What is the Effectiveness of Dialectical Behaviour Therapy in the Treatment of High-Risk Behaviours in Adolescents?

A Systematic Review

The Relationship Between Early Life Stress, Amygdala Reactivity and Coping Behaviour Across the Life Span: An fMRI Study


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I certify that all material in this thesis which is not my own work has been identified and that no material has previously been submitted and approved for the award of a degree by this or any other University.

Signature: [Signature]
Author’s Declaration

The literature review was completed independently by the author. For the empirical study, participants were recruited, and their data collected by the supervisor, Dr Pia Pechtel, in 2015. doi:10.1016/j.neuroimage.2014.04.025

All other aspects of the study were completed by the author, including development of the research question, data entry, analyses of clinical, behavioural and neuroimaging data, and write up.
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What is the Effectiveness of Dialectical Behaviour Therapy in the Treatment of High-Risk Behaviours in Adolescents?

A Systematic Review

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Abstract

High-risk behaviours (HRB) are understood to serve a function of regulating emotions in the absence of other adaptive coping strategies. Engagement in multiple HRBs during adolescence is known to contribute to increased risk of suicide and psychopathology. Dialectical Behaviour Therapy for adolescents (DBT-A) has received attention for treating HRB in adolescents over recent years. Previous reviews have either provided a narrow focus on one HRB in isolation, and/or have focused broadly on several interventions’ effectiveness in treating HRBs. This systematic review aimed to synthesise the literature across six databases, exploring the effectiveness of DBT-A (including both individual and group DBT sessions) on a range of HRBs in various settings. Eleven papers met the search criteria and were included within the review. A narrative synthesis of the findings provided evidence for DBT-A reducing a range of HRBs in comparison to control conditions, with particular benefits for suicidal ideation and self-harm. Improvements in self-harm were more likely to be maintained over follow-up, whereas between-group differences in other HRBs were often lost over time. Studies varied considerably in quality, treatment length, frequency, and intensity. The implications for future research and practice are discussed.

Keywords: Dialectical behaviour therapy, effectiveness, high risk behaviour, self-harm, systematic review, suicidality
Introduction

Suicide is the third leading cause of death in 15-19 year olds worldwide (World Health Organisation, 2019), and the leading cause of death in young people in the UK (Office for National Statistics, 2019). Suicidality (including suicidal ideation and suicide attempts; SAs) and self-harm/non-suicidal self-injury (NSSI) are some of the most frequently studied behaviours known to contribute to risk of death by suicide; however, these behaviours belong to a broader group of high-risk behaviours (HRBs) that deserve further attention. Research has noted links between emotion regulation difficulties, engagement in HRBs in adolescence, and wide-ranging difficulties that persist into adulthood, such as later psychopathology and increased utilisation of mental health (MH) services (Brière, Rohde, Seeley, Klein, & Lewinsohn, 2015). To aid understanding of these critical issues, the current systematic review (SR) aims to discuss the effectiveness of Dialectical Behaviour Therapy for adolescents (DBT-A); a multifaceted intervention that has appeared promising in decreasing HRBs to promote resilient functioning across the lifespan.

High-Risk Behaviour

HRBs have been defined as behaviours associated with a high risk of negative consequences for the person’s health, safety or wellbeing (Weller, Leve, Kim, Bhimji, & Fisher, 2015). HRBs can include impulsive and/or dangerous behaviours, including but not limited to NSSI, SAs, anti-social and aggressive behaviour, hazardous alcohol consumption, risky sexual behaviour, binge/restrictive eating, and gambling (Sadeh & Baskin-Sommers, 2017). Exposure to traumatic events including childhood maltreatment has been well-linked to engagement in HRBs (Adams et al., 2016; Ben-Zur & Zeidner, 2009). It is suggested that engagement in HRBs may occur for thrill or
pleasure-seeking, to cope with intense emotional distress, or a combination of both (Sadeh & Baskin-Sommers, 2017).

Though some risk-taking can be considered a usual part of adolescent development, the presence of multiple HRBs is associated with increased psychopathology, suicide risk, and likelihood of premature death and long-term disability (Gil, Wagner, & Artigues, 2003; Kipping, Campbell, MacArthur, Gunnell, & Hickman, 2012; Thullen, Taliaferro, & Muehlenkamp, 2016).

**Dialectical Behaviour Therapy**

Despite increasing numbers of suicides and SAs in young people, few interventions are known to be effective at decreasing factors that contribute to suicide risk. DBT has become a popular intervention in this domain over the past three decades (Linehan, 1993; Linehan, Armstrong, Suarez, Allmon, & Heard, 1991). DBT is an evidence-based psychotherapy, originally developed to treat suicide-related behaviour, emotion dysregulation, and borderline personality disorder (BPD) in adults, but has been adapted for use with adolescents with a range of HRB (DBT-A; Miller, Rathus, & Linehan, 2007; Miller, Rathus, Linehan, Wetzler, & Leigh, 1997, 2002).

DBT is based on biosocial theory, which suggests that emotional vulnerability (heightened sensitivity to experiencing emotion, and a slow return to baseline) coupled with an invalidating social environment (inconsistent, inappropriate, trivialising responses to emotions from caregivers) results in children not learning how to “adequately label or control emotional reactions” (Linehan, 1993, p. 51), therefore developing pervasive emotion dysregulation. HRBs may serve a function to manage such high levels of emotion, in the absence of more constructive coping strategies. DBT aims to reduce emotional, interpersonal, and behavioural dysregulation that
leads to engagement in what it defines as ‘life-threatening’ behaviours (e.g., SAs, NSSI), ‘quality-of-life interfering’ behaviours (e.g., aggressive/antisocial behaviour, depression, hopelessness), and ‘therapy-interfering’ behaviours (e.g., disengagement). By understanding the cause of such behaviours, blending both acceptance and change-based strategies, and teaching adaptive coping skills, it is hoped that reliance on these behaviours will reduce (Glenn, Esposito, Porter, & Robinson, 2019; Linehan, 1993).

DBT for adults includes four main treatment modes; skills training groups, individual therapy, telephone coaching, and team consultation. DBT-A is based on the same theory as DBT for adults, though differences are noted in the involvement of family members where possible, in both skills training groups and individual sessions. DBT-A is also significantly shorter than standard DBT (16 weeks versus one year); a shorter treatment was thought to be more appealing, since adolescents who attempt suicide are often difficult to engage in treatment (Trautman, Stewart, & Morishima, 1993). In practice, interventions usually follow the DBT-A manual (Miller et al., 2007), however elements are often adapted dependent on the client group, setting, and availability of resources; including length of treatment, frequency of sessions, presence of family members, and accessibility of telephone coaching. While we know that DBT-A has been developed with HRB in mind, the naturally occurring adaptations in clinical practice make it difficult to evaluate the specific therapeutic components that are linked to its effectiveness.

High-Risk Behaviour and Dialectical Behaviour Therapy: The Current Picture

Although some reviews on DBT-A have been published, several aspects are worth highlighting, since they limit the conclusions that can be drawn regarding the
effectiveness of DBT-A for HRB. First, previous SRs have provided a narrow focus, concentrating primarily on behaviours that DBT may classify as ‘life-threatening’ (NSSI and suicidal behaviour; DeCou, Comtois, & Landes, 2019; Glenn et al., 2019; Hawton et al., 2015; Iyengar et al., 2018; Ougrin, Tranah, Stahl, Moran, & Asarnow, 2015). The most recent SR by Glenn and colleagues (2019) included two studies that utilised DBT-A (McCauley et al., 2018; Mehlum et al., 2014). While this review confirmed DBT-A as a well-established’ treatment for decreasing SAs and NSSI, it did not address other HRBs known to contribute to the risk of suicide and poor long-term health outcomes. Second, many of the studies included in previous SRs have lacked a comparison/control condition, limiting conclusions that can be drawn about interventions’ effectiveness. Finally, a review of the literature by Groves and colleagues (2012) indicated some empirical support for DBT-A in reducing a range of HRBs in adolescents, however, few randomised controlled trials (RCTs) or controlled studies had been published at this time. Critically, several studies on DBT-A and HRB have been published within the last 12 months, highlighting the need for an updated review.

**Rationale and Aims**

Since DBT-A targets the problematic behaviours and pervasive emotion dysregulation that occur across individuals with a range of MH difficulties, it is largely accepted as a transdiagnostic approach (Ritschel, Lim, & Stewart, 2015). Support for assessing the effectiveness of interventions transdiagnostically comes from a move away from diagnosis and interventions for specific ‘disorders’, and towards the identification and understanding of patterns in emotional distress, troubling behaviour, and coping strategies (Johnstone et al., 2018).
The current SR aims to extend the work of previous reviews by considering DBT-A’s effectiveness on a range of HRBs, potentially addressing the same underlying construct of emotion dysregulation, to aid the application of transdiagnostic treatment approaches. The review aimed to answer the following question: What is the effectiveness of DBT-A in the treatment of HRBs in adolescents?

**Method**

This SR followed the Preferred Reporting Items for Systematic Review and Meta-analysis Protocol (PRISMA-P) to guide identification, screening, eligibility, and synthesis of studies (Moher, Liberati, Tetzlaff, & Altman, 2009; Moher et al., 2016).

**Information Sources**

In line with the Cochrane Library handbook (Higgins et al., 2019) guidance was sought from a librarian at the University of Exeter regarding databases and sources to search. Literature was identified using a computerised core search of multidisciplinary and subject-specific databases supplied by Ovid, Web of Science, and the Cochrane Library (Appendix A). Databases were searched from the first available article to 16th March 2020. No publications were excluded on the basis of the date they were published.

**Search Strategy**

Cochrane database and the International Prospective Register of Systematic Reviews (PROSPERO; https://www.crd.york.ac.uk/PROSPERO/) were checked to confirm that the review question had not been investigated. Guidance from the librarian, researchers, and clinicians enabled the iterative development of an accurate
and effective search strategy (National Institute of Health and Care Excellence [NICE], 2012).

A scoping review was used to generate search terms that could be used in combination. Keywords of seminal publications (Miller, Nathan, & Wagner, 2010; Miller et al., 2007) and searches in critical reviews (Iyengar et al., 2018; Ougrin et al., 2015) were checked for search strategies and additional search terms. Final search terms (Table 1) were reviewed and refined with consultation from researchers and clinicians.

The full electronic search strategy for one database (Ovid, Medline) is presented in Appendix B to ensure replicability. Generated titles and abstracts of records were screened for eligibility using PICOS criteria (Population, Intervention, Comparator, Outcome, Study design; Table 2; Higgins et al., 2019). Full texts of records included at title/abstract stage were further screened for eligibility for inclusion in the review. Reference lists of all included publications were hand-searched for relevant materials (NICE, 2012). All citations were stored on the electronic bibliographic software Mendeley. A second reviewer blind-rated six randomly selected records at the full text screening stage for reliability of eligibility for inclusion. An independent yes/no decision was made based on the PICOS criteria, which yielded 100% inter-rater reliability ($\kappa = 1.00$).
### Table 1

**Search Terms for Ovid Databases**

<table>
<thead>
<tr>
<th>Database search</th>
<th>Population Section 1 “OR”</th>
<th>Effectiveness Section 2 “OR”</th>
<th>DBT Section 3 “OR”</th>
<th>High-risk Behaviours Section 4 “OR”</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Individual search terms</strong> (in title or abstract)</td>
<td>child* OR adolesc* OR young person OR young people OR teenage* OR youth</td>
<td>effect* OR treat* OR intervention OR therap* OR psychotherap* OR outcome OR longitudinal stud* OR follow-up stud*</td>
<td>dialectical behavio?r therapy OR DBT</td>
<td>risk-taking OR risk* behavio?r OR high-risk behavio?r OR sexual* behavio?r OR sexual activit* OR alcoholism OR alcohol misuse OR alcohol abuse OR alcohol disorder OR addiction OR addictive behavio?r OR alcohol consumption OR binge drinking OR substance abuse OR substance misuse OR substance disorder OR drug abuse OR self-harm OR non-suicidal self-injur* OR self-mutilation OR self-destructive behavio?r OR suicid* OR overdose OR self-poison* OR eating disorder* OR eating behavio?r OR purg* OR binge-eat* OR restricted eat* OR weight loss OR gambling OR reckless driving OR antisocial disorder OR antisocial behavio?r OR aggressive behavio?r OR shoplifting OR vandalism OR impulsive behavio?r OR illegal behavio?r OR parasuicid* OR conduct disorder OR joy-rid* OR speeding OR stealing OR drink-driv* OR thrill-seeking</td>
</tr>
</tbody>
</table>

**Search combined** (in title or abstract)  
Section 1 AND Section 2 AND Section 3 AND Section 4

*Note. DBT = Dialectical Behaviour Therapy*
Table 2

*Inclusion and Exclusion Criteria for Eligibility for Systematic Literature Review*

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Participants</strong></td>
<td></td>
</tr>
<tr>
<td>• Studies involving adolescent participants, aged 12-18 years old</td>
<td>• Studies exclusively involving children under 12 years old</td>
</tr>
<tr>
<td>• Participants in all settings; including but not limited to clinical, community, research, university, hospital, and residential treatment centres</td>
<td>• Studies exclusively involving adults over 18 years old</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td></td>
</tr>
<tr>
<td>• Individuals who are enrolled in a full programme of DBT for Adolescents (DBT-A; including individual DBT sessions and a DBT skills group), either in its standard form or adapted to suit the targeted client group</td>
<td>• Studies that do not use DBT-A</td>
</tr>
<tr>
<td></td>
<td>• Studies that use DBT for Children (DBT-C)</td>
</tr>
<tr>
<td></td>
<td>• Studies that use only the skills group intervention of DBT-A (i.e., no individual DBT sessions alongside the skills group)</td>
</tr>
<tr>
<td></td>
<td>• Studies that combine DBT-A with another psychological therapy (i.e., DBT-A combined with mentalisation-based therapy)</td>
</tr>
<tr>
<td><strong>Comparisons</strong></td>
<td></td>
</tr>
<tr>
<td>• DBT-A compared with a control group (i.e., no treatment/waiting list/non-DBT-A control group) and/or:</td>
<td>• Studies where DBT-A is not compared to a control group (i.e., no treatment/waiting list) or:</td>
</tr>
<tr>
<td>• DBT-A compared with other psychological therapies</td>
<td>• Studies where data is not reported for the control group, therefore no comparisons can be made</td>
</tr>
<tr>
<td></td>
<td>• Studies where DBT-A is not compared to other psychological therapies</td>
</tr>
<tr>
<td></td>
<td>• Studies where DBT-A is compared to a ‘control’ group which still uses elements of DBT-A, (i.e., DBT-A ‘milieu’)</td>
</tr>
</tbody>
</table>
### Outcomes
- Studies that track and report changes in frequency or severity of HRBs over a period of time as a measure of effectiveness of DBT-A
- Quantitative data
- Studies where two different lengths of DBT-A are compared to each other without a non-DBT-A control group
- Studies that involve a ‘one-off’ assessment, i.e., the collection of one set of measures either before or after an intervention
- Studies that do not track or report prevalence and change in HRBs
- Studies that solely measured HRBs as part of a questionnaire assessing for BPD

### Study Design
- Quantitative studies
- Longitudinal or experimental designs involving repeated/continuous measurement of HRBs
- Randomised controlled trials
- Retrospective designs
- Qualitative studies
- Cross-sectional designs
- Feasibility studies that do not report effectiveness data
- Studies in any language other than English (to avoid translation requirements for feasibility reasons)
- Case studies/reports
- Previous systematic literature reviews and meta-analyses

*Note. DBT-A = Dialectical Behaviour Therapy for Adolescents; HRB = High-Risk Behaviour; BPD = Borderline Personality Disorder*
Eligibility Criteria

Characteristics of studies included in this review are based on PICOS criteria as outlined in Table 2.

**Population.** Rathus and Miller (2014) suggested that clients in their DBT-A programmes are generally aged between 13 to 18 years, however exceptions are allowed. For this review, identified participants were adolescents (12-18 years old); this was thought to increase homogeneity within groups, prevent outliers due to age, and capture the majority of studies using the DBT-A protocol.

**Intervention.** Only studies that implemented both individual DBT-A sessions and DBT-A skills groups were included in the review, since these arguably constitute the two main components of the full DBT-A model (Miller, Rathus, & Linehan, 2007). Studies including just the skills group would be likely to significantly differ in intensity to studies that included both skills groups and individual sessions, and would therefore not be comparable.

**Comparisons.** Solely including studies where there was a control/comparison group (e.g., another psychological therapy) enabled the effectiveness of DBT-A (and magnitude of the effect) to be investigated, while effects of other contributing factors were minimised.

**Outcome.** HRBs included but were not limited to NSSI, SAs, suicidal ideation, alcohol misuse, risky sexual behaviours, disordered eating patterns, illicit substance use, and antisocial or conduct difficulties (e.g., gambling, aggression). Although this is not a comprehensive list of all HRBs, the researcher sought guidance from standardised assessment measures such as the Risky, Impulsive, and Self-
Destructive Behaviour Questionnaire (Sadeh & Baskin-Sommers, 2017) and the Youth Self Report Questionnaire (Achenbach, 1991). Search terms were cross-checked with a member of the local National Health Service overdose and self-injury service to ensure the most frequent and dangerous HRBs observed in clinical settings were included. To quantify and provide evidence for the intervention under investigation, only studies reporting quantitative data on HRBs were included (Goertzen, 2017).

**Study design.** Studies considered for inclusion in the review included: (a) RCTs, where participants were randomly assigned to DBT-A or a control/comparison group; (b) prospective longitudinal or experimental designs where participants were allocated to conditions by the researcher; and (c) retrospective designs, whereby data was collected before/during/after the intervention and comparisons were made against a control/comparison group.

**Quality Evaluation and Risk of Bias**

Studies were evaluated using the standardised and validated Quality Assessment Tool for Quantitative Studies (QATQS; Armijo-Olivo, Stiles, Hagen, Biondo, & Cummings, 2012; Thomas, Ciliska, Dobbins, & Micucci, 2004; Appendix C & D). The QATQS evaluates studies within the domains of: (a) selection bias; (b) study design; (c) confounders; (d) blinding; (e) data collection method; and (f) study attrition/withdrawals and dropouts, and has been deemed appropriate for use in SRs of effectiveness (Deeks et al., 2003). The QATQS was used discuss the quality of articles rather than to exclude studies based on suboptimal quality, therefore all studies contributed towards the overall discussion of evidence.
To assess the reliability of quality ratings, a second rater blind-reviewed three randomly selected studies that were included in the review. This yielded 86% agreement. Discrepancies were discussed between the raters until 100% agreement was reached.

Bias may arise both through the actions of study investigators and the actions of review authors (Higgins et al., 2019). Bias was considered in the results of the individual studies and in the overall conclusions drawn in the SR (e.g., publication bias).

Data Extraction and Synthesis

Data were extracted using a data extraction form (Appendix E). As recommended by the Centre for Reviews and Dissemination (2009), findings are presented in narrative format due to the variation in included studies. It was expected that the included studies’ results would not be comparable due to differing outcome measures and analyses, and therefore a meta-analysis was not applicable.

Results

Study Selection

Figure 1 demonstrates the full study selection process. Searches were conducted using defined search terms across relevant databases and identified 1355 potentially relevant records. After duplicates were deleted (n = 523), 832 titles and abstracts were screened using PICOS criteria (Table 2). Of these, 746 did not meet criteria and were excluded from the review. Eighty-six articles were screened at the full text stage. Eleven records met PICOS criteria and were included in the review;
extracted information relating to PICOS criteria and study quality is summarised in Table 3. Exclusion criteria for 75 non-eligible studies are listed in Appendix F. No additional publications were identified through searching reference lists of included papers. Although all studies provided information regarding effectiveness of DBT-A on HRBs, papers were heterogeneous in aims and quality. Studies were published between 2004 and 2020, with nine of the 11 studies published in the last 10 years, suggesting a relatively new body of research.

Figure 1. Results of literature search strategy and eligibility screening

Note. Flowchart is based on PRISMA protocol (adapted Moher et al., 2009)
n = number; DBT-A = Dialectical Behaviour Therapy for Adolescents; DBT-C = Dialectical Behaviour Therapy for Children
### Table 3

**Summary of Articles Included for Analysis in Alphabetical Order by Author**

<table>
<thead>
<tr>
<th>Author and Location</th>
<th>Population</th>
<th>Intervention: DBT-A</th>
<th>Comparator</th>
<th>Outcome: HRB</th>
<th>Study Design</th>
<th>Results and Conclusion</th>
<th>Evaluation</th>
<th>QATQS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Apsche, Bass, and Houston (2006) USA</td>
<td>Adolescent males within a residential treatment centre. Referred to centre for anger, aggression, and externalising problem behaviours.</td>
<td>10 adolescent males ($M_{age} = 15.9$ years, SD = not provided) undergoing DBT-A for one year. This involved at least one DBT-A skills group per week and weekly individual therapy for one year.</td>
<td>10 adolescent males ($M_{age} = 16.1$ years, SD = not provided). Undergoing MDT for one year.</td>
<td>Pre, during (3 months), and post (6 months) treatment assessments measuring HRBs: (1) Average number of incidents of physical aggression in previous 60 days (2) Depression (BDI) (3) Suicidal ideation (SIQ)</td>
<td>Quasi-experimental design; a “coin toss” assigned the first client assigned to DBT-A, then the second assignment was to the MDT group. This alternated between groups until each group was filled.</td>
<td><strong>KEY FINDINGS:</strong> (1) Average number of incidents of physical aggression reduced after one year of treatment for both groups. Within-group analyses showed a statistically significant reduction in rates of aggression within the MDT group from baseline to post-treatment: Baseline $M_{incidents} = 11.8$, SD = 2.32, post-treatment $M_{incidents} = 11.8$, SD = 2.32. MDT showed a reduction of 92.23% in comparison to 27.9% in DBT-A. (2) Both MDT and DBT-A were effective at reducing depression. (3) Both MDT and DBT-A were effective at reducing suicidal ideation.</td>
<td><strong>Strengths:</strong> ‘Real world’ study in a clinical setting. Baseline comparisons between-groups were non-significant, indicating similar levels of severity of difficulties between groups. No dropouts due to being in a residential treatment centre. Good standard of DBT-A and MDT training delivered to therapists; MDT training delivered by the developer of MDT. <strong>Limitations:</strong> Not randomised. No statistical tests were utilised or reported to establish between-group differences. Possible errors in reporting of results. Limited reporting of methodology used; unable to assess treatment fidelity.</td>
<td>A – Weak B – Strong C – Weak D – Weak E – Moderate F – Strong Global: WEAK</td>
</tr>
</tbody>
</table>
2. Goldstein et al. (2015) USA

Adolescents with a diagnosis of bipolar disorder, recruited through a child and adolescent bipolar services specialty clinic. All participants had an acute manic/depressive/mixed episode within the last 3 months.

<table>
<thead>
<tr>
<th>Group</th>
<th>Participants</th>
<th>Treatment Description</th>
<th>Randomisation</th>
<th>Outcome Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>DBT-A</td>
<td>14 adolescents (M_{age} = 15.82 ± 2.1 years, no. of females = 11) were randomly assigned to DBT-A treatment consisting of 36 sessions (18 individual and 18 family skills training sessions) over the course of 12 months; weekly within the first 6 months, and tapered in frequency during the continuation phase. Individual and family sessions were alternated. Consisting of psychotherapy drawing from supportive, psychodidactic, family systems models. Individual and family sessions were spaced out by cases.</td>
<td>dbt = Psychotherapy drawing from supportive, psychodidactic, family systems models. Individual and family sessions were spaced out by cases.</td>
<td>2:1</td>
<td>1. Mood symptoms (K-SADS-DRS, K-SADS-MRS) 2. Affective symptoms (ALIFE) 3. Suicidal ideation (SADS-Jr) 4. Suicidal and non-suicidal self-injurious behaviour</td>
</tr>
<tr>
<td>TAU</td>
<td>6 adolescents (M_{age} = 16.83 ± 1.4 years, no. of females = 4) were randomly assigned to TAU consisting of psychotherapy drawing from supportive, psychodidactic, and family systems models. Individual and family sessions were scheduled as clinically indicated. Therapists also attended a weekly treatment team meeting where cases were discussed.</td>
<td>dbt = Psychotherapy drawing from supportive, psychodidactic, and family systems models. Individual and family sessions were scheduled as clinically indicated. Therapists also attended a weekly treatment team meeting where cases were discussed.</td>
<td>1:1</td>
<td>1. Mood symptoms (K-SADS-DRS, K-SADS-MRS) 2. Affective symptoms (ALIFE) 3. Suicidal ideation (SADS-Jr) 4. Suicidal and non-suicidal self-injurious behaviour</td>
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</table>

**Strengths:**
- DBT-A adapted for use with new client group – bipolar disorder.
- Sessions were videotaped for review during supervision to ensure fidelity to DBT model. Useful as a feasibility study to shape future services.

**Limitations:**
- On average, there was a between-group difference in severity of symptoms (including mania ratings, emotion dysregulation, and depression-free weeks in the 3 months before study intake). Small sample size precluded statistical analysis on outcome domains over time. Distribution of clinical characteristics between groups was not even since randomisation was purposely unequal. TAU

**Global:** MODERATE
Therapists provided telephone skills coaching and attended weekly DBT-A consultation team meetings. Participants in both conditions received medication management from a psychiatrist. (LIFE Self-Injurious/Suicidal Behaviour Scale) (5) Emotion dysregulation; Child-report (CALS-C) and parent-report (CALS-P) large effect sizes.

