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Relation between cannabis use and subcortical volumes in people at clinical high risk of psychosis

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ABSTRACT

Among people at genetic risk of schizophrenia, those who use cannabis show smaller thalamic and hippocampal volumes. We evaluated this relationship in people at clinical high risk (CHR) of psychosis. The Alcohol and Drug Use Scale was used to identify 132 CHR cannabis users, the majority of whom were non-dependent cannabis users, 387 CHR non-users, and 204 healthy control non-users, and all participants completed magnetic resonance imaging scans. Volumes of the thalamus, hippocampus and amygdala were extracted with FreeSurfer, and compared across groups. Comparing all CHR participants with healthy control participants revealed no significant differences in volumes of any ROI. However, when comparing CHR users to CHR non-users, a significant ROI × Cannabis group effect emerged: CHR users showed significantly smaller amygdala compared to CHR non-users. However, when limiting analysis to CHR subjects who reported using alcohol at a 'use without impairment' severity level, the amygdala effect was non-significant; rather, smaller hippocampal volumes were seen in CHR cannabis users compared to non-users. Controlling statistically for effects of alcohol and tobacco use rendered all results non-significant. These results highlight the importance of controlling for residual confounding effects of other substance use when examining the relationship between cannabis use and neural structure.

1. Introduction

Cannabis is the most extensively used illegal substance in people with schizophrenia. A recent review of the literature established that this is also true in people at clinical high risk (CHR) of developing psychosis (Addington et al., 2014), that is, individuals who present with attenuated or brief intermittent psychotic symptoms, or have a genetic risk for psychosis and decline in functioning. There is also some research implicating cannabis as one important factor in the onset of psychosis (Caspi et al., 2005; Fusar-Poli et al., 2012a; Kuepper et al., 2011; Moore et al., 2007). Prospective data suggests that among people at CHR of psychosis who use cannabis, those with higher baseline use severity (Buchy et al., 2015a) and frequency (Valmaggia et al., 2014), and a first use prior to age of 15 (Arseneault et al., 2002; Valmaggia et al., 2014) all confer a greater risk of transition to psychosis.

Recent work has established a link between cannabis use and subcortical volumes in people with schizophrenia. The thalamus, hippocampus and amygdala have been of particular interest as people with schizophrenia show volumetric reductions in these areas relative to healthy people (Bora et al., 2011; Chan et al., 2011; Ellison-Wright et al., 2008) and these regions are rich in cannabinoid 1 (CB1) receptors in the human brain (Glass et al., 1997). For

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example, chronic, heavy cannabis use has been associated with volumetric reductions in the hippocampus and amygdala (Lorenzetti et al., 2015). People with schizophrenia and a cannabis use disorder show cannabis-related shape differences in thalamus, striatum and globus pallidus, compared to patients without a cannabis use disorder (Smith et al., 2014), and cannabis users with schizophrenia show marked hippocampal shape deflation compared to healthy controls (Solowij et al., 2013). Several studies have established a link between subcortical volumes and cannabis use in people at familial risk of schizophrenia. One study reported that those who used cannabis frequently (i.e. at least once a month but not more than three times per week) had an enlarged third ventricle relative to other use frequencies, which could reflect gray matter loss in the adjacent anterior medial thalamus (Welch et al., 2011a). A second study used manual tracing technique and showed that people at familial risk of schizophrenia who consumed cannabis over a 2-year period showed bilateral volume loss in the thalamus, but not in the hippocampus or amygdala, compared to a non-exposed group (Welch et al., 2011b). A third study used an automated tensor-based morphometry analysis to detect gray matter loss in right anterior hippocampus (Welch et al., 2013). Together these finding suggest that people at familial risk of schizophrenia are particularly sensitive to the risk-modifying effects of cannabis on thalamic and perhaps hippocampal structure, but not on amygdala volumes. Very recent evidence suggests that thalamic functional connectivity may be impacted by cannabis use patterns in youth at clinical high risk of psychosis (Buchy et al., 2015b); however, it is unknown whether thalamic and other subcortical volumes are associated with cannabis use in this population. The CHR population offers a unique opportunity to study the relationship between cannabis use and subcortical volumes in people who are more likely to transition to psychosis than people at familial risk of psychosis or healthy people.

Based on the literature described above, the aim of the current report was to evaluate thalamic, hippocampal and amygdala volumes in CHR participants who used cannabis at baseline compared to CHR non-users. We hypothesized that CHR cannabis users would show significantly smaller thalamic and hippocampal volumes compared to CHR participants who did not use cannabis.

