Childhood adversity in bipolar disorder and psychosis.

A thesis submitted to The University of Manchester for the degree of Doctor in Clinical Psychology in the Faculty of Medical and Human Sciences

2015

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Section for Clinical and Health Psychology
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Thesis abstract

Title: Childhood adversity in bipolar disorder and psychosis.

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Doctorate in Clinical Psychology

The University of Manchester

2015

Study one is a meta-analysis of the relationship between childhood adversity and bipolar disorder. The results suggest that individuals with bipolar disorder are 2.63 times more likely to experience childhood adversity than non-clinical controls. This effect remained significant even when controlling for bias and when considering epidemiological and case control studies separately. Levels of adversity in bipolar disorder were comparable to those observed in samples diagnosed with unipolar depression and schizophrenia. In adversity subtype analysis, emotional abuse conveyed the greatest risk of bipolar disorder with an odds ratio of 4.04. The results suggest that childhood adversity, particularly emotional abuse, may play an important role in the development of bipolar disorder. This challenges the notion that bipolar disorder is solely the result of a genetic predisposition.

Study two is cross-sectional research investigating the association between childhood adversity and social functioning across the continuum of psychosis, and possible mediators of this relationship (i.e. attachment style, theory of mind ability, clinical symptoms). Fifty-four clinical and 120 non-clinical participants completed self-report questionnaires, interviews and tasks of theory of mind ability. The author used multiple group structural equation modelling to fit mediation models, whilst allowing for differential relationships across the samples. In the final model, only depression mediated the relationship between childhood adversity and social functioning. Childhood adversity did not significantly predict theory of mind ability in this data. The results suggest that psychosocial interventions for improving social functioning should also target low mood, particularly in individuals with a history of childhood adversity.

Taken together this thesis suggests that childhood adversity can have long-reaching and negative effects on individuals’ mental well-being. The author explores the wider clinical, academic and theoretical implications, and potential limitations, of the research in paper three. This section also contains the author’s reflections on the research process and a justification of key methodological and analytical decisions.
Declaration

Data collection for the Social Cognition Research in Bonding and Emotions (SCRiBE) study was shared with another trainee clinical psychologist. Her thesis will, however, concern predictors of anger in individuals with psychosis. I trained and co-supervised three undergraduate students who collected some of the non-clinical data (see Table 1 on page 113 for numbers recruited). The undergraduate students analysed a proportion of the non-clinical data as part of their theses.

I can confirm that no portion of the work referred to in the meta-analysis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.
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Acknowledgements

I would like to thank Katherine Berry and Sandra Bucci for their support and guidance over the past three years. They are top class academics, excellent supervisors and a pleasure to work with.

Special mentions go to Filippo Varese for his advice on the meta-analysis, Hannah Darrell-Berry for her involvement in the SCriBE study, Richard Emsley for his guidance on statistics and Warren Mansell for sharing his expansive knowledge of bipolar disorder. I would also like to express my gratitude to Sophie Parker and Richard Drake for their help with recruitment, and Shannon Couture for her feedback on the design of the empirical study.

This thesis would not have been possible without the altruistic input of clinicians and service users in the North West of England to whom I am very grateful. I am also indebted to all of the authors who kindly provided me with additional information for the meta-analysis.

Lastly, my thanks go to my partner Louise Laverty who has been incredibly supportive of me throughout my clinical training.

Note of published material

The protocol for paper one is available on the PROSPERO data repository website (http://www.crd.york.ac.uk/PROSPERO/; reference: CRD42015017201).
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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>CBT</td>
<td>Cognitive behavioural therapy</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
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<tr>
<td>CFI</td>
<td>Comparative fit index</td>
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<tr>
<td>CTQ</td>
<td>Childhood Trauma Questionnaire</td>
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<td>DSM</td>
<td>Diagnostic and Statistical Manual of Mental Disorders</td>
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<tr>
<td>ICC</td>
<td>Intra-class correlation</td>
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<tr>
<td>ICD</td>
<td>International Classification of Diseases</td>
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<tr>
<td>EIS</td>
<td>Early intervention service</td>
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<td>FEP</td>
<td>First episode psychosis</td>
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<tr>
<td>OR</td>
<td>Odds ratio</td>
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<tr>
<td>PAM</td>
<td>Psychosis Attachment Measure</td>
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<tr>
<td>PRISMA</td>
<td>Preferred Reporting Items for Systematic Reviews and Meta-Analyses</td>
</tr>
<tr>
<td>PSP</td>
<td>Personal and Social Performance Scale</td>
</tr>
<tr>
<td>RMSEA</td>
<td>Root mean square error of approximation</td>
</tr>
<tr>
<td>SCRIBE</td>
<td>Social Cognitive in Bonding and Emotions study</td>
</tr>
<tr>
<td>ToM</td>
<td>Theory of mind</td>
</tr>
<tr>
<td>TLI</td>
<td>Tucker Lewis Index</td>
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<tr>
<td>UHR</td>
<td>Ultra-high risk</td>
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</table>
Paper one: Literature review

The relationship between childhood adversity and bipolar disorder: A systematic review and meta-analysis.

For submission to World Psychiatry
Abstract:

The relationship between childhood adversity and bipolar disorder remains unclear. The authors statistically synthesised the available literature in order to understand the size of this effect. In line with the review protocol (PROSPERO reference: CRD42015017201), search terms relating to childhood adversity and bipolar disorder were entered into four electronic databases (Medline, Embase, PsychInfo, and Web of Science). Eligible studies included a sample formally diagnosed with bipolar disorder, a comparison sample (non-clinical, major depression or schizophrenia) and a quantitative measure of childhood adversity. Effect sizes were calculated and converted to odds ratios before being meta-analysed. From the 5395 identified articles, 13 case-control and six epidemiological studies were included in the main analysis. Childhood adversity was 2.63 (CI: 1.99 – 3.47, p<.001) times more likely to have occurred in bipolar disorder when compared to non-clinical controls. The effect sizes were similar for the case control (2.88; CI: 2.03 – 4.08) and epidemiological (2.24, CI: 1.41 – 3.55) studies. Emotional abuse showed the greatest effect size for any form of adversity with an odds ratio of 4.04 (CI: 3.12-5.22). Rates of childhood adversity in bipolar disorder were comparable to those in schizophrenia and unipolar depression. The findings suggest that childhood adversity, particularly emotional abuse, may play a key role in the development of bipolar disorder, comparable to that of other psychiatric conditions. This has implications for both the detection and treatment of bipolar symptomatology. There is a need for prospective cohort design research to better elucidate the causal nature of this relationship.

Key words: adversity, abuse, bipolar, mania, review, meta-analysis.
Introduction

Bipolar disorder is characterised by extreme depressive and manic affective states, which can be distressing and problematic to the individual. It is often associated with adverse outcomes, such as reduced functioning (1), impaired quality of life (2) and increased risk of death by suicide (3). Response to treatment is limited with high rates of relapse and symptom recurrence (4, 5). A better understanding of the factors leading to bipolar disorder is vital for refining detection, prevention and intervention strategies. Although past research has typically focused on the bio-genetic determinants of bipolar disorder, environmental risk factors are also increasingly being considered (6, 7). The current review and meta-analysis explores the association between a diagnosis of bipolar disorder and childhood adversity.

Childhood adversity is associated with a variety of negative outcomes in the general population (8, 9), where it may convey increased risk of developing psychopathology (10). This includes disorders characterised by emotional lability and low mood, such as borderline personality disorder (11) and major depression (12). In individuals with bipolar disorder, childhood adversity predicts increased mood cycling (13), greater numbers of affective episodes (14), poor cognitive functioning (15) and the presence of psychotic symptoms (16). However, the question of whether childhood adversity is a risk factor for developing bipolar disorder remains unresolved. Several systematic (17-20) and narrative (21, 22) reviews have summarised the available literature, observing high rates of adversity in most, but not all, bipolar samples. To date, no research has attempted to
integrate these empirical findings using meta-analytic methods. To do so would provide a more rigorous method for testing the null hypothesis, but also allow for consideration of the size (i.e. clinical importance) and consistency of the effects (23).

In addition to studies suggesting that exposure to childhood adversity might represent a non-specific risk factor for bipolar disorder, some authors have proposed that emotional abuse and neglect may convey greater risk of bipolar disorder than other forms of maltreatment (e.g. sexual abuse, physical abuse; 6). This is consistent with the theory that parental responsiveness shapes affect regulation strategies later in life (24). Comparison of effect sizes for different forms of adversity may help to understand the relative risk of bipolar disorder conveyed by specific adversity subtypes. Meta-analytic approaches might also clarify whether childhood adversity conveys greater risk for a particular form of bipolar disorder. Bipolar I is characterised by periods of mania (i.e. episodes of extremely elated mood, arousal and levels of activity, often in the presence of psychotic symptoms), whereas bipolar II only presents attenuated symptoms of mania with limited impact of the person’s functioning (i.e. hypomania). Given the evidence for a link between adversity and severe psychopathology, characterised by psychotic symptoms (25), one might expect greater levels of childhood adversity in patients with bipolar I disorder. Elevated levels of childhood adversity in bipolar disorder I, over bipolar II, could represent a dose-dependent effect of adversity on the severity of bipolar symptomatology. Lastly, diagnoses of major depression (26) and schizophrenia (25) appear more likely in individuals with a history of childhood adversity. It is possible
that childhood maltreatment conveys greater risk for one particular form of disorder. The final and exploratory aim of this review was therefore to compare rates of childhood adversity in individuals diagnosed with bipolar disorder to those diagnosed with schizophrenia and major depression.

In summary, this review examined three a-priori hypotheses: One, rates of childhood adversity would be elevated in samples with bipolar disorder compared to non-clinical controls; two, effect sizes for emotional abuse and neglect would be higher than that of other forms of adversity; and three, rates of childhood adversity would be greater in individuals with bipolar I, compared to bipolar II, disorder. The authors made no hypotheses regarding the rates of childhood adversity in bipolar disorder compared to the other clinical samples.

Method

Search strategy

The review was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards (27). A systematic search of four electronic databases (i.e. Medline, Embase, PsychInfo, Web of Science) was used to identify peer reviewed articles published between January 1980 and October 2014. The authors used blocks of search terms pertaining to bipolar disorder (bipolar, mani*, cyclothymi*, manic-depressi* or hypomani*) and childhood adversity (child abuse, physical abuse, sexual abuse, psychological abuse, emotional abuse, neglect*, trauma*, advers*, maltreat*, bully*, bullied, victim*, or parental loss). The search terms were partly adapted
from past systematic reviews (18, 19, 25). In the current review, searches in Medline, Embase and PsychInfo were ‘exploded’ in the field of Bipolar Disorder. The authors restricted the search in Web of Science to the areas of Psychiatry and Psychology by ‘Field’ in order to better detect relevant literature.

In addition to articles detected by the systematic search, the authors screened the reference lists of all included manuscripts and previous reviews (6, 17-22, 28). The authors also examined the reference lists of journal articles citing at least one of the included studies. In cases where the relevant information from which to assess eligibility or calculate an effect size was unavailable, the authors requested further information from the corresponding author of the manuscript.

**Eligibility criteria**

The review included case control and epidemiological (prospective and cross sectional) studies where a quantitative measure of childhood adversity was administered to a sample of individuals with a formal diagnosis of Bipolar disorder according to the Diagnostic and Statistical Manual (DSM-III, DSM-IIIR, DSM-IV, DSM-IV-TR & DSM-V) or the International Classification of Diseases (ICD-9 or ICD-10). The authors defined childhood adversity as experiencing neglect, abuse, bullying or the loss of parents before the age of 19. Studies exploring loss through separation (e.g. divorce of parents), expressed emotion, and/or stressful life events occurring in adulthood (i.e. after the age of 18) were not included in this review. After discussion, the authors also excluded relatively high frequency parenting practices (e.g. spanking, shouting), as these were assumed to be less traumatic to the
individual and subject to considerable cultural variability (29). The authors excluded case notes reviews that opportunistically assessed, rather than systematically measured, childhood adversity due to the increased likelihood of response bias (30). In cases where both 12-month and lifetime diagnoses were provided, the latter was selected for effect size extraction (31). Only articles published in peer review English language journals were included in the analysis.

The authors only included studies with at least one eligible control sample. Controls were defined \textit{a priori} as healthy individuals without an identified DSM or ICD diagnosis (in the epidemiological studies, this was defined as respondents known to be free of the outcome of interest, i.e. bipolar disorder), individuals with a DSM or ICD diagnosis of major depression, and individuals with a DSM or ICD diagnosis of a non-affective psychosis. The latter included schizophrenia, schizoaffective disorder, schizophreniform disorder, and delusional disorder.

\textit{Screening and data extraction}

The lead author screened identified articles in three stages: i) at the title level, ii) at the abstract level, and iii) at the article level. One third (33.4\%; n=1800) of titles were double rated by a postgraduate researcher with high levels of agreement (94.6\% of cases). Although the calculated Kappa was moderately high (k = .65) this metric can be distorted in unequally balanced binary variables (32). Positive agreement was .68 and negative agreement was .97 indicating acceptable levels of inter-rater reliability (33). All of the abstracts (n=446) were double rated by
a separate post-graduate researcher with similarly high levels of agreement (87.4% of cases). Kappa ($k = .71$), positive agreement (.81) and negative agreement (.91) scores were high for the ratings made at the abstract level. The majority of discrepancy between raters was due to the primary coder (JPC) being overly inclusive.

Two of the authors independently extracted data and calculated effect sizes for the identified articles using a data-collection spreadsheet. The intra-class correlation between the two sets of effect sizes indicated high levels of agreement (ICC: .98; $p<.001$). For the four cases where the primary authors were in disagreement, the wider team arbitrated and made a decision on how to generate the effect size. Extracted data included study and effect size descriptors (e.g. date published, bipolar type, diagnostic system, adversity assessment, sample size). When possible, the authors extracted binary (e.g. frequency tables, percentages), as opposed to $d$-family (e.g. means, standard deviations), effect sizes. The authors made this decision based on the use of odd ratios (OR) as the overall effect size statistic.

Methodological quality

Methodological quality was explored using the Newcastle Ottawa Assessment Scale (34), which assesses the selection and comparability of the samples, and the suitability of the adversity exposure. The purpose of performing a quality assessment in this review was to summarise methodological rigor, rather than to carry out additional sensitivity analysis. Item five of the Newcastle-Ottawa
Assessment Scale requires the assessor to select the single most important covariate or matching criteria. The authors selected gender given the plethora of studies showing greater levels of childhood trauma in women compared to men (35). The Newcastle-Ottawa scale has been used in a previous systematic review examining the relationship between childhood sexual abuse and bipolar disorder (19). The articles were independently rated by a postgraduate researcher demonstrating good inter-rater reliability with the lead author (ICC: .83, p<.001).

**Statistical analysis**

The authors used Comprehensive Meta-Analysis Version 2 (36) to compute the effect sizes and conduct the analyses. All effect sizes (e.g. d-family effects) were converted to OR in order to aid the interpretation of the results. The researchers used random-effects, rather than fixed effects, models, which are suitable when considering heterogeneous data gathered from a body of published literature (23). Visual inspection of funnel plots and regression tests of funnel plot asymmetry (Egger’s test) established the presence of publication and selection bias. In analyses where the authors identified likely selection bias, they employed Duval and Tweedie’s trim and fill method to identify hypothetically missing effects and subsequently estimate an adjusted OR (37, 38).

The authors conducted the analysis in four separate stages. In stage one, they considered the overall effects extracted from studies comparing bipolar and non-clinical samples on measures of childhood adversity. This analysis focused on the association between childhood adversity and bipolar disorder regardless of the
type of adversity exposure. Therefore, both studies considering single (e.g. sexual abuse) and multiple (e.g. sexual abuse, emotional abuse etc.) exposures were included. When extracting data in the presence of more than one measure of adversity, the authors used the most global or wide reaching assessment (e.g. total levels of adversity). In cases where this information was unavailable, the authors contacted the corresponding author of the primary manuscript to request information regarding an aggregated effect. In the absence of this information, the authors calculated separate effect sizes for each type of adversity, which they then merged into a single aggregated effect for the main analysis.

In the second stage of analysis, the authors explored the relative impact of different types of exposures on bipolar disorder. Multiple meta-analyses established the effects pertaining to each of the adversity subtypes. Due to the non-independence of the samples/reports, the authors did not directly compare these effects using meta-analytic methods, but rather considered each subtype in separate analysis.

In the third stage of the analysis, overall effects were extracted for studies that compared levels of childhood adversity between bipolar I and bipolar II disorder. The authors employed the same analysis strategy for dealing with multiple adversity types as in stage one. Lastly, in the fourth stage of analysis, the authors examined the impact of childhood adversity on bipolar disorder, relative to major depression and schizophrenia, using the same process as described for steps one and three.
In some cases, manuscripts contained both the results to the unadjusted analyses and the analyses adjusted for a number of covariates. Due to the range of reported covariates, and in order to increase comparability amongst the eligible studies, the authors included the unadjusted results in the main analyses and then performed a sensitivity analysis with the adjusted effects. In the presence of multiple levels of adjustment, the authors included the analysis with the largest number of demographics and/or covariates (e.g. age, gender, socioeconomic status, educational level). The majority of the aforementioned analyses explored the impact of childhood adversity generally, rather than the specific effects of adversity subtypes over and above the other forms of adversity. Therefore, we did not include effects that examined the impact of exposures whilst controlling for other types of childhood adversity (e.g. 39). The full review protocol is available on a data repository website (http://www.crd.york.ac.uk/PROSPERO/; reference: CRD420150172011).

1 Presented in appendix B; p125.
Results

Results to article screening

In total, the authors’ identified 6,347 articles through the systematic search. This number reduced to 5,395 articles when the authors removed duplicates. Figure 1 shows the number of articles excluded at each stage of the screening procedure. The primary reason for exclusion at all stages was the absence of a valid sample of patients with bipolar disorder or a quantitative measure of childhood adversity.

Description of identified research

The characteristics of the included articles are summarised in Table 1. Eleven authors provided clarification around methodological issues or further information from which to generate an effect size for the analyses. Only 11 studies reported the percentage of their bipolar sample that had experienced childhood adversity. Rates of childhood adversity in the bipolar samples ranged from 7.7% (40) to 77.1% (41). The weighted average exposure to childhood adversity in the bipolar sample included in this meta-analysis was 10.5%.

