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Concept Paper Form

Provisional Paper Title: Cognitive and Neural Reserve in Long-term Cannabis Users at Midlife: Implications for the Aging Brain
Proposing Author: Madeline Meier
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P.I. Sponsor: Terrie Moffitt, Avshalom Caspi (if the proposing author is a student or colleague of an original PI)
Today's Date: 10/24/2020

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

Objective of the study:

Research has shown that heavy cannabis users exhibit subtle cognitive deficits and brain structure differences (Schreiner et al., 2012; Scott et al., 2018; Lorenzetti et al., 2019), but these findings are the subject of much controversy (Kroon et al., 2020). Debate centers around several issues. The first is causality. Although observational studies cannot prove causality, studies have not sufficiently addressed commonly cited alternative explanations, including that cognitive and brain differences predate cannabis use or arise because of the effects of other substance use or early childhood risks common to both cannabis use and cognitive brain differences. The second issue concerns distinguishing problematic cannabis use from non-problematic recreational use. NESARC has shown that only about one third of cannabis users develop a problem use pattern (Hasin et al., 2015). Yet, prior studies have not adequately distinguished problem and non-problem users, thus tarring all cannabis use with the same brush in a way that greatly concerns policy makers. The third debated issue concerns cessation. Some studies have reported cognitive deficits and brain differences in cannabis users who quit (Medina et al., 2007; Meier et al., 2012), whereas others have not (Schreiner et al., 2012; Scott et al., 2018). In general, too few studies have addressed this question to make conclusions. The fourth debated issue is whether cannabis users' outcomes are benign compared to tobacco and alcohol users' outcomes. Cannabis advocates argue that cannabis should be legalized because it is far more benign than licit substances. However, this claim is rarely empirically tested. The proposed study aims to address these controversies by characterizing cognitive and brain differences in long-term cannabis users and informative subsets of comparison individuals selected from a representative cohort followed from birth to midlife.

Data analysis methods:

Analyses will use two complementary approaches: (1) comparison of long-term cannabis users with informative subgroups, and (2) tests of dose-response associations.

Subgroup comparisons. To test whether long-term cannabis users (currently using at least weekly at phase 45 plus at least 1 other phase of weekly or greater use) have compromised cognitive and brain function, analyses will compare long-term cannabis users with 5 informative, non-mutually exclusive groups:

(i) 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.

(ii-iii) Long-term tobacco dependent individuals and 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.

(iv) Midlife recreational cannabis users. This group was selected to distinguish long-term-regular cannabis users from recreational users. Midlife recreational users were 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

(v) 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.

Dose-response associations. To test dose-response associations between duration of cannabis use and cognitive and neural outcomes, analyses will test associations for two continuously-distributed exposures: persistent cannabis dependence and persistent regular cannabis use from age 18 to 45.

Outcomes are IQ change from childhood to adulthood (age 45), adult neuropsychological test performance (age 45), informant-reported cognitive problems (age 45), and both total and subregional hippocampal grey matter volume (age 45; this brain region was selected as a region of interest because of its high concentration of cannabinoid receptors and because it is the brain region that is most consistently found to be associated with cannabis use).

For both analytic approaches (group comparisons and dose-response associations), all analyses will adjust for sex and analyses of age-45 neuropsychological tests will additionally adjust for IQ in childhood, prior to cannabis initiation. For tests of dose-response associations, follow-up analyses of statistically significant associations will ascertain if dose-response associations are attributable to cannabis alone, or instead reflect the combination of cannabis and other substance use. To do this, associations will be adjusted for persistent tobacco, alcohol, and other illicit drug dependence. To ascertain if dose-response associations are attributable to early childhood risks, associations will be further adjusted for childhood SES, low childhood self-control, and family substance-use problems. Finally, to ascertain if dose-response associations are specific to cannabis, dose-response associations will also be tested for persistent tobacco dependence and

persistent alcohol dependence.

Variables needed at which ages:

Exposures:

1. Age-45 comparison groups: (i) long-term cannabis users, (ii) non-users of cannabis with no other substance use problems, (iii) long-term tobacco users, (iv) long-term alcohol users, (v) midlife recreational cannabis users, (vi) cannabis quitters.

2. Persistent cannabis dependence, persistent regular cannabis use, persistent tobacco dependence, persistent alcohol dependence (ages 18-45). (Persistent dependence on other illicit drugs is low prevalence and so will not be examined as an exposure but will be included as a covariate.)

Outcomes

1. IQ decline: childhood IQ, adult IQ (age 45), IQ decline (adult IQ minus child IQ)
2. Age-45 neuropsychological tests
    a. Executive function tests: WAIS-IV Working Memory Index, Wechsler Memory Scale Months of the Year Backward, Trail Making Test B
    b. Learning and memory: Rey Auditory Learning Total, Rey Auditory Delayed Recall
    c. Perceptual reasoning: WAIS-IV Perceptual Reasoning Index
    d. Verbal comprehension: WAIS-IV Verbal Comprehension Index
    e. Verbal fluency: Animal naming
    f. Motor Function: Grooved Pegboard
3. Informant-reported attention and memory problems (age 45)
4. Total hippocampal volume (age 45)
5. Subregional hippocampal volumes (age 45); 12 bilateral subregional volumes (Van der Meer, 2018) derived using the hippocampal subfields module in FreeSurfer 6.0 (Iglesias et al., 2015). (For the 7 regions in the subfields module with separate measures for head and body, the head and body measures will be combined.)

