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HUMAN DEVELOPMENT, BIRTH TO DEATH

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Concept Paper Form

Provisional Paper Title: Are childhood autistic traits associated with greater trauma exposure, post-traumatic stress responses, and impairment in young adult life?
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P.I. Sponsor: Andrea Danese (if the proposing author is a student or colleague of an original PI)
Today's Date: 11/4/2022

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

Objective of the study:

Despite the high prevalence of childhood traumatic experiences in the autistic population, research on trauma-related psychopathology in autistic children is severely lacking (Peterson et al., 2019); there is scarcely any research on how autistic traits relate to PTSD diagnosis, and none in children.

Autistic children and adults are at greater risk of exposure to negative life events, including bullying and trauma (Hoover & Kaufman, 2018). A recent study suggests that autistic adults who report experiencing traumatic events have a higher rate of clinical level PTSD symptoms (c. 45% pass cut-off on the PCL-5) than expected in trauma-exposed general population samples (c. 9%) (Rumball et al., 2020). Autistic adults with high levels of PTSD symptoms are also at higher risk of additional mental health problems (anxiety, depression), even compared to the already elevated risk for poor mental health amongst autistic people (Rumball et al., 2021). Additionally, autistic people may show post-traumatic stress reactions after experiences that are not traditionally recognised as traumas, thus not qualifying for PTSD diagnosis in DSM-5 (Brewin et al., 2019). These non-traditional traumas are associated with the same high rates of clinical level PTSD symptoms (43%) in autistic adults as the standard DSM-5 traumas (Rumball et al., 2020). It has been suggested that features of autism such as cognitive style (e.g., detail focus) and sensory memory encoding, alongside predisposition for emotional dysregulation and sensory arousal, may present a pathway to traumatic sequelae (Kerns et al., 2022).

Autistic children have high rates of bullying and victimization and enhanced risk of adverse childhood experiences (Hoover & Kaufman, 2018). Because of this greater exposure to negative events, autistic children are at elevated risk of developing trauma-related

psychopathology (Kerns et al., 2015). This was reflected in a systematic review showing that PTSD occurs in autistic children and young people at a somewhat higher rate than the general population (Rumball, 2019). In addition, both autism (Ringbom et al., 2022) and PTSD in young people (Lewis et al., 2019) are associated with long-term exclusion from education and employment; this may exacerbate functional impairment.

However, there are also several reasons why PTSD may be underdiagnosed in autistic children, meaning that PTSD diagnosis alone may not fully capture how autism impacts psychopathology and function after trauma. In children, symptoms of PTSD can be difficult to differentiate from features of autism (Stavropoulos et al., 2018); both involve avoidant behaviour, reactivity to sensory stimuli and repetitive play themes which can lead to diagnostic overshadowing. Additionally, autistic children may have difficulty disclosing their trauma (Kildahl et al., 2021), and struggle to communicate their symptoms, particularly as alexithymia commonly co-occurs with autism (Kinnaird et al., 2020).

Liability to trauma-related psychopathology likely extends beyond categorical/diagnostic definitions of autism. Autism is increasingly viewed dimensionally; for example, similar genetic factors influence diagnosed autism and subclinical autistic traits in the general population (e.g.,Robinson et al., 2011). Associations between dimensional measures of autistic traits and post traumatic stress symptoms have been demonstrated in adults (Haruvi-Lamdan et al., 2019; Stewart et al., 2022), but not in children. Therefore, this study aims to assess if high autistic traits in childhood predispose to the development of PTSD, and how autistic traits impact general psychopathology and functional impairment after trauma.

Objectives:

1. To determine if autistic traits put children at higher risk of experiencing trauma and developing PTSD.
2. To investigate if higher autistic traits put trauma-exposed young people at higher risk of developing more severe general psychopathological outcomes (as measured through the ‘p-factor’) and functional impairment (as measured through NEET status).

Hypotheses:
1. Higher autistic traits in childhood will be associated with greater likelihood of trauma exposure and PTSD in late adolescence/young adulthood
2. In children with higher autistic traits, exposure to trauma will result is more psychopathology and greater functional impairment compared to trauma-exposed children low in autistic traits.

Data analysis methods:

This study will draw longitudinal data from both E-RISK and TEDS databases to assess the influence of childhood autistic traits (from TEDS) on later PTSD diagnosis at age 18 years (from E-Risk). We will identify the subset of participants who are included in both datasets. Our sample will only include TEDS twins who are also in the E-RISK dataset, who have data for the key PTSD diagnosis variable and at least one TEDS ‘autism variable’ of interest. Preliminary checks showed that the overlapping group will be of n=1,440 out of

2,063 E-Risk Study member with full PTSD data. Based on previous epidemiological analyses of the E-Risk dataset (Lewis et al., 2019) and assuming missingness completely at random, we would therefore expect to find that (31.1%) n=448 study members in this subset reported experiencing trauma and (7.8%) n=112 met criteria for lifetime PTSD by age 18. Previous studies in adults with much smaller sample size have shown statistically significant associations between ASD traits and trauma exposure or PTSD risk (Haruvi-Lamdan et al., 2019; Stewart et al., 2022) but do not provide equivalent estimates to develop a formal power analysis without several assumptions.

Information from each data set will be matched and merged using participant IDs. To protect participant confidentiality, these IDs shall be encrypted prior to access being granted to lead researcher (AQ).

General psychopathology, 'p', will be derived by fitting a bifactor model to 11 symptom scales obtained at age 18 (Caspi et al., 2014). We will assess functional impairment by whether subject is not in education, employment, or training (NEET) (as in Lewis et al., 2019).