Thirteen case control and six epidemiological studies were included in the main analysis. The case control studies included 1259 cases and 1118 controls, whereas the epidemiological studies surveyed over 21 million respondents. The epidemiological research included three population based cross-sectional design studies (12, 39, 42), two retrospective cohort design studies (31, 40), and one quasi-prospective study (43). The latter examined childhood adversity as a predictor of
transition to psychosis over a three-year period in adulthood. The quasi-prospective design studies linked data on current diagnosis to registers on parental loss (40) and child protection status (31). The most commonly used measure of adversity in the case control studies was the Childhood Trauma Questionnaire (N=7; 44). Measures of childhood adversity in the epidemiological studies were generally single items derived from the validated trauma measures (e.g. the Conflict Tactics Scale (45)).
Records identified through search (n = 6347)

Records after duplicates removed (n = 5395)

Records screened at abstract level (n = 446)

Articles examined for coding (n = 153)

Records included in main analysis (n = 19)

Additional records included in secondary analyses (n = 11)

Figure 1. Flow chart showing rates of exclusion at different levels of screening.
Table 1. The characteristics of studies included in the main analysis.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Country</th>
<th>Bipolar sample characteristics</th>
<th>Diagnostic system</th>
<th>Sample sizes (n)</th>
<th>Measure</th>
<th>Adversity (type)</th>
<th>Diagnosis</th>
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</thead>
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<td><strong>Case control studies</strong></td>
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<tr>
<td>Agid et al., 1999</td>
<td>Israel</td>
<td>Bipolar patients</td>
<td>DSM-III-R</td>
<td>158</td>
<td></td>
<td>University Database Questionnaires (PL)</td>
<td>SCID</td>
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<td>Furukawa et al., 1999</td>
<td>Japan</td>
<td>Bipolar patients</td>
<td>DSM-III-R</td>
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<td></td>
<td>PISA or TOSHI (PL)</td>
<td>PISA</td>
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<tr>
<td>Rucklidge et al., 2006</td>
<td>New Zealand</td>
<td>Bipolar NOS, I &amp; II adolescent outpatients</td>
<td>DSM-IV-TR</td>
<td>63</td>
<td>24</td>
<td>CBC, KSADS-PL &amp; WASHU-K-SADS (SA, PA, N, EA)</td>
<td>KSADS</td>
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<td>Grandin et al., 2007</td>
<td>USA</td>
<td>Bipolar NOS, I &amp; II patients</td>
<td>DSM-IV</td>
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<td>155</td>
<td>Childrens Life Events Scale (maltreatment)</td>
<td>General Behaviour Inventory &amp; SADS-L</td>
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<td>Savitz et al., 2008</td>
<td>South Africa</td>
<td>Bipolar I &amp; II patients</td>
<td>DSM-IV</td>
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<td>68</td>
<td>CTQ (SA, PA, EA, EN, PN)</td>
<td>SCID</td>
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<td>Etain et al., 2010</td>
<td>France</td>
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<td>CTQ (SA, PA, EA, EN, PN)</td>
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<td>Country</td>
<td>Diagnosis</td>
<td>Scale</td>
<td>CTQ Items</td>
<td>From service</td>
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<td></td>
</tr>
<tr>
<td>Horesh &amp; Iancu, 2010</td>
<td>Israel</td>
<td>Bipolar outpatients</td>
<td>DSM-IV</td>
<td>90 30 60</td>
<td>Child Life Events List (PL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fowke et al., 2012</td>
<td>England</td>
<td>Bipolar patients</td>
<td>ICD-10</td>
<td>70 35 35</td>
<td>CTQ (SA, PA, EA, EN, PN)</td>
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<td></td>
</tr>
<tr>
<td>Konradt et al., 2013</td>
<td>Brazil</td>
<td>Bipolar I &amp; II patients</td>
<td>DSM-IV</td>
<td>149 54 95 82</td>
<td>MINI &amp; SCID</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aas et al., 2014</td>
<td>Norway</td>
<td>Bipolar NOS, I &amp; II patients</td>
<td>DSM-IV</td>
<td>66 42 14*</td>
<td>CTQ (SA, PA, EA, EN, PN)</td>
<td>SCID</td>
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<tr>
<td>Chen et al., 2014</td>
<td>Taiwan</td>
<td>Bipolar I &amp; II</td>
<td>DSM-IV</td>
<td>531 329 202</td>
<td>CIDI (PA)</td>
<td>CIDI</td>
<td></td>
</tr>
<tr>
<td>Watson et al., 2014</td>
<td>UK &amp; New Zealand</td>
<td>Bipolar I &amp; II outpatients</td>
<td>DSM-IV</td>
<td>115 60* 55*</td>
<td>CTQ (SA, PA, EA, EN, PN)</td>
<td>SCID</td>
<td></td>
</tr>
<tr>
<td>Janiri et al., 2015</td>
<td>Italy</td>
<td>Bipolar I &amp; II outpatients</td>
<td>DSM-III-R</td>
<td>207 104 103</td>
<td>CTQ (SA, PA, EA, EN, PN)</td>
<td>SCID</td>
<td></td>
</tr>
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</table>

**Epidemiological studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Diagnosis</th>
<th>Scale</th>
<th>Items from the CTS (SA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molnar et al., 2001</td>
<td>USA</td>
<td>Bipolar disorder</td>
<td>DSM-III-R</td>
<td>5866</td>
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</table>
### Studies included in comparisons with major depression and schizophrenia (stage four of analysis)

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Disorder</th>
<th>Classification</th>
<th>M</th>
<th>F</th>
<th>Cases</th>
<th>Controls</th>
<th>Method of Assessment</th>
<th>Rating Scale/Interviewing Schedule</th>
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<tbody>
<tr>
<td>Alnaes &amp; Torgersen, 1993 (57)</td>
<td>Norway</td>
<td>Bipolar and cyclothymic patients</td>
<td>DSM-III</td>
<td>156</td>
<td>59</td>
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<td>Anamnestic interview (PL)</td>
<td>SCID</td>
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<tr>
<td>Darvez-Bornoz et al., 1995 (58)</td>
<td>France</td>
<td>Bipolar patients</td>
<td>DSM-III-R</td>
<td>89</td>
<td>25</td>
<td>64</td>
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<td>Interview (SA)</td>
<td>Psychiatrist rated against criteria</td>
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<td>Hlastala &amp; McClellan, 2005 (59)</td>
<td>USA</td>
<td>Bipolar I</td>
<td>DSM-IV-TR</td>
<td>49</td>
<td>22</td>
<td>27</td>
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<td>PTSD module of SCID (SA, PA, N)</td>
<td>SCID</td>
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<tr>
<td>Study</td>
<td>Country</td>
<td>Diagnosis</td>
<td>Version</td>
<td>N (BD)</td>
<td>N (MD)</td>
<td>N (SCZ)</td>
<td>Method</td>
<td>Instrument/scale</td>
<td></td>
</tr>
<tr>
<td>------------------------------</td>
<td>-----------</td>
<td>---------------------</td>
<td>---------</td>
<td>--------</td>
<td>--------</td>
<td>---------</td>
<td>----------------------------------</td>
<td>------------------</td>
<td></td>
</tr>
<tr>
<td>Hyun et al., 2000</td>
<td>USA</td>
<td>Bipolar patients</td>
<td>DSM-IV</td>
<td>333</td>
<td>142</td>
<td>191</td>
<td>Semi-structured interview (SA, PA)</td>
<td>Diagnostic interview</td>
<td></td>
</tr>
<tr>
<td>Watson et al., 2007</td>
<td>UK</td>
<td>Bipolar patients</td>
<td>DSM-IV</td>
<td>40</td>
<td>30</td>
<td>10</td>
<td>CTQ (SA, PA, EA, EN, PN)</td>
<td>SCID</td>
<td></td>
</tr>
<tr>
<td>Angst et al., 2011</td>
<td>Switzerland</td>
<td>Bipolar disorder</td>
<td>Broad DSM-IV</td>
<td>287</td>
<td>104</td>
<td>183</td>
<td>Unclear (SA)</td>
<td>SCL-90-R</td>
<td></td>
</tr>
<tr>
<td>Alvarez et al., 2011</td>
<td>Spain</td>
<td>Bipolar patients</td>
<td>DSM-IV</td>
<td>92</td>
<td>40</td>
<td>52</td>
<td>Items from TLDEQ (SA, PA)</td>
<td>Unclear</td>
<td></td>
</tr>
<tr>
<td>Parker et al., 2013</td>
<td>Australia</td>
<td>Bipolar I &amp; II patients</td>
<td>DSM-IV</td>
<td>352</td>
<td>138</td>
<td>214</td>
<td>Unclear (SA, PA)</td>
<td>MINI</td>
<td></td>
</tr>
<tr>
<td>Perna et al., 2014</td>
<td>England</td>
<td>Bipolar I &amp; II patients</td>
<td>DSM-IV</td>
<td>74</td>
<td>47</td>
<td>27</td>
<td>CTQ (SA, PA, EA, EN, PN)</td>
<td>Clinical interview (unspecified)</td>
<td></td>
</tr>
</tbody>
</table>

Key: BD, Bipolar disorder; NC, Non-clinical controls; MD, unipolar or major depression; SCZ, schizophrenia; UK, United Kingdom; USA, United States of America; DSM, Diagnostic and Statistical Manual; PA, physical abuse; SA, sexual abuse; N, neglect; EN, emotional neglect; PN, physical neglect; EA, emotional abuse; PL, parental loss; ICD, International Classification of Diseases; SCID, Structured Clinical Interview for DSM Disorders; PISA, Psychiatric Initial Screening for Affective Disorders; TOSHI, Time-Ordered Stress and Health Interview; CBC, Child Behaviour Checklist; KSADS-PL, Kiddie-Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version; WASHU-K-SADS, Washington University in St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version; SADS-L, Schedule for Affective Disorders - Lifetime Diagnostic Interview (SADS-L); CTQ, Childhood Trauma Questionnaire; DIGS, Diagnostic Interview for Genetic Studies; MINI, Mini International Neuropsychiatric Interview; CIDI, Composite International Diagnostic Interview; CTS, Conflict Tactics Scales; CEVQ, Childhood Experiences of Violence Questionnaire; AUDADIS-IV, Alcohol Use Disorder and Associated Disabilities Interview Schedule-IV; PTSD, post-traumatic stress disorder; SCL, symptom checklist; TLDEQ, Traumatic Life Events and Distressing Event Questionnaires.
Stage one: Overall effect of childhood adversity on bipolar disorder.

Figure 2 shows the effect sizes (odds ratios) for each of the included studies, and the aggregated effects of childhood adversity on bipolar disorder. The analysis showed an overall effect of 2.63 (CI: 1.99 - 3.47, p<.001), suggesting that individuals with bipolar disorder are 2.6 times more likely to have experienced childhood adversity when compared to non-clinical controls. Similar effect sizes were observed for the case control (OR: 2.88, CI: 2.03 – 4.08, p<.001) and epidemiological studies (OR: 2.24, CI: 1.41 - 3.55, p= .001). There was no significant difference (Q (1) = 0.74, p=0.391) in the strength of the effect sizes between the two subgroups, attesting to the suitability of considering the study designs together in the same analysis.

Tests of heterogeneity

Tests of heterogeneity showed that the strength of the relationship between childhood adversity and bipolar disorder varied considerably across individual studies. Seventy seven percent of the variance (I^2) in the effect size could be attributed to true statistical heterogeneity for the overall effect size, which was greater than would be expected by error alone (Q (18) = 79.53, p<.001). This level of heterogeneity is generally thought to be high and should be considered when interpreting the results (66). One-study removed analysis suggested that the withdrawal of any particular study would not greatly alter the results of the analysis.
Selection bias analyses

In regards to publication bias, funnel plots of standard error by log odds ratios indicated a roughly symmetrical distribution of studies around the mean effect sizes. When combining the case control and epidemiological literature the result to Egger’s test was also non-significant (B: .12, SE: 1.08, p=.456) indicating the absence of publication bias or other selection bias. However, Duval and Tweedie’s trim and fill found two hypothetical missing studies, which brought the imputed OR to 2.47 (CI: 1.8-3.1).

Sensitivity analysis

Three of the epidemiological studies provided effect sizes adjusted for covariates in addition to unadjusted scores. Repeating the analysis using the adjusted scores yielded highly similar results (OR: 2.58, CI: 1.96 - 3.36, p <.001), with equivalent levels of statistical heterogeneity (Q (18) = 79.2, p <.001, \(I^2 = 77.27\)). This was also true when only including the epidemiological studies in the analysis (OR: 2.14, CI: 1.36-3.39, p =.001).
<table>
<thead>
<tr>
<th>Group by Design</th>
<th>Study name</th>
<th>Adversity</th>
<th>Statistics for each study</th>
<th>Odds ratio and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case control</td>
<td>Aas et al., 2014</td>
<td>Trauma total</td>
<td>5.58</td>
<td>1.67</td>
</tr>
<tr>
<td></td>
<td>Agid et al., 1999</td>
<td>Parental loss</td>
<td>2.65</td>
<td>0.89</td>
</tr>
<tr>
<td></td>
<td>Chen et al., 2014</td>
<td>Physical abuse</td>
<td>1.92</td>
<td>1.39</td>
</tr>
<tr>
<td></td>
<td>Elain et al., 2010</td>
<td>Trauma total</td>
<td>2.94</td>
<td>1.87</td>
</tr>
<tr>
<td></td>
<td>Fowke et al., 2012</td>
<td>Trauma total</td>
<td>5.81</td>
<td>2.37</td>
</tr>
<tr>
<td></td>
<td>Furukawa et al., 1999</td>
<td>Parental loss</td>
<td>0.68</td>
<td>0.30</td>
</tr>
<tr>
<td></td>
<td>Grandin et al., 2007</td>
<td>Maltreatment</td>
<td>2.53</td>
<td>1.68</td>
</tr>
<tr>
<td></td>
<td>Horesh &amp; Iancu, 2010</td>
<td>Parental loss</td>
<td>0.96</td>
<td>0.44</td>
</tr>
<tr>
<td></td>
<td>Janiri et al., 2015</td>
<td>Trauma total</td>
<td>3.60</td>
<td>2.16</td>
</tr>
<tr>
<td></td>
<td>Konrad et al., 2013</td>
<td>Trauma total</td>
<td>7.73</td>
<td>4.04</td>
</tr>
<tr>
<td></td>
<td>Rucklidge et al., 2006</td>
<td>Trauma total</td>
<td>1.68</td>
<td>0.22</td>
</tr>
<tr>
<td></td>
<td>Savitz et al., 2006</td>
<td>Trauma total</td>
<td>4.47</td>
<td>2.28</td>
</tr>
<tr>
<td></td>
<td>Watson et al., 2014</td>
<td>Trauma total</td>
<td>4.82</td>
<td>2.17</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.88</td>
<td>2.04</td>
</tr>
<tr>
<td>Epidemiological</td>
<td>Afifi et al., 2014</td>
<td>Trauma total</td>
<td>4.40</td>
<td>3.29</td>
</tr>
<tr>
<td></td>
<td>Gilman et al., 2014</td>
<td>Trauma total</td>
<td>2.74</td>
<td>2.08</td>
</tr>
<tr>
<td></td>
<td>Laurson et al., 2007</td>
<td>Parental loss</td>
<td>1.57</td>
<td>1.16</td>
</tr>
<tr>
<td></td>
<td>Molnar et al., 2001</td>
<td>Sexual abuse</td>
<td>4.37</td>
<td>1.70</td>
</tr>
<tr>
<td></td>
<td>Scott et al., 2010</td>
<td>Maltreatment</td>
<td>1.86</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>Sikkerbrook et al., 2012</td>
<td>Parental loss</td>
<td>0.77</td>
<td>0.38</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td>2.63</td>
<td>2.00</td>
</tr>
</tbody>
</table>

Figure 2. Forest plot of effect sizes.
Stage two: The relative impact of adversity subtypes.

Table 3 shows the results to the analyses exploring whether specific types of childhood adversity are elevated in bipolar disorder. Grandin (49) and Neeren (67) both report analyses from the Longitudinal Investigation of Bipolar Spectrum Disorders Project. For this analysis, the authors selected information from the Neeren and colleagues’ paper as this study specifically reported effects pertaining to the impact of adversity subtypes (i.e. emotional abuse, physical abuse and sexual abuse) on bipolar disorder. The results of these separate meta-analyses showed significant effects of all childhood adversity subtypes, with the exception parental loss, on bipolar disorder. Emotional abuse showed the strongest effect with an OR of 4.04 (CI: 3.12-5.22, \( p < .001 \)). This suggests that individuals with bipolar disorder were four times more likely to experience emotional abuse when compared to non-clinical samples.
Table 2. The results to the trauma subtype analysis.

<table>
<thead>
<tr>
<th>Trauma type</th>
<th>n</th>
<th>Odds Ratio</th>
<th>Lower</th>
<th>Upper</th>
<th>p-value</th>
<th>I^2</th>
<th>Q</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical abuse</td>
<td>12</td>
<td>2.86</td>
<td>2.22</td>
<td>3.69</td>
<td>&lt;.001</td>
<td>70</td>
<td>36.55</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Sexual abuse</td>
<td>12</td>
<td>2.58</td>
<td>2.08</td>
<td>3.20</td>
<td>&lt;.001</td>
<td>35</td>
<td>16.94</td>
<td>0.109</td>
</tr>
<tr>
<td>Emotional abuse</td>
<td>9</td>
<td>4.04</td>
<td>3.12</td>
<td>5.22</td>
<td>&lt;.001</td>
<td>23</td>
<td>10.40</td>
<td>0.238</td>
</tr>
<tr>
<td>Physical neglect</td>
<td>7</td>
<td>2.26</td>
<td>1.74</td>
<td>2.93</td>
<td>&lt;.001</td>
<td>0</td>
<td>5.41</td>
<td>0.492</td>
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<tr>
<td>Emotional neglect</td>
<td>7</td>
<td>2.62</td>
<td>2.03</td>
<td>3.38</td>
<td>&lt;.001</td>
<td>0</td>
<td>5.94</td>
<td>0.430</td>
</tr>
<tr>
<td>Parental loss</td>
<td>5</td>
<td>1.16</td>
<td>0.75</td>
<td>1.78</td>
<td>0.514</td>
<td>51</td>
<td>8.23</td>
<td>0.084</td>
</tr>
</tbody>
</table>
Stage three: Effect of childhood adversity on bipolar subtypes.

