GROWUPGROWOLD
HUMAN DEVELOPMENT, BIRTH TO DEATH

Moffitt & Caspi
Genes Environment Health Behavior

Concept Paper Form

Provisional Paper Title: Assessing the Developmental Taxonomy: Structural and functional neural correlates of life-course persistent vs. adolescence-limited antisocial behaviour in a longitudinal birth cohort
Proposing Author: Christina Carlisi
Author's Email: c.carlisi@ucl.ac.uk
P.I. Sponsor: Ahmad Hariri & Terrie Moffitt, with Essi Viding (if the proposing author is a student or colleague of an original PI)
Today's Date: 3/30/2020

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

Objective of the study:

Conduct disorder (CD) is characterized by persistent and pervasive antisocial behaviour which typically emerges early in life, usually during childhood or adolescence. Developmental Taxonomic Theory[1] suggests that there are two pathways by which antisocial behaviour arises, persists and desists, each linked to different hypothesized aetiological profiles. 'Life-course persistent' (LCP) antisocial behaviour characterizes a relatively small group of individuals who exhibit antisocial behaviour beginning in childhood which persists through adolescence and into adulthood. It is thought that LCP antisocial behaviour is neurodevelopmental in origin, characterized by neuropsychological impairment in executive functions and emotional reactivity. On the other hand, 'adolescence-limited' (AL) antisocial behaviour describes a comparatively larger group of individuals exhibiting such behaviour beginning in adolescence and primarily limited to this developmental window[2]. AL antisocial behaviour is thought to be developmentally normative in most cases, influenced by a gap in maturity between biological and social factors during adolescence[3,4]. In line with the Developmental Taxonomy[1], studies comparing these subtypes on neuropsychological function have shown that cognitive abnormalities are more pronounced in the LCP subtype[5,6]. Neuroimaging research into the Developmental Taxonomy is currently sparse, restricted mostly to studies focusing on a small sample of cognitively able adolescents from relatively high socioeconomic backgrounds. The neuroimaging findings (both functional and structural) from this sample regarding the Developmental Taxonomy have been mixed, with some analyses differentiating the LCP and AL groups, whilst others have not differentiated these individuals by age of onset[7,8]. These results are difficult to interpret given the demographic differences between the neuroimaging sample from these studies, and those derived empirically from longitudinal epidemiological cohorts.

Our recent work from the Dunedin Multidisciplinary Heath and Development Study[9] investigated cortical thickness and surface area in individuals with LCP and AL behaviour and found that at age-45, LCP individuals showed thinner cortex and smaller surface area compared to those with AL or no antisocial behaviour. Here, we propose to extend these findings by comparing volumetric differences in subcortical

structures, as well as general functional connectivity (GFC) in these individuals with a longitudinally-assessed history of LCP or AL antisocial behaviour. Although structure-function causation cannot be directly inferred, previous work in smaller samples[7,10] has implicated structural differences in subcortical regions, as well as altered connectivity in the Default Mode Network and orbitofrontal-amygdala circuitry,[11,12] and it is likely that alterations in the structural organization and connectivity of subcortical brain regions influences information processing through distributed brain circuitry, particularly given the neuropsychological dysfunction that has been proposed in individuals with a history of antisocial behavior and CD[10,13]. We aim to leverage the unique nature of this cohort to investigate whether abnormal subcortical brain structure and altered GFC is seen across subtypes or whether such abnormalities are specific to or more pronounced in LCP individuals.

Data analysis methods:

Analysis of structural and functional MRI data will be conducted in accordance with existing processing pipelines set up by Prof Hariri and colleagues (Annchen Knodt and Maxwell Elliot). Analyses outlined below will be conducted comparing groups of LCP or AL individuals as determined by longitudinal reports of antisocial behaviour. A series of analyses on extracted values (calculated per the pipelines outlined above) will be conducted comparing trajectory groups of antisocial behavior on:

1. Volumetric differences of subcortical regions of interest (as well as total brain volume)
2. Whole-brain General Functional Connectivity matrices investigating:
    a. Default mode network
    b. Networks and seed regions implicated in affect processing, violent/aggressive behaviour, and decision making (OFC-limbic (e.g. amygdala, striatum) circuitry, within-frontal (e.g. dorsal ACC-OFC) circuitry).
    c. A control comparison network (e.g. visual or auditory networks)

All analyses will include males and females and will be controlled for sex. In line with our previous study of cortical thickness and surface area in the Dunedin cohort, we will also conduct secondary analyses of total brain volume controlling for SES, IQ, history of head injury, and schizophrenia diagnosis to test for confounding effects of these factors which may relate to an antisocial lifestyle or might have brought about brain changes after childhood.

We will also conduct an exploratory data-driven connectome-wide association study (CWAS) to investigate multivariate connectivity patterns across the whole brain that vary with antisocial behaviour trajectory.

Variables needed at which ages:

- Antisocial conduct problems trajectory variable (LCP, AO, low – CDTraj7_26)[14,15]
- GFC matrices and extracted subcortical volumes from available regions (GFC from Glasser parcellation, subcortical volume from FreeSurfer's aseg pipeline)

Due to the fact that brain scans were collected at a later time point (age 45) compared to indices of antisocial behaviour (assessed at ages 7-26), it may be beneficial to conduct post-hoc analyses investigating the potential confounding impact of the following variables on structural and connectivity findings:

- Childhood SES - SESchildhd
- Childhood IQ – ChildIQ_STD
- Alcohol use history at age 45

- History of Traumatic Brain/head Injury at age 45 – HeadInjLT45
- Lifetime Schizophrenia diagnosis at age 45[16] – DxSzLT45
- Age 3 brain integrity – ZCHBR3
- Lifetime diagnosis of ADHD at age 45 - addliftm
- P factor scores (including sub-factor scores for internalizing, externalizing, thought disorder)
- Psychiatric diagnosis at age-45

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

It is unclear based on prior research to what degree the neurocognitive profile differs between LCP and AL groups. Most existing studies lack a reliable assessment of antisocial behaviour and associated brain abnormalities across the lifespan. This is due in part to the nature of the samples that have been used in existing studies, which is not representative of LCP and AL groups as derived from epidemiological samples. The Dunedin Study presents a unique opportunity to combine rich multi-source observational measures of behaviour with neuroimaging data to investigate the association between CD subtypes and neurostructural and functional connectivity profiles.