(3) Statistical trend for DBT-A group to be more likely to demonstrate improvement in suicidal ideation on the SIQ-Jr (F = 3.39, p = .07; OR = 2.9). 83% of DBT-A group participants reported a decrease in SIQ-Jr score (reflecting improvement/less suicidal ideation), 17% showed no change and 0% showed an increase in SIQ-Jr score, compared to a 50/50 split (increase/decrease) in the TAU group.

(4) DBT-A group reported no engagement in NSSI in the 3 months post-intervention (6 reported in the 3 months preceding the study). No change within the TAU group.

(5) DBT-A group and TAU group did not differ in terms of improvement on the CALS, however significant within-group differences were noted for DBT-A group only (CALS-C; F = 4.22, p = .008; partial $\eta^2 = 0.32$, CALS-P; F = 3.71, p = .01; partial $\eta^2 = 0.26$).

Conclusion: Support for DBT-A in significantly reducing depressive symptoms in comparison to psychotherapists had more years of experience than DBT-A therapists ($p = .02$). Content of TAU was not systematically assessed. Adolescents, parents, and psychiatrists were not blind to treatment assignment. No skills training component within TAU group, therefore different treatment intensity between groups. Limited reporting of outcomes at 3, 6 and 9 months (during treatment).
EFFECTIVENESS OF DBT IN THE TREATMENT OF HRBS

TAU. General support for DBT-A reducing emotion dysregulation and HRBs for clients with a diagnosis of bipolar disorder, though not significant between groups.

Adolescents (Mage of whole sample = 16.9 ± 1.8) with a diagnosis of anorexia nervosa, recruited through an ED unit.

24 adolescent females (ages per group not given) randomly assigned to 25 weeks of DBT-A involving 25 sessions of individual therapy (parents could take part in 5 sessions) and 25 sessions of DBT-A skills training groups (parents could take part in 8 sessions).

26 adolescent females (ages per group not given) randomly assigned to 25 weeks of CBT involving 25 sessions of individual therapy (parents could take part in 5 sessions) and 25 sessions of group therapy (parents could take part in 8 sessions).

All participants received medication management from a psychiatrist as necessary.

Assessments of HRBs at pre-treatment and post-treatment (25 weeks) measuring:

1) ED-specific psychopathology (EDI-2)
2) Symptoms in line with psychiatric diagnoses (SCL-90)
3) BMI

Secondary data analysis on a subsample of participants from RCT comparing CBT and DBT-A in individuals with anorexia (Salbach-Andrae et al., 2009) which could not be accessed in English. Participants were randomised to either CBT or DBT-A using a blocked randomisation procedure.

KEY FINDINGS:
No significant between-group differences, with generally greater effect sizes reported in CBT group:

1) Symptoms decreased significantly on the EDI-2 in the DBT-A group (t = 2.61; p = .016; d = −0.55) and the CBT group (t = 3.34; p = .003; d = −0.61).

2) SCL-90 general symptom strain lowered in the DBT-A group (t = 2.63; p = .015; d = 0.47) and the CBT group (t = 3.67; p = .001; d = 0.78).

3) BMI increased significantly in both groups; DBT-A group (t = −3.48; p = .002; d = 0.7) and CBT group (t = −3.35; p = .003; d = 1.04).

Conclusion:
Support for CBT and DBT-A in reducing HRBs in clients with EDs. Greater effect sizes for CBT within this population

Strengths:
Random assignment. Delivered two manualised therapies which are therefore replicable. Both therapies involved a skills group, therefore more likely to be matched in intensity.

Limitations:
Exclusively female sample. Small sample size and non-parametric statistical methods used resulted in relatively low power in the analyses. Ages not given per group. Treatment fidelity not measured. Study was a completer analysis; therefore ratings of dropouts were not assessed.

Global: WEAK
EFFECTIVENESS OF DBT IN THE TREATMENT OF HRBS

| Adults: Adolescents between 14 and 17 years of age (M[subscript]age of whole sample = 15.4 years, SD not specified, no. of females = 52) admitted to two general child and adolescent psychiatric inpatient units after having attempted suicide or having had suicidal ideation severe enough to warrant admission. 32 adolescents (ages per group not given) admitted to DBT-A led inpatient unit whereby they received 2 weeks of an adolescent DBT-A program modified from the 12-week adolescent outpatient program (Miller et al., 1997, 2002). DBT-A involved 10 daily, manualised DBT-A skills training sessions, twice-weekly individual DBT-A therapy, and a DBT-A milieu. Staff also attended regular DBT-A consultation meetings. 30 adolescents (ages per group not given) admitted to TAU; consisting of a daily psychodynamic psychotherapy group, individual psychodynamic therapy at least once per week, and a psychodynamically orientated milieu. TAU team also met regularly to discuss ward management issues. Assessments of HRBs at pre-treatment, post-treatment (2 weeks) and 1-year follow-up: (1) Depression (BDI), hopelessness (KHS), and suicidal ideation (SIQ) (2) Incident reports on the ward including violence towards self and/or others (3) Parasuicidal behaviours (LPC) (4) ER visits and re-hospitalisations during 1-year follow-up Quasi-experimental design; participants were not randomised to treatment groups due to bed availability. KEY FINDINGS: (1) Since both groups showed substantial symptomatic improvement at discharge on HRB outcome measures, there were no between-group differences. Absolute difference in effect sizes between the DBT-A and TAU groups on measures of HRBs: BDI (d = 1.67 – 1.05 = 0.62), KHS (d = 0.73 – 0.33 = 0.4), and SIQ (d = 2.12 – 1.36 = 0.76). No significant between-group differences at 1-year follow-up, though both groups continued to improve over time. (2) DBT-A group had significantly fewer incident reports filed on the ward than TAU group (t[subscript]1, 59 = 1.98, p = .052). (3) In the year after discharge, there was a significant reduction in the absolute number of parasuicidal behaviours in both groups. (4) Low numbers of re-hospitalisations and ER visits in both groups during 1-year follow-up. Conclusion: Support for DBT-A significantly

Strengths: First study adapting and evaluating DBT-A for use on adolescent inpatient wards. 100% retention rate of DBT-A participants; no dropouts. Mean length of stay in hospital was the same in both groups (18 days). Adherence to DBT-A model monitored through team consultation.

Limitations: Not randomised. DBT-A group appeared to differ to TAU group in baseline severity (higher baseline scores on all outcome measures), though this was not analysed or reported on. Small sample size not allowing for statistical differences to be detected on outcome measures of HRBs. Not randomised, use of pharmacotherapy only monitored during follow-up phase (not during hospitalisation).

Global: WEAK

A = Moderate
B = Strong
C = Weak
D = Weak
E = Weak
F = WEAK
### EFFECTIVENESS OF DBT IN THE TREATMENT OF HRBS

<table>
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<th>Study</th>
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<th>Limitations</th>
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<tr>
<td>5. McCauley et al. (2018) USA</td>
<td>86 adolescents recruited through community programs, inpatient and outpatient services, and hospital emergency departments, with at least 1 lifetime SA, elevated past-month suicidal ideation, self-injury repetition and 3 or more BPD features</td>
<td>87 adolescents ($\bar{x} = 15.04 \pm 1.43$ years, no. of females = 81) randomly assigned to 6 months of DBT-A, including multifamily skills group training, weekly individual sessions, telephone coaching and weekly team consultation.</td>
<td>HRB outcome measures were completed at baseline (pre-treatment), 3 months (middle of treatment), 6 months (end of treatment), 9 months, and 12 months (follow-ups).</td>
<td>Participants were randomised to treatment groups using a computerised adaptive minimisation randomisation procedure that matched participants across conditions within sites on no. of SAs, no. of previous self-injuries, age, and psychotropic medication use.</td>
<td>RCT;</td>
<td>(1) Significant advantages were found for DBT-A on all HRBs post-treatment. 90.3% of DBT-A group versus 78.9% of IGST reported no SAs (OR = 0.30), 54.2% of DBT-A group versus 36.9% of IGST group reported no self-harm (OR = 0.33). At 6 months, 46.5% of DBT-A and 27.6% of IGST group reported being self-harm free. Advantage of DBT-A decreased through follow-up with no statistically significant between-group differences from 6 to 12 months. However, secondary analyses did report that DBT-A was associated with significantly higher rates of clinically significant change at 12-months; one third (32.3%) of the youths in the IGST group reported no self-harm, compared to half (51.2%) of the youths in the DBT-A group.</td>
<td>Initially large sample size, good randomisation procedure and blinding. Intention-to-treat analysis used. Controlled for baseline severity in analysis. Both models were manualised and designed to be matched for treatment components. Adherence to models was assessed; reported to be strong within both conditions.</td>
<td>Low completion rates observed across both groups; 24.4% of DBT-A group and 44.8% of IGST group attended ≤16 individual sessions. However, intention-to-treat analysis was used. Overwhelmingly female sample. Changes in substance use (DUSI)</td>
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</table>
EFFECTIVENESS OF DBT IN THE TREATMENT OF HRBS

behaviours (CBCL)

Participants in both groups had improved on primary outcomes of HRBs over time, therefore there were no statistically significant group differences at 12 months.

Conclusion:
Significant advantages for DBT-A in reducing all HRBs in comparison to the control condition post-treatment. Advantages were no longer significant at 12-month follow-up since both groups improved over time.

Strengths:
Good method of randomisation. Blinding successful. No significant differences between groups on baseline outcome measures. Good adherence to treatment model and good retention of participants for the research (all completed pre and post measures). Intention-to-treat analysis used regardless of whether

Global: STRONG

6. Mehlum et al. (2014)

Norway

Adolescents were treated at community child and adolescent psychiatric outpatient clinics. Adolescents met at least 2 criteria of DSM-IV for BPD and had a history of at least 2 episodes of self-harm (at least 1 within the 12 weeks preceding the start of treatment). Adolescents (M_age = 15.9 ± 1.4 years, no. of females = 34) randomly assigned to 19 weeks of DBT-A consisting of 1 weekly multifamily skills training group (120 minutes), 1 weekly individual therapy session (60 minutes), and 1 weekly skills training session (120 minutes). Adolescents (M_age = 15.3 ± 1.6 years, no. of females = 34) randomly assigned to 19 weeks of treatment comprising EUC with at least one weekly treatment session (either individual, group, family therapy or telephone).

Assessments of HRBs carried out at pre-randomisation, 9 weeks, 15 weeks, and 19 weeks (end of treatment): (1) Self-harm (including SAs) and suicidal ideation

Single-blind RCT; Participants were allocated to treatment at random in a 1:1 ratio, stratified according to presence of suicide intent during the most serious episode of self-harm behaviour within the 16 weeks prior to randomisation. (treatment (6 months), a significant advantage for DBT-A on suicidal ideation emerged (t169 = 2.20, d = 0.34, p = .03). Participants in both groups had improved on primary outcomes of HRBs over time, therefore there were no statistically significant group differences at 12 months.

KEY FINDINGS:
(1) Frequency of self-harm episodes were measured from baseline to week 9, and from week 10 to 15. Only DBT-A group significantly decreased self-harm frequency (Δ slope = -1.28, 95% CI = -1.77 to -0.80, p < .001), and the between-group difference was statistically significant (Δ slope = -0.92, 95% CI = -1.69, -0.15, p = .021).

Suicidal ideation reduced similarly in both groups during the first 15 weeks, then continued to drop in the DBT-A and externalising behaviours (CBCL) not reported after baseline measurements; unclear whether or not these measures were collected post-treatment or purely used for baseline measurements.

Strengths:
Good method of randomisation. Blinding successful. No significant differences between groups on baseline outcome measures. Good adherence to treatment model and good retention of participants for the research (all completed pre and post measures). Intention-to-treat analysis used regardless of whether

Global: STRONG
EFFECTIVENESS OF DBT IN THE TREATMENT OF HRBS

7. Mehlm et al. (2016) Norway

Adolescents were treated at community child and adolescent psychiatric outpatient clinics. Adolescents met at least 2 criteria of Follow-up of original study (Mehlum et al., 2014).

Follow-up of original study (Mehlum et al., 2014).

Assessments of HRBs carried out at 1-year follow-up:

(1) Self-harm (including SAs) and suicidal ideation and

Prospective follow-up study on Mehlm et al. (2014) RCT

KEY FINDINGS:

(1) Over the follow-up year, DBT-A participants continued to report fewer self-harm episodes. A statistically significant difference for episodes of self-harm was found at both time intervals ($p < .05$).

(2) On most other outcomes, the group but levelled off in EUC group; statistically significant difference ($\Delta$ slope = -0.62 per week, $p = .010$).

(2) DBT-A significantly reduced scores on BHS, SMFQ, and MADRS (all $p < .001$) with generally large effect sizes, though there were only significant between-group differences in MADRS scores ($\Delta$ slope = -0.22, $p = .019$).

(3) There was a nonsignificant trend for DBT-A participants to have fewer ER visits, though overall there were few hospital admissions and ER visits in both groups.

Conclusion: Support for DBT-A significantly reducing self-harm, suicidal ideation, and depression (MADRS) in comparison to EUC.

Strengths: Prospective follow-up design, very high follow-up rate (97%), application of rigorous procedures for data collection.

Strengths mentioned in Mehlm et al. (2014) paper still apply; Good A = Moderate B = Strong C = Strong D = Moderate E = Strong

Limitations: Predominantly female sample. EUC was not monitored for fidelity, and was not a manualised treatment. Only DBT-A group received skills-training group sessions; different treatment intensity between groups. Self-harm data not reported at 19 weeks (only up to 15 weeks).

Follow-up of original study (Mehlum et al., 2014).

38 of the original 39 DBT-A participants took part in the follow-up; 37 of the original 38 EUC participants took part in the follow-up (97%).

Participants received full intervention.

(LPC; SIS; SIQ)

(2) Depression and hopelessness (MADRS; SMFQ; BHS)

(3) Hospital admissions and ER visits during treatment due to self-harm

All participants in both groups received pharmacotherapy as needed.

Delivered by therapists not trained in or practicing DBT-A; either psychodynamically oriented therapy or CBT.

Delivered by therapists not trained in or practicing DBT; either psychodynamically oriented therapy or CBT.

As needed family therapy sessions and telephone coaching.

Minutes), and as needed family therapy sessions and telephone coaching.
<table>
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<tr>
<th>8. Mehlum et al. (2019)</th>
<th>Adolescents were treated at community child and adolescent psychiatric</th>
<th>Follow-up of original study (Mehlum et al., 2014).</th>
<th>Follow-up of original study (Mehlum et al., 2014).</th>
<th>Assessments of HRBs carried out at 3-year follow-up: Prospective follow-up study on Mehlum et al. (2014) RCT</th>
<th><strong>KEY FINDINGS:</strong></th>
<th><strong>Strengths:</strong></th>
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<tr>
<td></td>
<td>DSM-IV for BPD and had a history of at least 2 episodes of self-harm (at least 1 within the last 16 weeks).</td>
<td>1-year follow-up.</td>
<td>1-year follow-up.</td>
<td>depression (LPC; SIS; SIQ; SMFQ; MADRS) (2) Hopelessness (BHS) (3) Hospital admissions and ER visits in 1-year post-randomisation</td>
<td>2 treatment groups had converged at the 1-year mark; DBT-A group maintained trial completion levels and EUC improved over the course of the year. (3) Limited use of ER and hospital admissions in both groups. No significant differences between groups. <strong>Conclusion:</strong> Support for DBT-A significantly reducing self-harm in comparison to EUC, retaining a significant difference between groups at 1-year follow-up.</td>
<td>All of the original participants were able to be traced. Prospective follow-up design, very high follow-up rate</td>
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</table>

**Strengths:**
- All of the original participants were able to be traced.
- Prospective follow-up design, very high follow-up rate

**Limitations:**
- Limitations of original study (Mehlum et al., 2014) still apply; predominantly female sample.
- EUC was not monitored for fidelity, and was not a manualised treatment.
- Only DBT-A group received skills-training group sessions; different treatment intensity between groups.
Norway outpatient clinics. Adolescents met at least 2 criteria of DSM-IV for BPD and had a history of at least 2 episodes of self-harm (at least 1 within the last 16 weeks).

37 of the original 39 DBT-A participants took part in the 3-year follow-up. 34 of the original 38 EUC participants took part in the 1-year follow-up.

(1) Self-harm (including SAs) and suicidal ideation, depression and hopelessness (LPC; SIS; SIQ; SMFQ; MADRS; BHS)
(2) Hospital admissions and ER visits in 3-years post-randomisation

significantly less episodes of self-harm at 3-year follow-up ($p < .001$).

For most outcomes, participants in both groups showed no sign of relapse and had retained treatment gains. There were no significant between-group differences for most outcomes.

(2) Over follow-up, participants in both groups had made a very limited use of the emergency services and psychiatric admissions.

Conclusion:
Support for DBT-A significantly reducing self-harm in comparison to EUC; lower post-treatment frequency of self-harm episodes reported by DBT-A participants was on average retained at 3 years post-randomisation follow-up.

(92%). Strengths mentioned in Mehlum et al. (2014) paper still apply: Good method of randomisation. Blinding successful. No significant differences between groups on baseline outcome measures. Good adherence to treatment model and good retention of participants for the research (all completed pre and post measures). Intention-to-treat analysis used regardless of whether participants received full intervention.

Limitations:
Limitations of original study (Mehlum et al., 2014) still apply; predominately female sample. EUC was not monitored for fidelity, and was not a manualised treatment. Only DBT-A group received skills-training group sessions; different treatment intensity between groups.

**Adolescents admitted to an acute-care inpatient unit within a private psychiatric hospital; admitted (either voluntarily or involuntarily) via local emergency departments because of imminent safety concerns.**

| 425 adolescents (M<sub>age</sub> = 15.67 ± 1.44 years, no. of females = 282) who were hospitalised during an 8-month period following implementation of DBT-A on the unit. DBT-A involved: A total of 9 DBT-A skills groups per week, intensive psychotherapy, including approximately 3 individual sessions per week and 1-2 family/collatera l therapy sessions per week. The ward had a DBT Milieu including DBT-A coaching. | 376 adolescents (M<sub>age</sub> = 15.59 ± 1.54 years, no. of females = 236) who were hospitalised during the exact same seasonal span of 8-months the year before DBT-A implementation. TAU involved: 3-4 CBT skills groups per week, 10 activity groups per week, 3 individual sessions per week, 1-2 family/collatera l sessions per week. The ward had a token. | Data was retrospectivel y collected from individuals’ electronic nursing records over an 8-month period:  
(1) Depression (HAMD)  
(2) Manic behaviours (YMRS)  
(3) Clinical impression (CGI-I; CGI-S)  
(4) Aggression (DASA) | Retrospectiv e chart review |

**KEY FINDINGS:**

(1) Both DBT-A and TAU reduced scores on all variables between pre-treatment and discharge. DBT-A group participants had significantly lower depression (HAMD) scores at discharge in comparison to the TAU group (F(1, 409) = 5.272, p = .022, n<sub>p<sup>2</sup> = 0.013).

(2) There were no significant differences between groups on the YMRS.

(3) Upon discharge, DBT-A group participants had significantly lower CGI-I scores (indicating improvement in mental health) TAU group participants, t<sub>(596) = 2.50, p < .001. There were no significant differences on the CGI-S.

(4) No significant differences on DASA discharge scores between groups.

**Conclusion:**

DBT-A did not provide a significant advantage over TAU in reducing aggression. General support for the use of DBT-A on inpatient units, in significantly reducing depression and in

**Strengths:**

Study aimed to reduce differences due to factors other than the intervention; TAU used exact same seasonal span of 8 months the year before DBT-A implementation, and same nine core MDT members provided treatment for both conditions. Admission scores were added as covariates in the analysis. Treatments were of a similar intensity; TAU also involved a robust programme of therapy; therefore, it appears results may be due to something about DBT-A treatment itself. Clinical and financial impact of results is substantial.

**Limitations:**

Non-randomised sample limiting generalisability of findings. Mean length of stay was 8 days for DBT-A group and 11 days for TAU group (much shorter duration of intervention than previously documented in the literature). Data was limited to what was

**Global:**

| A = Moderate  
| B = Moderate  
| C = Weak  
| D = Moderate  
| E = Weak  
| F = Not applicable

| E = Weak  
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| A = Moderate  
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EFFECTIVENESS OF DBT IN THE TREATMENT OF HRBS

10. Santamaria-Perez et al. (2020)

Spain

Adolescents deemed to be at current high risk of suicide referred to a community mental health team with repetitive NSSI and/or SAs over the last 12 months. 18 adolescents (Mage = 15.3 ± 1.2 years, no. of females = 16) received 16 weeks of DBT-A consisting of one weekly skills training group (attended separately by adolescents and their families), at least one biweekly 60-minute individual session, one weekly therapists team consultation. 17 adolescents (Mage = 15.2 ± 1.5 years, no. of females = 15) received 16 weeks of TAU plus GS and at least one biweekly 60-minute individual session including specific interventions, counselling, elements of CBT, or psychoeducation.

Pre and post (16 weeks) measurement of HRBs:

- Frequency of NSSI and SAs
- Suicidal ideation (SIQ-Jr)
- Depression (BDI-II)

Single-blind RCT; Participants were randomly assigned either DBT-A or TAU + GS, based on a computerised 1:1 simple randomisation.

**KEY FINDINGS:**

1. NSSI and SAs reduced in both groups over the course of treatment. The mean NSSI frequency in the last 4 weeks of treatment was 1.3 (0.7–1.9) in the DBT-A group and 2.1 (1.5–2.7) in the TAU + GS group (p = .045), with an estimated treatment effect of -0.8 (95% CI = 1.7 to -0.02) in favour of DBT-A. There was a reduction in SAs in both groups; reduction from 3 SAs in first month to 0 SAs in last month for DBT-A, and 2 in first month to 0 in last month for TAU + GS.

2. When analysed together, treatment (irrespective of type) significantly reduced mean scores on SIQ-Jr (t(28) = 2.583, p = .015) and the BDI-II (t(23) = 2.094, p = .048). There were no

**Strengths:**

- Clinical setting, hard-to-engage population, first study to adapt and validate Spanish DBT-A manual.
- Good randomisation procedure, intention-to-treat analysis used. Baseline scores were added as covariates in the analysis. Trial ended when predetermined sample size was achieved. DBT-A practitioners had 2-years’ experience before beginning the current study; good standard of training and therefore good adherence to DBT-A model (also assessed through weekly consultation meeting).
- Intensity of skills training groups in DBT-A were A = Moderate, B = Strong, C = Strong, D = Moderate, E = Weak, F = Moderate

**Global:** MODERATE
EFFECTIVENESS OF DBT IN THE TREATMENT OF HRBS

meeting; and routine consultation during office hours.

significant between-group differences.

Conclusion:
Support for DBT-A in reducing HRBs, specifically NSSI and SAs in comparison to TAU, in a “real world” community mental health setting.

Limitations:
Relatively small sample size. Telephone coaching not available 24 hours due to limited resources. TAU not manualised; fidelity to TAU not systematically assessed.

1. Tebbett-Mock, Saito, McGee, Woloszyn, and Venuti (2019) USA

Adolescents admitted to an acute-care inpatient unit within a private psychiatric hospital; admitted (either voluntarily or involuntarily) via local emergency departments because of imminent safety concerns

Same group of participants as Saito et al., 2020. 425 adolescents (Mage = 15.67 ± 1.44 years, no. of females = 282) who were hospitalised during an 8-month period following implementation of DBT-A on the unit. DBT-A involved: A total of 9 DBT-A skills groups per week, intensive psychotherapy, including approximately 3 individual

Same group of participants as Saito et al., 2020. 376 adolescents (Mage = 15.59 ± 1.54 years, no. of females = 236) who were hospitalised during the exact same seasonal span of 8-months the year before DBT-A implementation. TAU involved: 3-4 CBT skills groups per week, 10 activity groups per week focused on

Data was retrospectively collected from individuals’ electronic nursing records over an 8-month period:

(1) Number of constant observation hours for indications of self-injurious behaviour and aggression while hospitalised.

(2) Reported incidents of SA, self-injurious

Retrospective chart review

KEY FINDINGS:
(1) The 8-month period where DBT-A was implemented on the ward had reduced incidences on all outcome measures in comparison to the 8-month period of TAU. Number of constant observation hours for self-injury were significantly lower in the DBT-A group (mean = 0.72) compared with the TAU group (mean = 6.19) p = .01, d = 0.09. No significant differences between groups in constant observation hours for aggression.

(2) There were significantly fewer SAs for participants who received DBT-A (mean = 0) compared with the TAU group (mean = 0.02) p = .01, d = 0.1. There were also significantly fewer incidents of self-injury for participants who received DBT-

Strengths: Strengths described in Saito (2020) paper still apply; Study aimed to reduce differences due to factors other than the intervention; TAU used exact same seasonal span of 8 months the year before DBT-A implementation, and same nine core MDT members provided treatment for both conditions. Treatments were of a similar intensity; TAU also involved a robust programme of therapy; therefore, it appears results may be due to something about DBT-A treatment itself. Clinical and financial impact of results is substantial.

Strengths: Strengths described in Saito (2020) paper still apply; Study aimed to reduce differences due to factors other than the intervention; TAU used exact same seasonal span of 8 months the year before DBT-A implementation, and same nine core MDT members provided treatment for both conditions. Treatments were of a similar intensity; TAU also involved a robust programme of therapy; therefore, it appears results may be due to something about DBT-A treatment itself. Clinical and financial impact of results is substantial.