Four identified studies provided data to compare rates of childhood adversity across subtypes of bipolar disorder (50, 56, 64, 68). No significant difference in childhood adversity was observed between bipolar I and bipolar II disorder (OR: 0.93, CI: 0.48 - 1.81, \( p = .0.827 \); Q (3) = 6.91, \( p =.075 \), \( I^2 = 56.58 \)). In such a small number of studies, Eggers test would not have produced valid results.

Stage four: The impact of childhood adversity in bipolar disorder relative to major depression and schizophrenia.

Eleven studies were included in the analysis comparing rates of childhood adversity in bipolar and unipolar depression (Figure 3). The results showed that childhood adversity was significantly greater in bipolar disorder (OR: 1.24, CI: 1.02 - 1.50, \( p=.031 \)), with low levels of statistical heterogeneity (Q (10) = 12.83, \( p=.233 \), \( I^2 = 22.08 \)). Egger’s test approached significance (B: .75, SE: 0.43, \( p=.058 \)) indicating the possibility of publication bias. After Duval and Tweddie’s trim and fill adjusted for three hypothetical missing studies, the imputed OR fell to 1.09 (CI: 0.88 - 1.36).

Based on the identified articles, it was hypothesised post hoc that the absence of a significant difference in childhood adversity between bipolar and major depression was due to an over inclusion of studies focusing on parental loss (n=4). The authors therefore repeated the analysis including only those studies that measured other forms of adversity (n=7). This elevated the effect size (OR = 1.54,
CI: 1.19 - 2.00, \( p < .001 \); \( Q(6) = 4.30, p < .001, I^2 = 0 \) showing significantly higher rates of childhood adversity in bipolar disorder when compared to unipolar depression. No hypothetically missing studies were detected in this analysis with no indication of publication bias (B: -1.34, SE: 1.25, \( p = .166 \)).

The analysis of studies comparing bipolar patients to patients with diagnoses of schizophrenia is displayed in Figure 4. No significant difference in rates of childhood adversity was found when comparing bipolar disorder and schizophrenia in the analysis of five studies (OR = 0.89, CI: 0.79 – 1.01, \( p = .067 \); \( Q(4) = 2.32, p = .677, I^2 = 0 \)). Egger’s test was non-significant indicating the absence of publication bias (B: -0.52, SE: 0.42, \( p = .152 \)). This analysis identified no hypothetically missing studies. Due to a limited number of studies and range of adversity trauma measures, it was not possible to generate an effect size for individual adversity subtypes across clinical groups.

Quality assessment

Table 3 shows the results to the Newcastle Ottawa Quality Assessment Scale for the case control studies. Generally, the quality of the studies in the main analysis was high, with eight studies employing an appropriately matched control group and/or controlling for covariates in the analysis. Only one study failed to substantiate participants’ diagnoses through interview (41). Quality ratings for the case control studies included in the secondary analysis were lower than in the main analysis. This was largely due to studies not controlling for
covariates or employing a matched clinical control sample. Important to consider is that hospital controls score lower on item three of the Newcastle Ottawa Quality Assessment Scale. The majority of the studies included in the secondary analysis employed a rigorous method of ascertaining clients’ diagnoses.

The Newcastle Ottawa Quality Assessment Scale is designed for establishing the methodological quality of prospective cohort design research and was therefore incompatible with the cross sectional (12, 39, 42) and retrospective cohort (31, 40) epidemiological studies identified in the current review. To summarise this literature, all studies included a nationally representative sample with data obtained through structured interviews or record linkage. All epidemiological studies adequately controlled for a range of covariates in their analyses including gender.
<table>
<thead>
<tr>
<th>Study name</th>
<th>Outcome</th>
<th>Odds ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alnaes &amp; Torgersen, 1993</td>
<td>Parental loss</td>
<td>1.32</td>
<td>0.46</td>
<td>3.74</td>
<td>0.61</td>
</tr>
<tr>
<td>Agid et al., 1999</td>
<td>Parental loss</td>
<td>0.76</td>
<td>0.33</td>
<td>1.76</td>
<td>0.53</td>
</tr>
<tr>
<td>Furukawa et al., 1999</td>
<td>Parental loss</td>
<td>1.08</td>
<td>0.53</td>
<td>2.20</td>
<td>0.83</td>
</tr>
<tr>
<td>Hyun et al., 2000</td>
<td>Physical or sexual abuse</td>
<td>1.43</td>
<td>0.88</td>
<td>2.31</td>
<td>0.15</td>
</tr>
<tr>
<td>Watson et al., 2007</td>
<td>Trauma total</td>
<td>0.62</td>
<td>0.17</td>
<td>2.27</td>
<td>0.47</td>
</tr>
<tr>
<td>Savitz et al., 2008</td>
<td>Trauma total</td>
<td>1.29</td>
<td>0.64</td>
<td>2.63</td>
<td>0.48</td>
</tr>
<tr>
<td>Angst et al., 2011</td>
<td>Sexual abuse</td>
<td>1.54</td>
<td>0.77</td>
<td>3.08</td>
<td>0.22</td>
</tr>
<tr>
<td>Konradt et al., 2013</td>
<td>Trauma total</td>
<td>1.79</td>
<td>0.95</td>
<td>3.34</td>
<td>0.07</td>
</tr>
<tr>
<td>Parker et al., 2013</td>
<td>Physical or sexual abuse</td>
<td>2.48</td>
<td>1.24</td>
<td>4.98</td>
<td>0.01</td>
</tr>
<tr>
<td>Perna et al., 2014</td>
<td>Trauma total</td>
<td>1.40</td>
<td>0.59</td>
<td>3.30</td>
<td>0.45</td>
</tr>
<tr>
<td>Laurson et al., 2007</td>
<td>Parental loss</td>
<td>1.24</td>
<td>1.02</td>
<td>1.50</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Figure 3. Forest plot for the bipolar disorder compared to unipolar depression analysis.
## Study name | Outcome | Statistics for each study | Odds ratio and 95% CI
---|---|---|---
Darvez-Bornoz et al., 1995 | Sexual abuse | 0.66 | 0.24 | 1.80 | 0.41
Agid et al., 1999 | Parental loss | 1.06 | 0.44 | 2.57 | 0.90
Hlastala & McLellan, 2005 | Trauma total | 0.41 | 0.13 | 1.29 | 0.13
Alvarez et al., 2011 | Sexual & physical abuse | 0.83 | 0.30 | 2.28 | 0.72
Laurson et al., 2007 | Parental loss | 0.90 | 0.80 | 1.02 | 0.11

Figure 4. Forest plot for the bipolar disorder compared to schizophrenia analysis.
Table 3. Quality check for case control studies.

<table>
<thead>
<tr>
<th>Adequate case definition</th>
<th>Representativeness of the cases</th>
<th>Selection of controls</th>
<th>Definition of controls</th>
<th>Comparability of cases and controls</th>
<th>Ascertainment of exposure (trauma)</th>
<th>Same method for cases and controls</th>
<th>Non-response rate</th>
<th>Total stars</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agid et al., 1999</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>** N</td>
<td>N</td>
<td>N</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Furukawa et al., 1999</td>
<td>N</td>
<td>N</td>
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**Studies exploring the overall effect of childhood adversity on bipolar disorder (stage one).**

- Agid et al., 1999
- Furukawa et al., 1999
- Rucklidge et al., 2006
- Grandin et al., 2007
- Savitz et al., 2008
- Etain et al., 2010
- Horesh & Iancu, 2010
- Fowke et al., 2012
- Konradt et al., 2013
- Aas et al., 2014
- Chen et al., 2014
- Watson et al., 2014
- Janiri et al., 2015

**Studies exploring the effect of childhood adversity in bipolar disorder relative to major depression and schizophrenia (stage four).**

- Alnaes & Torgersen, 1993
- Darvez-Bornoz et al., 1995
- Hlastala & McClellan, 2005
- Hyun et al., 2000
- Watson et al., 2007
- Angst et al., 2011
- Alvarez et al., 2011
- Parker et al., 2013
- Perna et al., 2014

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Discussion

The results of the meta-analysis presented in this paper suggest that individuals with bipolar disorder are 2.63 times more likely to experience childhood adversity when compared to non-clinical controls. This effect did not appear to be the result of study design or bias, and remained robust and significant even when controlling for hypothetically missing studies. In the past, the genetic determinants of bipolar disorder have been emphasised in the research literature. However, the current findings suggest that childhood adversity may also play a key role in the development of this disorder.

The results showed that emotional abuse was four times more likely to occur in bipolar disorder when compared to healthy controls; an effect considerably larger than when considering other types of adversity. This is in contrast to a recent meta-analysis that observed roughly equivalent effect sizes for adversity subtypes on psychosis (25). The finding is consistent with key theoretical models (e.g. attachment theory), which suggest that a child’s early interactions with their primary caregivers can influence their ability to regulate emotions later in life (24). Despite a lack of research on attachment in bipolar disorder, there is some evidence to suggest that rates of insecure attachment are elevated in this population (69).

Individuals with bipolar disorder were more than twice as likely to experience sexual abuse, physical abuse and neglect when compared to non-clinical controls. However, parental loss did not significantly differ between bipolar and non-clinical samples. One explanation is that the impact of losing a parent is highly
dependent on the context and stage at which it occurs (6). Indeed, past research has suggested that a younger age at the time of parental loss, maternal loss in particular, and death by unnatural causes (e.g. suicide, murder) might convey greater risk of bipolar disorder (40, 70, 71). The way in which adverse events are interpreted and appraised may also influence their long-term impact (72). For example, maladaptive appraisals that adverse events could re-occur at any time could lead to greater distress and the use of unhelpful control strategies (73). Trauma appraisals have been relatively under-investigated in the context of bipolar spectrum disorders.

Rejecting our initial hypothesis, the effect of childhood adversity on bipolar II disorder, compared to bipolar I disorder, did not reach statistical significance. Although this analysis was based on only four studies, it is possible that childhood adversity represents a risk factor for both the more severe and attenuated form of bipolar symptoms. In the future research should investigate dose-response effects of adversity on bipolar symptomatology, which would strengthen inferences about a causal relationship (74). To the best of the author’s knowledge, no research has explored this in the context of bipolar disorder.

Rates of childhood adversity were significantly greater in bipolar disorder when compared to unipolar depression. However, this effect was not robust and became non-significant when controlling for hypothetically missing studies. The absence of a stronger effect may have been due to the overrepresentation of studies considering parental loss, which did not appear to be elevated in bipolar disorder more generally. When repeating the analysis without effects pertaining to parental loss, individuals with bipolar disorder presented with higher levels of
adversity compared to unipolar depression. Nevertheless, it is difficult to draw any firm conclusions on the specificity of childhood adversity on bipolar and unipolar depression.

The results showed no significant difference in the rates of childhood adversity between individuals diagnosed with bipolar disorder and schizophrenia. A wealth of past research has focused on the role of childhood adversity in the development of psychosis (25). The current findings suggest that early adversity may be equally as prevalent in bipolar disorder. Interestingly, correlational studies not included in this meta-analysis have suggested that childhood adversity, particularly sexual abuse, increases the likelihood of psychotic experiences in bipolar disorder (16, 75). In the future, research should explore the exact pathways by which specific forms of adversity lead to particular symptom clusters (76).

The systematic search failed to identify any longitudinal studies that measured adversity in childhood and prospectively measured outcome in later life; although, retrospective cohort design studies were included. The analysis revealed high levels of statistical heterogeneity, which is not surprising given the methodological and statistical differences in the identified studies. Measures of childhood adversity included national registers (31, 40), validated questionnaires (46, 50), survey items (39, 43) and semi-structured interviews (47, 77). Studies also differed in terms of diagnostic assessments (e.g. the Structure Clinical Interview for DSM Disorders, the Composite International Diagnostic Interview) and inclusion criteria (e.g. adolescents, adults), with two studies restricting their analysis to bipolar I disorder (43, 59). In the presence of further publications, future reviews
might wish to explore whether such methodological and clinical variations affect the strength of the observed effects.

The mechanism by which childhood adversity acts on bipolar symptomatology remains unclear. Adverse events may increase risk of bipolar disorder by sensitising individuals to subsequent stressors, increasing the volatility of emotional states (78). Physiological research in non-clinical populations has shown childhood adversity to predict aberrant hypothalamic-pituitary-axis functioning, and both structural and functional stress related brain changes (79). This includes increased amygdala activation (80) and changes to the prefrontal cortex (81); areas of the brain implicated in emotional dysregulation and impulse control respectively. In the future, it may be useful to develop, evaluate and refine a traumagenic neurodevelopmental model for bipolar disorder with a focus on emotional abuse (82). Further research is also needed to explore the clinical factors that might mediate the relationship between childhood adversity and bipolar disorder. Adverse events may lead to poorly integrated memories increasing the frequency of distressing trauma related intrusions (83). Alternatively, adverse events might lead to the development of maladaptive cognitive styles and belief systems (22). This includes extreme and conflicting beliefs about affective states, which could generate unhelpful control strategies that maintain affective instability over time (84, 85).

There are some limitations of this meta-analysis and of the research literature more generally. Recall bias and illness representations may confound retrospective reporting of childhood adversity (28). However, research has suggested that recall bias only explains a small amount of the variance in
retrospective childhood adversity assessments (86). Additionally, retrospective reports of adversity often show good convergent validity with clinical case notes and are relatively stable over time (87). In the absence of long-term prospective research, it is impossible to reach a definitive conclusion on the causal link between childhood adversity and bipolar disorder. In some cases, early or prodromal symptoms in childhood may place greater strain on parenting, which could contribute to dysfunctional relationships. Therefore, a genetic predisposition to bipolar disorder may increase levels of childhood adversity. Lastly, the adversity subtypes were not statistically independent. It is therefore impossible to draw any firm conclusions on the specificity of adversity subtypes on bipolar disorder from the current analysis.

The findings have several clinical implications. Policies and practices aimed at preventing childhood adversity could reduce rates of bipolar disorder and other mental health difficulties. Parenting programmes, such as ‘triple P’ (88) or ‘incredible years’ (89), could help to decrease unhelpful parenting styles that might eventually become abusive (90). Within services, clinicians should not be reluctant to enquire about their clients’ past adverse experiences, including emotional abuse and neglect. Read and colleagues (91) have provided guidance on how clinicians might conduct these conversations and sensitively respond to and deal with disclosures. Identification of childhood adversity should then lead to its integration into personalised formulations of clients’ difficulties, and the provision of appropriate support and interventions. One option is to provide assistance with the sequelae of childhood adversity through psychological therapy (92). For example,
trauma focused cognitive behavioural therapy (93) could be used to reduce post-traumatic stress disorder in individuals with bipolar disorder. However, evidence supporting the use of cognitive behavioural approaches, and psychological therapy more generally, in bipolar populations remains limited (94). The current findings suggest that cognitive models may benefit from considering the predisposing role of interpersonal stressors, in addition to the processes maintaining affective instability over time (95).

In conclusion, childhood adversity, particularly emotional abuse, appears to play an important role in the development of bipolar disorder. Rates of childhood adversity in bipolar disorder appear to be similar to those observed in psychosis and major depression. In the future, researchers should delineate this relationship by exploring potential mediators between adversity subtypes and both symptomatic and functional outcomes. Further prospective research exploring dose-response relationships would help to elucidate the causal relationship between childhood adversity and bipolar symptomatology. The findings have implications for the study and treatment of bipolar disorder.

Acknowledgements:

This research completed as part of the primary author’s doctorate in clinical psychology funded by the National Health Service. The authors would like to thank Louise Laverty and Rebecca Harrop for the assistance with reliability checking the data screening. They would also like to thank all of the authors who kindly supplied additional information about their research. This includes Alex Fowke, Daniela
Caldirola, Delfina Janiri, Gianfranco Spalletta, Jonathan Savitz, Lauren Alloy, Lize van der Merwe, Luciano de Souza, Monica Aas, Netta Horesh, Po-Hsiu Kuo, Stuart Watson, and Toshi Furukawa.
References


Paper two: Empirical study

Childhood adversity and social functioning in psychosis: The identification of clinical and cognitive mediators.

For submission to Psychiatry Research
Abstract

Childhood adversity may increase risk of impaired social functioning across the continuum of psychosis. However, the pathways by which adversity dictates functional outcome remain underexplored. The aim of this study was to investigate the relationship between childhood adversity and social functioning, and the clinical and cognitive mediators of this relationship. Fifty-four clinical (20 chronic, 20 first episode, 14 at ultra-high risk) and 120 non-clinical participants completed standardised questionnaires, semi-structured interviews and tests of theory of mind ability. The authors used multiple group structural equation modelling to fit mediation models allowing for differential relationships between the clinical and non-clinical samples. When examining each pathway separately, depression, paranoia and anxious attachment mediated the effect of childhood adversity on social functioning. However, in a combined model, depression was the only significant mediating variable. Childhood adversity did not significantly predict theory of mind ability. Childhood adversity may act on social functioning across the psychosis continuum by increasing levels of depression. Clinical interventions should target low mood in order to improve social functioning. Future research should further delineate the relationship between childhood adversity and functional outcomes in psychosis.
1. Introduction

Service user accounts have emphasised the importance of functional outcomes in recovery from psychosis (Pitt et al., 2007; Wood et al., 2010). This includes occupational change, but also improving interpersonal relationships and social behaviour. Impaired social functioning is common in individuals at different stages of psychotic disorder (Addington et al., 2008), where it is associated with increased risk of symptom reoccurrence (Robinson et al., 1999) and hospitalisation (Perlick et al., 1992). However, despite its clinical significance, the factors leading to poor social functioning in psychosis remain underexplored. The aim of this study was to investigate the relationship between childhood adversity and social functioning across the psychosis continuum, and to explore possible mediators of this relationship.

Childhood adversity (e.g. sexual abuse, physical abuse) is common in the general population (Kessler et al., 2010), but is particularly prevalent in individuals with non-affective psychosis (Varese et al., 2012). This has led some authors to propose that childhood adversity constitutes a risk factor for hallucinations and delusional beliefs (Read et al., 2001). Less understood is the association between childhood adversity and functional impairment in psychosis (Cotter et al., 2014). Existing research in this area has shown reduced social functioning in individuals who have experienced childhood interpersonal trauma or sexual abuse (Lysaker et al., 2001; Stain et al., 2013). Further research is required to delineate the pathways by which childhood adversity acts on social functioning in order to develop efficacious prevention and intervention strategies. In this article, the authors
explore attachment style, theory mind (ToM) impairment and clinical symptoms as mediators of this relationship.