We will take both a dimensional approach and a categorical approach (e.g., splitting the cohort into groups of with high versus low autistic traits, if the subgroups are large enough to enable this). We will control for the influence of confounding variables, such as socio-economic status, IQ and sex, as well as accounting for non-independent data (twinness).

Do higher autistic traits put children at higher risk of experiencing trauma and developing PTSD?

We will test univariate regression models to investigate the association between autistic traits and (1) report of criterion A trauma, and (2) lifetime PTSD diagnosis (from age 18 years assessment). We will then expand the analyses to account for the influence of possible confounding factors, such as socio-economic status, IQ, and sex.

If the subgroups are large enough to enable this, we will undertake sensitivity analyses to compare risk of (1) trauma exposure and (2) PTSD diagnosis between groups of participants with high and low autistic traits.

Within trauma exposed participants, are autistic traits associated with more severe psychopathology and functional impairment?

We will test univariate regression models to investigate the association of autistic traits with general psychopathology or functional impairment (NEET status) in trauma exposed young people. We will then expand the analyses to multivariate models to account for the influence of possible confounding factors, such as socio-economic status and IQ.

If the subgroups are large enough to enable this, we will undertake sensitivity analyses to compare general psychopathology scores or risk of functional impairment (NEET status) between groups of trauma-exposed participants with high and low autistic traits.

<u>Significance of the Study (for theory, research methods or clinical practice)</u>:

There is an unmet clinical need to develop evidence-based treatments for PTSD and trauma-related sequalae in autistic children, young people and adults. Identifying if high autistic traits in childhood impacts future risk of PTSD, broader psychopathology, and functional impairment after trauma will inform mental health care and support needed for autistic children (e.g., promoting screening for trauma and trauma related symptoms in autism services).

Variables needed at which ages:

Identifiers:

FAMILYID	[D]	Unique family identifier	Primary Family Level ID
FAMIDCK	[D]	Family ID (inc chkdig)	
FCHECK	[D]	Check Digit for FamilyID	
TWINAID	[D]	Twin A ID (inc chkdig)	
ATWINID	[D]	Twin A ID (ex chkdig)	Primary Elder Twin ID
TACHECK	[D]	Check Digit for AtwinID	
TWINBID	[D]	Twin B ID (inc chkdig)	
BTWINID	[D]	Twin B ID (ex chkdig)	Primary Younger Twin ID
TBCHECK	[D]	Check Digit for BtwinID	

PTSD:

DXPTSD5CUE18	[D][F]	PTSD Current dx, dsm5 - P18 - Elder
DXPTSD5CUY18	[D][F]	PTSD Current dx, dsm5 - P18 - Younger
DXPTSD5LFE18	[D][F]	PTSD Lifetime dx, dsm5 - P18 - Elder
DXPTSD5LFY18	[D][F]	PTSD Lifetime dx, dsm5 - P18 – Younger

PTSD Symptomology:

PTSD5_A_E18	[D][F]	PTSD (DSM5) - trauma exposure - P18 - Elder
PTSD5_A_Y18	[D][F]	PTSD (DSM5) - trauma exposure - P18 - Younger
PTSD5_B_E18	[D][F]	PTSD (DSM5) - reexperience the event - P18 - Elder
PTSD5_B_Y18	[D][F]	PTSD (DSM5) - reexperience the event - P18 - Younger
PTSD5_C_E18	[D][F]	PTSD (DSM5) - avoidance - P18 - Elder
PTSD5_C_Y18	[D][F]	PTSD (DSM5) - avoidance - P18 - Younger
PTSD5_D_E18	[D][F]	PTSD (DSM5) - negative alterations in cognition or mood - P18 - Elder
PTSD5_D_Y18	[D][F]	PTSD (DSM5) - negative alterations in cognition or mood - P18 - Younger
PTSD5_E_E18	[D][F]	PTSD (DSM5) - arousal/reactivity - P18 - Elder
PTSD5_E_Y18	[D][F]	PTSD (DSM5) - arousal/reactivity - P18 - Younger
PTSD5_F_E18	[D][F]	PTSD (DSM5) - gt 1 month duration - P18 - Elder
PTSD5_F_Y18	[D][F]	PTSD (DSM5) - gt 1 month duration - P18 - Younger
PTSD5_G_E18	[D][F]	PTSD (DSM5) - interference - P18 - Elder
PTSD5_G_Y18	[D][F]	PTSD (DSM5) - interference - P18 - Younger

General psychopathology ‘p’ factor:

PBF_E [F][M] P: Bi-Factor Model1, E-Twin
PBF_Y [F] P: Bi-Factor Model1, Y-Twin

Functional impairment (NEET status):

NEETE18 [D][F][M] NEET: Not in educ, employmt or training - P18 - Elder
NEETY18 [D][F] NEET: Not in educ, employmt or training - P18 - Younger

Co-founders

SAMPSEX [D][F] Sex of Twins: In sample
IQSUME5 [D][F] IQ scale - Elder
IQSUMY5 [D][F] IQ scale - Younger
SESDISM5 [D][F][M] SES Disadvantage, Age 5

Autism related measure (utilized with measures from TEDS):
TOMTOTE5 [D][F][M] TOM total score (elder)
TOMTOTY5 [D][F] TOM total score (younger)

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Data Security Agreement

Provisional Paper Title: Are childhood autistic traits associated with greater trauma exposure, post-traumatic stress responses, and impairment in young adult life?
Proposing Author: Quinton, Alice
Today's Date: 11/4/2022

☒	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: Alice Quinton