Concept Paper Template

Provisional Paper Title: The Influence of Pace of Aging on Pain Impact: Analysis of a Birth Cohort of Adults Approaching Middle Age

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P.I. Sponsor: TE Moffitt & A Caspi

Today's Date: 3-21-18

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

Objective of the study:

Among a birth cohort of individuals approaching middle age, to determine the extent to which pain impact is influenced by 12-year pace of aging; and to compare to influences of other accelerated aging markers (e.g. epigenetic clocks, telomere length).

Data analysis methods:

Data analyses will be completed using IBM SPSS Statistics for Mac software(IBM Corp, Armonk, New York). Alpha level will be set at P=.05 for all analyses. Pearson correlations will determine the relationship between 38y pain impact and accelerated aging markers, as well as secondary pain measures (e.g. sleep, mood, physical activity). Next, we will construct multivariable hierarchical OLS regression models to control for sex, 26y pain intensity and interference, and to compare strength of associations. 38y pain impact will be entered as the dependent variable; sex into the first block; 26y pain intensity and interference into the second block, and accelerated aging markers in the third block. Similar models will determine the association between accelerated aging markers and secondary pain markers. Standardized regression coefficients (beta) will provide comparative strength of the factors in the final model block. One thousand-sample bootstrapping will be used to calculate bias-corrected and accelerated 95% confidence intervals for the standardized regression coefficients. Absence of multicollinearity will be confirmed via *a priori* cutoff rules for inter-correlation (r<.70), tolerance (>.20), and variance inflation (<4).

Variables needed at which ages:

26y:

- Sex; Pain Intensity; Pain Interference; Physical Limitations; Self-Rated Health; Epigenetic Clocks (71, 353-CpG); Telomere Length

38y:

- Pain Impact; Physical Limitations; Self-rated Overall h=Health; Loneliness; Activity (METS – Occupational, Household, Sport/Leisure); Sleep; Depression; Pain Medication; Digit Symbol Coding Score; Digit Span Scaled Score; Epigenetic Clocks (71, 353-CpG); Telomere Length

26-38y:

- Pace of Aging;[1] Change in Epigenetic Clocks; Change in Telomere Length

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

Pain conditions are the most prevalent and disabling conditions in the world, surpassing diabetes, heart disease, stroke, and cancer.[2,3] Per capita, the greatest global disability and burden from pain conditions occurs among **older adults**.[3–5] Over 50% of community and institutional-dwelling older adults experience pain,[6–10] with many experiencing pain at multiple sites.[11–14] Age has also been associated with non-recovery from painful conditions;[15] meaning that older adults may be at greater risk for persistent pain. Coupled with the aging population,[16] persistent pain among older adults has contributed to exponential increases in health care costs. In U.S. Medicare beneficiaries alone, persistent pain management utilization over a decade has increased 177% per 100,000.[17]

Although the prevalence and impact of persistent pain has been attributed to age, very little is known the influence of **aging**. The primary limitation to date has been study design – the majority of previous studies have employed cross-sectional comparisons based on chronological age (e.g. younger versus older adults). Two problems exist with such models: 1) Chronological age comparisons lack the temporal component necessary to elucidate the influence of accelerating aging on persistent pain, and thus only determine differences across age cohorts; 2) Humans likely age at different rates, and accumulating evidence suggests a biological aging marker may be more predictive of morbidity and mortality than chronological age.[18,19]

Pain researchers have begun to consider biological markers of accelerated aging, such as epigenetic marks or leukocyte telomere length.[20–25] While few studies have been performed in humans, preliminary findings are that accelerated aging is positively associated with pain persistence.[22,23,25] **The problem** is that these studies utilized a cross-sectional design. Leukocyte telomere length measured at a single time point may be an indirect correlate of biological age, but not necessarily an indication of *the rate* of accelerated aging. Further, all studies to this point have been in small sample sizes.[22,23,25]

Recently, Belsky et al. utilized the Dunedin Study birth cohort to develop and validate a rate of accelerated aging measure (i.e. 'pace of aging').[1] **The purpose of this proposal** is to determine the extent to which pain impact at the onset of

middle-age is influenced by pace of aging. This study is innovative as, to my knowledge, it would be the first human longitudinal study of accelerated aging and pain. Moreover, the richness of the data will allow for comparisons to previously mentioned accelerated age markers assessed for pain associations (e.g. telomere length); as well as to secondary factors of pain - such as sleep,[26] cognitive performance,[27] mood,[28] and physical activity.[29] Finally, unlike previous pain investigations, this study will employ an adequate sample size of participants who are also at the same chronological age.

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Data Security Agreement

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Today's Date	3-1-18

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: