Altered Intrinsic Connectivity in the Default Mode Network and Central Executive Network in Borderline Personality Disorder and Low Resilient Functioning

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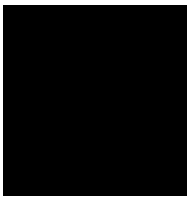
Thesis Declaration Form

I confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signature: 

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Overview

This thesis examines the neurobiological mechanisms associated with borderline personality disorder (BPD) and the efficacy of combined skills training and trauma-focussed interventions in two separate studies.

Part one comprises a systematic review and meta-analysis examining the efficacy and tolerability of combined skills training and trauma-focussed cognitive behavioural therapy (TFCBT) for adults with chronic posttraumatic stress disorder (PTSD). Seventeen randomised controlled trials were included in the meta-analysis. Results showed that combined skills training and TFCBT were superior to control conditions in reducing clinician-rated and self-reported PTSD symptom severity posttreatment. Based on preliminary comparison between combined skills training and TFCBT and TFCBT-only, there was no strong evidence to suggest that additional skills training provided additional benefits in terms of PTSD symptom reduction, attrition rate and quality of life. Given that there was considerable unexplained heterogeneity and the presence of risk across multiple domains on the risk of bias appraisal tool, findings were preliminary and further comparative studies were necessary to support the clinical rationale for skills training for individuals with chronic PTSD.

Part two examines resting-state intrinsic functional connectivity differences in individuals with BPD and healthy controls. In addition, resting-state intrinsic functional connectivity associated with resilient functioning were explored. Resting-state functional magnetic resonance imaging scans were obtained from 66 participants. Group independent component analysis, a multivariate data-driven approach, was performed to examine within and between network intrinsic functional connectivity in the default mode network, salience network and central executive network. Results revealed decreased intrinsic functional connectivity within the bilateral precuneus in the BPD group compared to healthy controls, which were potentially associated with impairments in self-referential processing in BPD.

Preliminary findings suggested different patterns of intrinsic functional connectivity within the default mode network and central executive network between healthy controls and the BPD group. The part concludes with the implications and limitations of the current study.

Part three details the critical appraisal of the research process. This included a reflective examination of the researcher's positionality on the current research, a discussion of the conceptual issues of resilience and the wider challenges in neuroimaging research. Considering the limitations discussed, several recommendations were detailed by the author.

Impact Statement

The current study has several key implications in the domains of academic research and clinical practice.

In the academic research domain, findings on resting-state intrinsic functional connectivity differences in borderline personality disorder (BPD) are an important step forward in understanding BPD-specific neurobiological mechanisms. Here, the study utilized Group Independent Component Analysis (GICA), a multivariate network analysis approach, in investigating resting-state intrinsic functional connectivity. As intrinsic functional connectivity networks can be consistently identified at rest or during task engagement, our findings allow future researchers to make comparisons of intrinsic functional connectivity in identical intrinsic networks from various neuroimaging studies with different paradigms (i.e., resting-state and task-based) and integrate findings on BPD-specific neurobiological mechanisms. The current study provided preliminary evidence suggesting that altered intrinsic functional connectivity in the precuneus may be neural-specific to individuals with BPD or specific to psychopathology symptoms characterised by BPD.

Furthermore, the current study highlighted the lack of inclusion of the BPD population in resilience research, which was often limited to healthy individuals and individuals with Axis I disorders of the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV). Preliminary findings affirmed that the BPD population were exposed to significant early adversity and showed more maladaptive functioning (i.e., psychopathology symptoms) than healthy individuals, which were indicative of severe impairments in general resilience mechanisms. In addition, current findings highlighted the importance of examining individual differences in resilient functioning. The quantitative measure of resilient functioning has research utility, as it takes into consideration of the individual differences in the severity of childhood trauma and psychopathology symptoms. The examination of

individual differences in the response to adversity would allow future research to examine the causal neurobiological processes underlying resilience mechanisms.

In the clinical practice domain, implicated regions in the current findings were associated with self-referential processing, autobiographical memory and cognitive control. Clinically, many psychological therapies have treatment components which may target these processes, such as reflecting on one's own thoughts and feelings, using a longitudinal formulation to understand current difficulties and the rehearsal of coping skills. It remains unknown whether such therapeutic components have an effect in strengthening and/or regulating intrinsic brain architecture associated with resilience and psychopathology. Further research on neurobiological changes associated with clinical interventions could elucidate change mechanisms in specific therapeutic components and facilitate specific and targeted interventions.

Given that neuroimaging findings are still in the early stages of development, there is inherent potential in neuroimaging research to translate the research into clinical utility. Understanding resilience mechanisms associated with intrinsic networks can inform clinical interventions in strengthening specific resilience mechanisms. With increased clarity in the relationship between intrinsic connectivity networks and resilience, interventions can potentially enhance resilience by targeting specific adaptive neural mechanisms using innovative techniques such as transcranial magnetic stimulation. Furthermore, identifying altered intrinsic networks associated with low resilient functioning could be clinically useful in the identification of vulnerable individuals for early intervention and the identification of resilience mechanisms that promote recovery in patient groups.

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Part 1: Literature Review

Skills Training and Trauma-Focussed Cognitive Behavioural Therapy for Chronic Posttraumatic Stress Disorder: A Meta-Analysis

Abstract

Background. Contemporary clinical conceptualisation of chronic posttraumatic stress disorder (PTSD) and clinical practice guidelines recommend the use of skills training to promote affect and interpersonal regulation and facilitate subsequent trauma-focussed interventions. However, there is little quantitative evidence to support the efficacy of skills training.

Objective. The study aimed to examine the efficacy and tolerability of skills training and trauma-focussed cognitive behavioural therapy (TFCBT) for adults with chronic PTSD and explore causes of heterogeneity in TFCBT studies.

Data Sources. A systematic review of relevant randomised controlled trials (RCT) of TFCBT for chronic PTSD were identified from PsychINFO, Pubmed and Web of Science. Relevant reviews on chronic PTSD and corresponding reference lists were hand searched by the author to identify additional studies.

Study selection: RCTs with a minimum sample size of 22 and at least one treatment arm of a combination of individual TFCBT and skills training for adults with chronic PTSD were included. The primary outcome measures were clinician-rated PTSD symptom severity and attrition rate. Secondary outcome measures were self-reported PTSD symptom severity and quality of life.

Data extraction. Data extraction and evaluation of risk of bias were conducted by the author.

Data Synthesis. All pooled effects were based on random-effects models. Seventeen studies (*N* = 1323) were included in the review. Combined TFCBT and skills training were superior to waitlist, treatment as usual and placebo conditions in reducing clinician-rated[1] and self-reported[2] PTSD symptom severity at posttreatment, [1]standardized mean difference (SMD) –1.47, 95% CI [–1.92, –1.02], 13 studies, *N* = 983; and [2]*SMD* –1.52, 95% CI [–2.37, –0.67], 11 studies, *N* = 794. Attrition rates did not differ between combined TFCBT and skills training group and control conditions. Based on preliminary comparison, there was no strong evidence

to suggest that additional skills training provided additional benefit in terms of PTSD symptom reduction, attrition rate and quality of life. There was considerable unexplained heterogeneity and the quality of evidence was low due to the presence of risk across multiple domains on the risk of bias appraisal tool.

Conclusions. Based on low quality evidence, large positive effects were found for combined TFCBT and skills training in reducing PTSD symptoms compared to waitlist, treatment as usual and placebo conditions. There was no strong evidence to suggest that combined TFCBT and skills training incurred greater attrition than waitlist or treatment as usual groups. As minimal comparative studies were available, more high-quality observational studies and comparative RCT studies are necessary to support the clinical rationale of skills training for chronic PTSD.

Keywords: meta-analysis, randomised controlled trials, chronic posttraumatic stress disorder, trauma-focussed cognitive behavioural therapy

Introduction

Posttraumatic Stress disorder, Chronic Posttraumatic Disorder and Complex Posttraumatic Disorder

Posttraumatic stress disorder (PTSD) is the persistent psychological distress presented in response to traumatic and threatening stressors. It is a debilitating condition characterised by the re-experiencing of trauma, avoidance of trauma reminders, hypervigilance, negative alterations in cognitions and mood persisting for at least one month (American Psychiatric Association, 2013). When PTSD symptoms persist for more than three months, it is considered chronic PTSD.

Complex PTSD is an emerging construct, where researchers proposed that complex PTSD is characteristically distinct from PTSD (Resick et al., 2012; van der Kolk, Roth, Pelcovitz, Sunday, & Spinazzola, 2005). Beyond the core PTSD symptoms discussed above, features of complex PTSD include: (1) emotion regulation difficulties, (2) disturbances in relational capacities, (3) alterations in attention and consciousness, (4) adversely affected belief systems, and (5) somatic distress and disorganisation (Cloitre et al., 2011; van der Kolk et al., 2005). However, other researchers have argued against a separate diagnosis of complex PTSD and instead, proposed that complex PTSD is a severe and chronic form of PTSD within a multidimensional spectrum of PTSD symptoms (Resick et al., 2012). Subsequently in the *Diagnostic Statistical Manual of Mental Disorders*, fifth edition (DSM–V), these symptoms were classified as associated features of PTSD (American Psychiatric Association, 2013; Cloitre et al., 2011). Nevertheless, complex PTSD remains a controversial construct and is beyond the scope of the current study. However, the recent conceptualisation of complex PTSD has influenced clinical interventions, which would be elaborated in later sections of the paper. Since complex PTSD is not a formal diagnosis in the DSM, the current scope of the study focusses on chronic PTSD.

Chronic Posttraumatic Stress Disorder

A recent epidemiological survey on PTSD across 26 populations reported an estimated lifetime prevalence of PTSD of 4% and 50% of the respondents with PTSD reported persistent symptoms (Koenen et al., 2017). Indeed, several longitudinal studies have described a subset of individuals with chronic trajectories (Bryant et al., 2015; Osenbach et al., 2014). The estimated prevalence of chronic PTSD is mixed, reportedly 4% (Bryant et al., 2015) to 27% (Osenbach et al., 2014) in two separate PTSD samples.

Trauma-focussed Cognitive Behavioural Therapy (TFCBT)

TFCBT is the first line psychological intervention for chronic PTSD (National Institute for Health and Care Excellence, 2005; Forbes et al., 2010). TFCBT is an aggregate of various theoretical approaches and its associated evidence-based psychological interventions aimed at processing specific trauma-related memories, cognition and symptoms (Lambert & Alhassoon, 2015). In order to process traumatic memories, four core components of TFCBT were identified in various evidence-based TFCBT interventions (Bisson, Roberts, Andrew, Cooper, & Lewis, 2013; Schnyder et al., 2015): (1) psychoeducation on PTSD, (2) emotion regulation and coping skills (i.e., anxiety management), (3) exposure and (4) cognitive restructuring and/or meaning making. The degree to which each component is emphasised in each TFCBT protocol varies, with a noticeable shift from behavioural (i.e., exposure) to cognitive components (i.e., cognitive restructuring and meaning making) over time. Examples of TFCBT include exposure therapy (Foa et al., 1999), cognitive therapy (Ehlers, Clark, Hackmann, McManus, & Fennell, 2005), cognitive processing therapy (Resick, Nishith, Weaver, Astin, & Feuer, 2002) and narrative exposure therapy (Neuner, Schauer, Klaschik, Karunakara, & Elbert, 2004).

Individual TFCBT was found to be effective in reducing clinician-rated PTSD symptom severity for individuals with chronic PTSD (Bisson et al., 2013). At

posttreatment, the review authors reported a large effect size, standardized mean difference (*SMD* –1.62; 95% CI –2.03 to –1.21) for individual TFCBT compared to waitlist in the reduction of PTSD symptoms (Bisson et al., 2013). Results suggest that the risk of meeting the criteria for PTSD diagnosis at posttreatment was 49% lower in the individual TFCBT group compared to the waitlist group (Bisson et al., 2013). Furthermore, anxiety and depressive symptoms were found to be alleviated alongside the reduction of PTSD symptoms (Bisson et al., 2013). Therefore, individual TFCBT appears to be as effective for individuals with chronic PTSD and individuals with non-chronic PTSD (Cusack et al., 2016).

Nonetheless, meta-analyses of TFCBT had reported high heterogeneity across TFCBT studies (Bisson et al., 2013; Ehring et al., 2014; Gerger, Munder, & Barth, 2014), which limits the validity of the conclusions on the efficacy of TFCBT in chronic PTSD. For example, clinical complexity was reported to moderate the efficacy of trauma-focussed psychological interventions (Gerger et al., 2014). Trauma-focussed psychological interventions were found to be more effective in individuals with non-complex presentations compared to individuals with clinical complexity (e.g. comorbid presentations, or exposure to multiple traumatic events). Indeed, individual TFCBT protocols possess considerable methodological variations, such as the recommended treatment dose, flexibility of treatment length, follow up duration and treatment components. Therefore, there is an urgent need to investigate the impact of characteristic and incidental moderators on outcomes to warrant the validity of conclusions from TFCBT RCTs.

Despite the reported efficacy of TFCBT, there is some evidence to suggest that individuals with chronic PTSD respond less optimally to conventional trauma-focussed interventions (Hembree, Street, Riggs, & Foa, 2004; Resick, Nishith, & Griffin, 2003). For instance, individuals with chronic PTSD are more likely to drop out from TFCBT compared to other non-trauma focussed psychological interventions (Bisson et al., 2013). Bisson et al. (2013) reported that there is a 1.39-

fold and 1.64-fold increase risk of dropout in individual TFCBT compared to other therapies and waitlist control respectively. Although subjective reasons for dropout may be heterogeneous, high attrition rates can be problematic as it may suggest poor tolerability of the specific psychological intervention, adverse reaction and unmet mental health needs.

Recent conceptualisation of complex PTSD and influence on clinical practice

Clinically, complex PTSD provides an alternative explanation of poor tolerability of TFCBT. Contemporary conceptualisation of chronic PTSD postulates that prolonged interpersonal trauma disrupts the development of effective affect regulation and interpersonal functioning (van der Kolk et al., 2005). Here, affect dysregulation refers to heightened sensitivity to intense negative emotions and the slow return to emotional baseline (Cloitre, Koenen, Cohen, & Han, 2002; Linehan, 1993). Affect dysregulation is widely documented in childhood abuse survivors (van der Kolk et al., 2005; Zlotnick et al., 1997), where difficulties such as high emotional reactivity, fearing the experience of emotions and dissociation are reported. In addition, interpersonal difficulties such as difficulties managing conflict, being assertive in relationships with differential power imbalance and managing interpersonal boundaries may result in pervasive and significant interpersonal difficulties for individuals with chronic PTSD (Cloitre et al., 2002; van der Kolk et al., 2005). Given the affect and interpersonal dysfunction described above, clinicians argued that individuals with complex PTSD may be at greater risk for dropping out from TFCBT interventions and respond less optimally to TFCBT (Cloitre et al., 2011).

More importantly, the recent conceptualisation of complex PTSD has informed clinical practice and treatment guidelines. A survey of 50 PTSD experts revealed that 84% of clinicians advocated the use of phase-based treatment for individuals with complex PTSD (Cloitre et al., 2011). Similarly, phased-based treatment was recommended as the first treatment option by The International

Society for Traumatic Stress Studies (ISTSS; Cloitre et al., 2012). As complex PTSD is clinically conceptualised as the consequence of impaired affect regulation, social and cognitive competencies, phased-based treatment aims to enhance these competencies and alleviate PTSD symptoms. The proposed phase-based treatment consists of three stages; (1) the stabilisation phase, where stability is promoted and the affect regulation, social and cognitive competencies are developed and strengthened, (2) the trauma-focussed phase, where traumatic memories are re-appraised and adaptively integrated in the individual's beliefs of the self, others and the world, and (3) the consolidation phase, where treatment gains are consolidated and functioning in other domains of life are improved (Cloitre et al., 2012). Clinically, the stabilisation phase intends to increase the tolerability of trauma-focussed interventions for individuals with more chronic and complex clinical presentations. Preliminary evidence suggests that affect and interpersonal skills training in the stabilisation phase followed by TFCBT was associated with lower dropout rates and greater PTSD remission rates compared to supportive counselling followed by TFCBT (Cloitre et al., 2010).

It is also important to note that the proposed interventions for stabilisation varies, with examples such as affect and interpersonal skills training (Cloitre et al., 2002), affect management group (Zlotnick et al., 1997), group CBT (Dorrepaal et al., 2013) and dialectical behavioural therapy skills group (Bradley & Follingstad, 2003). Other examples of skills training include breathing retraining, progressive muscle relaxation, relaxation techniques, stress inoculation training, mindfulness, dialectical behavioural therapy skills training (Linehan, 1993), anger management, anxiety management, social skills training and assertiveness training.

However, there is little quantitative evidence to support the need for a stabilisation phase (de Jongh et al., 2016). Through a critical review of selected empirical evidence, de Jongh et al. (2016) asserted that individuals with chronic PTSD with comorbid presentations benefit from trauma-focussed psychological

interventions without the stabilisation phase. Yet, there were a number of flaws in the review. First, the review authors did not conduct a systematic search to ensure that all existing relevant literature had been included. Second, the review did not investigate treatment efficacy and tolerability with the use of quantitative methods. We argue that it is premature to conclude the effect or non-effect of skills training in the treatment of chronic PTSD.

Study Aims

Therefore, the present study aimed to address the research gap by: (1) evaluating the efficacy and tolerability of combined skills training and TCBT interventions in the treatment of chronic PTSD and, (2) exploring the causes of heterogeneity in TFCBT studies. The scope of the review targets skills training specifically, due to the greater availability of generated research compared to other forms of proposed interventions for stabilisation. Given that complex PTSD is not a formal diagnosis and is an unlikely inclusion criterion in most randomised controlled trials, the scope of the current study is limited to chronic PTSD. The current study had three research questions. First, whether combined skills training and TFCBT were more efficacious in reducing PTSD symptoms and improving quality of life compared to control conditions. Secondly, whether combined skills training and TFCBT were more efficacious and tolerable than TFCBT-only. Finally, whether clinical complexity, treatment dose, flexibility of treatment length, follow up duration, gender and type of skills training accounted for the heterogeneity observed in TFCBT studies. Clinical complexity was selected as a moderator of interest as a meta-analysis reported that individuals with complex presentation benefitted from nonspecific psychological interventions, while non-complex individuals benefitted from specific trauma-focussed intervention (Gerger et al., 2014). Clinical complexity is defined in the later sections of the paper. The other moderators of interest selected were exploratory.

Method

Inclusion Criteria

Randomised controlled trials (RCTs) of TFCBT for chronic PTSD were included in the study. The inclusion criteria for participants were: (1) adults aged 18 to 65, (2) a formal diagnosis of PTSD according to the DSM or International Classification of Diseases (ICD), (3) PTSD symptoms of at least three months in order to meet the criteria for chronic PTSD, (4) comorbid presentations were included in the study given the high prevalence of comorbidity in chronic PTSD, and (5) a minimum sample size of 22 after the random assignment of eligible participants. To ensure that the included studies were sufficiently powered, power calculations reported in studies meeting the inclusion criteria were recorded and the minimum sample size to detect the treatment effect was selected as an additional inclusion criterion. Four studies reported power calculations and the minimum sample size reported was 22 (Asukai, Saito, Tsuruta, Kishimoto, & Nishikawa, 2010).

The inclusion criteria for methodological characteristics include: (1) individual face to face TFCBT as a component of a treatment arm, (2) additional components such as group skills training were allowed, (3) studies with at least one treatment arm of a combination of TFCBT and skills training, (4) skills training should be an explicit and distinct intervention component delivered before or after TFCBT components and should be described in the study's intervention protocol.

The study's exclusion criteria were: (1) psychopharmacological interventions or combined psychopharmacological and psychological interventions (e.g. TFCBT and sertraline), (2) psychological interventions targeting specific PTSD symptoms instead of the overall cluster of PTSD symptoms (e.g. CBT for insomnia, or CBT for panic), (3) RCTs with only group TFCBT offered in the treatment arm, (4) eye movement desensitisation and reprocessing (EMDR; Shapiro, 2001) and brief eclectic psychotherapy (Gersons, Carlier, Lamberts, & van der Kolk, 2000) were

excluded as they possess characteristically discrete treatment components (i.e., bilateral stimulation and psychodynamic components) from the core components of TFCBT described above. This exclusion criteria was to ensure that the pooled effect sizes of psychological interventions were as similar as possible for inferences to be valid.

Study Identification and Selection

Studies were accessed from PsychINFO, Pubmed and Web of Science using the following search terms: ((chronic OR complex OR multiple OR severe OR "treatment resistant") AND ("posttraumatic stress disorder" OR "post-traumatic stress disorder" OR PTSD OR "combat disorder")) AND (("cognitive behavio* therapy" OR "cognitive therapy" OR "behavio* therapy" OR "prolong* exposure" OR "exposure therapy" OR "imaginal exposure" OR CBT OR "cognitive processing therap*")) AND ((RCT or "randomi* control* trial")) NOT TOPIC: ("young" OR "adolescent" OR "youth"). Relevant reviews on chronic PTSD and their corresponding reference lists were hand searched by the author to identify additional RCT studies. The cut-off date for the article search was 31 July 2018, with no prior time criteria established.

Outcome Measures

The primary outcome measures of interest in the current study were: (1) clinician rating of PTSD symptom severity on a standardized measure (e.g. the Clinician-administered PTSD scale (Blake et al., 1995) and the PTSD Symptom Scale-Interview (Foa, Riggs, Dancu, & Rothbaum, 1993) and (2) attrition rate, which was defined as the number of individuals who dropped out of the study for any reason after random assignment. Clinician rated PTSD symptom severity was selected as a primary outcome measure as many RCTs reported clinician ratings instead of self-report measures. Secondary outcomes of interest were self-reported PTSD symptoms on a standardized measure, such as the Impact of Events Scale (Horowitz, Wilner, & Alvarez, 1979), and self-reported quality of life.

Data Extraction and Analysis

1. Extracting and Coding of Information

Relevant data as described were extracted and recorded (refer to Appendix A). Sample characteristics such as the total number of participants, number of participants in each group, gender (at least 80% of the study's sample were males, at least 80% of the study's sample were females or mixed), duration since trauma event and PTSD symptom duration were extracted. To categorize studies according to clinical complexity, we adapted the criteria reported by Gerger et al. (2014). Studies were categorized as clinically complex when 80% or more of the sample met one of the following criteria: (1) presence of multiple problems (i.e., two or more comorbid mental disorders, being in an ongoing violent relationship, being a refugee) or (2) presence of complex psychological traumatization such as childhood trauma or multiple intentional trauma. Attrition rate was defined as the number of participants who dropped out for any reason after random assignment. The attrition rate for control and treatment arms were extracted separately.

Intervention characteristics such as modality (individual or combined individual and group), number of intervention sessions, total intervention duration, and flexibility of intervention sessions offered (yes/no) were coded. Flexibility referred to variability in treatment length (i.e., number of intervention sessions offered) based on clinician evaluation, participant's reported reduction in PTSD symptoms or participant's preferences. Comparison groups were divided into two groups, namely (1) waitlist control or treatment as usual or placebo (i.e., non-trauma focussed psychological intervention), and (2) comparative TFCBT intervention (e.g. prolonged exposure vs cognitive processing therapy). In addition, maximum follow up duration was recorded. Primary outcome measures of interest were changes in PTSD symptom severity based on a standardized measure rated by a clinician (e.g. the Clinician Administered PTSD Symptom Scale) and attrition rates. Secondary outcome measures of interest were self-reported measures on PTSD symptom

severity and quality of life. Skills training were coded into the following groups: (1) affect regulation skills such as breathing retraining, progressive muscle relaxation, diaphragmatic breathing, stress inoculation training and mindfulness, (2) interpersonal skills, such as assertive communication, self-advocacy and empowerment and (3) affect and interpersonal regulation skills training, such as dialectical behavioural therapy skills, social and emotional rehabilitation.

Methodological aspects of studies were coded as such: random assignment of participants (unclear how random assignment was conducted, invalid method, yes and clearly reported), power calculation (yes/no), manual-based intervention (yes/no), adherence of treatment (none, monitored in supervision, tapes reviewed for adherence), therapist's experience (novice, graduate students, qualified clinicians), blinding of personnel at baseline and posttreatment assessment (yes/no) and intent to treat analysis (yes/no). In addition, treatment of missing values was recorded.

2. Measures of Treatment Effect

Sample sizes, means and standard deviations of continuous outcomes were extracted from intent to treat data at posttreatment. When intent to treat analyses were not available, sample sizes, means and standard deviations were extracted from completers data. If the study has more than two arms, relevant individual TFCBT treatment arms were combined to allow for pairwise comparison between control group (i.e., waitlist or treatment as usual or placebo) and treatment arms (i.e., TFCBT). The combination of groups was completed based on the formulae provided by the Cochrane Handbook (Higgins & Green, 2011; refer to Appendix B1). SMD was used to allow the comparison of various outcome measures across studies. Corresponding standard errors and confidence intervals were calculated. Study authors were contacted to provide information for any missing data.

As for categorical outcomes (i.e., attrition rate), relative risk and corresponding confidence intervals were calculated. Relative risk represents the

probability of an event (i.e., dropout) occurring and was utilised in the current study as it is commonly used in medical studies as compared to odds ratio (Bisson et al., 2013).

3. Assessment of Risk of Bias in Included Studies

The risk of bias tool described in the Cochrane Handbook for Systematic Review of Interventions (Higgins et al., 2011) was utilised to assess risk of bias in included studies (refer to Appendix C). The tool was selected as it is widely used to evaluate the validity of RCTs. Additional criterion specific to assess the quality of psychological interventions in RCTs (Yates, Morley, Eccleston, & Williams, 2005) were included, as the appraisal tool from the Cochrane Handbook was designed for general medical trials and lack specific assessment domains relevant to psychological interventions. Additional assessment domains, namely therapist allegiance, treatment fidelity and therapist qualification, were used in a Cochrane Review of interventions for torture survivors (Patel, Kellezi, & Williams, 2014). The author conducted the assessment by judging each assessment domain in three categories (i.e., high risk, low risk and unclear risk) and constructed the risk of bias table for each study. Assessment domains were: (1) random sequence generation, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessment, (5) incomplete outcome data, (6) selective reporting, (7) therapist allegiance, (8) treatment fidelity, (9) therapist qualification and (10) other bias.

4. Statistical Analysis

A random effects model was selected for analysis based on the considerable heterogeneity reported in meta-analyses of TFCBT studies (Bisson et al., 2013; Ehring et al., 2014). Therefore, a random effects model using the Restricted Maximum Likelihood (REML; Langan et al., 2019) with the estimate of heterogeneity based on the inverse variance method was conducted on R (R core team, 2018; https://www.R-project.org) with the metafor package (Viechtbauer, 2010). Using the

inverse variance method, each study is weighted in the inverse proportion to its variance. Through the inverse variance method, both sample size and the variability of outcomes measured were accounted for in the calculation of study weights. Instead of weighting studies by sample size, the inverse variance method yields more accurate effect size estimates (Marín-Martínez & Sánchez-Meca, 2010). The REML method was selected as it provides higher accuracy in estimating heterogeneity variance compared to other methods, such as the DerSimonian and Laird method (Kosmidis, Guolo, & Varin, 2017; Langan et al., 2019). Estimates of heterogeneity were reported through the I^2 statistic and *Q*-test statistic.

First, a random-effects meta-analysis was performed based on the extracted SMD to establish the overall relative effect between combined TFCBT and skills training and waitlist, treatment as usual or placebo. Next, to investigate the incremental benefit of TFCBT and skills training relative to TFCBT-only, a random-effects meta-analysis was performed comparing combined TFCBT and skills training to TFCBT-only. To explore causes of heterogeneity across studies, subgroup analyses and meta-regression analyses were conducted for categorical variables (i.e., clinical complexity, flexibility of treatment length, gender and type of skills training) and continuous variables (i.e., follow up duration and number of intervention sessions) respectively. Finally, comparisons with at least 10 studies were subjected to the Egger's test for publication bias. This is in line with recommendations from the Cochrane Handbook, as using the test on a small number of studies would likely result in insufficient power in distinguishing real asymmetry from random chance (Higgins & Green, 2011).

Results

Results of Search

The search of the electronic databases Web of Science, PubMed and PsychInfo yielded 526 references (refer to Figure 1). In addition, reference lists of

relevant review papers and meta-analyses (Bisson et al., 2013; Cloitre, 2009; Creamer & Forbes, 2004; Cusack et al., 2016; de Jongh et al., 2016; Dorrepaal et al., 2014; Dossa & Hatem, 2012; Gerger et al., 2014; Lambert & Alhassoon, 2015; McFarlane & Kaplan, 2012; Nickerson, Bryant, Silove, & Steel, 2011; Nose et al., 2017; Palic & Elklit, 2011; Patel et al., 2014; Thompson, Vidgen, & Roberts, 2018) were checked and yielded 100 references. After removing 88 duplicate references, 538 references were screened, where the titles and abstracts were screened for relevance. 438 references were excluded as many titles and abstracts were irrelevant to the study, with topics such as sleep difficulties, whiplash, acute stress disorder, psychopharmacological interventions and technology-based interventions. The remaining 100 references were reviewed and assessed for eligibility. Eighty-three studies did not meet the inclusion criteria and were excluded (refer to Appendix D). Two studies (Feske, 2008; Hinton et al., 2004) were excluded based on the criterion of a minimum sample size of 22. A total of 17 RCT studies were included in the meta-analysis (refer to Figure 1).

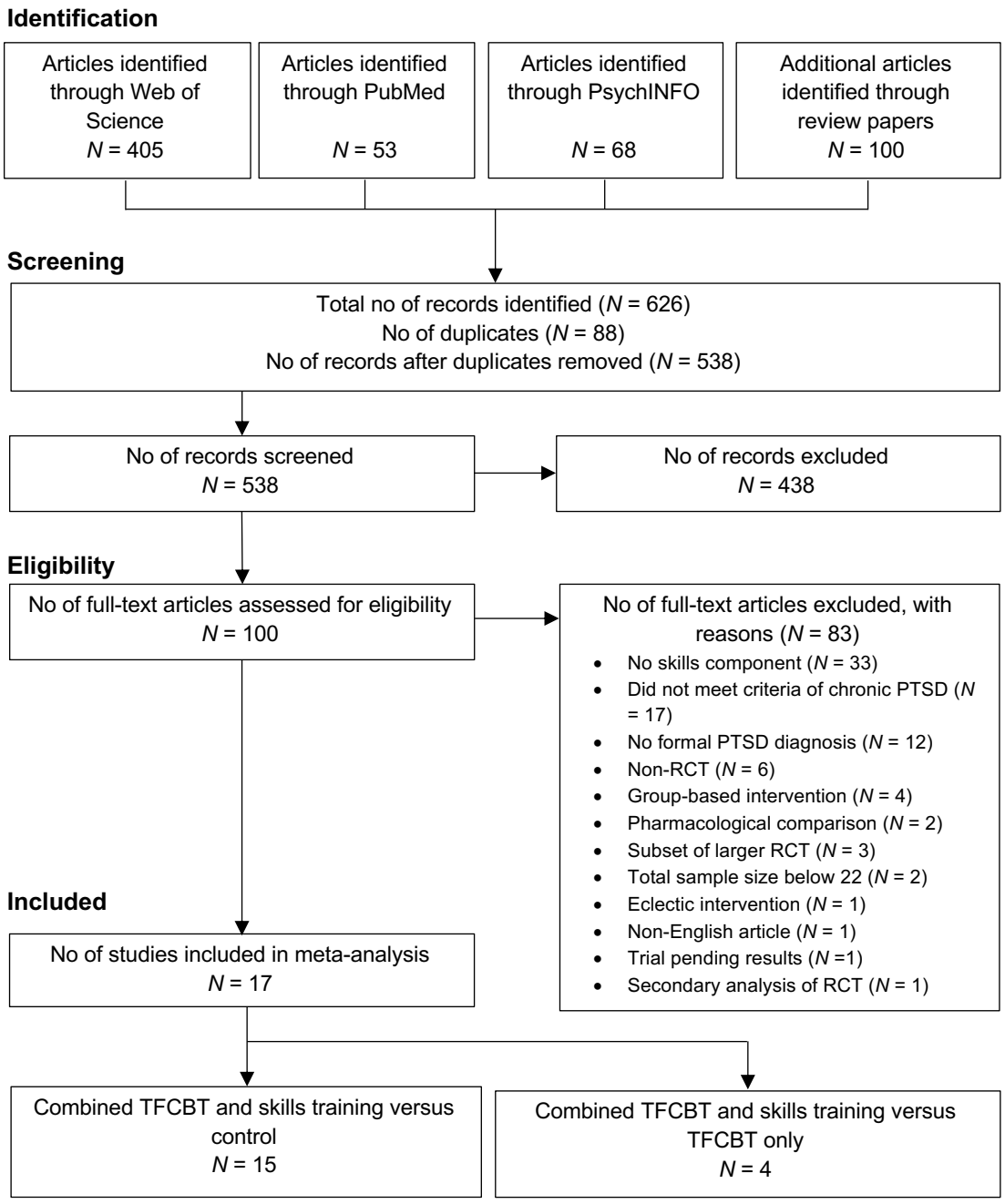

Figure 1. Flow chart of the identification and selection of studies. PTSD = posttraumatic stress disorder; RCT = randomized controlled trial; TFCBT = trauma-focussed cognitive behavioural therapy.

Study Characteristics

Characteristics of the included studies were detailed in Table 1. Majority of the studies were published after year 2000 (*N* = 15). Fifteen studies (17 active treatment conditions, 15 control conditions) compared combined TFCBT and skills training to control (i.e., waitlist, treatment as usual or placebo). Control conditions

were waitlist (*N* = 12), treatment as usual (*N* = 2) and placebo (*N* = 1, with supportive therapy as the control arm). Four studies (4 active treatment conditions, 4 comparative conditions) compared combined TFCBT and skills training to TFCBT-only. Total sample sizes across studies ranged from 23 (Fecteau & Nicki, 1999) to 179 (Foa et al., 2005).

Study samples were predominantly female; samples of eleven studies had 80% or more females and one study with 80% or more males. Five studies used combined modalities (i.e., individual TFCBT and group skills training) in their treatment arms. Types of trauma reported by study samples include childhood abuse (including sexual, physical and emotional abuse; *N* = 9), sexual and/or physical assault (*N* = 4), refugees with war or conflict related psychological trauma (*N* = 2), domestic violence (*N* = 2), motor vehicle accident (*N* = 1), military combat-related psychological trauma (*N* = 1) and mixed trauma (*N* = 2).

Table 1
Overview of included studies

Study	Intervention	Control	N	Female/Male	Clinical complexity	PTSD measure	Modality	No of sessions	Flexibility of treatment	Follow up (months)
Asukai (2010)	Prolonged exposure	TAU	24	21/3	N	CAPS	Individual	8 to 15	Y	12
Beidel (2011)	Trauma Management Therapy with exposure therapy	Exposure therapy	35	0/35	–	CAPS[c]	Combined	28	N	0
Bohus (2013)	Dialectical Behaviour Therapy for PTSD	TAU	74	74/0	Y	CAPS	Combined	91	N	3
Buhmann (2016)	Cognitive Behavioural Therapy	Waitlist	138	36/64[a]	Y	None[c]	Individual	16	N	0
Chard (2005)	Cognitive Processing Therapy	Waitlist	71	71/0	Y	CAPS[c]	Combined	27	N	12
Cloitre (2002)	Skills training in affect and interpersonal regulation (STAIR) modified prolonged exposure	Waitlist	58	58/0	Y	CAPS	Combined	16	N	9
Cloitre (2010)	Skills training in affect and interpersonal regulation (STAIR) modified prolonged exposure	Supportive counselling/Exposure	66	66/0	Y	CAPS	Combined	16	N	6
Cottraux (2008)	Cognitive Behavioural Therapy	Supportive Therapy	60	42/18	N	None	Individual	10 to 16	Y	24
Fecteau (1999)	Cognitive Behavioural Therapy	Waitlist	23	14/6[b]	N	CAPS[c]	Individual	4	Y	6
Foa (1999)	Prolonged exposure and stress inoculation training	Waitlist	70	70/0	N	PSS-I[c]	Individual	9	N	12
Foa (2005)	Prolonged exposure; Prolonged exposure and cognitive restructuring	Waitlist	179	179/0	N	PSS-I[c]	Individual	9 to 12	N	12
Hinton (2005)	Cognitive Behavioural Therapy	Waitlist	40	24/16	N	CAPS	Individual	12	Y	3
Kubany (2003)	Cognitive Trauma Therapy	Waitlist	37	37/0	Y	CAPS	Individual	8 to 11	N	3
Kubany (2004)	Cognitive Trauma Therapy	Waitlist	125	125/0	N	CAPS	Individual	8 to 11	Y	6
McDonagh (2005)	Cognitive Behavioural Therapy	Waitlist	52	52/0	Y	CAPS	Individual	14	Y	6
Resick (2002)	Prolonged exposure; Cognitive Processing Therapy	Waitlist	171	171/0	Y	CAPS	Individual	9/12	N	9
van den Berg (2015)	Prolonged exposure	Waitlist	100	54/46	Y	CAPS	Individual	8	N	6

Note. CAPS = clinician-administered PTSD scale; PSS-I = PTSD symptom scale – Interview; TAU = treatment as usual; Y = yes, N = no; – No information available.

[a, b] Studies did not report the gender of participants who dropped out and the numbers reflect participants at baseline (i.e., attended first session) and who completed the intervention respectively.

[c] Posttreatment scores were based on completers instead of intent to treat analysis.

Included studies compared (1) combined TFCBT and skills training versus waitlist, treatment-as-usual or placebo, and (2) combined TFCBT and skills training versus TFCBT-only. The following specific comparisons were made:

1. Combined TFCBT and skills training versus waitlist, treatment as usual or placebo: Fifteen studies (Asukai et al., 2010; Bohus et al., 2013; Buhmann, Nordentoft, Ekstroem, Carlsson, & Mortensen, 2016; Chard, 2005; Cloitre et al., 2002; Cottraux et al., 2008; Fecteau & Nicki, 1999; Foa et al., 1999; Foa et al., 2005; Hinton et al., 2005; Kubany, Hill, & Owens, 2003; Kubany et al., 2004; McDonagh et al., 2005; Resick et al., 2002; van den Berg et al., 2015).
2. Combined TFCBT and skills training versus TFCBT-only: Four studies (Beidel, Frueh, Uhde, Wong, & Mentrikoski, 2011; Cloitre et al., 2010; Foa et al., 1999; Resick et al., 2002).

Two studies (Foa et al., 1999; Resick et al., 2002) had two treatment arms and a waitlist condition. We combined the two treatment arms to allow for the first comparison. For example, in Foa et al., (1999), we combined two treatment arms (1) the prolonged exposure group and (2) prolonged exposure and stress inoculation training group, and compared the combination of treatment arms to the waitlist condition. For the second comparison (i.e., combined skills training and TFCBT versus TFCBT-only), we contrasted the intervention arm with more emphasis on skills training with the intervention with less emphasis on skills training.

An overview of skills training interventions was presented in Table 2. Skills training components include breathing retraining (*N* = 5), mindfulness (*N* = 3), dialectical behavioural skills training (*N* = 3), diaphragmatic breathing (*N* = 2), progressive muscle relaxation (*N* = 2), self-advocacy and empowerment (*N* = 2), social and emotional rehabilitation (*N* = 1), relaxation technique (*N* = 1), assertive communication (*N* = 1) and stress inoculation training (*N* = 1). Number of intervention sessions dedicated for skills training were rarely reported and largely varied, ranging from one session to 68 sessions.