Attachment theory suggests that traumatic or suboptimal parenting styles influence individuals’ interpretations and expectations of future relationships. These internal working models (i.e. cognitive and emotional representations) of relationships are thought to persist into adulthood, where they shape social interactions and behaviour (Bowlby, 1969). Several authors have posited that insecure attachment exists on two continua (Bartholomew, 1990; Mikulincer & Shaver, 2002). Attachment avoidance derives from consistently unresponsive caregiving, where the individual learns to be overly self-reliant and reject intimate relationships. Conversely, attachment anxiety is the result of inconsistent or contradictory caregiving, leading to an excessive need for approval and fear of rejection. It is thought that both anxious and avoidant attachment styles are associated with impaired interpersonal functioning.

Past research has demonstrated associations between insecure attachment and social problems, such as hostility towards others, interpersonally demanding behaviour and social distancing (Berry et al., 2008; MacBeth et al., 2008). There is also evidence to suggest that insecure attachment styles can result from childhood adversity (Gumley et al., 2014). Indeed, studies have observed positive associations between the number of negative events in childhood and adult attachment anxiety (Berry et al., 2009; Picken et al., 2010); an effect that appears amplified in cases of intra-familial and severe forms of adversity (Swanson & Mallinckrodt, 2001). To the best of our knowledge, no research has explored whether attachment style
mediates the relationship between childhood adversity and social functioning in psychosis.

A further pathway to impaired social functioning may be through ToM impairment. ToM represents an individual’s ability to understand and make accurate inferences about the intentions and thoughts of others (Corcoran, 2001; Couture et al., 2006). It includes the ability to see things from others’ perspectives and to understand social cues (Pinkham et al., 2014), which may be essential skills for developing and maintaining relationships (Couture et al., 2006). Although ToM ability has sometimes been found to predict social functioning in individuals with psychosis (Bora et al., 2006; Morosini et al., 2002), the strength of this relationship appears to be highly contingent of the choice of assessments and covariates included in the analysis (Fett et al., 2011).

Some authors have proposed that ToM deficits are the result of a genetic predisposition (Bora et al., 2009). However, the authors predict that childhood environmental factors may also influence ToM development. Childhood adversity may limit ToM enriching experiences, whilst directly preventing skills acquisition. This is consistent with key theories of child development, whereby the individual learns to navigate social encounters through the behaviour and reactions of others (Bandura & Walters, 1963; Vygotsky, 1978). Such opportunities may be limited or absent in cases of neglect, whereas volatile and contradictory early interpersonal exchanges may make it difficult for the child to generalise, and therefore learn, from social experiences. Childhood adversity may also have a more direct impact on ToM ability. There is now a wealth of literature suggesting that childhood adversity, and associated stress, can lead to hypo-thalamic-pituitary axis dysregulation, which
can have a deleterious effect on neuronal development (Corcoran et al., 2003; Teicher et al., 2003). Past studies have suggested that childhood adversity is associated with impaired cognitive ability, limiting attention, memory, and language abilities (De Bellis et al., 2009). There is also some indication that adverse events can disrupt higher-order cognitive processes, including social perception (Nazarov et al., 2014) and emotion processing (Lysaker et al., 2011). A recent study found that children with a history of early life deprivation had depleted ToM ability (Colvert et al., 2008). Further research is necessary in order to understand the impact of childhood adversity on ToM in the context of psychosis.

In addition to attachment style and ToM ability, the authors propose that depression and paranoia will act as mediators between childhood adversity and social functioning. Depression is characterised by low motivation and social withdrawal, whereas paranoia is often associated with active social avoidance and anxiety in social situations. Both may affect individuals’ ability to engage in social situations. Past research in this area has shown negative associations between these symptoms and a wide range of social processes (Combs et al., 2013; Corcoran et al., 2011). Additionally, rates of depression (Scott et al., 2010) and paranoia (Bentall et al., 2012) are elevated in individuals with a history of childhood adversity, suggesting a possible causative link between these variables.

In this study, the authors examined predictors of social functioning in both clinical and non-clinical populations. For the clinical sample, they recruited individuals with varying severities of psychosis, which had the advantage of being able to explore the cross-continuum determinants of social functioning. There is
now considerable evidence to support a continuum model of psychosis, which extends to the general population (Johns & Van Os, 2001).

The first hypothesis was that there would be a direct effect of childhood adversity on social functioning. The second hypothesis was that attachment anxiety, attachment avoidance, ToM ability, paranoia and depression would mediate this relationship. In the absence of a mediation effect, the authors tested whether these variables would independently predict levels of social functioning.

2. Methods

2.1. Sample

The clinical sample comprised of three a-priori defined groups. Group 1 consisted of individuals meeting the criteria for a Diagnostic and Statistical Manual (Fourth Edition; DSM-IV) diagnosis of schizophrenia, schizoaffective, schizophreniform, or delusional disorder who had been experiencing psychotic symptoms for at least two years. The research team obtained these diagnoses from the referring clinician and the clients’ clinical records. Group 2 consisted of individuals who had recently experienced a first episode of psychosis (FEP) and were receiving treatment from an Early Intervention Service (EIS). EIS are specialist services aimed at supporting individuals aged 16-35 in the first three years after their initial psychotic episode. EIS operationally define psychosis based on cut-off scores on the Positive and Negative Syndrome Scale (Kay et al., 1987). Therefore, at entry to service, all clients had scored four or greater on the delusional thinking, hallucinations, or suspicious thoughts items of this interview. Group 3 consisted of
individuals who met criteria for being at ultra-high risk (UHR) of developing psychosis according to the Comprehensive Assessment of At Risk Mental State (Yung et al., 2005) at some point in the past 12 months and who were enrolled with an EIS or Early Detection and Intervention Team. These individuals had not yet made transition to FEP, but were experiencing attenuated psychotic experiences, which were causing distress and disability.

In addition to the three clinical samples, the researchers opportunistically recruited non-clinical participants through adverts placed around a University campus and an online research participation system. All participants were aged 16 or older. The exclusion criteria for all groups were: i) a neurological disorder; ii) a moderate or severe learning disability; iii) organic or substance induced psychosis; or iv) known visual or hearing difficulties.

2.2. Measures

The variables presented in the current analysis were from a wider number of assessments administered as part of a study examining the impact of early life adversity, attachment styles, and social cognition on key outcomes in psychosis. The authors administered the PANSS to the chronic and FEP samples for descriptive purposes.

2.2.1. Independent variable

The Childhood Trauma Questionnaire (CTQ; Bernstein et al., 2003) is a validated 28-item self-report measure childhood adversity. Respondents indicate whether they experienced a range of events on a scale from 1 (never true) to 5
(very often true). The CTQ consists of five subscales assessing physical abuse, emotional abuse, sexual abuse, physical neglect, and emotional neglect. Past research has attested to the reliability and validity of the CTQ in psychiatric (Bernstein et al., 1997) and non-clinical (Paivio & Cramer, 2004) samples.

2.2.2. Dependent variable

The Personal and Social Performance Scale (PSP; Morosini et al., 2000) was employed to assess participant social functioning over the previous month. The interviewer scores the participant from one (absent) to six (very severe) on four dimensions of social functioning: socially useful activities, personal and social relationships, self-care and disturbing and aggressive behaviour. Based on these ratings, they then score the participant on a single scale ranging from zero to 100 using set criteria. The PSP has been shown to have adequate reliability and validity in individuals with non-affective psychosis (Nasrallah et al., 2008; Patrick et al., 2009). For the current study, the lead author trained four researchers in the administration and scoring of this interview. Prior to recruitment starting, all researchers provided ratings for 12 clinical vignettes in order to assess inter-rater reliability\(^2\). The intra-class correlation (two way mixed effects; absolute agreement) for the total PSP score was 0.92 \(p<0.001\), suggesting excellent levels of agreement. The lead author reviewed audio recordings of the interviews and provided feedback throughout recruitment.

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\(^2\) Examples presented in appendix D; p134
2.2.3. Proposed mediators

The Psychosis Attachment Scale (PAM; Berry et al., 2006) is a 16-item questionnaire measure of anxious and avoidant attachment in adults, which does not require the respondents to be involved in romantic relationships. Berry and colleagues have established the construct validity of the PAM subscales in two non-clinical samples (Berry et al., 2007; Berry et al., 2006), and its concurrent validity and test re-test reliability in individuals with psychosis (Berry et al., 2008).

In order to assess different aspects of ToM ability the authors employed two measures of this construct. The Hinting Task (Corcoran et al., 1995) consists of 10 passages depicting scenarios involving two people that are read out loud to the respondent. At the end of each passage, one of the characters makes a hint. The participant is then required to identify the hidden meaning in the character’s statement. The Mind in the Eyes task (Baron-Cohen et al., 2001) presents participants with 36 images of people’s eyes and asks them to choose which of four words best describes the emotion that they are showing. The Hinting and Mind in the Eyes tasks were highlighted as key measures of ToM by a recent expert panel (Pinkham et al., 2014).

The Calgary Depression Scale (Addington et al., 1990) is a semi-structured interview with good internal consistency. It has less overlap with the positive and negative symptoms of psychosis than other measures of depression (Addington et al., 1996). Paranoia was assessed using the Green Paranoid Thought Scales (Green et al., 2008), which was designed to assess suspicious thoughts across the psychosis continuum. It contains items relating to social reference and ideas of persecution,
and has acceptable internal consistency, and good concurrent and convergent validity.

2.3. Procedure

Clinicians from inpatient and community mental health services in the North West of England identified and invited eligible clients to take part. All clients provided written consent prior to completing the tasks, questionnaires and interviews. The researchers then reviewed the participants’ medical notes for demographic and background information. An NHS Research Ethics Committee approved this research study.

2.4. Statistical analysis

All analyses were conducted in Stata 12.0 (Stata Corporation, 2011). Initially, in the presence of non-normally distributed variables, the authors used non-parametric analyses to detect differences in the independent (childhood adversity), mediating (anxious attachment style, avoidant attachment style, paranoia, depression, Hinting Task, and Mind in the Eyes Task) and dependent (social functioning) variables across the samples. This included Kruskal-Wallis H tests to determine the presence of statistically significant differences, and post-hoc Mann-Whitney tests in order to ascertain which of the groups, in particular, differed in their scores. A Bonferroni correction was used to account for multiple hypotheses testing ($p < 0.001$).
The authors conducted the mediation analysis in three steps. Firstly, partial correlations assessed the independence of the mediators, whilst controlling for levels of childhood adversity, age, gender and clinical status (i.e. psychosis or non-clinical). Bootstrapping with 2000 replications was used to estimate the standard error and 95% confidence intervals, accounting for the data not being normally distributed (Mooney & Duval, 1993).

Secondly, the authors conducted mediation analysis using the SEM command in Stata, which fitted the statistical models across subgroups of the data and allowed testing for differential relationships between the clinical and non-clinical samples. Clinical status was entered as the grouping variable. The authors tested differences in the model chi-square (\(X^2\)), and the number of model parameters tested against the \(X^2\) distribution (i.e. Score Test), to ascertain whether there were significant differences in the strength of the structural coefficients between groups. In the absence of significant differences, all structural coefficients were constrained to be equal providing single estimates of the coefficients.

Mediation analysis involves estimating three regression models: one, a regression of the outcome on the independent variable; two, a regression of the mediating variable on the independent variable; and three, a regression of the outcome on the independent and mediating variables (MacKinnon, 2008). The second and third models can be fitted simultaneously using structural equation modelling. Mediation is present if the indirect effect is statistically significant, or if the strength of the independent variable on outcome is smaller in the presence of the mediating variable.
In the present analysis, Model 1 contained the total effect of childhood adversity on social functioning. The subsequent six models then contained a single mediating variable in addition to a direct effect. Figure 1 shows the structure of the models. Model 2 estimated the regression coefficients between childhood adversity and social functioning, childhood adversity and paranoia, and paranoia and social functioning. Subsequently, the authors replaced paranoia with depression in Model 3, attachment anxiety in Model 4, attachment avoidance in Model 5, Mind in the Eyes score in Model 6 and the Hinting Task score in Model 7.

Thirdly, variables found to successfully mediate the relationship between childhood adversity and social functioning at the previous stage of analysis were entered into a final multiple mediation model. The purpose of this was to consider the relative impact of the different mediators on social functioning in addition to the direct effect of childhood adversity. In the presence of statistically significant partial correlations, the mediators were non-independent and permitted to covary.

The authors controlled for the effects of age and gender on the mediating and outcome variables in the mediation analyses. Bootstrapping with 2000 replications was used to estimate the standard error and 95% confidence intervals. Variables were manually standardised for ease of interpretation. In addition to the $X^2$, the authors report three goodness of fit for each model: the Tucker Lewis Index (TLI), the Comparative Fit Index (CFI), and the Root Mean Square Error of Approximation (RMSEA). Although using cut-offs for other goodness of fit indices has been criticised (Barrett, 2007), an approximate RMSEA of less than 0.10, and CFI
and TLI scores approaching 1.000, are generally considered to indicate good statistical fit.

Figure 1. i) A representation of the total effect of childhood adversity on social functioning (Model 1). ii) A representation on the mediation models (Models 2-7).

3. Results

3.1. Sample characteristics

Clinicians approached approximately 80 individuals to take part in the study with 24 (14 chronic, three FEP, seven UHR) subsequently declining and two individuals ineligible based on their diagnoses. The final samples therefore consisted of 54 clinical (20 chronic, 20 FEP, 14 UHR) and 120 non-clinical participants. Table 1 shows demographic information and summary statistics for the clinical and non-clinical samples. The authors subdivided the clinical sample into its three constituent groups for descriptive purposes. The majority of individuals

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3 Further rationale for analysis presented on page 103
with chronic and FEP fell into the mildly to moderately ill symptom range on the PANSS (Leucht et al., 2005).

3.2. Group differences in the mean scores of key variables.

Kruskal-Wallis analysis indicated that the median of the measures differed significantly across the samples. Mann-Whitney tests then showed that social functioning was significantly lower, and childhood trauma and depression significantly higher, in the clinical compared to the non-clinical participants. The UHR and FEP samples also experienced significantly greater levels of attachment anxiety, attachment avoidance and paranoia when compared to the non-clinical sample. The chronic group performed significantly worse than the non-clinical participants on both the Hinting Task and the Mind in the Eyes measures. The FEP group performed worse on the Mind in the Eyes task only.
Table 1. Demographic information and summary statistics for the clinical and non-clinical samples.

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<td>6</td>
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<tr>
<td>Inpatient status, n</td>
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<td>0</td>
<td>0</td>
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<td>PANSS score, mean (SD)</td>
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<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Positive</td>
<td>17.1 (6.1)</td>
<td>14.5 (3.9)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>N/S</td>
</tr>
<tr>
<td>Negative</td>
<td>15.2 (5.8)</td>
<td>12.3 (3.3)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>N/S</td>
</tr>
<tr>
<td>General</td>
<td>32.7 (7.8)</td>
<td>27.5 (5.4)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Chronic &gt; FEP</td>
</tr>
<tr>
<td>PSP, mean (SD)</td>
<td>55.3 (10.3)</td>
<td>57.6 (9.2)</td>
<td>56.0 (10.9)</td>
<td>76.1 (9.9)</td>
<td>88.07</td>
<td>NC &gt; chronic, FEP, UHR</td>
</tr>
<tr>
<td>CTQ, mean (SD)</td>
<td>45.1 (15.5)</td>
<td>39.9 (12.3)</td>
<td>45.8 (16.2)</td>
<td>31.2 (7.5)</td>
<td>37.72</td>
<td>chronic, FEP, UHR &gt; NC</td>
</tr>
<tr>
<td>Avoidant attachment, mean (SD)</td>
<td>1.6 (0.5)</td>
<td>1.8 (0.6)</td>
<td>1.8 (0.5)</td>
<td>1.2 (0.6)</td>
<td>31.85</td>
<td>FEP, UHR &gt; NC</td>
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<tr>
<td>Anxious attachment, mean (SD)</td>
<td>1.3 (0.8)</td>
<td>1.5 (0.6)</td>
<td>1.8 (0.8)</td>
<td>1.0 (0.6)</td>
<td>24.40</td>
<td>FEP, UHR &gt; NC</td>
</tr>
<tr>
<td>CDS, mean (SD)</td>
<td>4.5 (4.1)</td>
<td>6.0 (4.2)</td>
<td>7.0 (5.4)</td>
<td>1.7 (2.3)</td>
<td>45.39</td>
<td>chronic, FEP, UHR &gt; NC</td>
</tr>
<tr>
<td>GPTS, mean (SD)</td>
<td>66.7 (29.3)</td>
<td>82.6 (33.8)</td>
<td>88.3 (31.8)</td>
<td>47.0 (15.6)</td>
<td>44.29</td>
<td>FEP, UHR &gt; NC</td>
</tr>
<tr>
<td>The Hinting Task, mean (SD)</td>
<td>14.8 (3.8)</td>
<td>17.8 (2.5)</td>
<td>17.8 (1.5)</td>
<td>18.7 (1.6)</td>
<td>33.82</td>
<td>NC &gt; chronic</td>
</tr>
<tr>
<td>Mind in the Eyes, mean (SD)</td>
<td>19.8 (5.6)</td>
<td>22.5 (5.0)</td>
<td>22.6 (5.0)</td>
<td>26.8 (3.9)</td>
<td>39.56</td>
<td>NC &gt; FEP, chronic</td>
</tr>
</tbody>
</table>

Key: n, number of participants; NC, non-clinical psychosis; FEP, first episode psychosis; UHR, ultra-high risk; SD, Standard Deviation; PANSS, Positive and Negative Syndrome Scale; PSP, Personal and Social Performance Scale; CTQ, Childhood Trauma Questionnaire; PAM, Psychosis Attachment Measure; CDS, Calgary Depression Scale; GPTS, Green et al., Paranoid Thought Scales; N/S, non-significant.

*Only results significant at p <.001 after a Bonferoni correction was carried out.
3.3. Partial correlations

Table 2 shows the results of the partial correlations between the mediating variables. In total, there were eight statistically significant positive partial correlations, the strongest of which was between anxious attachment style and paranoia. The Hinting Task showed the weakest associations with the clinical mediators, but significantly correlated with participants’ scores on the Mind in the Eyes task.

Table 2. Partial correlations between mediating variables when controlling for childhood adversity, age, gender and clinical status.

<table>
<thead>
<tr>
<th></th>
<th>Avoidant attachment</th>
<th>Anxious attachment</th>
<th>Depression</th>
<th>Paranoia</th>
<th>Hinting Task</th>
<th>Mind in the Eyes</th>
</tr>
</thead>
<tbody>
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<td>Avoidant attachment</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxious attachment</td>
<td>0.13</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>0.19*</td>
<td>0.34**</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paranoia</td>
<td>0.18*</td>
<td>0.46**</td>
<td>0.43**</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hinting Task</td>
<td>-0.05</td>
<td>-0.03</td>
<td>-0.08</td>
<td>-0.12</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Mind in the Eyes</td>
<td>-0.09</td>
<td>0.20*</td>
<td>0.22*</td>
<td>0.09</td>
<td>0.24*</td>
<td>1.00</td>
</tr>
</tbody>
</table>

*p <0.05 **p <0.001

3.4. Individual mediation models

Table 3 contains the results of Models 1-7 constrained across groups. In Model 1, there was a significant negative total effect of childhood adversity on social functioning. Therefore, the results confirmed the hypothesis that a history of childhood adversity would predict worse social functioning in adulthood. Subsequent models tested the role of clinical and cognitive mediators between
childhood adversity and social functioning. In Model 2, childhood adversity significantly predicted greater paranoia, which predicted worse social functioning. Additionally, the strength of the relationship between childhood adversity and social functioning weakened and became non-significant in the presence of the paranoia variable supporting a mediation effect. The results also supported mediation when depression (Model 3) or attachment anxiety (Model 4) were entered in the place of paranoia. Although childhood adversity predicted attachment avoidance (Model 5), this did not predict levels of social functioning, therefore rejecting an indirect effect through this variable.

The relationship between childhood adversity and Hinting Task scores was non-significant, disconfirming the presence of a mediation effect (Model 7). The relationship between Hinting Task performance and social functioning approached statistical significance ($p = 0.067$). Inclusion of the Hinting Task in this model did not reduce the strength of the relationship between childhood adversity and social functioning. Childhood adversity did not predict worse Mind in the Eyes assessment scores, which was not related to social functioning (Model 6).

Table 3 shows the goodness of fit scores for the individual mediation models. All $X^2$ scores were non-significant, and TLI and CFI generally approached 1.000, indicating that the models generally adequately fitted the data. Model 6 examining Mind in the Eyes scores was the worst fitting model with an RMSEA of 0.064 and a CFI of 0.810.
Table 3. Table of mediation models where the coefficients are constrained to be equal across groups.

<table>
<thead>
<tr>
<th>Model</th>
<th>IV</th>
<th>DV</th>
<th>Beta</th>
<th>BS SE</th>
<th>p</th>
<th>Lower</th>
<th>Upper</th>
<th>$\chi^2$</th>
<th>$p$</th>
<th>RMSEA</th>
<th>CFI</th>
<th>TLI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>Childhood adversity</td>
<td>Social functioning</td>
<td>-0.17</td>
<td>0.07</td>
<td>0.021</td>
<td>-0.31</td>
<td>-0.03</td>
<td>2.10</td>
<td>0.553</td>
<td>&lt;0.001</td>
<td>1.000</td>
<td>1.178</td>
</tr>
<tr>
<td>Model 2</td>
<td>Childhood adversity</td>
<td>Paranoia</td>
<td>0.43</td>
<td>0.14</td>
<td>0.003</td>
<td>0.15</td>
<td>0.7</td>
<td>4.51</td>
<td>0.720</td>
<td>&lt;0.001</td>
<td>1.000</td>
<td>1.101</td>
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<tr>
<td></td>
<td>Paranoia</td>
<td>Social functioning</td>
<td>-0.20</td>
<td>0.07</td>
<td>0.005</td>
<td>-0.34</td>
<td>-0.06</td>
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</tr>
<tr>
<td></td>
<td>Childhood adversity</td>
<td>Social functioning</td>
<td>-0.08</td>
<td>0.08</td>
<td>0.311</td>
<td>-0.24</td>
<td>0.07</td>
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<tr>
<td>Model 3</td>
<td>Childhood adversity</td>
<td>Depression</td>
<td>0.48</td>
<td>0.15</td>
<td>0.001</td>
<td>0.19</td>
<td>0.77</td>
<td>2.88</td>
<td>0.896</td>
<td>&lt;0.001</td>
<td>1.000</td>
<td>1.132</td>
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<td>Depression</td>
<td>Social functioning</td>
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<td>0.07</td>
<td>&lt;0.001</td>
<td>-0.42</td>
<td>-0.14</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Childhood adversity</td>
<td>Social functioning</td>
<td>-0.04</td>
<td>0.08</td>
<td>0.583</td>
<td>-0.19</td>
<td>0.11</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Model 4</td>
<td>Childhood adversity</td>
<td>Anxious attachment</td>
<td>0.47</td>
<td>0.10</td>
<td>&lt;0.001</td>
<td>0.28</td>
<td>0.67</td>
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<td>-0.02</td>
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<tr>
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<td>Childhood adversity</td>
<td>Social functioning</td>
<td>-0.11</td>
<td>0.08</td>
<td>0.205</td>
<td>-0.27</td>
<td>0.06</td>
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<td>Model 5</td>
<td>Childhood adversity</td>
<td>Avoidant attachment</td>
<td>0.31</td>
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<td>&lt;0.001</td>
<td>0.15</td>
<td>0.47</td>
<td>7.30</td>
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<td>Avoidant attachment</td>
<td>Social functioning</td>
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<td>0.07</td>
<td>0.086</td>
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<td>0.02</td>
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<tr>
<td></td>
<td>Childhood adversity</td>
<td>Social functioning</td>
<td>-0.13</td>
<td>0.08</td>
<td>0.090</td>
<td>-0.28</td>
<td>0.02</td>
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</tr>
<tr>
<td>Model 6</td>
<td>Childhood adversity</td>
<td>Mind in the Eyes</td>
<td>0.14</td>
<td>0.08</td>
<td>0.091</td>
<td>-0.02</td>
<td>0.30</td>
<td>9.38</td>
<td>0.226</td>
<td>0.063</td>
<td>0.815</td>
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<td>0.969</td>
<td>-0.11</td>
<td>0.11</td>
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<tr>
<td></td>
<td>Childhood adversity</td>
<td>Social functioning</td>
<td>-0.17</td>
<td>0.07</td>
<td>0.022</td>
<td>-0.31</td>
<td>-0.02</td>
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<tr>
<td>Model 7</td>
<td>Childhood adversity</td>
<td>Hinting Task</td>
<td>0.15</td>
<td>0.08</td>
<td>0.062</td>
<td>-0.01</td>
<td>0.31</td>
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<td>&lt;0.001</td>
<td>1.000</td>
<td>1.037</td>
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<td>Hinting Task</td>
<td>Social functioning</td>
<td>0.17</td>
<td>0.09</td>
<td>0.065</td>
<td>-0.01</td>
<td>0.35</td>
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<tr>
<td></td>
<td>Childhood adversity</td>
<td>Social functioning</td>
<td>-0.19</td>
<td>0.07</td>
<td>0.006</td>
<td>-0.32</td>
<td>-0.05</td>
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</table>

Key: IV, independent variable; DV, dependent variable; BS SE, Bootstrapped standard error; CI, confidence interval; RMSEA, root mean square error of approximation; CFI, comparative fit index; TLI, Tucker-Lewis Index; $\chi^2$, Chi-squared.
3.5. Mediation analysis – final model.

Based on the analysis of each mediator separately, attachment anxiety, depression and paranoia were included in the final mediation model (Figure 2). To summarise, a history of childhood adversity significantly predicted greater levels of paranoia ($\beta$: 0.41, $p = 0.003$, $SE$: 0.14, $CI$: 0.14 to 0.68), depression ($\beta$: 0.46, $p = 0.001$, $SE$: 0.14, $CI$: 0.19 to 0.74) and attachment anxiety ($\beta$: 0.47, $p < 0.001$, $SE$: 0.10, $CI$: 0.27 to 0.67). However, only depression ($\beta$: -0.24, $p = 0.001$, $SE$: 0.07, $CI$: -0.38 to -0.09), but neither paranoia ($\beta$: -0.09, $p = 0.273$, $SE$: 0.08, $CI$: -0.24 to 0.07) nor attachment anxiety ($\beta$: -0.03, $p = 0.661$, $SE$: 0.06, $CI$: -0.16 to 0.10) significantly predicted levels of social functioning. There was no direct effect of childhood adversity on social functioning in this model ($\beta$: -0.01, $p = 0.884$, $SE$: 0.09, $CI$: -0.18 to 0.16). The final model had excellent goodness of fit ($X^2$: 12.58, $p = 0.637$; RMSEA: <0.001; CFI: 1.000; TLI: 1.026).

Figure 5. The final mediation model.

Non-significant Scores Tests for all models indicated that there were no significant differences in the strength of the coefficients between the clinical and non-clinical samples. Nevertheless, in sensitivity analysis, the authors repeated the mediation analysis allowing the parameters to vary across the subgroups of the data. Most notably, this analysis showed a non-significantly ($X^2$: 1.084, $p$>$X^2$: 0.298) stronger effect of childhood adversity on social functioning in the non-clinical ($\beta$: -0.29, $p$ = 0.003, SE: 0.10, CI: -0.49 to -0.10) compared to the clinical ($\beta$: -0.12, $p$ = 0.252, SE: 0.10, CI: -0.32 to 0.08) sample. Conversely, Hinting Task performance more strongly predicted social functioning in the clinical ($\beta$: 0.24, $p$ = 0.005, SE: 0.08, CI: 0.07 to 0.40) compared to the non-clinical ($\beta$: 0.05, $p$ = 0.795, SE: 0.18, CI: -0.30 to 0.41) group, although this difference remained non-significant ($X^2$: 2.706, $p$>$X^2$: 0.100).
4. Discussion

This first aim of this study was to test the hypothesis that childhood adversity would predict social functioning. The second aim was then to establish whether paranoia, depression, attachment styles and ToM ability mediate this relationship. The purpose of this study was therefore to delineate the pathway by which childhood adversity might lead to impaired social functioning across the psychosis continuum.

In support of the primary hypothesis, the analysis showed that a history of childhood adversity significantly predicted worse social functioning. This supports the prediction that early life experiences have a long-reaching effect on social impairment, even into adulthood. The strength of this relationship was similar to that observed in individuals with first episode (Stain et al., 2013) and more chronic psychosis (Lysaker et al., 2001). Interestingly, the effect of childhood adversity on social functioning was greater in the non-clinical, compared to the clinical, sample, although this difference did not reach statistical significance. It is possible that in patient populations factors unrelated to childhood adversity play a greater role in determining social impairment.

The authors carried out the mediation analysis in two stages. In the first stage, paranoia, depression, and attachment anxiety mediated the relationship between childhood adversity and social functioning. However, in the second stage when entering all significant mediators into a single model, only depression predicted functional outcome. Childhood adversity may lead to greater levels of
depression, increasing the chronicity (Wiersma et al., 2009) and number (Bernet & Stein, 1999) of affective episodes. In turn, depressive symptomatology, such as feelings of hopelessness, demotivation and anhedonia, may act as a major barrier to engaging in meaningful social behaviour. The results may explain the mechanism by which childhood adversity acts on social functioning across the psychosis continuum. Important to note is that the mediators were significantly correlated and non-independent. Therefore, childhood adversity may have acted on depression by increasing levels of suspicious thoughts (Drake et al., 2004) and attachment anxiety (Kvrgic et al., 2012).

Avoidant attachment style did not significantly predict social functioning in the current data. Additionally, although statistically significant, the effect of anxious attachment on social functioning was relatively small. This might be due to the PSP assessing a global construct that is insensitive to fine-grained social difficulties (e.g. an under reliance on others). Interestingly, childhood adversity significantly predicted both forms of insecure attachment with a stronger coefficient for attachment anxiety that was consistent with past research (Berry et al., 2009; Picken et al., 2010). Early life events may therefore shape individuals’ working models of relationships, affecting how they relate to significant others in psychosis and the general population.

The analysis showed that childhood adversity did not significantly predict either measure of theory of mind, rejecting a mediation effect. This suggests that early life experiences may not be responsible for the theory of mind deficits sometimes observed in individuals with psychosis. Instead, these may be the result
of factors unrelated to childhood adversity (e.g. access to peer relationships, a genetic predisposition; Bora et al., 2009). Interestingly, and contrary to previous findings (Bora et al., 2006; McGlade et al., 2008; Pinkham & Penn, 2006; Sullivan et al., 2013), there was no significant effect of ToM ability of social functioning in this data, although the coefficient for Hinting Task scores did approach significance ($p = 0.062$). The Mind in the Eyes requires skills in mental state decoding ability, which is likely to be heavily reliant on instinctive emotion perception (Bora et al., 2006). Conversely, the Hinting Task is a measure of indirect speech and assesses an individual’s ability to reason about the hidden mental states of others. The latter is likely to be less automatic and more reliant on the individual’s pragmatic language ability, and may have a greater, albeit still weak, effect on social functioning. The absence of a greater effect of ToM on social functioning in this sample may have represented a ceiling effect in the non-clinical sample for this measure. Indeed, the effect of the Hinting Task on social functioning was non-significantly greater in the clinical participants.

There are a number of limitations to this research. First, the sample size was somewhat limited, but sufficient, for conducting structural equation modelling. The RMSEA is typically elevated in small samples, but remained low for all models, indicating that they adequately fitted the data. Second, the observed mediation effects may have been the result of an absent variable (Emsley et al., 2010). For example, negative symptoms have been found to significantly predict social function in psychosis (Corcoran et al., 2011), but were not included in this analysis. Third, the presented statistical models did not control for certain covariates (e.g.
medication, history of therapy). In particular, neurocognitive ability and social
cognition are likely to be related constructs (Penn et al., 1997). However, the
purpose of the study was to explore whether ToM ability tasks mediated the
association between childhood adversity and social functioning, rather than the
degree to which social cognition predicted functional outcome over and above
indices of neurocognitive ability. Fourth, recall bias may confound retrospective
measures of childhood adversity. Contrary to this notion, there is some indication
that memory bias explains little variance in measures of childhood adversity
(Fergusson et al., 2011). Lastly, the study was cross sectional limiting inferences
about causality. It is possible that poor premorbid social functioning in childhood
led to greater rates of adversity.

In regards to the clinical implications of this research, policies aimed at
preventing childhood abuse may help to ameliorate social impairment in psychosis
and the general population. In the past, interventions for improving functional
outcomes in psychosis have received limited empirical support (Cather et al., 2005).
However, the findings of the current study suggest that targeted treatments for
depression may hold some utility in improving social functioning. This might include
medication, but also psychosocial interventions such as cognitive behavioural
therapy (CBT). CBT techniques, such as activity scheduling, could have a direct
impact on levels of social contact, which in turn could elevate mood through
behavioural activation. There is evidence to suggest that CBT can improve affective
outcomes in psychosis with small to moderate effects (Wykes et al., 2008).
Interventions aimed at improving mental reasoning, such as Social Cognition and
Interaction Training (Combs et al., 2007), may help to improve theory of mind deficits in psychosis (Couture et al., 2006).

In conclusion, childhood adversity predicted worse social functioning across the continuum of psychosis. Depression mediated this relationship. The data did not support the hypothesised link between childhood adversity and ToM ability. Future research should explore the causal nature of these relationships through prospective longitudinal design research.
References


Bora, E., Eryavuz, A., Kayahan, B., Sungu, G., & Veznedaroglu, B. 2006. Social function, theory of mind and neurocognition in outpatients with schizophrenia; mental state decoding may be a better predictor of social functioning than mental state reasoning. Psychiatry Research 145(2), 95-103.


of psychosis: the Comprehensive Assessment of At-Risk Mental States.

Australian and New Zealand Journal of Psychiatry 39(11-12), 964-971.
Paper three: Critical evaluation
1. Summary of findings.

In this thesis, the trainee explored the role of childhood adversity in two related psychiatric disorders. The first paper comprised of a meta-analysis exploring rates of adversity in individuals who had received a diagnosis of bipolar disorder. In total, the author screened 5395 articles with 19 eligible studies included in the final analysis. The results suggested that individuals with bipolar disorder were 2.63 times more likely to have experienced a history of childhood adversity than non-clinical samples. Interestingly, the greatest observed effect was for emotional abuse, where the odds ratio was 4.04. The data also showed comparable rates of adversity in individuals diagnosed with bipolar disorder to those with a diagnosis of schizophrenia or major depression.

The second paper contained the results of the Social Cognition in Bonding and Emotions (SCriBE) Study. The trainee investigated whether levels of childhood adversity predicted social functioning across the psychosis continuum. He also explored whether certain candidate variables mediated this relationship. Participants completed self-report questionnaires, interviews and tests of theory of mind ability. The available data were analysed using the structural equation modelling module for Stata 12.0 (Stata Corporation, 2013). Depression mediated the relationship between childhood adversity and social functioning. Childhood adversity did not predict theory of mind (ToM) ability, which did not significantly predict social functional, although the effect for the Hinting Task did approach significance.
2. Diagnostic vs continuum models of psychosis.

There is considerable diagnostic overlap between bipolar and psychotic disorders. Recent estimates suggest that 70% of individuals with a diagnosis of bipolar disorder will experience some form of psychosis (Upthegrove et al., 2015). Conversely, individuals with diagnoses of psychotic disorders will often experience periods of mania and/or depression (Drake et al., 2004). This has led some authors to advocate a dimensional approach to psychosis and mental health difficulties (van Os et al., 1999; Vieta & Phillips, 2007). In regards to the current findings, it is probable that childhood adversity holds little specificity for bipolar disorder, but rather represents a general risk factor for psychological dysfunction. Regarding paper two, the finding of increased rates of emotional abuse in bipolar disorder may be suggestive of an association with emotional instability, rather than a distinct nosological entity. It is also possible that ToM ability represents a common cause of impaired social functioning across the psychosis continuum, including bipolar disorder. Indeed, ToM deficits are also present in bipolar samples (Bora et al., 2009). Therefore, although papers one and two focused on separate diagnoses, the findings may generalise to both the diagnostic categories of bipolar disorder and schizophrenia. The commonalities and differences that might exist between individuals with differing symptom profiles require further investigation through large and well-designed research.

3.1. Paper one.

3.1.1. The strengths and limitations of meta-analysis.

The considerable number of systematic reviews and meta-analyses that had examined childhood adversity in psychosis (Matheson et al., 2013; Read et al., 2005; Varese et al., 2012) initially made the choice of topic for paper one difficult. The trainee settled on the area of childhood adversity in bipolar disorder based on its potential impact and importance to the field. He made the decision to do a meta-analysis, as opposed to a narrative review, based on the research question and a scoping search of the literature. This identified multiple studies that contained a quantitative measure of childhood adversity in bipolar and control samples. In many cases, meta-analysis is preferable to a narrative approach in that it estimates the size, but also the consistency, of the effects (Borenstein et al., 2011). In support of this assertion, the online Cochrane Manual (Green et al., 2011) states:

‘Many systematic reviews contain meta-analyses. Meta-analysis is the use of statistical methods to summarize the results of independent studies... By combining information from all relevant studies, meta-analyses can provide more precise estimates of the effects of health care than those derived from the individual studies included within a review’ (section 1.2.2.; Green et al., 2011)

Like all systematic reviews, the strength of any meta-analysis is somewhat determined by the included studies. A higher quality of available literature is likely
to lead to more accurate and valid conclusions. Systematic reviews and meta-analyses are also highly reliant on the authors accurately presenting the results to their analyses in a way that facilitates effect size extraction. Failure to do so can lead to the exclusion of relevant studies increasing levels of bias.

3.1.2. The strengths and limitations of paper one.

There are several strengths to the review presented in this thesis. To the best of the trainee’s knowledge, he has conducted the first meta-analysis to explore the effect of childhood adversity on bipolar disorder. The trainee performed a wide scoping search of the research literature, which identified the majority of studies included in the final analysis. Eligibility criteria were determined a-priori and published in an online protocol, which allowed for transparency in the review process. The trainee attended regular meetings in order to reach consensus on study inclusion with his supervisors. An independent researcher extracted the effect sizes with high levels of agreement, reducing the possibility that the results were due to individual error at this level. The main analysis showed a moderate effect of childhood adversity on bipolar disorder with relatively narrow confidence intervals, which remained significant even after controlling for bias, allowing for greater confidence in the findings.

There are also some limitations to paper one. The eligibility criteria only included published English Language journal articles, and not books or dissertations. The trainee made this decision based on his workload and time pressures. Only including peer-reviewed studies may have provided greater quality assurance. However, excluding unpublished work could also have led to a file
drawer effect (Rosenthal, 1979). Rates of agreement between the trainee and two postgraduate students who double coded the articles were adequate, but contained some discrepancy. This was largely due to the trainee being overly inclusive in the screening process. In the analysis, there were high levels of heterogeneity in the effects, which may have been due to differences in the included study designs. This is unsurprising given the variety of measures, samples and statistical techniques that authors’ employed, and is common in meta-analysis. In the presence of a larger number of studies, the trainee could have used meta-regression to explore which study characteristics had the greatest impact on the effect sizes.

In order to establish the quality of the included studies, the trainee used the Newcastle-Ottawa Quality Assessment, which has received criticism for a lack of validation and subjective scoring criteria (Stang, 2010). Unfortunately, all quality assessments are largely arbitrary and open to bias. For example, the trainee had considered the criteria presented by Hawker and colleagues (Hawker et al., 2002), which he rejected based on its unclear anchor points. After careful deliberation, the trainee judged this the most appropriate available quality assessment available at the time of review. Other weaknesses of the findings derive largely from problems with the literature as a whole. For example, the systematic search found no prospective cohort design studies exploring the role of childhood adversity in determining bipolar disorder, which would have allowed for stronger causal inferences to be made. Lastly, the trainee used the presence or absence of a diagnosis of bipolar disorder as the outcome for the meta-analysis. Bentall (2004)
has questioned the validity and utility of psychiatric diagnoses. In the future, it may be useful to consider a more dimensional approach to bipolar symptomatology across diagnostic groups (van Os et al., 1999; Vieta & Phillips, 2007).

3.2. Paper two.

3.2.1. Strengths and limitations of paper two.

The second paper has some commendable attributes, including a large non-clinical sample and sophisticated analytical techniques. The mixed sample allowed the trainee to explore the relationship between variables across the psychosis continuum. Participants had varying severities and durations of psychosis, reducing the likelihood that the findings were an artefact of a particular stage of disorder. However, the heterogeneity of the sample could also be criticised for introducing hidden sources of error to the analysis. The trainee held regular training sessions for the other researchers in the Personal and Social Performance Scale (PSP; Morosini et al., 2000) ensuring high levels of inter-rater reliability. This reduced the possibility that the findings were due to inconsistent scoring styles.

The trainee discussed available measures with his supervisors and independent experts in the field before deciding on the inclusion of particular assessments. He employed the Hinting Task and the Mind in the Eyes Task in order to assess potentially distinct, but related, aspects of ToM ability. Authors have sometimes labelled these mental state decoding and mental state reasoning (Bora et al., 2006). In the presence of strong correlations between the task scores, the
trainee could have considered ToM as a single latent variable. Unfortunately, only a subset of participants (i.e. FEP and chronic groups) provided data on negative symptoms and this variable was not included in the final analysis. Negative symptoms have found it to be strongly associated with social functioning in psychosis (Corcoran et al., 2011) and may have some conceptual overlap with depression. Given the large number of measures already included in the study protocol, the trainee felt that adding additional assessments would have been too burdensome for participants. The trainee sought advice from the service user panel in the department who also felt that additional measures would be taxing on participants.

The cross sectional and retrospective nature of the empirical paper is a limitation of the current research. Social desirability effects, recall bias and forgetting may confound retrospective self-report measures of childhood adversity (Hardt & Rutter, 2004). Prospective longitudinal design research was beyond the scope of a doctoral thesis given the time and financial constraints. There is some research attesting to the accuracy of retrospective measures of adversity (Fergusson et al., 2011) and the use of self-report assessments in psychosis (Palmier-Claus et al., 2012b). The researchers recruited the non-clinical, largely female, sample from around the University campus, which was unlikely to be representative of the general population. Opportunistic sampling helped to facilitate recruitment by the undergraduate student researchers. The relatively modest size of the clinical samples, particularly the ultra-high risk (UHR) group, may have limited statistical power reducing the possibility of detecting small effect sizes.
3.2.2. Analytical decisions.

The choice to investigate mediation effects, and the presence of multiple groups, complicated the analysis. The trainee, his supervisors and a statistician corresponded regularly to establish an appropriate analysis plan. The trainee decided that it would be important to use the structural equation modelling command in Stata 12.0 to test multiple mediation models. This approach provided single estimates of the coefficients, whilst controlling for the non-independence of multiple samples. It also enabled the trainee to establish whether there were significant differences in the strength of the coefficients between the clinical and non-clinical subgroups. The analysis lent greater power than if the trainee had fitted the models in the two samples separately. Unfortunately, there was insufficient power to group the analysis by the individual clinical subsamples (UHR, FEP, chronic), which represents a limitation of the current research.

In the mediation analysis, the trainee only controlled for covariates that were a-priori hypothesised not to be the result of childhood adversity (i.e. age, gender). The presence of certain additional variables would have complicated the models. This is particularly true of variables that might have mediated the mediation effects, or had negative effects on the dependent variable. For example, childhood adversity may have predicted depression, causing individuals to engage in medication use and therapy, which could have mitigated the impact of symptoms on social functioning. It is important to consider the absence of certain covariates when interpreting the results. The wider pathways to impaired social functioning require further exploring through more advanced structural equation models in
larger samples (Emsley et al., 2010). These might include additional variables such as neurocognition, negative symptoms, social comparisons, feelings of shame and voice hearing.

4. Theoretical and conceptual implications.

The results of paper one suggest that childhood adversity may play a key role in the development of bipolar disorder. In the past, the genetic determinants of bipolar disorder, and mental health difficulties, have been emphasised (Bentall & Jones, 2006). However, the current findings indicate that environmental factors may also increase an individual’s risk of developing bipolar symptomatology. In the future, there may be some value in considering bipolar disorder from a biopsychosocial, as opposed to a purely biogenetic, model. Cognitive models should attempt to explain the role of predisposing factors, in addition to the beliefs and behaviours maintaining affective instability over time (Mansell et al., 2007).

In the empirical study, the trainee observed that a history of childhood adversity was associated with impaired social functioning in individuals with varying levels of psychosis. Depression mediated the impact of early life experiences on functional outcome. Childhood adversity may therefore increase depressive symptoms (e.g. sadness, hopelessness, demotivation), which reduce socially meaningful behaviour. This is consistent with cognitive models of psychosis, which suggest that early life experiences may affect mood through beliefs and associated negative automatic thoughts (Morrison, 2001). The results highlight the importance
and impact of affective symptoms across the psychosis continuum regardless of diagnosis.

The data did not support the hypothesised effect of attachment styles on social functioning. Attachment avoidance did not significantly predict social functioning in this sample. Additionally, the relationship between attachment anxiety and social functioning became non-significant in the presence of depression. Attachment theory suggests that early or suboptimal parenting can lead to unhelpful working models and patterns of behaviour within relationships (Bowlby, 1969). The current findings indicate that attachment style has less of an impact on social behaviour than low mood. However, it is possible that attachment anxiety has an indirect effect on social functioning through depression. Indeed, depression and attachment anxiety showed a significant correlation when controlling for certain covariates, which is consistent with past research (Kvrgic et al., 2012). Unfortunately, the trainee could not ascertain the direction of the effect in this cross sectional data.

Childhood adversity did not predict ToM ability in the current data. Therefore, adversity may not be an important determinant of ToM ability across the psychosis continuum. Instead, ToM may be the result of other factors (e.g. access to educational support, exposure to peers). Bora and colleagues (Bora et al., 2009) have proposed that ToM ability may represent a genetic marker for psychosis and bipolar disorder. The determinants of ToM ability require further investigation in the context of adult mental health populations. The absence of a significant association between ToM and social functioning could have been due to a number
of factors, including a ceiling effect on the Hinting Task, insufficient power to detect a small effect size, or less pronounced ToM deficits in the non-clinical, first episode and UHR samples. The latter is somewhat surprising given that reviews have suggested comparable ToM deficits in chronic and FEP, with elevated rates in UHR samples compared to controls (Bora & Pantelis, 2013). This may represent differences between service and study inclusion criteria, possible sample/recruitment biases (e.g. care coordinators only recruiting cognitively able clients) or the choice of measures employed.

5. Clinical implications.

As discussed in papers one and two, the research presented in this thesis has certain clinical implications. Firstly, policies aimed at preventing childhood abuse may reduce rates of bipolar disorder and social impairment in psychosis. Parenting interventions could ameliorate unhelpful behaviours that might become abusive over time (Bendall et al., 2013; Webster-Stratton et al., 2001). Assessing childhood adversity in clients with psychosis and bipolar disorder could help to facilitate personally meaningful formulations, which in turn, could guide psychological therapy and support (Read et al., 2007). Trauma focused cognitive therapy (Cohen et al., 2012) and eye movement desensitisation and reprocessing (Laugharne et al., 2014) have received some empirical support for the treatment of trauma in psychiatric populations.

In the past, healthcare professionals have considered psychosis and bipolar disorder to be the result of individuals’ genes, which has led to the adoption of
more medicalised treatments (e.g. medication). If bipolar disorder and psychosis are also the result of environmental and psychological factors, then clinicians and policy makers may wish to place greater emphasis on psychosocial interventions. On a service development level, clients may benefit by inclusion in services that adopt a less medicalised approach (e.g. early intervention) with greater access to psychological therapy.

The results of paper two suggest that targeted interventions for low mood in psychosis may improve social outcomes, particularly in individuals with a history of childhood adversity. There are now several options for treating depression in psychiatric populations. Cognitive behavioural therapy (CBT) has received support in the treatment of depression in psychosis (Wykes et al., 2008). Within this model, therapists attempt to break unhelpful maintenance cycles by challenging maladaptive thoughts and the use of certain behaviours. CBT techniques include graded exposure and activity scheduling, which could also have a direct effect on social contact. Other relevant approaches might include metacognitive therapy and psychodynamic interpersonal therapy. The former attempts to reduce depressive rumination (Wells et al., 2009; Wells & Papageorgiou, 2004), whilst the latter promotes awareness and tolerance of emotional states (Guthrie, 1999).

Compassion focused therapy may also reduce levels of depression in individuals with psychosis (Braehler et al., 2013). Antidepressant medication has also received some, albeit limited, support for improving low mood in this population (Whitehead et al., 2003).
In paper two, ToM tasks did not significantly predict social functioning, although the Hinting Task did approach significance. Past research has shown stronger associations between these constructs (Bora et al., 2006; Pinkham & Penn, 2006). Therefore, although not strongly supported by the current data, there may be some utility of boosting ToM ability in order to improve social functioning in psychosis. Consistent with this conclusion, researchers have developed cognitive rehabilitation packages for improving ToM ability (Bechi et al., 2012; Combs et al., 2007; Roncone et al., 2004). These generally involve clients participating in role-plays, video exercises and group discussions. Although pilot studies have produced promising findings, these interventions require further validation through randomised controlled trials before integration into clinical settings (Couture et al., 2006).

6. Future research.

The results to paper one highlight the need for further research exploring the association between childhood adversity and bipolar disorder. Longitudinal prospective design research would elucidate the causal nature of this relationship. Similar to samples diagnosed with non-affective psychosis (Trauelsen et al., 2015), the identification of dose-response effects would strengthen inferences about causality (Hill, 1965). The systematic search identified no studies that explored the impact of childhood bullying on bipolar disorder. Additionally, the trainee failed to identify epidemiological datasets that included assessments of emotional abuse. The specificity of adversity subtypes and the role of associated appraisals represent
clear avenues of further investigation. Researchers may wish to consider and measure the perceived severity, nature (e.g. familial or non-familial) and timing (e.g. age of occurrence) of adverse childhood events.

In the future, meta-analyses should explore the association between childhood adversity and the clinical symptoms associated with bipolar disorder, including affective instability, age of onset, number of hospitalisations, frequency of affective episodes, rapid vs non-rapid mood cycling, and suicidality. Studies should examine the factors mediating and moderating the relationship between childhood events and bipolar symptomatology. This might involve examining interactions between cognitive (e.g. attribution bias), behavioural (e.g. cannabis use) and biological (e.g. candidate genes) factors. To the best of the trainee’s knowledge, no research has explored the instability, rather than the severity or level, of parental hostility on symptoms. Inconsistently abusive relationships (both within and between parents) could lead to extreme and conflicting beliefs about affective states, which in turn could generate and maintain affective instability over time (Mansell et al., 2007).

There is a dearth of research exploring the association between childhood adversity and functional outcomes across the psychosis continuum. Future research should explore the exact pathways by which adverse events contribute to social impairment. Prospective and longitudinal research is required, in addition to larger epidemiological investigation. It may also be useful to examine the association between adversity subtypes and particular indices of social functioning, and their relative mediators. The trainee is currently performing secondary analysis of the
SCRIBE data to investigate whether adversity subtypes predict particular attachment styles and psychotic symptoms. Research should explore the role of neurocognition and negative symptoms on the development of social functioning across diagnostic groups and stages of disorder. Analysis of larger clinical datasets would allow more complex structural equation models to be tested. This in turn could help to understand the chain of events leading to impaired social functioning.

The Personal and Social Performance Scale (Morosini et al., 2000) may only provide a general assessment of social functioning. In the future, it may be useful to develop a more ecologically valid and sensitive measure of social impairment. For example, the trainee has previously published research suggesting that experience sampling is feasible and acceptable in individuals with non-affective psychosis (Hartley et al., 2014; Palmier-Claus et al., 2012a; Palmier-Claus et al., 2012b). The development of a momentary assessment scale for social functioning would allow researchers to investigate the impact of macro-level variables (e.g. adversity, attachment, social cognition) on micro-level performance (e.g. self-reported success of social interactions, levels of social contact). There may also be some utility in developing in vivo assessments of social cognition for electronic handheld devices, which could provide more accurate and representative assessments of ToM.

Future research should explore and differentiate the effects of social cognition on functional outcomes. A recent expert panel highlighted the wide range of measures and tests of social cognition used in psychosis research (Pinkham et al., 2014). This is also a limitation of the social functioning literature, where there is
considerable methodological heterogeneity (Burns & Patrick, 2007). Greater consistency in study designs would allow for more comparable and consistent effect sizes. Within this area, it may be useful to explore the interactions that exist between different forms of social cognition. For example, ToM deficits may increase the likelihood and prevent disconfirmation of negative attribution biases (Bentall et al., 2001; Couture et al., 2006). Impairments in both may therefore convey the greatest risk of social impairment. This could also be true of the relationship between childhood adversity and social cognition: Social cognitive ability may moderate, rather than mediate, the impact of adversity on social functioning, which requires investigation in individuals with psychosis and related disorders.

7. Personal reflections.

Conducting research as part of a Doctorate in Clinical Psychology was very different to completing research within a PhD or postdoctoral position. The trainee had to manage competing demands and deadlines, which required flexible and adaptable working. The following section outlines some personal reflections on the research process.

Paper one offered an excellent opportunity for the trainee to develop skills in meta-analysis, which nevertheless, required him to spend considerable time becoming familiar with effect size computation and the Comprehensive Meta-Analysis software package. The trainee screened a large number of articles at both the title and abstract levels, and held regular meetings in order to gain team consensus on the inclusion of certain papers. A systematic review of this scale
would not have been possible without supportive and dedicated supervisors who, through regular meetings and reliability checking, were active participants in the review process. In the future, it may be useful to conduct meta-analysis as part of a wider team, where multiple researchers share the workload, including article screening, effect size extraction and correspondence with authors. It might also be helpful to select appropriate search terms that identify a large proportion of the research literature, whilst reducing the number of false positive results.

