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Concept Paper Form

Provisional Paper Title: Persistent cannabis use and midlife brain integrity
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Today's Date: 10/26/2020

Please describe your proposal in 2-3 pages with sufficient detail for helpful review.

Objective of the study:

In the United States, increased legalization of cannabis for recreational and therapeutic use has been accompanied by a decrease in the perceived risks for harm associated with the drug (Gruber et al., 2017). However, cannabis use is concomitantly emerging as a risk factor for a number of negative outcomes, especially in older adults with a long history of persistent use. In particular, impaired brain function associated with chronic cannabis use has been consistently revealed through cognitive testing (Hall, 2015; Volkow et al., 2016). Consistent with these findings, chronic cannabis use has been associated with structural alterations in the brain's gray matter and white matter supporting cognitive functions, as ascertained via neuroimaging. However, existing neuroimaging results are mixed and the cumulative evidence is inconclusive. For example, while reviews have highlighted fairly consistent gray matter alterations in cannabinoid receptor-dense regions including the hippocampus and amygdala (Batalla et al., 2013, Gruber et al., 2017, Lorenzetti et al., 2016), a recent study that carefully controlled for alcohol use found no evidence of alterations associated with cannabis use (Weiland et al., 2015). Similarly, studies of white matter have generally linked cannabis use to lower microstructural integrity in several areas of the brain, but regions with higher integrity have also been observed in some analyses (Gruber et al., 2017).

These mixed results can in part be attributed to several limitations of existing studies. First, conclusions drawn from existing neuroimaging studies of links between chronic cannabis use and brain structure are limited by factors plaguing much of the neuroimaging literature, including heterogeneity of protocols and small samples that are underpowered and unrepresentative of true population variation (Weiland et al., 2015). Additionally, these studies face limitations common in the study of cannabis use, including difficulties with accurately quantifying drug exposure and reliance on cross-sectional retrospective reports of use (Stringer et al., 2016). Further, more work is needed to determine 1) whether observed differences in brain structure simply reflect

differences preceding onset of cannabis use (i.e., selection effects); 2) whether associations between cannabis and brain are confounded by use of other substances such as alcohol and tobacco; 3) the extent to which effects are limited to chronic users or also apply to recreational or therapeutic users; and 4) how associations between cannabis use and brain compare to that of other substances such as alcohol and tobacco (Volkow et al., 2016).

Here, we propose to begin to fill these gaps by conducting exploratory analyses of the associations between cannabis use and measures of brain structure in the Dunedin Study, a large, longitudinal, population-representative birth cohort. The Dunedin Study's rich dataset of health and behavioral measures collected from early childhood through age 45 offer the opportunity to address existing limitations as follows. First, we are able to leverage prospective measures of early life risk factors, such as childhood health and SES, to test for selection effects. Second, the study's detailed prospective measures of alcohol and tobacco use allow us to test for confounding effects of these substances. Third, the extensive interviews with which cannabis use was assessed also allow us to distinguish between heavy and recreational users, enabling us to test whether associations with brain depend on level of use. Fourth, we can additionally leverage the study's alcohol and tobacco use data to compare the magnitude of associations between brain and these substances to those with cannabis use. Finally, the availability of high-quality MRI-derived measures of gray matter (cortical thickness, surface area, and volume) at age 45 in 860 study members, 617 of whom reported some level of cannabis use, and 154 of whom received a diagnosis of cannabis dependence at one or more of the eight assessments affords us power to conduct unbiased whole-brain analyses to ascertain the breadth of associations between cannabis use and brain. Quality measures of white matter integrity (fractional anisotropy, derived from diffusion-weighted imaging) are available in 853 study members. We are additionally able to calculate brainAGE, a machine-learning-based prediction of an individual's chronological age from their brain structure, which represents a novel contribution to the existing literature. Such high-quality measures in a relatively large number of individuals position us to provide a more accurate and complete picture of the effects of lifetime cannabis use on midlife brain integrity, which may be important in shaping trajectories of healthy and unhealthy aging.

Data analysis methods:

To test for associations between persistent cannabis use and measures of brain structure, we will follow a two-part analysis strategy. For all analyses, the outcome variables will include global measures of total brain volume (TBV), mean cortical thickness (CT), total surface area (SA), average fractional anisotropy (FA), and brainAGE, as well as regional measures of CT, SA, FA, and subcortical volumes.

Our primary analyses will use linear regressions to test for dose-response associations between the brain measures and two continuous measure of cannabis use: (1) the number of assessments where Study members met criteria for cannabis dependence and (2) the number of assessments where Study members reported weekly-to-daily use. For each significant association, we will further exploration the association by:

1) Testing for selection effects, i.e. pre-cannabis-use differences in early-life risk factors, including low childhood SES, low IQ, poor self-control, poor childhood health, and family substance use problems. Risk factors will be added to the linear regression model as covariates.