Table 2
Overview of skills training

Study	Skills training	Number of skills training sessions
Asukai (2010)	Breathing retraining	–
Beidel (2011)	Social and emotional rehabilitation	14
Bohus (2013)	DBT skills training, mindfulness	68
Buhmann (2016)	Mindfulness and acceptance commitment therapy	–
Chard (2005)	Assertive communication	–
Cloitre (2002)	Affect and interpersonal regulation skills derived from generic CBT and DBT skills training	8
Cloitre (2010)	Affect and interpersonal regulation skills derived from generic CBT and DBT skills training	8
Cottraux (2008)	Relaxation techniques	4
Fecteau (1999)	Diaphragmatic breathing technique	–
Foa (1999)	Stress inoculation training	–
Foa (2005)	Breathing retraining	1
Hinton (2005)	Diaphragmatic breathing, mindfulness, imagery, progressive muscle relaxation	–
Kubany (2003)	Progressive muscle relaxation, self-advocacy and empowerment	–
Kubany (2004)	Progressive muscle relaxation, self-advocacy and empowerment	–
McDonagh (2005)	Breathing retraining	–
Resick (2002)	Breathing retraining	–
van den Berg (2015)	Breathing retraining	–

Note. – No information available; CBT = cognitive behavioural therapy; DBT = dialectical behavioural therapy.

Effect Size Calculation

Six studies (Beidel et al., 2011; Buhmann et al., 2016; Chard, 2005; Fecteau & Nicki, 1999; Foa et al., 1999; Foa et al., 2005) reported posttreatment outcomes for completers instead of intent to treat analysis. Consequentially, sample sizes, means and standard deviations were extracted from the treatment completers in these six studies. The remaining studies' sample sizes, means and standard deviations were extracted from intent to treat data. One paper (Fecteau & Nicki, 1999) presented the subscales of self-reported PTSD symptom severity instead of the total score (i.e., Impact of Events Scale intrusion and avoidance subscales) and the means and standard deviations of subscales were combined in line with the

formula presented in Appendix B1. One paper (van den Berg et al., 2015) reported confidence intervals instead of standard deviations, and within-group standard deviations were calculated based on reported means, sample size and confidence intervals (refer to Appendix B2 for formulae). As all information required were reported, it was not necessary to contact study authors.

Risk of Bias

Overall risk of bias of the included studies were presented in Figure 2 and Figure 3. Characteristics of included studies and their respective risk of bias tables were included in Appendix E. Generally, more recent studies showed lower risk of bias compared to older studies.

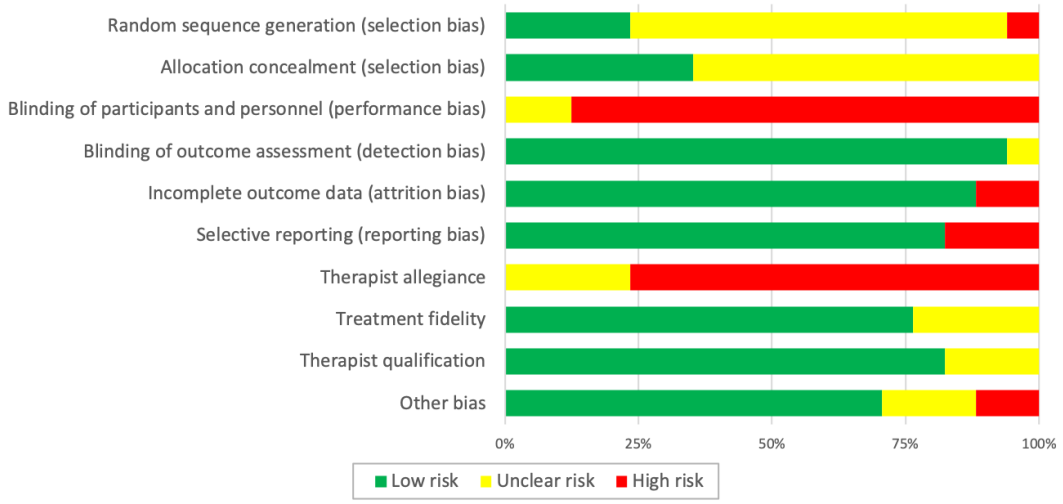

Figure 2. Risk of bias graph. Review author's judgements about each risk of bias item presented as percentages across all included studies.

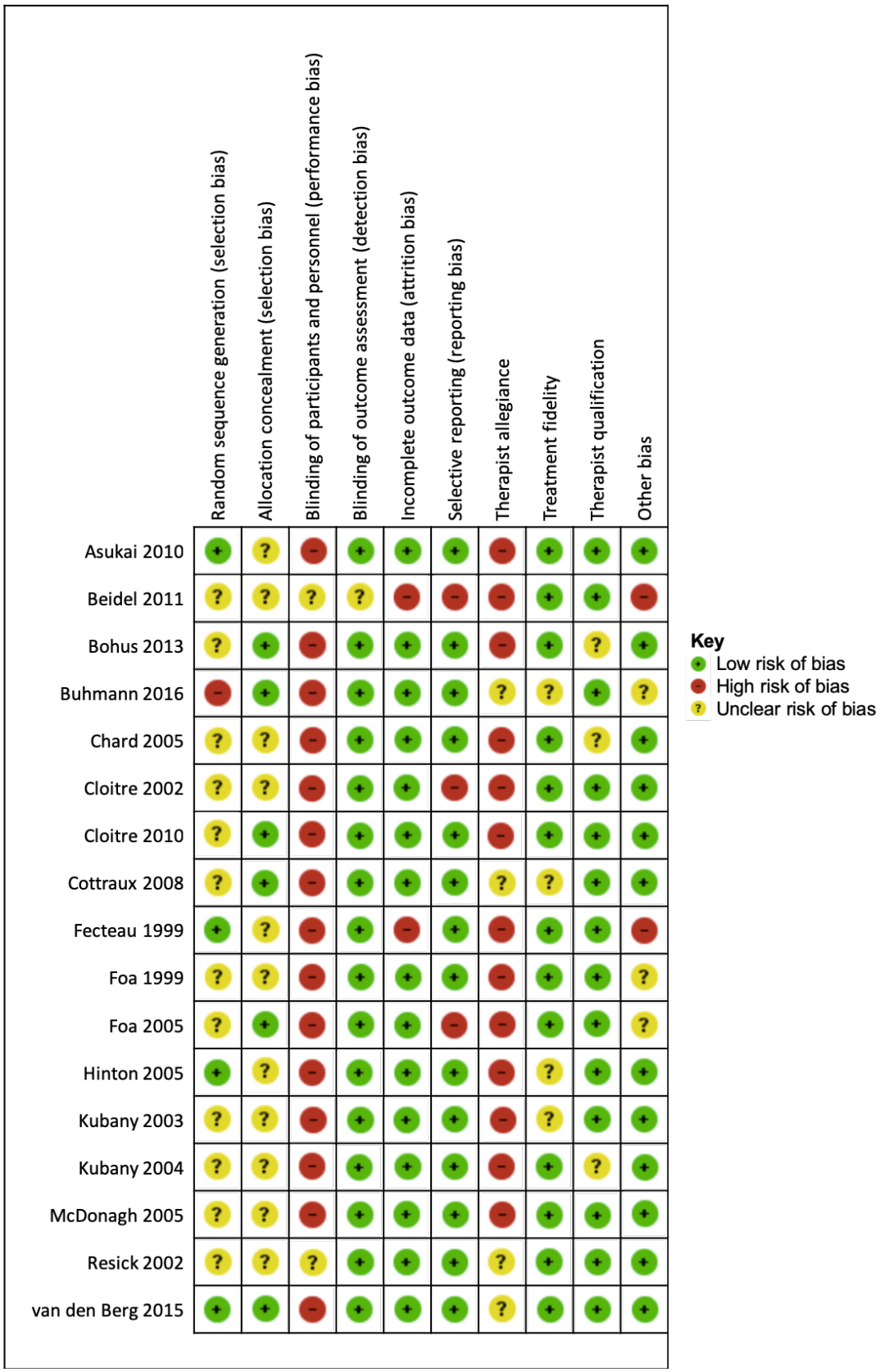

Figure 3. Risk of bias summary. Review author's judgements about each risk of bias item for each included study.

Risk of bias was judged to be high across included studies in the following domains: random sequence generation, allocation concealment, blinding of participants and personnel and therapist allegiance. Many studies did not sufficiently report the method of random assignment (Beidel et al., 2011; Bohus et al., 2013; Chard, 2005; Cloitre et al., 2002; Cloitre et al., 2010; Cottraux et al., 2008; Foa et al., 1999; Foa et al., 2005; Kubany et al., 2003; Kubany et al., 2004; McDonagh et al., 2005; Resick et al., 2002) and the method of concealing allocation of participants to intervention or control arms (Asukai et al., 2010; Beidel et al., 2011; Chard, 2005; Cloitre et al., 2002; Fecteau & Nicki, 1999; Foa et al., 1999; Hinton et al., 2005; Kubany et al., 2003; Kubany et al., 2004; McDonagh et al., 2005; Resick et al., 2002). As expected, double blinding of participants and personnel were often challenging in psychological interventions and majority of the included studies were judged to be at high risk. However, well-designed studies measured and controlled for participant's expectations of intervention (Beidel et al., 2011; Resick et al., 2002).

In relation to therapist allegiance, nine studies were rated as high risk as the authors developed the treatment protocol (Beidel et al., 2011; Bohus et al., 2013; Chard, 2005; Cloitre et al., 2002; Cloitre et al., 2010; Foa et al., 1999; Foa et al., 2005; Kubany et al., 2003; Kubany et al., 2004; McDonagh et al., 2005). In three studies, the first author provided treatment to all participants in the treatment arm (Fecteau & Nicki, 1999; Hinton et al., 2005; Kubany et al., 2003) and were rated as high risk. Six studies had therapists provide interventions to both treatment and control arms (Beidel et al., 2011; Chard, 2005; Cloitre et al., 2010; Cottraux et al., 2008; Resick et al., 2002; van den Berg et al., 2015). Within these six studies, three studies were rated as unclear risk as they did not present with other high-risk indicators (Cottraux et al., 2008; Resick et al., 2002; van den Berg et al., 2015). One study (Buhmann et al., 2016) did not report any information on the author's links to the interventions provided or descriptions of the therapists and received a risk rating of unclear risk.

Risk of bias was judged to be low across included studies in the following domains: blinding of outcome assessment, incomplete outcome data, selective reporting, treatment fidelity, therapist qualification and other bias. All but one study (Beidel et al., 2011) had assessors blinded to the participant's allocation assessed outcomes at pre, post and follow up. Two studies excluded dropouts from analysis and did not perform intent to treat analysis (Beidel et al., 2011; Fecteau & Nicki, 1999) and were rated as high risk in the incomplete outcome data domain. However, reasons for dropout were underreported. Out of 17 studies, 12 studies did not report reasons for dropout (Asukai et al., 2010; Bohus et al., 2013; Chard, 2005; Cloitre et al., 2002; Cloitre et al., 2010; Foa et al., 1999; Foa et al., 2005; Kubany et al., 2003; Kubany et al., 2004; McDonagh et al., 2005; Resick et al., 2002). In addition, majority of the studies reported the outcomes listed in their methods section.

In relation to treatment fidelity, all studies utilised a treatment manual or protocol and 13 studies selected intervention tapes randomly for adherence rating (Asukai et al., 2010; Beidel et al., 2011; Bohus et al., 2013; Chard, 2005; Cloitre et al., 2002; Cloitre et al., 2010; Fecteau & Nicki, 1999; Foa et al., 1999; Foa et al., 2005; Kubany et al., 2004; McDonagh et al., 2005; Resick et al., 2002; van den Berg et al., 2015). Two studies (Buhmann et al., 2016; Cottraux et al., 2008) assessed adherence to treatment through supervision and the remaining two studies (Hinton et al., 2005; Kubany et al., 2003) did not assess for treatment adherence. Majority of the studies had trained or qualified therapists provide intervention for participants in treatment arms. Two studies were rated as high risk in the domain of other bias due to the presence of disability benefit incentives (Beidel et al., 2011) and small sample size (Fecteau & Nicki, 1999). Two studies had uneven sample sizes across conditions (Foa et al., 1999; Foa et al., 2005) and received an unclear risk rating. In addition, one study received an unclear risk rating due to the use of translated self-

report measures and real-time translation of outcome measures (Buhmann et al., 2016).

Effects of Intervention

Comparison 1: Combined TFCBT and Skills Training versus Control

Thirteen studies (N = 983) considered clinician-rated PTSD symptoms as an outcome of interest (refer to Figure 4). At posttreatment, the combined TFCBT and skills training group showed improved clinician-rated PTSD symptoms compared to waitlist, treatment as usual and placebo control, *SMD* –1.47; 95% CI [–1.92, –1.02], $p < .01$. There was significant heterogeneity between studies, $Q(12) = 63.2$, $p < .01$, $I^2 = 88\%$.

Fifteen studies (N = 1216) reported attrition rates of individuals who dropped out of the study post allocation (refer to Figure 5). Attrition rate was not significantly different between combined TFCBT and skills training group and control groups, relative risk (RR) 1.15, 95% CI [0.66, 2.02], $p = .619$. Significant heterogeneity was detected, $Q(14) = 52.47$, $p < .01$, $I^2 = 73\%$.

Eleven studies (N = 794) considered self-reported PTSD symptoms as an outcome of interest (refer to Figure 6). Overall, eight self-report measures were used and these measures were reviewed to ensure that scores from respective measures had the same direction (i.e., higher scores meant higher self-reported PTSD symptoms). At posttreatment, the combined TFCBT and skills training group showed significant improvements in PTSD symptoms compared to control conditions, *SMD* –1.52, 95% CI [–2.37, –0.67], $p < .01$. Substantial heterogeneity was detected, $Q(10) = 107.95$, $p < .01$, $I^2 = 96\%$.

Only three studies (N = 194) considered self-reported quality of life as an outcome of interest (refer to Figure 7). All three studies used different self-report measures and these measures had the same direction (i.e., higher scores were indicative of higher quality of life). Self-reported quality of life did not differ between combined TFCBT and control conditions at posttreatment, *SMD* 0.01, 95% CI [–

0.28, 0.29], p = .967. Non-significant heterogeneity between the studies was observed, $Q(2) = 0.339$, p = .844, I^2 = 0%.

Comparison 2: Combined TFCBT and Skills Training versus TFCBT-only

Four studies (N = 265) contributed to this comparison and considered clinician-rated PTSD symptom severity as an outcome of interest (refer to Figure 8). There was no difference between combined TFCBT and skills training and TFCBT-only groups in terms of clinician-rated PTSD symptoms severity posttreatment, *SMD* 0.04, 95% CI [–0.25, 0.33], p = .792. Heterogeneity between studies was non-significant, $Q(3) = 3.74$, p = .292, I^2 = 26%. In terms of attrition rate (refer to Figure 9), both combined TFCBT and skills training and TFCBT-only groups did not significantly differ, *RR* 1.19, 95% CI [0.43, 3.28], p = 0.731). Moderate to substantial heterogeneity was detected, $Q(3) = 8.36$, p = .039, I^2 = 70%.

Three studies (N = 220) considered self-reported PTSD symptoms severity as an outcome of interest (refer to Figure 10). There was no significant difference between groups in terms of self-reported PTSD symptom severity, *SMD* –0.11, 95% CI [–0.77, 0.54], p = .732. Moderate to substantial heterogeneity between studies was detected, $Q(2) = 12.21$, $p < .01$, I^2 = 80%. All three studies did not measure quality of life as an outcome of interest.

Research Question 3: Investigating Causes of Heterogeneity

Given the considerable heterogeneity observed between the included TFCBT studies, subgroup analyses (refer to Appendix F) and meta-regression analyses were conducted for categorical variables (i.e., clinical complexity, flexibility of treatment length, gender and type of skills training) and continuous variables (i.e., follow up duration and number of intervention sessions). The meta-analysis model which compares clinician-rated PTSD symptom severity between combined TFCBT and skills training and control conditions (i.e., comparison one) was selected for subgroup analysis and meta-regression analyses as the model included the most

studies and had used the most consistent measure (i.e., the Clinician-administered PTSD scale). The outcome measure of attrition rate was not selected for subgroup analyses as there were no statistically significant difference in attrition rate between combined TFCBT and skills training and control conditions.

Subgroup analyses revealed that clinical complexity, flexibility of treatment length, gender and type of skills training were not significantly associated with observed SMD (refer to Table 3). Similarly, meta-regression analyses revealed that follow up duration and number of intervention sessions did not significantly predict observed SMD.

Publication Bias

The potential effect of publication bias was tested through funnel plots and the Egger's test to test for funnel plot asymmetry. Three funnel plots were constructed based on the comparison between combined TFCBT and skills training versus waitlist, treatment as usual and supportive therapy.

The first funnel plot examined the measure of clinician-rated PTSD symptom severity (refer to Figure 11) and the Egger's test detected significant asymmetry, $z = -4.57$, $p < .001$. This suggests the likelihood of publication bias, as indicated by the asymmetrical appearance of the funnel plot and significant results from the Egger's test of asymmetry. The second funnel plot examined the measure of attrition rate (refer to Figure 12) and the Egger's test was non-significant, $z = 1.13$, $p = .258$. The third funnel plot examined the measure of self-reported PTSD symptom severity (refer to Figure 13) and the Egger's test detected significant asymmetry, $z = -4.68$, $p < .001$. Overall, funnel plots suggest an absence of smaller studies in favour of waitlist, treatment as usual or supportive therapy. The absence of smaller studies may be partly attributed to the selection process as we only included studies with a minimum sample size of 22.

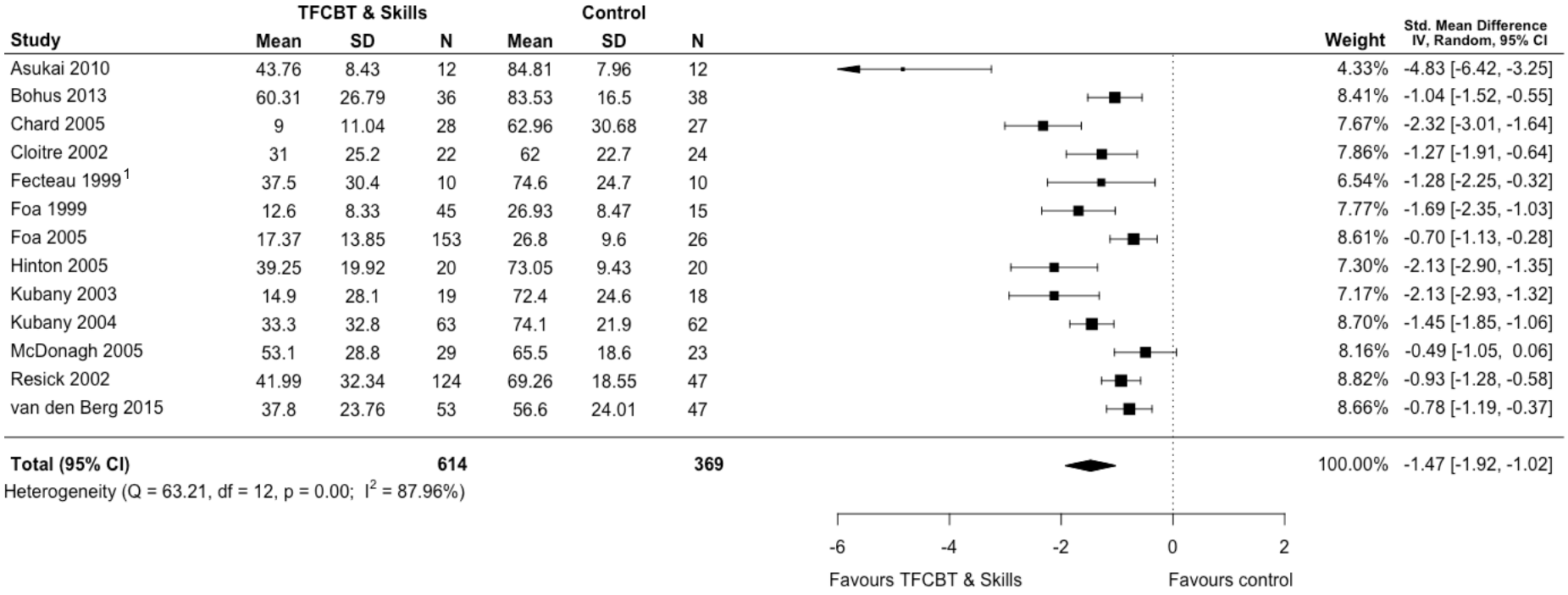

Figure 4. Comparison 1: Combined TFCBT and skills training versus control**;** Outcome: Clinician-rated PTSD symptom severity; Random Effects Model. CI = confidence interval; Std = standardized; TFCBT = trauma-focussed cognitive behavioural therapy.

[1] The study only reported completers' means and standard deviations and excluded dropouts.

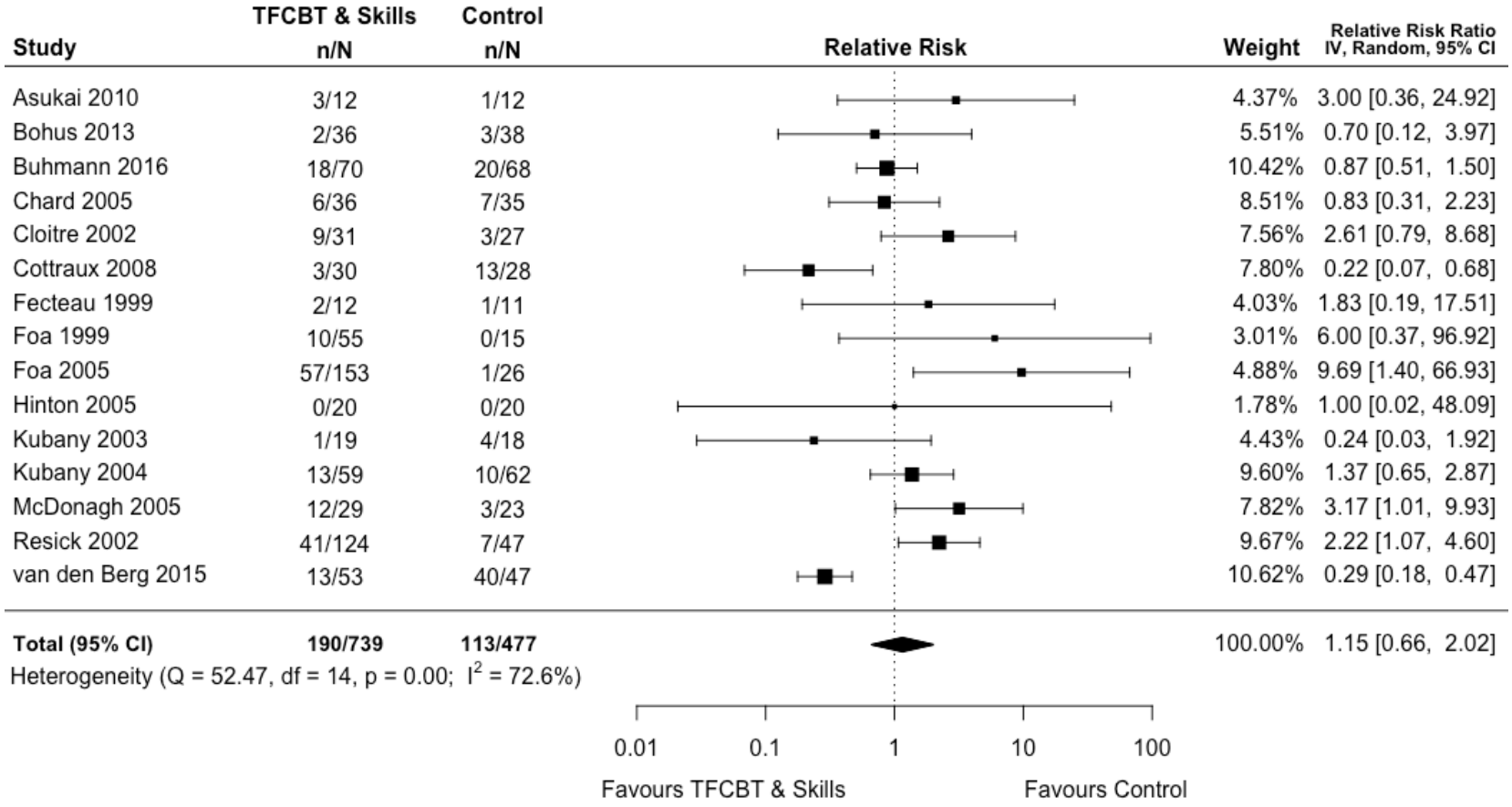

Figure 5. Comparison 1: Combined TFCBT and skills training versus control**;** Outcome: Attrition rate; Random Effects Model. CI = confidence interval; TFCBT = trauma-focussed cognitive behavioural therapy.

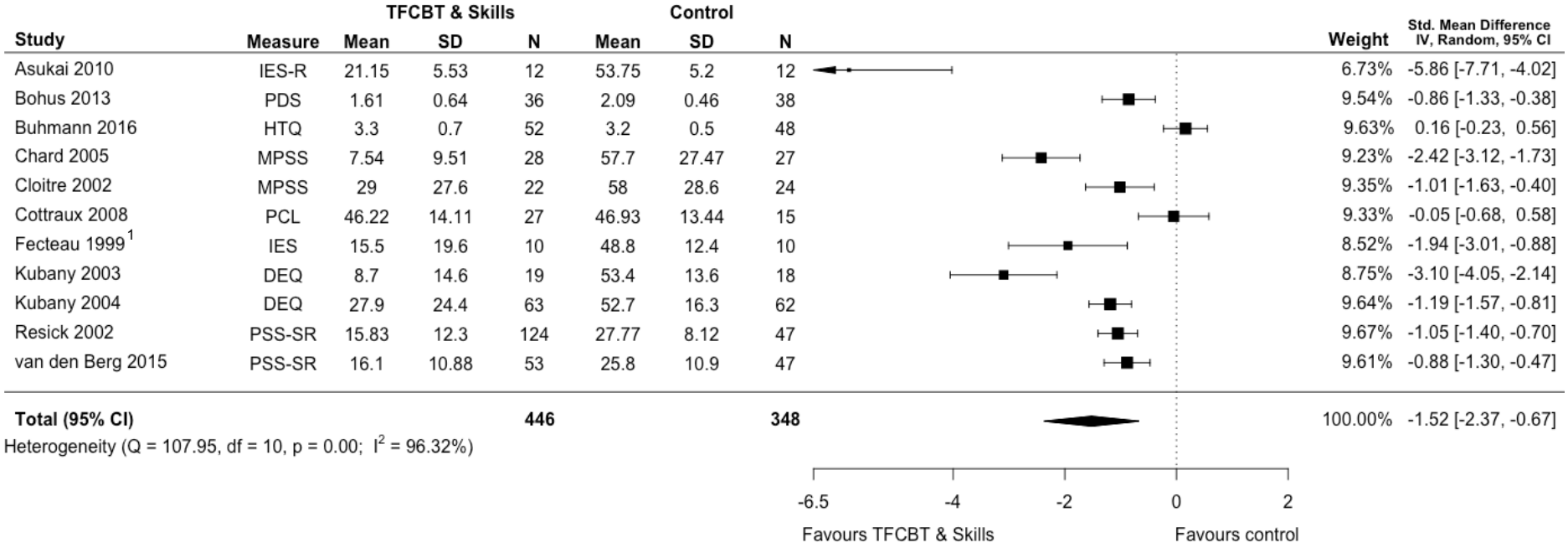

Figure 6. Comparison 1: Combined TFCBT and skills training versus control**;** Outcome: Self-reported PTSD symptom severity; Random Effects Model. CI = confidence interval; Std = standardized; DEQ = distressing event questionnaire; HTQ = harvard trauma questionnaire; IES = impact of events scale; IES-R = impact of events scale-revised; MPSS = modified PTSD symptom scale; PCL = post-traumatic checklist scale; PDS = posttraumatic stress diagnostic scale; PSS-SR = PTSD symptom scale – self-report; TFCBT = trauma-focussed cognitive behavioural therapy.

[1] The study only reported completers' means and standard deviations and excluded dropouts.

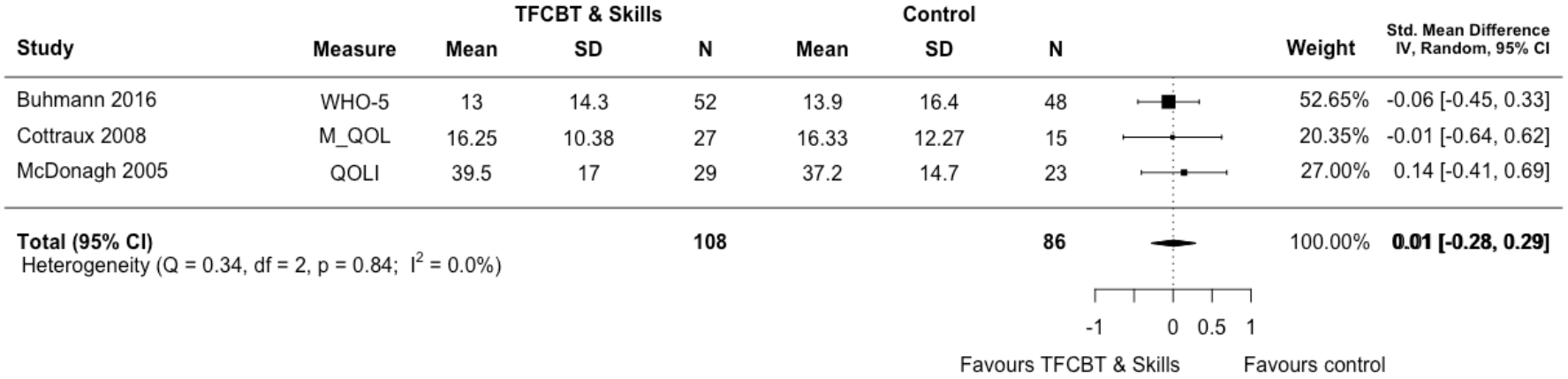

Figure 7. Comparison 1: Combined TFCBT and skills training versus control**;** Outcome: Self-reported quality of life; Random Effects Model. CI = confidence interval; Std = standardized; M_QOL = mark's quality of life scale; QOLI = quality of life inventory; TFCBT = trauma-focussed cognitive behavioural therapy; WHO-5 = world health organization-five well-being index.

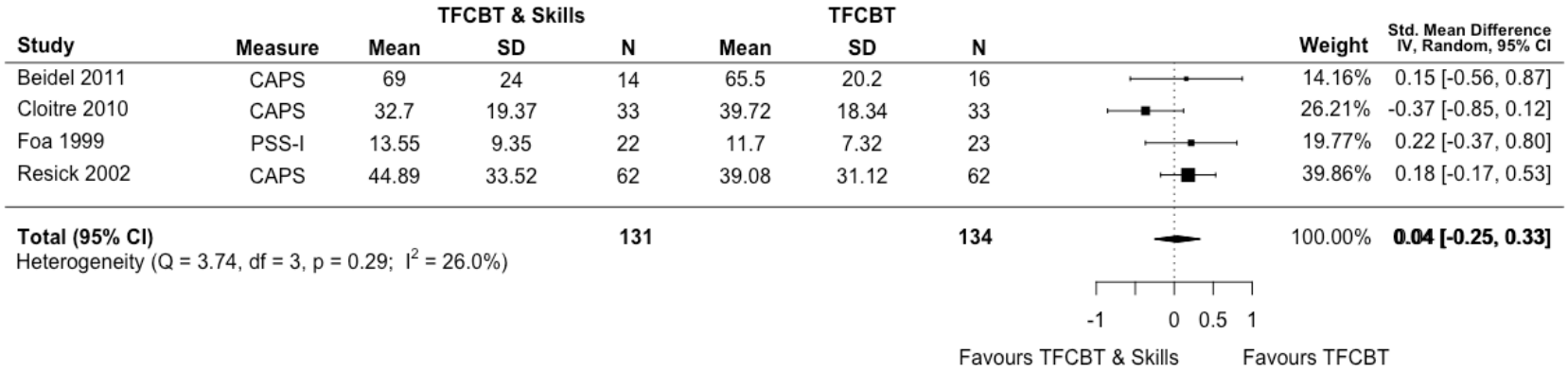

Figure 8. Comparison 2: Combined TFCBT and skills training versus TFCBT-only**;** Outcome: Clinician-rated PTSD symptom severity; Random Effects Model. CI = confidence interval; Std = standardized; TFCBT = trauma-focussed cognitive behavioural therapy.

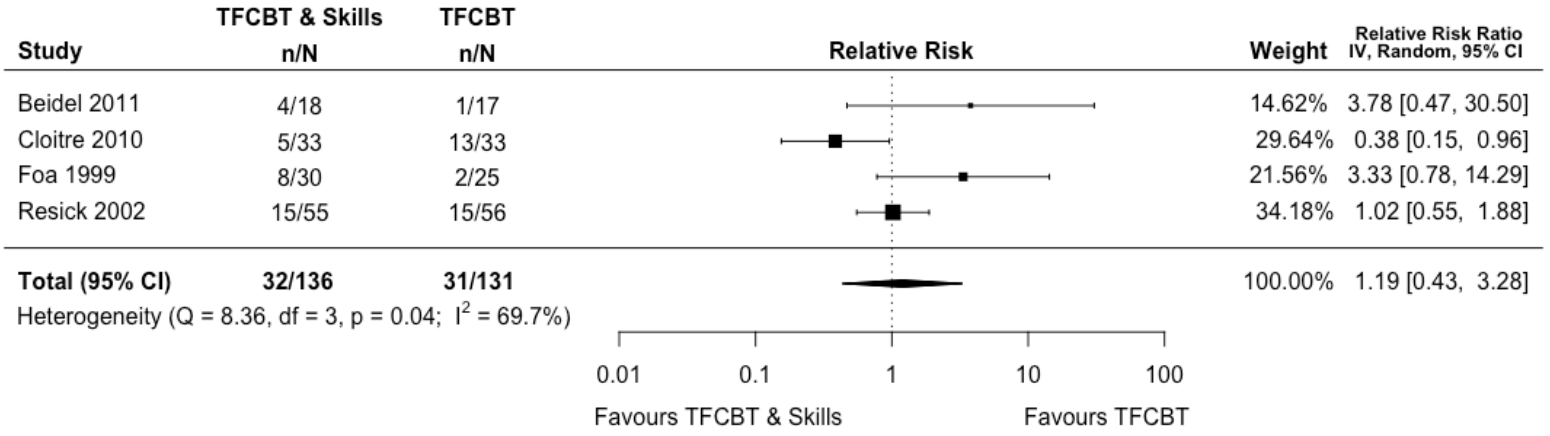

Figure 9. Comparison 2: Combined TFCBT and skills training versus TFCBT-only**;** Outcome: Attrition rate; Random Effects Model. CI = confidence interval; Std = standardized; TFCBT = trauma-focussed cognitive behavioural therapy.

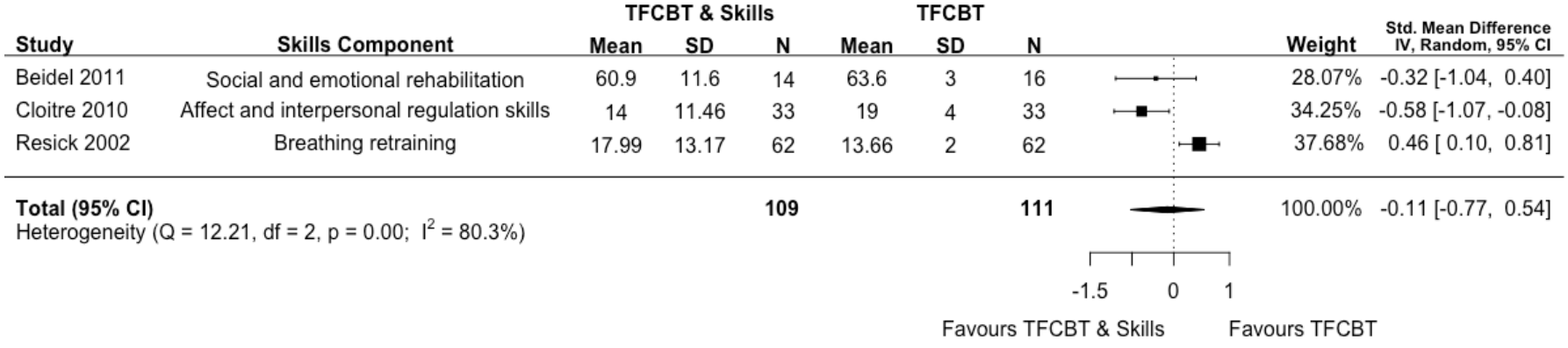

Figure 10. Comparison 2: Combined TFCBT and skills training versus TFCBT-only**;** Outcome: Self-reported PTSD symptom severity; Random Effects Model. CI = confidence interval; Std = standardized; TFCBT = trauma-focussed cognitive behavioural therapy.

Table 3

Subgroup analyses and meta-regression results with potential moderators as predictors
Outcome: Clinician-rated PTSD symptom severity; Random effects model

Predictors	*N*	SMD	95% CI		*p*	*Q*	p^1	Tau^2	I^2
Clinical complexity						1.23	0.267	0.052	19%
Complex	8	-1.26	-1.67	-0.85	<.001				
Non-complex	5	-2.00	-3.25	-0.75	0.0017				
Gender						0.13	0.716	0	0%
Females (≥ 80% of	10	-1.54	-2.12	-0.95	<.001				
sample)	3	-1.35	-2.17	-0.53	0.0012				
Mixed									
Type of skills training						5.72	0.057	0.168	65%
Affect regulation	8	-1.46	-2.24	-0.67	<.001				
Interpersonal	1	-2.32	-3.01	-1.64	<.001				
Affect & interpersonal	4	-1.39	-1.74	-1.04	<.001				
Flexibility of sessions						0.36	0.547	0	0%
Yes	7	-1.72	-2.78	-0.67	0.0013				
No	6	-1.37	-1.85	-0.89	<.001				
Follow up duration	13					0.59	0.444	0.655	89%
Number of sessions	13					0.06	0.807	0.671	89%

Note. SMD = standardized mean difference; CI = confidence interval; *p* = level of significance from subgroup meta-analyses; p^1 = level of significance for moderator; *Q* = Q-test statistic, I^2 = percentage of variation attributed to heterogeneity.