A = Moderate B = Moderate C = Weak D = Moderate E = Weak F = Not applicable

Global: WEAK
sessions per week and 1-2 family/collateral therapy sessions per week. The ward had a DBT Milieu including DBT-A coaching.

general coping skills and mental health wellness, and intensive psychotherapy (approximately 3 individual sessions per week and 1-2 family/collateral sessions per week). The ward had a token economy system Milieu.

All participants in both groups received medication management if necessary.

behaviour, aggression patient-to-patient, aggression patient-to-staff while hospitalised.

(3) Number of restraints while hospitalised

A (mean = 0.04) than the TAU group (mean = 0.09) \( p = .04, d = 0.07 \). No significant between-group differences for incidents of aggression.

(3) The number of restraints was significantly lower for participants who received DBT-A (mean = 0.14) compared with the TAU group (0.16) \( p = .01, d = 0.09 \).

A cost-saving analysis was also performed and indicated savings of approximately $251,609 in the DBT-A group.

**Conclusion:**
Support for the use of DBT-A on inpatient units, in significantly reducing number of constant observation hours for incidents of self-injury, SAs, and restraints during admission in comparison to TAU.

**Limitations:**
Limitations of Saito (2020) paper still apply; Non-randomised sample limiting generalisability of findings. Mean length of stay was 8 days for DBT-A group and 11 days for TAU group (much shorter duration of intervention than previously documented in the literature). Data was limited to what was available on electronic records (lots of missing data). No follow-up; unable to discern maintenance of treatment outcomes. Only approximately half of the DBT-A group were given DBT-A-specific individual therapy due to lack of availability of clinicians.

Although data were collected prospectively, it is a retrospective chart review and therefore not a direct comparison between DBT-A and TAU.

**Note.** A = selection bias, B = study design, C = confounders, D = blinding, E = data collection method, F = withdrawals and dropouts; ALIFE = Adolescent Longitudinal Interval Follow-up Evaluation; BDI = Beck Depression Inventory; BDI-II = Beck Depression Inventory.
EFFECTIVENESS OF DBT IN THE TREATMENT OF HRBS

Inventory, 2nd edition; BHS = Beck Hopelessness Scale; BMI = Body Mass Index; BPD = borderline personality disorder; CALS = Children's Affective Lability Scale; CALS-C = Children's Affective Lability Scale Child Self-Report; CALS-P = Children's Affective Lability Scale Parent Report; CBCL = Child Behaviour Checklist; CBT = Cognitive Behavioural Therapy; CGI-I = Clinical Global Impressions-Improvement; CGI-S = Clinical Global Impressions-Severity for Symptoms; DASA = Dynamic Appraisal of Situational Aggression; DBT-A = Dialectical Behaviour Therapy; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, 4th edition; DUSI = Drug Use Screening Inventory; ED = eating disorder; EDI-2 = EDI-2 = Eating Disorder Inventory-2; ER = emergency room; EUC = enhanced as usual care; GS = group sessions; HAMD = Hamilton Depression Rating Scale; HRB = high risk behaviour; IGST = individual and group supportive therapy; K-SADS-DRS = Schedule for Affective Disorders and Schizophrenia for School-Aged Children Depression Rating Scale; K-SADS-MRS = Schedule for Affective Disorders and Schizophrenia for School-Aged Children Mania Rating Scale; KHS = Kazdin Hopelessness Scale for Children; LIFE = Longitudinal Interval Follow-up Evaluation; LPC = Lifetime Parasuicide Count; M = mean; MADRS = Montgomery-Asberg Depression Rating Scale; MDT = Mode Deactivation Therapy; no. = number; NSSI = non-suicidal self-injury; OR = odds ratio; QATQS = Quality Assessment Tool for Quantitative Studies; RCT = randomised controlled trial; SA = suicide attempt; SASII = Suicide Attempt Self-Injury Interview; SCL-90 = Symptom Checklist-90; SD = standard deviation; SIQ = Suicidal Ideation Questionnaire; SIQ-Jr = Suicidal Ideation Questionnaire-Junior; SIS = Suicide Intent Scale; SMFQ = Short Mood and Feelings Questionnaire; TAU = treatment as usual; USA = United States of America; YMRS = Young Mania Rating Scale
Study Characteristics

**Population.** Individuals were recruited from inpatient units (1, 4, 9, 11), outpatient/community-based MH services (6, 7, 8), clinics for bipolar disorder (2) and eating disorders (EDs; 3), or a mixture of these settings, including admissions to emergency departments (5, 10). Participants were referred to interventions due to increased suicidal ideation/SAs/NSSI (4, 5, 6, 7, 8, 9, 10, 11), problems with anger and aggression (1), bipolar disorder (2), and anorexia nervosa (3). Six studies were conducted in outpatient clinics (2, 3, 6, 7, 8, 10), four in inpatient/residential treatment units (1, 4, 9, 11), and one in an academic medical centre (5).

**Intervention.** Although DBT-A was based on Miller et al. (1997, 2002, 2007) and involved both DBT-A skills groups and individual sessions, the format still varied. Five studies involved multifamily skills training groups (2, 5, 6, 7, 8), four studies involved adolescent-only skills training groups (1, 4, 9, 11), and one study held separate skills training groups for adolescents and parents (10). Study three allowed parents to attend five individual sessions (20%) and eight group sessions (32%).

The majority of studies consisted of interventions between 16 and 26 weeks in total (3, 5, 6, 7, 8, 10). Two studies used DBT-A interventions over a 12-month period (1, 2), one study shortened the intervention to 2 weeks (4), and two studies were limited to the amount of time individuals spent on an inpatient ward, which ranged between eight and 11 days (9, 11).

The intensity of treatment varied across studies. Six studies involved once-weekly individual and once-weekly group skills training sessions (1, 3, 5, 6, 7, 8). One 12-month study involved weekly sessions over the first six months, but alternated
between individual and family skills training sessions, followed by more infrequent sessions over the latter six months (2). One two-week inpatient study delivered ten skills group sessions per week and at least two individual sessions per week (4). Other inpatient studies delivered nine skills training groups per week, at least three individual sessions per week, and approximately one to two family sessions per week (9, 11). One study offered at least one biweekly individual DBT-A session, alongside one weekly skills training group (10). Family sessions were offered in five studies (6, 7, 8, 9, 11), telephone coaching was available to participants in six studies (2, 5, 6, 7, 8, 10), and team consultation in six studies (2, 4, 5, 9, 10, 11).

**Comparator.** Control/comparison groups also varied. Eight studies used a treatment as usual (TAU) or enhanced as usual care (EUC) comparison group. All except two studies (6, 10) provided at least one weekly individual psychotherapy session (including supportive therapy, psychodynamic therapy, psychoeducation). Alongside individual sessions, family sessions were provided in four studies (2, 5, 9, 11), and group therapy sessions in three studies (4, 5, 10). Two studies offered cognitive behavioural therapy (CBT) skills training groups in the TAU condition (9, 11). Study six (followed up by studies seven and eight) offered on average no less than one weekly treatment session which could be individual, group, family therapy, or telephone format, and Study 10 provided biweekly individual sessions alongside group therapy. Study one used mode deactivation therapy (MDT) as a comparator, Study five used individual and group supportive therapy (IGST), and Study three used CBT. Anecdotally, seven studies could be considered reasonably ‘matched’ in intensity to the DBT-A group, since they included individual and group components of similar frequency, however these were not always ‘skills’ groups (1, 3, 4, 5, 9, 10, 11).
**Outcome.** Although all studies measured and reported change in HRB, this was not always the primary outcome, and there were variations in the HRBs measured. All studies except one (11) used self-report measures, however, some also used interviewer-administered measures (2, 4, 5, 6, 7, 8, 10), and clinically recorded data (e.g., behaviour incident reports and/or hospital admissions/emergency room (ER) use; 1, 4, 6, 7, 8, 11), and Body Mass Index (BMI) scores (3). The most commonly studied HRBs were suicidal ideation (1, 2, 4, 5, 6, 7, 8, 10) and self-harm (2, 4, 5, 6, 7, 8, 10, 11). Aggression was measured by four studies (1, 4, 9, 11), hospital/ER use by four studies (4, 6, 7, 8), and eating behaviour by one study (3). Four studies provided follow-up data at different time periods following intervention (4, 5, 7, 8). Other clinical presentations often associated with HRB were measured in several studies (e.g., depression, hopelessness, and emotion dysregulation), however since these are not classified as HRBs the results were not included in the main findings of the SR (Appendix G).

**Study design.** Studies were conducted in the United States of America (1, 2, 5, 9, 11), Norway (6, 7, 8), Germany (3), Canada (4), and Spain (10). Sample sizes were between 20 and 77 for the majority of studies (1, 2, 3, 4, 6, 7, 8, 10), although three studies had larger sample sizes of between 173 and 801 participants (5, 9, 11). The median sample size was 71 participants. The majority of studies were RCTs (2, 3, 5, 6, 10) and quasi-experimental designs (1, 4). Two studies (7, 8) were follow-ups of another included RCT (6) and two were part of the same retrospective chart review (9, 11).
Quality of Included Studies

Each of the eleven studies were evaluated using the QATQS. Quality varied with scores ranging from weak (n = 5), moderate (n = 3), to strong (n = 3; Appendix H). The QATQS rating system regards RCTs or quasi-experimental designs as strong methodological approaches. As noted, nine out of the 11 included studies used either RCT or quasi-experimental design. This said, sample sizes were relatively small, and few commented on the confounders that were adjusted. Based on the reported statistics of studies it was unclear whether power was sufficient to accurately detect differences, therefore inferences that could be drawn were often limited. Three studies were unable to conduct between-group statistical analyses on several outcomes due to small/unequal sample sizes (1, 2, 3).

Main Findings and Implications

Within this section, studies are grouped to consider the impact of DBT-A on specific HRBs. It should be noted that some standardised measures assess a range of HRBs, usually with a specific focus on one behaviour (i.e., measures of self-harm also including questions regarding suicidal ideation/SAs). Since it was not possible to further separate these behaviours, the measure’s primary focus has been utilised to aid grouping for initial outcome data. Follow-up data is reported separately.

Suicidal ideation. Consistent with previous reviews exploring suicidality (DeCou et al., 2019; Glenn et al., 2015; Quinn, 2009), all studies showed within-group improvements following DBT-A intervention.

Significant between-group differences in suicidal ideation were found in two studies (5, 6); with other studies reporting general reductions in suicidal ideation
across both conditions, therefore not reaching between-group significance (1, 2, 4, 7, 8, 10). Study six was a particularly strong study, with good blinding, randomisation procedures, and adherence to the DBT-A model; DBT-A participants improved at a linear, steady rate through all data collection points (pre-treatment to 19 weeks), whereas the EUC group did not improve in the last 4 weeks. Study five also reported a significant advantage for DBT-A towards the end of active treatment (3-6 months; \( t_{169} = 2.20, p = .03, d = 0.34 \)). While not significant, study two reported a trend for DBT-A to decrease suicidal ideation in individuals with bipolar disorder. Where significant group differences were not observed, this could be due to differences in methodological quality (1) and better comparator therapies (i.e., matched in intensity; 4, 10). Studies seven and eight were follow-ups of Study six, where the EUC group had improved over time, therefore there was no longer a between-group significant difference. In summary, significant between-group differences were demonstrated in two studies of stronger methodological quality, indicating that DBT-A was more effective than IGST and EUC comparators, but was similar to other treatments within the non-significant studies.

**Self-harm.** Significant between-group differences in frequency of self-harm (often including SAs) were found in six studies (5, 6, 7, 8, 10, 11), favouring DBT-A in comparison to the control condition. Reductions were found in the other two studies, though these did not meet between-group significance (2), and low numbers precluded statistical analysis (4).

Study five additionally reported on a secondary analysis of clinically significant change, defined as the absence of any self-harm; 40 out of 86 participants (46.5%) in the DBT-A group versus 24 out of 87 participants (27.6%) in the IGST group reported being ‘self-harm free’ at the end of the intervention (6 months). In Study six, the
significant reduction in self-harm frequency was only present in the DBT-A group. Since the EUC group in this condition did not receive skills-training sessions, this could indicate support for the skills-training component of DBT-A in explicitly teaching skills to reduce self-harm behaviours. In both Studies 5 and 6, the most dramatic reductions in self-harm episodes were between the beginning and middle of treatment (3-4 months), with the DBT-A groups reducing the number of self-harm episodes to approximately 50% of baseline number by the middle of treatment.

Study 11 was a retrospective chart review of a period of time where DBT-A had been implemented on an inpatient ward in comparison to TAU. The DBT-A group required significantly fewer constant observation hours for self-injury, and there were significantly fewer incidents of self-harm and SAs. This is particularly noteworthy considering the brief average admission time (8.36 days). Although there was no follow-up analysis, it would be interesting to explore whether these results were maintained after discharge. Cost-savings within this study were also noteworthy; less money was spent on staff time for constant observation hours, resulting in a $251,609 saving over the 8-month period. In sum, DBT-A was shown to consistently and significantly reduce self-harm behaviours in comparison to control conditions, in both outpatient and inpatient settings.

**Aggression.** Studies found significant between-group differences in levels of aggression towards others (1, 4), self (4), and number of restraints required (11). In inpatient settings, one study (4) showed significant advantages for DBT-A in reducing ‘behavioural' incident reports, including other and self-directed violence. However, two studies did not demonstrate significant differences in self-reported aggression or incidents of aggression between groups (9, 11). Study one found fewer improvements in physical aggression following DBT-A than MDT, yet this study displayed various
methodological concerns, with noticeable errors in the reporting of the results and a likely bias, since the authors developed MDT. Study four showed a significant difference when comparing the 6-month period before DBT-A implementation to the 6-month period after DBT-A implementation on the DBT-A ward ($\chi^2 = 43.11, p < .001$), thus supporting DBT-A as a mechanism of change rather than something related to non-DBT ward phenomena. Though findings regarding aggression are mixed, the mean length of stay in Study four was significantly longer (18 days) than in the other inpatient studies (9, 11; 8-11 days), perhaps indicating the benefit of a longer period of treatment and time on the ward in reducing aggression.

**Hospital admissions and ER use.** Studies generally reported low rates of hospital admissions and ER use in both conditions, with no significant differences between groups. Study six showed a non-significant trend for DBT-A participants to have fewer hospital visits.

**Eating behaviour.** One study used DBT-A within a specialist ED community team (3). ED symptoms were reported to have decreased significantly in both CBT and DBT-A groups, with larger effect sizes in CBT ($d = -0.61$) than DBT-A ($d = -0.55$). Furthermore, BMI increased significantly in both the CBT group ($d = 1.04$) and in the DBT-A group ($d = 0.7$).

**Follow-up data.** Four studies provided follow-up data at different time periods post-intervention (4, 5, 7, 8). Study four showed no between-group differences at 12-month follow-up, since both groups demonstrated substantial reductions in HRBs over this period. Due to a low base-rate of re-hospitalisations and ER visits, statistical analysis did not detect differences between groups, however, raw numbers showed the total number of hospitalisations at follow-up had tripled in the TAU group (from n
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= 2 to n = 6), and DBT-A group had remained the same (n = 6). The total number of ER visits in the TAU group had also increased from three to 14, whereas the DBT-A group had increased from six to eight.

Studies five, seven, and eight reported that the DBT-A group retained a significant advantage in terms of self-harm, however treatment groups had converged on most other HRB outcomes, due to the DBT-A group maintaining their completion levels and EUC improving over the course of follow-up. In Study seven, a trend was noted for EUC participants to have more treatment from MH services over the follow-up year than DBT-A participants, which could have affected their improvement over this period. Follow-up analyses in Study five reported fewer SAs in the DBT-A group (7%) than the IGST group (10.3%) between the end of the intervention and 12-month follow-up; one individual in the IGST group died by suicide in the follow-up period. Study eight reported that at the 3-year mark, participants in both groups had retained treatment gains on measures of HRBs, with no sign of relapse and no significant between-group differences on outcomes except self-harm, which was retained from the previous years. In sum, the limited findings suggest that reductions in self-harm in particular are maintained over follow-up for DBT-A, but improvements on other HRBs were seen and maintained irrespective of treatment condition.

Treatment completion rates. Five studies provided information regarding treatment completion/dropouts (2, 4, 5, 6, 10). Two studies reported significantly higher rates of adherence to treatment in DBT-A group (2, 5), and two studies reported no significant differences in adherence between groups (6, 10). Study six had a more relaxed definition of ‘dropout’ within the TAU group, which could contribute to an underestimation of attrition within this group. While Study four did not provide data regarding dropout in the TAU group, they reported no dropouts in the DBT-A group.
Overall, considering the data provided, DBT-A appears to engage and retain adolescents in treatment better than control conditions.

**Discussion**

This review aimed to evaluate available evidence for the effectiveness of DBT-A in the treatment of HRBs in adolescents. Although previous reviews have been conducted around this topic (DeCou et al., 2019; Glenn et al., 2019; Groves et al., 2012), to current knowledge, this is the first SR in the last 8 years to consider effectiveness of DBT-A with a minimum of two critical DBT components (individual and skills group) on a range of HRBs in adolescents. A total of 11 studies were included and a variety of HRBs were identified; suicidal ideation, SAs, self-harm, aggression, hospital admissions, ER use, and eating behaviour. Surprisingly, no studies were found for some HRB (e.g., risky sexual behaviour, drug and alcohol misuse) highlighting the need for further research. The reviewed studies provide vital information about practical effectiveness, with findings indicating that DBT-A has an overall positive effect on a range of HRBs in adolescents. Findings support DBT-A’s theoretical assumptions that in order to effectively target various HRB, a possible shared mechanism of emotion dysregulation can be addressed. As emotion dysregulation is common in a range of MH presentations, this further lends promise to DBT-A’s transdiagnostic utility. However, the findings remain tentative due to methodological complexities identified within the reviewed research. Specifically, included studies varied in methodological quality, power to detect meaningful differences, and measures used to assess HRBs, thus making it difficult to draw firmer conclusions. Notwithstanding this, seven of the 11 studies reported at least one significant between-group finding on a measure of HRB, in favour of DBT-A.
Findings suggested significant improvements in suicidal ideation and self-harm in particular, with reductions in self-harm being the most likely to remain significant in comparison to the control group over follow-up (McCauley et al., 2018; Mehlum et al., 2016, 2019). This fits with DBT’s main treatment targets of reducing ‘life-threatening’ and ‘quality of life interfering’ behaviours, through addressing underlying emotion dysregulation (Linehan, 1993). A pattern of reductions in suicidal ideation and self-harm across studies appeared to emerge, with greater improvements noted in the first 12-16 weeks of the intervention than the rest of the intervention and follow-up (McCauley et al., 2018; Mehlum et al., 2014). This could suggest that a relatively short intervention may still have a significant impact on reducing HRBs, which is likely to be more appealing for adolescents, families, and services.

Although three studies were limited to a short period of time individuals spent on inpatient wards (Katz et al., 2004; Saito et al., 2020; Tebbett-Mock et al., 2019), significant group differences were found on measures of self-harm and aggression. Interestingly, adolescents in both groups made similar improvements on other outcomes, even though the DBT-A group had a significantly shorter stay on the ward (Saito et al., 2020; Tebbett-Mock et al., 2019). These findings perhaps lend support towards the benefit of shorter, more intense adaptations of DBT-A for inpatient settings. The cost-savings noted in Tebbett-Mock et al. (2019) further suggest that DBT-A could be a more cost-effective treatment than TAU.

The variation in intensity between comparator conditions and DBT-A also contributed difficulties in interpreting the findings. However, even in studies where DBT-A was felt to be reasonably ‘matched’ in intensity to the control group, significant between-group differences were noted, thus indicating something specifically about the DBT-A model/intervention that likely contributed to changes in HRB. Since DBT-A
is a complex, multi-faceted intervention, a growing body of literature is investigating which elements may be most important in effecting change (Neacsiu, Rizvi, & Linehan, 2010; Rudge, Feigenbaum, & Fonagy, 2020). The DBT model suggests that deficits in interpersonal skills, distress tolerance skills and emotion regulation underlie engagement in HRBs, therefore it could be suggested that improvement in HRBs may be attributable to the skills group component of DBT (Saito et al., 2020). In sum, shorter, more intensive interventions with emphasis on the skills group element could be worth further investigation in their effectiveness for specifically targeting HRB.

Strengths and Limitations

The review took a broad approach to exploring the impact of DBT-A across several settings on a range of HRBs. By combining studies that examine a range of HRBs, rather than focusing on one HRB in isolation (e.g., NSSI), the SR provided tentative support regarding a possible shared mechanism underlying different HRB which will need further rigorous exploration. By summarising different DBT-A adaptations across a range of settings, some preliminary conclusions about clinical optimisation (i.e., short, intense treatment) could be drawn.

The findings of this review should be considered in the context of several limitations on both a review and study level. First, while search terms were carefully selected, it is possible that not every study assessing effectiveness of DBT-A on HRBs was identified, particularly unpublished studies with null findings. Second, quality assessment ratings were not used to exclude studies, and the methodological quality of included studies varied significantly, thus limiting the generalisability of findings. Third, although this review attempted to ensure consistency in interventions by only including studies that involved both the individual and group skills training elements of
DBT-A, studies still varied in terms of intervention length, number of sessions, intensity, and presence of family members. Fourth, small sample sizes and low base rates on certain measures meant that some studies were not able to analyse all outcomes, and often lacked power to detect between-group differences. Furthermore, studies differed in their descriptions of their adherence to (or deviation from) the DBT-A model; some provided clear evidence of assessment of fidelity, others were vague. Overall, these variations limit the conclusions that can be drawn, thus further research into this area is needed.

**Clinical and Theoretical Implications**

The results from this SR highlight the need for outcome measures in studies on DBT-A to assess a range of HRBs, rather than solely focusing on behaviours such as NSSI, SAs, and suicidal ideation, which have most commonly been researched due to their classification as 'life-threatening' behaviours. More assessment of outcomes during interventions (rather than just before and after) could allow for further investigation of the different trajectories (e.g., early decrease in HRB with DBT-A) that were discovered between DBT-A and control groups in some studies. The results highlight that DBT-A could be useful in supporting individuals who engage in a range of HRBs across a variety of psychiatric diagnoses, since it may be targeting a common mechanism that contributes to psychological distress (difficulties with emotion regulation) possibly resulting in the development of maladaptive coping strategies (HRBs). However, more research is needed on HRBs that may fall under the same mechanism but are not frequently studied (e.g., substance misuse, risky sexual behaviours).
Most current interventions for adolescents at risk of suicide are intensive and use a variety of treatment components (Glenn et al., 2015). All studies in the current SR included both individual and group skills training elements of DBT-A. In clinical practice, ‘skills group only’ DBT is becoming more popular, and further research into this area, including controlled trials, would be useful in order to examine which elements are necessary in order to meaningfully impact adolescents and yield significant results. If shorter, less intensive versions of DBT-A were able to provide similar effects, this could have a dramatic effect on the costs and availability of such a resource within clinical settings.

DBT-A could serve an important function as a Phase one ‘stabilisation’ therapy for individuals with trauma histories who are at increased risk of engaging in HRBs; decreasing multiple HRBs and increasing use of adaptive coping strategies in readiness for exposure therapy if required. New protocols combining DBT with trauma-specific approaches are emerging (e.g., DBT-Prolonged Exposure; Harned, Korslund, Foa, & Linehan, 2012), and research in this area is growing in adolescent populations (Lang, Edwards, Mittler, & Bonavitacola, 2018).

Conclusion

With a recent shift towards interventions that address transdiagnostic patterns, there is a growing interest to understand the effectiveness of interventions on a range of difficulties that may have a shared underlying mechanism. This SR explored the effectiveness of DBT-A on a range of HRBs, expanding on previous reviews which have examined interventions more broadly, or focused on one HRB in isolation. The literature on DBT-A has expanded considerably in recent years, with six of the 11 included studies published in the last two years. Despite being limited in
generalisability, the review demonstrated that DBT-A can have a positive benefit on a number of HRBs, with improvements in self-harm most likely to be maintained over follow-up. The review raises a number of limitations within studies, and proposes preliminary ideas on how to continue building the evidence-base for interventions that reduce HRBs, in order to prevent poor long-term outcomes that persist into adulthood.
References


https://doi.org/10.1016/j.cbpra.2017.12.005


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https://doi.org/10.1111/jora.12199


Appendices

Appendix A: List of All Databases Searched in the Review

Appendix B: Full Search Strategy for Ovid Medline Database

Appendix C: Effective Public Health Practice Project Quality Assessment Tool for Quantitative Studies

Appendix D: Effective Public Health Practice Project Quality Assessment Tool Dictionary

Appendix E: Data Extraction Form

Appendix F: Exclusion Criteria for Studies not Eligible for Review in Alphabetical Order by Author

Appendix G: Main Findings Regarding Clinical Presentations Associated with HRBs

Appendix H: EPHPP Quality Rating Full Table

Appendix I: Journal of Clinical Child and Adolescent Psychology Submission Guidelines
Appendix A

List of All Databases Searched in the Review

- Ovid included the following databases: Embase, Ovid Medline(r) In-Process & Other Non-indexed Citation and Ovid Medline(r), APA PsycINFO and APA PsycExtra.

- Web of Science included the following databases: Science Citation Index Expanded (1900-present), Social Sciences Citation Index (1956-present), Arts & Humanities Citation Index (1975-present), Conference Proceedings Citation Index – Science (1990-present), Conference Proceedings Citation Index – Social Science & Humanities (1990-present), Emerging Sources Citation Index (2015-present).

- Cochrane library included the following databases: Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials
### Appendix B

**Full Search Strategy for Ovid Medline Database**

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<td>Advanced</td>
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<tr>
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Appendix C

Effective Public Health Practice Project Quality Assessment Tool for Quantitative Studies

QUALITY ASSESSMENT TOOL FOR QUANTITATIVE STUDIES

COMPONENT RATINGS

A) SELECTION BIAS

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B) STUDY DESIGN

Indicate the study design

| 1. Randomized controlled trial |
| 2. Controlled clinical trial |
| 3. Cohort analytic (two group pre + post) |
| 4. Case control |
| 5. Cohort (one group pre + post [before and after]) |
| 6. Interrupted time series |
| 7. Other specify |
| 8. Can't tell |

Was the study described as randomized? If NO, go to Component C

<table>
<thead>
<tr>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
</table>

If Yes, was the method of randomization described? (See dictionary)

<table>
<thead>
<tr>
<th>No</th>
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</tr>
</thead>
</table>

If Yes, was the method appropriate? (See dictionary)

<table>
<thead>
<tr>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>RATE THIS SECTION</th>
<th>STRONG</th>
<th>MODERATE</th>
<th>WEAK</th>
</tr>
</thead>
<tbody>
<tr>
<td>See dictionary</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>
C) CONFOUNDERS

(Q1) Were there important differences between groups prior to the intervention?
1 Yes
2 No
3 Can’t tell

The following are examples of confounders:
1 Race
2 Sex
3 Marital status/family
4 Age
5 SES (income or class)
6 Education
7 Health status
8 Pre-intervention score on outcome measure

(Q2) If yes, indicate the percentage of relevant confounders that were controlled (either in the design (e.g. stratification, matching) or analysis)?
1 80 – 100% (most)
2 60 – 79% (some)
3 Less than 60% (few or none)
4 Can’t Tell

D) BLINDING

(Q1) Was (were) the outcome assessor(s) aware of the intervention or exposure status of participants?
1 Yes
2 No
3 Can’t tell

(Q2) Were the study participants aware of the research question?
1 Yes
2 No
3 Can’t tell

E) DATA COLLECTION METHODS

(Q1) Were data collection tools shown to be valid?
1 Yes
2 No
3 Can’t tell

(Q2) Were data collection tools shown to be reliable?
1 Yes
2 No
3 Can’t tell

See dictionary
F) WITHDRAWALS AND DROP-OUTS

(Q1) Were withdrawals and drop-outs reported in terms of numbers and/or reasons per group?
1  Yes
2  No
3  Can’t tell
4  Not Applicable (i.e. one time surveys or interviews)

(Q2) Indicate the percentage of participants completing the study. (If the percentage differs by groups, record the lowest).
1  80 - 100%
2  60 - 79%
3  less than 60%
4  Can’t tell
5  Not Applicable (i.e. Retrospective case control)

RATE THIS SECTION

<table>
<thead>
<tr>
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<th>MODERATE</th>
<th>WEAK</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

See dictionary

G) INTERVENTION INTEGRITY

(Q1) What percentage of participants received the allocated intervention or exposure of interest?
1  80 - 100%
2  60 - 79%
3  less than 60%
4  Can’t tell

(Q2) Was the consistency of the intervention measured?
1  Yes
2  No
3  Can’t tell

(Q3) Is it likely that subjects received an unintended intervention (contamination or co-intervention) that may influence the results?
1  Yes
2  No
3  Can’t tell

H) ANALYSES

(Q1) Indicate the unit of allocation (circle one)
community organization/institution practice/office individual

(Q2) Indicate the unit of analysis (circle one)
community organization/institution practice/office individual

(Q3) Are the statistical methods appropriate for the study design?
1  Yes
2  No
3  Can’t tell

(Q4) Is the analysis performed by intervention allocation status (i.e. intention to treat) rather than the actual intervention received?
1  Yes
2  No
3  Can’t tell
GLOBAL RATING

COMPONENT RATINGS
Please transcribe the information from the gray boxes on pages 1-4 onto this page. See dictionary on how to rate this section.

<table>
<thead>
<tr>
<th>Component</th>
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<th>Moderate</th>
<th>Weak</th>
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<tr>
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<td>2</td>
<td>3</td>
</tr>
<tr>
<td>B STUDY DESIGN</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>C CONFOUNDERS</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>D BLINDING</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>E DATA COLLECTION METHOD</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>F WITHDRAWALS AND DROPOUTS</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

GLOBAL RATING FOR THIS PAPER (circle one):

1 STRONG [no WEAK ratings]
2 MODERATE [one WEAK rating]
3 WEAK [two or more WEAK ratings]

With both reviewers discussing the ratings:

Is there a discrepancy between the two reviewers with respect to the component (A-F) ratings?
No
Yes

If yes, indicate the reason for the discrepancy:

1 Oversight
2 Differences in interpretation of criteria
3 Differences in interpretation of study

Final decision of both reviewers (circle one):

1 STRONG
2 MODERATE
3 WEAK
Appendix D

Effective Public Health Practice Project Quality Assessment Tool Dictionary

Quality Assessment Tool for Quantitative Studies Dictionary

The purpose of this dictionary is to describe items in the tool thereby assisting raters to score study quality. Due to under-reporting or lack of clarity in the primary study, raters will need to make judgements about the extent that bias may be present. When making judgements about each component, raters should form their opinion based upon information contained in the study rather than making inferences about what the authors intended. Mixed methods studies can be quality assessed using this tool with the quantitative component of the study.

A) SELECTION BIAS

(Q1) Participants are more likely to be representative of the target population if they are randomly selected from a comprehensive list of individuals in the target population (score very likely). They may not be representative if they are referred from a source (e.g. clinic) in a systematic manner (score somewhat likely) or self-referred (score not likely).

(Q2) Refers to the % of subjects in the control and intervention groups that agreed to participate in the study before they were assigned to intervention or control groups.

B) STUDY DESIGN

In this section, raters assess the likelihood of bias due to the allocation process in an experimental study. For observational studies, raters assess the extent that assessments of exposure and outcome are likely to be independent. Generally, the type of design is a good indicator of the extent of bias. In stronger designs, an equivalent control group is present and the allocation process is such that the investigators are unable to predict the sequence.

Randomized Controlled Trial (RCT)

An experimental design where investigators randomly allocate eligible people to an intervention or control group. A rater should describe a study as an RCT if the randomization sequence allows each study participant to have the same chance of receiving each intervention and the investigators could not predict which intervention was next. If the investigators do not describe the allocation process and only use the words ‘random’ or ‘randomly’, the study is described as a controlled clinical trial.

See below for more details.

Was the study described as randomized?

Score YES, if the authors used words such as random allocation, randomly assigned, and random assignment.

Score NO, if no mention of randomization is made.

Was the method of randomization described?

Score YES, if the authors describe any method used to generate a random allocation sequence.

Score NO, if the authors do not describe the allocation method or describe methods of allocation such as alternation, case record numbers, dates of birth, day of the week, and any allocation procedure that is entirely transparent before assignment, such as an open list of random numbers of assignments.

If NO is scored, then the study is a controlled clinical trial.
Was the method appropriate?

Score YES, if the randomization sequence allowed each study participant to have the same chance of receiving each intervention and the investigators could not predict which intervention was next. Examples of appropriate approaches include assignment of subjects by a central office unaware of subject characteristics, or sequentially numbered, sealed, opaque envelopes.

Score NO, if the randomization sequence is open to the individuals responsible for recruiting and allocating participants or providing the intervention, since those individuals can influence the allocation process, either knowingly or unknowingly.

If NO is scored, then the study is a controlled clinical trial.

Controlled Clinical Trial (CCT)
An experimental study design where the method of allocating study subjects to intervention or control groups is open to individuals responsible for recruiting subjects or providing the intervention. The method of allocation is transparent before assignment, e.g. an open list of random numbers or allocation by date of birth, etc.

Cohort analytic (two group pre and post)
An observational study design where groups are assembled according to whether or not exposure to the intervention has occurred. Exposure to the intervention is not under the control of the investigators. Study groups might be non-equivalent or not comparable on some feature that affects outcome.

Case control study
A retrospective study design where the investigators gather ‘cases’ of people who already have the outcome of interest and ‘controls’ who do not. Both groups are then questioned or their records examined about whether they received the intervention exposure of interest.

Cohort (one group pre + post (before and after)
The same group is pretested, given an intervention, and tested immediately after the intervention. The intervention group, by means of the pretest, act as their own control group.

Interrupted time series
A study that uses observations at multiple time points before and after an intervention (the ‘interruption’). The design attempts to detect whether the intervention has had an effect significantly greater than any underlying trend over time. Exclusion: Studies that do not have a clearly defined point in time when the intervention occurred and at least three data points before and three after the intervention.

Other:
One time surveys or interviews

C) CONFOUNDERS

By definition, a confounder is a variable that is associated with the intervention or exposure and causally related to the outcome of interest. Even in a robust study design, groups may not be balanced with respect to important variables prior to the intervention. The authors should indicate if confounders were controlled in the design (by stratification or matching) or in the analysis. If the allocation to intervention and control groups is randomized, the authors must report that the groups were balanced at baseline with respect to confounders (either in the text or a table).

D) BLINDING

(Q1) Assessors should be described as blinded to which participants were in the control and intervention groups. The purpose of blinding the outcome assessors (who might also be the care providers) is to protect against detection bias.

(Q2) Study participants should not be aware of (i.e. blinded to) the research question. The purpose of blinding the participants is to protect against reporting bias.
E) DATA COLLECTION METHODS

Tools for primary outcome measures must be described as reliable and valid. If 'face' validity or 'content' validity has been demonstrated, this is acceptable. Some sources from which data may be collected are described below:

- **Self reported data** includes data that is collected from participants in the study (e.g. completing a questionnaire, survey, answering questions during an interview, etc.).
- **Assessment/Screening** includes objective data that is retrieved by the researchers (e.g. observations by investigators).
- **Medical Records/Vital Statistics** refers to the types of formal records used for the extraction of the data.

Reliability and validity can be reported in the study or in a separate study. For example, some standard assessment tools have known reliability and validity.

F) WITHDRAWALS AND DROP-OUTS

Score **YES** if the authors describe BOTH the numbers and reasons for withdrawals and drop-outs.
Score **NO** if either the numbers or reasons for withdrawals and drop-outs are not reported.
Score **NOT APPLICABLE** if the study was a one-time interview or survey where there was not follow-up data reported.

The percentage of participants completing the study refers to the % of subjects remaining in the study at the final data collection period in all groups (i.e. control and intervention groups).

G) INTERVENTION INTEGRITY

The number of participants receiving the intended intervention should be noted (consider both frequency and intensity). For example, the authors may have reported that at least 80 percent of the participants received the complete intervention. The authors should describe a method of measuring if the intervention was provided to all participants the same way. As well, the authors should indicate if subjects received an unintended intervention that may have influenced the outcomes. For example, co-intervention occurs when the study group receives an additional intervention (other than that intended). In this case, it is possible that the effect of the intervention may be over-estimated. Contamination refers to situations where the control group accidentally receives the study intervention. This could result in an under-estimation of the impact of the intervention.

H) ANALYSIS APPROPRIATE TO QUESTION

Was the quantitative analysis appropriate to the research question being asked?

An intention-to-treat analysis is one in which all the participants in a trial are analyzed according to the intervention to which they were allocated, whether they received it or not. Intention-to-treat analyses are favoured in assessments of effectiveness as they mirror the noncompliance and treatment changes that are likely to occur when the intervention is used in practice, and because of the risk of attrition bias when participants are excluded from the analysis.
Component Ratings of Study:
For each of the six components A – F, use the following descriptions as a roadmap.

A) SELECTION BIAS
   Good: The selected individuals are very likely to be representative of the target population (Q1 is 1) and there is greater than 80% participation (Q2 is 1).
   Fair: The selected individuals are at least somewhat likely to be representative of the target population (Q1 is 1 or 2); and there is 60 - 79% participation (Q2 is 2). 'Moderate' may also be assigned if Q1 is 1 or 2 and Q2 is 5 (can’t tell).
   Poor: The selected individuals are not likely to be representative of the target population (Q1 is 3); or there is less than 60% participation (Q2 is 3) or selection is not described (Q1 is 4); and the level of participation is not described (Q2 is 5).

B) DESIGN
   Good: will be assigned to those articles that described RCTs and CCTs.
   Fair: will be assigned to those that described a cohort analytic study, a case control study, a cohort design, or an interrupted time series.
   Weak: will be assigned to those that used any other method or did not state the method used.

C) CONFOUNDERS
   Good: will be assigned to those articles that controlled for at least 80% of relevant confounders (Q1 is 2); or (Q2 is 1).
   Fair: will be given to those studies that controlled for 60 – 79% of relevant confounders (Q1 is 1) and (Q2 is 2).
   Poor: will be assigned when less than 60% of relevant confounders were controlled (Q1 is 1) and (Q2 is 3) or control of confounders was not described (Q1 is 3) and (Q2 is 4).

D) BLINDING
   Good: The outcome assessor is not aware of the intervention status of participants (Q1 is 2); and the study participants are not aware of the research question (Q2 is 2).
   Fair: The outcome assessor is not aware of the intervention status of participants (Q1 is 2); or the study participants are not aware of the research question (Q2 is 2).
   Poor: The outcome assessor is aware of the intervention status of participants (Q1 is 1); and the study participants are aware of the research question (Q2 is 2); or blinding is not described (Q1 is 3 and Q2 is 3).

E) DATA COLLECTION METHODS
   Good: The data collection tools have been shown to be valid (Q1 is 1); and the data collection tools have been shown to be reliable (Q2 is 1).
   Fair: The data collection tools have been shown to be valid (Q1 is 1); and the data collection tools have not been shown to be reliable (Q2 is 2) or reliability is not described (Q2 is 3).
   Poor: The data collection tools have not been shown to be valid (Q1 is 2) or both reliability and validity are not described (Q1 is 3 and Q2 is 3).

F) WITHDRAWALS AND DROP-OUTS - a rating of:
   Good: will be assigned when the follow-up rate is 80% or greater (Q1 is 1 and Q2 is 1).
   Fair: will be assigned when the follow-up rate is 60 – 79% (Q2 is 2) OR Q1 is 4 or Q2 is 5.
   Poor: will be assigned when a follow-up rate is less than 60% (Q2 is 3) or if the withdrawals and drop-outs were not described (Q1 is No or Q2 is 4).
   Not Applicable: if Q1 is 4 or Q2 is 5.
Appendix E

Data Extraction Form

Reference Number:

Title:

Author(s):

Date:

Objective:

Target group:

Setting:

Population

Study population:

Sampling method:

Power Calculation:

Entry and exclusion criteria:

Representative of sample:

Size of intervention and control groups:

Comparability of intervention and control groups:

Description of Intervention

Experimental intervention (including timescale and any aspects of complexity):

Control (including timescale and any aspects of complexity):

Outcomes: Measures and Instruments

Timing of measures:

Nature of measures:

Baseline:

Instruments used:

Were instruments validated?:

Length of follow up:
Study Design

Study Quality:

Method of randomisation:
Method of allocation concealment:
Blinding of assessors:
Intention to treat analysis:
Raw means and standard deviations presented at baseline:
Raw means and standard deviations presented at follow up:

Results

Means and SDs of primary outcomes by group:
Attrition (D/O) from study and from intervention and control groups:
What statistical tests were used?

Conclusions

Author’s conclusions:
Reviewer’s commentary:
Strengths:
Weaknesses:
Generalisability of findings:

Quality Assessment Tool Rating

A =
B =
C =
D =
E =
F =

Global rating:
### Appendix F

Exclusion Criteria for Studies not Eligible for Review in Alphabetical Order by Author

<table>
<thead>
<tr>
<th>No.</th>
<th>Author</th>
<th>Reason for Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Adrian et al. (2019)</td>
<td>Part of another study already included - not reporting HRB statistics in this paper</td>
</tr>
<tr>
<td>2</td>
<td>Agnew (2013)</td>
<td>No control/comparison group</td>
</tr>
<tr>
<td>3</td>
<td>Anestis, Charles, Lee-Rowland, Barry &amp; Gratz (2019)</td>
<td>DBT-A skills group only</td>
</tr>
<tr>
<td>4</td>
<td>Beckstead, Lambert, DuBose &amp; Linehan (2015)</td>
<td>No control/comparison group</td>
</tr>
<tr>
<td>5</td>
<td>Berk (2016)</td>
<td>No control/comparison group</td>
</tr>
<tr>
<td>6</td>
<td>Berk, Starace, Black &amp; Avina (2018)</td>
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<td>Castellanos (2015)</td>
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<td>Cooney (2010)</td>
<td>Feasibility study - not reporting change in HRBs</td>
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<td>Uses DBT-C</td>
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<td>Reason for Exclusion or Comment</td>
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<td>Rathus &amp; Miller (2002)</td>
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<tr>
<td>75</td>
<td>Zapolski &amp; Smith (2017)</td>
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**Note.** No. = number; HRB = high-risk behaviour; DBT-A = Dialectical Behaviour Therapy for Adolescents; DBT-C = Dialectical Behaviour Therapy for Children
Appendix G

Main Findings Regarding Clinical Presentations Associated with HRBs

**Depression**

Three studies reported between-group significant differences in depressive symptoms, in favour of DBT-A (2, 6, 9). Study nine is of importance due to being on an inpatient ward, whereby the mean length of stay for DBT-A participants (8 days) was significantly shorter than for TAU participants (11 days). In Study two, the trajectories for the two groups of individuals with bipolar disorder were noticeably different, with the DBT-A group improving in a consistent and linear fashion over the 12-month period, and the TAU group experiencing initial improvements until the middle of treatment, whereby their scores increased again, and finally tapered off to scores similar to baseline at the end of treatment. Support could again be suggested for the skills-training element of DBT-A in reducing depressive symptoms, since the control groups in studies two and six did not involve a skills-training component.

**Hopelessness**

While there were no between-group significant differences reported in terms of hopelessness, Study four reported absolute differences in effect sizes, in favour of DBT-A ($d = 0.73$ compared to $d = 0.33$ for TAU); DBT-A participants had higher scores at baseline ($M_{KHS} = 9.13$) than TAU ($M_{KHS} = 8.27$), however their scores at discharge were less ($M_{KHS} = 5.87$) than the TAU group ($M_{KHS} = 6.55$). Study six reported significant within-group reductions for the DBT-A group but not for TAU, with greater effect sizes for the DBT-A group (0.97) compared to TAU group (0.22).
**General Symptoms of Psychopathology**

Study three reported consistent reductions in symptoms of psychopathology in both groups, with no significant differences between groups, however effect sizes were greater for the CBT group than DBT-A group (CBT; $d = 0.78$; DBT-A; $d = 0.47$). Study 11 found that participants who received DBT-A showed significant improvement in presentation of symptoms of psychopathology upon discharge compared to the TAU condition ($p < .001$), but both groups showed equal improvements in severity of symptoms. Again, this is interesting given the significantly shorter duration of treatment in the DBT-A group in comparison to TAU (9, 11).

**Manic Behaviour**

Two studies looked at the effectiveness of DBT-A on mood symptoms, and in particular, manic behaviour (2, 9). Neither reported between group significant differences in mania ratings, however the study with stronger methodology (2) reported a significant effect of time on mania rating scores among the DBT-A group ($F = 7.10, p = 0.0003$; partial $n^2 = 0.39$) but not TAU ($F = 0.25, p = 0.90$; partial $n^2 = 0.11$).

**Emotion Dysregulation**

Though significant between-group differences were not found in emotion dysregulation, study two noted that only the DBT-A group had within-group differences on this measure (CALS-C, $p = 0.008$; CALS-P, $p = .01$).
### Appendix H

**EPHPP Quality Rating Full Table**

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<th>No.</th>
<th>Author</th>
<th>A - Selection Bias</th>
<th>B - Study Design</th>
<th>C - Confounders</th>
<th>D - Blinding</th>
<th>E - Data Collection Method</th>
<th>F - Withdrawals and Dropouts</th>
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*Note. No. = number; N/A = not applicable*
Appendix I

Journal of Clinical Child and Adolescent Psychology Submission Guidelines

About the Journal

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Preparing Your Paper

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- Should be written with the following elements in the following order: title page; abstract; main text; references; appendices (as appropriate); table(s) with caption(s) (on individual pages); figures; figure captions (as a list)
- Should contain a structured abstract of 250 words.
- Read making your article more discoverable, including information on choosing a title and search engine optimization.
- A Regular Article may not exceed 11,000 words (i.e., 35 pages), including references, footnotes, figures, and tables. Brief Reports include empirical research that is soundly designed, but may be of specialized interest or narrow focus. Brief Reports may not be submitted in part or whole to another journal of general circulation. Brief Reports may not exceed 4,500 words for text and references. These limits do not include the title page, abstract, author note, footnotes, tables, and figures. Manuscripts that exceed these page limits and that are not prepared according to the guidelines in the Manual will be returned to authors without review.
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All Regular Article and Brief Report submissions must include a title of 15 words or less that identifies the developmental level of the study participants (e.g., children, adolescents, etc.). JCCAP uses an unstructured abstract format. For studies that report randomized clinical trials or meta-analyses, the abstract also must be consistent with the guidelines set forth by CONSORT or MARS, respectively. The Abstract should include up to 250 words, presented in paragraph form. The Abstract should be typed on a separate page (page 2 of the manuscript), and must include each of the following label sections: 1) Objective (i.e., a brief statement of the purpose of the study); 2) Method (i.e., a detailed summary of the participants, N, age, gender, ethnicity, as well as a summary of the study design, measures, and procedures; 3) Results (i.e., a detailed summary of the primary findings that clearly articulate comparison groups (if relevant); 4) Conclusions (i.e., a description of the research and clinical implications of the findings). Avoid abbreviations, diagrams, and reference to the text in the abstract. JCCAP will scrutinize manuscripts for a clear theoretical framework that supports central study hypotheses.

In addition, a clear developmental rationale is required for the selection of participants at a specific age. The Journal is making diligent efforts to insure that there is an appropriately detailed description of the sample, including a) the population from which the sample was drawn; b) the number of participants; c) age, gender, ethnicity, and SES of participants; d) location of sample, including country and community type (rural/urban), e) sample identification/selection; f) how participants were contacted; g) incentives/rewards; h) parent consent/child assent procedures and rates; i) inclusion and exclusion criteria; j) attrition rate. The Discussion section should include a comment regarding the diversity and generality (or lack thereof) of the sample. The Measures section should include details regarding item content and scoring as well as evidence of reliability and validity in similar populations.

All manuscripts must include a discussion of the clinical significance of findings, both in terms of statistical reporting and in the discussion of the meaningfulness and clinical relevance of results. Manuscripts should a) report means and standard deviations for all variables, b) report effect sizes for analyses, and c) provide confidence intervals wherever appropriate (e.g., on figures, in tables), particularly for effect sizes on primary study findings. In addition, when reporting the results of interventions, authors should include indicators of clinically significant change. Authors may use one of several approaches that have been recommended for capturing clinical significance, including (but not limited to) the reliable change index.
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The Relationship Between Early Life Stress, Amygdala Reactivity and Coping Behaviour Across the Life Span: An fMRI Study

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Target Journal: Neuroimage
Word Count: 7999 words

Submitted in partial fulfilment of requirements for the Doctorate Degree in Clinical Psychology, University of Exeter
Abstract

Objective: Following early life stress (ELS), individuals have been shown to develop maladaptive coping strategies including externalising behaviours such as aggression that persist across the life span. Yet, little is known about the possible underlying mechanisms for this association. This study explored these relationships using neuroimaging methods and clinical data from a 30-year longitudinal dataset investigating adults with ELS and cross-sectional controls without ELS.

Methods: Forty-one participants ($M_{age} = 25.66$ years, $SD = 2.96$) participated in the study: 15 participants with ELS, and 26 controls. Participants completed the Amygdala Reactivity Paradigm while a functional magnetic resonance imaging (fMRI) scan was recorded to probe amygdala reactivity and behavioural responses to emotionally salient stimuli. Blood-oxygen-level-dependent signals from bilateral amygdala and relevant subfields were analysed and correlated with clinical measures of coping in adulthood, and aggressive/hostile behaviour across the lifespan.

Results: Although fMRI data showed no significant between-group differences on contrasts of interest, key differences were noted on trials of neutral faces. Compared to controls, individuals with ELS demonstrated significantly faster reaction time on all trials with greatest difference for neutral faces, and significantly less accuracy on trials with negative faces and shapes, but not neutral faces. Higher amygdala reactivity to neutral faces was significantly positively correlated with emotion-oriented methods of coping in adulthood, and aggressive and hostile behaviours during mid-adolescence and adulthood but not childhood or late-adolescence.

Conclusion: Although the current study did not find significant differences between groups on contrasts of interest, results emphasise the critical role of individuals’
reactions to neutral, but not negative, cues in their environment and how this relates to emotion-oriented coping and aggressive/hostile behaviours following ELS. Findings support theories highlighting the initially adaptive changes that happen in the amygdala, potentially leading to increased reliance on maladaptive coping mechanisms into adulthood.