In order to meet recruitment targets, two trainee clinical psychologists worked together to collect data for the SCRiBE study. They then analysed different components of the data. The author of this thesis examined social functioning, whereas the other trainee investigated predictors of anger. As part of the recruitment process, the author assisted with supervising three undergraduate students who collected a proportion of the data in the non-clinical sample (see Table 1 for a breakdown of recruitment numbers). Although he had initially hoped that joint recruitment would save time, it did raise certain challenges. For example, the trainee had to train all of the researchers in administering and scoring the assessments, whilst ensuring inter-rater reliability. This included regular training sessions, listening to audio recordings and observing interviews. Data cleaning sessions ensured that there were no obvious errors or inconsistencies in the scoring across raters. Although this approach yielded high levels of reliability on the primary outcome for paper two (i.e. PSP scores) it was also time-consuming. In future studies when directing multiple researchers/students, the trainee will use questionnaires, rather than interviews, in order to remove the need to establish
inter-rater reliability. Nevertheless, the trainee enjoyed his experience of supervising undergraduates and training researchers in clinical assessments, which he hopes to continue in the future.

Table 1. The number of participants recruited by each researcher.

<table>
<thead>
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<th>Group</th>
<th>Author of thesis</th>
<th>Other trainee</th>
<th>Undergraduates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-clinical</td>
<td>21</td>
<td>11</td>
<td>88</td>
</tr>
<tr>
<td>Ultra-high risk</td>
<td>13</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>First episode psychosis</td>
<td>3</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>Chronic</td>
<td>5</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>42</td>
<td>44</td>
<td>88</td>
</tr>
</tbody>
</table>

Recruitment within clinical services can be challenging. Care coordinators are often busy and inundated with research requests. Other research projects conducted at the time of the SCRiBE study had preferential levels of reimbursements or offered an active treatment arm. In order to overcome barriers to recruitment, the trainee made frequent telephone calls, attended regular team meetings, and held PANSS training sessions at early intervention services. The trainee also regularly attended hospital wards in order to become familiar to the teams. This was a time consuming process, with an attendance to referral ratio of about 3:1. One key learning point from this process was the need to provide sufficient incentives to staff/clients (e.g. reimbursement, treatments), whilst
making participation as easy as possible (e.g. reducing assessment times, meeting in places of mutual convenience). In the future, researchers could gain ethical approval to share the results of assessments with the referring clinical team in order to inform practice and incentivise clinicians to make referrals. This should be done with the clients’ consent and whilst carefully considering the impact that it might have on the information they provide. The trainee believes that greater dissemination of findings to clinical services would help to endear them to the research process. He is currently disseminating the results of the SCRiBE study through oral presentations and written summaries. In the future, it may also be useful to recruit client groups that are less researched (e.g. older adults).

Originally, the trainee had hoped to recruit the majority of the UHR participants through the Early Detection and Intervention Teams in Salford and Wigan. Unfortunately, these services were in a state of transition at the time of recruitment, culminating in many of the therapists and the trainee’s original field supervisor, leaving their positions. These difficulties may explain why the trainee did not meet his recruitment target of 20 UHR participants. In order to account for a shortfall in referrals, the trainee attempted to recruit additional participants within Early Intervention Services in Lancashire Care (e.g. Blackpool) with some success \((n = 3)\). This highlighted the value of flexible recruitment strategies and ethical approval within multiple National Health Service trusts.

The trainee received the advice of a service user panel within the department of clinical psychology. This was invaluable in deciding on the number of measures included in the protocol and has led him to consider the possible merits
of setting up a young people’s service user group in order to provide advice on research into early psychosis. On a personal note, it was sometimes difficult for the trainee to administer clinical interviews, without offering further help and assistance to clients. This was particularly true of cases where the participant was not currently receiving any psychological therapy. Lastly, clinicians are expected to make detailed notes of their clinical contacts, which is somewhat lacking in research domains. It might be helpful for the generation of a protected and confidential electronic or paper notes system for clinical researchers. This could safeguard clinicians against litigation, but also provide a useful reminder of session content.

8. Concluding remarks.

The research presented in this thesis suggests that childhood adversity can have wide-reaching negative effects on psychological wellbeing. This includes increased chances of receiving a diagnosis of bipolar disorder and impaired social functioning. Research illuminating how adversity affects mental health outcomes is important for the development of effective prevention and treatment strategies. The planned injection of funds to mental healthcare over the next year (NHS England, 12 February 2015) represents an opportunity for services to improve support to individuals with a history of childhood adversity. National initiatives should attempt to prevent abuse and maltreatment more widely. Childhood maltreatment represents an important area of consideration in both clinical and research arenas.
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Appendices

Appendix A. Calculations for positive and negative agreement.
Appendix B. Review protocol.
Appendix C. Inter-rater reliability scores for PSP subscales.
Appendix D. Example PSP inter-rater reliability vignettes.
Appendix E. The PSP assessment.
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Appendix I. Example slides from the Mind in the Eyes test.
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Appendix K. Participant information sheet for first episode and chronic participants.
Appendix L. Participant information sheet for non-clinical participants.
Appendix M. Participant information sheet for ultra-high risk participants.
Appendix N. Consent form for non-clinical participants.
Appendix O. Consent form for clinical participants.
Appendix P. Ethics approval letter.
Appendix A. Calculations for positive and negative agreement.

**Title level:**

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</tr>
<tr>
<td>Trainee</td>
<td>Negative</td>
<td>40</td>
<td>1596</td>
</tr>
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</table>

Equation:

Positive agreement = \( \frac{2a}{2a+b+c} = \frac{212}{212+38+40} = .68 \)

Negative agreement = \( \frac{2d}{2d+b+c} = \frac{3192}{3192+58+40} = .97 \)

Kappa = .65

**Abstract level:**

<table>
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<td>117</td>
<td>36</td>
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<tr>
<td>Trainee</td>
<td>Negative</td>
<td>20</td>
<td>273</td>
</tr>
</tbody>
</table>

Equation:

Positive agreement = \( \frac{2a}{2a+b+c} = \frac{254}{254+36+20} = .81 \)

Negative agreement = \( \frac{2d}{2d+b+c} = \frac{316}{316+26+20} = .91 \)

Kappa = .71
Appendix B: Review protocol.

**Proposed title**

Childhood trauma and bipolar disorder: A systematic review and meta-analysis.

**Author and affiliations list**

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**Author contributions**

The following list of possible author contributions has been taken from the Cochrane Handbook, which in turn was adapted from Yank and colleagues’ (1999) article. The initials of authors contributing to a particular section are provided.

Conceiving the review: JPC, SB, KB and FV.

Designing the review: JPC, SB, KB and FV.

Coordinating the review: JPC, SB, KB and FV.

Data collection for the review.

Designing search strategies: JPC, SB, KB and FV.

Undertaking searches: JPC.

Organizing retrieval of papers: JPC.

Screening retrieved papers against eligibility criteria: JPC. Additionally, two postgraduate students (Louise Laverty and Rebecca Harrop) will double screen a proportion of the identified article titles and abstracts.
Extracting data from papers: JPC, SB & FV.
Writing to authors of papers for additional information: JPC.
Providing additional data about papers: JPC.
Obtaining and screening data on unpublished studies: JPC.
Data management for the review.
Entering data: JPC (FV to double code data)
Study quality assessment: JPC & FV.
Analysis of data: JPC.
Interpretation of data.
Providing a methodological perspective: JPC & FV.
Providing a clinical perspective: SB & KB.
Providing a policy perspective: SB & KB.
Providing a consumer perspective: TBC.
Writing the review (or protocol): JPC
Providing general advice on the review: FV, KB & SB.
Securing funding for the review: N/A
Performing previous work that was the foundation of the current review: FV.

**Rationale**

Childhood adverse experiences has been implicated in the development of severe mental illness (Read et al., 2001). Despite the association between early adversity and non-affective psychosis being relatively well established (Varese et al., 2012) the link with bipolar disorder type symptoms (e.g. mania) is less well understood. This study represents a systematic review and meta-analysis of studies exploring the association between early childhood trauma and diagnoses of bipolar disorder.

Some authors have recently discussed the mechanism by which social-environmental risk factors might lead to specific symptoms seen in severe mental illness (Bentall et al., 2014). In bipolar disorder, exaggerated emotional activation and hyperactivity may be maladaptive attempts to avoid specific trauma related intrusions (Maniglio, 2013).
Trauma may also sensitise an individual to later stressors, increasing the volatility of affective states in response to everyday events (Glaser et al., 2010; Mijn-Germeys et al., 2003). For example, traumatic events may sometimes lead to poorly integrated memories, which are subsequently triggered by emotion laden dialog (Mansell & Hodson, 2009). Indeed, intrusive memories and images have been found to be common during both euthymic and depressive mood states in individuals with bipolar disorder (Gregory et al., 2010).

Existing narrative and systematic reviews have suggested an association between childhood trauma and bipolar symptomatology (e.g. Alloy et al., 2005, 2006; Daruy-Filho et al., 2011; Etain et al., 2008; Maniglio, 2013a, 2013b; Tsuchiya, 2003). However, to the best of the authors’ knowledge there have been no meta-analyses investigating the size or nature of this effect through meta-analytic approaches. Furthermore, the publishing of new and potentially illuminating studies (e.g. Perna et al., 2014; Watson et al., 2014) suggests that an updated review of the literature is warranted.

**Aims**

**Primary objectives**

The purpose of this review is to explore the role of childhood trauma in bipolar disorder. The primary objectives are:

To investigate whether exposure to childhood trauma is elevated in individuals with bipolar disorder compared to non-clinical samples.

To investigate whether exposure to childhood trauma is elevated in individuals with bipolar disorder compared to individuals diagnosed with major depression or non-affective psychosis.

The secondary objectives are:

To investigate which forms of childhood trauma are most elevated in bipolar disorder when compared to non-clinical populations.

To investigate which forms of childhood trauma are most elevated in bipolar disorder compared to individuals with major depression or non-affective psychosis.

To investigate whether exposure to childhood trauma is greater in bipolar one compared to bipolar II disorder.
To investigate the prevalence of total trauma and trauma subtypes in bipolar samples.

In exploratory analysis, we will also the associations between childhood trauma and key characteristics of bipolar disorder. No a-priori hypotheses will be made as to these relationships.

**Type of review**

This study represents a systematic review and meta-analysis of the available quantitative literature.

**Eligibility criteria**

Case control, prospective cohort and epidemiological studies will be included in the review.

Studies will include a sample of psychiatric patients diagnosed with bipolar disorder. Studies on mixed samples will not be included unless separate analysis has been conducted on a bipolar disorder subsample. Neurological disorders and substance induced psychosis will be excluded from this review due to having potentially different aetiologies to bipolar disorder. Non-clinical and attenuated bipolar type symptoms will not be included unless a formal diagnosis has been given according to Diagnostic and Statistical Manual (DSM-III, DSM-IIIR, DSM-IV, DSM-IV-TR & DSM-V) or the International Classification of Diseases (ICD-9 or ICD-10).

Studies will include a quantitative measure of childhood trauma such as sexual abuse, physical abuse, emotional abuse, physical neglect, emotional neglect, bullying or loss of parents. Studies focusing on traumatic events occurring within adulthood will not be included. Consistent with previous reviews in psychosis (Varese et al., 2012), parental loss is defined as the death of a parent. Studies focusing on “parental separation” will not be included as it is potentially difficult to operationally define (e.g. whether the term refers to parental death, divorce or other type of separation from parents in childhood, e.g. being taken in LA care).

Studies will be published in a peer reviewed journal as a full article or short report. Editorials, comments, letters to the editor, book chapters, case series, and dissertations/theses (i.e. grey literature) will not be included in this review.
Studies will be written in the English language. Unfortunately, this review does not have the resources to facilitate the translation of journal articles.

Studies will be published in or after 1980 in order to coincide with the release of the DSM-III and current classifications of mental disorder.

Studies will contain sufficient statistical information from which to generate an effect size. In the absence of this data we shall contact the lead/contact author in an attempt to obtain this information.

Studies will not share the same participants as other studies. In the case of multiple analyses conducted on the same data, the most comprehensive and largest study will be selected.

**Database searches**

Separate systematic searches will be conducted using four electronic databases (Medline, Embase, PsychInfo and Web of Science). Two groups of search terms will be used. In group one, terms relating to bipolar disorder will be entered: *Bipolar, Mani* or *cyclothymi* or *manic-depressi* or *hypomani*. In group two, terms relating to childhood trauma will be entered: *Child abuse, physical abuse, sexual abuse, psychological abuse, emotional abuse, neglect*, *trauma*, *advers*, *maltreat*, *bully*, *bullied*, *victim*, and *parental loss*. The search terms were chosen based on the researchers’ clinical experience and past systematic reviews (Varese et al., 2012). Searches in Medline, Embase and PsychInfo will be exploded in the field of *Bipolar Disorder*. The search in Web of Science it will be restricted by ‘Field’ to the areas of Psychiatry and Psychology in order to focus the search on articles that are likely to be more relevant to the research question. Scoping search identified 12 potentially eligible studies, attesting to the suitability of the review and meta-analysis.

**Hand searches**

In addition to the articles detected through the systematic search, the authors will consider articles identified and cited in previous reviews (e.g. Alloy et al., 2005, 2006; Daruy-Filho et al., 2011; Etain et al., 2008; Maniglio, 2013a, 2013b; Tsuchiya, 2003). The reference lists of eligible papers will also be screened to identify further studies of interest. Journal articles citing the eligible papers will also be examined.
**Article access**

Articles will be obtained from libraries at the University of Manchester, the University of Liverpool and Lancaster University. This will include electronic and hard copies of the original articles. In cases where neither University subscribes to a particular journal, the first authors will be contacted for a copy of the manuscript. We will also attempt to retrieve relevant articles through inter-library loan services available at our HEIs. This will take place following the full journal article screening stage of the review.

**Reliability check**

Louise Laverty (doctoral student) will code 33% of all titles identified by the systematic search in order to assess reliability with the first author (JPC). Rebecca Harrop (postgraduate student) will then double rate 100% of the available abstracts. Articles included in the review will be discussed between the whole research team at regular meetings to resolve any discrepancy in coding decisions (SB, KB, FV, JPC).

**Timeframe**

Title, abstract and article level screening is expected to be completed by April 2015. Coding and meta-analysis of the extracted data will be completed by May 2015. The final article is likely to be submitted by June 2015.

**Data extraction**

Data will be extracted separately by two members of the research team (FV and JPC). Discrepancy in the data extracted will be discussed at regular team meetings (FV, JPC, SB and KB in attendance) until a consensus is reached. Information will be extracted from eligible articles and incorporated into Excel, Stata 12.0, Comprehensive Meta-analysis and SPSS data files. Methodological features of the studies, thought to influence the computed effect sizes, coded alongside statistical information (e.g. measure of trauma, diagnostic system, and sample characteristics). The type of trauma will be recorded in order to test secondary hypotheses regarding the type of trauma most prevalent in bipolar patient samples.
Effect size computation and statistical analyses

Quantitative information (e.g. binary data from 2 x 2 Tables) will be extracted in order to compute effect sizes in the form of an Odds Ratio (OR). When statistical information suited for the direct computation of this effect size metric will not be available, alternative effect sizes (e.g. d-family effects) will be computed based on the statistics reported in the primary studies, and will then be converted into ORs.

Meta-analyses will be conducted using a random effects model; this integration method is appropriate for meta-analyses presenting considerable statistical heterogeneity, and leads to more conservative findings (i.e. broader CIs) compared to fixed-effect meta-analysis. Our primary analyses will integrate effects regardless of type of exposure, and separate analyses will consider studies which contrasted bipolar patients to psychiatric and non-psychiatric controls. Cases where a study presents multiple effect sizes (e.g. studies reporting both group differences on sexual abuse and physical abuse exposure) these will be merged to form a single effect size in order to avoid violating the assumption of independent observations. We will subsequently conduct appropriate subgroup analyses (see below) to scrutinise in more detail associations between bipolar and specific types of childhood adversities. Visual examination of funnel plots and linear regression tests of funnel plot asymmetry will be used to assess for publication and selection bias, and effect size imputation methods (“trim and fill” analyses) will be used as appropriate to estimate the impact of these potential biases on our meta-analytic findings.

Heterogeneity, quality assessment, subgroup and sensitivity analyses

We will examine and quantify statistical heterogeneity using the Q test and the $I^2$-squared statistics. The Newcastle Ottawa Quality assessment will be used to classify the quality of eligible studies. Meta-regression techniques (mixed effects model) will be employed to establish and control for the influence of study quality indices and methodological characteristics on effect sizes. We will conduct a series of subgroup analyses to explore systematic differences emerging from (i) studies which compared bipolar patients to non-psychiatric controls and (ii) studies which compared bipolar patients to patients with unipolar depression and/or non affective psychosis. Separate analyses will be also carried out for specific types of
exposures, i.e. sexual abuse, physical abuse, neglect etc. Throughout, we will conduct one study removed analyses will be used to assess whether any included study will exert undue influence on our meta-analytic findings

Note: Published on PROSPERO: reference CRD42015017201
Appendix C: Inter-rater reliability scores for PSP subscales.

<table>
<thead>
<tr>
<th>Intra-class correlation (two way mixed effects; absolute agreement) between five raters:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total PSP ICC:</strong></td>
</tr>
<tr>
<td>0.92, <em>p</em> &lt;0.001.</td>
</tr>
<tr>
<td><strong>Subscales:</strong></td>
</tr>
<tr>
<td><strong>Socially Useful Activities ICC:</strong></td>
</tr>
<tr>
<td>0.76, <em>p</em> &lt;0.001.</td>
</tr>
<tr>
<td><strong>Personal and Social Relationships ICC:</strong></td>
</tr>
<tr>
<td>0.82, <em>p</em> &lt;0.001.</td>
</tr>
<tr>
<td><strong>Self-Care ICC:</strong></td>
</tr>
<tr>
<td>0.93, <em>p</em> &lt;0.001.</td>
</tr>
<tr>
<td><strong>Disturbing and Aggressive Behaviour ICC:</strong></td>
</tr>
<tr>
<td>0.90, <em>p</em> &lt;0.001.</td>
</tr>
</tbody>
</table>
Appendix D. Example PSP inter-rater reliability vignettes.

Mrs A. is a 43-year-old housewife, married and mother of a 17-year-old son. In the previous month she has had difficulties in household activities to such an extent that her relatives had to do all the housework themselves. In addition, her social relationships had decreased: she has gone out only to visit her hairdresser, has met only people invited by her husband and has not taken care of her son at all. She has had no problem in self-care.