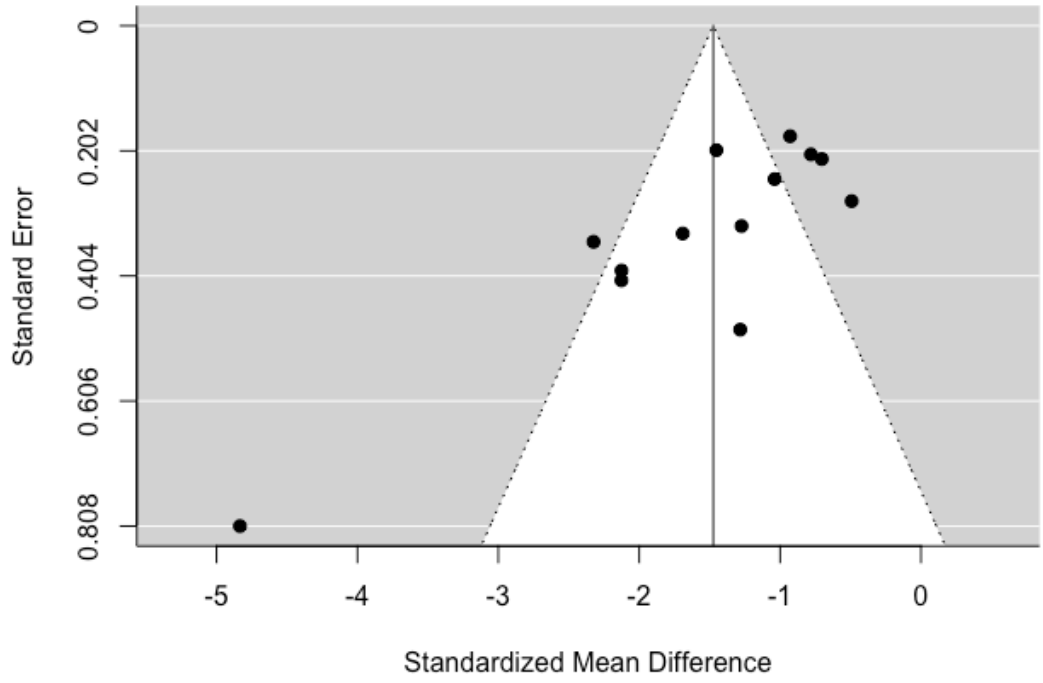

Figure 11. Funnel plot of comparison 1: Combined TFCBT and skills training versus waitlist/treatment as usual/ supportive therapy, outcome – clinician-rated PTSD symptom severity.

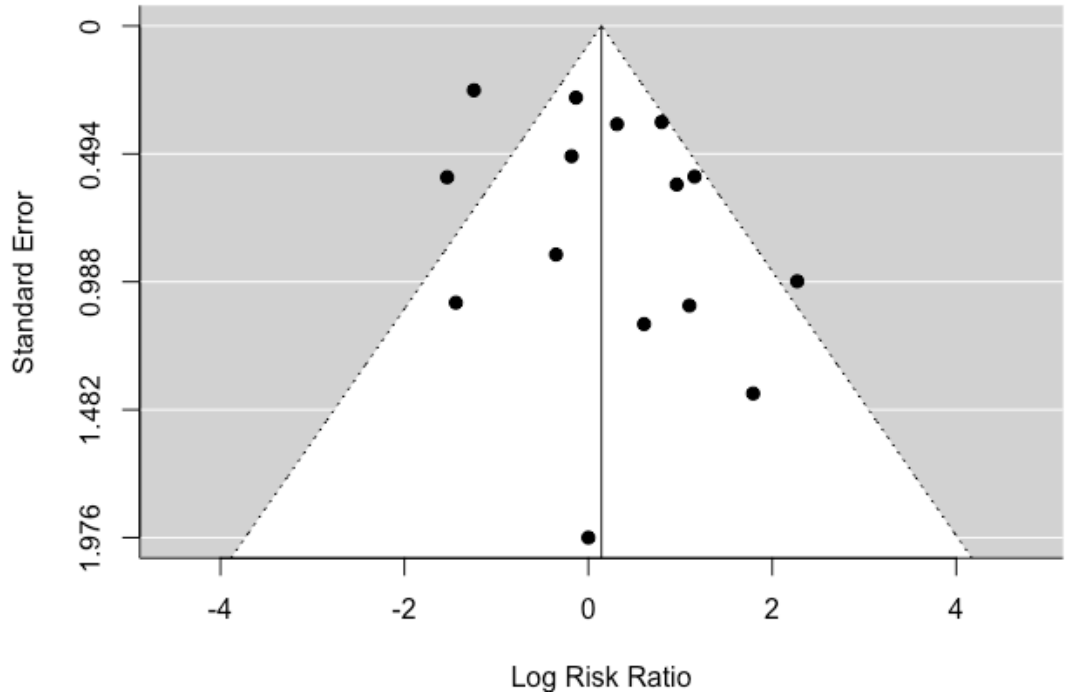

Figure 12. Funnel plot of comparison 1: Combined TFCBT and skills training versus waitlist/treatment as usual/ supportive therapy, outcome – attrition rate.

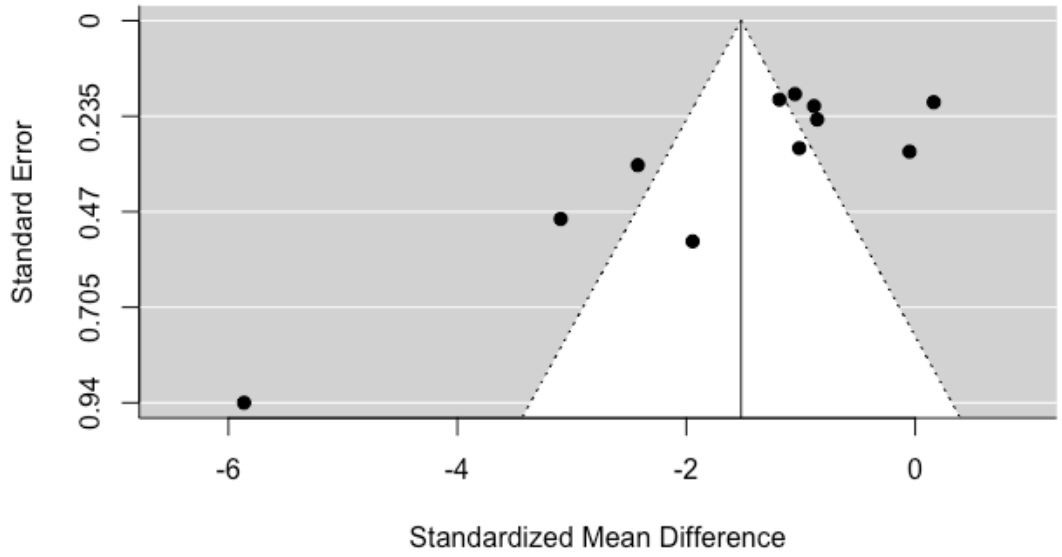

Figure 13. Funnel plot of comparison 1: Combined TFCBT and skills training versus waitlist/treatment as usual/ supportive therapy, outcome – self-reported PTSD symptom severity.

Discussion

The current study examined the efficacy and tolerability of combined TFCBT and skills training and examined potential moderators which may account for the treatment effects observed. Seventeen studies of 1323 participants were included for this review. Combined TFCBT and skills training were superior to control conditions in reducing both clinician-rated and self-reported PTSD symptom severity posttreatment. In line with previous meta-analyses on TFCBT (Bisson et al., 2013; Ehring et al., 2014), combined TFCBT and skills training had a strong positive effect size on the reduction of PTSD symptom severity (i.e., both clinician-rated and self-reported) at posttreatment. There was no difference between combined TFCBT and skills training and control groups on measures of quality of life at posttreatment. Attrition rates did not differ between combined TFCBT and skills training group and control conditions. Comparisons between combined TFCBT and skills training and TFCBT-only could only be considered as preliminary due to the small number of studies available. Based on preliminary comparisons, there was no strong evidence to suggest that additional skills training provided additional benefit in terms of PTSD

symptom reduction, attrition rate and quality of life. There was considerable unexplained heterogeneity detected in these comparisons and cautious interpretation of findings were necessary. Clinical complexity, flexibility of treatment, gender, number of intervention sessions, follow up duration and type of skills training did not significantly account for the heterogeneity observed across studies.

However, the quality of the body of evidence was low given the limitations in study design and unexplained heterogeneity of results. Several limitations in study design were identified and contributed to the downgrading of randomised trial evidence, namely: (1) the lack of blinding of participants and personnel, (2) the lack of controlling for treatment expectancy, and (3) presence of unclear risk associated with researcher allegiance.

Potential Explanations for Heterogeneity in TFCBT Studies

Unexplained heterogeneity across studies reduces the quality of evidence and the validity of findings. In clinical contexts, the heterogeneity of chronic PTSD is commonly observed (Zoellner, Pruitt, Farach, & Jun, 2014). Given that the diagnostic criteria of PTSD in the DSM consist of 17 to 20 symptoms (American Psychiatric Association, 2013), the included TFCBT studies may consist of heterogenous samples with varying degrees of symptom severity across the diagnostic criteria. Variation in the inclusion and exclusion criteria across included studies may also contribute to the high levels of heterogeneity observed. For example, the strict exclusion criteria in Asukai et al., (2010) excluded individuals with past childhood abuse. This may indirectly contribute to the superior response to TFCBT and skills training compared to other study samples exposed to childhood trauma. In contrast with other included studies, van den Berg et al., (2015) included individuals with severe mental illness, such as schizophrenia and psychosis. The study reported less variability in estimated effect sizes on outcome measures (i.e., clinician-rated and self-reported PTSD symptom severity, attrition rate) compared to most studies. Perhaps, individuals with severe mental illness are a distinct clinical

group and respond differently to combined TFCBT and skills training. Thus, heterogeneity may be attributable to the distinct clinical groups resulting from the variation in inclusion and exclusion criteria between studies.

Although the magnitude of the pooled effect size of combined skills training and TFCBT on clinician-rated PTSD symptom severity was large, two studies (Foa et al., 2005; McDonagh et al., 2005) had considerably smaller effect sizes. Both studies had greater attrition rates in active treatment arms compared to waitlist and used pretreatment CAPS scores to substitute posttreatment scores in intent to treat analysis. The combination of the conservative method of handling missing data and uneven attrition rate between groups may have contributed to the smaller effect sizes observed in the two studies.

The range of estimated effect sizes (i.e., standardized mean difference) was observed to be more varied in studies with considerably smaller sample size per condition (i.e., 12 participants or less per condition; Asukai et al., 2010; Fecteau & Nicki, 1999). Statistically, smaller sample sizes were expected to have greater variability and result in more extreme effect sizes. Furthermore, it has been noted that the amount of weight given to smaller studies were proportionately greater in the random effects model compared to fixed effect models (Higgins & Green, 2011). Therefore, the influence of small study effects could have contributed to the large heterogeneity observed.

In addition, cultural influences may be a potential moderator of treatment effects. The majority of included studies were conducted in North America (N = 12) and Europe (N = 4). Interestingly, Asukai et al. (2010), a Japanese study, reported considerably larger effect sizes compared to other studies. Possibly, the efficacy of TFCBT may be moderated by cultural differences such as power differences in social hierarchies and the degree of mental health stigma.

Limitations

The presence of limitations at study, outcome and review levels warrant conservative interpretation of the current findings. At study level, we did not extract the stage of treatment where skills training was implemented. This was not feasible as many studies did not report the specific treatment stage where skills training was implemented or reported the use of skills training throughout treatment (e.g. breathing retraining taught in the first session and used as an affect regulation skill during exposure to traumatic memory). Thus, we were unable to make inferences on the efficacy of phased-based treatment for chronic PTSD.

At outcome level, the use of attrition rate as an indirect measure of treatment tolerability was limited. Non-completers represent a heterogenous group – where it does not solely represent individuals who have difficulties tolerating TFCBT. Practical barriers to treatment exist, such as childcare needs, accessibility of treatment site and mobility difficulties. Therefore, there is an urgent need for the direct assessment of treatment tolerability. Qualitative feedback from non-completers and qualitative studies on reasons for dropout can provide more accurate measures of treatment tolerability. We recommend future RCTs to document reasons for dropout to allow for such qualitative investigations.

In addition, we did not examine the long-term efficacy of combined TFCBT and skills training. The practice and generalisation of affect regulation and interpersonal skills may provide clinical benefits over time. As outcomes of interest were of a narrow scope in the current study, we did not examine the wider impacts of affect regulation and interpersonal skills training on overall functioning or well-being. Additional comparisons with follow up data are necessary in understanding the trajectory of therapeutic gains.

At review level, publication bias was likely to be present in the review, as it was not feasible to conduct additional searches into “grey” literature such as dissertations and conference papers due to the time constraints. Furthermore, a

separate reviewer was not involved in the review process as it was beyond the scope and feasibility of the project. Therefore, the process of systematic literature search, study selection, data extraction and assessment of risk of bias was undertaken by a single reviewer. This increases the likelihood of errors and subjective bias.

The effect of methodological decisions underpinning the review process were not examined through sensitivity analyses. Methodological decisions which may affect the findings of the current study may include: (1) the inclusion of RCTs with multicomponent treatment beyond skills training and individual TFCBT (e.g., access to social worker, non-specific group interventions such as music and art therapy groups), (2) the inclusion of interventions implemented through translators, (3) the inclusion of studies with the minimum sample size of 22, (4) the selection of random effects instead of fixed-effect model, (5) the combination of waitlist, treatment as usual and placebo as a control arm and (6) the inclusion of RCTs using non-intent to treat methods. As sensitivity analyses were manpower intensive, it was not feasible to repeat the meta-analysis to test the effects of the above methodological decisions. As treatment as usual and waitlist conditions are characteristically distinct and could affect the estimated effect size of TFCBT, secondary analysis contrasting treatment as usual and waitlist conditions should be considered in future meta-analyses.

Furthermore, the presence of unclear risk may threaten the validity of the study's conclusion. Areas of unclear risk include researchers as developers of the psychological intervention, a single therapist providing treatment to all participants and therapists administering treatment to both treatment arms. It is unclear whether these methodological characteristics had influence on treatment outcomes, and there is a need for researchers to actively reduce the risk of bias. Future RCTs can reduce the risk through transparent reporting of the authors and therapists' personal

interest and position of specific therapeutic models, measure and statistically control for the therapist's expectations of treatment efficacy.

Conclusion

The study is the first systematic and quantitative review to synthesize the treatment efficacy and tolerability of combined skills training and TFCBT for chronic PTSD. Findings suggest that combined skills training and TFCBT is an effective intervention for chronic PTSD, but there was no strong evidence to suggest that it is superior to TFCBT-only. Implications for clinical practice and research were summarised below.

Implications for Clinical Practice

1. Combined TFCBT and skills training showed large positive effects in reducing PTSD symptoms in individuals with chronic PTSD compared to waitlist, treatment as usual and placebo at posttreatment. There was no strong evidence to suggest that combined TFCBT and skills training incurred greater attrition than waitlist or treatment as usual groups. However, the low quality of evidence, presence of publication bias and significant unexplained heterogeneity warrant cautious interpretation of findings.
2. There was no strong evidence to suggest the added benefit of skills training in optimising the efficacy and tolerability of traditional TFCBT interventions for chronic PTSD. However, the conclusion is limited given the small number of comparative studies between combined TFCBT and skills training and TFCBT-only.

Implications for Research

1. More high-quality observational studies and comparative RCT studies are necessary to support the clinical rationale of skills training for chronic PTSD.

2. Direct assessment of treatment tolerability, reporting of reasons for dropout and qualitative studies on reasons for dropout can provide more precise measurement of treatment tolerability.
3. In order to reduce the risk of therapist allegiance influencing study outcomes, we recommend future RCTs to report authors' and therapists' personal interest and alignment towards specific therapeutic models, measure and statistically control for therapist's and client's expectations of treatment efficacy.

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Part 2: Empirical Paper

Altered Intrinsic Connectivity in the Default Mode Network and Central Executive Network in Borderline Personality Disorder and Low Resilient Functioning

Abstract

Background. Recent synthesis of neuroimaging evidence proposed that aberrant intrinsic functional connectivity in three large-scale neurocognitive networks; the default mode network, salience network, and central executive network, contributes to psychopathology. Current findings from rest-state functional magnetic resonance imaging (fMRI) studies on borderline personality disorder (BPD) were inconsistent and limited to BPD-specific differences.

Objective. The study aims to identify resting-state intrinsic functional connectivity differences in BPD. The secondary aim was to explore resting-state intrinsic functional connectivity associated with resilience.

Method. Resting-state fMRI scans were obtained from 66 participants (29 healthy controls and 37 individuals with BPD). Group independent component analysis was conducted to examine intrinsic functional connectivity within and between the default mode network, salience network and central executive network associated with group and resilient functioning. Resilience was quantified as the residual resulting from the difference between the participant's predicted and observed psychopathology symptoms, based on the severity of their self-reported childhood trauma. The participant's predicted psychopathology symptoms were derived from a linear regression model which examined the relationship between psychopathology and childhood trauma (N = 198; 111 individuals with BPD and 87 healthy controls).

Results. Healthy individuals showed increased intrinsic functional connectivity within the bilateral precuneus compared to individuals with BPD, $p < .05$, false discovery rate (FDR) corrected, and these group differences remained after controlling for childhood trauma and psychopathology symptoms. Higher resilient functioning in the healthy individuals was associated with decreased intrinsic functional connectivity within the left ventral central executive network, $p < .05$, FDR corrected. Furthermore, the association between decreased intrinsic functional

connectivity in the anterior cingulate and high resilient functioning were only replicated in the healthy individuals and not in the BPD group.

Conclusion. Preliminary findings suggest different patterns of intrinsic functional connectivity within the default mode network and central executive network between healthy individuals and individuals with BPD. Implicated regions were associated with self-referential processing, autobiographical memory and cognitive control. The findings contribute to future investigations on BPD-specific differences and general resilience mechanisms in intrinsic brain architecture.

Introduction

Borderline Personality Disorder

Borderline personality disorder (BPD) is a debilitating condition associated with the need for intensive treatment, use of extensive healthcare resources and up to 10% completed suicide rate (American Psychiatric Association, 2013; Grant et al., 2008). BPD is characterized by a "pervasive pattern of instability of interpersonal relationships, self-image, and affects, and marked impulsivity that begins by early adulthood and is present in a variety of contexts" (American Psychiatric Association, 2013, p. 663). Given the high impact of BPD on individuals and the systems surrounding them, it is necessary to investigate the pathophysiology of BPD to better inform intervention. A recent synthesis of neuroimaging evidence proposed that aberrant intrinsic functional connectivity within and between three large-scale neurocognitive networks contribute to psychopathology (Menon, 2011).

Intrinsic Functional Connectivity Networks

Before elaborating on the neurocognitive networks implicated in BPD, a brief description of intrinsic functional connectivity will be provided. Intrinsic functional connectivity networks are fundamental, large-scale networks of functionally connected, interdependent brain areas (Menon, 2011). Intrinsic functional connectivity networks include a set of large-scale functionally connected brain networks that can be captured in either resting state or during task engagement (Laird et al., 2011). Recent neuroimaging evidence suggested that intrinsic functional activity accounts for a significant 60 to 80% of overall brain energy consumption, which is significantly greater than evoked brain activity during task engagement (Raichle & Mintun, 2006). Indeed, researchers estimated that task-related brain activations account for less than 5% of overall brain energy consumption (Raichle & Mintun, 2006). In addition, there is evidence that intrinsic

functional connectivity networks act as a “basic operating system” for task-related brain activation (Keller et al., 2011), where intrinsic brain architecture sustains and updates the brain’s range of task-relevant functional responses.

Synthesising neuroimaging evidence from multiple disorders, Menon (2011) proposed that aberrant functional connectivity within and between three intrinsic networks contribute to cognitive and affective dysfunction across multiple disorders, such as autism, schizophrenia, anxiety, depression and dementia. Known as the triple network model, the three networks of interest are the default mode network, salience network and central executive network.

In the next section, specific brain regions and functions associated with each intrinsic network were elaborated. In addition, neuroimaging findings associated with BPD were reviewed using the triple network model. As the scope of the current study was limited to resting-state intrinsic functional connectivity, only resting-state functional connectivity studies were included. The review of resting-state functional connectivity differences in BPD was informed by the systemic review and meta-analysis conducted by Visintin et al. (2016) and a scoping search conducted by the author to include more recent resting-state studies. There were ten studies investigating resting-state functional connectivity in BPD to date (Das, Calhoun, & Malhi, 2014; Doll et al., 2013; Duque-Alarcón, Alcalá-Loranzo, González-Olvera, Garza-Villarreal, & Pellicer, 2019; Krause-Utz et al., 2014; Lei et al., 2017; O’Neill et al., 2015; Sarkheil, Ibrahim, Schneider, Mathiak, & Klasen, 2019; Salvador et al., 2016; Taha, 2015; Wolf et al., 2011).

Given that intrinsic functional networks are a recent development, six studies used seed-based analysis to examine the resting-state functional connectivity between selected brain regions (Duque-Alarcón et al., 2019; Krause-Utz et al., 2014; Lei et al., 2017; O’Neill et al., 2015; Sarkheil et al., 2019; Taha, 2015). The seed-based analysis approach selects a priori brain regions, known as seeds, to examine functional connectivity from the selected seeds to other brain regions.

Since the areas selected differ across studies, findings from seed-based analysis can be hard to synthesize. More recent methods such as independent component analysis (ICA) permitted researchers to take a whole-brain network approach in examining intrinsic functional connectivity specific to BPD. Nevertheless, seed-based studies were considered in the review below because they add to our understanding of aberrant functional connectivity associated with BPD.

Default Mode Network

The default mode network consists of the medial prefrontal cortex, posterior cingulate cortex and precuneus and extends to the medial temporal lobe (i.e., the hippocampus) and angular gyrus (Menon, 2011). Traditionally, the default mode network was viewed as a surveillance system which monitored our internal and external environment, which allowed us to react flexibly and effectively. The default mode network showed increased functional connectivity at rest and decreased functional connectivity during task engagement, and this observation was replicated across numerous resting-state studies in the healthy population (Raichle et al., 2001; Spreng, Mar, & Kim, 2008). Contemporary research also indicated the significant role of the default mode network in self-referential and autobiographical processes (Menon, 2011).

Increased functional connectivity in BPD involving the medial prefrontal cortex was reported in five studies (Das et al., 2014; Duque-Alarcón et al., 2019; Salvador et al., 2016; Taha, 2015; Wolf et al., 2011). A meta-analysis of seven resting-state functional connectivity studies in BPD also reported increased functional connectivity in the BPD group relative to healthy controls in the medial prefrontal cortex, anterior cingulate and precuneus (Visintin et al., 2016). Aberrant intrinsic functional connectivity in the default mode network was proposed to reflect significant difficulties in self-referential processes, such as distorted views of the self and others typically observed in individuals with BPD (Visintin et al., 2016).

Aberrant intrinsic functional connectivity in the other nodes such as the anterior cingulate and precuneus associated with BPD were inconsistent. Two studies reported decreased functional connectivity in the precuneus (Das et al., 2014; Lei et al., 2017) and one study reported increased functional connectivity in the precuneus (O'Neill et al., 2015). Altered functional connectivity in the precuneus was speculated to be associated with extensive internal thoughts related to the self (O'Neill et al., 2015) and impaired integration of information to form a stable internal representation of the self (Das et al., 2014; Lei et al., 2017). However, the inconsistent direction of altered intrinsic functional connectivity in the precuneus may be attributed to the use of different analysis methods across the three studies mentioned above and the findings could only be considered preliminary.

Salience Network

The salience network mainly comprises the anterior insula, posterior insula and anterior cingulate (Menon, 2011). The insula plays an important role in detecting salient events from a large stream of sensory stimuli, activating autonomic responses and initiating control signals to engage higher cognitive processes such as attention (Menon & Uddin, 2010). In addition, the insula plays a prominent role in interoceptive awareness: the awareness of bodily processes and subjective emotional states, such as anxiety and disgust (Critchley, Wiens, Rotshtein, Öhman, & Dolan, 2004; Menon & Uddin, 2010). Increased activation in the salience network was observed when healthy participants viewed others in pain (Singer, 2006). In contrast, the anterior cingulate plays an important role in response selection, as it is associated with sensory and motor areas (Menon & Uddin, 2010). In combination, the insula and anterior cingulate identifies relevant internal and external sensory information and guides behaviour (Menon, 2011). In addition, it is important to note that regions of the anterior cingulate overlap with the default mode network; specifically, the ventral anterior cingulate showed increased functional connectivity

at rest and showed significant functional connectivity with the posterior cingulate cortex and medial prefrontal cortex (Greicius, Krasnow, Reiss, & Menon, (2003).

Three studies reported increased functional connectivity in the salience network in individuals with BPD compared to healthy controls (Doll et al., 2013; Sarkheil et al., 2019; Wolf et al., 2011). Researchers speculated that increased functional connectivity in the salience network in individuals with BPD may reflect heightened negative emotional states and emotional sensitivity presented by individuals with BPD.

Central Executive Network

The central executive network, also known as the frontoparietal network, comprises the dorsolateral prefrontal cortex and posterior parietal cortex (Menon, 2011). Consistent neuroimaging evidence has established the central role of the central executive network in cognitive control, which refers to the ability to select actions consistent with internally driven goals (Koechlin & Summerfield, 2007; Seeley et al., 2007).

Four resting-state studies reported aberrant functional connectivity between the default mode network and the central executive network, with most studies reporting an increased functional connectivity between these networks (Duque-Alarcón et al., 2019; Lei et al., 2017; O'Neill et al., 2015; Taha, 2015). However, the specific brain regions varied across studies.

Only one study reported aberrant functional connectivity between the salience and central executive network. Doll et al. (2013) reported that individuals with BPD displayed greater functional connectivity between the salience network and the central executive network and between the salience network and the default mode network compared to healthy controls. In contrast, healthy controls displayed greater functional connectivity between the central executive network and the salience network and between the central executive network and the default mode

network (Doll et al., 2013). These findings led the researchers to conclude that between-network connectivity was dominated by connections with the salience network in individuals with BPD (Doll et al., 2013). Another study reported that reduced functional connectivity between the salience network and the central executive network was significantly associated with greater impulsivity in individuals with BPD (Das et al., 2014). This may reflect heightened emotional processing and impairments in cognitive reasoning, distancing and control observed in individuals with BPD (Doll et al., 2013).

In summary, the triple network comprises large-scale neurocognitive networks proposed to be the “core” networks implicated in BPD. The default mode network drives cognitive processes related to the self, such as self-referential and autobiographical processes. The salient network is implicated in sensory and emotion processing, such as interoceptive awareness and empathy. Finally, the central executive network is associated with higher order cognitive function such as cognitive control. These three neurocognitive networks underlie self, emotion and cognitive processing and are fundamental neural processes that are associated with psychopathology. Current resting-state functional connectivity studies revealed significant alterations within and between the default mode, salience and central executive networks in individuals with BPD. The ten resting-state studies reviewed above provided preliminary evidence of altered intrinsic networks across the three core neurocognitive networks relevant to impairments in emotional and cognitive processes in BPD.

Critique on Current Resting-State Studies on BPD

However, there are three main methodological shortcomings embedded in the current literature. Firstly, nearly half of the resting-state studies utilised a small sample size of 20 participants or less per group (Das et al., 2014; Doll et al., 2013; Krause-Utz et al., 2014; Wolf et al., 2011). Studies with small sample sizes are

susceptible to inflated effect size estimates, which increase the risk of false positives (Button et al., 2013).

Secondly, six out of ten of the resting-state studies reviewed here utilised the seed-based analysis approach (Duque-Alarcón et al., 2019; Krause-Utz et al., 2014; Lei et al., 2017; O'Neill et al., 2015; Sarkheil et al., 2019; Taha, 2015). The scope of functional connectivity findings in seed-based analysis was limited by the prior selection of brain areas, which may be potentially biased (Lv et al., 2018). Given that many brain regions do not have specific distinct functions, inferences based on the subjective selection of specific brain regions are speculative (Schleim & Roiser, 2009). Since cognitive and/or psychological processes are rarely exclusive to a specific brain region, a network perspective was necessary.

Thirdly, the narrow focus on BPD-specific neural correlates failed to elucidate the neural resources that protect individuals from psychopathology. The development of psychopathology is not limited to dysfunction in disorder-specific mechanisms, but impairments in general resilience mechanisms as well (Kalisch, Müller, & Tüscher, 2015). If intrinsic functional connectivity networks are the brain's basic operating system, they are potentially relevant in resilience mechanisms that protect individuals from developing psychopathology. Given that the triple network had been implicated in psychopathology and BPD, these intrinsic networks may play an important role in resilience mechanisms.

In the next section, the concept of resilience, the relationship between early adversity and psychopathology and the current neuroimaging evidence associated with resilience were detailed.

Resilience, Early Adversity and Psychopathology

Resilience is defined as "an interactive concept that is concerned with the combination of serious risk experiences and a relatively positive psychological outcome despite those experiences" (Rutter, 2006, p. 1). Two conditions are

essential to the construct of resilience: first, exposure to significant adversity; second, positive psychological outcome, such as the absence of psychopathology symptoms. Thus, the argument follows that resilience is an empirically observable outcome of the absence of psychopathology despite the experience of significant adversity (Kalisch et al., 2015).

The experience of significant adversity, such as childhood trauma, plays a significant role in BPD (McLaughlin et al., 2010). In a study of 209 inpatients diagnosed with BPD, more than half of the inpatients reported being sexually abused or physically abused in early childhood and adolescence (Zanarini et al., 2002). In another large study of 653 individuals with a personality disorder diagnosis, the BPD group reported the highest rate of traumatic exposure and posttraumatic stress disorder (PTSD) comorbidity (Yen et al., 2002). In addition, the researchers found that the severity of clinical symptoms is significantly correlated with the severity of traumatic exposure (Yen et al., 2002). Furthermore, within clinical populations, individuals with childhood trauma reported greater distress, functional impairment, comorbidity and chronicity of symptoms as compared to individuals with no childhood trauma (Danese & Baldwin, 2017).

However, studies also showed that not all individuals exposed to childhood trauma develop psychopathology. An epidemiological study with a 30-year follow-up reported that 45% of individuals who experienced childhood maltreatment did not develop psychopathology in adulthood (Collishaw et al., 2007). Given that early adversity is experienced in individuals with and without BPD, how do we explain individual differences in the development of psychopathology? Potentially, the combination of impairments in resilience mechanisms, BPD-specific dysfunction in neural mechanisms and high trauma exposure may explain the individual differences in the developmental trajectory of psychopathology.

Intrinsic Functional Connectivity and Resilience

However, little is known about the role of intrinsic functional connectivity and resilience in the context of adversity. In a systematic review of current neuroimaging findings associated with resilience to stress, the default mode network and salience network were implicated (van der Werff, van den Berg, Pannekoek, Elzinga, & van der Wee, 2013b). The systematic review identified structural, resting-state and task-based functional neuroimaging evidence associated with resilience; two studies relevant to resting-state intrinsic functional connectivity are elaborated below.

van der Werff et al. (2013a) conducted a preliminary rest-state functional magnetic resonance imaging (fMRI) study that investigated functional connectivity in the default mode network and salience network among three groups: (1) healthy individuals who reported having experienced childhood maltreatment and had no mental health diagnosis (i.e., resilient group); (2) individuals with mental health diagnosis (i.e., depression and/or anxiety disorders) who had experienced childhood maltreatment (i.e., vulnerable group); and (3) healthy individuals with no childhood maltreatment (i.e., healthy control group). Using seed-based analysis, the researchers found that the resilient group displayed decreased functional connectivity between the left dorsal anterior cingulate (part of the default mode network) and the lingual gyrus and occipital fusiform gyrus compared to the vulnerable group and healthy control group (van der Werff et al., 2013a). As each group had a sample size of 11, the findings were preliminary; the results suggested that functional connectivity in the default mode network may be associated with resilience to early adversity. However, the severity of early adversity was not accounted for in the study and the distribution of childhood trauma reported by the resilient group was greater than the distribution reported by the vulnerable group. Given that individuals in the resilient group were exposed to varied degrees of childhood maltreatment, the degree of resilient functioning may differ within the resilient group. Therefore, it may be too simplistic to group individuals as “resilient”

without quantitatively accounting for the degree of childhood maltreatment and symptom severity.

Another study examined the relationship between regional homogeneity (i.e., the degree of coherence of low frequency fluctuations in specific brain regions) and resilience. Increased regional homogeneity in the salience network was associated with lower psychological resilience in healthy individuals (Kong, Wang, Hu, & Liu, 2015). Specifically, increased regional homogeneity in the bilateral insula, right dorsal and rostral anterior cingulate cortex predicted lower psychological resilience in healthy individuals (Kong et al., 2015). Although the findings seemed to affirm the involvement of the salience and default mode networks in resilience, it is crucial to note that the study relied on self-report measures of resilience (i.e., the Connor-Davidson Resilience Scale). Potentially, self-report measures of resilience may measure traits like optimism, which may be a mediating variable for positive adaptation instead of resilience itself. In addition, higher scores on self-report measures may not transfer to positive psychological outcomes (i.e., the absence of psychopathology) in the context of adversity. Furthermore, the study was limited to the healthy population and neural mechanisms associated with resilience may not be transferable in the BPD population.

In summary, the current state of resting-state neuroimaging findings associated with resilient functioning is in the early stages of development and constrained by limited studies. Given the flaws in the measurement of resilience in the two studies reviewed above, we do not know if the aberrations found in the resting-state intrinsic functional connectivity in the default mode network and salience network are associated with resilient functioning. Furthermore, the studies reviewed above and in the systematic review by van der Werff et al. (2013b) did not examine the BPD population, where resilient functioning was expected to be low, while trauma exposure was expected to be high. The study of neurobiological contributions to resilient functioning was limited to Axis I disorders of the *Diagnostic*

and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), such as PTSD, anxiety and depression. To gain a comprehensive understanding of neurobiological mechanisms associated with resilient functioning, individuals with global and severe maladaptive functioning, such as the BPD population, should be included in resilience research.

Study Rationale

Two constructs were of interest to the current study; resilient functioning and BPD. Both constructs converge on childhood trauma, where early adversity is prominent and considered in the context of current functioning. Both constructs diverge in outcome, where severe psychopathology is observed in the BPD population and low psychopathology is observed in healthy "resilient" populations. Given that childhood trauma is experienced across the two populations and individual differences are present in outcomes (i.e., psychopathology), the current study aims to address the research gap by including the BPD population in resilience research and examine individual differences in the development of psychopathology in the context of childhood trauma.

Study Aims and Hypotheses

The current study aimed to: (1) identify resting-state intrinsic functional connectivity network differences between individuals with BPD and healthy individuals, (2) explore intrinsic networks associated with resilient functioning, and (3) explore whether intrinsic networks associated with resilience were similar or different in individuals with BPD compared to healthy individuals.

Based on the previous neuroimaging studies on BPD reviewed above, we expected the following intrinsic functional connectivity profile specific to BPD: (1) increased intrinsic functional connectivity within the default mode network, particularly regions such as the medial prefrontal cortex and anterior cingulate, and (2) increased intrinsic functional connectivity within the salience network. In line with

the findings from van der Werff et al. (2013a), we hypothesized that higher resilient functioning was associated with decreased intrinsic functional connectivity within the anterior cingulate. Given that this was an exploratory study on resilient functioning in individuals with BPD and healthy individuals, we expected intrinsic functional connectivity associated with resilient functioning to differ between the healthy controls and the BPD group. Specifically, we hypothesized that decreased intrinsic functional connectivity within the anterior cingulate would be observed in healthy individuals with high resilient functioning, but not in the BPD group with high resilient functioning.

Since resilient functioning is an empirically observable outcome of an absence of psychopathology in the context of adversity, the current study examined the relationship between self-reported general psychopathology symptoms and self-reported childhood traumatic experience across a large sample of healthy individuals and individuals with BPD. Resilient functioning was quantified as the difference between predicted general psychopathology symptoms and observed psychopathology symptoms given the individual's reported childhood trauma. This yielded an index of resilient functioning from which we could ascertain the degree to which an individual's current functioning is better or worse than expected given their self-reported experience of childhood trauma. We used a data-driven approach to measure resilient functioning that was adapted from Overstreet et al. (2017) and van Harmelen et al. (2017). This measure of resilient functioning emphasised the outcomes (i.e., degree of psychopathology symptoms) instead of self-reported resilience to adversity, which is more likely to be biased. Instead of using specific measures of personality psychopathology symptoms such as the Personality Assessment Inventory (Morey, 1991), the study used general psychopathology symptoms as a broader measure of psychological outcome. The intention was to examine broad psychological outcomes, which may be more relevant to both healthy individuals and individuals with BPD.

Group independent component analysis (GICA) was selected as this study used a multivariate, data-driven, whole-brain network approach to examine intrinsic functional connectivity. Instead of examining simple pairwise correlations between pre-selected voxels in seed-based analysis, GICA takes into consideration the relationship between all voxels. Previous literature suggested that the GICA approach is more suitable for detecting subtle differences between subjects (Allen et al., 2011), and would probably be more appropriate in the investigation of the relationship between intrinsic functional connectivity and resilient functioning. Two dependent variables characterising intrinsic functional connectivity were of interest in the current study: (1) spatial maps, which reflected the degree of connectivity within the network, and (2) functional network connectivity, which reflected the degree of connectivity between networks (Jafri, Pearlson, Stevens & Calhoun, 2008).

Method

Design

This study is part of a larger research study investigating neurobiological and behavioural underpinnings of BPD and anti-social personality disorder (ASPD) within a computational psychiatry framework (Montague and Fonagy, Wellcome Trust). The larger study protocol includes structured interviews, self-report measures, as well as obtaining structural and fMRI and in-scanner cognitive tasks. The larger study was approved by the Research Ethics Committee for Wales (REC reference 12/WA/0281; see Appendix G). The current study had a cross-sectional design and used a subset of the data obtained.

Power Analysis

Current power calculations available for fMRI studies, such as Neuropower and fMRIpower, utilise complex statistical models based on event-related designs and group contrasts. Since ICA, a multivariate connectivity analysis approach that

involves multiple testing of all voxels across the whole brain at rest, these complex statistical models became inappropriate. Furthermore, power calculations on Neuropower have not been validated for connectivity data (Durnez et al., 2016). The estimation of effect sizes and power analysis for connectivity studies remains unanswered in current literature (Durnez et al., 2016) and was beyond the scope of the current study. Therefore, we relied on the classic power analysis method using G*Power 3 (Faul, Erdfelder, Buchner & Lang, 2009).

We anchored the estimated effect size from the meta-analysis of resting-state functional connectivity differences in the BPD population reported by Visintin et al. (2016), where researchers reported medium effect sizes for functional connectivity differences between the BPD group and healthy controls in the precuneus. Based on an a priori power analysis, the target sample size for the GICA analysis was 82 participants. The sample size was estimated to detect an effect of medium magnitude (r = .30) with .80 Power (two-tailed bivariate correlation test, α = .05). We did not anchor the effect size from the resting-state connectivity study by van der Werff et al. (2013a) as the study did not report its effect size and we were unable to extract effect sizes from resting-state parametric maps from the study with Neuropower.

In relation to the regression analysis to examine the relationship between childhood trauma and psychopathology symptoms, we adapted a moderate effect size estimate reported by Wingenfeld et al. (2011). Based on an a priori power analysis, the target sample size for the regression analysis was 68 participants. The sample size was estimated in order to detect an effect of medium magnitude (F = .15) with .80 Power (linear multiple regression with one predictor, α = .05).

Participants

Individuals with BPD were recruited from outpatient specialist personality disorder services across London. Mental health practitioners across clinical sites identified potential participants and disseminated basic information about the study

and contact information of the research team. Clinical staff and researchers emphasised that participation was completely voluntary and would not affect the clinical care or interventions received. Healthy controls were recruited through posters and other advertising materials distributed publicly.

The larger study inclusion criteria were as listed:

1. age from 18 to 60 years at the time of assessment
2. with normal corrected vision
3. met the diagnostic criteria of BPD according to DSM-5 for the clinical population
4. negative screening results for psychopathology for healthy participants
5. fluent in written and spoken English.

The exclusion criteria for the study included individuals with current or historical neurological disorders including epilepsy, head injury and loss of consciousness, or learning disability requiring specialist educational support. All participants with MRI contraindications such as metallic implants, pacemakers and known history of claustrophobia were excluded from the study.

Overall Procedures

Participants were assessed by researchers at the Wellcome Trust Centre for Neuroimaging at University College London (UCL). Informed consent was obtained from participants (refer to Appendix H) at the initial session. Participants were asked to give their consent for the research team to inform their clinical team of their participation in the study, and to inform their clinical team if there was any clinically relevant information obtained in the course of their participation in the study. Participants were required to complete two sessions of assessments at the research site; each session took approximately four hours. Participants were then reimbursed for their time at £10 per hour and any travel expenses incurred. At the end of their participation in the study, participants were provided with a debrief sheet (see Appendix I).

Resting-State fMRI Procedure

A stationary standard *Windows* desktop screen was used during resting-state acquisition and the participants were instructed to “keep their eyes open and let their mind wander, think of whatever that comes to mind” for five minutes.

fMRI Data Acquisition

Structural and functional images were obtained using three different 3.0 Tesla Siemens Trio scanners with a 32-channel head coil. Scanning parameters were kept constant across the three scanners. Resting-state functional T2-weighted images were obtained using a multi-echo echo-planar imaging (EPI) sequence using the following parameters: repetition time (TR) = 2000ms, echo time (TE) = 25ms, flip angle = 90°, field-of-view (FOV) = 220mm, voxel size = 3.4mm x 3.4mm x 3.4mm, slice thickness = 4mm, 37 axial slices. An fMRI run of five minutes acquired 150 functional images per participant.

High resolution T1-weighted structural images were acquired from each participant as anatomical references for resting-state scans. Using a magnetization-prepared rapid acquisition with gradient echo (MPRAGE) imaging sequence, the following parameters were used: TR = 1200ms, TE = 2.66ms, flip angle = 12°, voxel slice = 1mm x 1mm x 1mm, slice thickness = 1mm, 192 slices. An off-resonance Gaussian-shaped radio frequency pulse (4ms duration, 220° nominal flip angle, 2kHz frequency offset) was applied prior to non-selective excitation.

Measures

Demographics information included age, ethnicity, gender, number of years of education, education level and employment status were obtained.

1. Childhood Trauma Questionnaire

The Childhood Trauma Questionnaire (CTQ) is a 28-item self-report measure of five distinct types of maltreatment: physical abuse, emotional abuse, sexual abuse, emotional neglect and physical neglect (Bernstein et al., 1994; refer

to Appendix J). Participants were instructed to retrospectively report experiences of abuse and neglect in childhood and respond on a 5-point Likert scale (1 = never true, 2 = rarely true, 3 = sometimes true, 4 = often true, 5 = very often true). The CTQ yields a total raw score which ranges from 5 to 25, and is then classified into severity of maltreatment of none, low, moderate and severe. The CTQ demonstrates high internal consistency reliability (α = .95), high test-retest reliability (*r* = .88) and convergent validity with interview ratings from the Childhood Trauma Interview (Bernstein et al., 1994).

2. Brief Symptom Inventory

The Brief Symptom Inventory (BSI), a 53-item self-report questionnaire, was used to measure the severity of psychopathology across nine dimensions: somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation and psychoticism (Derogatis & Melisaratos, 1983, refer to Appendix K). Participants were instructed to rate their degree of distress on a variety of difficulties, such as “trouble remembering things”, on a 5-point scale (0 = not at all, 1 = a little bit, 2 = moderately, 3 = quite a bit, 4 = extremely). The BSI yields three global indexes: (1) the Global Severity Index (GSI), a weighted frequency score based on the sum of the ratings of each item; (2) the Positive Symptom Total (PST), the total frequency of the number of symptoms reported; and (3) the Positive Symptom Distress Index (PSDI), the intensity of distress corrected for the number of symptoms reported.

The BSI GSI was selected to reflect the severity of psychopathology symptoms because it is the most sensitive indicator of the degree of distress and psychopathology symptoms (Derogatis & Melisaratos, 1983). The BSI showed moderate to high internal consistency reliability (α = .75 to .89) and moderate convergent validity with the Minnesota Multiphasic Personality Inventory (*r* = .50 to .53; Boulet & Boss, 1991).

Raven's Standard Progressive Matrices. Recent literature reported the association between intelligence and increased resting-state functional connectivity, implicating several resting-state networks such as the default mode network, salience network and central executive network (Dubois, Galdi, Paul, & Adolphs, 2018; Hearne, Mattingley, & Cocchi, 2016). Given the global impact of intelligence on resting-state functional connectivity, intelligence was measured using the Raven's Standard Progressive Matrices (SPM; Raven, Raven, & Court, 2003), and statistically controlled as a covariate of no interest. The Raven's SPM measured general cognitive ability (Raven et al., 2003), and takes approximately 20 minutes to complete. It consists of 60 matrices of increasing difficulty and yields a total score ranging from 0 to 60. Participants were provided with six to eight options and were asked to identify a missing element that completes a pattern. The Raven's SPM possessed high internal consistency reliability, r = .88 (Pearson, 2007), and high convergent validity with the Wechsler Adult Intelligence Scale-Revised full-scale IQ, r = .74 to .84 (O'Leary, Rusch, & Guastello, 1991).

Image Preprocessing

An overview of the analysis pipeline was shown in Figure 1. Preprocessing was conducted with the CONN toolbox (www.nitrc.org/projects/conn/) based on Statistical Parametric Mapping software (SPM12, Wellcome Trust Centre for Neuroimaging, UCL, UK; http://www.fil.ion.ucl.ac.uk/spm). Details of the complete analysis pipeline were provided in Appendix L.

For functional data, each participant's functional images were visually inspected for scanner and motion artefacts using the Artifact Detection Toolbox. To control for head motion, an exclusion criteria of excessive head motion was applied. Participants with more than 3mm linear shift and/or rotation more than 1.5° from INRIAlign motion estimates were excluded. Controlling for motion artefacts was important as head motion results in systematic effects on functional connectivity results (Van Dijk, Sabuncu, & Buckner, 2012). The first three functional images for

each participant were discarded due to magnetization effects (Allen et al., 2011). Slice timing correction, motion correction and spatial normalisation were performed to ensure that all image data from each participant were placed in the same reference point of time and space (Calhoun, Adali, Pearlson, & Pekar, 2001).

A custom preprocessing pipeline in the CONN toolbox was used and comprised: (1) reorientation, (2) realignment using INRIAlign, (3) direct coregistration to structural scans, (4) slice timing correction, (5) segmentation and normalisation, where functional data were spatially normalised into the stereotactic space of Montreal Neurological Institute (MNI) with the resampling voxel size of 3mm x 3mm x 3mm and (6) spatial smoothing using a Gaussian kernel with a full width at half maximum (FWHM) of 8mm. INRIAlign was used because simulation studies had shown its robustness in motion correction compared to standard realignment packages in SPM (Freire, Roche, & Mangin, 2002). Previous studies also demonstrated that spatial smoothing does not affect ICA analysis and it is a useful preprocessing step because it reduces high frequency spatial noise and desensitizes the images to errors in the motion correction and normalization (Calhoun et al., 2001). For structural data, reorientation, segmentation and spatial normalisation were added to the preprocessing pipeline in the CONN toolbox.

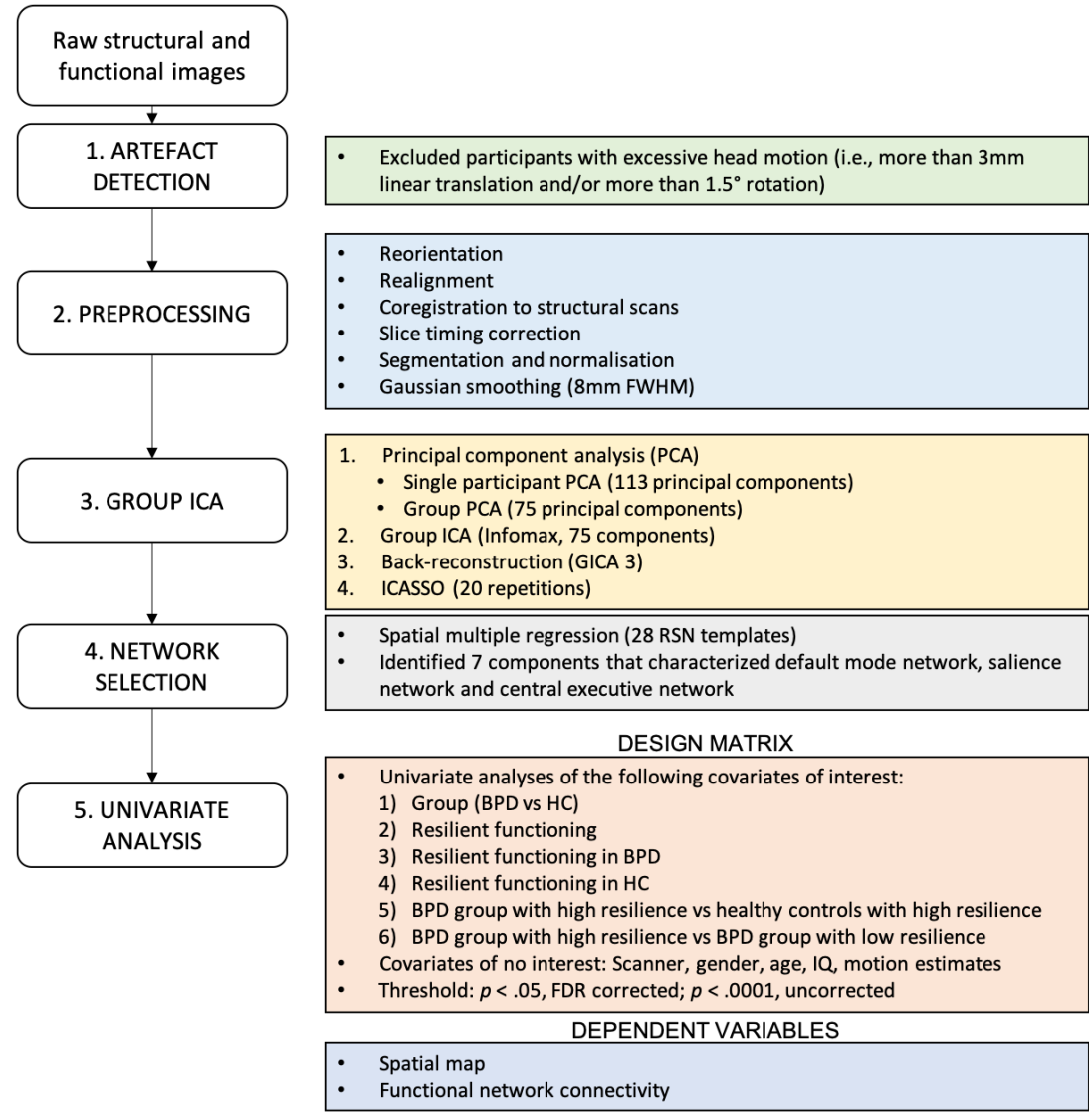

Figure 1. Analysis pipeline. Coloured boxes refer to the methodological decisions made. BPD = borderline personality disorder; FDR = false discovery rate; FWHM = full width at half maximum; GICA = group independent component analysis; HC = healthy controls; ICA = independent component analysis; PCA = principal component analysis; RSN = resting-state networks.

Independent Component Analysis (ICA)

High-model order ICA was applied to preprocessed functional data in accordance with precedent ICA protocols (Allen et al., 2011; Doll et al., 2013; Manoliu et al., 2013) using the GICA fMRI toolbox (GIFT) toolbox (http://icatb.sourceforge.net).

GICA was conducted in three stages. First, a two-step principal component analysis (PCA) was conducted, where participant-specific functional data were

concatenated and reduced. Subject-specific data reduction PCA retained 113 principal components, while group data reduction retained 75 principal components. Group level PCA was necessary to reduce the dimensions of the data to fit the number of components to be estimated with ICA (Allen et al., 2011). In the second stage, ICA was performed with the Infomax algorithm (Bell & Sejnowski, 1995) on group data to yield the independent components. Similar to precedent ICA studies (Allen et al., 2011; Doll et al., 2013; Manoliu et al., 2013), 75 independent components were extracted. Previous studies have shown that high-order models of ICA produce more robust components which correspond to anatomical and functional sub-networks (Allen et al., 2011; Doll et al., 2013; Manoliu et al., 2013). In the third stage, back reconstruction of each participant's time courses and spatial maps based on the group components identified in stage two was performed. The GICA 3 back reconstruction approach was selected as previous literature suggested that it is more robust compared to older back reconstruction approaches (Erhardt et al., 2011). Each back-reconstructed component consisted of a spatial *z*-map which reflects the component's functional connectivity pattern across space in each voxel within this component and a corresponding time course which reflects the blood-oxygen-level-dependent (BOLD) signal fluctuations of the component across time (Manoliu et al., 2013).

To ensure that the number of ICA components identified (i.e., 75 independent components) were reliable, the Infomax algorithm was repeated 20 times in the ICASSO toolbox. The ICASSO toolbox generates a quality index, I_q (ranging from 0 to 1), which reflects the reliability of each independent component. Independent components with a quality index greater than 0.8 were suggested to be highly reliable (Allen et al., 2011).

Network Selection

Multiple spatial regression was conducted on the identified 75 independent components using the T-maps from a previously established set of intrinsic

functional connectivity networks in Allen et al. (2011) as regressors of interest. T-maps of 28 intrinsic connectivity networks were developed from 603 healthy participants and were available online from the Medical Image Analysis Laboratory (MIALAB; http://mialab.mrn.org/data/hcp/RSN_HC_unthresholded_tmaps.nii). For each intrinsic connectivity network, the independent component with the largest correlation coefficient was chosen.

Components which characterised the default mode network, salience network and central executive network were selected through multiple spatial regression. Consistent with previous ICA studies investigating the three resting-state networks (Doll et al., 2013; Manoliu et al., 2013), seven components were of interest in the current study (refer to Table 1).

Table 1
Network selection

Intrinsic network	Component number[a]	Regions
Default mode network		
Anterior default mode network	25	Bilateral medial prefrontal cortex
Inferior-posterior default mode network	53	Medial posterior parietal cortex Angular gyrus
Superior-posterior default mode network	50	Bilateral precuneus
Salience network	55	Bilateral insula Anterior cingulate cortex
Central executive network		
Left ventral central executive network	34	Left inferior parietal lobule Left superior frontal gyrus
Right ventral central executive network	60	Right inferior parietal lobule Right middle frontal gyrus
Dorsal central executive network	52	Bilateral supramarginal gyrus Left inferior frontal gyrus

Note. [a] Components from T-maps of intrinsic networks reported in Allen et al. (2011).

Statistical Analysis

1. Resilient functioning

Linear regression analyses were conducted to examine the relationship between psychopathology (measured by the BSI GSI) and childhood trauma (measured by the CTQ total score). Statistically, the regression model would predict

the participant's psychopathological symptoms based on his/her reported childhood trauma. All regression analyses were conducted in R version 3.5.1 (R Core Team, 2018; https://www.R-project.org/). R-based source packages used for analysis included dplyr (Wickham, Francois, Henry & Müller, 2019) and ggplot2 (Wickham, 2016). Model selection was guided by two indicators. The first indicator was the root mean square error (RMSE), an accuracy indicator, which was derived from the standard deviation of residuals. Residuals refer to the difference between observed values (i.e., observed BSI scores) and predicted values based on the regression model. Lower RMSE values indicate higher accuracy in the regression model as the difference between observed and predicted values were minimised. The second indicator was the Akaike information criterion (AIC), a goodness of fit indicator, which measured the relative quality of the model compared to other models (Spiess & Neumeyer, 2010). The use of AIC in the selection of linear regression models was found to be more robust than standard measures such as the R^2 (Spiess & Neumeyer, 2010). Similarly, lower AIC values suggest that the model has a better fit with observed values relative to other models.

Resilient functioning was extracted for each participant based on the difference between their observed psychopathological symptoms and their predicted psychopathological symptoms given the degree of self-reported childhood trauma. This was calculated through extracting residuals from the final regression model. Negative residual scores reflected higher resilient functioning, while positive residual scores reflected lower resilient functioning. Additionally, participants were grouped into high resilience (i.e., negative residual scores) and low resilience groups (i.e., positive residual scores).

2. Intrinsic functional connectivity associated with BPD and resilient functioning

Two outcome variables were of interest from the identified components associated with the default mode, salience and central executive networks: (1)

spatial maps, reflecting the degree of functional connectivity within the component; and (2) functional network connectivity, the degree of functional connectivity between components of interest.

The MANCOVAN toolbox in GIFT was used to conduct univariate analyses. Six univariate analyses were conducted to examine the relationship between the covariate of interest and intrinsic functional connectivity: (1) correlates of group (i.e., BPD vs healthy controls), (2) correlates of resilient functioning, (3) resilient functioning in individuals with BPD, (4) resilient functioning in healthy controls, (5) BPD group with high resilience vs healthy controls with high resilience, and (6) BPD group with high resilience vs BPD group with low resilience. All univariate analyses controlled for scanner, gender, age, IQ and motion estimates (i.e., average motion estimates from INRIAlign) as nuisance predictors. Given that there was no consensus on the recommended threshold to use for significance testing in resting-state functional connectivity studies (Garrison, Scheinost, Finn, Shen, & Constable, 2015), two thresholds were used in the current study. First, a more conservative threshold set at $p < .05$ and corrected for multiple comparisons using the false discovery rate (FDR) was reported. Second, a less conservative threshold set at $p < .0001$, uncorrected, was reported.

Results

Sample Characteristics

The sampling process for the current secondary analysis was described in Figure 2. The larger dataset contained 587 participants of which 349 participants were excluded as we were unable to retrieve their resting-state scans from the server and/or the researchers noted scanning issues during fMRI acquisition. Behavioural data were missing for 40 participants. The remaining 198 participants (111 individuals with BPD and 87 healthy controls) were included for regression analysis. From the 198 participants, we were unable to retrieve structural and/or

functional data for 89 participants. To minimise the potential confounding effect of different fMRI scanners on resting-state scans obtained, we excluded 10 participants whose resting-state scans were acquired from a different 3.0 Tesla Siemens scanner. Transgender individuals (*n* = 2) were excluded given the small sample sizes and potential differences in resting-state functional connectivity (Spies et al., 2016). There were 97 participants whose fMRI data were available for preprocessing and GICA analysis. From the 97 participants, 14 participants were excluded due to excessive head motion as defined by scans with more than 3mm linear shift and/or rotation of more than 1.5°. Seven participants were excluded as their structural T1 scans were visibly different and were likely to be a different scan parameter. Another 10 participants were excluded as their fMRI identifiers did not match the participant identification numbers in the behavioural dataset. Therefore, 66 participants were included in the GICA analysis (29 healthy controls and 37 individuals with BPD).

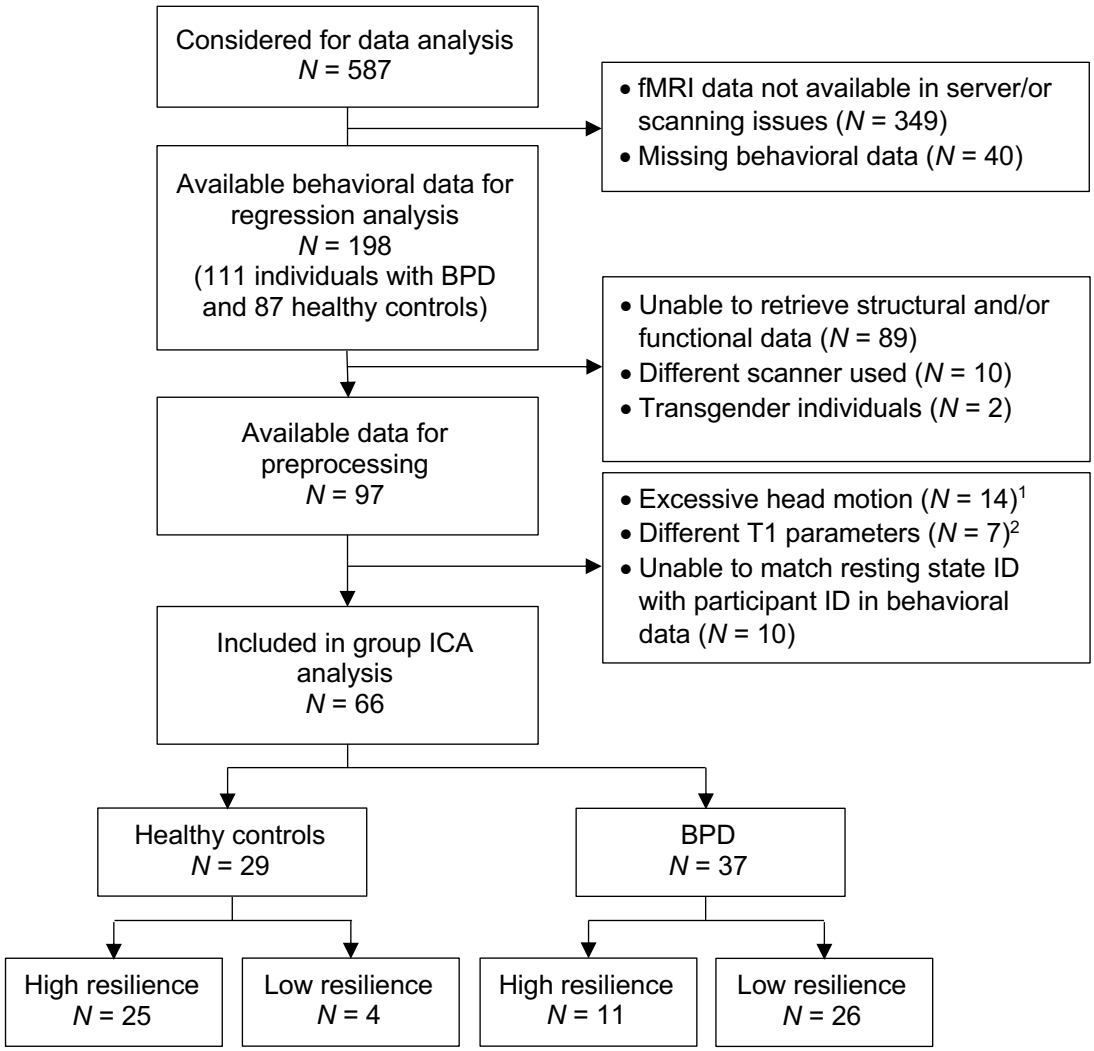

Figure 2. Participant flowchart. Participants with positive residual scores from the regression model (N = 198) were grouped as "low resilience" and participants with negative residual scores were grouped as "high resilience". BPD = borderline personality disorder; fMRI = functional magnetic resonance imaging; ICA = independent component analysis; ID = identifier.

[1] Participants with more than 3mm linear shift and/or rotation more than 1.5°.

[2] T1 scans were visually different and likely to be diffusion tensor imaging (DTI) scan parameters.

There were significantly more females in the BPD group (89%) compared to healthy controls (59%), $p < .01$ (refer to Table 2). The Fisher's exact test revealed significant differences on employment status between BPD and healthy controls, $p < .01$ (refer to Table 2). There were more participants who were unemployed in the BPD group than in the healthy control group. Significant age differences were also detected between BPD group (M = 29.92, SD = 8.52) and healthy controls (M =

25.66, *SD* = 8.33), *t*(64) = 2.04, *p* < .05 (refer to Table 3). There were no significant differences between groups for ethnicity, education level, years of education and head motion (refer to Table 3 and Table 4).

Table 2
*Demographic data (*N = *66)*

	HC (*n* = 29) *n* (%)	BPD (*n* = 37) *n* (%)	*F* statistic	*p* value
Gender				
Male	12 (41%)	4 (11%)	0.008	.01**
Female	17 (59%)	33 (89%)		
Ethnicity				
White British	10 (35%)	24 (65%)	9.36	.08
White Other	6 (21%)	2 (5%)		
Black British, British-Caribbean, British-African	3 (10%)	4 (11%)		
Mixed	3 (10%)	3 (8%)		
Asian	6 (21%)	2 (5%)		
Any other background not stated	1 (3%)	2 (5%)		
Education level				
No qualifications	1 (3%)	1 (3%)	5.49	.34
Vocational	0 (0%)	2 (5%)		
GCSE or equivalent	5 (17%)	5 (13%)		
A Level or equivalent	15 (52%)	11 (30%)		
Higher education or equivalent	6 (21%)	12 (32%)		
Postgraduate education	2 (7%)	6 (16%)		
Employment status				
Employed	14 (48%)	11 (30%)	12.09	.00**
Student	11 (38%)	8 (22%)		
Carer	1 (3%)	0 (0%)		
Unemployed	3 (10%)	18 (49%)		
Currently seeing mental health services	3 (10%)	37 (100%)	.00	.00**

Note. BPD = borderline personality disorder; HC = healthy controls.
** Refers to statistical significance at *p* < .01.

Table 3
*Demographic data (*N = *66)*

	HC *n* = 29		BPD *n* = 37		*t*	*p*
	M	*SD*	*M*	*SD*	Statistic	value
Age	25.66	8.33	29.92	8.52	2.04	.05*
Females	25.06	9.83	29.70	8.40	1.75	.09
Males	26.50	5.92	31.75	10.63	1.27	.23
Years in education[m]	14.52	2.95	14.83	3.72	0.36	.72
Females (HC = 17, BPD = 32)	14.94	2.56	14.50	3.19	0.49	.63
Males (HC = 10, BPD = 4)	13.80	3.55	17.50	6.76	1.37	.20

Note. BPD = borderline personality disorder; HC = healthy controls. [m] Three missing values.
* Refers to statistical significance at $p < .05$.

Table 4
*Group comparisons for motion estimates (*N = *66)*

	HC *n* = 29		BPD *n* = 37		*t*	*p*
	M	*SD*	*M*	*SD*	Statistic	value
Translation (*x*)	0.18	0.21	0.22	0.28	0.61	.54
Translation (*y*)	0.24	0.19	0.28	0.16	0.97	.33
Translation (*z*)	0.56	0.45	0.53	0.53	0.20	.84
Rotation (pitch)	0.01	0.01	0.01	0.01	0.36	.72
Rotation (roll)	0.002	0.003	0.002	0.003	0.97	.33
Rotation (yaw)	0.002	0.003	0.003	0.004	0.76	.45

Note. Motion estimates were extracted from INRIAlign. BPD = borderline personality disorder; HC = healthy controls.

Behavioural Measures

An independent sample t-test revealed that BSI GSI was significantly greater in the BPD group ($M = 1.98$, $SD = 0.74$) than in healthy controls ($M = 0.43$, $SD = 0.34$), $t(53.08) = 11.34$, $p < .01$, Bonferroni corrected (refer to Table 5). CTQ was significantly higher in the BPD group ($M = 58.08$, $SD = 20.02$) as compared to the healthy controls ($M = 42.66$, $SD = 20.01$), $t(64) = 3.11$, $p < .01$, Bonferroni corrected. The Kolmogorov–Smirnov test was used to test for normality, and both BSI GSI and CTQ scores were not normally distributed, $p < .01$.

Table 5

*Profile of BSI and CTQ (*N = *66)*

	HC *n* = 29				BPD *n* = 37						
	M	*SD*	Min	Max	*M*	*SD*	Min	Max	*t*	*p* value	*d*
Brief Symptom Inventory (BSI)											
Somatization	0.53	0.47	0	1.86	1.41	0.86	0	3.29	5.28	.00**[c]	1.27
Obsessive-compulsive	0.87	0.74	0	3.17	2.46	0.96	0.33	3.83	7.56	.00**[c]	1.86
Interpersonal sensitivity	0.37	0.46	0	1.50	2.52	1.01	0	4.00	11.42	.00**[c]	2.74
Depression	0.47	0.59	0	2.67	2.61	1.03	0.50	4.00	10.62	.00**[c]	2.55
Anxiety	0.34	0.36	0	1.33	2.04	1.01	0.17	4.00	9.49	.00**[c]	2.24
Hostility	0.29	0.29	0	1.00	1.40	1.03	0	3.40	6.26	.00**[c]	1.47
Phobic anxiety	0.09	0.17	0	0.60	1.83	1.05	0	4.00	9.91	.00**[c]	2.31
Paranoid ideation	0.28	0.49	0	2.40	1.69	0.97	0	3.60	7.73	.00**[c]	1.83
Psychoticism	0.32	0.49	0	2.20	1.74	0.88	0.40	3.60	8.25	.00**[c]	1.99
BSI Global Severity Index	0.43	0.34	0.04	1.21	1.98	0.74	0.53	3.21	11.34	.00**[c]	2.69
BSI Positive Symptom Total	15.28	9.71	2.00	33.00	41.03	8.52	20.00	53.00	11.46	.00**[c]	2.82
BSI Positive Symptom Distress Total	1.37	0.43	1.00	2.40	2.49	0.60	1.38	3.33	8.87	.00**[c]	2.15
Childhood Trauma Questionnaire (CTQ)											
Emotional abuse	10.38	6.44	5.00	25.00	15.43	5.55	7.00	25.00	3.42	.00**[c]	0.84
Physical abuse	8.00	4.87	5.00	21.00	8.30	5.22	5.00	23.00	0.24	.81	0.06
Sexual abuse	6.03	2.38	5.00	13.00	8.51	5.76	5.00	24.00	2.37	.02**	0.56
Emotional neglect	10.69	5.11	5.00	23.00	16.57	5.79	5.00	25.00	4.31	.00**[c]	1.08
Physical neglect	7.55	3.92	5.00	18.00	9.23	3.90	5.00	20.00	1.77	.08	0.43
CTQ total	42.66	20.01	25.00	89.00	58.08	20.02	31.00	110.0	3.11	.00**	0.77

Note. BPD = borderline personality disorder; *d* = Cohen's d; HC = healthy controls; Min = minimum; Max = maximum; *t* = t statistic.

** Refers to statistical significance at $p < .01$

[c] Bonferroni corrected, $p < .01$.

Resilient Functioning

Linear regression was conducted with the larger dataset (*N* = 198, 111 BPD and 87 healthy controls) to minimise error. Cubic linear regression was selected as the following assumptions necessary for linear regression were not met: (1) the distributions of CTQ and BSI were non-normally distributed, (2) the residuals of the linear regression model were non-normally distributed, (3) there was no clear linear relationship between CTQ and BSI GSI and (4) outliers were present in CTQ scores. Transformations (i.e., log-transformed CTQ and square root-transformed BSI) were applied as the distributions of CTQ and BSI were highly positively skewed (refer to Appendix M). Given that the measurement unit for resilient functioning (i.e., residuals) derived from the regression model was arbitrary, the transformation of the variables was unlikely to affect the interpretation of results. The relationship between self-reported CTQ and BSI scores could be best described as cubic (refer to Figure 3 and Table 6). Although the quartic model showed the lowest RMSE and AIC values, it was not selected as the predictors in the quartic model were non-significant.

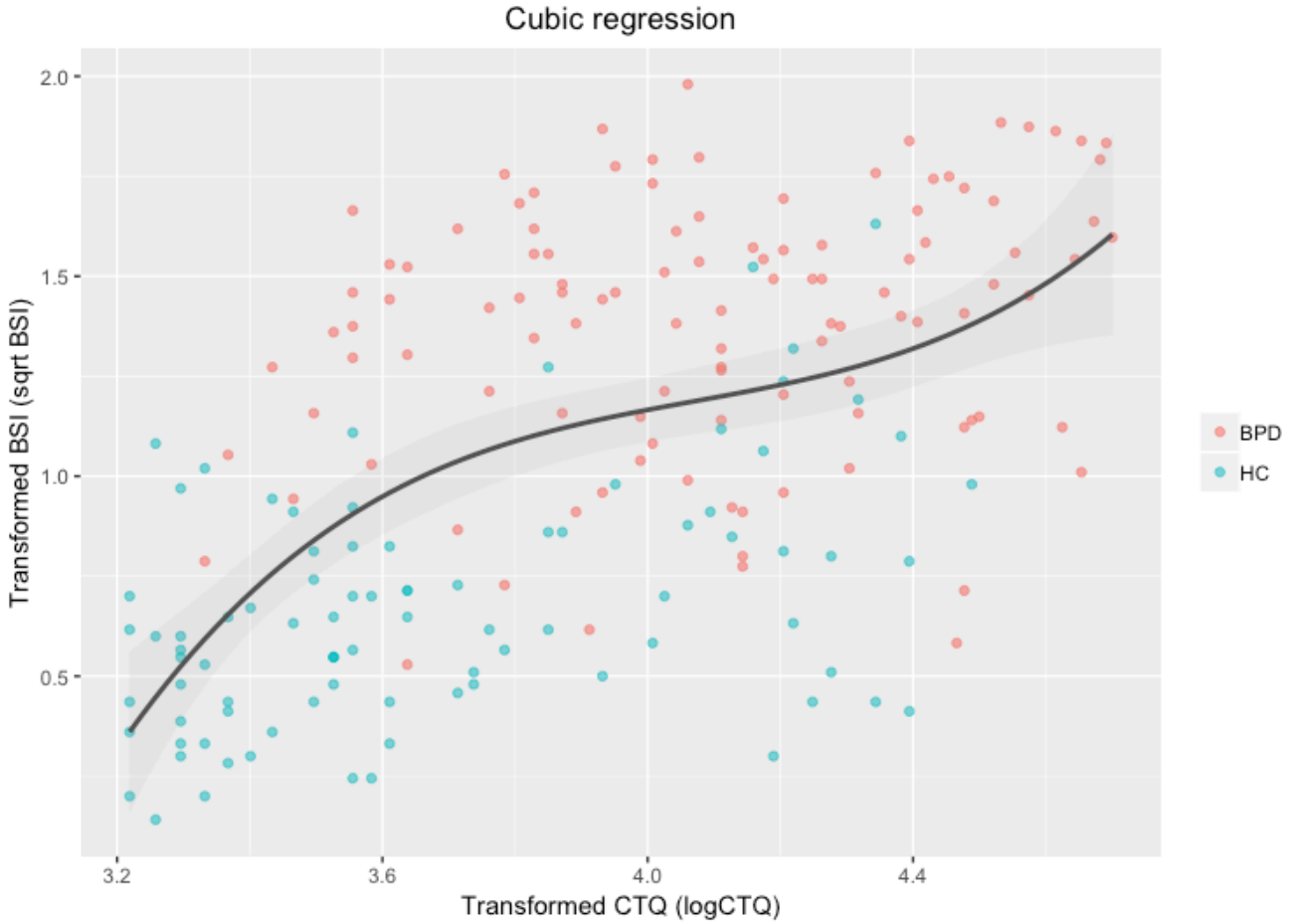

Figure 3. Cubic relationship between BSI GSI and CTQ (N = 198). Grey regions above and below the regression curve represent 95% confidence interval. BPD = borderline personality disorder; BSI GSI = brief symptom inventory global severity index; CTQ = childhood trauma questionnaire; HC = healthy controls; log = logarithm to base 10; sqrt = square-root.

Table 6
Model selection for regression models predicting psychopathology symptoms with childhood trauma (N = *198*)

Model	β	*p* value	*F* statistic	R^2	RMSE	AIC
1. Linear						
Constant	−1.49	<.01**	93.14	0.32	0.39	194.01
CTQ	0.65	<.01**				
2. Quadratic						
Constant	−6.85	<.05*				
CTQ	3.41	<.05*	49.35	0.34	0.39	191.94
CTQ^2	−0.35	<.05*				
3. Cubic						
Constant	−61.94	<.05*				
CTQ	45.90	<.05*	34.98	0.35	0.38	189.43
CTQ^2	−11.20	<.05*				
CTQ^3	0.92	<.05*				
4. Quartic						
Constant	452.22	.10				
CTQ	−483.51	.08				
CTQ^2	192.16	.07	27.51	0.36	0.38	187.71
CTQ^3	−33.62	.06				
CTQ^4	2.19	.06				

Note. Superscripts accompanying CTQ refer to exponentiation, specifically: CTQ^2 = CTQ raised to the power of 2; CTQ^3 = CTQ raised to the power of 3; CTQ^4 = CTQ raised to the power of 4. AIC = akaike information criterion; CTQ = childhood trauma questionnaire; RMSE = root mean square error. * $p < .05$.
** $p < .01$

ICA Analysis

Sixty-six participants (29 healthy controls and 37 individuals with BPD) were included in the GICA analysis. Automated selection of components through multiple spatial regression revealed seven components of interest that were spatially consistent with Allen et al. (2011) and Manoliu et al. (2013). These components were highly stable, with a reliability index of 0.95 or more. Spatial maps of the seven components of interest were shown in Figure 4 and regions of peak activations of each component were presented in Table 7.

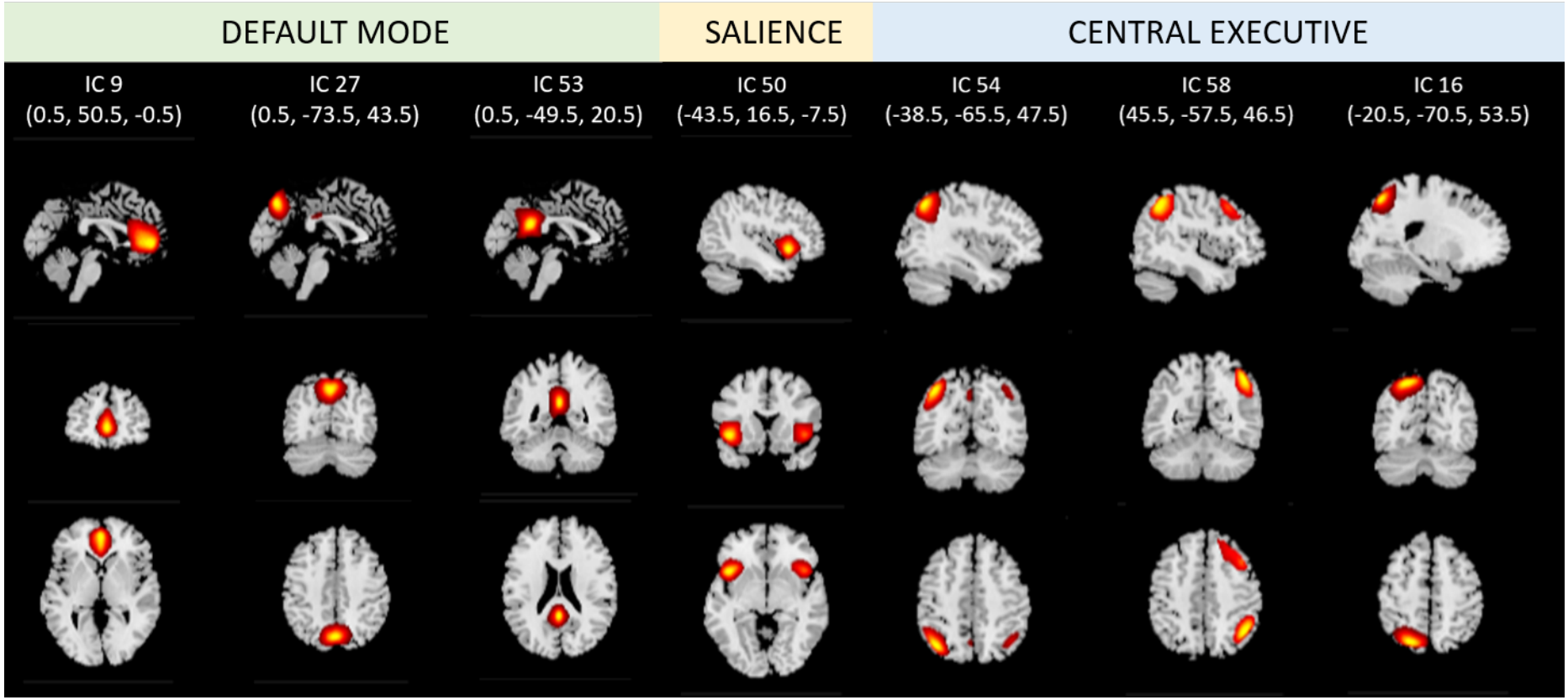

Figure 4. Spatial maps of selected components reflecting the default mode, salience and central executive networks. Spatial maps were converted to *z*-scores and thresholded at $z > 4$. Peak coordinates of components were reported in Montreal Neurological Institute (MNI) coordinates.

Table 7

Peak activations of resting networks spatial maps (N = *66*)

Networks and brain regions	k_{voxels}	t_{max}	MNI coordinates		
Default mode network					
Anterior default mode network: IC 9 (0.98)					
B Anterior cingulate	10478	61.44	−4	40	0
L Middle cingulate cortex	969	12.02	0	−14	40
L Inferior frontal gyrus	391	9.5	−56	16	16
R Insula	234	10.06	32	16	−14
L Mid occipital gyrus	33	6.75	−30	−78	12
Superior-posterior default mode network: IC 27 (0.97)					
B Precuneus	8434	37.03	4	−70	40
Inferior-posterior default mode network: IC 53 (0.96)					
B Posterior cingulate cortex	10128	49.18	−4	−48	26
L Precuneus		52.03	−6	56	22
L Medial frontal gyrus	756	13.39	−2	52	−8
R Middle occipital gyrus	182	8.89	30	−84	26
L Cerebellum crus 2	103	6.99	−38	−58	−42
Salience network					
IC 50 (0.97)					
L Insula	7717	47.48	−36	22	−4
R Insula	6081	37.11	40	20	−4
L Middle frontal gyrus	622	14.59	−28	52	28
R Angular gyrus	1260	15.32	56	−50	34
L Angular gyrus and supramarginal gyri	420	10.57	−50	−50	36
Central executive network					
Dorsal central executive network: IC 16 (0.97)					
L Superior parietal gyrus	7050	37.68	−16	−66	46
R Superior parietal gyrus	696	14.08	24	−68	54
R Cerebellum crus 1	1881	13.92	34	−64	−28
L Inferior temporal gyrus	950	17.02	−52	−62	−10
R Inferior frontal gyrus	284	7.99	50	36	−10
Left ventral central executive network: IC 54 (0.96)					
L Angular gyrus	8213	43.64	−42	−60	42
L Middle frontal gyrus	3957	18.29	−44	16	44
R Angular gyrus	2301	31.64	48	−58	44
R Insula	1785	17.32	48	4	2
L Middle temporal gyrus	1218	19.17	−60	−38	−4
Right ventral central executive network: IC 58 (0.95)					
R Superior frontal gyrus	11226	31.02	20	24	56
R Angular gyrus	3653	42.55	50	−52	38
R Precuneus	2803	19.6	6	−66	42
L Fusiform	1606	12.91	32	−90	14
B Inferior parietal lobule	542	14.01	−40	−60	52
R Middle temporal gyrus	507	11.69	60	−36	−8

Note. One-sample *t*-test for individual ICA components, $p < .05$, with family-wise error rate (FWE) correction. Stability index of components were reported in brackets. Peak coordinates of components were reported in Montreal Neurological Institute coordinates. B = bilateral; ICA = independent component analysis; k_{voxels} = number of voxels in each cluster; L = left; MNI = Montreal Neurological Institute; R = right;. t_{max} = maximum *t*-statistic in each cluster.

1. Correlates of group and intrinsic functional connectivity

Controlling for scanner, gender, age, IQ and motion estimates, univariate analysis of group revealed significant effects of group, $p < .05$, FDR corrected. Healthy controls showed increased intrinsic functional connectivity within the bilateral precuneus compared to BPD, $p < .05$, FDR corrected (refer to Figure 5) and $p < .0001$, uncorrected. Group differences in intrinsic functional connectivity within the bilateral precuneus remained after controlling for self-reported psychopathology symptoms and childhood trauma separately (refer to Appendix N). There were no significant group differences on functional network connectivity between components.

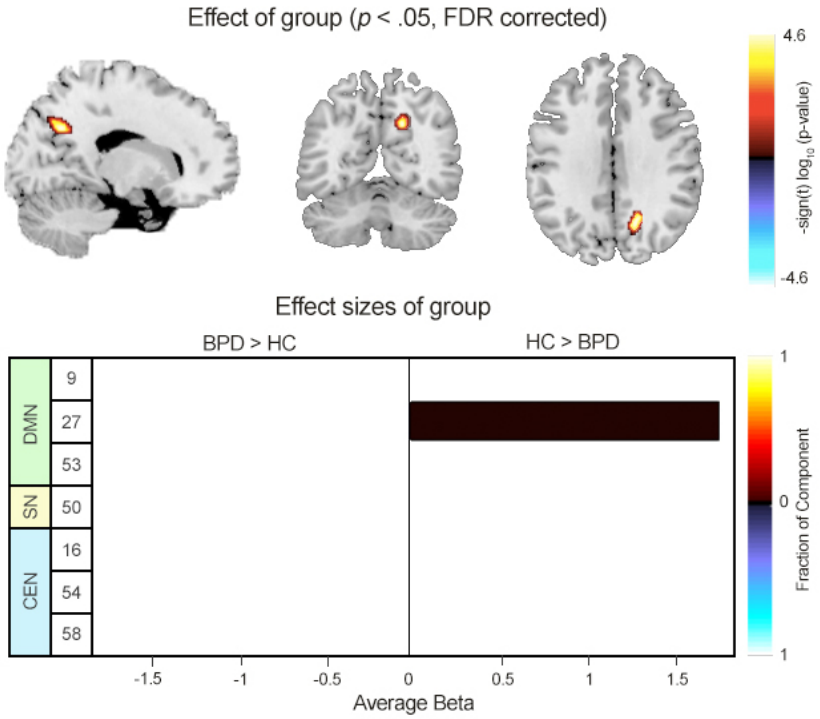

Figure 5. Univariate results showed significant effects of group in spatial map. The top row showed composite maps of significant effects and are displayed as -sign(t)log$_{10}$(p). The bottom row showed average β-values for group and the colour of the bar is proportional to the fraction of component voxels contributing to each effect. Healthy controls showed increased functional connectivity within the precuneus (component 27) compared to BPD, $p < .05$, FDR corrected. *BPD* = borderline personality disorder; CEN = central executive network; DMN = default mode network; FDR = false discovery rate; HC = healthy controls; SN = salience network.

2. Correlates of resilient functioning and intrinsic functional connectivity

Univariate analyses revealed that there were no significant effects of resilient functioning on spatial maps and functional network connectivity, based on both thresholds of $p < .05$, FDR corrected, and $p < .0001$, uncorrected.

3. Resilience in BPD

Low resilient functioning in the BPD group was associated with increased intrinsic functional connectivity within the right ventral central executive network, $p < .0001$, uncorrected (refer to Figure 6). However, this finding did not survive the conservative threshold of $p < .05$, FDR corrected. There was no significant difference on functional network connectivity between components.

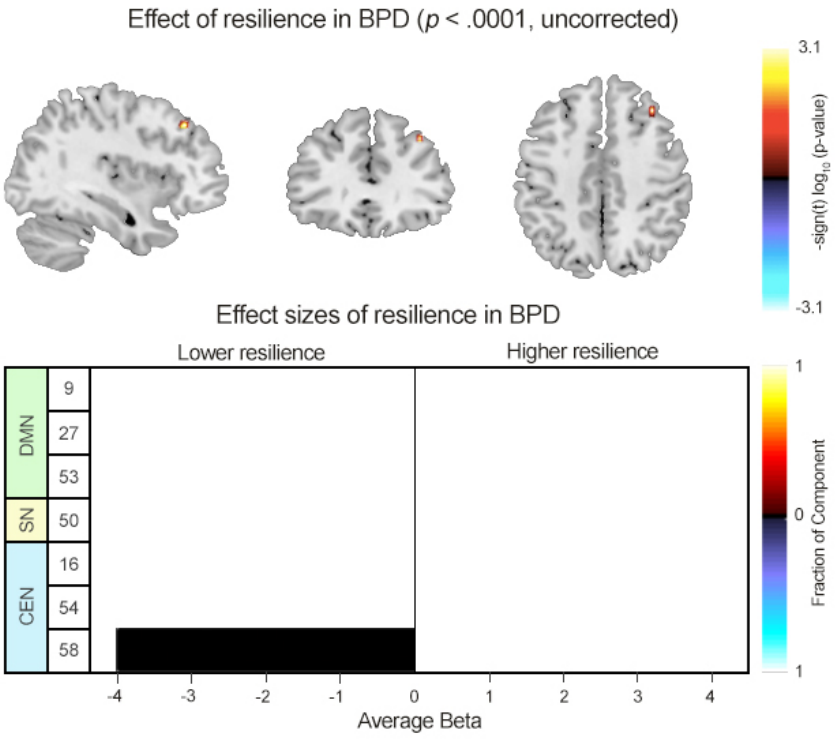

Figure 6. Univariate results showed significant effects of resilience within the BPD group (n = 37). The top row showed composite maps of significant effects and are displayed as -sign(*t*)log$_{10}$(*p*). The bottom row showed average β-values for resilient functioning and the colour of the bar is proportional to the fraction of component voxels contributing to each effect. Low resilient functioning in the BPD group was associated with increased functional connectivity within the right ventral central executive network (component 58), $p < .0001$, uncorrected. *BPD* = borderline personality disorder; CEN = central executive network DMN = default mode network; SN = salience network.

4. Resilience in healthy controls

Higher resilient functioning in the healthy controls was associated with decreased functional connectivity within the left ventral central executive network, $p < .05$, FDR corrected (refer to Figure 7). In addition, low resilient functioning in the healthy controls was associated with increased functional connectivity within the posterior cingulate cortex, $p < .0001$, uncorrected (refer to Figure 8). Similarly, there was no significant difference in functional network connectivity between components.

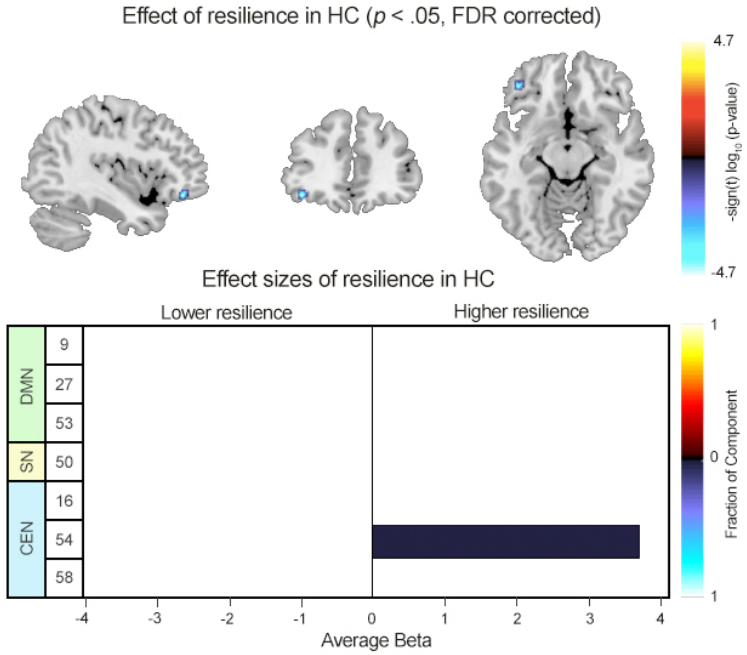

Figure 7. Univariate results showed significant effects of resilience within the HC group (n = 29).). The top row showed composite maps of significant effects and are displayed as -sign(*t*)log$_{10}$(*p*). The bottom row showed average β-values for resilient functioning and the colour of the bar is proportional to the fraction of component voxels contributing to each effect. High resilient functioning in the healthy controls was associated with decreased functional connectivity within the left ventral central executive network (component 54), *p* < .05, FDR corrected. CEN = central executive network; DMN = default mode network; FDR = false discovery rate; HC = healthy controls; SN = salience network.

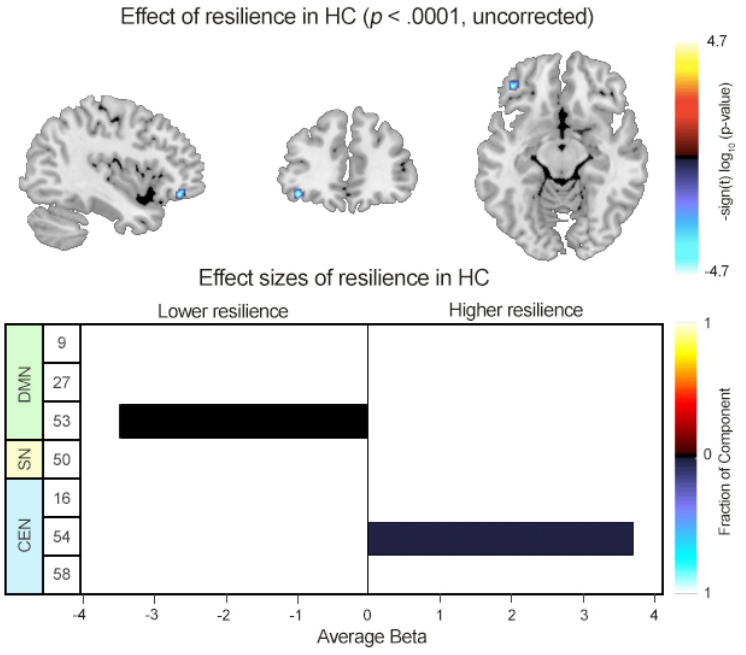

Figure 8. Univariate results showed significant effects of resilience within the HC group (n = 29). The top row showed composite maps of significant effects and are displayed as -sign(*t*)log$_{10}$(*p*). The bottom row showed average β-values for resilient functioning and the colour of the bar is proportional to the fraction of component voxels contributing to each effect. Low resilient functioning in the healthy controls was associated with increased functional connectivity within the posterior cingulate cortex (component 53), *p* < .0001, uncorrected. CEN = central executive network; DMN = default mode network; HC = healthy controls; SN = salience network.

5. Healthy controls with high resilience versus BPD group with high resilience

Healthy controls with high resilient functioning (*N* = 25) showed decreased functional connectivity within the anterior cingulate compared to BPD group with high resilient functioning (*N* = 11), *p* < .0001, uncorrected (refer to Figure 9). In addition, healthy controls with high resilient functioning showed increased connectivity within the precuneus compared to BPD group with high resilient functioning, *p* < .0001, uncorrected. However, both findings did not survive the conservative threshold of *p* < .05, FDR corrected.

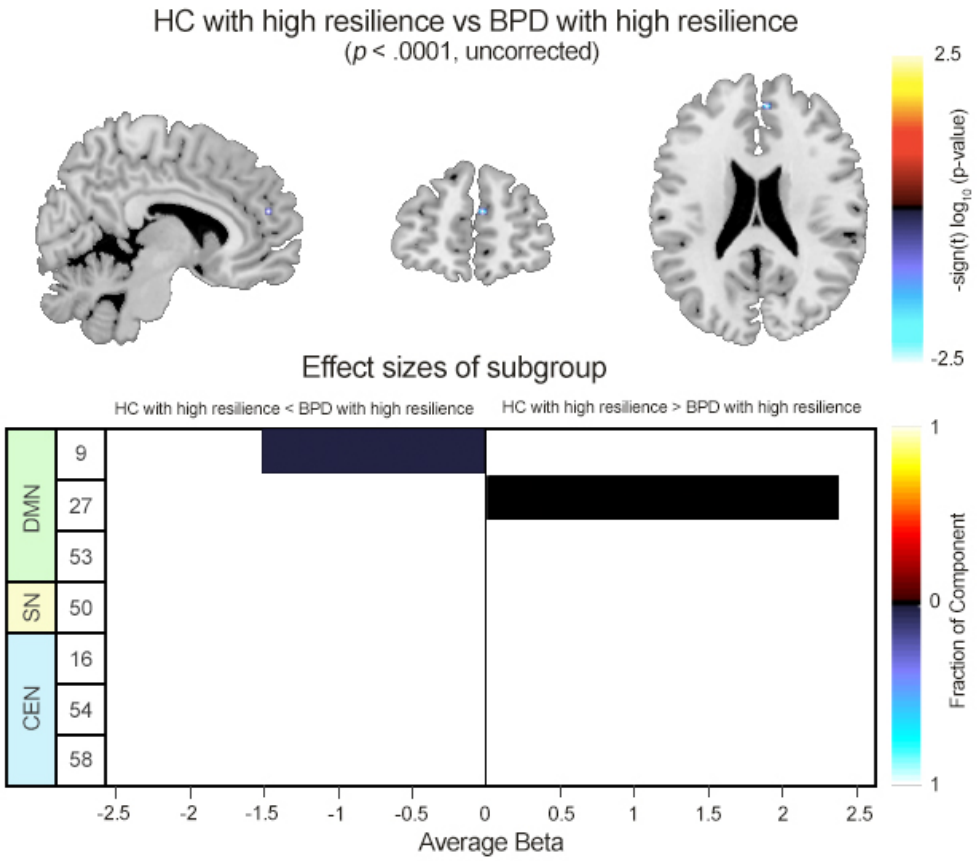

Figure 9. Healthy controls with high resilience (n = 25) versus BPD group with high resilience (n = 11). The top row showed composite maps of significant effects and are displayed as -sign(*t*)log$_{10}$(*p*). The bottom row showed average β-values for subgroup and the colour of the bar is proportional to the fraction of component voxels contributing to each effect. *BPD* = borderline personality disorder; CEN = central executive network; DMN = default mode network; HC = healthy controls; SN = salience network.

6. BPD group with low resilience versus BPD group with high resilience

The BPD group with low resilient functioning (*N* = 26) displayed decreased functional connectivity within the anterior cingulate compared to BPD group with high resilient functioning (*N* = 11), $p < .0001$, uncorrected (refer to Figure 10). This finding did not survive the conservative threshold with corrections for multiple comparisons.

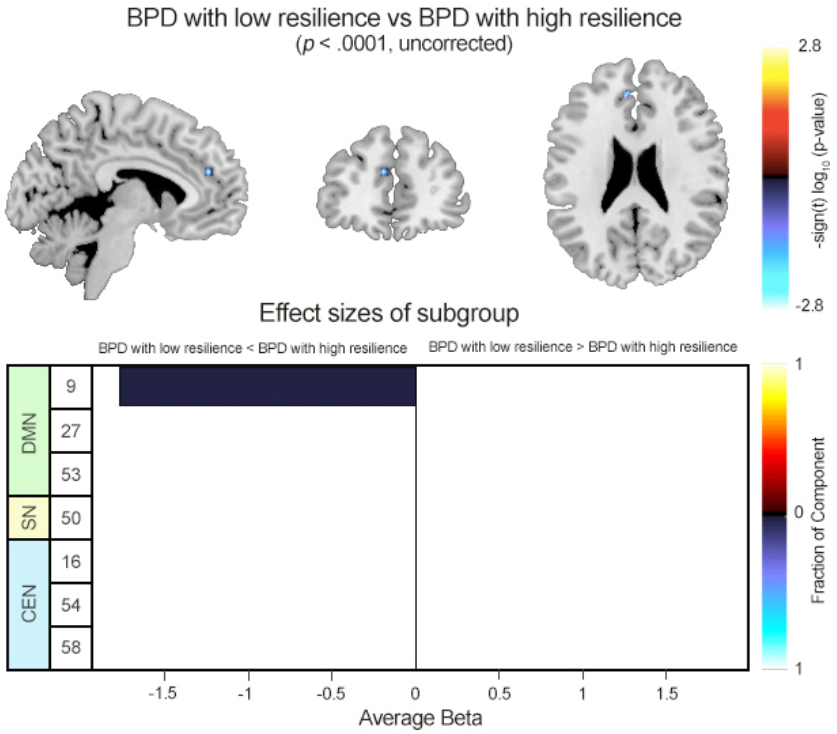

Figure 10. BPD group with low resilience (n = 26) versus BPD group with high resilience (n = 11). The top row showed composite maps of significant effects and are displayed as -sign(*t*)log$_{10}$(*p*). The bottom row showed average β-values for subgroup and the colour of the bar is proportional to the fraction of component voxels contributing to each effect. *BPD* = borderline personality disorder; CEN = central executive network; DMN = default mode network; SN = salience network.

Discussion

In this section, key findings of the current study, limitations of the research, and implications for research and clinical practice were discussed. The current study examined the role of intrinsic functional connectivity networks associated with BPD and resilient functioning. GICA was conducted to examine intrinsic functional connectivity within and between the triple network associated with BPD and resilient

functioning. Overall, findings suggest different patterns of intrinsic functional connectivity within the default mode network and central executive network associated with resilient functioning between healthy individuals and individuals with BPD. There were no significant findings for between-network intrinsic functional connectivity associated with group and resilient functioning. Contrary to resting-state studies, there were no significant findings for intrinsic functional connectivity within the salience network. The study utilised a novel data-driven approach in measuring resilience, where resilient functioning was extracted for each individual based on the difference between reported psychopathology and predicted psychopathology given the individual's reported childhood trauma. Linear regression revealed a cubic relationship between psychopathology and childhood trauma in healthy individuals and individuals with BPD. Findings and their relevance to the current literature are discussed in the section below.

Altered Intrinsic Functional Connectivity in the Default Mode Network Associated with BPD

Contrary to previous resting-state studies, results indicated decreased intrinsic functional connectivity within the precuneus in the BPD group compared to healthy controls. Similarly, individuals with BPD who reported lower psychopathology symptoms than expected given their reported childhood trauma showed decreased intrinsic functional connectivity within the precuneus. Furthermore, group differences (i.e., individuals with BPD vs healthy individuals) in intrinsic functional connectivity within the precuneus remained after controlling for psychopathology symptoms and childhood trauma. Inconsistencies in the direction of intrinsic functional connectivity in the precuneus may be attributed to small sample sizes in the resting-state studies (*N* = 36 in O'Neil et al., 2015; *N* = 27 in Das et al., 2014; *N* = 34 in Wolf et al., 2011), as small sample studies had lower statistical power and limited replicability (Cremers, Wager, & Yarkoni, 2017). Despite the inconsistencies with the directionality of neural findings in BPD, aberrant

intrinsic functional connectivity in the precuneus has been implicated. Thus, the current study provided preliminary evidence suggesting that aberrant intrinsic functional connectivity in the precuneus may be neural-specific to individuals with BPD or specific to psychopathology symptoms characterised by BPD.

Alterations in the precuneus may reflect impairments in the recall of autobiographical memories (Raichle, 2015). In a resting-state study, researchers found decreased intrinsic functional connectivity within the precuneus in individuals with major depression who were treatment naïve (Zhu et al., 2012). Decreased intrinsic functional connectivity in the precuneus was significantly associated with greater overgeneral autobiographical memory (Zhu et al., 2012), which is the tendency to recall broad autobiographical events over specific ones. Low specificity in the recall of autobiographical events was also associated with increased duration and greater chronicity of depression symptoms (Sumner, Griffith, & Mineka, 2010).

In the context of BPD, findings on overgeneral autobiographical memory were inconsistent (Bech, Elklit, & Simonsen, 2015). However, some studies reported that individuals with BPD displayed the tendency to recall specific negative autobiographical events (Bech et al., 2015) and their recall of autobiographical events were more disorganized than healthy individuals (Adler, Chin, Kolisetty, & Oltmanns, 2012). The capacity to recollect autobiographical memories is integral in the development of self-awareness and forming a stable sense of identity (Levine, 2004). Based on the characteristics of autobiographical memory recall in individuals with BPD, Adler et al. (2012) argued that the disorganised recall of autobiographical memories and impairments in the integration of autobiographical memories may be associated with the unstable sense of self presented by individuals with BPD.

Similar hypoactive intrinsic functional connectivity in the precuneus was observed in individuals with chronic PTSD related to early childhood trauma (Bluhm et al., 2009), but not observed in individuals with PTSD related to adversity in adulthood (Akiki et al., 2018). Given that intrinsic functional connectivity within the

default mode network develops over the first nine years of life (Daniels, Frewen, McKinnon, & Lanius, 2011), exposure to early adversity may disrupt the developmental trajectory of connectivity within the default mode network. Thus, aberrant intrinsic functional connectivity within the precuneus may also be associated with exposure to early adversity in individuals with BPD.

Bringing together the different explanations for altered intrinsic functional connectivity in the precuneus discussed above, the relationship between altered intrinsic functional connectivity in the precuneus and impaired self-referential processing in BPD could support the theory of latent vulnerability (McCory, Gerin, & Viding, 2017). The theory postulated that significant early adversity results in alterations in neurobiological systems that are adaptive in early adverse environments (McCory et al., 2017). However, altered neurobiological systems may obstruct the individual's ability to navigate through the demands of normative environments. Thus, the experience of childhood trauma combined with alterations in neurobiological systems increases the individual's latent vulnerability in developing psychopathology later in adulthood (McCory et al., 2017).

In the current study, alterations found in the precuneus may reflect neurobiological changes in response to early adversity. In the context of challenging environments, such as early adversity and caregiver high emotional involvement (Bailey & Grenyer, 2015), privileging specific negative autobiographical memories could be adaptive as it may be an important cognitive process for trauma processing (Schnurr, 2017) and potentially increase emotional involvement from significant others. However, in normative environments, maladaptive self-referential processes may obstruct the individual's ability to accurately infer the mental states of themselves and others. Impaired self-referential processing may lead to long-term consequences of interpersonal, self and emotion dysregulation observed in the BPD population. However, empirical support for the theory of latent vulnerability requires future longitudinal studies to clarify the causal relationship between early adversity,

altered neurobiological mechanisms, and the associated adaptive and/or maladaptive processes.

Predicting Psychopathology Based on Early Adversity

The current study identified a cubic relationship between early childhood trauma and general psychopathology symptoms. As expected, individuals with BPD reported higher levels of childhood trauma as compared to healthy controls. Yet, a substantial minority of healthy individuals were observed to report lower psychopathology symptoms than expected given the higher levels of childhood trauma reported. This finding is similar to the cohort study by Collishaw et al. (2007).

The cubic relationship between early adversity and psychopathology may suggest that general resilience mechanisms were most effective at moderate levels of trauma. At moderate levels of reported childhood trauma, predicted psychopathology symptoms appear to plateau. Indeed, the stress inoculation theory postulated that moderate levels of stress in early life may promote resilience to adversity in later life through the development of necessary coping skills (Branchi & Cirulli, 2014; Eysenck, 1983; Seery, Leo, Lupien, Kondrak, & Almonte, 2013). Animal studies have shown that mice exposed to early stressors were more resistant to stressors in adulthood compared to mice which were not exposed to early stressors (Santarelli et al., 2017). Indeed, Rutter (2006) argued that controlled exposure to adversity may increase resilience to psychopathology. Potentially, the absence of any form of early adversity and severe early adversity may have a significant impact on general resilience mechanisms necessary for positive adaptation in the context of adversity later in adulthood.

Altered Intrinsic Functional Connectivity in the Default Mode Network Associated with Resilient Functioning

The current findings suggest that the association between decreased intrinsic functional connectivity in the anterior cingulate and high resilient functioning were only replicated in the healthy individuals and not in the BPD group. Both

healthy controls with high resilience and the BPD group with low resilience displayed decreased intrinsic functional connectivity in the anterior cingulate (i.e., midline cortical structures) compared to BPD group with high resilience. Similar findings in healthy individuals were reported by van der Werff et al. (2013a), where resilient healthy individuals (i.e., individuals who experienced childhood maltreatment and did not develop psychiatric disorders in adulthood) showed decreased functional connectivity in the anterior cingulate at rest compared to two other groups (i.e., individuals exposed to trauma who developed psychopathology and healthy controls without psychopathology). The researchers argued that decreased functional connectivity in the anterior cingulate may be specific to resilience (van der Werff et al., 2013a).

The anterior cingulate plays a significant role in self-awareness, and the observed decreased intrinsic functional connectivity in both groups (i.e., healthy individuals with high resilience and BPD group with low resilience) may reflect different thought content related to self-referential processing. Increased functional activity in the anterior cingulate displayed by individuals with major depression was found to be positively correlated with rumination (Nejad, Fossati, & Lemogne, 2013). Simultaneously, self-reflection in healthy individuals was associated with increased activation in the anterior cingulate (Herwig, Kaffenberger, Schell, Jäncke, & Brühl, 2012). Although speculative, both adaptive self-reflection and maladaptive rumination may be associated with similar neurological changes. Possibly, increased intrinsic functional connectivity in the anterior cingulate displayed by resilient individuals with BPD may reflect adaptive self-reflection and/or self-awareness. Given that the current study did not provide explicit instructions for self-reflection or asked participants to describe their thoughts during the resting-state scan, the functional significance of decreased intrinsic functional connectivity in the anterior cingulate is speculative. Further investigations on the neurological changes that occur during adaptive self-reflection and maladaptive rumination are warranted.

Though the anterior cingulate is part of the salience network, it was spatially sorted as part of the default mode network in the current study and was consistent with precedent studies (Allen et al., 2011; Manoliu et al., 2014). As mentioned in the review, the ventral regions of the anterior cingulate overlap with the default mode network and salience network. Thus, future studies can use seed-based analysis to distinguish the specific function of different regions within the anterior cingulate.

Low resilient functioning in healthy individuals was associated with increased intrinsic functional connectivity in the posterior cingulate cortex. The posterior cingulate cortex is a hub with extensive influence over other brain regions (Buckner & Vincent, 2007; Fransson & Marrelec, 2018; Uddin, Kelly, Biswal, Castellanos, & Milham, 2009), such as the motor network and the central executive network. Furthermore, the posterior cingulate is a hub within the default mode network which was proposed to act as a "convergence node" where information from the anterior default mode network and posterior default mode network converges (Fransson & Marrelec, 2018). In an fMRI study, functional connectivity in the ventral posterior cingulate cortex decreased as attention was externally directed to a cognitive task, while the functional connectivity in the dorsal posterior cingulate cortex increased as the task became more demanding and required more externally directed attention (Leech, Kamourieh, Beckmann, & Sharp, 2011). Given the connections of the posterior cingulate within the default mode network and beyond the default mode network, researchers suggested that it plays a significant role in switching between internally directed and externally directed attention (Leech et al., 2011). Perhaps, healthy individuals who reported more psychopathology symptoms than expected had more internally directed thoughts or may have had difficulties switching from internally directed attention to externally directed attention to meet task demands. As the current study did not examine the correlations between intrinsic functional connectivity and cognitive processes (e.g., attention), future task-

based fMRI studies can clarify the role of the posterior cingulate in attention and resilient functioning.

Altered Intrinsic Functional Connectivity in the Central Executive Network Associated with Resilient Functioning

Current findings revealed: (1) low resilience in BPD group was associated with increased intrinsic functional connectivity in the right ventral central executive network, and (2) high resilience in healthy individuals was associated with decreased intrinsic functional connectivity in the left ventral central executive network. These preliminary findings suggest that neural correlates of resilience appear to be different between healthy individuals and individuals with BPD. Since functional connectivity in the central executive network typically decreases at rest, increased intrinsic functional connectivity in the central executive network observed in both low resilience subgroups may reflect compensatory mechanisms, where additional neural resources (i.e., central executive network) were recruited at rest. Alternatively, the downregulation of intrinsic functional connectivity in the central executive network at rest may be impaired in individuals with low resilient functioning. As there were limited studies examining the central executive network from a network perspective (Menon, 2011), the functional significance of aberrant intrinsic functional connectivity in the central executive network during resting-state remains unknown.

Limitations

Concurrently, the study had several limitations. Firstly, the study's definition of resilient functioning was narrowed to the degree of general psychopathology symptoms the individual presents given their reported childhood trauma experience. The impact of childhood trauma is not solely dependent on the frequency of traumatic experiences in childhood. Empirical and clinical evidence suggested that the subjective appraisal of the traumatic experience mediates the relationship between trauma and psychopathology (Meiser-Stedman, Dalgleish, Glucksman,

Yule, & Smith, 2009; Palosaari, Punamäki, Diab, & Qouta, 2013; Park, 2010). Subjective appraisals of threat and coping resources have a significant impact on psychopathology. Indeed, Kalisch et al. (2015) proposed appraisal and reappraisal of threat and coping as integral resilience mechanisms, which the current study did not examine.

Secondly, the CTQ, which is a retrospective self-report measure for childhood trauma, possessed inherent limitations such as: (1) the questionnaire was unable to distinguish between "normative" levels of adversity and childhood trauma, particularly in the domain for emotional abuse (McCory et al., 2017); (2) the questionnaire provided no information as to when maltreatment occurred; and (3) the questionnaire was vulnerable to biases in the process of retrospective retrieval of autobiographical memories. Indeed, the construct validity of retrospective measures of childhood trauma has been challenged as a recent meta-analysis revealed poor agreement between prospective and retrospective measures of childhood trauma (Baldwin, Reuben, Newbury, & Danese, 2019). Inconsistencies in self-reported childhood trauma exist — the researchers reported that more than half of the individuals with prospective records of childhood maltreatment did not report childhood maltreatment on retrospective measures, while more than half of the individuals who reported childhood maltreatment on retrospective measures did not have corroborating data on prospective records (Baldwin et al., 2019). Although the CTQ scores obtained in the current study may not be an accurate reflection of actual childhood trauma, we argue that: (1) retrospective measures such as the CTQ measured subjective experiences of childhood trauma; and (2) retrospective reports of childhood trauma may not meet the higher thresholds of childhood trauma used in prospective reports (in Baldwin et al., 2019), which were highly dependent on official records from child protection services.

Thirdly, resilience extends beyond the absence of psychopathology and encompasses well-being in other domains such as emotional, cognitive, behavioural

and social functioning (van Harmelen et al., 2017). Furthermore, external factors that may mediate or moderate resilient functioning were not accounted for, such as parental involvement, nature of peer and parent relationships, and socioeconomic status (Fritz, de Graaff, Caisley, van Harmelen, & Wilkinson, 2018). The presence of external factors contributing to resilient functioning may explain the lack of statistical fit of the observed data in the current study's regression model. Furthermore, resilience may be a dynamic construct that changes across time and context (Masten, 2014; van der Werff et al., 2013b), which further constrained our inferences on static resting-state intrinsic networks associated with resilience.

Fourth, the study design was cross-sectional and correlational in nature and we cannot draw conclusions on the causal relationship between BPD, resilient functioning and intrinsic functional connectivity in the triple network. We were unable to conclude if aberrations in the default mode network and central executive network represented vulnerability to psychopathology, or if these aberrations were products of psychopathology and/or exposure to early adversity. Neural markers of resilient functioning in the context of early adversity can only be established through longitudinal studies, where causal relationships between early adversity, resilient functioning and intrinsic functional connectivity can be ascertained.

Fifth, limitations exist in the data-driven approach. Given that resilient functioning was extracted from the regression model and GICA was conducted using a subset of participants from the same regression model, the measure of resilient functioning and the subsequent interpretation of intrinsic functional connectivity differences may be potentially circular. Instead, the use of separate datasets for modelling resilient functioning and GICA analysis could prevent circularity. This was not completed due to the limited data available. In addition, findings of the current study may be restricted to the dataset and may not be transferable across populations.

Sixth, the study did not control for the effects of medication. The effects of medication on intrinsic networks are not fully understood. Antipsychotic medication was found to be associated with increased functional connectivity in the anterior cingulate and medial prefrontal cortex (Kraguljac et al., 2016). As we did not control for medication, the findings of the study may be confounded by effects of medication on intrinsic networks.

Finally, given the small sample size of the current study, results can only be considered preliminary and require replication in other resting-state studies. The final sample size for GICA analysis (N = 66) was below the target sample size estimated from the power analysis. Despite the small sample size, group differences in the precuneus were still detected. Subgroup comparisons with healthy controls with low resilient functioning (n = 4) were not feasible due to the small sample size. Furthermore, there was limited resting-state fMRI data available for healthy individuals who reported moderate to severe levels of trauma (n = 7), which limited the possibility of investigating the triple network across participants with higher levels of childhood trauma regardless of diagnosis.

Implications for Research and Clinical Practice

Current findings contribute to our understanding of the role of intrinsic functional connectivity in the triple network associated with BPD and resilient functioning. At rest, the current study found altered intrinsic functional connectivity within the precuneus in individuals with BPD compared to healthy individuals. Hypoactive intrinsic functional connectivity of the default mode network in individuals with BPD at baseline may impair task engagement. Since intrinsic functional connectivity in the default mode network is typically suppressed during task engagement, further investigations on the effect of hypoactive intrinsic functional connectivity in the precuneus on task engagement in individuals with BPD is warranted.

Although alterations in the triple network specific to BPD were implicated in several resting-state studies, neural findings remain inconsistent. There is an urgent need for the synthesis and replication of neural markers that are specific to BPD. As intrinsic functional connectivity networks can be consistently identified at rest or during task engagement, GICA allows researchers to make comparisons between specific intrinsic networks across neuroimaging studies and synthesize findings. Understanding the clinical relevance of aberrant intrinsic functional connectivity in the triple network associated with BPD could inform future psychopharmacological interventions to target BPD-specific neural markers.

Furthermore, the current literature review of resilience research highlighted the lack of inclusion of the BPD population, which was often limited to healthy individuals and individuals with DSM VI Axis I diagnoses. Preliminary findings affirmed that the BPD population were exposed to more significant early adversity and showed more maladaptive functioning (i.e., psychopathology symptoms) than healthy individuals, which could be indicative of severe impairments in general resilience mechanisms. We argue that the inclusion of the BPD population was necessary in clarifying neurobiological mechanisms associated with resilience. Future resilience research should take a transdiagnostic approach to examine general resilience mechanisms in individuals across the spectrum of psychopathology symptoms. In addition, current findings highlighted the importance of examining individual differences in resilient functioning. The quantitative measure of resilient functioning has research utility, as it takes into consideration of the individual differences in the severity of childhood trauma and psychopathology symptoms. Grouping individuals based on diagnosis or trauma exposure oversimplifies the construct of resilience. More importantly, the examination of individual differences in the response to adversity would allow future research to examine the causal neurobiological processes underlying resilience mechanisms.

Current findings suggested that altered intrinsic functional connectivity in the anterior cingulate, posterior cingulate and frontoparietal regions in the central executive network were associated with resilient functioning. Implicated regions were associated with self-referential processing, autobiographical memory and cognitive control. Clinically, many psychological therapies have treatment components which may target these processes, such as reflecting on one's own thoughts and feelings, using a longitudinal formulation to understand current difficulties and the rehearsal of coping skills. It remains unknown whether such therapeutic components have an effect in strengthening and/or regulating intrinsic brain architecture associated with resilience and psychopathology. Further research on neurobiological changes associated with clinical interventions could elucidate change mechanisms in specific therapeutic components and facilitate specific and targeted interventions.

