Concept Paper

Provisional Paper Title: Does psychiatric illness predict signs of accelerated aging at mid-life?

Proposing Author: Jasmin Wertz

Author's Email: jasmin.wertz@duke.edu

P.I. Sponsor: Terrie E. Moffitt & Avshalom Caspi
(if the proposing author is a student or colleague of an original PI)

Today's Date: December 16, 2019

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

Objective of the study:

The overall aim of this study is to test the hypothesis, proposed by Moffitt & Caspi (JAMA-Psychiatry 2019) that Dunedin study members who have experienced more psychiatric illness in adulthood (as indicated by higher scores on a general factor of psychopathology, the p-factor[1], reflecting transdiagnostic liability to mental disorder) show signs of accelerated aging by mid-life (as indicated by measures of biological pace of aging, sensorimotor function, and cognitive function)[2].

Specifically, we propose three aims:

Aim 1: To test whether individuals who have experienced psychiatric illness show a faster pace of biological aging by age 45.
Aim 2: To test whether individuals who have experienced psychiatric illness show reduced sensory and motor function in mid-age.
Aim 3: To test whether individuals who have experienced psychiatric illness show reduced cognitive function in mid-age.

Data analysis methods:

Operationalization of constructs

To measure psychiatric illness, we propose to use a general factor of psychopathology (the p-factor), which summarizes the severity of one's propensity to develop any and all disorders during the life course[1]. The p-factor has been developed and used in previous Dunedin studies[1]. We propose to use the p-factor instead of individual diagnoses of psychiatric illness, because research consistently shows that most people who present with a specific psychiatric disorder also experience other preexisting, co-occurring, and future-occurring mental disorders.[3] Furthermore, findings pointing to accelerated aging in psychiatric illness (as reviewed below) are evident across mental disorders. However, we will perform supplementary analyses to test whether associations with aging outcomes hold for individual domains of psychopathology (i.e., externalizing, internalizing and thought disorder problems) (see analysis plan below).

To measure signs of accelerated aging, we will use three sets of outcomes: a) pace of aging; b) sensory and motor function, and c) cognitive function. Each outcome will be assessed using a self-report measure as well as a lab-test assessment (i.e., for cognitive function, we would use self-report of cognitive difficulties at age 45, and IQ scores at age 45). First, we will analyze measures capturing study members' pace of aging. We propose to use a cross-phase measure of biological pace of aging, that has been developed and used in previous Dunedin studies[6], as well as a measure of self-reported age, as assessed at age 45. Second, we will analyze self-report and lab test measures capturing study members' sensory and motor function (i.e., hearing, vision, motor, balance). Third, we will analyze self-report and lab test measures of cognitive functioning.

Analysis plan

For each of the 3 aims outlined above, the analyses will follow a series of steps as follows:

a) Test whether higher scores on the p-factor are associated with i) self-reports of the outcome; and ii) lab-test assessments of the outcome. This analysis will use regression models predicting each outcome from p-scores, adjusted for study members' sex.

b) Test whether any association observed in step a are specific to any one domain of psychopathology, i.e. internalizing, externalizing or thought disorder problems. This analysis will use regression models, predicting each outcome from the separate domains of psychopathology (i.e. internalizing, externalizing, and psychotic experiences predicting the respective outcome), adjusted for sex.

c) Test reverse causality, i.e. whether associations between p-scores and indices of accelerated aging could be explained by pre-existing problems in childhood that preceded the onset of psychopathology. For this analysis, we will use childhood-equivalent measures for each mid-age outcome, which have been prospectively collected when Dunedin study members were young. For example, when testing association between p-factor scores and cognitive function at age 45, we would include measures of cognitive function assessed in childhood in the model. This analysis will use the same regression models as in step a), but will additionally adjust for the childhood equivalent of the age-45 outcome measure.

Questions for hearing and vision investigators

1) *Question for hearing investigators*:
- At age 45, would it make sense to integrate the cue-sensitivity and advantage scores into an overall measure of 'social' hearing ability?
- Would we need to control for overall hearing ability when assessing associations with cue sensitivity and advantage score?

2) *Question for vision investigators*:
- The vision protocol describes visual acuity, contrast sensitivity and matrix visual field testing as the 'major components of visual function'. Therefore, would you recommend including all three of these measures (and if so, can they be integrated into an overall measure of visual function, or are to be used separately?), or is there one particular measure that you would recommend that is perhaps particularly sensitive to showing age-related decline in visual functioning?

- If we would only use one measure (say, contrast sensitivity) would we need to control for the other measures (e.g. visual acuity) when testing associations?