Keywords: Amygdala reactivity, early life stress, coping, fMRI
Early life stress (ELS) has been defined as exposure to events during childhood that exceed a child’s coping resources and cause prolonged phases of stress (Pechtel & Pizzagalli, 2011). ELS can include but is not limited to emotional, verbal, physical or sexual abuse, neglect, social deprivation, disaster, household mental illness and household dysfunction (e.g., witnessing domestic violence, parental separation; Brown et al., 2009). ELS can have significant long-term consequences for individuals’ emotional, behavioural, and cognitive functioning (Vachon, Krueger, Rogosch, & Cicchetti, 2015). This can include the development of maladaptive coping strategies such as avoidance, and engagement in aggressive/hostile behaviours (Loeber & Stouthamer-Loeber, 1998; Seiffge-Krenke, 2000).

Although research acknowledges the long-term impact of ELS, possible neurobiological mechanisms by which ELS is linked to maladaptive coping and aggressive behaviour remain unclear (McCrory & Viding, 2015). By looking at functional changes in the amygdala, a brain region critically implicated in emotional reactivity, it is hoped that poor long-term outcomes could be better understood, therefore better targeted by interventions earlier in development. As retrospective data only provides a limited insight, the current study uses data from a 30-year longitudinal sample to investigate if ELS is associated with altered amygdala reactivity, and whether such changes are related to maladaptive coping styles in adulthood, as well as aggressive and hostile behaviours across the lifespan.
Early Life Stress and Coping Behaviour

Children who experience ELS often develop coping strategies to prevent them being overwhelmed by high levels of emotion (Ullman & Peter-Hagene, 2014). While such strategies may initially provide protection in threatening environments, when used into adulthood, they can solidify as maladaptive styles of coping with negative sequelae (Segrin, Woszidlo, & Givertz, 2013; Seiffge-Krenke, 2000). Measures such as the Coping Inventory for Stressful Situations (CISS; Endler & Parker, 1990a) have highlighted the link between ELS and high levels of emotion-oriented coping (i.e., responding emotionally to stressful circumstances) and high levels of avoidance-oriented coping (i.e., escaping stressful circumstances; Higgins & Endler, 1995; O’Brien, Margolin, John, & Krueger, 1991). Though initially useful, emotion-oriented and avoidance-oriented coping have been associated with increased anxiety and depression (Christensen & Kessing, 2005; Suls & Fletcher, 1985). Equally, research has found links between ELS and aggressive/hostile behaviours across the lifespan, possibly as a means to manage high levels of emotion (Éthier, Lemelin, & Lacharité, 2004; Fonagy, 2004; Jonson-Reid et al., 2010). When aggressive/hostile behaviour continues throughout development, risk of anxiety, depression, and suicidal behaviour can increase (Browne & Finkelhor, 1986; Lewis, 1992).

Although research has indicated a relationship between ELS, maladaptive coping styles, and aggressive/hostile behaviour, the underlying mechanism by which ELS contributes to such behaviours remains unclear (Winiarski, Engel, Karnik, & Brennan, 2018).
Early Life Stress and Amygdala

ELS can alter stress responsivity, which may help to understand the neurobiological effect of ELS on coping and aggressive behaviour (Lupien, McEwen, Gunnar, & Heim, 2009; Teicher et al., 2003). ELS has been shown to cause disruptions to the regulatory process of the hypothalamic-pituitary-adrenal (HPA) axis; a major neuroendocrine system involved in regulating bodily processes including reactions to stress and emotions. The HPA axis reaction to ELS is thought to lead to excessive glucocorticoid release, which can interfere with critical developmental processes such as neurogenesis, synaptogenesis, and myelination, ultimately changing the maturing brain’s structure and function (De Bellis et al., 1999; Teicher & Samson, 2016).

Excessive release of glucocorticoids can have a neurotoxic effect on the amygdala, due to its high glucocorticoid receptor density and prolonged postnatal development (Peiffer, Veilleux, & Barden, 1991). The amygdala is a complex structure of the limbic system composed of distinct heterogeneous nuclei, including the basolateral (BL), centromedial (CM), and superficial regions (SF; Amunts et al., 2005). It plays a critical role in fear learning, threat detection, and neural regulation of emotion (Davis & Whalen, 2001; Doretto & Scivoletto, 2018; LeDoux, 2000). Interestingly, ventral (BL) and dorsal (CM) volumetric subfields of the amygdala have been shown to differentially relate to impulsivity and aggression, while the SF region is suggested to be implicated in various affective processes (Heimer & Van Hoesen, 2006). The amygdala and its subfields are therefore key regions-of-interest (ROI) when investigating links between ELS, maladaptive coping, and aggressive/hostile behaviour (Gopal et al., 2013).
The amygdala is susceptible to change from ELS due to rapid growth and high developmental plasticity during infancy and preadolescence (Payne, Machado, Bliwise, & Bachevalier, 2010; Uematsu et al., 2012; Ulfig, Setzer, & Bohl, 2006). According to the theory of latent vulnerability, altered threat processing and changes in amygdala reactivity are intended to benefit and protect the individual by prioritising threat-related stimuli and reacting to threat more quickly (McCrory & Viding, 2015). However, when threat subsides, research has suggested hypervigilance may become maladaptive, leaving the individual with greater distress and vulnerability to psychopathology (Gaffrey, Barch, & Luby, 2016; Suzuki et al., 2014).

Task-based functional magnetic resonance imaging (fMRI) studies have assessed the relationship between ELS and altered amygdala reactivity to emotional information, with mixed findings. Studies have reported heightened amygdala reactivity to negative/threat-related stimuli following ELS (e.g., angry/fearful faces; Dannlowski et al., 2013; McCrory et al., 2011, 2013; Swartz, Williamson, & Hariri, 2015; Tottenham et al., 2011), potentially due to the amygdala engaging in enhanced processing of threatening information (McCrory & Viding, 2015; Tottenham & Sheridan, 2010). Research has also indicated heightened reactivity to neutral facial expressions following ELS (Evans et al., 2016; Mattson, Hyde, Shaw, Forbes, & Monk, 2016; Van Harmelen et al., 2013), perhaps due to individuals overcautiously attributing threat or harm to emotionally ambiguous stimuli to ensure safety. Conversely, studies have shown lower amygdala reactivity to negative cues in individuals with ELS compared to controls (Taylor, 2010; Taylor, Eisenberger, Saxbe, Lehman, & Lieberman, 2006).

In addition to differences in timing/type of ELS, mixed results could be attributed to the amygdala often being analysed as a unitary structure, rather than evaluating
specific functions of the respective subfields (Ball et al., 2007; Brown et al., 2014; Kim et al., 2004; Roy et al., 2013).

**Study Aims and Rationale**

The study aims to add to the existing literature by investigating the relationship between ELS, amygdala function in various subfields, and coping styles, including aggressive/hostile behaviours across the life span (age 5, 8, 15, 19, and 29).

To date, we know that the amygdala’s structural development is vulnerable to the effects of ELS, but have less consistent evidence how ELS affects the amygdala’s function into adulthood (Gorka, Hanson, Radtke, & Hariri, 2014; Hanson et al., 2015; Pechtel, Lyons-Ruth, Anderson, & Teicher, 2014; Van Tieghem et al., 2019). We also know that ELS is related to increased maladaptive coping strategies and aggressive/hostile behaviour, however we do not know if changes in amygdala reactivity may contribute to this. Understanding such relationships could provide an early window of opportunity to tailor therapeutic interventions to increase their effectiveness, when the amygdala is undergoing maturational changes.

**Research Questions and Hypotheses**

1. Do adults with a history of ELS show amplified amygdala reactivity to negative and neutral faces compared to healthy controls (HCs)?

   Hypothesis 1: Compared to HCs, ELS group will have greater amygdala reactivity to negative and neutral faces, but not non-emotive shapes.

2. Do adults with a history of ELS show different behavioural responses to negative and neutral faces compared to HCs?
Hypothesis 2: Compared to HCs, ELS group will demonstrate shorter reaction time (RT) and lower accuracy in matching negative and neutral faces, but not non-emotive shapes.

3. Are adults with elevated amygdala reactivity to negative and neutral faces more likely to use maladaptive coping styles?

Hypothesis 3: Higher levels of amygdala reactivity to negative and neutral faces will be associated with greater use of emotion-orientated and avoidance-oriented coping, but less use of task-oriented coping as measured by the CISS.

4. Among adults with history of ELS, is increased amygdala reactivity to negative and neutral faces in adulthood associated with aggressive or hostile behaviour across the life span?

Hypothesis 4: Those with altered levels of amygdala reactivity to neutral and negative faces (age 29) will have shown greater aggressive and hostile behaviours in childhood (age 5 and 8), adolescence (age 15 and 19), and adulthood (age 29).

Method

Design

The research utilised secondary data from an experimental study in a between-subject design. Participants with ELS were recruited from the Family Pathways Project (FPP); a longitudinal study on child development and social risk factors conducted over a 30-year period in the United States of America (USA; Lyons-Ruth et al., 1990). Control participants with no/very low ELS and no psychopathology were recruited from a cross-sectional study of maltreatment-related effects on neurobiology (HC; Teicher et al., 2014).
Participants

The initial FPP longitudinal cohort consisted of 76 families at or below 200% of the federal poverty line. Participants were recruited as infants (8.5 ± 5.6 months) to study their cognitive, affective and physical development in multiple waves during infancy, childhood, and adolescence, with a 74% follow-up rate (Lyons-Ruth et al., 1997; Lyons-Ruth et al., 1990; Obsuth et al., 2014).

In 2012, at approximately age 29, 18 of the original participants were screened for inclusion into the current study. Participants were representative of the longitudinal cohort, since they did not differ from the larger cohort in family demographic characteristics (Appendix A). Thirty-six unmedicated control participants with no past or present psychopathology and no or low exposure to maltreatment were recruited using community advertisement (HC; Teicher et al., 2014).

Participants were excluded if they reported substance abuse in the past six months, a significant medical or neurological condition, or did not meet MRI safety criteria. Thirteen participants were excluded in total due to excess movement (ELS = 1), corrupt MRI/behavioural data (HC = 8; ELS = 2) or significant signal dropout (HC = 2).

The final sample consisted of 15 ELS participants (8 females/7 males, M\text{age} = 29.27 ± 0.46 years) and 26 HC participants (19 females/7 males, M\text{age} = 23.59 ± 1.26 years). HC participants were on average approximately six years younger than ELS participants. This difference was thought to be acceptable since amygdala development should be stable within this age range (Uematsu et al., 2012). Participants were fluent in English and compliant with the MRI safety protocol. Three studies published anatomical findings in subsamples of the current study but no
publications derived from the functional MRI data (Khoury et al., 2019; Lyons-Ruth et al., 2016; Pechtel et al., 2014; Appendix B).

Power Analysis

Using G*Power (Erdfelder, Faul, Buchner, & Lang, 2009) and the overall sample of 41 participants (Hypotheses 1-3), effect sizes were calculated using a power level of .80 and an alpha level of .05. As the sample size is relatively small, there is only power to detect medium-large effect sizes (Cohen, 1992). Moreover, as Hypothesis 4 explored relationships among longitudinal assessments from the ELS group only (n = 15), correlations would require large effect sizes to be detected at a power of .80 and alpha level of .05. Since fMRI studies have been criticised for their lack of statistical power, Appendix C provides a further discussion.

Measures and Materials

Amygdala Reactivity Paradigm (ARP). To examine amygdala reactivity to emotionally salient stimuli, participants completed an experimental block-design paradigm while a fMRI scan was recorded (Figure 3; Brown et al., 2005; Fakra et al., 2009; Hariri et al., 2009; Hariri, Mattay, et al., 2002). Research has indicated the ARP elicits robust and replicable amygdala responses in populations with ELS (Evans et al., 2016; Swartz et al., 2015) and without ELS (Carré, Fisher, Manuck, & Hariri, 2012; Hariri, Tessitore, Mattay, Fera, & Weinberger, 2002). The task was programmed using E-Prime (Psychology Software Tools Inc., Pennsylvania) and presented in the MRI suite using a projector system. Participants viewed the task using an angled mirror attached to their head coil while lying in the bore of the scanner. Responses were selected with participants’ index and middle finger, using a fibre-optic button box.
The ARP consisted of 13 blocks in total; six blocks of a face-processing task interleaved with seven blocks of a sensorimotor control task. During the face-processing blocks, participants viewed a trio of faces with either emotionally ‘neutral’ or ‘negative’ (anger or fear) expressions. Each face-processing block consisted of six trios of the same expression, balanced for gender, derived from a standard set of pictures of facial affect (Ekman & Friesen, 1976). During the sensorimotor control blocks, participants viewed six trios of simple geometric shapes (circles, vertical and horizontal ellipses).

Blocks began with the brief instruction (‘match faces’ or ‘match shapes’) that lasted two seconds. Participants were asked to indicate which of the two images in the bottom row was identical to the target image in the top row. Each trial was presented for four seconds with a fixed inter-stimulus interval (ISI) of two seconds. A
fixation cross was presented for 10 seconds at the start of the task and between each block. Total task time was 624 seconds. Accuracy and RT were collected.

**Magnetic resonance imaging acquisition.** Anatomical and functional neuroimaging data were collected using a Siemens 3Tesla TIM Trio scanner (Siemens AG Erlangen, Germany) fitted with a 32-channel head coil. During the ARP, 42 brain slices were acquired using an interleaved and tilted slice acquisition. T2* weighted echoplanar images were acquired with the following key parameters: TR/TE = 3000/30ms, 208 volumes, FOV = 22mm, 3.5 mm isotropic voxels, slice thickness 3.5mm, Flip angle = 90°. Functional imaging data for each participant were aligned with their high-resolution T1-weighted anatomical image for registration into standard space and functional localisation (TR/TE = 21/2.25ms; 128 slices, FOV = 256mm; voxel size = 1.0 x 1.0 x 1.3mm; slice thickness = 1.33mm; flip angle = 12°). Scanning parameters were developed by a MR physicist at Harvard Medical School to optimise statistical power and psychological validity.

**Early life stress.** The Maltreatment and Abuse Chronology of Exposure scale (MACE; Teicher & Parigger, 2015) consists of 52 items to measure timings (age 1-18) and severity of exposure to maltreatment. Category scores are summed to provide a total sum score (MACE-SUM) indicating overall severity of exposure (ranging from 0-100). MACE was developed using item response theory and MACE-SUM demonstrated excellent test re-test reliability (r = 0.91) and high convergent validity (r = .71) with the Childhood Trauma Questionnaire (Bernstein & Fink, 1998).

**Coping styles in adulthood.** The Coping Inventory for Stressful Situations (CISS; Endler & Parker, 1990a) is a 48-item self-report inventory measuring task-oriented, emotion-oriented, and avoidance-oriented coping styles (16 items each).
Task-oriented coping is considered adaptive as individuals directly approach the stressful situation through problem-solving. Emotion-oriented coping (i.e., blaming self, becoming angry), and avoidance-oriented coping (i.e., delaying or avoiding the problem) are considered maladaptive. Items are scored on a 5-point Likert scale from 1 (not at all) to 5 (very much). Item scores per scale are added (range 16-80); higher scores represent greater use of that particular coping strategy. CISS shows high internal consistency reliabilities for all subscales ($rs$ between .76 and .91) and high convergent validity with other coping measures (Endler & Parker, 1990b; Endler, Parker, & Butcher, 1993).

**Aggression/hostility across the lifespan.** Aggressive and hostile behaviours in the ELS group were measured at multiple time-points using developmentally appropriate measures (Appendix D). The Preschool Behaviour Questionnaire (PBQ; Behar & Stringfield, 1974) was completed by teachers when participants were approximately five years old. The Punitive subscale of the Middle Childhood Disorganisation and Control Scales (MCDC; Bureau et al., 2009) was used to code an interaction between mother and child when participants were eight years old. The Hostility subscale of the Personality Research Form (PRF; Jackson, 1967, 1974, 1984) was completed by participants when they were 15 years old. The Punitive behaviour scale of the Goal Corrected Partnership in Adolescence Coding System (GPACS; Obsuth et al., 2014) was used to code the security of an interaction between mother and adolescent when participants were 19 years old. Finally, the Anger-hostility subscale of the Symptoms Questionnaire (SQ; Kellner, 1987) was completed by participants at the time of the current study (age 29).
Procedure

**Data collection and organisation.** The principal investigator (PI) of the longitudinal study confirmed collected data complied with USA data protection guidelines. General Data Protection Regulations were followed for accessing and analysing the data in the United Kingdom (UK). The study was approved by Harvard Medical School, Cambridge Hospital, and McLean Hospital institutional review boards, and University of Exeter Department of Psychology Ethics Committee (Appendix E).

**MRI session.** In the original study, participants completed a phone screen before attending a three-hour research session which included additional measures not discussed here. Participants provided written informed consent and were reimbursed $100 for their time (Appendix F). Data were collected at the Neuroimaging Center at McLean Hospital, USA. Longitudinal measures were collected at different time points at the Cambridge Health Alliance, USA.

Before the MRI scan at age 29, participants completed coping (CISS) and hostility (SQ) measures and a practice round of the ARP. Participants were visually monitored during the task and were able to communicate with the researcher via intercom; they were given a panic button to stop the scan at any time. Participants were debriefed at the end of the study and MRI images were inspected by a radiographer for any abnormalities.

**Outliers and influential statistics.** MRI and ARP showed no missing data. MACE-SUM data (7.32%) was missing at complete random as determined by Little’s Missing Completely at Random (MCAR) test ($x^2(3) = .82, p = .85$). A non-significant MCAR test implied that variables could be imputed using Expectation Maximisation algorithms in SPSS. Estimation used auxiliary variables (gender, age, ethnicity) in the
imputation model. Longitudinal data for measures of aggression/hostility was also missing at random (range: 6.7%-33.3%; $x^2(52) = 46.34, p = .70$). Estimation used all variables included in the correlational model plus auxiliary variables, i.e., age, gender, and ethnicity (Hypothesis 4).

All data were checked for outliers by calculating standardised z-scores and boxplots. Univariate outliers (z-score ± 3.29) were found for one ELS and one control participant’s ARP accuracy scores, and one control participant’s SQ scores. Outliers were replaced with the value of the next not-outlying score (nearest neighbour).

**Parametric assumptions.** Distribution of data (including normality, skewness, and kurtosis) were checked separately within each group using histograms and Q-Q plots (Quinn & Keough, 2002). As a result, RT and accuracy data for the ARP were log-transformed to reduce impact of skewness. Scatterplots of relevant variables were inspected to confirm linearity assumptions. Homogeneity of variances was assessed using Levene’s test; results were appropriately adjusted for unequal variances where required.

**fMRI data analysis.**

**Pre-processing.** Nifti files were converted using MRI Convert software (MRICron; Version 2.1.0; https://lcni.uoregon.edu/downloads/mriconvert). Blood-oxygen-level-dependent (BOLD) fMRI data were pre-processed and analysed according to standardised pipelines in Statistical Parametric Mapping software (SPM; Version 12; https://www.fil.ion.ucl.ac.uk/spm/) running on MATLAB (version 9.6.0.1 R2019a; https://uk.mathworks.com/products/matlab.html). Standard pre-processing steps for each individual included setting the origin to the anterior commissure on structural and functional scans, realignment, slice time correction with middle volume,
co-registration to the participants’ anatomical (T1-weighted) image, segmentation, normalisation into standardised stereotactic space (Montreal Neurological Institute (MNI) template), and spatial smoothing using a Gaussian filter kernel of 6mm full-width at half-maximum to improve the signal-to-noise ratio.

The Artifact Detection Toolbox (Version 2015-10; https://www.nitrc.org/projects/artifact_detect) was used to identify outliers in global signal intensity and translational/rotational movement parameters. Realignment generated six movement regressors for volumes with high motion or artefact, which were included in the general linear model as nuisance covariates, to control for residual movement. The complete fMRI processing pipeline is detailed in Appendix G.

First-level (within-subject) analysis. Linear contrasts using canonical haemodynamic response functions were used to estimate condition-specific BOLD activation for each individual using a boxcar model. Pre-processed time series data for each participant were analysed using t-statistics and statistical maps to test for main effects of task at each voxel (whole brain) for the contrasts of interest: (a) negative faces > shapes; (b) neutral faces > shapes; and (c) shapes > all faces.

Second-level (group difference) analysis. To determine group-level main effects (Hypothesis 1), contrast images from each participant (summary measures of participant responses) were entered into the second level analysis. The model included a regressor for each contrast of interest, for example ‘negative faces > shapes’, thus for each voxel, activation = $\text{BOLD}_{\text{negative faces}} - \text{BOLD}_{\text{shapes}}$. To control for age, these were entered into the model as nuisance covariates. Differences in statistical maps between the ELS and HC group in response to emotional stimuli were acquired by two-sample t-tests. First and second-level analyses were performed with
a $p < .05$ cluster-defining threshold, minimum extent threshold of 15 contiguous voxels, and a cluster-wise threshold of $p < .05$, uncorrected.

**Region of interest analyses.** BOLD contrast estimates were extracted from functional clusters exhibiting a main effect of task within anatomically defined ROI. To examine the role of amygdala activation in ELS (Hypothesis 1), predetermined ROI focused on the bilateral amygdala and three bilateral subfields (BL, CM, SF). Masks for bilateral amygdala were created using Harvard-Oxford Subcortical Structural Atlas in MNI space (binarised and thresholded to include voxels with at least 10% probability of being part of the ROI). Masks for subfields were obtained from authors of a seminal paper investigating amygdala reactivity (Nikolova & Hariri, 2012). Percentage signal change from the first-level analysis were extracted, and ROI analyses were performed using MarsBar toolbox for SPM (Version 0.44; http://marsbar.sourceforge.net/; $p < .05$, peak-Family Wise Error (pFWE) and cluster-False Discovery Rate (cFDR).

**Descriptive and Clinical Data**

Data were analysed using SPSS (Version 25.0; https://www.ibm.com/uk-en/analytics/spss-statistics-software). Chi-Square tests, Fisher’s exact test (two-tailed) and independent t-tests examined group differences in demographic information. To examine Hypothesis 2, a Group (ELS, HC) x Condition (negative, neutral, shapes) mixed Analysis of Variance (ANOVA) was run separately for accuracy and RT. To account for significant group-differences in age, analyses were repeated with age as a covariate (Analysis of Covariance; ANCOVA). Greenhouse-Geisser correction was used where applicable (McCall & Appelbaum, 1973).

To test Hypothesis 3, independent t-tests examined group differences in CISS scores, and these were correlated with bilateral ROI signal intensities ($n = 41$), using
age as a covariate. To test Hypothesis 4, Pearson’s bivariate correlations examined the relationships between signal intensities derived from the amygdala ROIs and measures of hostility and aggressive behaviour across the life span in the ELS sample only (age 5, 8, 15, 19, 29; n = 15).

Results

Demographic Data

Participants mainly described themselves as Caucasian and were on average 25.66 years old (SD = 2.96), with the ELS group being significantly older than HC (p < .001). ELS participants were less likely to be single (p = .04), less likely to have a college degree (p < .001) and more likely to report maltreatment than HCs (p < .001; Table 1). No group differences emerged in gender, ethnicity, or handedness.

Six ELS participants reported current anxiety and mood disorders (generalised anxiety disorder = 1; social phobia = 1; panic disorder = 1; major depressive disorder = 2; dysthymia = 1). Two ELS participants were previously diagnosed with attention-deficit-hyperactivity disorder but were not taking medication at the time of the scan.
Table 1

Demographics for Participants in the Early Life Stress and Healthy Control Groups

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Early Life Stress (n = 15)</th>
<th>Healthy Controls (n = 26)</th>
<th>Statistical value</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, M years (SD)</td>
<td>29.27 (0.46)</td>
<td>23.59 (1.26)</td>
<td>(t = 20.81)</td>
<td>&lt;.001***</td>
</tr>
<tr>
<td>MACE-SUM, M score (SD)</td>
<td>31.53 (16.17)</td>
<td>12.47 (6.82)</td>
<td>(t = 4.35)</td>
<td>&lt;.001***</td>
</tr>
<tr>
<td>Females, N (%)</td>
<td>8 (53.3)</td>
<td>19 (73.1)</td>
<td>N/A</td>
<td>.31a</td>
</tr>
<tr>
<td>White, N (%)</td>
<td>11 (73.3)</td>
<td>20 (76.9)</td>
<td>(x^2 = 7.18)</td>
<td>.127</td>
</tr>
<tr>
<td>Single, N (%)</td>
<td>9 (60)</td>
<td>24 (92.3)</td>
<td>N/A</td>
<td>.04*a</td>
</tr>
<tr>
<td>College degree, N (%)</td>
<td>1 (6.67)</td>
<td>24 (92.3)</td>
<td>N/A</td>
<td>&lt;.001***a</td>
</tr>
<tr>
<td>Right-handed, N (%)</td>
<td>14 (93.3)</td>
<td>26 (100)</td>
<td>N/A</td>
<td>.37a</td>
</tr>
</tbody>
</table>

Note. n = number; M = mean; SD = standard deviation; MACE-SUM = Maltreatment and Abuse Chronology of Exposure Scale: Overall Severity of Exposure; N/A = not applicable

*aFisher’s Exact Test (two-tailed)

*p < .05
**p < .01
***p < .001

fMRI Data

Whole brain analysis. As Hypothesis 1 specifically investigated amygdala activation, results mainly focus on the ROI analyses. In brief, whole-brain analysis did not reveal any differences between ELS and HC groups on main contrasts of interest. Significant clusters for each group are included in Appendix H.

Region of interest analysis. ROI group analyses were performed for each contrast of interest on bilateral amygdala (left and right) and subfields (BL, CM, SF).
There were no significant group differences in amygdala activity on any of the contrasts of interest (Table 2).

However, within-group analyses showed that both ELS and HC groups demonstrated significantly higher activation in bilateral amygdala and all subfields during the negative faces condition than the Shapes condition (Appendix I), demonstrating that task manipulation worked as expected from previous research (Hariri, Tessitore, et al., 2002). Since both groups showed similar levels of activation, there were no significant differences between groups, thus no support was found for Hypothesis 1.

Table 2

*Between-group Region of Interest Analysis for Negative Faces > Shapes Contrast*

<table>
<thead>
<tr>
<th>Region of Interest</th>
<th>ELS &gt; Controls</th>
<th>ELS &lt; Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Contrast estimate</td>
<td>t</td>
</tr>
<tr>
<td>Left Amygdala</td>
<td>0.10</td>
<td>0.23</td>
</tr>
<tr>
<td>Right Amygdala</td>
<td>-0.18</td>
<td>-0.38</td>
</tr>
<tr>
<td>Left Centromedial</td>
<td>0.26</td>
<td>0.60</td>
</tr>
<tr>
<td>Right Centromedial</td>
<td>0.14</td>
<td>0.33</td>
</tr>
<tr>
<td>Left Basolateral</td>
<td>0.19</td>
<td>0.43</td>
</tr>
<tr>
<td>Right Basolateral</td>
<td>-0.06</td>
<td>-0.16</td>
</tr>
<tr>
<td>Left Superficial</td>
<td>0.04</td>
<td>0.08</td>
</tr>
<tr>
<td>Right Superficial</td>
<td>-0.03</td>
<td>-0.05</td>
</tr>
</tbody>
</table>

*Note.* ELS = Early life stress

On the neutral faces > shapes contrast, both groups showed higher activation in bilateral amygdala and subfields when viewing neutral faces than shapes, though results were not significant between-groups, therefore not supporting Hypothesis 1 (Table 3). It is worth noting that the Neutral faces > Shapes within-group contrast was
significant in multiple regions in the ELS group (right amygdala, $p = .04$; left BL amygdala, $p = .05$; right SF amygdala, $p = .02$) but was not significant for any regions within the HC group (Appendix I). A lack of group differences to reach significance may be related to the relatively small sample.

Table 3

*Between-group Region of Interest Analysis for Neutral Faces > Shapes Contrast*

<table>
<thead>
<tr>
<th>Region of Interest</th>
<th>ELS &gt; Controls</th>
<th>ELS &lt; Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Contrast estimate</td>
<td>$t$</td>
</tr>
<tr>
<td>Left Amygdala</td>
<td>0.24</td>
<td>0.60</td>
</tr>
<tr>
<td>Right Amygdala</td>
<td>0.34</td>
<td>0.86</td>
</tr>
<tr>
<td>Left Centromedial</td>
<td>0.20</td>
<td>0.50</td>
</tr>
<tr>
<td>Right Centromedial</td>
<td>0.29</td>
<td>0.80</td>
</tr>
<tr>
<td>Left Basolateral</td>
<td>0.42</td>
<td>1.04</td>
</tr>
<tr>
<td>Right Basolateral</td>
<td>0.28</td>
<td>0.77</td>
</tr>
<tr>
<td>Left Superficial</td>
<td>0.20</td>
<td>0.43</td>
</tr>
<tr>
<td>Right Superficial</td>
<td>0.38</td>
<td>0.98</td>
</tr>
</tbody>
</table>

*Note.* ELS = Early life stress

Supporting Hypothesis 1, both groups showed similar levels of activation for the shapes > all faces contrast. No within or between-group differences were found (Table 4).
### Table 4

**Between-group Region of Interest Analysis for Shapes > All Faces Contrast**

<table>
<thead>
<tr>
<th>Region of Interest</th>
<th>ELS &gt; Controls</th>
<th>ELS &lt; Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Contrast estimate</td>
<td>t</td>
</tr>
<tr>
<td>Left Amygdala</td>
<td>-0.17</td>
<td>-0.46</td>
</tr>
<tr>
<td>Right Amygdala</td>
<td>-0.05</td>
<td>-0.13</td>
</tr>
<tr>
<td>Left Centromedial</td>
<td>-0.22</td>
<td>-0.65</td>
</tr>
<tr>
<td>Right Centromedial</td>
<td>-0.21</td>
<td>-0.63</td>
</tr>
<tr>
<td>Left Basolateral</td>
<td>-0.33</td>
<td>-0.93</td>
</tr>
<tr>
<td>Right Basolateral</td>
<td>-0.13</td>
<td>-0.38</td>
</tr>
<tr>
<td>Left Superficial</td>
<td>-0.08</td>
<td>-0.18</td>
</tr>
<tr>
<td>Right Superficial</td>
<td>-0.12</td>
<td>-0.33</td>
</tr>
</tbody>
</table>

*Note.* ELS = Early life stress

### Behavioural Data

**Accuracy.** It was hypothesised that the ELS group would be less accurate in identifying negative and neutral faces, but not non-emotive shapes compared to HCs (Hypothesis 2).

A mixed ANOVA showed that there was a significant main effect of condition ($F(2, 78) = 5.49, p = .006, \eta^2_p = .12$) and of group ($F(1,39) = 16.47, p < .001, \eta^2_p = .30$) on accuracy scores. There was also a significant interaction of group x condition for accuracy scores ($F(2, 78) = 6.75, p = .002, \eta^2_p = .15$).

Follow-up tests showed the ELS group provided significantly less accurate responses on the negative faces trial ($M = 95.29, SD = 4.49$) than the HC group ($M = 99.15, SD = 2.04; t(17.23) = -3.13, p = .006$), partially supporting Hypothesis 2. However, in contrast to Hypothesis 2, no group differences in accuracy scores emerged between the ELS ($M = 98.89, SD = 2.30$) and HC ($M = 98.93, SD = 2.23$);
EARLY LIFE STRESS, AMYGDALA REACTIVITY AND COPING

$t(39) = -0.059, p = .953$ on neutral trials. Moreover, on the shapes trials, the ELS group provided significantly less accurate responses ($M = 97.14, SD = 2.73$) than the HC group ($M = 99.54, SD = 0.96$), $t(15.93) = -3.29, p = .005$ (Figure 2), thus not supporting Hypothesis 2.

![Figure 2. Accuracy data for participants with early life stress (ELS) and healthy controls (HC)](image)

Note.

** $p < .01$

When entering age as a covariate, there was no significant main effect of condition ($F(2, 76) = .512, p = .601, \eta^2_p = .013$) or group ($F(1,38) = 2.29, p = .139, \eta^2_p = .057$) or interaction effect ($F(2, 76) = .126, p = .882, \eta^2_p = .003$).

**Reaction Time.** It was hypothesised that the ELS group would show shorter RT identifying negative and neutral faces, but not non-emotive shapes compared to HCs (Hypothesis 2).

A mixed ANOVA showed that there was no significant main effect of condition ($F(1.70, 66.20) = 1.59, p = .213, \eta^2_p = .039$), but a main effect of group membership
on RT \((F(1, 39) = 9.34, p = .004, \eta_p^2 = .193)\). Results also showed a group \times condition interaction \((F(1.70, 66.20) = 3.52, p = .042, \eta_p^2 = .083)\).

Follow-up tests only partially support Hypothesis 2, as although ELS were faster to respond, this applied to both emotive and non-emotive stimuli (Figure 3). The largest group difference was found on the neutral faces trial, where the ELS group were significantly faster at responding \((M = 971.98, SD = 134.34)\) than the HC group \((M = 1253.15, SD = 303.46; t(39.00) = -3.75, p = .001)\). The ELS group were also significantly faster at responding to negative faces \((M = 956.77, SD = 179.15)\) than the HC group \((M = 1220.32, SD = 302.79; t(36.40) = -3.39, p = .002)\). Although showing a smaller group difference, the ELS group were still significantly faster at responding to shapes \((M = 986.22, SD = 154.47)\) than the HC group \((M = 1136.21, SD = 239.51; t(39) = -2.09, p = .04)\).

![Figure 3](image.png)

*Figure 3. Reaction time data for participants with early life stress (ELS) and healthy controls (HC)*

*Note.*

* p < .05
** p < .01
*** p ≤ .001
An ANCOVA for RT with age as covariate showed no main effect of condition \((F(1.70, 64.52) = .609, p = .521, n_p^2 = .016)\), group \((F(1,38) = 2.71, p = .108, n_p^2 = .067)\), or group x condition interaction \((F(1.70, 64.52) = .223, p = .764, n_p^2 = .006)\).

**Clinical Data**

**Coping styles.** On the CISS, the ELS group used significantly greater emotion-oriented coping and significantly less task-oriented coping than the HC group. No significant differences in avoidant coping were found between ELS and HC (Table 5).

Table 5

*Coping Inventory for Stressful Situations (CISS) Data for Participants with Early Life Stress and Healthy Controls*

<table>
<thead>
<tr>
<th>CISS Subscale</th>
<th>Early Life Stress (n = 15)</th>
<th>Healthy Controls (n = 26)</th>
<th>Statistical value</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emotion-oriented</td>
<td>47.40 (8.87)</td>
<td>39.23 (10.05)</td>
<td>( t = 2.61 )</td>
<td><strong>.01</strong></td>
</tr>
<tr>
<td>Task-oriented</td>
<td>47.13 (6.70)</td>
<td>54.97 (12.05)</td>
<td>( t = -2.67 )</td>
<td><strong>.01</strong></td>
</tr>
<tr>
<td>Avoidance</td>
<td>54.73 (10.90)</td>
<td>53.46 (10.30)</td>
<td>( t = .37 )</td>
<td>.71</td>
</tr>
</tbody>
</table>

*Note.* CISS = Coping Inventory for Stressful Situations; n = number; M = mean; SD = standard deviation.

\*p < .05

To address Hypothesis 3, partial correlations (age as covariate) were run to investigate the relationship between coping styles (CISS) and ROI amygdala activation. Table 6 demonstrates results for bilateral amygdala; Appendix J contains a table of all trials and subfields. Results partially support Hypothesis 3, since higher levels of emotion-oriented coping were associated with greater activation in bilateral
amygdala and all bilateral subfields (p < .01) when viewing neutral faces. For the negative faces trial, only amygdala activation in the CM subfield was correlated with emotion-oriented coping (p < .05). Task-oriented coping (considered an adaptive form of coping), was not significantly correlated with amygdala activation (bilateral or subfields) on any trial.

Table 6

Partial Correlations Among Coping Inventory for Stressful Situations (CISS) Scores and Region of Interest Signal Intensities for Negative and Neutral Faces with Age as Covariate

<table>
<thead>
<tr>
<th>Variable</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAmy Negative</td>
<td></td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>RAmy Negative</td>
<td></td>
<td></td>
<td>0.85**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAmy Neutral</td>
<td></td>
<td>0.36*</td>
<td>0.27</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAmy Neutral</td>
<td></td>
<td>0.27</td>
<td>0.16</td>
<td>0.94**</td>
<td>0.52**</td>
<td>0.47**</td>
<td></td>
</tr>
<tr>
<td>CISS Emotion</td>
<td></td>
<td>0.22</td>
<td>0.13</td>
<td>0.52**</td>
<td>0.47**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CISS Task</td>
<td></td>
<td>-0.14</td>
<td>-0.08</td>
<td>0.00</td>
<td>0.06</td>
<td>-0.40**</td>
<td>0.28</td>
</tr>
<tr>
<td>CISS Avoidance</td>
<td></td>
<td>0.12</td>
<td>0.17</td>
<td>0.07</td>
<td>0.10</td>
<td>0.28</td>
<td>0.12</td>
</tr>
</tbody>
</table>

Note. LAmy = Left Amygdala; RAmy = Right Amygdala; CISS = Coping Inventory for Stressful Situations

*p < .05

**p < .01

Aggressive and hostile behaviour across the life span. Developmentally appropriate measures of aggression/hostility were collected from ELS group at age 5, 8, 15, 19, and 29 (Appendix K). Table 7 shows correlations between amygdala activation (ROI) and measures of aggressive/hostile behaviour across the lifespan (Hypothesis 4).
Table 7

Correlations Among Early Life Stress Group Scores on Measures of Aggression/Hostility Across the Lifespan and Region of Interest Signal Intensities for Negative and Neutral Faces

<table>
<thead>
<tr>
<th>Variable</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 LAmy Negative</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 RAmy Negative</td>
<td>.81**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 LAmy Neutral</td>
<td>.46</td>
<td>.19</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 RAmy Neutral</td>
<td>.25</td>
<td>-.02</td>
<td>.92**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 PBQ</td>
<td>-.07</td>
<td>.13</td>
<td>.08</td>
<td>.07</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 MCDC</td>
<td>-.18</td>
<td>.05</td>
<td>.01</td>
<td>.23</td>
<td>.08</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 PRF</td>
<td>.35</td>
<td>.46</td>
<td>.52*</td>
<td>.41</td>
<td>.07</td>
<td>.01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 GPACS</td>
<td>-.29</td>
<td>-.31</td>
<td>.24</td>
<td>.30</td>
<td>-.06</td>
<td>.24</td>
<td>-.08</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 SQ</td>
<td>.09</td>
<td>.06</td>
<td>.57*</td>
<td>.56*</td>
<td>-.19</td>
<td>.18</td>
<td>.67**</td>
<td>.31</td>
<td></td>
</tr>
</tbody>
</table>

Note. LAmy = Left Amygdala; RAmy = Right Amygdala; PBQ = Preschool Behaviour Questionnaire: Hostility Subscale; MCDC = Middle Childhood Disorganisation and Control Scales: Punitive Subscale; PRF = Personality Research Form: Hostility subscale; GPACS = Goal Corrected Partnership in Adolescence Coding System: Punitive Behaviour subscale; SQ = Symptoms Questionnaire: Anger-Hostility Subscale.

*p < .05
**p < .01

There was a significant positive correlation of moderate magnitude between activation in the left amygdala when viewing neutral faces and aggression/hostile behaviour during mid-adolescence (PRF; age 15). There were also significant positive correlations of moderate magnitude between aggression/hostile behaviour during adulthood (SQ; age 29) and activation in left and right amygdala when viewing neutral faces. Results partially support Hypothesis 4, since increased adult amygdala reactivity to neutral cues but not negative cues were correlated to aggressive/hostile behaviour in adulthood (age 29; SQ) and mid-adolescence (age 15; PRF), but not during childhood (age 5, PBQ; age 8, MCDC) or late adolescence (age 19; GPACS).
Extended correlations of subfields and amygdala activation (Appendix L) showed significant positive correlations between PRF scores (age 15) and activation for neutral faces in left ventral (BL; \( r = .61, p < .05 \)), right ventral (\( r = .59, p < .05 \)) left dorsal (CM; \( r = .62, p < .05 \)) and right dorsal (\( r = .65, p < .01 \)) subregions of the amygdala but not SF. PRF scores were also significantly positively correlated with lateral amygdala reactivity for negative faces in right ventral (\( r = .54, p < .05 \)) and right SF subfields (\( r = .54, p < .05 \)). There were also significant correlations between levels of aggression at age 29 (SQ) in all bilateral subfields (BL, CM, SF; all \( p < .05 \) except left CM (\( p < .01 \))) when viewing neutral faces, yet no correlations for negative faces, emphasising the key role of neutral cues when trying to understand aggressive/hostile behaviour.

**Discussion**

This study investigated the relationship between ELS and amygdala reactivity, exploring whether adult amygdala reactivity to emotive cues could be related to maladaptive coping styles in adulthood, and aggressive/hostile behaviour across the lifespan. First, no differences in amygdala reactivity to emotive cues were found between adults with and without ELS, thus not supporting Hypothesis 1. Second, partially supporting Hypothesis 2, adults with ELS made more errors on trials displaying angry/fearful faces and shapes, but achieved comparable results to controls when viewing neutral faces. Those with ELS reacted significantly faster than controls on all trials, with the greatest difference when viewing neutral faces. However, behavioural group differences were lost when analysis controlled for age. Third, partial correlations found that bilateral amygdala reactivity to neutral faces was associated with emotion-oriented coping but not avoidance, partially supporting Hypothesis 3.
Finally, higher bilateral amygdala reactivity to neutral faces was significantly positively correlated with aggressive/hostile behaviour during adolescence (age 15) and adulthood (age 29) but not during childhood or late adolescence, partially supporting Hypothesis 4.

Both groups showed significantly higher amygdala activation during the negative faces versus shapes condition, however differences between groups did not reach significance. Although this does not fit with initial hypotheses of greater sensitivity to threat following ELS, findings are consistent with Taylor et al. (2006) who found low amygdala reactivity in response to negative faces, potentially due to individuals learning to shut out/avoid threatening stimuli (Redlich et al., 2018; Taylor, 2010). Another explanation for not finding significant between-group differences could rest in the small sample size, as power analysis indicated that only medium-large effects could be detected.

Though there were no significant between-group differences, significant activation emerged in several subfields of the amygdala on the neutral faces versus shapes condition for the ELS group, but not for HCs. Higher amygdala activation to neutral facial expressions in adults with ELS in comparison to HCs has been indicated in previous studies (Evans et al., 2016; Mattson et al., 2016), suggesting that stress-related increases in amygdala reactivity are not limited to direct threat, but critically extend to neutral socio-emotional cues. Given the high number of neutral cues in our daily environment, individuals who have experienced ELS may therefore experience higher levels of stress if they perceive neutral cues as negative and threatening.

Analysis of the behavioural data again emphasised specific differences in ELS group responses to neutral faces compared to HCs; the greatest difference in RT was
found on the neutral faces trial, whereby the ELS group were significantly faster to respond than HCs. Findings could suggest that the ELS group may perceive neutral faces as threatening, thus needing to respond faster than on other trials. This is consistent with literature suggesting that individuals who experienced childhood maltreatment show faster RT than controls when detecting threatening stimuli (Maheu et al., 2010). Interestingly, while the ELS group were faster in response to neutral faces, their accuracy scores on this trial were similar to the HC group, while they showed significantly more errors when matching negative faces or shapes. This could indicate that the ELS group paid greater attention to ambiguous, neutral stimuli in order to decipher their meaning and recognise potential threat, thus responding faster and making fewer mistakes compared to clearly marked negative cues.

Findings should be interpreted with caution as results were no longer significant when controlled for age. Hence, group differences in accuracy and RT could be due to age, rather than ELS. Future research could use a case-matched control sample to explore this further.

Individuals with ELS utilised significantly more emotion-oriented coping, and significantly less task-oriented coping than HCs. Engagement in emotion-oriented coping has been linked with depression, anxiety, and somatic symptoms (Cosway, Endler, Sadler, & Deary, 2000; McWilliams, Cox, & Enns, 2003). Reverse associations have been found regarding task-oriented coping, resulting in good outcomes for psychological wellbeing, including positive associations with life-satisfaction and self-esteem (Christensen & Kessing, 2005; Smith, Saklofske, Keefer, & Tremblay, 2016).

Critically, individuals who rely heavily on emotion-oriented methods of coping showed greater amygdala activation to neutral faces, but not negative faces. This is
interesting in the context of current literature, suggesting that neutral facial
expressions may trigger traumatic memories in individuals with dissociative identity
disorder and borderline personality disorder; clinical presentations that are well-linked
to severe childhood trauma (Donegan et al., 2003; Schlumpf et al., 2013). It has been
suggested that neutral facial expressions may be communicated by a perpetrator
before, during, or after traumatic experiences (Pfaltz et al., 2019), affecting individuals’
ability to trust the apparent calmness of neutral expressions. This perhaps indicates
that individuals who are more likely to feel threatened by ambiguous cues in their
environments may need to rely on emotion-oriented coping methods to manage high
levels of amygdala activity. Alternatively, as correlations do not imply causality, it could
mean that utilising emotion-oriented coping reinforces reactions to neutral cues with
amplified emotions, leading to higher amygdala reactivity.

Finally, the relationship between amygdala activation at age 29 and
aggressive/hostile behaviour was investigated in the longitudinal sample. Adults who
showed higher amygdala reactivity to neutral faces also showed greater
aggressive/hostile behaviours during mid-adolescence and adulthood, but not during
childhood or late adolescence. Mid-adolescence is a key developmental phase of
increased emotional reactivity and decreased regulation, and could therefore
represent a ‘sensitive period’ for the development of maladaptive patterns of
responses including aggressive behaviours, to manage overwhelming emotions
(Lickley & Sebastian, 2018). A significant relationship between amygdala activation to
neutral faces and aggressive/hostile behaviours in adulthood potentially supports the
neurobiological mechanism of amygdala reactivity to neutral cues in the development
of aggressive behaviour, in an attempt to manage high levels of emotion.
There are several things to consider when interpreting the null findings between amygdala reactivity to emotive cues in adulthood and aggressive behaviour in childhood and late adolescence. First, it could be true that amygdala reactivity in adulthood is less relevant to understanding early life behaviours; potentially since the amygdala undergoes rapid changes during this time, functioning differently in early life than adulthood. Second, different styles of questionnaires were used to assess aggressive behaviour; indeed, only self-report questionnaires (PRF, SQ) were related to amygdala activation, compared to null findings with observational measures (MCDC, GPACS) and teacher-reported questionnaires (PBQ). Finally, other methodological challenges may arise from using different measures at each assessment point rather than standardised measures that allow follow-up across development (e.g., Child Behaviour Checklist; Achenbach & Rescorla, 2001).

**Strengths and Limitations**

This study expands on one of the few prospective longitudinal studies of infants from adverse environments (FPP), which has been collecting data in the USA over a period of 30 years. It sought to overcome limitations of previous research by following children beyond adolescence into adulthood, to consider the relationship between ELS and altered amygdala reactivity at a time when the amygdala is expected to have completed the majority of its maturation process. Moreover, the study uses the ARP, which can be considered the gold-standard assessment to probe amygdala reactivity to various emotive cues, thus allowing findings to be interpreted in light of other research utilising the same paradigm.

However, several limitations need to be considered. First, due to the relatively small sample size, the study only had power to detect medium-large effects, and
smaller differences between groups may not have been detected (e.g., Hypothesis 1). Second, since longitudinal studies such as the FPP collect data on many variables over a long period of time, the chance of error extracting variables from databases increases. Limited information was available to explain some variables, which would have been useful for the interpretation of scores. To minimise the chance of error and maximise utility of available data, extracted data was checked thoroughly with the FPP’s PI, and literature were consulted regarding interpretation. Third, since the ARP used a fixed ISI between images on each trial, the amygdala may be subjected to habituation (Plichta et al., 2014). Additional analysis could include only the first images of each block to empirically investigate the potential for habituation. Finally, as correlations are limited in identifying causal mechanism underlying ELS and maladaptive coping and behaviours, future research could utilise different methods (e.g., mediation).

**Theoretical Implications**

Support was largely found for the theory of latent vulnerability (McCrory & Viding, 2015); one of the critical theories within this field. The theory suggests that functional brain changes occur in order to adapt to the environment when under threat, however when the threat is removed, prolonged hypervigilance can leave individuals vulnerable to psychopathology and increased stress responsivity. While no direct link was found between ELS and amygdala reactivity to negative/neutral cues as results did not meet group significance (likely due to power), differences were noted in the way individuals with ELS responded to neutral cues. This could therefore support the possibility that the tendency to perceive neutral cues as threatening initially developed as a protective strategy (i.e., 'better safe than sorry'), but might have detrimental
consequences on how the individual views the world as an adult. The link between heightened amygdala reactivity and greater use of emotion-oriented coping, as well as aggressive and hostile behaviours during mid-adolescence and adulthood adds to the theory by suggesting how the ‘vulnerability’ and long-term consequences mentioned in the literature may be translated into specific clinical behaviours that are seen in practice.

The sensitive period theory also suggests that the timing when ELS occurred may have an effect on whether individuals show heightened or blunted amygdala reactivity in later life (Pechtel et al., 2014; Zhu et al., 2019). Future analysis of this dataset could explore this further, since the MACE questionnaire collected information regarding timing of ELS.

**Implications for Practice**

Acknowledging potential changes in behavioural and amygdala reactivity to neutral stimuli following ELS could help clinicians comprehend how these individuals interpret neutral cues, and how they may be forced to cope as a result. Since the world is full of neutral cues, it could be proposed that individuals who have experienced ELS are likely to be emotionally activated on a minute-to-minute basis, which requires use of maladaptive coping strategies. Such strategies are known to have short-term benefits of reducing distress but can have negative long-term consequences. Negative cues are more obviously recognised as triggers for heightened emotional reactivity in individuals with ELS, thus, individuals are likely to be aware of the impact of obvious threats on their levels of distress. Yet, individuals may be less aware of the impact of neutral cues on their emotional state. Similarly, the common emotion regulation
strategies offered in clinical practice may not be powerful enough to impact the consistent and amplified emotional reactions experienced by those with ELS.

Asking specific questions regarding neutral stimuli during psychological assessments and holding these ideas in mind when developing formulations could help clinicians to understand the world of those who have heightened emotional responses in a different light. Interventions such as Dialectical Behaviour Therapy (DBT) that aim to reduce emotional, interpersonal, and behavioural dysregulation associated with engagement in maladaptive coping may be guided by this understanding, potentially increasing effectiveness for individuals who have experienced ELS. Integrating this knowledge into clinical practice could help to (a) predict and monitor the distress that may be experienced by individuals when exposed to neutral cues (such as a clinician or group member’s body language or facial expressions); (b) validate the differences in experiences of neutral cues in individuals who have experienced trauma; (c) reduce the need for engagement in emotion-oriented coping and aggressive/hostile behaviour (e.g., learning DBT strategies for neutral cues); and (d) increase individuals’ confidence in managing emotional distress through teaching adaptive coping strategies.

**Conclusion**

This study utilised data from a longitudinal sample of participants, contributing to a growing body of research regarding the impact of ELS on amygdala reactivity and associated long-term outcomes. Although findings did not support the initial hypotheses, interestingly, results highlighted the critical role of individuals’ reactions to neutral cues in their environment. Amygdala reactivity to neutral, but not negative, cues in adulthood was associated with emotion-oriented coping, and
aggressive/hostile behaviours during mid-adolescence and adulthood. Findings support theories highlighting the initially adaptive changes that happen in the amygdala, potentially leading to increased reliance on maladaptive coping mechanisms into adulthood. The study highlighted potential critical implications associated with building an understanding of individual differences in brain-behaviour reactions to neutral cues into clinical practice to promote adaptive functioning.
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Appendices

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Appendix B: Relevant Publications

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Appendix I: Region of Interest Analysis

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Appendix A

Longitudinal Family Demographic Characteristics

ELS participants did not differ from the larger cohort in family demographic characteristics (effect sizes: family income $\mu=.04$, ns; gender $\varphi=.14$, ns; mother single parent $\varphi=.02$, ns; mother high school only $\varphi = .03$, ns; ethnic minority status $\varphi = .05$, ns), quality of parent–child interaction in infancy, childhood, or adolescence ($\eta = .01–.05$, all ns), severity of childhood maltreatment ($\eta= .01$, ns) or in extent of Axis I or Axis II psychopathology on the Structured Clinical Interview in adulthood (.00–.00, all ns).
Appendix B

Relevant Publications

Publications utilising data as part of the Family Pathways Project:
https://www.researchgate.net/profile/Karlen_Lyons-Ruth

Publication utilising functional MRI data collected when participants were mean age 24.58 ± 0.88 years:


Publications utilising structural MRI data from same sample of participants:


Appendix C

FMRI Statistical Power Discussion

FMRI studies have been criticised for their lack of statistical power due to small sample sizes and challenges in determining meaningful effect sizes using traditional methods (Cremers, Wager, & Yarkoni, 2017; Turner, Paul, Miller, & Barbey, 2018). Yet, Poldrack et al. (2017) investigated the sample sizes used in fMRI research over the past two decades, showing sample sizes are steadily increasing, with a median sample size of 28.5 in 2015 (Figure B1). Since this time, even the most highly cited fMRI studies have reported small sample sizes (medians of 23 and 24 in 2017-18), and are often constrained by practical factors including the expense of fMRI data collection and time needed to analyse data (Szűcs & Ioannidis; 2019). The current sample, although perhaps underpowered in a traditional sense, remains considerably larger than this and therefore should not be discounted when discussing results in comparison to earlier published research.

Figure C1. Sample sizes in fMRI research.
Note. Figure produced by Poldrack et al. (2017; p. 19).
Preschool Behaviour Questionnaire: Hostility Subscale

In the longitudinal sample, the 30-item Preschool Behaviour Questionnaire (PBQ; Behar & Stringfield, 1974) was completed by teachers of children aged 49-71 months ($M_{age} = 59$ months). The PBQ identifies behaviours that suggest the emergence of emotional problems using three subscales: hostile-aggressive, anxious, and hyperactive-distractible. Only data from the 11-item hostile-aggressive subscale were analysed for this study. Each behaviour was scored as either 0 (does’t apply), 1 (applies sometimes), or 2 (certainly applies). Procedures and other longitudinal results of PBQ have been detailed in previous publications (Lyons-Ruth, Alpern, & Repacholi, 1993). The measure shows acceptable inter-rater reliability ($r = .81$), and test-rest reliability ($r = .87$; Behar, 1977; Behar & Stringfield, 1974).

Middle Childhood Disorganisation and Control Scales: Punitive Subscale

At age eight, a standardised attachment assessment was used to observe mother and child’s reunion following a one-hour separation (Main & Cassidy, 1988). Child attachment behaviour was coded using the Middle Childhood Disorganisation and Control Scales (MCDC; Bureau et al., 2009), with scales ranging from 1 (low) 9 (high) to rate the extent of three dimensions of children’s behaviour toward their parent: controlling-punitive, controlling-caregiving, and disorganised behaviour. For the current study, only the controlling-punitive subscale was analysed, with scores in the high range indicating hostility toward the parent (i.e., being challenging, humiliating, cruel). The controlling-punitive subscale shows high internal reliability
(0.97), and high construct validity with other measures of attachment and punitive disorganised attachment (Bureau et al., 2009).

**Personality Research Form: Hostility Subscale**

Participants completed the Personality Research Form (PRF; Jackson, 1967, 1974, 1984) when they were 15 years old. The PRF is a self-report personality inventory assessing the normal range of personality, based on Murray's (1938) taxonomy of needs. The PRF employs 16-item scales in a true-false format for 20 content areas including an aggression scale used in this study. A high score on the aggression scale describes a person who is threatening, aggressive, and willing to hurt others (Jackson, 1984). Acceptable convergent and discriminant validity as well as test retest reliabilities for the PRF (.50 and .91) have been reported (Edwards, Abbott, & Klockars, 1972; Wiggins & Broughton, 1985).

**Goal Corrected Partnership in Adolescence Coding System: Punitive Behaviour Scale**

At age 19, adolescents and their mothers were videotaped during a five-minute unstructured reunion and ten-minute discussion of a conflict in their relationship. The security of interaction between adolescents and parents were coded with the Goal Corrected Partnership in Adolescence Coding System (GPACS; Obsuth et al., 2014). The adolescent punitive behaviour scale was analysed for the current study as it assessed hostile, punitive or devaluing behaviour towards the parent (e.g., mocking, rejecting, dictating). Scores range between 0 and 5, with higher scores indicating higher levels of hostility. Acceptable psychometric properties of this measure in the
longitudinal sample have recently been published (Khoury, Rajamani, Bureau, Easterbrooks, & Lyons-Ruth, 2020).

**Symptom Questionnaire: Anger-Hostility Symptoms Subscale**

At the time of the current study (age 29), participants completed the Symptom Questionnaire (SQ; Kellner, 1987). The SQ is a 92-item self-rating questionnaire across four main scales: Anxiety, depression, anger-hostility, and somatic. This research focused on the SQ anger-hostility symptom scale. Answers on this subscale are dichotomous ("yes"/"true" = 1, maximum score = 17) with a higher score indicating greater hostility. Symptom subscales of the SQ have shown greater sensitivity than their wellbeing counterparts in detecting treatment changes, and greater discriminant validity differentiating patients from healthy controls (Benasi, Fava, & Rafanelli, 2020).
Appendix E

Ethics Documentation

Dear Charlotte Marr,

Application ID: eCLESPsy000879 v2.1
Title: The impact of early life stress on amygdala reactivity and coping behaviour across the life span

Your e-Ethics application has been reviewed by the CLES Psychology Ethics Committee.

The outcome of the decision is: Favourable

Potential Outcomes

<table>
<thead>
<tr>
<th>Favourable:</th>
<th>The application has been granted ethical approval by the Committee. The application will be flagged as Closed in the system. To view it again, please select the tick box. View completed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favourable, with conditions:</td>
<td>The application has been granted ethical approval by the Committee conditional on certain conditions being met, as detailed below. Unless stated otherwise, please resubmit the requested amendments via the online system before beginning the research.</td>
</tr>
<tr>
<td>Provisional:</td>
<td>You have not been granted ethical approval. The application needs to be amended in light of the Committee's comments and re-submitted for ethical review.</td>
</tr>
<tr>
<td>Unfavourable:</td>
<td>You have not been granted ethical approval. The application has been rejected by the Committee. The application needs to be amended in light of the Committee's comments and resubmitted, or you need to complete a new application.</td>
</tr>
</tbody>
</table>

Please view your application here and respond to comments as required. You can download your outcome letter by clicking on the 'PDF' button on your e-Ethics Dashboard.

If you have any queries please contact the CLES Psychology Ethics Chair:
Nick Webster
n.webster@exeter.ac.uk

Kind regards,
CLES Psychology Ethics

CLES – Psychology
Psychology
College of Life and Environmental Sciences
University of Exeter
Washington Singer Building
Perry Road
Exeter
EX4 4QG
Web: www.exeter.ac.uk

Dear Charlotte Marr

Ethics application - eCLESPsy000879

The impact of early life stress on amygdala reactivity and coping behaviour across the life span

Your project has been reviewed by the CLES – Psychology Ethics Committee and has received a Favourable opinion.

The Committee has made the following comments about your application:

- Please view your application at https://eethics.exeter.ac.uk/CLESPsy/ to see comments in full.

If you have received a Favourable with conditions, Provisional or unfavourable outcome you are required to re-submit for full review and/or confirm that committee comments have been addressed before you begin your research.

If you have any further queries, please contact your Ethics Officer.

Yours sincerely

CLES – Psychology Ethics Committee
Appendix F

Consent Form Given to Participants

INFORMED CONSENT AND
AUTHORIZATION TO USE AND DISCLOSE
PROTECTED HEALTH INFORMATION
FOR RESEARCH

We try to make this form easy to understand. But it may still have words or ideas that are not clear to you. Please feel free to ask the study doctor or the study staff to explain anything that you do not understand.

Your name (Subject): __________

Today's Date: __________

Home Address: __________

Are you now taking part in any Research Studies?  Yes  No

Title of Study:  Neurobiological Effects of Childhood Adversity: A 20-year Prospective Study

Name of Principal Investigator: Dr. Karlen Lyons-Ruth

Name of Co-Investigator(s): Dr. Martin Teicher, Dr. Pia Pechtel

Name of Study Staff: Sarah Richardt

IRB Protocol No.: CHA-IRB-0447/05/10
IRB Approval Date: May 17, 2011
IRB Expiration Date: May 17, 2012

Study Sponsor(s):

Neurobiological Effects of Childhood Adversity: A 20-year Prospective Study

Study description

You are invited to take part in a research study done by Dr. Karlen Lyons-Ruth and colleagues. As part of this study, we are interested in learning more about the human development from infancy through to early adulthood based on early parental interactions.

Taking part is voluntary. You have the choice to take part or not. If you take part in the study, you may also leave the study at any time. If you don't want to take part, there will be no disadvantages for you. Although you can leave the study at any time, we will be able to use any information about you that we got while you were part of the research. You will always be proportionally reimbursed for the amount of time you participated.

Revised: April 2011
**Purpose for the Study:**

The purpose of this Research Study is to improve our understanding on the long-term outcomes that may be related to early experiences. We would therefore like to invite you to complete two study components: Firstly, we will ask you to participate in an interview and complete some questionnaires to view your recent well-being and stressful life events. Secondly, we would like to take an anatomical scan of your brain to compare it to other young adults in the study with similar experiences. Finally, findings will be compared to an already existing database on early life experiences that will broaden our understanding on how the brain might be affected by different care giving styles. Long-term, we hope that the findings from this research will ultimately lead to the development of intervention to can assist children who experience early adversity.

**Reasons why you have been selected for the Study:**

The reasons why you have been selected for this Research Study is your previous involvement in the Family Pathway Project. As we have already collected information about your early childhood, we are now interested to see how this may affect you today.

**Period of Participation (how long you will be involved in the study):**

If you choose to participate in this study, the study procedures will last for 2.5 hours and consist of only one session. There will be 40 young adults participating in this research all of whom have been studied since infancy.

**Procedures (what we will do):**

If you decide to take part in this research study, the following will be done:

First we would like you complete nine questionnaires. The Perceived Stress Scale and Coping in Stressful Situations will tell us about any recent stressful life events and how you chose to deal with them. The Dissociation Experiences Scale will tell us how you respond to other situations in your everyday life. Furthermore, we would like you to complete questionnaires about your perception of your family relationships (Parental Bonding Inventory, Parent-Child Relationship Scale, and Modified Adverse Childhood Experiences Scale). We will also ask you to fill out questionnaires to let us know how you are feeling (State-Trait Anxiety Inventory, Limbic System Function Questionnaire, and Symptoms Questionnaire). Following the questionnaires, we would then like to invite you to participate in an interview to update our knowledge on your mental and physical well-being since your last visit as part of this longitudinal study.

Then we would ask you to participate in a brain scan to look at the structural and functional properties of your brain. For most of the scan, you will be able to relax and watch a short entertainment video. For the remaining portion, we will ask you to play a matching game with shapes and faces. The method we use for this is called Magnetic Resonance Imaging (MRI) and uses a magnetic field to scan your brain. Physicians commonly use Magnetic Resonance imaging scanners as they allow us to produce extremely accurate images of the brain or other organs.

Revised: April 2011
such as knee or heart. The scan for this study will take place at the research facilities at McLean hospital using a 3T MRI scanner. While MRI scans are a common and safe procedure, it is important to CAREFULLY read through the MRI safety form handed out with this document. The MRI scanner produces a very strong magnetic field and the magnet is always in use, so it is important not to have any metal on your body or carry any metal into the scanning room with you. The investigator will thoroughly instruct you on all necessary procedures and will address any concerns or questions you may have about this part of the study.

We will then combine the MRI data that we collected from you with other participants who had similar early experiences. Furthermore, we will compare it to young adults with different early experiences both from the present study as well as and from an already existing neuroimaging database on early life experiences.

Some subjects should not participate in MRI studies. These include persons with metallic implants, such as artificial limbs, aneurysm clips, or persons with electronic implants, such as cardiac pacemakers. The magnetic field generated by the MRI machine can cause these objects to move or malfunction. Women who are pregnant must not participate in the study.

Birth Control:
Are you Pregnant or think you are Pregnant? [ ] Yes [ ] No
Are you able to get Pregnant? [ ] Yes [ ] No
Are you planning to get Pregnant? [ ] Yes [ ] No

Although the data suggests that it is perfectly safe for embryos or fetuses to be scanned, there is still much that remains unknown. For this reason, we believe that it is safer to be cautious and not allow anyone who suspects they might be pregnant to participate in the study. We will therefore ask you to take a pregnancy test on the day of the study prior to the MRI scan.

We know of no risk or adverse effects from the radio signals used in this study.

Possible Risk, Discomforts, Side Effects, and Inconveniences:

Questionnaires and Interview:
You may ask to see the questions before deciding whether or not to participate in this study. If you experience uneasiness during the completion of the questionnaires or the interview, please address this with the investigator. You may decide not to answer questions that you feel uncomfortable with.

Revised: April 2011
Occasionally, some individuals experience feelings of claustrophobia, or fatigue and/or physical discomfort from lying still on their back during the scanning session. We will try to position you comfortably at the beginning of the scan using additional pillows. If you feel anxious or scared when in an enclosed space, these feelings could occur while in the MRI. You will be able to communicate any discomfort experienced during the scan through an intercom system that connects you with the investigator. If you become too uncomfortable you should tell the researchers and the procedure will be stopped.

If you have any metal in your body such as a pacemaker or surgical pins or clips, or if you work with materials or tools that could leave small pieces of metal in your eyes or skin, you may not be in the MRI study. Women who are pregnant must not participate in the study. If you are not using reliable contraception and you have engaged in sexual intercourse between your last menstrual period and the day of the scan, we will ask you to take a pregnancy test if you like to participate.

**POSSIBLE DISCOVERY OF FINDINGS RELATED TO MEDICAL IMAGING:**
It is very important that you understand that the MRI recordings are performed for research purposes only; the results cannot be used to make decisions related to any diagnosis or treatment. The MRI scan is designed to answer research questions and cannot examine your brain medically. This MRI is not a substitute for one your medical doctor would order. It may not show problems that would be picked up by a medical MRI scan. However, if we believe that we have found a medical problem in your MRI scan, we will ask a doctor who is trained in the reading of MRI scans, a radiologist, to help us review the scan. If the radiologist thinks there may be an abnormality in your MRI scan, we will contact you and will help you to get medical follow-up for the problem. If you have a primary care doctor, we can contact your doctor, with your permission, and help him or her to get the right follow-up for you. No information generated in this study, will become part of a hospital record routinely. However, if the study detects an abnormality in your MRI scan, then this information may become part of the hospital record. It is possible that you could be unnecessarily worried if a problem were suspected, but not actually found.

Overall, we are very happy to talk with you about any questions or concerns you may have about these risks.

**Alternatives to Participation:**
Participation in this study is voluntary. The alternative is not to participate in this study.

**Benefits:** (What good may come from the research)
This research may not help you directly. However, what we learn may help others.

**Costs:**
You will not have any added costs from being in this study.

Revised: April 2011
Compensation (reward for taking part):

You will be paid $100 for your time and travel expenses for being in this study. If you do not complete the entire study, you will be paid proportionally for the time that you did participate. Payment will be made at the end of the study or when you end your participation. If all parts of the study are not completed during the 2.5-hour study day, you will be given the option to extend the study day or to come back a different day to finish the study materials. If you choose to do so, you will be compensated an additional $10 for every 15 minute increment, and increments will be rounded up.

Voluntary Participation:

If you choose to take part, then your participation is voluntary and you may leave the study at any time without any further consequences.

To leave you must:

Send a letter to the research team. If you decide to leave the study, then you must send a signed letter saying that you want to leave the research study or

Fill out and sign a “Notice to Withdraw” form. However, any information collected from you before the date of you leaving will be used in the research study.

The research team may decide that you are no longer needed in the study. Then the research team must notify you in writing. This could be for example, because you did not follow all the rules while in the study.

Privacy / Confidentiality:

There are laws (state and national) that protect your health information to keep it private. We always follow those laws.

We will protect all of your health information, including your Protected Health Information or “PHI”. (Your PHI is information that might identify you, such as your name, address, phone number, etc.)

If you take part in this study, you agree to let the research team use your medical information. Do not agree to take part if you don’t want the research team to access your health information. The research team agrees always to follow these guides:

- The research team will view your health information only during the life of this study.
- We will not include any information that could identify you in any publication.
- At the end of the study, the research team will remove all of your identifiable information (name, address, phone number, etc.) from our database.

The Cambridge Health Alliance’s Institutional Review Board (IRB) is responsible for making sure that researchers follow federal laws to protect human subjects. Staff of the IRB may at any time ask to look at any records to make sure the research staff is following the laws to protect you.

Sometimes, we are required to share the results of your study tests and procedures with:

Revised: April 2011
Period of Authorization:

Your authorization on this research project will expire on: 6/15/2011. As part of the study, your information will be added to the longitudinal database that contains all of your data since infancy. There is no expiration date of your data as information may be analyzed and re-analyzed in light of scientific and medical advances, or reviewed for quality assurance, oversight, or other purposes.

Getting Help (Contacts):

If you have questions about this study, then you have the right to ask for help. Some of the concerns that people have are:
• What are the benefits or risks of the research?
• What are my rights as a research subject?
• What should I do if I feel pressured to take part against my will?
• How will health information be protected?

At any point you are invited to address any of your concerns. Listed below are the contact details of the key personnel on this project.

Dr. Karlon Lyone-Ruth Cambridge Health Alliance 617-547-3116
Dr. Martin Teicher McLean Hospital 617-865-2871
Dr. Pia Pechtel Department of Psychology 617-865-4234
Nancy Brooks McLean Hospital 617-865-4238
Sarah Richards Cambridge Health Alliance 617-855-4240

If you have these or any other concerns, please contact either a member of the IRB or the Patient Relations Department. The offices are open Monday to Friday (not holidays) from 8:30 in the morning until 5:00 in the evening:

IRB Chair Person: Dr. Lor Givon
Telephone: 617-498-8302
Address: 1492 Cambridge Street, Cambridge, MA 02138

Patient Relations Manager: Lorraine Vendetti
Telephone: 817-665-1396
Address: 1492 Cambridge Street, Cambridge, MA 02138

Revised: April 2011
Certification from Person Obtaining Consent:
The subject has been informed of:
(i) The procedure, purpose and risks of the study as described above,
(ii) How his/her Health information may be used, shared and reported, and
(iii) His/her privacy rights.

The subject has been provided with a signed copy of this Form.

Signature of Person Obtaining Consent ___________________________ Date __________

Subject's Signature ___________________________ Date __________

Patient's Legal Representative (if applicable) ___________________________ Date __________

Interpreter (if used) Print Name ___________________________ Interpreter Role

This form is valid only if it has the IRB Committee's stamp of approval.

IRB APPROVED UNTIL
MAY 17 2012
CAMBRIDGE HEALTH ALLIANCE

Revised: April 2011
Appendix G

Full fMRI Pipeline used in SPM

**fMRI Pre-processing**

1. Set origin to anterior commissure on both anatomical and functional images

**Pre-processing Steps**

1. **Realignment** (*Realign → est & res*)
   a. New session → Session
   i. Specify files – all functional images (208 images)
   ii. Estimation options
      Interpolation → 6th degree
   iii. Resliced options
      1. Resliced images → All images + Mean Image
      2. Interpolation → 6th degree
   iv. All others default inc. Estimation options → num passes → register to mean
   b. Save job ‘realign.mat’ (if using batch for each individual with dependencies, save batch after smoothing)
   c. Press Run
   d. Check translation / movement parameters – write down how much they have moved, e.g. 0.6mm etc.

2. **Slice timing correction** (*Slice timing*)
   a. New sessions
   i. Sessions → Specify files and select ^r.* (208 files) (if using batch, select ‘DEP Realign: Estimate & Reslice: Resliced Images (Sess 1)’)
   ii. Number of slices – 42
   iii. TR: 3
   iv. TA: 3-(3/42)
   v. Slice order: 2:2:42 1:2:42
   vi. Reference slice: 42 (middle slice)
   b. Save job ‘slice_timing.mat’
   c. Press run

3. **Co-register** (*Coregister → Estimate*)
   b. Source image: structural image within structural folder (image that had origin reset – morph…)
   c. Save job ‘coreg.job’
   d. Press Run
e. Check reg reference and source image – check areas align with one another – particularly the ventricles etc. and check outskirts of boundaries to ensure the brains are in the same spaces, e.g.

