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Provisional Paper Title: Cortical and subcortical neural correlates of intimate partner violence in a longitudinal birth cohort
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Data analysis for this project will be carried out at Duke University by Renate Houts and Annchen Knodt.

Objective of the study:

Intimate partner violence (IPV) is a global public health problem that remains one of the most widespread human rights violations around the globe[1]. IPV is defined as a "behavior within an intimate relationship that causes physical, sexual or psychological harm, including acts of physical aggression, sexual coercion, psychological abuse and controlling behaviors"[1]. The negative consequences of IPV on health, such as mood disorders (depressive episodes), anxiety disorders (including posttraumatic stress disorder and obsessive-compulsive disorder), lower self-esteem, physical injuries, substance use disorders, or socioeconomic issues have been well-established[1], as well as the risk of re-victimization[2]. Recent evidence also indicates that experiencing (i.e., being victim of) physical, but not psychological IPV is associated with faster biological ageing[3]. Due to the significant negative impact that IPV has on the individual and society as a whole, unsurprisingly an extensive body of research has focused on the psychological, biological, and social impact of IPV on the victims[4]. However, far less research has focused on the neurobiological correlates of IPV perpetrators[5, 6], as we propose to do here. Specifically, while an extensive neuroimaging literature has focused on antisocial[7] or violent[8] behaviours in general, or psychiatric disorders[9] associated with those behaviours in particular, few studies have examined the structural neural *correlates*[#] of individuals who have perpetrated IPV[5]. This state of affair is likely to be partly due to the ethical and methodological challenges associated with the recruitment of participants.

To date, only four studies[10-13] have been published, all focusing on male participants with

[#] The term 'correlates' here is used to highlight that, to our knowledge, no study exists that can establish whether structural brain abnormalities are causally related to IPV, despite one prospective longitudinal study showing that the presence of neuropsychological deficits in childhood, as measured by low verbal intelligence, is directly related IPV (verbal and physical aggression) decades later[25].

small samples. One study[10] relying on the independent assessment of two neuroradiologists surprisingly concluded that structural brain abnormalities in grey or white matter are not strongly or specifically associated with IPV in offenders (n=21) who were compared to non-IPV offenders (n=20) and, therefore, unlikely explaining fMRI findings in previous studies on this population. However, in another study[11] on the same sample, IPV offenders were found to exhibit decreased cortical thickness in the orbitofrontal, insular, anterior and posterior cingulate cortices, as well as in the parahippocampal gyrus when compared to non-IPV offenders; lower thickness of the posterior cingulate was associated with poorer recognition of emotional facial expressions. The third study[13] found that, compared to non-offenders, IPV offenders exhibited lower volume of the accumbens and dorsal anterior cingulate cortex, which were associated with poorer emotion regulation and lower empathy scores. The final study[12] showed that alcoholic patients with IPV (n=27) had reduced right amygdala volume as compared with non-violent alcoholic patients (n=14) and health controls (n=13). The dearth of structural neuroimaging studies is surprising, but taken together the above findings are consistent with meta-analytic work showing that perpetrators of IPV have higher rates of traumatic brain injury than the general population and with the increasing neuropsychological literature documenting impaired neuropsychological functioning in perpetrators of IPV, particularly in executive functions.

In addition to the small sample size, four other important limitations characterize this literature and pertain to the nature of the sample, the data analytic strategy, and the study design. First, in terms of sample, the existing studies have exclusively relied either on males recruited from forensic or clinical settings, which make those participants unrepresentative from the general population because (1) they only reflect the most extreme cases of clinically abusive IPV[14] and, relatedly, (2) do not include females despite evidence that females can also engage in clinically abusive forms of IPV[14]. A large epidemiological sample from the general population, including both males and females and spanning the entire continuum of intimate relationships (from non-abusive through nonclinically abusive forms to clinically abusive forms of IPV) would address this limitation. Second, despite evidence that both males and females engage in IPV[14], no study has compared the sexes to clarify to what extent the neural correlates are the same or different across sexes. Third, in terms of data analytic strategy, while there is good evidence that IPV perpetrators are also victim of IPV themselves[14], the above studies were unable to examine the structural brain correlates associated with *experiencing (i.e., being victim of)* IPV vs *perpetrating* IPV. Finally, in terms of study design, because all the studies have been cross-sectional, they have not been able to examine if, and to what extent, some factors (e.g., history of head injury, substance use disorders), which predate the scan and are known risk factors for IPV[5, 6], might contribute to some of the observed effects on the brain. This is not an exhaustive list of the limitations, but highlight some of the most important problems with this literature, which limit its theoretical and translational impact.