Early childhood covariates

1. Childhood SES
2. Low childhood self-control
3. Family substance-use problems

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

As stated in the grant application, this study has implications for research, prevention, treatment, and policy.

Implications for future research: Positive findings of poor outcomes will attract attention to priority questions warranting further research investment. Conversely, negative findings will help the field identify hypotheses of cannabis harm that are unfruitful so that scientific resources can be directed elsewhere.

Implications for prevention: Knowledge of harms that do or do not characterize long-term users of cannabis will inform substance-abuse preventions. Preventing adolescent cannabis use is a major focus now, but this study can inform whether cessation programs for midlife adults ought to be added to the prevention toolkit. More generally, findings from the Dunedin Study are convincing aging researchers that the first half of the life course has untapped potential for prevention of late-life disease and disability. The proposed work asks if this prevention principle extends to reducing harms from cannabis use in the first half of the life course.

Implications for treatment: Positive findings of low reserve will point to issues that should be addressed when treating patients diagnosed with cannabis dependence, or when prescribing medicinal cannabis.

Implications for policy: Cannabis legalization is well underway and findings of harm are unlikely to reverse this trend. What is needed now is information about the likely circumstances of the generation of baby boomer cannabis users who continue to use it today as they enter late life. If our work reveals that their cognitive and neural reserves look inadequate to sustain their health and wellbeing into old age, this will inform service-provision policy. If the work shows their reserves are not linked to cannabis history, this news will inform policy too.

References

Cole JH, Franke K. Predicting age using neuroimaging: innovative brain ageing biomarkers. Trends in neurosciences. 2017. **40**(12):681-90.

Franke K, Ziegler G, Klöppel S, Gaser C, Alzheimer's Disease Neuroimaging Initiative. Estimating the age of healthy subjects from T1-weighted MRI scans using kernel methods: exploring the influence of various parameters. Neuroimage. 2010.**15**;50(3):883-92.

Han BH, Palamar JJ. Trends in cannabis use among older adults in the United States, 2015-2018. JAMA Internal Medicine. 2020.**180**(4):609-11.

Hasin, D.S., et al., Prevalence of marijuana use disorders in the United States between 2001-2002 and 2012-2013. JAMA Psychiatry. 2015. **72**(12):1235-1242.

Iglesias JE, Augustinack JC, Nguyen K, Player CM, Player A, Wright M, Roy N, Frosch MP, McKee AC, Wald LL, Fischl B, Van Leemput K; Alzheimer's Disease Neuroimaging Initiative. A computational atlas of the hippocampal formation using ex vivo, ultra-high resolution MRI: Application to adaptive segmentation of in vivo MRI. Neuroimage. 2015. 15;115:117-37.

Kroon E, Kuhns L, Hoch E, Cousijn J. Heavy cannabis use, dependence and the brain: a

clinical perspective. Addiction. 2020. **115**(3):559-72.

Liem F, Varoquaux G, Kynast J, Beyer F, Masouleh SK, Huntenburg JM, Lampe L, Rahim M, Abraham A, Craddock RC, Riedel-Heller S. Predicting brain-age from multimodal imaging data captures cognitive impairment. Neuroimage. 2017. **148**:179-88.

Lorenzetti V, Chye Y, Silva P, Solowij N, Roberts CA. Does regular cannabis use affect neuroanatomy? An updated systematic review and meta-analysis of structural neuroimaging studies. European Archives of Psychiatry and Clinical Neuroscience. 2019. **269**(1):59-71.

Medina KL, Hanson KL, Schweinsburg AD, Cohen-Zion M, Nagel BJ, Tapert SF. Neuropsychological functioning in adolescent marijuana users: subtle deficits detectable after a month of abstinence. Journal of the International Neuropsychological Society. 2007 **13**(5):807.

Meier MH, Caspi A, Ambler A, Harrington H, Houts R, Keefe RS, McDonald K, Ward A, Poulton R, Moffitt TE. Persistent cannabis users show neuropsychological decline from childhood to midlife. Proceedings of the National Academy of Sciences. 2012. **109**(40):E2657-64.

Schreiner AM, Dunn ME. Residual effects of cannabis use on neurocognitive performance after prolonged abstinence: a meta-analysis. Experimental and clinical psychopharmacology. 2012. **20**(5):420.

Scott JC, Slomiak ST, Jones JD, Rosen AF, Moore TM, Gur RC. Association of cannabis with cognitive functioning in adolescents and young adults: a systematic review and meta-analysis. JAMA Psychiatry. 2018. **75**(6):585-95.

Van der Meer D, Rokicki J, Kaufmann T, Córdova-Palomera A, Moberget T, Alnæs D, Bettella F, Frei O, Doan NT, Sønderby IE, Smeland OB. Brain scans from 21,297 individuals reveal the genetic architecture of hippocampal subfield volumes. Molecular psychiatry. 2018 2:1-3.

Whalley LJ, Deary IJ, Appleton CL, Starr JM. Cognitive reserve and the neurobiology of cognitive aging. Ageing research reviews. 2004. **3**(4):369-82.

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.
☒	I have read the Data Use Guidelines and agree to follow the instructions.

Signature: Madeline H. Meier