References cited:

1. Moffitt, T. E. Adolescence-limited and life-course-persistent antisocial behavior: A developmental taxonomy. *Psychological Review* **100**, 674–701 (1993).
2. APA. *Diagnostic and statistical manual of mental disorders: DSM-5*. (American Psychiatric Publishing, 2013).
3. Galambos, N. L., Barker, E. T. & Tilton-Weaver, L. C. Who gets caught at maturity gap? A study of pseudomature, immature, and mature adolescents. *International Journal of Behavioral Development* **27**, 253–263 (2003).
4. Piquero, A. R. & Brezina, T. Testing Moffitt's Account of Adolescence-Limited Delinquency*. *Criminology* **39**, 353–370 (2001).
5. Fairchild, G. *et al.* Decision Making and Executive Function in Male Adolescents with Early-Onset or Adolescence-Onset Conduct Disorder and Control Subjects. *Biological Psychiatry* **66**, 162–168 (2009).
6. Passamonti, L. *et al.* Neural Abnormalities in Early-Onset and Adolescence-Onset Conduct Disorder. *Arch Gen Psychiatry* **67**, 729–738 (2010).
7. Fairchild, G. *et al.* Brain Structure Abnormalities in Early-Onset and Adolescent-Onset Conduct Disorder. *AJP* **168**, 624–633 (2011).
8. Fairchild, G., Van Goozen, S. H., Stollery, S. J. & Goodyer, I. M. Fear Conditioning and Affective Modulation of the Startle Reflex in Male Adolescents with Early-Onset or Adolescence-Onset Conduct Disorder and Healthy Control Subjects. *Biological Psychiatry* **63**, 279–285 (2008).
9. Carlisi, C. O. *et al.* Associations between life-course-persistent antisocial behaviour and brain structure in a population-representative longitudinal birth cohort. *The Lancet Psychiatry* **7**, 245–253 (2020).
10. Fairchild, G., Goozen, S. H. M. van, Calder, A. J. & Goodyer, I. M. Research Review: Evaluating and reformulating the developmental taxonomic theory of antisocial behaviour. *Journal of Child Psychology and Psychiatry* **54**, 924–940 (2013).
11. Sethi, A. *et al.* Anatomy of the dorsal default-mode network in conduct disorder: Association with callous-unemotional traits. *Dev Cogn Neurosci* **30**, 87–92 (2018).
12. Craig, M. C. *et al.* Altered connections on the road to psychopathy. *Molecular Psychiatry* **14**, 946–953 (2009).
13. Moffitt, T. E. Male antisocial behaviour in adolescence and beyond. *Nature Human Behaviour* **2**, 177–186 (2018).
14. Odgers, C. L. *et al.* Prediction of Differential Adult Health Burden by Conduct Problem Subtypes in Males. *Arch Gen Psychiatry* **64**, 476–484 (2007).

15. Odgers, C. L. *et al.* Predicting Prognosis for the Conduct-Problem Boy: Can Family History Help? *Journal of the American Academy of Child & Adolescent Psychiatry* **46**, 1240–1249 (2007).
16. Meier, M. H. *et al.* Neuropsychological Decline in Schizophrenia From the Premorbid to the Postonset Period: Evidence From a Population-Representative Longitudinal Study. *AJP* **171**, 91–101 (2014).

Data Security Agreement

Provisional Paper Title: Assessing the Developmental Taxonomy: Structural and functional neural correlates of life-course persistent vs. adolescence-limited antisocial behaviour in a longitudinal birth cohort
Proposing Author: Christina Carlisi
Today's Date: 3/30/2020

☒	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: Christina O. Carlisi

CONCEPT PAPER RESPONSE FORM

A

Provisional Paper Title	Assessing the Developmental Taxonomy: Structural and functional neural correlates of life-course persistent vs. adolescence-limited antisocial behaviour in a longitudinal birth cohort
Proposing Author	Christina Carlisi
Other Contributors	Terrie E. Moffitt, Annchen R. Knodt, Honalee Harrington, David Ireland, Tracy R. Melzer, Richie Poulton, Sandhya Ramrakha, Avshalom Caspi, Ahmad R. Hariri, Essi Viding
Potential Journals	Click or tap here to enter text.
Today's Date: 3/30/2020	
Intended Submission Date: Click here to enter date	

Please keep one copy for your records and return one to the proposing author

B. To be completed by potential co-authors:

☐	Approved
☐	Not Approved
☐	Let's discuss, I have concerns

Comments: Click here to enter text

Please check your contribution(s) for authorship:

☐	Conceptualizing and designing the longitudinal cohort study
☐	Conceptualizing data collection protocols and creating variables
☐	Data collection
☐	Conceptualizing and designing this specific paper project
☐	Statistical analyses and interpretation (or reproducibility check)
☐	Writing
☐	Reviewing manuscript drafts
☐	Final approval before submission for publication
☐	Agreement to be accountable for the work
☐	Acknowledgment only, I will not be a co-author

Signature: Click here to enter text