2. Methods

2.1. Participants

Participants were recruited for the second phase of the multisite North American Prodrome Longitudinal Study (NAPLS-2) (Addington et al., 2012), a 2-year longitudinal study which was established to investigate predictors and mechanisms of transition to psychosis. The final NAPLS sample consists of 764 CHR participants and 280 healthy controls (HC). The present paper reports on the 519 CHR participants in NAPLS-2 who provided baseline magnetic resonance (MR) scans and also completed a baseline assessment on cannabis use, as well as 204 HC participants who were not using cannabis at a baseline and provided MR scans. All CHR participants were required to meet the Criteria of Prodromal Syndromes (COPS) using the Structured Interview for Prodromal-Risk Syndromes (SIPS) (McGlashan et al., 2010).

Participants were excluded if they met criteria for any current or lifetime axis I psychotic disorder, IQ < 70, past or current history of central nervous system disorder or DSM-IV criteria for current substance dependence disorder. HC participants were also excluded if they had a first-degree relative with a current or past psychotic disorder. A more detailed description of ascertainment, inclusion and exclusion criteria, and participant details is provided elsewhere (Addington et al., 2012).

2.2. Measures

The SIPS and the Scale of Prodromal Symptoms (SOPS) (McGlashan et al., 2010) were used to assess criteria for a prodromal syndrome and severity of attenuated positive symptoms. Post-training agreement on determining the prodromal diagnoses was excellent (kappa = 0.90) (Addington et al., 2012).

Cannabis use in the last month was rated using the Alcohol and Drug Use Scale (AUS/DUS) (Drake et al., 1996) which records severity (1 = abstinent, 2 = use without impairment, 3 = abuse, 4 = dependence) and frequency of use (0 = no use, 1 = once or twice per month, 2 = 3–4 times per month, 3 = 1–2 times per week, 4 = 3–4 times per week, 5 = almost daily) in the last month. Alcohol and tobacco use were also recorded.

2.3. MRI scans

Scanning was performed at eight sites. Five sites (UCLA, Emory, Harvard, UNC, and Yale) used Siemens-Trio 3T scanners, two sites (Zucker-Hillside Hospital and UCSD) used GE HDx scanners, and one site (Calgary) used a GE Discovery scanner. All Siemens sites used a 12-channel head coil and all GE sites used an 8-channel head coil. Sequence parameters were optimized for each scanner manufacturer, software version and coil configuration according to the ADNI protocol (http://adni.loni.usc.edu/methods/documents/mri-protocols/). Scans were acquired in the sagittal plane with a 1 mm*1 mm in-plane resolution and 1.2 mm slice thickness. Siemens scanners used an MPRAGE sequence with a 256 (axial) $\times$ 240 (sagittal) $\times$ 176 (coronal) mm field of view, TR/TE/TI = 2300/2.91/900 ms and a 9° flip angle, while GE scanners used an IR-SPGR sequence with a 26 cm field of view, TR/TE/TI = 7.0/minimum full/400 ms and an 8° flip angle.

2.4. Image processing

Subcortical volumetric segmentation of the thalamus was processed using FreeSurfer version 5.2 (http://surfer.nmr.mgh.harvard.edu/) at Yale University by investigators who had participated in the FreeSurfer training course at the Martinos Center for Biomedical Imaging. The subcortical segmentation procedure assigns a neuroanatomical label to each voxel of the MRI volume using a probabilistic atlas and a Bayesian classification rule (Fischl et al., 2002). See Cannon et al. (2014) for details on the quality assurance procedure.

2.5. Statistical analyses

A regression analysis adjusted “raw” ROI volumes for normal variation in age based on observed relationships of the ROIs with age in the HC sample (Mathalon et al., 2003; Pfefferbaum et al., 1995). Specifically, for each ROI, volumetric data were linearly regressed on age in the HC group, and the resulting regression equation was used to derive predicted ROI volumes based on age for all subjects. These age-specific predicted volumes were then subtracted from observed volumes, and the difference was divided by the standard error of regression from the HC age-regression model. This resulted in an age-adjusted z-score for each participant based on the normative data provided by the HC group. By definition, the mean $\pm$ standard deviation for age-adjusted z-scores in the HC group equals 0 ± 1. For CHR participants, z-scores provide volume estimates relative to that which would be expected from healthy individuals of a particular age. For all groups, z-scores express deviations of ROI volumes from the age-specific normative ROI volume estimates in standard units. Accordingly, the profile of ROI z-score means for the HC's used herein in group comparisons was nearly flat (i.e., all ROI means equal to