2) Testing for the influence of persistent use of other substances, including alcohol, tobacco, and other illicit drugs. Measures of lifetime alcohol, tobacco, and illicit drug use will be added to the linear regression model as covariates.
3) Comparing the effects of cannabis use to those of alcohol and tobacco use. Effect sizes of alcohol and tobacco use will be generated by mirroring the primary cannabis analyses.

Our secondary analyses will use pairwise t-tests to test for differences in brain structure between persistent cannabis users and Study members with other patterns of use. Study members with other use patterns will be divided into 5 non-mutually exclusive groups for comparison to persistent users as follows:

1) Life-long non-users of cannabis who have never been dependent on other substances. This group was selected to replicate the control group most often reported in the literature.
2) Long-term tobacco dependent individuals and
3) long-term alcohol dependent individuals, both currently free from cannabis (<12x a year) and with no history of weekly cannabis use and no history of cannabis dependence. These two groups were selected to serve as benchmark comparisons for any cannabis findings and to help disentangle potential cannabis effects from potential alcohol and tobacco effects.
4) Midlife recreational cannabis users. This group was selected to distinguish long-term-regular cannabis users from recreational users. Midlife recreational users are defined as 6 to 51 days per year at age 32 OR 38 OR 45, non-user or less than weekly at 45, AND never cannabis dependent, never 'daily' (4+ days per week) cannabis user.
5) Formerly cannabis dependent quitters. Previously cannabis dependent OR 'daily user', no cannabis reported at 45 and NOT dependent on other drugs at 45. This group is used to test whether any poor outcomes diminish after cessation.

We will use sex as a covariate in all analyses.

Variables needed at which ages:

Primary Independent Variables, Dose-response Analyses

1. potDxgrp45 – Number of adult study phases with a cannabis dependence diagnosis
2. DailyPotGp45 – Number of adult study phases with self-reported weekly-to-daily use

Primary Independent Variables, Subgroup Comparisons

1. comp0_ltuser45 - long-term cannabis users
2. comp1_noSUD - cannabis non-users with no other substance use problems
3. comp2_lttobv2 - long-term tobacco users
4. comp3_ltalcv2 - long-term alcohol users
5. comp4_recreatn - midlife recreational cannabis users
6. comp5_quit - cannabis quitters

Primary Dependent Variables

Global measures of brain structure:

1. Mean Cortical Thickness
2. Total Surface Area
3. Average Fractional Anisotropy

4. Brain-Age Gap Estimate (brainAGE) – difference between estimated brain age and chronological age

Regional measures of brain structure:

1. Regional measures of cortical thickness from the 360 regions in the multi-modal cortical parcellation described in Glasser et al. 2016
2. Regional measures of surface area from the same 360 regions
3. Tract-wise measures of fractional anisotropy from the Johns Hopkins University white matter atlas (24 bilateral tracts; Wakana et al., 2007).
4. Regional GMV of 20 subcortical structures from Freesurfer (Fischl et al., 2002)

Covariates

The following covariates will be added into our regression models as described above:

1. Sex
2. ChldhdIQ
3. SESchildhd
4. lscuw311
5. zChildPoorHlth
6. ProACEs_trunc
7. Number of adult study phases with a tobacco dependence diagnosis
8. Number of adult study phases with an alcohol dependence diagnosis
9. Persistent illicit drug dependence

Significance of the Study (for theory, research methods or clinical practice):

The Dunedin Study's rich dataset of detailed, prospective assessments of lifetime cannabis use and high-quality neuroimaging measures at midlife in a large, population-representative birth cohort offers a unique opportunity to add needed clarity to the literature on cannabis-related alterations in brain structure. Unbiased whole-brain analyses of possible associations between cannabis and midlife brain integrity will help provide targets of focus for future work. These efforts to better understand the impact of cannabis use on brain health are becoming especially important as trends toward increased legalization continue, and bases for informed policy and decision-making are needed.

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Data Security Agreement

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☒	I am current on Human Subjects Training (CITI (www.citiprogram.org) or equivalent)
☒	My project is covered by the Duke ethics committee OR I have /will obtain ethical approval from my home institution.
☒	I will treat all data as "restricted" and store in a secure fashion. My computer or laptop is: a) encrypted (recommended programs are FileVault2 for Macs, and Bitlocker for Windows machines) b) password-protected c) configured to lock-out after 15 minutes of inactivity AND d) has an antivirus client installed as well as being patched regularly.
☒	I will not "sync" the data to a mobile device.
☒	In the event that my laptop with data on it is lost, stolen or hacked, I will immediately contact Moffitt or Caspi.
☒	I will not share the data with anyone, including my students or other collaborators not specifically listed on this concept paper.
☒	I will not post data online or submit the data file to a journal for them to post. *Some journals are now requesting the data file as part of the manuscript submission process. Study participants have not given informed consent for unrestricted open access, so we have a managed-access process. Speak to Temi or Avshalom for strategies for achieving compliance with data-sharing policies of journals.*
☒	I will delete all data files from my computer after the project is complete. Collaborators and trainees may not take a data file away from the office. This data remains the property of the Study and cannot be used for further analyses without an approved concept paper for new analyses.

Signature: Annchen Knodt