Given that neuroimaging findings are still in the early stages of development, there is inherent potential in neuroimaging research to translate the research into clinical utility. Understanding resilience mechanisms associated with intrinsic networks can inform clinical interventions in strengthening specific resilience mechanisms. With increased clarity in the relationship between intrinsic connectivity networks and resilience, interventions can potentially enhance resilience by targeting specific adaptive neural mechanisms using innovative techniques such as transcranial magnetic stimulation. Furthermore, identifying intrinsic networks associated with low resilient functioning could be clinically useful in the identification of vulnerable individuals for early intervention and the identification of resilience mechanisms that promote recovery in patient groups. Further research is warranted to understand the underlying causalities and mechanisms of intrinsic functional connectivity networks, early adversity and psychopathology.

Conclusion

Overall, preliminary findings suggest resting-state intrinsic functional connectivity differences in individuals with BPD compared to healthy controls in the default mode network, specifically within the precuneus. Given the functional significance of self-referential processing associated with the default mode network, further investigations in the causal relationship between intrinsic functional connectivity within the default mode network and psychopathology symptoms are warranted. In addition, findings implicate intrinsic functional connectivity in other nodes within the default mode network, such as the anterior cingulate and posterior cingulate, and the central executive network that were associated with resilient functioning. The current study highlighted the importance of examining individual differences in resilient functioning and the need for a transdiagnostic approach in the study of resilience mechanisms. The findings contribute to future investigations on BPD-specific differences and general resilience mechanisms in intrinsic brain architecture.

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Part 3: Critical Appraisal

Critical Appraisal

Overview

This critical appraisal explores key issues that arose during the research process. First, personal and professional experiences relevant in shaping the research project are detailed. Second, conceptual issues related to resilience are discussed. In particular, the definition of resilience in resilience research and its broader implications are explored. Third, I discuss the wider challenges in neuroimaging research and, fourth, explore future research directions.

Researcher Positionality on Current Research

Prior to clinical training, I was a research assistant in a clinical neuroscience laboratory involved in several functional magnetic resonance imaging (fMRI) and electroencephalogram (EEG) studies. These studies investigated the neurobiological basis of autism spectrum disorder, dyslexia, cognitive impairment in older adults and obsessive-compulsive disorder. Although the research area was challenging, it was exciting to harness innovative and modern neuroimaging techniques to understand brain and behaviour. Beyond disorder-specific neurobiological abnormalities, the current study provided the opportunity to explore intrinsic brain architecture associated with resilience.

As a researcher, understanding the neurological mechanisms that promote positive adaption was intriguing. As a trainee clinical psychologist, I had the privilege of working with individuals with borderline personality disorder (BPD) presenting with high levels of risk. As a witness of my clients' stories of early adverse experiences and persistent levels of emotional distress, the goal of identifying inherent resilience mechanisms to improve the possibility of positive adaption in the context of early adversity was personally important. Thus, the current study was

congruent with my previous research and clinical experience, and my desire to expand my knowledge and skills in the area of neuroscience.

Definition of Resilience and Measuring Resilience: Strengths and Weaknesses

The definition of resilience utilised in the current study was, “an interactive concept that is concerned with the combination of serious risk experiences and a relatively positive psychological outcome despite those experiences” (Rutter, 2006, p. 1). Resilience was quantified using residuals from a linear regression model, where residuals reflected the difference between participants’ predicted and reported psychopathology symptoms based on their self-reported childhood trauma experiences.

A quantitative approach to measuring resilient functioning was advantageous as resilient functioning was triangulated using two self-report measures (i.e., outcomes of psychopathology symptoms and experiences of childhood trauma). The measure avoided self-reported trait resilience, which can be confounded by personality traits such as optimism. In addition, the approach allowed resilient functioning to be measured as a construct based on a continuum. This was not possible in previous research studies on resilience in which researchers compared the following three groups: (1) resilient individuals who were exposed to adversity and did not develop psychopathology, (2) vulnerable individuals who were exposed to adversity and developed psychopathology, and (3) healthy individuals with no exposure to adversity and with no psychopathology. The comparison of three different participant groups did not enable researchers to account for individual differences within each group, such as the severity of childhood trauma and psychopathology symptoms. Thus, the quantitative approach was superior in accounting for individual differences.

However, the assumption that psychopathology is a maladaptive response to adversity is flawed. Evolutionary perspectives on psychopathology postulated that

symptoms of psychopathology are adaptive mechanisms evolved to respond to loss and threat (Gilbert, 2001). For instance, behavioural inactivation and withdrawal may be adaptive responses to situations where danger is present and escape is unlikely. From an evolutionary perspective, submissive behaviours such as inactivity and withdrawal can minimise harm as it signals to the aggressor that there is no challenge. This adaptive response may de-escalate aggression and violence, which promotes the individual's survival. However, persistent behavioural inactivation could lead to unintended consequences when there is no actual danger. Therefore, the presence of psychopathology symptoms in the current study may serve an adaptive function within the individual's context. Following from this argument, judgements of adaptive or maladaptive responses (i.e., psychopathology) are context-dependent and time-dependent.

The flipside of the study's definition of resilience was the implication of low resilient functioning. Given that individuals with BPD reported more severe psychopathology symptoms than healthy individuals, a large proportion of individuals with BPD were categorised in the "low resilient functioning" group. As a clinician, the classification was a dilemma as I had witnessed immense resilience in the face of unimaginable early adversity in many of the clients with whom I had worked. The term "low resilient functioning" had negative connotations, which may implicitly blame individuals for their mental health difficulties. Therefore, the current study considered the neurobiological abnormalities, intrinsic brain architecture associated with resilience and the severity of childhood trauma that may influence resilient functioning. Indeed, based on my clinical experience, clinicians relate neuroimaging findings pertinent to a client's presenting difficulties to help clients make sense of the inherent neural mechanisms that are impaired. In my experience, clients appreciate formulations that are informed by neurobiological findings. Certainly, there is clinical utility in understanding the neurobiological mechanisms of

psychopathology and resilience as it aids individuals and the systems surrounding the individual to make sense of mental health difficulties.

Although the operationalisation of resilience was objective and useful in the research, the relationship between psychopathology and childhood trauma may differ between healthy individuals and individuals with BPD. Healthy individuals were observed to cluster on the lower ends of psychopathology and childhood trauma, while the BPD group was observed to cluster on the moderate to higher ends of psychopathology and childhood trauma. Statistically, it may be possible that pooling two characteristically distinct groups may have underestimated the resilient functioning of individuals with BPD.

On the other hand, the quantitative measurement of resilient functioning allowed the recognition of high resilient functioning individuals in the BPD group. These were individuals who reported lower psychopathology symptoms than expected given the individuals' self-reported childhood trauma. Although the measure of resilient functioning is dependent on the dataset and would vary across datasets, the recognition of positive adaptation in BPD in the current study is unique, as many comparative studies between healthy individuals and individuals with various mental health diagnoses do not acknowledge resilient functioning in the patient group. The measure of resilient functioning has research utility as it provides opportunities for future investigations on the underlying resilience mechanisms that promote recovery in patient groups.

Challenges of Neuroimaging Research

1. 1000 Degrees of Freedom

In the process of reviewing the current literature on resting-state functional connectivity abnormalities in BPD, several key issues were observed: (1) none of the individual resting-state studies reported power analysis to estimate the sample size required to identify activations of interest, (2) methodological decisions made at

different stages of the studies, such as preprocessing, first-level analysis (i.e., within-subject) and second-level analysis (i.e., between-subjects), varied widely across studies, and (3) the thresholds for statistical significance varied across studies and there was no consensus on the need for correcting for multiple comparisons.

Indeed, a random sample of 241 recent neuroimaging studies revealed 207 unique analysis pipelines – there were almost as many analysis methods as studies (Carp, 2012a). Excessive flexibility in methodological decisions had large effects on study outcomes (Carp, 2012b). Carp (2012b) argued that researchers could make small changes to methodological decisions in order to present the most significant findings. Furthermore, as the flexibility of analysis pipelines increases, the risk for false-positive findings increases (Carp, 2012b). Indeed, some researchers suggested that even after correcting for multiple comparisons in resting-state studies, many statistical packages generated cluster level results whereby false-positive rates were up to 70% (Eklund, Nicols, & Knutsson, 2016). Therefore, neuroimaging studies were more vulnerable to false-positive findings and possessed limited replicability of study findings.

In the current study, I attempted to minimise the flexibility of the analysis pipeline by adhering closely to precedent analysis pipelines from Allen et al. (2011), Doll et al. (2013) and Manoliu et al. (2013). In addition, I provided detailed information on data acquisition and the complete analysis pipeline. Furthermore, reporting of the research process was informed by the recommended guidelines in neuroimaging research (Poldrack et al., 2008). These steps aimed to increase the transparency of methodological decisions and increase replicability in future studies. Furthermore, it was necessary to explicitly describe the caveats of the current study, such as being a preliminary exploratory study on intrinsic networks associated with resilience that was limited by a small sample size. Retrospectively, preregistration of

the study detailing the study's hypotheses and analysis pipeline could have increased research transparency.

Nevertheless, methodological variability and the lack of reporting guidelines in neuroimaging studies remain a challenge and require action across different systemic levels of research. It is imperative for neuroscience experts to develop guidelines, similar to Consolidated Standards of Reporting Trials (CONSORT) guidelines, for reporting fMRI research. Existing guidelines (e.g., Poldrack et al., 2008) should be revised to include newer techniques, including functional connectivity analysis and group independent component analysis. Guidelines ensure that research is rigorous and enables future research to use the same methodologies to replicate results. Further research and development in power calculations for resting-state functional connectivity studies are warranted, as the current state of power calculations for fMRI studies are limited to task-based fMRI paradigms. Since power calculations are not validated for functional connectivity studies, researchers do not have the tools necessary to estimate sample sizes required and calculate effect sizes of resting-state functional connectivity results.

2. Post hoc Inferences

The search for brain and behaviour links is complex, as many brain regions do not have a distinct specific function (Schleim & Roiser, 2009). The significant regions of aberrant intrinsic functional activity in the current study, such as the precuneus, anterior cingulate and posterior cingulate, had multiple functions. However, it is common in neuroimaging research to identify specific neurobiological abnormalities and, subsequently, link the specific neurobiological abnormality to a function (i.e., psychological, cognitive or behavioural process) that may fit with the patient group.

The strategy of inferring cognitive processes based on observed neural activation was termed "reverse inference" by Poldrack (2006). The logic behind reverse inference is fallacious because the brain activations (or inactivations)

observed were *not exclusive* to the specific cognitive process or the specific disorder group examined. Given that specific behavioural, psychological and cognitive processes do not map cleanly onto activations in brain regions, the strategy of reverse inference does not allow research to deduce the underlying neural mechanisms necessary for the specific process to occur. The consequence of a cognitive process (i.e., brain activations observed) is an inadequate explanation of how the cognitive process emerged. Therefore, conclusions from many neuroimaging studies were limited to descriptions of the neural activations that supported the specific process (i.e., cognitive, psychological or behavioural), and did not explain *how* the neural activation supported the cognitive process.

3. Missing translation between brain and behaviour

The current study described different patterns of intrinsic functional connectivity between groups (i.e., healthy individuals versus individuals with BPD). However, describing *how* intrinsic networks differ does not mean we: (1) understand how intrinsic functional connectivity causes psychopathology symptoms, and/or (2) know how to change disease-specific mechanisms. The design of the current study only allowed preliminary descriptions of aberrant intrinsic functional connectivity associated with BPD and resilient functioning. However, the bigger questions remained unanswered: Why were intrinsic networks displaying these differences? What were these intrinsic networks for? What do intrinsic networks produce? How do these networks generate the psychopathology symptoms? To what degree do intrinsic networks relate to psychopathology symptoms?

Indeed, researchers have criticised many neuroimaging studies for their narrow focus on describing the properties of neurobiological mechanisms and describing the complex methodologies that led to their findings (Krakauer, Ghazanfar, Gomez-Marin, MacIver, & Poeppel, 2017). Given that computation methods have rapidly advanced during the past 25 years in neuroimaging, a shift towards technique-driven neuroscience was observed (Krakauer et al., 2017).

Krakauer and colleagues used a wonderful metaphor that perfectly encapsulated the problem: *To understand the adaptive behaviour of flight in birds, we do not dissect an ostrich's feathers in detail. Understanding the bird's ability to fly requires understanding a bird's behaviour of flapping its wings and the aerodynamic rules that impact on the properties of the bird's feathers. We can understand flight by studying behaviour and the objective rules of nature that the bird's wings were subjected to, without necessarily having to analyse all the physical parts.* Another metaphor adapted from Woese (2004) expressed the consequence of a reductionist approach: *neuroscience could read notes in the score, but it couldn't hear the music*. Automated big data approaches without regard for the individual are reductionist (Krakauer et al., 2017). Thus, Krakauer et al. (2017) advocated that behavioural work (i.e., understanding behaviour and its component processes) needed to be as detailed as neural work in order to bridge the explanation gap between brain and behaviour.

Reflecting on the research process, the dominance of technique was apparent. As a novice in the area of neuroscience, most resources were directed to: (1) understand the various computation techniques used in the current literature, (2) form an understanding of resting-state studies describing the properties of neural correlates of BPD and resilient functioning, (3) understand precedent group independent component analysis pipelines, and (4) test the current study's analysis pipeline and troubleshoot technical difficulties. With most resources dedicated to technique-related processes, it was difficult to keep a psychological/behavioural framework in mind to guide hypothesis-driven analysis. Possibly, it was easier as a researcher to focus on the analysis process than attempt to look for answers to bridge the colossal gap between brain and behaviour. As Woese (2004, p. 173) aptly pointed out, "*Science is impelled by two main factors, technological advance and a guiding vision. … Without the proper technological advances, the road ahead*

is blocked. Without a guiding vision there is no road ahead". Given the complexities of techniques in the current study, it was easy to lose sight of the road ahead.

Recommendations for Future Research

Consistent with the recommendations from Krakauer et al. (2017), neuroimaging research needs to be guided by a theoretical framework that explains the phenomena (i.e., psychopathology), and supported by carefully crafted experiment paradigms to examine the neural properties associated with the target phenomena. Perhaps, we have not studied psychopathology symptoms in enough detail to develop an overarching biopsychosocial framework that explains BPD symptoms. It is possible that a reliance on self-reported clinical measures was ecologically constrained and did not provide enough detailed information about psychopathology symptoms and the function they serve. Perhaps, we have not studied the behaviours of our clients and/or study participants in enough detail to understand component processes that underpin psychopathology in order to deduce brain and behaviour relationships. Therefore, current research could benefit from the refining of a biopsychosocial framework to explain how altered neurobiological systems lead to the psychopathology observed in BPD or vice versa.

Bridging the immense gap between neural mechanisms and psychopathology requires an interdisciplinary approach. It requires collaborative working and an exchange of ideas across clinicians, researchers using qualitative approaches, statisticians, engineers, and so on. The role of clinical psychology is well situated in the detailed study of psychopathology and the development of theoretical frameworks that explain psychopathology. In retrospect, the current research would have benefited from interdisciplinary input. Seeking for collaborators, especially with the technical aspects of neuroimaging research, could result in better study outcomes, such as combining of datasets to increase the

statistical power of the study and better preprocessing techniques to improve the accuracy of neuroimaging findings.

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Appendix A: Study Coding Sheet

Study ID: _____
Author: _____
Title: _____
Journal: _____
Year: _____ Volume: _____

A. SAMPLE CHARACTERISTICS				
1	Number of participants (N)			
2	Number of participants in treatment arm 1			
3	Number of participants in treatment arm 2 (if any)			
4	Number of participants in control arm			
5	Gender	1 ≥ 80% of N were males	2 ≥ 80% of N were females	3 Mixed gender
6	Duration since trauma event (months)			
7	PTSD symptom duration (years)			
8	Clinical complexity	1	Clinically complex ≥ 80% of the sample met one of the following criteria: (1) presence of multiple problems (i.e., two or more comorbid mental disorders, or being in an ongoing violent relationship, or being a refugee, (2) presence of complex psychological traumatization such as childhood trauma or multiple, or intentional trauma	
		0	Non-complex (i.e., did not meet criteria for 1)	
B. INTERVENTION CHARACTERISTICS				
9	Comparison type	1 waitlist control or treatment as usual or placebo	2 comparative TFCBT intervention	
10	Name of treatment 1			
11	Name of treatment 2			
12	Name of control / comparison			
13	Intervention modality	1 Individual	2 Combined individual and group	
14	Number of intervention sessions offered			
15	Number of skills training sessions offered			
16	Flexibility of treatment	1	Yes, varied number of intervention sessions offered based on clinician	

			evaluation, client's reported reduction in PTSD symptoms or client's preferences.
		0	No
17	Skills training	1	Affect regulation skills E.g. breathing retraining, progressive muscle relaxation, diaphragmatic breathing, stress inoculation training and mindfulness
		2	Interpersonal skills E.g. assertive communication, self-advocacy and empowerment
		3	Affect and interpersonal regulation skills E.g. dialectical behavioural therapy skills, social and emotional rehabilitation
18	Maximum follow up duration (months)		
C. OUTCOME MEASURES OF INTEREST			
19	Clinician-rated PTSD symptom severity at posttreatment	(A)	Name of measure
		(B)	Mean and standard deviation of treatment arm at posttreatment
		(C)	Mean and standard deviation of control arm at posttreatment
20	Attrition rate	(A)	Number of participants in treatment arm who dropped out for any reason after random assignment
		(B)	Number of participants in control arm who dropped out for any reason after random assignment
21	Self-reported PTSD symptom severity at posttreatment	(A)	Name of measure
		(B)	Mean and standard deviation of treatment arm at posttreatment
		(C)	Mean and standard deviation of control arm at posttreatment
22	Self-reported quality of life at posttreatment	(A)	Name of measure
		(B)	Mean and standard deviation of treatment arm at posttreatment
		(C)	Mean and standard deviation of control arm at posttreatment
D. STUDY QUALITY			
23	Random assignment	1	Invalid method used
		2	Unclear how random assignment was conducted
		3	Yes, and clearly reported
24	Power calculation	0	No
		1	Yes
25	Manual-based intervention	0	No
		1	Yes
26	Adherence	0	None
		1	Monitored through supervision only
		2	Session tapes reviewed for adherence
27	Therapist's experience	1	Novice

		2	Graduate students
		3	Qualified clinicians
28	Blinding of personnel at baseline and posttreatment assessment	0	No
		1	Yes
29	Intent to treat analysis	0	No
		1	Yes
30	Treatment of missing values		

Appendix B1: Formulae for Combining Groups

	Group 1 (e.g. males)	Group 2 (e.g. females)	Combined groups
Sample size	N_1	N_2	$N_1 + N_2$
Mean	M_1	M_2	$\frac{N_1M_1 + N_2M_2}{N_1 + N_2}$
SD	SD_1	SD_2	$\sqrt{\frac{(N_1 - 1)SD_1^2 + (N_2 - 1)SD_2^2 + \frac{N_1N_2}{N_1 + N_2}(M_1^2 + M_2^2 - 2M_1M_2)}{N_1 + N_2 - 1}}$

Appendix B2: Formulae for Calculating Within-Group Standard Deviation

From t value to standard error

The t value is the ratio of the difference in means to the standard error of the difference in means. The standard error of the difference in means can therefore be obtained by dividing the difference in means (MD) by the t value:

$$SE = \frac{MD}{t}$$

In the example, the standard error of the difference in means is obtained by dividing 3.8 by 2.78, which gives 1.37.

From confidence interval to standard error

If a 95% confidence interval is available for the difference in means, then the same standard error can be calculated as:

$$SE = (\text{upper limit} - \text{lower limit})/3.92$$

as long as the trial is large. For 90% confidence intervals 3.92 should be replaced by 3.29, and for 99% confidence intervals it should be replaced by 5.15. If the sample size is small then confidence intervals should have been calculated using a t distribution. The numbers 3.92, 3.29 and 5.15 need to be replaced with larger numbers specific to both the t distribution and the sample size, and can be obtained from tables of the t distribution with degrees of freedom equal to $N_E + N_C - 2$, where N_E and N_C are the sample sizes in the two groups. Relevant details of the t distribution are available as appendices of many statistical textbooks, or using standard computer spreadsheet packages. For example, the t value for a 95% confidence interval from a comparison of a sample size of 25 with a sample size of 22 can be obtained by typing =**tinv(1-0.95,25+22-2)** in a cell in a Microsoft Excel spreadsheet.

From standard error to standard deviation

The within-group standard deviation can be obtained from the standard error of the difference in means using the following formula:

$$SD = \frac{SE}{\sqrt{\frac{1}{N_E} + \frac{1}{N_C}}}$$

In the example,

$$SD = \frac{1.37}{\sqrt{\frac{1}{25} + \frac{1}{22}}} = 4.69$$

Note that this standard deviation is the average of the standard deviations of the experimental and control arms, and should be entered into RevMan twice (once for each intervention group).

Appendix C: Risk of Bias Critical Appraisal Tool

RANDOM SEQUENCE GENERATION **Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence.**	
Criteria for a judgement of 'Low risk' of bias.	The investigators describe a random component in the sequence generation process such as: • Referring to a random number table; • Using a computer random number generator; • Coin tossing; • Shuffling cards or envelopes; • Throwing dice; • Drawing of lots; • Minimization*. *Minimization may be implemented without a random element, and this is considered to be equivalent to being random.
Criteria for the judgement of 'High risk' of bias.	The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example: • Sequence generated by odd or even date of birth; • Sequence generated by some rule based on date (or day) of admission; • Sequence generated by some rule based on hospital or clinic record number. Other non-random approaches happen much less frequently than the systematic approaches mentioned above and tend to be obvious. They usually involve judgement or some method of non-random categorization of participants, for example: • Allocation by judgement of the clinician; • Allocation by preference of the participant; • Allocation based on the results of a laboratory test or a series of tests; • Allocation by availability of the intervention.
Criteria for the judgement of 'Unclear risk' of bias.	Insufficient information about the sequence generation process to permit judgement of 'Low risk' or 'High risk'.
ALLOCATION CONCEALMENT **Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment.**	
Criteria for a judgement of 'Low risk' of bias.	Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation:

	• Central allocation (including telephone, web-based and pharmacy-controlled randomization); • Sequentially numbered drug containers of identical appearance; • Sequentially numbered, opaque, sealed envelopes.
Criteria for the judgement of 'High risk' of bias.	Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on: • Using an open random allocation schedule (e.g. a list of random numbers); • Assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or nonopaque or not sequentially numbered); • Alternation or rotation; • Date of birth; • Case record number; • Any other explicitly unconcealed procedure.
Criteria for the judgement of 'Unclear risk' of bias.	Insufficient information to permit judgement of 'Low risk' or 'High risk'. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement – for example if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed.
BLINDING OF PARTICIPANTS AND PERSONNEL **Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.**	
Criteria for a judgement of 'Low risk' of bias.	Any one of the following: • No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; • Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
Criteria for the judgement of 'High risk' of bias.	Any one of the following: • No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; • Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
Criteria for the judgement of 'Unclear risk' of bias.	Any one of the following: • Insufficient information to permit judgement of 'Low risk' or 'High risk'; • The study did not address this outcome.
BLINDING OF OUTCOME ASSESSMENT **Detection bias due to knowledge of the allocated interventions by outcome assessors.**	
Criteria for a judgement	Any one of the following:

of 'Low risk' of bias.	• No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; • Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
Criteria for the judgement of 'High risk' of bias.	Any one of the following: • No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; • Blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
Criteria for the judgement of 'Unclear risk' of bias.	Any one of the following: • Insufficient information to permit judgement of 'Low risk' or 'High risk'; • The study did not address this outcome.
INCOMPLETE OUTCOME DATA **Attrition bias due to amount, nature or handling of incomplete outcome data.**	
Criteria for a judgement of 'Low risk' of bias.	Any one of the following: • No missing outcome data; • Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); • Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; • For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; • For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; • Missing data have been imputed using appropriate methods.
Criteria for the judgement of 'High risk' of bias.	Any one of the following: • Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; • For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; • For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; • 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomization; • Potentially inappropriate application of simple imputation.

Criteria for the judgement of 'Unclear risk' of bias.	Any one of the following: • Insufficient reporting of attrition/exclusions to permit judgement of 'Low risk' or 'High risk' (e.g. number randomized not stated, no reasons for missing data provided); • The study did not address this outcome.

SELECTIVE REPORTING

Reporting bias due to selective outcome reporting.

Criteria for a judgement of 'Low risk' of bias.	Any of the following: • The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; • The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
Criteria for the judgement of 'High risk' of bias.	Any one of the following: • Not all of the study's pre-specified primary outcomes have been reported; • One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; • One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); • One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; • The study report fails to include results for a key outcome that would be expected to have been reported for such a study.
Criteria for the judgement of 'Unclear risk' of bias.	Insufficient information to permit judgement of 'Low risk' or 'High risk'. It is likely that the majority of studies will fall into this category.

THERAPIST ALLEGIANCE

Adapted from Yates et al. (2005) and Patel et al. (2014)

Criteria for a judgement of 'Low risk' of bias.	Any of the following: • None of the below markers for high risk
Criteria for the judgement of 'High risk' of bias.	Any one of the following: • Authors developed the treatment • Authors advocates the treatment • Study declaring allegiance to model/intervention • Therapists or supervisors were also researchers and authors

Criteria for the judgement of 'Unclear risk' of bias.	• Therapists provided both control and treatment interventions

TREATMENT FIDELITY

Adapted from Yates et al. (2005) and Patel et al. (2014)

Criteria for a judgement of 'Low risk' of bias.	Any of the following: • Use of treatment manual • use of unspecified manual / adapted manual produced for trial • Tapes reviewed for adherence
Criteria for the judgement of 'High risk' of bias.	• No markers of the above

THERAPIST QUALIFICATIONS

Adapted from Yates et al. (2005) and Patel et al. (2014)

Criteria for a judgement of 'Low risk' of bias.	Any of the following: • Trained therapists (with or without supervision)
Criteria for the judgement of 'uncertain risk' of bias.	Any of the following: • Therapists in training and supervised

OTHER BIAS

Bias due to problems not covered elsewhere in the table.

Criteria for a judgement of 'Low risk' of bias.	The study appears to be free of other sources of bias.
Criteria for the judgement of 'High risk' of bias.	There is at least one important risk of bias. For example, the study: • Had a potential source of bias related to the specific study design used; or • Has been claimed to have been fraudulent; or • Had some other problem. • e.g. asylum seeker incentive, disability benefit incentives/very small sample size/significant differences in baseline characteristics or poorly reported baseline/ treatment delivered by 1 therapist
Criteria for the judgement of 'Unclear risk' of bias.	There may be a risk of bias, but there is either: • Insufficient information to assess whether an important risk of bias exists; or • Insufficient rationale or evidence that an identified problem will introduce bias. • e.g. real-time translation of assessments (not standardized)

Appendix D: Characteristics of Excluded Studies

No.	Study	Reason for exclusion
1	Adenauer (2011)	No skills training component
2	Arntz (2007)	No skills training component
3	Bedard-Gilligan (2018)	Prolonged exposure vs pharmacological treatment (setraline), with no control group
4	Basoglu (2005)	No skills training component
5	Bischescu (2007)	No skills training component
6	Belleau (2017)	Duration of PTSD symptoms were not reported, thus chronicity of PTSD were unclear.
7	Blanchard (2003)	17.3% of sample were severe sub-syndromal PTSD
8	Boudewyns (1990)	Group-based exposure intervention
9	Brom (1989)	Duration of PTSD symptoms were not reported, thus chronicity of PTSD were unclear. 83 out of 112 participants are bereaved of a loved one due to suicide/murder and complex bereavement / prolonged grief were not assessed.
10	Bryant (2003)	No skills training component
11	Bryant (2011)	24 out of 26 participants were bereaved of a family member due to terrorist attacks and presented with complicated grief.
12	Cigrang (2017)	Only 59% of treatment group and 67% of control group met PTSD criteria.
13	Coffey (2016)	All groups, including control group, received substance abuse treatment as usual, which included daily 3 hour groups, daily recreation therapy, AA and NA meetings and individual drug counseling sessions.
14	Cooper (1989)	No skills training component
15	Cooper (2017)	Non-RCT and comparison of prolonged exposure vs setraline without a control group
16	Crombach (2018)	Non-RCT - non-random assignment into treatment and control groups on the basis of PTSD severity.
17	Darnell (2017)	No PTSD diagnosis
18	de Bont (2016)	Secondary analysis of van den Berg (2015)
19	Devilly (1999)	Large variance in PTSD symptom duration and proportion of chronic PTSD participants were unknown.
20	Dorrepaal (2012)	Group TFCBT
21	Duffy (2007)	No skills training component
22	Dunne (2012)	Duration of PTSD symptoms were not reported, thus chronicity of PTSD were unclear.
23	Echeburua (1996)	Trauma event occurred less than 3 months before entry into study.
24	Echeburua (1997)	No skills training component
25	Ehlers (2003)	No skills training component
26	Ehlers (2005)	No skills training component
27	Ehlers (2014)	No skills training component
28	Feeny (2002)	Subset of larger RCT (Foa et al., 1999)

No.	Study	Reason for exclusion
29	Feske (2008)	Small sample size below 22 (N = 21)
30	Foa (1991)	No skills training component
31	Foa (2006)	Recent trauma event not meeting the PTSD symptom duration criteria.
32	Forbes (2012)	No skills training component
33	Ford (2011)	No skills training component
34	Ford (2018)	No skills training component
35	Galovski (2012)	No skills training component
36	Gesteira (2018)	Journal article written in Spanish.
37	Hendriks (2018)	Non-RCT with no control group.
38	Hensel-Dittmann (2011)	No skills training component
39	Hien (2004)	Non-RCT
40	Hijazi (2014)	No PTSD diagnosis
41	Hinton (2004)	Small sample size below 22 (N = 21)
42	Hinton (2011)	Group TFCBT
43	Jerud (2014)	Prolonged exposure vs pharmacological treatment (setraline), with no control group
44	Keane (1989)	Duration of PTSD symptoms were not reported, thus chronicity of PTSD were unclear.
45	Kruger (2014)	Subset of larger RCT (Bohus et al., 2013)
46	Maercker (2006)	47% of participants (20 out of 42) did not meet full PTSD criteria.
47	Markowitz (2015)	No skills training component
48	Marks (1998)	No skills training component
49	McGovern (2011)	Duration of PTSD symptoms were not reported, thus chronicity of PTSD were unclear.
50	Mills (2012)	Duration of PTSD symptoms ranged from 1 month to 40 years (unclear proportion of individuals with chronic PTSD)
51	Monson (2006)	No skills training component
52	Morath (2014)	Duration of PTSD symptoms were not reported, thus chronicity of PTSD were unclear.
53	Mueser (2015)	Duration of PTSD symptoms were not reported, thus chronicity of PTSD were unclear.
54	Mueser (2008)	Duration of PTSD symptoms were not reported, thus chronicity of PTSD were unclear.
55	Nacasch (2011)	No skills training component
56	Najavits (2018)	No skills training component
57	Neuner (2004)	No skills training component
58	Neuner (2008)	Duration of PTSD symptoms were not reported, thus chronicity of PTSD were unclear.
59	Neuner (2010)	Duration of PTSD symptoms were not reported and only 85% of participants had PTSD diagnosis according to the DSM-IV.

No.	Study	Reason for exclusion
60	Nijdam (2013)	Eclectic psychotherapy included main components of TFCBT, grief therapy, directive therapy and psychodynamic approach.
61	Nordahl (2018)	Trial pending results.
62	Paunovic (2001)	No skills training component
63	Paunović (2011)	No skills training component
64	Polak (2015)	Non-RCT, TFCBT vs TFCBT and biofeedback
65	Power (2002)	No skills training component
66	Rabe (2008)	Subset of larger RCT (Maercker, 2006), only 48.5% of participants met PTSD criteria
67	Resick (2008)	No skills training component
68	Sannibale (2013)	No skills training component
69	Schnurr (2007)	No skills training component
70	Steel (2017)	Duration of PTSD symptoms were not reported, thus chronicity of PTSD were unclear.
71	Stenmark (2013)	Duration of PTSD symptoms were not reported, thus chronicity of PTSD were unclear.
72	Tarrier (2000)	No skills training component
73	Taylor (2003)	No skills training component
74	Tecic (2009)	No PTSD diagnosis
75	van Dam (2013)	61.8% of the total sample met DSM-IV criteria of PTSD
76	van den Berg (2016)	Subset of larger RCT (van den Berg, 2015)
77	van Emmerik (2008)	46.4% of the sample met criteria for chronic PTSD.
78	Vaughan (1994)	78% of the total sample met DSM-III criteria of PTSD.
79	Wang (2016)	61.5% of the intervention group met DSM-IV criteria for PTSD and integrated treatment group included TFCBT, biofeedback, vitamins and group physiotherapy.
80	Weiss (2015)	No PTSD diagnosis
81	Wells (2015)	No skills training component
82	Yehuda (2009)	Non-RCT with no control group.
83	Zang (2013)	No skills training component

Appendix E: Characteristics of Included Studies

Asukai (2010)

Methods	Randomised controlled trial
Participants	24 individuals (Japanese) with PTSD related to crime and accident-related single trauma (3 males, 21 females)
Interventions	8 to 15 sessions (each 90 minute) of prolonged exposure (*N* = 12) vs treatment as usual (*N* = 12)
Outcomes	CAPS, IES-R, CES-D, GHQ-28
Notes	10 out of 12 of the participants in the treatment group received treatment as usual. Treatment as usual included supportive counselling and psychopharmacology. Both groups were similar at baseline on all measures.

Risk of bias table

Bias	Author's judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Allocation of the eligible patients to one of the two treatment groups: the PE group and the control group (TAU only), was randomized by the study site based on computer-generated random digit numbers by permuted blocks between 4 and 8."
Allocation concealment (selection bias)	Unclear risk	Comment: There were no reported measures of allocation concealment.
Blinding of participants and personnel (performance bias)	High risk	Comment: Participants were aware of their allocation. Study did not measure and control for treatment expectancy.
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Two independent female masters-level psychologists, who were unaware of the patients' treatment group, performed all assessments at pretreatment, posttreatment, and 3- and 6-month follow-up. The 12-month follow-up assessment was conducted via mail. Blindness was maintained by ensuring that the assessors had no access to group allocation and never talked with patients about which group they were in."
Incomplete outcome data (attrition bias)	Low risk	Quote: "intention-to-treat analysis was performed to determine the relative effect between the two treatment groups for each periodic post-treatment assessment, and those between pre-PE (after the waiting period) and post-PE treatment in the control group (CAPS total score, IES-R, CES-D, and GHQ-28)." Comment: However, reasons for dropout were not fully reported.

Selective reporting (reporting bias)	Low risk	Comment: All specified outcomes have been reported.
Therapist allegiance	High risk	Comment: All therapists were authors of paper.
Treatment fidelity	Low risk	Quote: “All sessions were videotaped and reviewed weekly by the first author to ensure treatment integrity.”
Therapist qualification	Low risk	Comment: Trained therapists
Other bias	Low risk	Comment: No other source of bias was found.

Beidel (2011)

Methods	Randomised controlled trial
Participants	35 veterans with combat-related PTSD (all males)
Interventions	28 sessions – 14 individual and 14 group (each 90 minutes) of trauma management therapy with exposure therapy (*N* = 18) vs exposure therapy (*N* = 17)
Outcomes	CAPS, PCL-M, QLQ, HAMA, HAMD
Notes	Both groups were similar at baseline on all measures.

Risk of bias table

Bias	Author’s judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: “Among the 35 veterans who were randomly assigned and began treatment…” Comment: Method of random assignment was not sufficiently reported.
Allocation concealment (selection bias)	Unclear risk	Comment: There were no reported measures of allocation concealment.
Blinding of participants and personnel (performance bias)	Unclear risk	Quote: “Assessment of treatment credibility did not indicate any differences between groups.”
Blinding of outcome assessment (detection bias)	Unclear risk	Comment: Insufficient information on whether assessors for primary outcome measures were blinded. Authors reported, “independent evaluators, blinded to treatment condition, completed the following rates at pre- and posttreatment” specific to secondary measures such as the HAMA and HAMD.
Incomplete outcome data (attrition bias)	High risk	Comment: Dropouts were excluded from analysis and not properly accounted for in statistical analysis. Reasons for dropout were reported.
Selective reporting (reporting bias)	High risk	Quote: “although we collected follow-up data on 10 of the 30 participants, a number of patients declined to return to the clinic simply for assessments, coupled with the move of the first

		author to a different university, did not allow collection of follow-up data on the majority of participants." Comment: Follow up duration was not specified in protocol.
Therapist allegiance	High risk	Comment: First author developed treatment protocol and supervised all therapists providing intervention. All therapists provided interventions to both treatment arms.
Treatment fidelity	Low risk	Quote: "To determine treatment fidelity, 20% of the sessions were randomly selected for review by the first author. There were no protocol violations."
Therapist qualification	Low risk	Qualified and trained therapists
Other bias	High risk	Quote: "many participants in the current study expressed concerns about losing their disability benefits if their hospital records reflected significant improvement in PTSD symptoms." Comment: Participant's concerns with disability benefits may influence their responses on outcome measures.

Bohus (2013)

Methods	Randomised controlled trial
Participants	74 individuals with childhood sexual abuse related PTSD (all females)
Interventions	91 sessions – 23 individual sessions (each 45 minutes) and 65 group sessions (ranging from 25 to 90 minutes) Dialectical Behaviour Therapy for Post-traumatic Stress Disorder (*N* = 36) vs treatment as usual/waitlist (*N* = 38)
Outcomes	CAPS, PDS, BSL, DES, BDI-II, GAF, SCL-90R
Notes	Study was conducted in residential setting. Treatment as usual / waitlist included psychosocial and/or psychopharmacology. Sleep disorders and major depressive episodes were treated with psychopharmacology in the DBT-PTSD group. Both groups were similar at baseline on all measures.

Risk of bias table

Bias	Author's judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "… eligible participants were randomly assigned in a 1:1 ratio to either the DBT- PTSD arm or the TAU-WL arm." Comments: Method of random assignment was not sufficiently reported.

Allocation concealment (selection bias)	Low risk	Quote: “Participants and all persons involved in the study were blinded to treatment assignment until written informed consent had been obtained.”
Blinding of participants and personnel (performance bias)	High risk	Comment: Participants were aware of their allocation. Study did not measure and control for treatment expectancy.
Blinding of outcome assessment (detection bias)	Low risk	Quote: “the clinicians who conducted the posttreatment assessments remained blinded to treatment assignment throughout the study.”
Incomplete outcome data (attrition bias)	Low risk	Quote: “For the intention-to-treat effect sizes, we chose a conservative approach (last observation carried forward).” Comment: However, reasons for dropouts were not reported.
Selective reporting (reporting bias)	Low risk	Comment: All specified outcomes have been reported.
Therapist allegiance	High risk	Quote: “All therapists were involved in the treatment development. DBT-PTSD will be published as a manual and is distributed by workshops for which five authors receive income.”
Treatment fidelity	Low risk	Quote: “All individual sessions were videotaped. Video-based live online supervision was provided weekly to ensure therapists’ adherence and competence.”
Therapist qualification	Unclear risk	Quote: “Therapists were graduate and post-graduate psychologists who had been trained in DBT and in trauma-focused CBT.”
Other bias	Low risk	Comment: No other source of bias was found.