Variables needed at which ages:

Cross-phase		
	Snum	
	Sex	
	P_BF45	P-Factor Scores
	EXT_CF45	Externalizing Factor Scores
	INT_CF45	Internalizing Factor Scores
	THD_CF45	Thought Disorder Factor Scores
	zChildPoorHlth	Childhood poor health z-score
	ZMotor39	Motor score ages 3-9
	PaceOfAging	Pace of Aging (Age 45)
	wfsiq711std	Childhood IQ
Age 7		
	PTAcode_rt7	Pure tone code, continous, right ear at 7
	PTAcode_lt7	Pure tone code, continous, left ear at 7
	VAcuity_rt7	Visual acuity right eye
	VAcuity_lt7	Visual acuity left eye
Age 9		
	PTAcode_rt9	Pure tone code, continous, right ear at 9
	PTAcode_lt9	Pure tone code, continous, left ear at 9
	VAcuity_rt9	Visual acuity right eye
	VAcuity_lt9	Visual acuity left eye
Age 11		
	spin11_nn	SPIN11 no noise, mean of 2 trials
	spin11_10db	SPIN11 10db, mean of 2 trials
	spin11_5db	SPIN11 5db, mean of 2 trials
	PTAave_rt11	PureTone ave of .5, 1K, 2K & 4K, right ear, age 11
	PTAave_lt11	PureTone ave of .5, 1K, 2K & 4K, left ear, age 11
	VAcuity_rt11	Visual acuity right eye
	VAcuity_lt11	Visual acuity left eye
Age 45		
	srAgePercp45	Self-perceived age in years
	SRHearing45	Hearing difficulty screen
	lisnslcsrtscp45	LiSNS_LowCueSRT_Score [low is good] - P45
	lisnshcsrtscp45	LiSNS_HighCueSRT_Score [low is good] - P45
	lisnstkadvscp45	LiSNS_TalkerAdvantage_Score [low is poor] - P45
	lisnsspadvscp45	LiSNS_SpatialAdvantage_Score [low is poor] - P45
	lisntotadvscp45	LiSNS_TotalAdvantage_Score [low is poor] - P45
	SRvision45	SR vision difficulty screen, high = much difficulty
	VisAcuBest45	Visual acuity 45, best of either eye, LOW is GOOD
	ContrastSens45	Contrast sensitivity score, p45
	Velocity_avg45	Velocity: Avg of walk/cog/max, p45, cm/second

	PhyLimts45	SF36 physical limitations (RAND version), p45
	Dizzy45	Dizziness scale, high = freq dizzy triggers - hlh scale
	balClsMax45	One-legged balance, Eyes closed, max of three trials
	fsIQ45_STD	Full Scale IQ at 45, standardized to Mean 100, SD 15
	CogDiffSc45expd	Expanded Cog complaints scl at 45

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

As the population ages, this increases the public-health significance of chronic age-related diseases such as heart disease, type 2 diabetes, stroke, pulmonary disease, and dementia, which are major drivers of poor quality of life and high healthcare costs[4]. In order to design interventions that can protect an aging population from disease and disability, more knowledge is needed about preventable risk factors that predict the accelerated pace of aging that is thought to underpin susceptibility to age-related diseases[5,6]. The aim of our study is to test the hypothesis, as recently laid out in a viewpoint article by Moffitt & Caspi[2], that psychiatric illness is a risk factor for accelerated pace of aging.

The hypothesis builds on three sets of findings from previous research: first, individuals who experience psychiatric illness have higher mortality rates and shorter lifespans, even after accounting for suicide[7,8]. Second, individuals who experience psychiatric illness have higher rates and an earlier onset of age-related diseases[9,10]. Third, individuals who experience psychiatric illness are exposed to many of risk factors that are associated with poor aging and the onset of age-related disease, including chronic stress[11], harsher environmental exposures (such as victimization or poverty)[12], a less healthy lifestyle (including higher rates of smoking, drinking, and drug use)[13] and side effects of psychiatric medication[14].

There is currently little research testing whether a history of psychiatric illness earlier in life predicts signs of accelerated aging that are already evident by mid-age. The viewpoint article that first laid out the hypothesis of accelerated aging in psychiatric illness reported preliminary evidence that higher scores on the p-factor are associated with a measure of accelerated biological pace of aging in the Dunedin cohort[2], but here we would like to undertake a more comprehensive test of the hypothesized psychiatric illness-aging link.

Early identification of accelerated aging in people with psychiatric illness has implications for public health intervention and planning: first, because it identifies a population at risk of following a trajectory of poor aging that could be preferentially targeted with interventions; and second, because it can inform the forecasting of future burden of poor aging outcomes based on population prevalence estimates of psychiatric illness.

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Data Security Agreement

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Today's Date	December 16, 2019

Please keep one copy for your records and return one to the PI Sponsor

Please initial your agreement

x	I am current on Human Subjects Training (CITI (www.citiprogram.org) or equivalent)
x	My project is covered by Duke or Otago ethics committee OR I have /will obtain ethical approval from my home institution.
x	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.
x	I will not "sync" the data to a mobile device.
x	In the event that my laptop with data on it is lost, stolen or hacked, I will immediately contact Professor Moffitt or Caspi. (919-684-6758, tem11@duke.edu, ac115@duke.edu)
x	I will not share the data with anyone, including my students or other collaborators not specifically listed on this concept paper.
x	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. The Dunedin Study Members have not given informed consent for unrestricted open access, so we have a managed-access process. Speak to Terrie or Avshalom for strategies for achieving compliance with data-sharing policies of journals.*
x	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. The data remains the property of the Study and cannot be used for further analyses without an approved concept paper for new analyses.

Signature: _____**Jasmin Wertz** _____