4. Segmentation (Segment)
   a. Volumes: Coreg structural file from previous step (Morph_....swap.nii) (if using batch, select ‘DEP Coregister: Estimate: Coregistered images’)
   b. Change Save Bias Corrected to ‘Save Bias Corrected’
   c. Native tissue: change all to Native + Dartel imported (for all)
   d. Warped tissue: change to modulated + unmodulated (for all)
   e. Deformation fields: Inverse + Forward
   f. Save job ‘segment.mat’
   g. Press run

5. Normalisation (Normalise → Write)
   a. Data → New subject -> subject
   b. Deformation field: ‘y_...nii’ in structural folder created in previous section (if using batch, select ‘DEP Segment: Forward Deformations’)
   c. Images to write: ‘^ar*.img’ i.e. realigned, slice time corrected functional images + ‘mean....nii’ i.e. mean functional image all from functional folder – 209 images altogether (if using batch, select ‘DEP Realign: Estimate & Reslice: Mean Image’ and ‘Slice Timing Corr. Images (Sess1)’)
   d. Writing options → voxel sizes: change to [3.5 3.5 3.5]
   e. Save job ‘normalise.mat’
   f. Press run

6. 2nd Normalise (Write)
   a. Data → New subject
   b. Deformation field: ‘y_...nii’ (if using batch, select ‘DEP Segment: Forward Deformations’)
   c. Images to write: ‘mMorph.....nii’ i.e. bias corrected structural (if using batch, select ‘DEP Segment: Bias Corrected (1)’)
   d. Writing options → voxel sizes: change to 1.0 1.0 1.3
   e. Save job ‘norm_struct.mat’
   f. Press run
   g. Check reg again – use ‘wmmorph’ file and ‘wmean’ functional image

7. Smoothing (Smooth)
   a. Images to smooth: war*.nii i.e. spatially normalised files (if using batch, select the first Normalised images (if the slice time corrected images were in the normalised first) ‘DEP Normalise: Write: Normalised Images (Subj 1)’)
   b. FWHM → 6 (6mm smoothing kernel)
   c. Save job ‘smooth.mat’
d. Press run

8. Review all pre-processed data

9. Checking for movement:
   a. Start within ‘functional’ directory for participant
   b. Load Art toolbox
   c. Set Matlab path to functional directory
   d. Sessions: 1
   e. Which global mean to use -> Regular
   f. Select type of motion params file -> txt(SPM)
   g. Select functional volumes for session 1 -> select all 208 (original) functional images (unprocessed) - ^fMRI – click done
   h. Select movement params file for session 1 -> choose rp_ file
   i. Produces image with details of outliers – movement threshold – volume numbers are stated
   j. Save -> select all – save and rename with art1, art2, art3
   k. Use new movement parameter file for 1st level analysis (e.g. art_regression_outliers_and_movement_fMRI_025swap_00001)

fMRI Modelling

   o Matlab files created for onset times:
      ▪ sot1 : shapes
      ▪ sot2: negative
      ▪ sot3: neutral

1. 1st level analysis (individual):

   1. Load stimulus onset times to Matlab – stored in each participants’ ‘categorical’ folder – choose this as the path
   2. Matlab prompt: load sots
   3. SPM: Specify 1st-level
      i. Directory: categorical
      ii. Timing parameters
         ▪ Units for design: seconds
         ▪ Interscan interval: 3
         ▪ Microtime resolution: 42 (number of slices)
         ▪ Microtime onset: 42 (reference slice as per slice time correction)
         ▪ Data and design → New subject/session
           I. Scans: Use ^swar.* filter to select all 208 smoothed, normalised, slice-time corrected, realigned functional images
           II. Conditions → New condition
              i. Name: shapes
                 1. Onsets: sot{1}
2. Durations: 36
   ii. Conditions → Replicate conditions
      1. Open new ‘condition’ option
      2. Name: negative
      iii. Onsets: sot{2}
      iv. Durations: 36

III. Conditions → Replicate conditions
   i. Open new ‘condition’ option
   ii. Name: neutral
   iii. Onsets: sot{3}
   iv. Duration: 36

IV. Multiple regressors: Use ART motion parameters file.
V. Model derivatives: No derivatives
VI. Save as ‘1stlevel.mat’
VII. Run

   iii. Review: Design tab -> Design Matrix -> Explore -> Session 1 ->
   iv. Estimate
      ▪ SPM.mat: SPM.mat in categorical
      ▪ Run
   v. Batch -> SPM -> Stats -> Contrast manager
      ▪ Contrast Sessions -> New T contrast….
      ▪ Set up new T contrasts sessions as below:
      ▪ Delete existing contrasts -> Yes (unless adding contrasts)

<table>
<thead>
<tr>
<th>Number</th>
<th>Name</th>
<th>Contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>001</td>
<td>Negfaces_v_Nothing</td>
<td>0 1</td>
</tr>
<tr>
<td>002</td>
<td>Neutral faces_v_Nothing</td>
<td>0 0 1</td>
</tr>
<tr>
<td>003</td>
<td>Shapes_v_Nothing</td>
<td>1 0 0</td>
</tr>
<tr>
<td>004</td>
<td>Negative faces &gt; Shapes</td>
<td>-1 1</td>
</tr>
<tr>
<td>005</td>
<td>Shapes &gt; Negative faces</td>
<td>1 -1</td>
</tr>
<tr>
<td>006</td>
<td>Neutral faces &gt; Shapes</td>
<td>-1 0 1</td>
</tr>
<tr>
<td>007</td>
<td>Shapes &gt; Neutral faces</td>
<td>1 0 -1</td>
</tr>
<tr>
<td>008</td>
<td>Negative faces &gt; Neutral faces</td>
<td>0 1 -1</td>
</tr>
<tr>
<td>009</td>
<td>Neutral faces &gt; Negative faces</td>
<td>0 -1 1</td>
</tr>
<tr>
<td>010</td>
<td>All faces &gt; Shapes</td>
<td>-1 0.5 0.5</td>
</tr>
<tr>
<td>011</td>
<td>Shapes &gt; All faces</td>
<td>1 -0.5 -0.5</td>
</tr>
</tbody>
</table>
- Save
- Run for each participant

Results
- Select SPM.mat from categorical
- Apply masking: none
- P value adjust to control: none
- Uncorrected p value: 0.001 (default)
- Extent threshold: 15

2. 2nd level analysis (group):
   - Run separate analyses for each contrast of interest (4, 5, 6, 7, 8, 9, 10, 11)
   - Click specify 2nd level
   - Select the correct directory e.g. …2nd level analysis_con004
   - Select ‘Design’ and choose ‘two sample t test’
   - Select Cells -> New cell x3
     - Group 1 Scans – select relevant con files for controls (e.g. con4 = negative faces vs. shapes)
     - Group 2 Scans – Select relevant con files for ELS
   - Covariates
     - New: Covariate
     - Vector: Ages (enter all ages in order include both groups one after the other)
     - Name: Ages
     - Others: default
     - Save as e.g. con0004.mat
   - Run

4. Estimate
   - SPM.mat: SPM.mat in relevant directory
   - Run

5. Batch -> SPM -> Stats -> Contrast manager
   - Contrast Sessions -> New T contrast…. 
   - Set up new T contrasts sessions as below:
   - Delete existing contrasts -> Yes (unless adding contrasts)

<table>
<thead>
<tr>
<th>Group</th>
<th>Contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
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</tr>
<tr>
<td>ELS</td>
<td>0 1</td>
</tr>
<tr>
<td>-Controls</td>
<td>-1</td>
</tr>
<tr>
<td>-ELS</td>
<td>0 -1</td>
</tr>
<tr>
<td>Controls &lt; ELS</td>
<td>-1 1</td>
</tr>
<tr>
<td>Controls &gt; ELS</td>
<td>1 -1</td>
</tr>
</tbody>
</table>
iv. Save as contrasts.mat
v. Repeat steps from 'Click specify 2nd level' for other 1st level contrasts

3. ROI analysis:
   a. Open Marsbar toolbox
   b. ‘ROI definition’ dropdown click build -> choose how you want to build an ROI e.g. from image -> create relevant ROIs for each image or region
   c. ‘Design’ -> ‘set design from file’ -> choose the relevant SPM.mat file
   d. ‘Data’ -> ‘Extract ROI data (default)’ -> Select ROI image
   e. ‘Results’ -> ‘Estimate results’
   f. ‘Results’ -> ‘Import contrasts’ -> Select SPM.mat file and select all contrasts of interest
   g. ‘Results’ -> Statistics table -> Select all contrasts of interest
   h. Results -> Save results to file
   i. In Matlab window load results file
      i. Type SPM.marsY.Y
      ii. Beta weights for each ROI per participant
   j. Run bilateral amygdala and all 3 subfields (LB, CM, SF) for each contrast
Appendix H

Whole Brain Analysis Tables

Anatomical labels derived from the SPM Neuromorphometrics Atlas.

Table H1

Negative Faces > Shapes Contrast for Control Group

<table>
<thead>
<tr>
<th>Brain Region</th>
<th>P value (FDR-corr)</th>
<th>k</th>
<th>t</th>
<th>MNI coordinates (mm)</th>
<th>x</th>
<th>y</th>
<th>z</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right cerebral white matter</td>
<td>0.001</td>
<td>25,233</td>
<td>8.20</td>
<td>-16  -98  -7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>7.78</td>
<td>12  -94  -4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>7.76</td>
<td>18  -91  -7</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table H2

Negative Faces > Shapes Contrast for Early Life Stress Group

<table>
<thead>
<tr>
<th>Brain Region</th>
<th>P value (FDR-corr)</th>
<th>k</th>
<th>t</th>
<th>MNI coordinates (mm)</th>
<th>x</th>
<th>y</th>
<th>z</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right cerebral white matter</td>
<td>0.001</td>
<td>15486</td>
<td>5.27</td>
<td>-34  -84  -10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5.17</td>
<td>1   14   -10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5.04</td>
<td>-34 -10  -28</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table H3

Neutral Faces > Shapes Contrast for Control Group

<table>
<thead>
<tr>
<th>Brain Region</th>
<th>P value (FDR-corr)</th>
<th>k</th>
<th>t</th>
<th>MNI coordinates (mm)</th>
<th>x</th>
<th>y</th>
<th>z</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right cerebral white matter</td>
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<td>1086</td>
<td>5.6</td>
<td>18   -91  -10</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>5.56</td>
<td>-6   -94  -4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5.31</td>
<td>40  -49  -21</td>
<td></td>
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<td></td>
</tr>
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</table>
Table H4

*Neutral Faces > Shapes Contrast for Early Life Stress Group*

<table>
<thead>
<tr>
<th>Brain Region</th>
<th>P value (FDR-corr)</th>
<th>k</th>
<th>t</th>
<th>MNI coordinates (mm)</th>
<th>x</th>
<th>y</th>
<th>z</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left cerebral white matter</td>
<td>.001</td>
<td>2341</td>
<td>5.26</td>
<td>-34</td>
<td>-84</td>
<td>-10</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>4.34</td>
<td>-38</td>
<td>-52</td>
<td>-21</td>
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<tr>
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<td></td>
<td>4.22</td>
<td>36</td>
<td>-74</td>
<td>-18</td>
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</tr>
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</table>
Appendix I

Region of Interest Analysis Tables

Table I1

*Within-group Differences in Region of Interest Activation on Negative Faces > Shapes Contrast*

<table>
<thead>
<tr>
<th>Region of Interest</th>
<th>Early Life Stress</th>
<th>Healthy Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Contrast estimate</td>
<td>t</td>
</tr>
<tr>
<td>Left Amygdala</td>
<td>0.80</td>
<td>2.75</td>
</tr>
<tr>
<td>Right Amygdala</td>
<td>0.67</td>
<td>2.24</td>
</tr>
<tr>
<td>Left Centromedial</td>
<td>0.84</td>
<td>2.94</td>
</tr>
<tr>
<td>Right Centromedial</td>
<td>0.75</td>
<td>2.69</td>
</tr>
<tr>
<td>Left Basolateral</td>
<td>0.82</td>
<td>2.87</td>
</tr>
<tr>
<td>Right Basolateral</td>
<td>0.64</td>
<td>2.33</td>
</tr>
<tr>
<td>Left Superficial</td>
<td>0.86</td>
<td>2.45</td>
</tr>
<tr>
<td>Right Superficial</td>
<td>0.85</td>
<td>2.53</td>
</tr>
</tbody>
</table>

Table I2

*Within-group Differences in Region of Interest Activation on Neutral Faces > Shapes Contrast*

<table>
<thead>
<tr>
<th>Region of Interest</th>
<th>Early Life Stress</th>
<th>Healthy Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Contrast estimate</td>
<td>t</td>
</tr>
<tr>
<td>Left Amygdala</td>
<td>0.39</td>
<td>1.46</td>
</tr>
<tr>
<td>Right Amygdala</td>
<td>0.49</td>
<td>1.85</td>
</tr>
<tr>
<td>Left Centromedial</td>
<td>0.31</td>
<td>1.18</td>
</tr>
<tr>
<td>Right Centromedial</td>
<td>0.34</td>
<td>1.43</td>
</tr>
<tr>
<td>Left Basolateral</td>
<td>0.45</td>
<td>1.71</td>
</tr>
<tr>
<td>Right Basolateral</td>
<td>0.37</td>
<td>1.57</td>
</tr>
<tr>
<td>Left Superficial</td>
<td>0.42</td>
<td>1.38</td>
</tr>
<tr>
<td>Right Superficial</td>
<td>0.57</td>
<td>2.14</td>
</tr>
</tbody>
</table>
Table I3

*Within-group Differences in Region of Interest Activation on Shapes > All Faces*

<table>
<thead>
<tr>
<th>Region of Interest</th>
<th>Early Life Stress</th>
<th>Healthy Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Contrast estimate</td>
<td>t</td>
</tr>
<tr>
<td>Left Amygdala</td>
<td>-0.59</td>
<td>-2.51</td>
</tr>
<tr>
<td>Right Amygdala</td>
<td>-0.56</td>
<td>-2.36</td>
</tr>
<tr>
<td>Left Centromedial</td>
<td>-0.57</td>
<td>-2.55</td>
</tr>
<tr>
<td>Right Centromedial</td>
<td>-0.54</td>
<td>-2.51</td>
</tr>
<tr>
<td>Left Basolateral</td>
<td>-0.65</td>
<td>-2.86</td>
</tr>
<tr>
<td>Right Basolateral</td>
<td>-0.52</td>
<td>-2.30</td>
</tr>
<tr>
<td>Left Superficial</td>
<td>-0.62</td>
<td>-2.23</td>
</tr>
<tr>
<td>Right Superficial</td>
<td>-0.67</td>
<td>-2.71</td>
</tr>
</tbody>
</table>
Appendix J

Partial Correlations Among Coping Inventory for Stressful Situations (CISS) Scores and All Region of Interest (ROI) Signal Intensities for All Trials with Age as Covariate

|     | 1   | 2   | 3   | 4   | 5   | 6   | 7   | 8   | 9   | 10  | 11  | 12  | 13  | 14  | 15  | 16  | 17  | 18  | 19  | 20  | 21  | 22  | 23  | 24  | 25  | 26  | 27  |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| 1 LAmy Negative | .28  | .95** | .05  | .03  | .01  | .02  | .00  | .01  | .02  | .03  | .05  | .07  | .09  | .11  | .12  | .13  | .15  | .17  | .18  | .19  | .20  | .21  | .22  | .23  | .24  | .25  | .26  | .27  |
| 2 RAmy Negative | .36  | .78** | .05  | .03  | .01  | .02  | .00  | .01  | .02  | .03  | .05  | .07  | .09  | .11  | .12  | .13  | .15  | .17  | .18  | .19  | .20  | .21  | .22  | .23  | .24  | .25  | .26  | .27  |
| 3 SF LAmy Negative | .43** | .77** | .05  | .03  | .01  | .02  | .00  | .01  | .02  | .03  | .05  | .07  | .09  | .11  | .12  | .13  | .15  | .17  | .18  | .19  | .20  | .21  | .22  | .23  | .24  | .25  | .26  | .27  |
| 4 SF RAmy Negative | .53** | .80** | .05  | .03  | .01  | .02  | .00  | .01  | .02  | .03  | .05  | .07  | .09  | .11  | .12  | .13  | .15  | .17  | .18  | .19  | .20  | .21  | .22  | .23  | .24  | .25  | .26  | .27  |
| 5 BL LAmy Negative | .54** | .82** | .05  | .03  | .01  | .02  | .00  | .01  | .02  | .03  | .05  | .07  | .09  | .11  | .12  | .13  | .15  | .17  | .18  | .19  | .20  | .21  | .22  | .23  | .24  | .25  | .26  | .27  |
| 6 BL RAmy Negative | .52** | .81** | .05  | .03  | .01  | .02  | .00  | .01  | .02  | .03  | .05  | .07  | .09  | .11  | .12  | .13  | .15  | .17  | .18  | .19  | .20  | .21  | .22  | .23  | .24  | .25  | .26  | .27  |
| 7 CM LAmy Negative | .60** | .83** | .05  | .03  | .01  | .02  | .00  | .01  | .02  | .03  | .05  | .07  | .09  | .11  | .12  | .13  | .15  | .17  | .18  | .19  | .20  | .21  | .22  | .23  | .24  | .25  | .26  | .27  |
| 8 CM RAmy Negative | .68** | .85** | .05  | .03  | .01  | .02  | .00  | .01  | .02  | .03  | .05  | .07  | .09  | .11  | .12  | .13  | .15  | .17  | .18  | .19  | .20  | .21  | .22  | .23  | .24  | .25  | .26  | .27  |

Note. LAmy = Left Amygdala; RAmy = Right Amygdala; SF = Superficial; BL = Basolateral; CM = Centromedial; CISS = Coping Inventory for Stressful Situations

*p < .05

**p < .01
Appendix K

Clinical Data on Aggression and Hostility Measures for Longitudinal Participants with Early Life Stress

Table K1

Clinical Data on Aggression and Hostility Measures for Longitudinal Participants with Early Life Stress

<table>
<thead>
<tr>
<th>Measure of Aggression/Hostility</th>
<th>Age (years)</th>
<th>Mean</th>
<th>Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBQ</td>
<td>5</td>
<td>5.12</td>
<td>4.98</td>
</tr>
<tr>
<td>MCDC</td>
<td>8</td>
<td>3.53</td>
<td>1.58</td>
</tr>
<tr>
<td>PRF</td>
<td>15</td>
<td>23.17</td>
<td>3.95</td>
</tr>
<tr>
<td>GPACS</td>
<td>19</td>
<td>2.13</td>
<td>0.74</td>
</tr>
<tr>
<td>SQ</td>
<td>29</td>
<td>7.72</td>
<td>3.51</td>
</tr>
</tbody>
</table>

Note. PBQ = Preschool Behaviour Questionnaire: Hostility Subscale; MCDC = Middle Childhood Disorganisation and Control Scales: Punitive Subscale; PRF = Personality Research Form: Hostility subscale; GPACS = Goal Corrected Partnership in Adolescence Coding System: Punitive Behaviour subscale; SQ = Symptoms Questionnaire: Anger-Hostility Subscale.
Appendix L

Correlations Among Early Life Stress (ELS) Group Scores on Measures of Hostility/Aggression Across the Lifespan and All Region of Interest (ROI) Signal Intensities for All Trials

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 |
| LAmy Negative | .81** | 3 | SF LAmy Negative | .53** .74** | 4 | SF RAmy Negative | .79** .93** .79** | 5 | BL LAmy Negative | .92** .88** .79** .75** | 6 | BL RAmy Negative | .76** .79** .83** .90** | 7 | CM LAmy Negative | .92** .72** .78** .77** .89** .64** | 8 | CM RAmy Negative | .76** .74** .71** .77** .73** .73** |
| LAmy Neutral | .46 .19 .44 .23 .36 .22 .45 .31 | 9 | LAmy Neutral | .25 .02 .19 .02 .16 .02 .18 .16 | 10 | RAmy Neutral | .25 .02 .19 .02 .16 .02 .18 .16 | 11 | SF LAmy Neutral | .38 .13 .33 .20 .26 .26 .26 .25 .38* .98** .89** | 12 | SF RAmy Neutral | .2 .01 .11 .01 .09 .05 .15 .17 .89** .96** .85** |
| BL LAmy Neutral | .45 .20 .36 .29 .26 .32 .24 .37* .97** .88** .84** .74** | 13 | BL LAmy Neutral | .42 .15 .34 .29 .25 .34* .23 .34* .95** .91** .77** .71** .95** | 14 | BL RAmy Neutral | .23 .15 .15 .16 .11 .18 .15 .27 .83** .80** .84** .86** .84** .79** | 15 | CM LAmy Neutral | .19 .18 .13 .11 .10 .16 .10 .29 .78** .70** .84** .84** .83** .77** .89** |
| LAmy Shapes | .38 .20 .15 .04 .14 .01 .24 .11 .71** .57** .43** .52** .48** .42** .44** .47** | 16 | CM LAmy Neutral | .34 .18 .12 .03 .13 .02 .24 .14 .61** .45 .34* .48** .49** .37** .38 .43** .96** | 17 | CM LAmy Neutral | .47 .29 .19 .05 .12 .01 .28 .15 .57** .36 .42** .50** .41** .36 .41** .45** .97** .95** | 18 | SF RAmy Shapes | .36 .20 .07 .03 .07 .06 .21 .11 .56** .40 .31 .50** .34 .31 .37 .45** .91** .97** .93** |
| BL LAmy Neutral | .31 .17 .20 .10 .22 .09 .24 .16 .71** .59** .42** .48** .53** .46** .44** .46** .97** .92** .89** .84** .64** | 19 | BL RAmy Neutral | .35 .13 .17 .07 .15 .05 .22 .11 .66** .53** .31 .38 .44** .42** .34** .36 .92** .92** .86** .84** .93** | 20 | CM LAmy Shapes | .36 .14 .10 .01 .05 .06 .24 .03 .74** .65** .43** .56** .42** .39** .48** .47** .93** .90** .92** .90** .87** .88** |
| CM LAmy Neutral | .25 .10 .07 .01 .07 .07 .21 .11 .71** .61** .47** .58** .45** .41** .47** .54** .90** .91** .86** .90** .85** .85** .93** | 21 | PBQ | .07 .13 .03 .28 .21 .03 .04 .08 .08 .07 .11 .12 .11 .08 .24 .30 .16 .34 .18 .30 .13 .13 .29 .02 .12 | 22 | MCDC | .18 .05 .24 .10 .05 .04 .31 .18 .01 .23 .01 .20 .08 .01 .08 .02 .08 .13 .20 .14 .10 .21 .12 .08 .08 | 23 | PRF | .35 .46 .29 .64** .49 .54** .36 .49 .52** .41 .48 .36 .61** .62** .65** .54** .52** .41 .49 .64** .68** .63** .68** .07 .01 |
| GPACS | -.29 -.31 -.30 -.36 -.36 -.31 -.34 -.43 .24 .30 .23 .22 .16 .31 .09 .02 .29 .26 .17 .17 .19 .23 .29 .28 -.06 .24 -.08 | 24 | SQ | .09 .06 .05 .13 .16 .20 .11 .15 .57** .56** .58** .60** .55** .62** .72** .59** .49 .54** .38 .52** .48 .63** .68** 56** .19 .18 .67** 31 |

* p < .05
** p < .01
Appendix M
Dissemination Statement

Dissemination to Participants and Services

The results of this study will be disseminated to interested parties through feedback, journal publication and presentation.

Feedback

As agreed in the original Family Pathways Project, participants will be informed of the results of the study. Participants will be provided with details of who to contact, should they require further information.

Journal Publication

It is expected that the study will be submitted for publication in Neuroimage.

Presentation

On 8th June 2020, the research findings are due to be presented to an academic audience, for peer review, as part of the Doctorate in Clinical Psychology at the University of Exeter.
Appendix N

Neuroimage Submission Guidelines

Retrieved from

Article structure: Original research papers

Original research papers should confirm to the following guidelines. The structure of Review, Comments and ToolBox papers should be adapted to their content.

Subdivision - numbered sections
Divide your article into clearly defined and numbered sections. Subsections should be numbered 1.1 (then 1.1.1, 1.1.2, ...), 1.2, etc. (the abstract is not included in section numbering). Use this numbering also for internal cross-referencing: do not just refer to 'the text'. Any subsection may be given a brief heading. Each heading should appear on its own separate line.

Introduction
State the objectives of the work and provide an adequate background, avoiding a detailed literature survey or a summary of the results.

Material and methods
Provide sufficient details to allow the work to be reproduced by an independent researcher. Methods that are already published should be summarized, and indicated by a reference. If quoting directly from a previously published method, use quotation marks and also cite the source. Any modifications to existing methods should also be described.

Results
Results should be clear and concise.

Discussion
This should explore the significance of the results of the work, not repeat them. A combined Results and Discussion section is often appropriate. Avoid extensive citations and discussion of published literature.

Conclusions
The main conclusions of the study may be presented in a short Conclusions section, which may stand alone or form a subsection of a Discussion or Results and Discussion section.
Appendices
Appendices can be employed for mathematical derivations or formulations that are important for the paper but are not the primary focus of the paper. Appendices are subject to peer review. If there is more than one appendix, they should be identified as A, B, etc. Formulae and equations in appendices should be given separate numbering: Eq. (A.1), Eq. (A.2), etc.; in a subsequent appendix, Eq. (B.1) and so on. Similarly for tables and figures: Table A.1; Fig. A.1, etc.

Essential title page information

- **Title.** Concise and informative. Titles are often used in information-retrieval systems. Avoid abbreviations and formulae where possible.
- **Author names and affiliations.** Please clearly indicate the given name(s) and family name(s) of each author and check that all names are accurately spelled. You can add your name between parentheses in your own script behind the English transliteration. Present the Authors' affiliation addresses (where the actual work was done) below the names. Indicate all affiliations with a lower-case superscript letter immediately after the author's name and in front of the appropriate address. Provide the full postal address of each affiliation, including the country name and, if available, the e-mail address of each author.
- **Corresponding author.** Clearly indicate who will handle correspondence at all stages of refereeing and publication, also post-publication. This responsibility includes answering any future queries about Methodology and Materials. Ensure that the e-mail address is given and that contact details are kept up to date by the corresponding author.
- **Present/permanent address.** If an author has moved since the work described in the article was done, or was visiting at the time, a 'Present address' (or 'Permanent address') may be indicated as a footnote to that author's name. The address at which the author actually did the work must be retained as the main, affiliation address. Superscript Arabic numerals are used for such footnotes.

Abstract

A concise and factual abstract is required. The abstract should state briefly the purpose of the research, the principal results and major conclusions. An abstract is often presented separately from the article, so it must be able to stand alone. For this reason, References should be avoided, but if essential, then cite the author(s) and year(s). Also, non-standard or uncommon abbreviations should be avoided, but if essential they must be defined at their first mention in the abstract itself.

**Graphical abstract**
Although a graphical abstract is optional, its use is encouraged as it draws more attention to the online article. The graphical abstract should summarize the contents of the article in a concise, pictorial form designed to capture the attention of a wide
readership. Graphical abstracts should be submitted as a separate file in the online submission system. Image size: Please provide an image with a minimum of 531 × 1328 pixels (h × w) or proportionally more. The image should be readable at a size of 5 × 13 cm using a regular screen resolution of 96 dpi. Preferred file types: TIFF, EPS, PDF or MS Office files. You can view Example Graphical Abstracts on our information site.

Authors can make use of Elsevier's Illustration Services to ensure the best presentation of their images and in accordance with all technical requirements.

**Highlights**

Highlights are mandatory for this journal. They consist of a short collection of bullet points that convey the core findings of the article and should be submitted in a separate editable file in the online submission system. Please use 'Highlights' in the file name and include 3 to 5 bullet points (maximum 85 characters, including spaces, per bullet point). You can view example Highlights on our information site.

**Keywords**

Immediately after the abstract, provide a maximum of 6 keywords, using American spelling and avoiding general and plural terms and multiple concepts (avoid, for example, 'and', 'of'). Be sparing with abbreviations: only abbreviations firmly established in the field may be eligible. These keywords will be used for indexing purposes.

**Abbreviations**

Define abbreviations that are not standard in this field in a footnote to be placed on the first page of the article. Such abbreviations that are unavoidable in the abstract must be defined at their first mention there, as well as in the footnote. Ensure consistency of abbreviations throughout the article.

**Acknowledgements**

Collate acknowledgements in a separate section at the end of the article before the references and do not, therefore, include them on the title page, as a footnote to the title or otherwise. List here those individuals who provided help during the research (e.g., providing language help, writing assistance or proof reading the article, etc.).

**Formatting of funding sources**

List funding sources in this standard way to facilitate compliance to funder's requirements:
EARLY LIFE STRESS, AMYGDALA REACTIVITY AND COPING ACROSS THE LIFESPAN

Funding: This work was supported by the National Institutes of Health [grant numbers xxxx, yyyy]; the Bill & Melinda Gates Foundation, Seattle, WA [grant number zzzz]; and the United States Institutes of Peace [grant number aaaa].

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