Buhmann (2016)

Methods	Pragmatic Randomised controlled trial
Participants	280 refugees with war-related PTSD (128 males, 89 females post allocation)
Interventions	16 sessions (duration not reported) of Cognitive Behavioural Therapy (*N* = 70) vs waitlist (*N* = 68) vs psychopharmacology and CBT (*N* = 71) and psychopharmacology (*N* = 71)
Outcomes	HTQ, HSCL-25, HAMA, HAMD, SCL-90, VAS, SDS, WHO-5
Notes	Two treatment arms were not included in the meta-analysis (i.e., psychopharmacology group, psychopharmacology and CBT group). Both groups were similar at baseline on all measures.

Risk of bias table

Bias	Author’s judgement	Support for judgement

Random sequence generation (selection bias)	High risk	Quote: “Randomisation was stratified by gender and total score on HTQ (above or below 3.2), so that patients with equal illness severity were allocated to all groups.”
Allocation concealment (selection bias)	Low risk	Quote: “Allocation was concealed by using sequentially numbered sealed envelopes. The envelopes were kept in an office physically separate from the clinic and were administered by secretaries, who were not associated with the research project.”
Blinding of participants and personnel (performance bias)	High risk	Comment: Participants were aware of their allocation. Study did not measure and control for treatment expectancy.
Blinding of outcome assessment (detection bias)	Low risk	Comment: Primary outcome measures were based on participant’s self-report.
Incomplete outcome data (attrition bias)	Low risk	Quote: “To conduct intention-to-treat analyses with all 280 patients, a full information maximum likelihood (FIML) was used in analyses, which included both pre- and posttreatment scores.” Comment: Reasons for dropouts were reported.
Selective reporting (reporting bias)	Low risk	Comment: All specified outcomes have been reported.
Therapist allegiance	Unclear risk	Comment: No information about author’s links to interventions provided, or descriptions about psychologist providing CBT.
Treatment fidelity	Unclear risk	Quote: “Even though treatment was manualised there was some variability in the treatment offered.”
Therapist qualification	Low risk	Quote: “Psychologists trained in CBT and receiving supervision by specialists in CBT conducted the psychotherapeutic treatment.”
Other bias	Unclear risk	Comment: Primary outcome measure, HTQ, was a self-report measure which was translated into six common languages. 48% of CBT group required translation in therapy.

Chard (2005)

Methods	Randomised controlled trial
Participants	71 individuals with childhood sexual abuse related PTSD (all females)
Interventions	27 sessions – 10 individual sessions (each 60 minutes) and 17 group sessions (each 90 minutes) of Cognitive Processing Therapy for sexual abuse survivors (CPT-SA, *N* = 36) vs waitlist (*N* =35)
Outcomes	CAPS, MPSS, BDI-II, DES-II
Notes	Participants in the waitlist group received 5 to 10

	minutes weekly phone calls providing supportive counselling. Both groups were similar at baseline on all measures.

Risk of bias table

Bias	Author's judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comments: Method of random assignment was not sufficiently reported.
Allocation concealment (selection bias)	Unclear risk	Comment: There were no reported measures of allocation concealment.
Blinding of participants and personnel (performance bias)	High risk	Comment: Participants were aware of their allocation. Study did not measure and control for treatment expectancy.
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Research assistants blind to the assigned condition of the subject conducted all interviews, and treatment completers were asked not to mention having been in therapy at posttreatment assessments."
Incomplete outcome data (attrition bias)	Low risk	Comment: Intent to treat analyses were conducted and all specified outcomes were reported. However, reasons for dropout were not reported.
Selective reporting (reporting bias)	Low risk	Comment: All specified outcomes have been reported.
Therapist allegiance	High risk	Comment: Author developed treatment manual adapted for childhood sexual abuse survivors and was involved in delivering group and individual interventions.
Treatment fidelity	Low risk	Quote: "All sessions were videotaped, and the principal investigator provided weekly adherence supervision."
Therapist qualification	Unclear risk	Quote: "The therapy groups were run by seven therapists, including the principal investigator and six graduate students in psychology with a background in cognitive–behavioral interventions."
Other bias	Low risk	Comment: No other source of bias was found.

Cloitre (2002)

Methods	Randomised controlled trial
Participants	58 individuals with childhood sexual abuse related PTSD (all females)
Interventions	16 sessions – 8 sessions (each 60 minutes) of Skills Training in Affect and Interpersonal Regulation and 8 sessions (90 minutes) of modified prolonged exposure (*N* = 31) vs waitlist (*N* = 27)
Outcomes	CAPS, MPSS, NMR, BDI, DISS, IIP, SAS, ISEL, Ax/Ex, TAS-20, STAI-S

Notes	Participants in waitlist group received weekly phone calls (each 15 minutes) with the clinical coordinator. Both groups were similar at baseline on all measures.

Risk of bias table

Bias	Author's judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comments: Method of random assignment was not sufficiently reported.
Allocation concealment (selection bias)	Unclear risk	Comment: There were no reported measures of allocation concealment.
Blinding of participants and personnel (performance bias)	High risk	Comment: Participants were aware of their allocation. Study did not measure and control for treatment expectancy.
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Clinician raters were blind to treatment condition at pre- and posttreatment."
Incomplete outcome data (attrition bias)	Low risk	Comment: Intent to treat analysis were conducted. However, reasons for dropout were not provided.
Selective reporting (reporting bias)	High risk	Bisson et al. (2013): "There is emphasis on reporting improvements in affect regulation and interpersonal skills as opposed to PTSD symptoms. The Methods section does not seem to indicate that these were the primary outcome measures."
Therapist allegiance	High risk	Comment: Author supervised all therapists delivering intervention and developed STAIR modified PE treatment protocol.
Treatment fidelity	Low risk	Quote: "Audiotapes of 44 therapy sessions (11% of 408 sessions) were rated."
Therapist qualification	Low risk	Quote: "Treatment sessions were conducted by five female doctoral-level clinical psychologists. Therapists were trained using manuals with treatment guidelines and received weekly supervision."
Other bias	Low risk	Comment: No other source of bias was found.

Cloitre (2010)

Methods	Randomised controlled trial
Participants	104 individuals with childhood sexual abuse related PTSD (all females)
Interventions	16 sessions – 8 sessions (each 60 minutes) of Skills Training in Affect and Interpersonal Regulation and 8 sessions (90 minutes) of modified prolonged exposure (STAIR/PE; *N* = 33) vs 16 sessions of supportive counselling and modified prolonged

	exposure (Support/Exposure; *N* = 33) vs 16 sessions of STAIR and supportive counselling (*N* = 38)
Outcomes	CAPS, PSS, NMR, BDI, DISS, IIP, ISEL, Ax/Ex, STAI-S
Notes	All groups were similar at baseline on all measures. The STAIR and supportive counselling group were not considered in the meta-analysis as the effect of skills training alone was not included in the research question.

Risk of bias table

Bias	Author's judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomization blocks of nine (three instances of each of the three conditions) were employed, generated by an individual not otherwise involved with the study."
Allocation concealment (selection bias)	Low risk	Quote: "Randomization blocks of nine (three instances of each of the three conditions) were employed, generated by an individual not otherwise involved with the study."
Blinding of participants and personnel (performance bias)	High risk	Comment: Participants were aware of their allocation. Study did not measure and control for treatment expectancy.
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Diagnostic assessments were conducted by independent raters who were blind to treatment condition."
Incomplete outcome data (attrition bias)	Low risk	Quote: "Analyses for all symptom outcome measures were performed on the intent-to-treat sample using data from all participants according to their randomization assignment. Missing data were imputed using PROC MI in SAS to generate 10 imputed data sets. Comment: Intent to treat analysis conducted. However, reasons for dropout were not reported.
Selective reporting (reporting bias)	Low risk	Comment: All specified outcomes were reported.
Therapist allegiance	High risk	Comment: Author supervised all developed STAIR modified PE treatment protocol. All therapists provided intervention in each treatment arm.
Treatment fidelity	Low risk	Quote: "Ten percent of all treatment sessions were randomly selected and rated by graduate-level research assistants trained to an adherence protocol."
Therapist qualification	Low risk	Quote: "The therapy was conducted by one of nine female master's

		degree-level or doctorate-level clinical psychologists or social work staff who were manual trained and received weekly supervision by the first author or expert clinicians trained by the first author."
Other bias	Low risk	Comment: No other source of bias was found.

Cottraux (2008)

Methods	Randomised controlled trial
Participants	60 outpatients with DSM-IV chronic PTSD (18 males, 42 females)
Interventions	10 to 16 sessions (each 60 to 120 minutes) of Cognitive Behaviour Therapy (*N* = 31) vs 16 sessions (each 60 minutes) of Supportive Therapy (*N* = 29)
Outcomes	PCL, BDI-13, FQ, HAMA, Mark's Quality of Life Scale
Notes	Data was collected from two sites. Validated French versions of outcome measures were used. Both groups were similar at baseline on all measures.

Risk of bias table

Bias	Author's judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomization was performed using blocks of 4 patients for each center."
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was concealed and organized by the Statistics Department at the 'Hospices Civils de Lyon'. The Statistics Department informed the center's secretary of each patient's group allocation by phone. After initial assessment by a psychologist, the secretary then informed the patient about his or her group allocation."
Blinding of participants and personnel (performance bias)	High risk	Comment: Participants were aware of their allocation. Study did not measure and control for treatment expectancy.
Blinding of outcome assessment (detection bias)	Low risk	Quote: "An independent evaluator performed the assessment at weeks 0, 16, 52 and 104. The evaluator did not take part in the treatment and was blind to the nature of each therapeutic condition."
Incomplete outcome data (attrition bias)	Low risk	Comment: Intent to treat analysis was conducted with the last observation carried forward procedure.
Selective reporting (reporting bias)	Low risk	All specified outcomes appear to be reported. Reasons for dropout were reported.

Therapist allegiance	Unclear risk	Quote: “The same therapists administered both CBT and ST. All were CBT-oriented therapists and this may have biased the treatment in favor of CBT as the therapists were requested to use methods they judged as noneffective.”
Treatment fidelity	Unclear risk	Quote: “The therapists had homemade manuals on CBT or ST written according to the methods reported in the classical books on the topic.”
Therapist qualification	Low risk	Quote: “The therapists were senior psychologists or psychiatrists with a CBT diploma (i.e., 3 years of training).”
Other bias	Low risk	Comment: No other source of bias was found.

Fecteau (1999)

Methods	Randomised controlled trial
Participants	23 individuals with motor vehicle accident related chronic PTSD (6 males, 14 females). The study did not report how many males and females were originally included in the study.
Interventions	4 sessions (each 1.5 to 3 hours) of Cognitive Behavioural Therapy (*N* =12) vs waitlist (*N* = 11)
Outcomes	CAPS, IES, BAI, BDI, AFQ
Notes	Both groups were similar at baseline on all measures.

Risk of bias table

Bias	Author’s judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “Participants were then randomly assigned to the treatment or waitlist groups by a flip of coin.”
Allocation concealment (selection bias)	Unclear risk	Comment: There were no reported measures of allocation concealment.
Blinding of participants and personnel (performance bias)	High risk	Comment: Participants were aware of their allocation. Study did not measure and control for treatment expectancy.
Blinding of outcome assessment (detection bias)	Low risk	Quote: “These interviews were conducted by a trained independent rater, a licensed psychologist, who was unaware of participants’ group assignment.”
Incomplete outcome data (attrition bias)	High risk	Comment: Dropouts (2 from treatment group and 1 from waitlist) were excluded from analysis. However, reasons for dropout were reported. Dropouts were excluded from analysis and no intent to treat analysis were completed.
Selective reporting (reporting bias)	Low risk	Comment: All specified outcomes were reported.

Therapist allegiance	High risk	Comment: The first author provided therapy for all participants.
Treatment fidelity	Low risk	Quote: “Eight sessions, two for each of sessions 1 to 4, were chosen randomly and taped for independent review.”
Therapist qualification	Low risk	Quote: “Therapist is a licensed psychologist with 15 years clinical experience at the time of starting the project, including some experience providing assessment and therapy for this population over the past 9 years.”
Other bias	High risk	Comment: Small sample size

Foa (1999)

Methods	Randomised controlled trial
Participants	96 assault victims with chronic PTSD (all females)
Interventions	9 sessions (two 120 minute sessions, seven 90 minute sessions) of Prolonged exposure and Stress Inoculation Training (PE-SIT; *N* = 30) vs 9 sessions (two 120 minute sessions, seven 90 minute sessions) of Prolonged exposure only (PE; *N* = 25) vs 9 sessions (two 120 minute sessions, seven 90 minute sessions) of Stress Inoculation Training only (SIT; *N* = 26) vs 15 waitlist
Outcomes	PSS-I, BDI, STAI, SAS
Notes	Participants in waitlist group received one phone call from a therapist during waiting period to determine their current status. The SIT only group were excluded from the meta-analysis. Means and standard deviations of the PE and PE-SIT group were combined as both groups had components of TFCBT and skills training (i.e., breathing retraining and/or stress inoculation training.) All groups were similar at baseline on all measures.

Risk of bias table

Bias	Author’s judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comments: Method of random assignment was not reported, and the study assigned more participants into treatment groups after enrolling 10 participants in the waitlist.
Allocation concealment (selection bias)	Unclear risk	Comment: There were no reported measures of allocation concealment.
Blinding of participants and personnel (performance bias)	High risk	Comment: Participants were aware of their allocation. Study did not measure and control for treatment expectancy.
Blinding of outcome assessment (detection bias)	Low risk	Quote: “Independent evaluators were female clinicians with at least a master’s degree who received extensive training in administration of the instruments and were unaware of

		treatment assignment."
Incomplete outcome data (attrition bias)	Low risk	Comment: Intent to treat analyses were conducted using a last value carried forward procedure to impute missing data due to dropout. However, reasons for dropout were not reported.
Selective reporting (reporting bias)	Low risk	Comment: All specified outcomes were reported.
Therapist allegiance	High risk	Comment: Supervisors supervising therapists providing treatment developed treatment manual and were authors of the paper.
Treatment fidelity	Low risk	Quote: "Videotapes of 63 therapy sessions (9% of the 702 sessions) were randomly selected and rated. Raters were familiar with the treatment programs but had not treated any participants in this study."
Therapist qualification	Low risk	Quote: "Individual treatment was conducted by seven female PhD-level clinical psychologist."
Other bias	Unclear risk	Comment: Uneven group size as waitlist sample was considerably small.

Foa (2005)

Methods	Randomised controlled trial
Participants	179 assault survivors with chronic posttraumatic stress disorder (all females)
Interventions	9 to 12 sessions (each 90 to 120 minutes each) Prolonged exposure (*N* = 79) vs 9 to 12 sessions (each 90 to 120 minutes each) Prolonged exposure and cognitive restructuring (*N* = 74) vs waitlist (*N* = 26)
Outcomes	PSS-I, BDI, SAS, PSS-SR
Notes	PE/CR group showed lower PSS-I scores than PE group at baseline. PE and PE/CR groups were combined in the meta-analysis.

Risk of bias table

Bias	Author's judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The study statistician assigned participants who provided informed consent to one of the three conditions using a weighted randomization procedure such that participants were assigned to one of the active treatment conditions at a greater rate than to waitlist." Comment: Method of random sequence generation was not sufficiently reported.
Allocation concealment	Low risk	Comment: Study statistician assigned

(selection bias)		participants who provided informed consent to condition and therapists made contact with the participants after assignment.
Blinding of participants and personnel (performance bias)	High risk	Comment: Participants were aware of their allocation. Study did not measure and control for treatment expectancy.
Blinding of outcome assessment (detection bias)	Low risk	Quote: "All evaluations were conducted by trained doctoral or master's level CTSA clinicians who were blind to the study condition."
Incomplete outcome data (attrition bias)	Low risk	Comment: Intent to treat analysis was conducted. However, reasons for dropout were not reported and dropout rate was high in treatment groups (1 from waitlist, 30 from PE/CR and 27 from PE group).
Selective reporting (reporting bias)	High risk	Comment: PSS-SR was specified as a secondary outcome measure and not reported in results section, apart from the within treatment group comparisons.
Therapist allegiance	High risk	Comment: Supervisors supervising therapists providing treatment developed treatment manual and were authors of the paper.
Treatment fidelity	Low risk	Quote: "Using adherence manuals, we randomly selected and rated videotapes of 141 therapy sessions (11.5% of 1227 sessions) for fidelity to treatment manual.
Therapist qualification	Low risk	Quote: "Five clinicians with doctoral degrees in clinical psychology administered the treatments at CTSA; six clinicians with master's degrees in counselling or social work administered the treatments at WOAR."
Other bias	Unclear risk	Comment: Uneven group size as waitlist sample was considerably small.

Hinton (2005)

Methods	Randomised controlled trial
Participants	40 Cambodian refugees with treatment-resistant PTSD and panic attacks (16 males, 24 females)
Interventions	12 sessions of Cognitive Behavioural Therapy (*N* = 20) vs delayed treatment (*N* = 20)
Outcomes	CAPS, ASI, SCL-90, N-PASS, O-PASS, N-FSS, O-FSS
Notes	All participants received supportive psychotherapy which consisted of fortnightly meetings with a social worker and psychopharmacology. All groups were similar at baseline on all measures.

Risk of bias table

Bias	Author's judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Eligible participants who agreed to participate were stratified by gender, with random allocation to either the Immediate treatment or the Delayed treatment group decided by a coin toss."
Allocation concealment (selection bias)	Unclear risk	Comment: There were no reported measures of allocation concealment.
Blinding of participants and personnel (performance bias)	High risk	Comment: Participants were aware of their allocation. Study did not measure and control for treatment expectancy.
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Blind to treatment condition, all assessments were made by a Cambodian bicultural worker."
Incomplete outcome data (attrition bias)	Low risk	Quote: "All randomised participants completed the study, and there were no missing data."
Selective reporting (reporting bias)	Low risk	Comment: All specified outcomes were reported.
Therapist allegiance	High risk	Comment: First author developed treatment protocol and delivered intervention for all participants.
Treatment fidelity	Unclear risk	Comment: It is unclear whether treatment adherence was assessed.
Therapist qualification	Low risk	Comment: Therapist was an experienced doctoral level practitioner and researcher.
Other bias	Low risk	Comment: No other source of bias was found.

Kubany (2003)

Methods	Randomised controlled trial
Participants	37 individuals with partner-abuse related PTSD (all females)
Interventions	8 to 11 sessions (each 1.5 hours) of Cognitive Trauma therapy (*N* = 19) vs delayed treatment (*N* = 18)
Outcomes	CAPS, BDI, RSES, TRGI, STRGS-PA, PFQ
Notes	All groups were similar at baseline on all measures.

Risk of bias table

Bias	Author's judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "After these assessments, the women were randomly assigned to either an Immediate or a Delayed CTT-BW condition." Comment: Method of random sequence generation was not sufficiently reported.

Allocation concealment (selection bias)	Unclear risk	Comment: There were no reported measures of allocation concealment.
Blinding of participants and personnel (performance bias)	High risk	Comment: Participants were aware of their allocation. Study did not measure and control for treatment expectancy.
Blinding of outcome assessment (detection bias)	Low risk	Quote: "The assessors were blind to participants' condition assignments."
Incomplete outcome data (attrition bias)	Low risk	Comment: Intent to treat analysis was conducted. However, reasons for dropout were not reported.
Selective reporting (reporting bias)	Low risk	Comment: All specified outcomes were reported.
Therapist allegiance	High risk	Comment: First author developed treatment manual and delivered intervention for all participants.
Treatment fidelity	Unclear risk	Comment: It is unclear whether treatment adherence was assessed.
Therapist qualification	Low risk	Comment: Qualified and experienced therapist delivered intervention.
Other bias	Low risk	Comment: No other source of bias was found.

Kubany (2004)

Methods	Randomised controlled trial
Participants	125 individuals with partner-abuse related PTSD (all females)
Interventions	8 to 11 sessions (each 1.5 hours) of Cognitive Trauma therapy (*N* = 63) vs delayed treatment (*N* = 62)
Outcomes	CAPS, BDI, RSES, TRGI, STRGS-PA, PFQ
Notes	All groups were similar at baseline on all measures.

Risk of bias table

Bias	Author's judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Every 2 consecutive women determined to be eligible were randomly assigned either to an immediate CTT-BW condition or to a delayed CTT-BW condition." Comment: Method of random sequence generation was not sufficiently reported.
Allocation concealment (selection bias)	Unclear risk	Comment: There were no reported measures of allocation concealment.
Blinding of participants and personnel (performance bias)	High risk	Comment: Participants were aware of their allocation. Study did not measure and control for treatment expectancy.
Blinding of outcome assessment (detection bias)	Low risk	Quote: "The assessors were blind to participants' condition assignments and none served as therapists in the study."
Incomplete outcome data	Low risk	Comment: Intent to treat analysis was

(attrition bias)		conducted. However, reasons for dropout were not reported.
Selective reporting (reporting bias)	Low risk	Comment: All specified outcomes were reported.
Therapist allegiance	High risk	Comment: First author developed treatment manual and was part of the team of therapist delivering intervention. First author supervised all therapist as well.
Treatment fidelity	Low risk	Quote: "Using CTT-BW therapist-adherence rating scales, therapist adherence ratings were obtained for 60 therapy sessions (approximately 7.5% of all sessions)."
Therapist qualification	Unclear risk	Comment: Treatment was conducted by therapists with varied qualifications (qualified clinical psychologist with postdoctoral training in PTSD, nursing, counselling and education degrees).
Other bias	Low risk	Comment: No other source of bias was found.

McDonagh (2005)

Methods	Randomised controlled trial
Participants	74 individuals with childhood sexual abuse related PTSD (all females)
Interventions	14 sessions (first 7 sessions were 2 hours each, final 7 sessions were 1.5 hours each) of Cognitive Behavioural Therapy (*N* = 29) vs 14 sessions (first 7 sessions were 2 hours each, final 7 sessions were 1.5 hours each) of Present-centered therapy (*N* = 22) vs waitlist (*N* = 23)
Outcomes	CAPS, BDI, STAI, TSI, DES, STAXI, QOLI
Notes	There was no significant difference between groups at baseline with the exception of distorted cognitions (measured by TSI), where the CBT group had lower scores on the TSI compared to the waitlist group at baseline.

Risk of bias table

Bias	Author's judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Following the initial laboratory evaluation, women were randomly assigned to one of the following three conditions for 14 weeks. When it became clear that the dropout rate was greater for CBT, we changed the random assignment process to increase the chance of assignment to CBT." Comment: Method of random sequence generation was not sufficiently reported.

Allocation concealment (selection bias)	Unclear risk	Comment: There were no reported measures of allocation concealment.
Blinding of participants and personnel (performance bias)	High risk	Comment: Participants were aware of their allocation. Study did not measure and control for treatment expectancy.
Blinding of outcome assessment (detection bias)	Low risk	Quote: "A separate group of female clinicians, who were blind to treatment condition and who had no other role in the study conducted the four CAPS interviews. The participants completed the self-report questionnaires at the time of the CAPS interview."
Incomplete outcome data (attrition bias)	Low risk	Comment: Intent to treat analysis was conducted. However, reasons for dropout were not reported.
Selective reporting (reporting bias)	Low risk	Comment: All specified outcomes were reported.
Therapist allegiance	High risk	Quote: "Separate pools of therapists provided CBT or PCT treatment." Comment: Three authors developed PCT manual and one author (who developed manual) provided supervision for therapists delivering PCT.
Treatment fidelity	Low risk	Quote: "Adherence to CBT or PCT was measured by experienced clinicians who watched selected videotapes of therapy sessions and rated each session for the presence or absence of particular therapeutic interventions using a form that listed all required, unacceptable, and overlapping interventions for both treatments."
Therapist qualification	Low risk	Quote: "All therapists were female clinicians experienced in conducting therapy with trauma survivors. Three psychologists, all of whom had prior training in CBT, received training on implementation of the CBT manual. Three clinical social workers with master's degrees received PCT training from the authors of that manual."
Other bias	Low risk	Comment: No other source of bias was found.

Resick (2002)

Methods	Randomised controlled trial
Participants	171 rape victims with chronic PTSD (all females)
Interventions	13 hours of Cognitive Processing Therapy (*N* = 62) vs 9 sessions (1 hour for first session, 1.5 hours each for subsequent 8 sessions) Prolonged Exposure (*N* = 62) vs waitlist (*N* = 47)

Outcomes	CAPS, BDI, PSS-SR, TRGI
Notes	Waitlist group was encouraged to call for client-centered telephone counselling and received fortnightly calls from an interviewer to assess for immediate risks requiring emergency services. All groups were similar at baseline on all measures. The CPT group was excluded from the meta-analysis as there were no component of skills training in the protocol.

Risk of bias table

Bias	Author's judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: Method of random sequence generation was not sufficiently reported.
Allocation concealment (selection bias)	Unclear risk	Comment: There were no reported measures of allocation concealment.
Blinding of participants and personnel (performance bias)	High risk	Comment: Participants were aware of their allocation. However, treatment expectancy was measured at pre and post treatment. Quote: "The group effect was nonsignificant; there were no differences between the two therapies on the therapeutic expectation questions at either pretreatment or posttreatment."
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Independent assessments were made at pretreatment, posttreatment, and 3 and 9 months posttreatment."
Incomplete outcome data (attrition bias)	Low risk	Comment: Intent to treat analysis was conducted. However, reasons for dropout were not reported.
Selective reporting (reporting bias)	Low risk	Comment: All specified outcomes were reported.
Therapist allegiance	Unclear risk	Quote: "Assignments were balanced so that each therapist handled an approximately equal number of therapy cases in each condition."
Treatment fidelity	Low risk	Quote: "Independent raters who were not otherwise involved in the project conducted assessments of treatment adherence and therapist competence. The tapes were viewed by experts in each specific therapy who were not a part of the project and who were not affiliated with the university where the study was being conducted."
Therapist qualification	Low risk	Quote: "Therapists were eight women with doctorates in clinical or counseling psychology and a background in cognitive– behavioral

		therapy.”
Other bias	Low risk	Comment: No other source of bias was found.

van den Berg (2015)

Methods	Randomised controlled trial
Participants	155 outpatients with psychosis and comorbid PTSD (71 males, 84 females)
Interventions	8 sessions (each 1.5 hours) of prolonged exposure (*N* = 53) vs 8 sessions (each 1.5 hours) of eye movement desensitization and reprocessing (*N* = 55) vs waitlist (*N* = 47)
Outcomes	CAPS, PSS-SR, PTCI
Notes	EMDR treatment arm was not included in the current meta-analysis. All groups received treatment as usual, consisting of medication, treatment and/or support by therapists, caseworkers, nurses and/or coaches, with the exclusion of trauma-focussed interventions. All groups were similar at baseline on all measures.

Risk of bias table

Bias	Author’s judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “An independent randomization bureau randomized the treatment condition using stratified randomization blocks per therapist with equal strata sizes.”
Allocation concealment (selection bias)	Low risk	Comment: Central allocation by independent randomization bureau.
Blinding of participants and personnel (performance bias)	High risk	Comment: Participants were aware of their allocation. Study did not measure and control for treatment expectancy.
Blinding of outcome assessment (detection bias)	Low risk	Quote: “Assessors were blinded to treatment allocation. 27 incidents of unblinding occurred. In case of unblinding, another assessor repeated the entire measurement.”
Incomplete outcome data (attrition bias)	Low risk	Comment: Intent to treat analysis was conducted using linear mixed models. However, reasons for dropouts were not reported.
Selective reporting (reporting bias)	Low risk	Comment: All specified outcomes were reported.
Therapist allegiance	Unclear risk	Quote: “All therapists delivered both treatments.”
Treatment fidelity	Low risk	Quote: “All treatment sessions were videotaped and 10% was randomly selected and rated by trained and blinded raters.”
Therapist qualification	Low risk	Quote: “The therapists were 19 clinical psychologists and 1 psychiatrist.”

Other bias	Low risk	Comment: No other source of bias was found.

Legend

AFQ	Accident Fear Questionnaire
ASI	Anxiety Sensitivity Index
Ax/Ex	Anger Expression subscale of the State-Trait Anger Expression Inventory
BSL	Borderline Symptom List
CAPS	Clinician-Administered PTSD scale
CES-D	Center for Epidemiologic Studies Depression Scale
BAI	Beck Anxiety Inventory
BDI-II	Beck Depression Inventory-II
DES-II	Dissociative Experiences Scale-II
DEQ	Distressing Event Questionnaire
DISS	Dissociation scale
FQ	Fear Questionnaire
GAF	Global Assessment of Functioning
GHQ-28	General Health Questionnaire (28-item)
HAMA	Hamilton Rating Scale for Anxiety
HAMD	Hamilton Rating Scale for Depression
IES	Impact of Events Scale
IES-R	Impact of Events Scale-Revised
IIP	Inventory of Interpersonal Problems
ISEL	Interpersonal Support Evaluation List
HSCL-25	Hopkins Symptom Checklist-25
HTQ	Harvard Trauma Questionnaire
MPSS	Modified PTSD Symptom Scale
N-FSS	Neck Panic Flashback Severity Scale
NMR	General Expectancy for Negative Mood Regulation
N-PASS	Neck Panic Attack Severity Scale
O-FSS	Orthostatic Panic Flashback Severity Scale
O-PASS	Orthostatic Panic Attack Severity Scale
PCL-M	PTSD Checklist - Military Version
PCL	Post-traumatic Checklist Scale
PDS	Posttraumatic Stress Diagnostic Scale
PFQ	Personal Feelings Questionnaire
PSS-I	PTSD Symptom Scale - Interview
PSS-SR	PTSD Symptom Scale – Self-report
PTCI	Post-traumatic Cognitions Inventory (PTCI)
QOLI	Quality of Life Inventory
QLQ	Quality of Life Questionnaire
RSES	Rosenberg Self Esteem Scale
SAS	Social Adjustment Scale
SCL-90R	Symptom Checklist-90 - Revised
SDS	Sheehan Disability Scale
STAI	State-Trait Anxiety Inventory
STAI-S	State subscale of the State-Trait Anxiety Inventory
STAXI	State-Trait Anger Expression Inventory
STRGS-PA	Sources of Trauma-Related Guilt Survey – Partner Abuse Version
TAS-20	Toronto Alexithymia Scale-20 item version
TRGI	Trauma-Related Guilt Inventory

TSI	Traumatic Stress Institute Beliefs Scale
WHO-5	World Health Organization-Five Well-being Index
VAS	Visual analogue pain scales

Appendix F: Subgroup Analyses

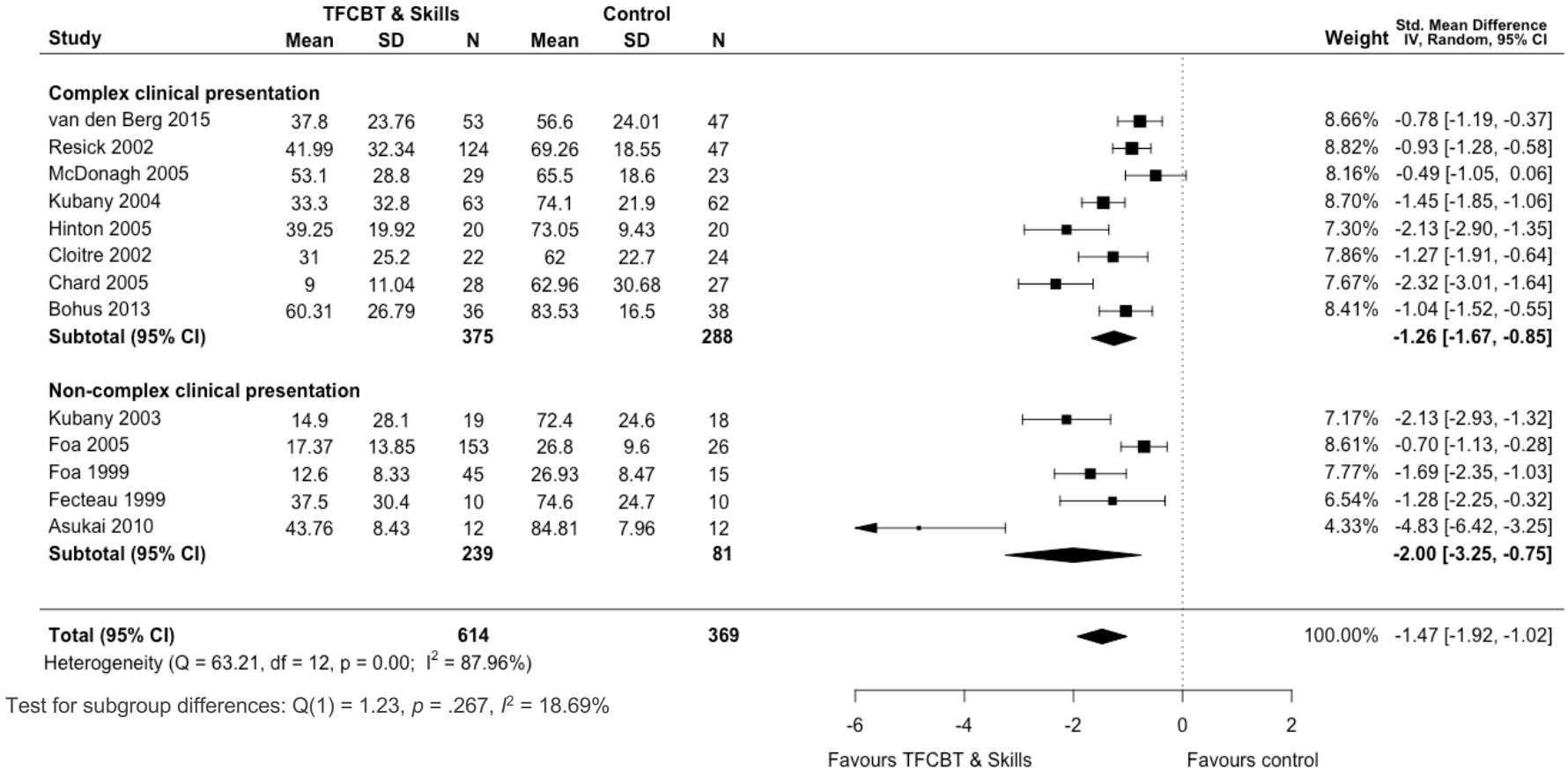

Figure 1. Forest plot of relative effects between complex and non-complex presentations on standardized mean difference. CI = confidence interval; Std = standardized; TFCBT = trauma-focussed cognitive behavioural therapy.

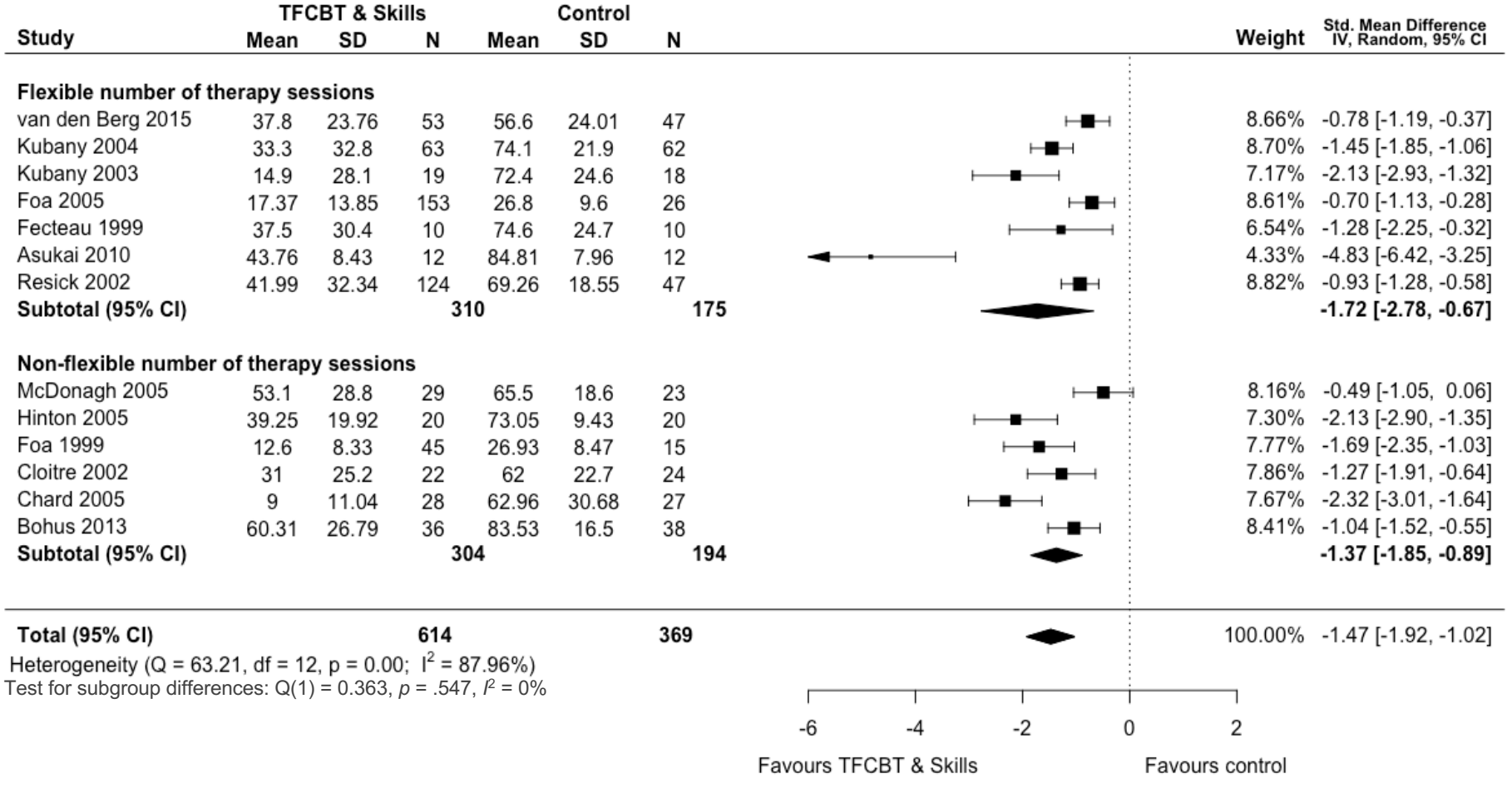

Figure 2. Forest plot of relative effects between flexible and non-flexible number of therapy sessions on standardized mean difference. CI = confidence interval; Std = standardized; TFCBT = trauma-focussed cognitive behavioural therapy.

