.0$, $p < 0.001$) and PSY-NonACU ($\chi^2_{(2)} = 58.0$, $p < 0.001$).

Cannabis Dependence: There was a higher proportion of Cannabis Dependence among HC-ACU compared to HC-NonACU ($\chi^2_{(1)} = 4.78$, $p = 0.029$) and PSY-NonACU ($\chi^2_{(1)} = 5.21$, $p = 0.022$); and among PSY-ACU compared to HC-NonACU ($\chi^2_{(1)} = 12.1$, $p = 0.001$) and PSY-NonACU ($\chi^2_{(1)} = 13.13$, $p < 0.001$).

Other Substance Use: There was a higher proportion of Other Substance Use among HC-ACU compared to HC-NonACU ($\chi^2_{(1)} = 9.08$, $p = 0.003$); and among PSY-ACU compared to HC-ACU ($\chi^2_{(1)} = 10.41$, $p = 0.001$) and HC-NonACU ($\chi^2_{(1)} = 41.6$, $p < 0.001$) and PSY-NonACU ($\chi^2_{(1)} = 25.31$, $p < 0.001$); and among PSY-NonACU compared to HC-NonACU ($\chi^2_{(1)} = 4.62$, $p = 0.032$).

b. Diagnosis Groups:

Cannabis use – Age of first use: HC-NonACU > HC-ACU ($p < 0.001$), SZ-ACU ($p < 0.001$); BP-ACU ($p < 0.001$); BP-ACU < SZ-NonACU ($p < 0.05$); BP-NonACU ($p < 0.05$).

Cannabis use – Amount of use: There was a higher proportion of heavy users among HC-ACU compared to HC-NonACU ($\chi^2_{(2)} = 44.0$, $p < 0.001$) and SZ-NonACU ($\chi^2_{(2)} = 34.0$, $p < 0.001$) and BP-NonACU ($\chi^2_{(2)} = 24.0$, $p < 0.001$); and among SZ-ACU compared to HC-NonACU ($\chi^2_{(2)} = 49.0$, $p < 0.001$) and SZ-NonACU ($\chi^2_{(2)} = 39.0$, $p < 0.001$) and BP-NonACU ($\chi^2_{(2)} = 29.0$, $p < 0.001$); and among BP-ACU compared to HC-NonACU ($\chi^2_{(2)} = 39.0$, $p < 0.001$) and SZ-NonACU ($\chi^2_{(2)} = 29.0$, $p < 0.001$) and BP-NonACU ($\chi^2_{(2)} = 19.0$, $p < 0.001$).

Cannabis Dependence: There was a higher proportion of Cannabis Dependence among HC-ACU compared to HC-NonACU ($\chi^2_{(1)} = 4.78$, $p = 0.029$); and among SZ-ACU compared to HC-NonACU ($\chi^2_{(1)} = 12.29$, $p < 0.001$) and SZ-NonACU ($\chi^2_{(1)} = 9.12$, $p = 0.003$) and BP-NonACU ($\chi^2_{(1)} = 5.08$, $p = 0.024$); and among BP-ACU compared to HC-NonACU ($\chi^2_{(1)} = 9.64$, $p = 0.002$) and SZ-NonACU ($\chi^2_{(1)} = 7.04$, $p = 0.008$) and BP-NonACU ($\chi^2_{(1)} = 3.83$, $p = 0.05$).

Other Substance Use: There was a higher proportion of Other Substance Use among HC-ACU compared to HC-NonACU ($\chi^2_{(1)} = 9.08$, $p = 0.003$); and among SZ-ACU compared to HC-ACU ($\chi^2_{(1)} = 9.33$, $p = 0.002$) and HC-NonACU ($\chi^2_{(1)} = 37.6$, $p < 0.001$) and SZ-NonACU ($\chi^2_{(1)} = 20.92$, $p < 0.001$) and BP-NonACU ($\chi^2_{(1)} = 11.81$, $p = 0.001$); and among BP-ACU compared to HC-NonACU ($\chi^2_{(1)} = 22.24$, $p < 0.001$) and SZ-NonACU ($\chi^2_{(1)} = 9.46$, $p = 0.002$) and BP-NonACU ($\chi^2_{(1)} = 4.87$, $p = 0.027$); and among BP-NonACU compared to HC-NonACU ($\chi^2_{(1)} = 5.44$, $p = 0.02$).

HC: healthy controls; PSY: volunteers with psychosis; SZ: volunteers with schizophrenia or schizoaffective disorder; BP: volunteers with psychotic bipolar I disorder, HC: healthy controls; ACU: adolescent onset cannabis use; Non-ACU: cannabis non-users.

gray matter reductions in the middle frontal regions in patients with schizophrenia and concurrent cannabis use (Schnell et al., 2012). Two meta-analyses confirm the observation that previous cannabis use in schizophrenia is associated with less cognitive impairment (Rabin et al., 2011; Yucel et al., 2012). This association is more consistent in studies that focused on adolescent cannabis use (ACU), which was found to be associated with milder cognitive impairment compared to non-users (Hanna et al., 2016; Yucel et al., 2012), contrary to the observation of poorer cognition associated with ACU in otherwise healthy individuals (Meier et al., 2012).

We recently reported that in individuals with psychosis (schizophrenia/schizoaffective disorder [SZ] and psychotic bipolar I disorder [BP]), ACU was associated with less impaired global cognitive function, as measured by the Brief Assessment of Cognition in Schizophrenia (BACS), compared to cannabis non-users (Hanna et al., 2016). Further, we found that this effect on cognition was specifically driven by differences between the SZ with and without history of ACU, and not the BP, subgroups.

Here, we extended our work by examining brain structure characteristics—whole brain and regional gray matter density (GMD)—in