In this context, using a person-centered approach, we propose first to examine the cortical and subcortical neural correlates of perpetrators of IPV and compare them to individuals with no history of IPV from the Dunedin Multidisciplinary Heath and Development Study[3, 14]. The inclusion of both females and males will enable us to also test for potential sex-by-group interactions. Finally, consistent with recent work on this dataset[3], we will use a variable-centered approach to investigate the structural brain correlates associated with *experiencing (i.e., being victim of)* IPV vs *perpetrating* IPV. In terms of brain metrics, given

recent evidence on this cohort that IPV is associated with faster biological ageing[3], we will first use brainAGE (i.e., the difference between chronological age and age predicted from machine-learning models of brain-imaging data), a well-validated and reliable proxy of biological ageing[15]. Any significant group differences or associations with this metric will then be followed-up by secondary analyses with mean cortical thickness, global surface area, and subcortical volumes to clarify which of those features might be accounting for the effects on brainAGE.

Hypotheses:

1. Given recent evidence in this cohort that IPV is associated with faster biological ageing[3], we predict that, in comparison with individuals who have never perpetrated IPV, perpetrators of IPV will show greater brainAGE, which will be mostly underpinned by a combination of *reductions* in cortical thickness, surface area, and subcortical volume.
2. Based on prior work indicating that (1) a history of conduct problems/disorder and the presence of deviant personality traits (e.g., high psychopathic traits) increase the risk of perpetrating IPV[14, 16, 17] and (2) that those clinical features have been linked to reduced grey matter volume[9, 18] in cortical and subcortical regions, we hypothesize that, in comparison with individuals who have never perpetrated IPV, perpetrators of IPV will exhibit reduced cortical thickness and surface area in the prefrontal and temporal cortices, as well as reduced volume of the amygdala and the striatum.
3. Given our prior work examining sex differences in cortical and subcortical structure in relation to conduct disorder[19], we predict that, compared with males with no history of IPV as perpetrators, male perpetrators of IPV will show lower cortical thickness in the temporal cortex, while female perpetrators of IPV will show the opposite pattern. In terms of surface area, we predict that, compared with males with no history of IPV as perpetrators, male perpetrators of IPV will show higher surface area in the superior frontal gyrus, whereas the opposite pattern will be seen in female perpetrators of IPV.
4. Based on a recent paper in this cohort[3], we hypothesize that *experiencing* IPV will be related to some of the decrease in cortical thickness, surface area or subcortical volume seen in perpetrators of IPV.

Data analysis methods:

We will use IPV data collected at ages 21, 26, 32, 38, and 45 to construct a summative measure of IPV involvement over time to classify the participants into one of two mutually exclusive types: Perpetrator of IPV vs no history of IPV as a perpetrator.

sMRI analyses will be conducted in accordance with existing preprocessing pipelines set up by Prof Hariri and colleagues as used in previous publications[20-22]. Analyses will first compare the two groups in terms of brainAGE. We will then test for group-by-sex interactions. Finally, consistent with a previous paper[3] on this dataset, we will use a regression model to investigate if *experiencing* IPV vs *perpetrating* IPV predict brainAGE. Any significant group differences or associations with brainAGE, will then be followed-up by secondary analyses, but with mean cortical thickness, global surface area, and subcortical volumes to clarify which of those metrics might be accounting for the effects on brainAGE. Finally, if cortical thickness or surface area account for brainAGE, follow-up analyses with parcellations of cortical thickness and surface area will be conducted to characterize the

nature of the spatial distribution for those metrics. Consistent with Carlisi et al.[21], we will correct for multiple comparisons across each set of regional tests performed (i.e., cortical thickness, surface area) by using a false discovery rate (FDR) procedure[23].

Consistent with our prior structural work on antisocial groups[24], in a regression model restricted to the IPV group only, we will examine the extent to which a history of head injury and substance use disorders contribute to the variance in brain data where there is a group difference.

Variables needed at which ages:

- Intimate partner violence
    - At phase 26, 32, 38, and 45

- BrainAGE at 45 years
- Grey matter at 45 years:
    - Cortical (thickness and surface area) measures, subcortical and total intracranial volume.
- Covariates
    - Childhood SES
    - History of head injury
    - History of substance use disorders

We will also need other variable to show the overall demographic, cognitive and psychiatric characteristics of the two groups at age 45. In addition to the above-mentioned variables, we would like to include the following variables in a table for each group:

- IQ
- Alcohol use at age 45
- Psychiatric diagnosis at age-45

Significance of the Study (for theory, research methods or clinical practice):
As highlighted above, the neuroimaging literature on IPV is small and the existing studies suffer from several important limitations, which have limited the theoretical and translational impact of this body of work. The Dunedin Study presents a unique opportunity to combine rich multi-source assessment of IPV with neuroimaging data in the context of prospective longitudinal study to investigate the structural neural correlates of IPV.

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