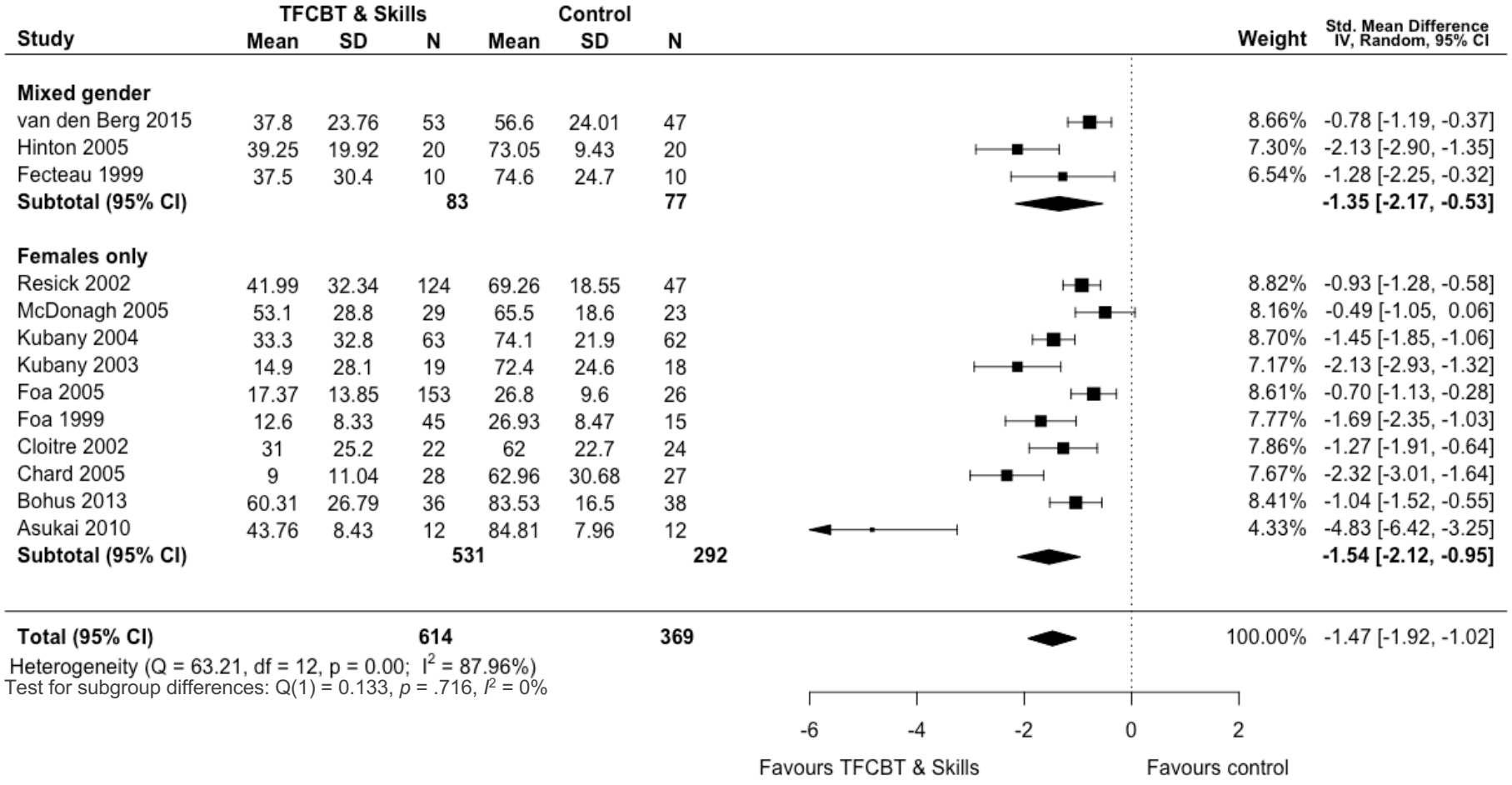

Figure 3. Forest plot of relative effects between mixed gender and only females on standardized mean difference. CI = confidence interval; Std = standardized; TFCBT = trauma-focussed cognitive behavioural therapy.

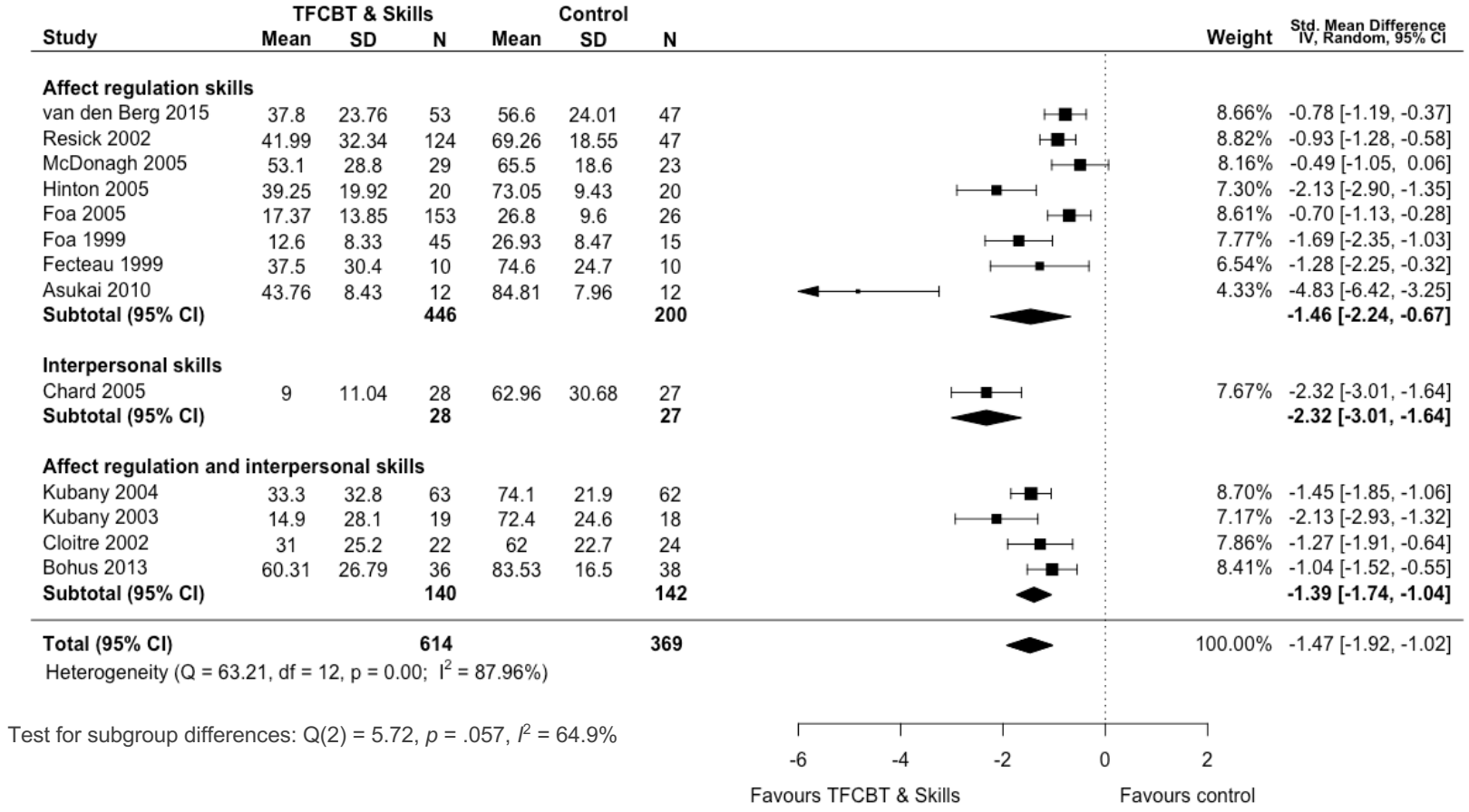

Figure 4. Forest plot of relative effects between types of skills training on standardized mean difference. CI = confidence interval; Std = standardized; TFCBT = trauma-focussed cognitive behavioural therapy.

Appendix G: Ethics Approval

Part of the research infrastructure for Wales funded by the National Institute for Social Care and Health Research, Welsh Government.
Yn rhan o seilwaith ymchwil Cymru a ariannir gan y Sefydliad Cenedlaethol ar gyfer Ymchwil Gofal Cymdeithasol ac Iechyd, Llywodraeth Cymru

NISCHR

Gwasanaeth Moeseg Ymchwil | RES | Research Ethics Service

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09 October 2012

Professor Peter Fonagy
HoD, Department of Clinical, Educational and Health Psychology, UCL
UCL
Gower Street
London WC1N 3BG

Dear Professor Fonagy

Study title: **Probing Social Exchanges – A Computational Neuroscience Approach to the Understanding of Borderline and Anti-Social Personality Disorder**
REC reference: **12/WA/0283**

Thank you for your letter of 25 September 2012, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information was considered by a sub-committee of the REC at a meeting held on 05 October 2012. A list of the sub-committee members is attached.

Confirmation of ethical opinion
On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites
NHS sites
The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Conditions of the favourable opinion
The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the

Appendix H: Informed Consent

Please complete this form after you have read the Information Sheet and/or listened to an explanation about the research.

Project Title:

Understanding the Social Brain in Healthy Volunteers and People with Psychological Difficulties.

This study has been approved by the Research Ethics Committee for Wales (Project ID): 12/WA/0283.

Thank you for your interest in taking part in this research. Before you agree to take part, the person organising the research must explain the project to you.

If you have any questions arising from the Information Sheet or explanation already given to you, please ask the researcher before you to decide whether to join in. You will be given a copy of this Consent Form to keep and refer to at any time.

Participant's Statement

I

- have read the notes written above and the Information Sheet, and understand what the study involves. I am also aware that I can consent to certain aspects of the study in order to participate in them whereas I can withhold my consent for others parts.
- understand that if I decide at any time that I no longer wish to take part in this project, I can notify the researchers involved and withdraw immediately.
- consent to the processing of my personal information for the purposes of this research study.
- understand that such information will be treated as strictly confidential and handled in accordance with the provisions of the Data Protection Act 1998.
- understand that some of the MRI data will be transferred for analysis to the Principal Investigator's second laboratory at Virginia Tech University in the USA and will therefore no longer be subject to EEA data protection laws but that this data will be anonymised and no identifiable personal information will be shared or transferred.
- agree that the research project named above has been explained to me to my satisfaction and I agree to take part in this study.
- I agree that my non-personal research data may be used by others for future research. I am assured that the confidentiality of my personal data will be upheld through the removal of identifiers.

- I understand that part of my participation will be audio-recorded (the interviews) and I consent to the anonymous use of this material as part of the project.
- I agree to be contacted in the future by UCL researchers who would like to invite me to participate in follow-up studies.
- I understand that the information I have submitted will be published as a report and that I can request a copy. Confidentiality and anonymity will be maintained and it will not be possible to identify me from any publications.
- I agree that the research team might re-contact me in case that additional data has to be obtained or for follow-up studies.

Please initial the statements below if you agree with them:	**Initial here**
I agree to take part in the general part of the PD-CPA study as outlined in the information Sheet and to all points listed above. (a separate consent for the MRI, tattoo component, and genetics component follows below).	☐
I agree to the audio recording of interviews and I consent to the anonymous use of this material as part of the project.	☐
I agree that some of the study data will be shared with the collaborating laboratory at Virginia Tech University in the USA.	☐
I understand that relevant sections of medical and or probation notes and data collected during my clinical assessment and during the study from me, may be looked at by individuals from the PD-CPA research team, my clinician or from the NHS Trust, where it is relevant to our taking part in this research. I give permission for these individuals to have access to my records.	☐
I agree that the PD-CPA research team can contact me about coming in for up to two follow-up sessions over the next three years.	☐
I agree that I can be contacted after the end of this study about possible future research and follow-up with PD-CPA and related groups.	☐
I agree that my GP can be told that I am participating in this study.	☐

GP's name: _____ Surgery: _____

Address: _____

MRI and Cognition:

I agree to have an MRI scan and I understand what will happen in the scan. ☐

I have had an MRI safety check and I am confident that there is no reason why I can't have a scan, such as a recent operation. ☐

I agree that my test results can be held by the Wellcome Trust and shared with other research groups, and I understand that this data will be anonymous and not contain any personal information. ☐

Genetics:

You do not have to agree to provide blood or saliva samples to take part in the research. You do not have to agree that any samples you do give can be stored for future testing.
By giving a sample, you consent to be contacted by BioResource about the possibility of joining their panel, but you are under no obligation to join BioResource.

I agree to give a sample of **blood and saliva** (delete as appropriate) for medical research and for details about me and any samples I provide to be kept on a secure database. I agree that BioResource, the study collaborator on genetics, can store my samples and can contact me to invite me to join their panel. ☐

I agree that the samples and information I provide can be stored for use in future medical research, subject to ethical approval. ☐

I understand that I will not benefit financially if my samples are used in research leading to a new treatment or medical test being developed. ☐

In the unlikely event that an abnormality is picked up from tests carried out on my sample, I agree to be informed, and with my consent my GP can be told. ☐

Thank you for your help.

By completing and returning this form, you are giving us your consent that the personal information you provide will be treated as strictly confidential and handled in accordance with the provisions of the Data Protection Act 1998.

Participant:

Signed: Date:

Researcher:

Signed: Date:

Appendix I: Participant's Debrief Sheet

Understanding the Social Brain in Healthy Volunteers and People with Psychological Difficulties.

Thank you for taking part in our study, we appreciate that you gave up your time to take part and hope that you found it interesting.

Summary of the Research Project

The aim of our study is to understand how mind and brain work in order to better understand patients with psychological difficulties. We hope that this will have an impact on the development of specific treatment interventions.

Most of our tasks are designed to look at how we think about ourselves and others (called "mentalisation"), how we regulate our emotions, value co-operation or experience close relationships and how problems can sometimes develop in these relationships.

Getting a better sense of the different strategies that people apply in these areas can help us understand more about when people experience mental health problems that can lead them to find certain social interactions and situations challenging. We hope to use these findings so that treatments can be tailored to help improve the domains where a patient's difficulties may lie.

We are also interested in how someone's experiences in childhood and his or her parenting at that time impact on the performances in the tasks and the functioning of the brain areas that underpin them. For instance, the long interview can tell us more about the quality of your bonding with parents.

Some of the topics discussed in the course of the study may have brought about thoughts or feelings which you had not previously considered or may have made you recall memories which could be perceived as distressing or lead you to feel tense or ruminate on thoughts. Therefore, we have provided some exercises at the back of this sheet which may help you to cope with any such feelings which you may experience.

What to do if you continue to feel concerned

If you continue to feel concerned after taking part in the study it may be useful to talk to a family member, a friend or your GP. Your Lead Clinician (care co-ordinator) or Probation Worker will also be able to support you, if you have one.

In addition to this support there is also free and confidential advice provided by the Mental Health charity Mind which can be found on their website: http://www.mind.org.uk/ or by calling their advice line 0300 123 3393.

If you feel at immediate risk do not hesitate to contact Dr Janet Feigenbaum (details overleaf).

Appendix J: Childhood Trauma Questionnaire (CTQ)

These questions ask about some of your experiences growing up as a child and a teenager. Although these questions are of a personal nature, please try to answer as honestly as you can. For each question select the circle under the response that best describes how you feel.

	Never True	Rarely True	Sometimes True	Often True	Very Often True
I didn't have enough to eat.					
I knew there was someone to take care of me and protect me.					
People in my family called me things like "stupid", "lazy", or "ugly".					
My parents were too drunk or high to take care of the family.					
There was someone in my family who helped me feel that I was important or special.					
I had to wear dirty clothes.					
I felt loved.					
I thought that my parents wished I had never been born.					
I got hit so hard by someone in my family that I had to see a doctor or go to hospital.					
There was nothing I wanted to change about my family.					
People in my family hit me so hard that it left me with bruises or marks.					
I was punished with a belt, a board, a cord, or some other hard object.					
People in my family looked out for each other.					
People in my family said hurtful or insulting things to me.					
I believe that I was physically abused.					
I had the perfect childhood.					

I got hit or beaten so badly that it was noticed by someone like a teacher, neighbour, or doctor.					
I felt that someone in my family hated me.					
People in my family felt close to each other.					
Someone tried to touch me in a sexual way, or tried to make me touch them.					
Someone threatened to hurt me or tell lies about me unless I did something sexual with them.					
I had the best family in the world.					
Someone tried to make me do sexual things or watch sexual things.					
Someone molested me.					
I believe that I was emotionally abused.					
There was someone to take me to the doctor if I needed it.					
I believe that I was sexually abused.					
My family was a source of strength and support.					

Appendix K: Brief Symptom Inventory (BSI)

Instructions
The BSI test consists of a list of problems people sometimes have. Read each one carefully and tick the box of the response the best describes how much that problem has distressed or bothered you during the past seven days including today.

Do not skip any items.

If you have any questions, please ask them now.
In the last 7 days, how much were you distressed by:

	Not at all	**A little bit**	**Moderately**	**Quite a bit**	**Extremely**
1. Nervousness or shakiness inside					
2. Faintness or dizziness					
3. The idea that someone else can control your thoughts					
4. Feeling others are to blame for most of your troubles					
5. Trouble remembering things					
6. Feeling easily annoyed or irritated					
7. Pains in the heart or chest					
8. Feeling afraid in open spaces					
9. Thoughts of ending your life					
10. Feeling that most people cannot be trusted					
11. Poor appetite					
12. Suddenly scared for no reason					
13. Temper outbursts that you could not control					
14. Feeling lonely even when you are with people					
15. Feeling blocked in getting things done					
16. Feeling lonely					
17. Feeling blue					
18. Feeling no interest in					

things					
19. Feeling fearful					
20. Your feelings being easily hurt					
21. Feeling that people are unfriendly or dislike you					
22. Feeling inferior to others					
23. Nausea or upset stomach					
24. Feeling that you are watched or talked about by others					
25. Trouble falling asleep					
26. Having to check and double check what you do					
27. Difficulty making decisions					
28. Feeling afraid to travel on buses, subways, or trains					
29. Trouble getting your breath					
30. Hot or cold spells					
31. Having to avoid certain things, places, or activities because they frighten you					
32. Your mind going blank					
33. Numbness or tingling in parts of your body					
34. The idea that you should be punished for your sins					
35. Feeling hopeless about the future					
36. Trouble concentrating					
37. Feeling weak in parts of your body					
38. Feeling tense or keyed up					
39. Thoughts of death or dying					
40. Having urges to beat, injure, or harm someone					
41. Having urges to break or smash things					
42. Feeling very self-conscious with others					
43. Feeling uneasy in crowds					
44. Never feeling close to another person					

45. Spells of terror or panic					
46. Getting into frequent arguments					
47. Feeling nervous when you are left alone					
48. Others not giving you proper credit for your achievements					
49. Feeling so restless you couldn't sit still					
50. Feelings of worthlessness					
51. Feeling that people will take advantage of you if you let them					
52. Feeling of guilt					
53. The idea that something is wrong with your mind					

Appendix L: Complete Analysis Pipeline

1. Dicom convert ima files to nifty using MRI convert software

- Select input folder (main folder with all subjects)
- Convert to NIFTI
- Select output folder (main folder)
- Options:

Select – save each subject in separate directory
Select – save each series in separate directory
Select – save as .nii file
*Run once without 4d files, run second time selecting – save multivolume series as 4d files (So that we have the 3d structural files x 6 ; and 4d resting state file for input into conn)

- T1 nii output: subjectID.nii (1 x 4d.nii file), subjectID_01 to subjectID_06.nii (6 x 3d.nii file), 1 subjectID_info.txt file
- T2 nii output: subjectID.nii (1x 4d.nii file), 150 x subjectIDnii files, 1 x subjectID_info.txt
- location of nii T1 files: subjectID > anat > preproc
- location of nii T2 files: subjectID > func > preproc

2. Input structural and functional files into CONN

- New Project
- Enter number of subjects (N = 97)
- Number of sessions = 1
- Repetition time (TR) = 2

- Acquisition type = Continuous
- Structural files: To select 3d.nii files (subjectID_06.nii)
- Functional files: To select 4d.nii files (subjectID.nii)

*keep order of subject files the same in both structural and functional files

3. Data review in artrepair toolbox

> view data with contrast movie
> select individual subject > func > preproc > select 150 .nii files
> slice orientation = axial
> select range = 1:150
> select slices = all
> select data magnification = contrast (best for artefact detection in raw images)
> choose reference image = automatic
> select viewing mode = movie (motage movie in matlab)
> Frames/second? = 4

4. Preprocessing in CONN

- CONN preprocessing modules:

• functional center to (0,0,0) coordinates (translation)
• functional realignment & unwarp
• functional outlier detection (art-based)
• - edit settings > global signal z-value threshold = 5
> subject motion mm threshold = 3
> subject rotation rad threshold = 1.5
> Use diff global, Use diff motion, uncheck ‘use comp motion’
> Drop first scans > Remove first 3 initial scans
• functional direct coregistration to structural (rigid body transformation)
• functional slice-timing correction
> slice timing parameters > interleaved (top-down)
• functional direct segmentation & normalization
• structural center to (0,0,0) coordinates (translation)
• structural segmentation and normalization
>>> segment/normalize/ resample: structural target resolution = 3mm
>>> functionals target resolution = 3mm
>>> Bounding box - [-90 -126 -72;90 90 108] mm (default)
• functional smoothing = 8mm

*save art results on matlab

5. Quality check in output
- CONN > covariates (2nd level) > remove outliers of excessive head motion - linear translation > 3mm and/or rotation > 1.5 degrees
    - Review artrepair output to screen out outliers of excessive head motion
    - Update accrual to reflect outliers removed
    - Record motion estimates to keep as covariates
    - Review individual structural and functional images for ACPC origin
    - Review individual coregistration of structural and functional images

6. Extract motion estimates from CONN
CONN toolbox > Covariates (first level) > covariate tools > compute summary measures
> consider covariate realignment > raw values
> summarize across timepoints > maximum
> summarize across dimensions > do not aggregate
> ok
Covariates (2nd level) > select all 6 covariates (maximum of realignment raw values measure)
> covariate tools > export covariate data to file

7. GIFT ICA setup
Select data file – select swau.nii files (preprocessed func scans)
Is your data stored in one group folder? > No
Number of subjects: 66
Number of sessions per subject: 1
Do you want to estimate the number of independent components: No
Number of IC = 75
Do you want to autofill data reduction values? No
Which Algorithm do you want to use: Infomax
Select stability analysis type: Regular
How do you want to run group ICA: Serial

8. GIFT ICA - SetupDefaults
Select type of data pre-processing: Remove mean per timepoint
Which mask do you want to use?: Default mask
Select type of PCA: Standard
Do you want to stack datasets?: Yes
Select matrix storage type: full
Select precision: Double
Select eigen solver type: selective
Select type of group PCA: Subject specific
Select the backreconstruction type: GICA
Do you want to scale the results?: z-scores
Select group ICA type: spatial
How many data reduction PCA steps do you want to run?: 2
Number of PC (step 1): 113
Number of PC/IC (Step 2): 75

9. Select the options for the Infomax algorithm (all left to default options)
Select block less than 218152 where default = 251: 251
Select stop where default=1e-06: 1e-06
Select weight where Maxweight=100000000: 0
Select lrate where min=0.000001 and max=0.1: 0.0034742
Select maxsteps where Default=512: 512
Select anneal between (0 1]: 0.9
Select annealdeg between [0 180]: 60
Select momentum between [0 1]: 0
Select extended where default=0: 0

Number of components: 75
Select Posact: off
Select Sphering: on
Select bias: on
Select verbose: on

10. Exit ICA
Change working directory > setup new GUI > open parameter file
> backrecontype > change to 'gica3'
> save workspace

11. EXIT matlab to customise back construction method to GICA3
Reopen matlab > reopen parameter.mat file to check that backrecontype has been changed to GICA3

Reopen gift ICA
Run analysis > Select Parameter file > Select ica_parameter_info.mat
Select analysis step/steps: All
Group PCA performance settings: User specified settings
Analysis info > check that back reconstruction type was GICA3

12. Toolboxes > ICASSO
Select Mode: Both
Enter no. of times (>1)you want ICA to be run: 20
Enter min cluster size to get the most stable run (recommended option is ceil (0.8*number of runs): 16
Enter max cluster size to get the most stable run. Recommended option is number of runs: 20

13. Review analysis information
Got parameters from user: yes
Parameters initialized: Yes
Number of subjects: 66
Number of sessions: 1
Number of independent components: 30
ICA algorithm: Infomax
Number of scans/timepoints: 150
Mask file: Default mask created from functional data
Data pre-processing type: Remove mean per timepoint
PCA type: standard
Group PCA type: subject specific
Group ICA type: spatial
Back reconstruction type: GICA3
Scaling components: z-scores
Stability analysis type: ICASSO
Group analysis mode: serial

Reduction step info
Reduction step 1 info:
Number of groups before concatenation: 66
Number of groups after concatenation: 66
Number of previous groups in new groups: 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
Number of PC before data reduction: 113 113 113 113 113 113 113 113 113 113 113 113 113 113 113 113 113 113 113 113 113 113 113 113 113 113 113 113 113 113 113 113 113 113 113 113 113 113 113 113 113 113 113 113 113 113 113 113 113 113 113 113 113 113 113 113 113 113 113 113 113 113 113 113 113 113
Number of PC after data reduction: 75 75 75 75 75 75 75 75 75 75 75 75 75 75 75 75 75 75 75 75 75 75 75 75 75 75 75 75 75 75 75 75 75 75 75 75 75 75 75 75 75 75 75 75 75 75 75 75 75 75 75 75 75 75 75 75 75 75 75 75 75 75 75 75 75 75

Reduction step 2 info:
Number of groups before concatenation: 66
Number of groups after concatenation: 1
Number of previous groups in new groups: 66
Number of PC before data reduction: 113
Number of PC after data reduction: 75

Toolbox > ICASSO
Select parameter file (.mat)
Select mode: RandInit (default)
Enter no. of times you want ICA to be run: 20
Enter min cluster size to get the most stable run (recommended 0.8*number of runs): 16
Enter max cluster size to get the most stable run (recommended option is number of runs): 20

14. GIFT spatial sorting
Component > Sorting > Yes > Display
Select sorting criteria: Multiple regression
Sorting type: Spatial
Select template: RSN_HC_unthresholded_tmaps
Select component set to sort: mean_component_ica_s_all

15. GIFT MANCOVAN
Toolboxes > MANCOVAN > Create design matrix
> Select ICA/Mancovan parameter file >ica5_parameter_file.mat
> Select output directory to place mancovan results > MANCOVAN_Group
> Select design criteria > MANCOVA
> Add covariates
> Select covariates > +
> Enter covariate name > Group
> Select type of covariate > categorical
> Enter covariate name > scanner
> Select type of covariate > categorical
> Enter covariate name > gender
> Select type of covariate > categorical
> Enter covariate name > age (centered)
> Select type of covariate > continuous
> Enter covariate name > IQ (centered)
> Select type of covariate > continuous

Setup features > Select model interactions > cancel
> Spatial maps
> Type of mask? > Default
> Center spatial maps> Yes
> Statistic for thresholding > T
> Select Z threshold > 1.0
> FNC correlations
> Detrend number > 3
> Despike timecourses? > Yes
> Filter cutoff (Hz) > 0.15
> Regress covariates > None
Select features > Spatial maps and FNC correlations
Add components > Select component 9, 27, 53 (name: default mode)
> Select component 50 (name: salience)
> Select component 16, 54, 58 (name: central executive)
Enter P-value significance threshold > 0.05 / 0.0001
Enter TR in seconds > 2
Enter no. of components for each feature in a vector > 66 66

Run MANCOVAN >

> Select nuisance variables > select average motion estimate from CONN
> Do you want to skip multivariate tests > No
> Selected covariate > Group (or other covariate of interest)

Display > Select results to display > Features (T-maps, FNC)

> T-threshold (Tmap) > 1.0
> Select image values to display (tmap) > Positive and negative
> Threshold criteria (univariate results) > fdr / none
> Low and high frequency limits to compute fALFF > 0.1, 0.15
> Display (generate result summary in PDF)

Appendix M: Distributions of CTQ and BSI GSI

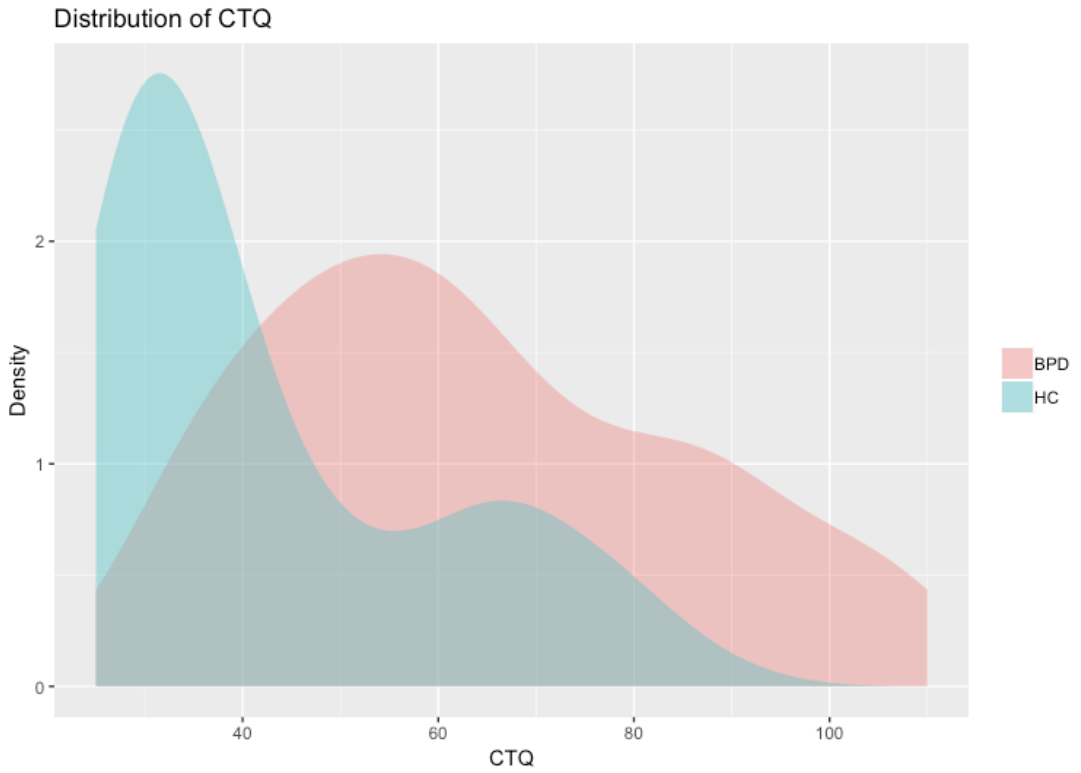

Figure 5. Distribution of self-reported raw scores on the Childhood Trauma Questionnaire (N = 198). BPD = borderline personality disorder; CTQ = childhood trauma questionnaire; HC = healthy controls.

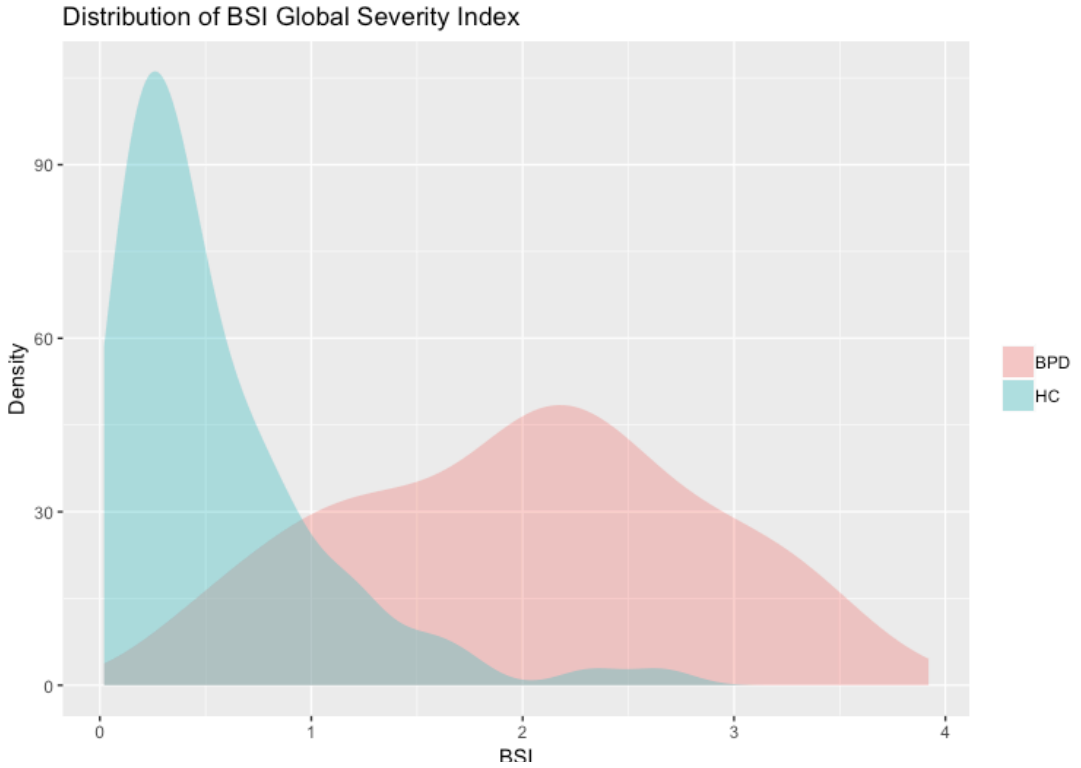

Figure 6. Distribution of brief symptom inventory global severity index (N = 198). BPD = borderline personality disorder; BSI = brief symptom inventory; HC = healthy controls.

Appendix N: Group Differences after Controlling for Self-Reported Psychopathology and Childhood Trauma

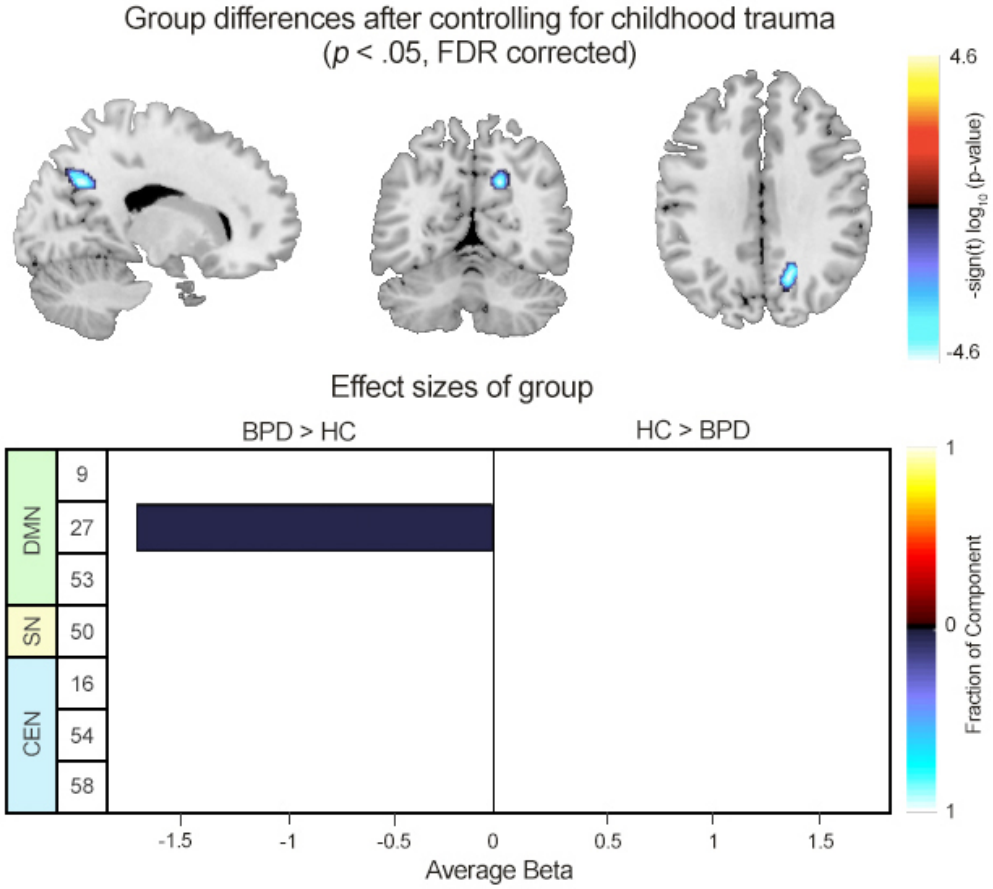

Figure 7. Univariate results showed significant effects of group in spatial map after controlling for childhood trauma. The top row showed composite maps of significant effects and are displayed as -sign(t)log$_{10}$(p). The bottom row showed average β-values for group and the colour of the bar is proportional to the fraction of component voxels contributing to each effect. Controlling for childhood trauma as measured by the CTQ, the BPD group showed decreased intrinsic functional connectivity within the precuneus (component 27) compared to healthy controls, p < .05, FDR corrected.
BPD = borderline personality disorder; CEN = Central executive network; DMN = default mode network; FDR = false discovery rate; HC = healthy controls SN = salience network.

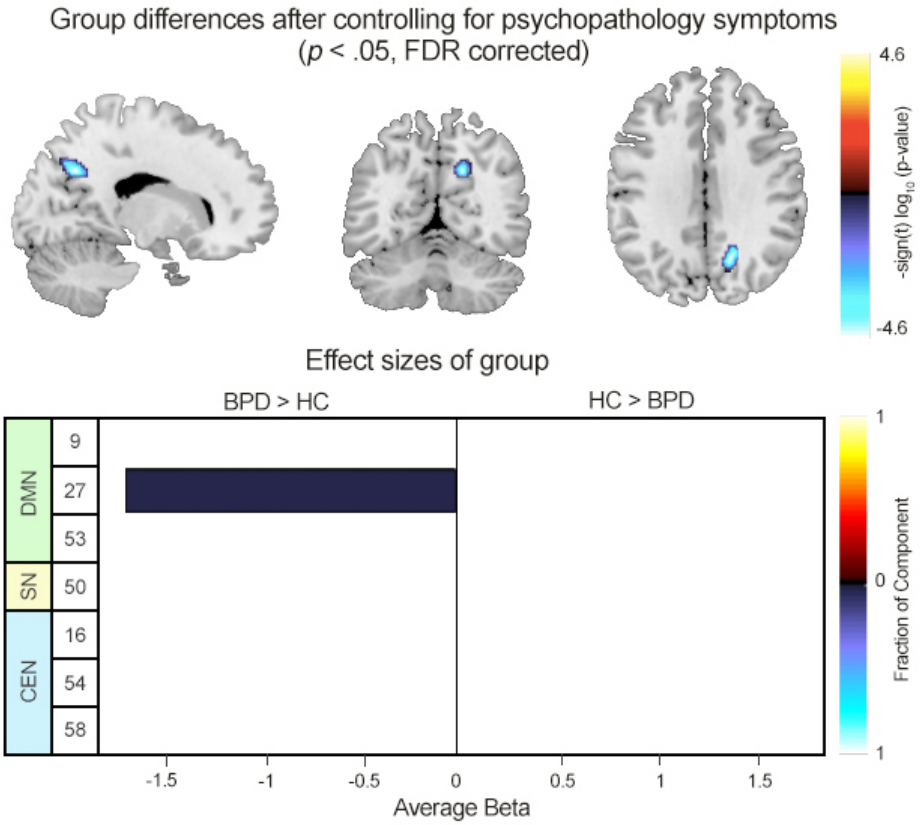

Figure 8. Univariate results showed significant effects of group in spatial map after controlling for psychopathology symptoms. The top row showed composite maps of significant effects and are displayed as -sign(t)$\log_{10}$(p). The bottom row showed average β-values for group and the colour of the bar is proportional to the fraction of component voxels contributing to each effect. Controlling for psychopathology symptoms as measured by the BSI, the BPD group showed decreased intrinsic functional connectivity within the precuneus (component 27) compared to healthy controls, p < .05, FDR corrected. BPD = borderline personality disorder; CEN = Central executive network; DMN = default mode network; FDR = false discovery rate; HC = healthy controls SN = salience network.