Mrs B. is a 54-year-old woman, working in her family business, living with her husband. In the past month she has done some housework and performed household activities, but less regularly and efficiently than in the past, and she has not been able to work in her husband’s shop; self-care has been normal. In the same period, she has had several episodes of substance abuse (thrychloroethylene inhalation, drinking alcohol) and of disturbing behaviour toward her relatives (repeated quarrels and verbal assaults). Family relationships were so strained that her sons, who lived elsewhere, refused to meet or telephone her. Although her previous social relationships were very rewarding, she has met only one friend regularly in the past month.

Mr C. is a 45-year-old man, divorced, with adult sons, living in a rehabilitation centre. In the past month he has taken part in the activities of the centre (meetings, performance of collective tasks, participation in common decisions, etc.) and has
attended a sheltered job regularly, performing so well that he was considered eligible for a competitive job. He has maintained family relationships regularly with his daughters, wife and sister. He has had poor, only formal, social relations with the other guests at the rehabilitation centre, poor self-care and living space care.

Gary is a 55 year old divorcee who has been living alone for three years. His wife left him and they are no longer in contact. He has also fallen out with all of his friends since the breakup and no longer socialises with others. He has held three very short-term jobs in the past 18 months, losing them all after displaying violent behaviour. He had a part-time job as a caretaker at an office building and after being fired punches a member of staff in the face Gary believes had put in a complaint about him. When confronted by a member of the public Gary physically assaults him knocking him to the ground and kicking him repeatedly in the head and stomach. The police are called and arrive at his house to find him living in squalor, with no food in the fridge and the lounge full of rotting food and rubbish.

All vignettes were generated by a postgraduate researcher or were adapted/taken from the article by Morosini and colleagues (p.325-326, 2011).

Appendix E. The PSP assessment.

**PSP Questions**

The PSP measures four types of social functioning. These are:

a. Socially useful activities (i.e. ability to work and study)

b. Personal and social relationships (i.e. the person’s ability to form and maintain relationships)

c. Self-care (i.e. the person’s ability to look after themselves; wash/clean)

d. Disturbing and aggressive behaviour.

**Step one: Ask all of the following questions.**

**Area a)**
- How would you say you usually spend your time?
- Do you work or study? How many times a week? Paid or voluntary?
- If unemployed – how long for? Actively looking for work?
- Have you had any difficulties in work/study in the past month e.g taking time off?
- What other activities do you do? How often? (Hobbies, housework, cooking, shopping etc)

**Area b)**
- Who do you live with? Do you generally get on?
- How often do you see/speak to family members? Do you get on?
- Do you like socialising with people?
- Do you have friends that you socialise with? How often? What activities?

**Area c)**
- How do you generally get on with looking after yourself?
- E.g eating regular meals, showering, clean clothes?
- Do you have any help or prompting with this?

**Area d)**
- In the last month, did you behave in a way that some people may have thought rude or insensitive?
- In the last month have you behaved in a way that some people might consider rude/offensive?
- Do you ever lose your temper/shout at people/throw or destroy things?
- Do you get irritable/snappy with people?
- Do you ever get physically aggressive with people?
**Step two:** If necessary, ask a selection of the following questions to make your ratings (these questions are optional). Feel free to go back to these questions after starting scoring.

1) Socially Useful Activities

**Work or Study**

Do you work/study? In the last month? Where? How many days/hours? Any difficulties at work/place of study? If unemployed, how long for?

**Socially Useful Activities**

Apart from work, do you do anything else that other people may find useful? E.g cooking, cleaning, housework, voluntary work?  
What do you tend to do with your days?  
Any hobbies or activities?

2) Personal and Social Relationships

**Family**

Do you have a partner? Do you live together? How do you get along?  
Do you have close family members? In the last month, have you been in touch with any of your relatives? How often do you see them? Do you get along well or do you have problems? Do they help you, do you help them?

**Social Relationships**

How often do you go out to meet other people? Do you like socialising with people? Do you have a close friendship group, how often do you see mates?  
Do you do things together? Do you have somebody who can help if you need it?  
Is there anyone you are particularly close to?

3) Self Care

How do you get on with looking after yourself e.g eating regular meals, remembering to shower and look after house?

**Personal Hygiene**

In the last month, how often have you taken a shower or a bath?  
Did you wash alone or did someone remind you or help you?  
Have you cleaned your teeth everyday?

**Care of Ones Appearance**

For men without a beard...Do you shave regularly
For women...Have you used a little make up, at least on special occasions? Have you gone to the hairdressers?

**Ways of Dressing**

In the last month, did you always put on clean clothes? Did you ever go out in pjammas or not dressed properly?

4) **Disturbing and Aggressive Behaviour**

**Disturbing Behaviour**

In the last month, did you behave in a way that some people may have thought rude or insensitive?
Did you take something belonging to others without asking permission?
While drunk, did you do something that could annoy others?
Did you ever do something strange that other people may find worrying?
Did you ever speak loudly or have your record playing or the TV too loud?
Did you keep asking other people for money or gifts?
Did you complain often about your condition?

**Destructive and Aggressive Behaviour**

Has there been any times over the past month where you have got irritable/snappy with people? Is it just with people you know, or sometimes with strangers?
In the last month, did you ever lose control over your temper?
Did you shout at anybody?
Did you throw and destroy objects?
Do you ever get physically aggressive with people? Did you hit or hurt anybody? How severe was it? Did you really want to hurt them?
How often did it happen?
Do you think that is going to happen again in the near future?

Adapted/taken from materials used in the Recovery trial and the article by Morosini and colleagues (2011). For scoring guidance see validation article.

Appendix F: Green and colleagues’ Paranoid Thought Scales.

PTSS (Green et al. 2007)

Please read each of the statements carefully.
They refer to thoughts and feelings you may have had about others over the last month.
Think about the last month and indicate the extent of these feelings from 1 (Not at all) to 5 (Totally).
Please complete both Part A and Part B.
(N.B. Please do not rate items according to any experiences you may have had under the influence of drugs.)

<table>
<thead>
<tr>
<th>Part A</th>
<th>Not at all</th>
<th>Somewhat</th>
<th>Totally</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. I spent time thinking about friends gossiping about me</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2. I often heard people referring to me</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3. I have been upset by friends and colleagues judging me critically</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>4. People definitely laughed at me behind my back</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>5. I have been thinking a lot about people avoiding me</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>6. People have been dropping hints for me</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>7. I believed that certain people were not what they seemed</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>8. People talking about me behind my back upset me</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>9. I was convinced that people were singling me out</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>10. I was certain that people have followed me</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>11. Certain people were hostile towards me personally</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>12. People have been checking up on me</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>13. I was stressed out by people watching me</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>14. I was frustrated by people laughing at me</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>15. I was worried by people’s undue interest in me</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>16. It was hard to stop thinking about people talking about me behind my back</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>
Appendix G. Psychosis Attachment Measure.

SELF-REPORT MEASURE

We all differ in how we relate to other people. This questionnaire lists different thoughts, feelings and ways of behaving in relationships with others.

PART A

Thinking generally about how you relate to other key people in your life, please use a tick to show how much each statement is like you. Key people could include family members, friends, partner or mental health workers.

There are no right or wrong answers

<table>
<thead>
<tr>
<th>Statement</th>
<th>Not at all</th>
<th>A little</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. I prefer not to let other people know my ‘true’ thoughts and feelings.</td>
<td>(..)</td>
<td>(..)</td>
<td>(..)</td>
<td>(..)</td>
</tr>
<tr>
<td>2. I find it easy to depend on other people for support with problems or difficult situations.</td>
<td>(..)</td>
<td>(..)</td>
<td>(..)</td>
<td>(..)</td>
</tr>
<tr>
<td>3. I tend to get upset, anxious or angry if other people are not there when I need them.</td>
<td>(..)</td>
<td>(..)</td>
<td>(..)</td>
<td>(..)</td>
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<tr>
<td>4. I usually discuss my problems and concerns with other people.</td>
<td>(..)</td>
<td>(..)</td>
<td>(..)</td>
<td>(..)</td>
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<tr>
<td>5. I worry that key people in my life won’t be around in the future.</td>
<td>(..)</td>
<td>(..)</td>
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<tr>
<td>6. I ask other people to reassure me that they care about me.</td>
<td>(..)</td>
<td>(..)</td>
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<td>(..)</td>
</tr>
<tr>
<td>7. If other people disapprove of something I do, I get very upset.</td>
<td>(..)</td>
<td>(..)</td>
<td>(..)</td>
<td>(..)</td>
</tr>
<tr>
<td>8. I find it difficult to accept help from other people when I have problems or difficulties.</td>
<td>(..)</td>
<td>(..)</td>
<td>(..)</td>
<td>(..)</td>
</tr>
<tr>
<td>9. It helps to turn to other people when I’m stressed.</td>
<td>(..)</td>
<td>(..)</td>
<td>(..)</td>
<td>(..)</td>
</tr>
<tr>
<td>10. I worry that if other people get to know me better, they won’t like me.</td>
<td>(..)</td>
<td>(..)</td>
<td>(..)</td>
<td>(..)</td>
</tr>
</tbody>
</table>
11. When I’m feeling stressed, I prefer being on my own to being in the company of other people.

<table>
<thead>
<tr>
<th>Not at all</th>
<th>A little</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>(..)</td>
<td>(..)</td>
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<td>(..)</td>
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</table>

12. I worry a lot about my relationships with other people.

<p>| | | | |</p>
<table>
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<tr>
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<td>(..)</td>
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13. I try to cope with stressful situations on my own.

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<td>(..)</td>
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</table>

14. I worry that if I displease other people, they won’t want to know me anymore.

<p>| | | | |</p>
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<tr>
<td>(..)</td>
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</table>

15. I worry about having to cope with problems and difficult situations on my own.

<p>| | | | |</p>
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<tbody>
<tr>
<td>(..)</td>
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</table>

16. I feel uncomfortable when other people want to get to know me better.

<p>| | | | |</p>
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<tbody>
<tr>
<td>(..)</td>
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</table>

PART B

In answering the previous questions, what relationships were you thinking about?

(E.g. relationship with mother, father, sister, brother, husband, wife, friend, romantic partner, mental health workers etc)

Appendix H. Link to Calgary Depression Scale.


Appendix I. Example slides from the Mind in the Eyes test.
Appendix J. The Hinting Task.

**Hinting Task (Corcoran et al., 1995)**

**Hinting Task**

<table>
<thead>
<tr>
<th>Name:</th>
<th>Sex:</th>
<th>Age:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Story</strong></td>
<td><strong>Verbatim Response 1 and score</strong></td>
<td><strong>Verbatim Response 2 and score</strong></td>
</tr>
<tr>
<td>Long, hot journey</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dirty bath</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treacle toffees</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creased shirt</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flat broke!</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Project at work</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birthday present</td>
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<tr>
<td>Ornaments</td>
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<td>Train set</td>
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<tr>
<td>Heavy cases</td>
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</table>

**Instructions**

Say, "I'm going to read out a set of 10 stories involving two people. Each story ends with one of the characters saying something. When I've read the stories out I'm going to ask you some questions about what the character said. Here's the first story. Listen carefully to it."
Hinting Task (Corcoran et al, 1995)

Story 1

George arrives in Angela’s office after a long and hot journey down the motorway. Angela immediately begins to talk about some business ideas. George interrupts Angela saying:

“‘My, my! It was a long, hot journey down that motorway!’

QUESTION: What does George really mean when he says this?

Answer:
George means either “Can I have a drink” and/or “Can I have a few minutes to settle down after my journey before we start talking business”.

Either of these responses would score 2.

If a correct response is not given for the first hint (eg. the participant just replies something like “He means exactly what he says”) then introduce next part of the story / hint.

ADD: George goes on to say:

“I’m parched!”

QUESTION: What does George want Angela to do?

Answer: George wants Angela to get him or offer to get him a drink.

This response would score 1. Anything else would be given a score of 0.
Hinting Task (Corcoran et al, 1995)
Story 2

Melissa goes to the bathroom for a shower. Anne has just had a bath. Melissa notices the bath is dirty so she calls upstairs to Anne:

"Couldn't you find the cleaning products, Anne?"

QUESTION: What does Melissa really mean when she says this?

Answer: Melissa means "Why didn't you clean out the bath" or "Go and clean out the bath now". → This response would be given a score of 2 and next item would be introduced

If the participant fails to give the correct answer at this stage then add:

ADD: Melissa goes on to say:
   "You're very lazy sometimes, Anne!"

QUESTION: What does Melissa want Anne to do?

Answer: Melissa wants Anne to clean out the bath.  
→ This response would score 1. Any other response would be given a score of 0.
Hinting Task (Corcoran et al, 1995)
Story 3

Gordon goes to the supermarket with his mum. They arrive at the sweetie aisle. Gordon says:

"Cor! Those treacle toffees look delicious."

QUESTION: What does Gordon really mean when he says this?

Answer:
Gordon means "Please buy me some sweets, mum"

"If the participant fails to give the correct answer at this stage then add:

ADD: Gordon goes on to say:
"I'm hungry, mum."

QUESTION: What does Gordon want his mum to do?

Answer: Buy him some sweets.
Hinting Task (Corcoran et al, 1995)

Story 4

Paul has to go to an interview and he’s running late. While he is cleaning his shoes, he says to his wife, Jane:

"I want to wear that blue shirt but it’s very creased."

**QUESTION:** What does Paul really mean when he says this?

**Answer:**
Paul means "Will you iron my shirt for me please?"

"If the participant fails to give the correct answer at this stage then add:

**ADD:** Paul goes on to say:
"It’s in the ironing basket."

**QUESTION:** What does Paul want Jane to do?

**Answer:** Iron his shirt.
Hinting Task (Corcoran et al, 1995)
Story 5

Lucy is broke but she wants to go out in the evening. She knows that David has just been paid. She says to him:

"I'm flat broke! Things are so expensive these days."

QUESTION: What does Lucy really mean when she says this?

Answer: Lucy means "Will you lend me some money David?" OR "Will you take me out tonight and pay?"

**If the participant fails to give the correct answer at this stage then add:

ADD: Lucy goes on to say:
   "Oh well, I suppose I'll have to miss my night out."

QUESTION: What does Lucy want David to do?

Answer: She wants David to lend her money or offer to take her out and pay.
Hinting Task (Corcoran et al, 1995)

Story 6

Donald wants to run a project at work but Richard, his boss, has asked someone else to run it. Donald says:

"What a pity. I'm not too busy at the moment."

**QUESTION** What does Donald really mean when he says this?

Answer: Donald means "Please change your mind Richard and give the project to me"

"If the participant fails to give the correct answer at this stage then add:

**ADD:** Donald goes on to say:

"That project is right up my street."

**QUESTION** What does Donald want Richard to do?

Answer: Change his mind and give the project to him to run
Hinting Task (Corcoran et al., 1995)

Story 7

Rebecca's birthday is approaching. She says to her Dad:

"I love animals, especially dogs."

QUESTION: What does Rebecca really mean when she says this?

Answer: "Will you buy me a dog for my birthday Dad?"

**If the participant fails to give the correct answer at this stage then add:

ADD: Rebecca goes on to say:

"Will the pet shop be open on my birthday, Dad?"

QUESTION: What does Rebecca want her dad to do?

Answer: to say he'll buy her a dog for her birthday! buy her a dog for her birthday
Betty and Michael moved into their new house a week ago. Betty has been unpacking some ornaments. She says to Michael:

"Have you unpacked those shelves we bought, Michael?"

**QUESTION:** What does Betty really mean when she says this?

**Answer:** Betty means "Will you put those shelves up now please?"

**If the participant fails to give the correct answer at this stage then add:

**ADD:** Betty goes on to say:

"If you want something doing you have to do it yourself!"

**QUESTION:** What does Betty want Michael to do?

**Answer:** Put the shelves up.
Hinting Task (Corcoran et al, 1996)

Story 9

Jessica and Max are playing with a train set. Jessica has the blue train and Max has the red one. Jessica says to Max:

"I don't like this train."

QUESTION: What does Jessica really mean when she says this?

Answer: Jessica means "I want your train and you can have mine."

"If the participant fails to give the correct answer at this stage then add:

ADD: Jessica goes on to say:

"Red is my favourite colour."

QUESTION: What does Jessica want Max to do?

Answer: swap trains
Appendix K. Participant information sheet for first episode and chronic participants.

Participant Information Sheet (Groups 1 & 2)

The SCRIBE (Social Cognition Research in Bonding and Emotions) study

We would like to invite you to take part in a research study. Before you decide you need to understand why the research is being done and what it would involve for you. Please take time to read the following information carefully. Talk to others about the study if you wish. Thank you for reading this.

What is the study about?

This study looks at something called ‘social cognition’. Social cognition is a person’s ability to understand the intentions and behaviours of others. We think that a person’s social cognition abilities might have been influenced with experiences in their childhood. We are interested in looking at how a person’s childhood experiences effects their social cognition and then how social cognition effects a person’s emotions and ability to socialise.

Why have I been invited to take part?

You have been invited to take part in this study because you have been having or have had unusual experiences (e.g. hearing things) and or suspicious thoughts. You will also be aged 16 or older. We hope to recruit 120 people to take part in this study.

Do I have to take part?

No, it is your decision whether you take part or not. If you do decide to take part, you will be given this information sheet to keep and asked to sign a consent form saying you agree to take part. If you decide to take part, you are still free to withdraw at any time, without giving a reason. This would not affect the standard of care that you receive.

What will participation involve?

If you choose to take part, a researcher will arrange to meet with you at a place that is convenient for you (e.g. your home or a health centre). The study will take no longer than 1 hour and 45 minutes and will involve completing some questionnaires, short
interviews and tasks. Additionally, you will be asked for some personal details (e.g. age, ethnicity, diagnosis, medication, months since first contact with services and number of criminal convictions), which with your permission we will also access through your healthcare case-notes.

- **Questionnaires:**
  The questionnaires in this study look at a number of different things, such as difficult experiences that you may (or may not) have had during childhood and how you tend to feel and act. There are no right or wrong answers. Some examples of the things that you will be asked to rate on the questionnaires are ‘I believe that I was emotionally abused’ and ‘when I get mad I say nasty things’.

- **Short interviews:**
  The interviews will help the researchers learn a little about how you feel and experiences you may (or may not) have. Some examples of the questions that you will be asked are ‘do you sometimes feel in danger?’ and ‘do you once in a while have strange or unusual experiences?’ We may wish to audio record the interviews in order to go over it at a later date, but this is optional and completely up to you. If you are audio recorded, tapes will be kept for a maximum of 6 months before being wiped clean. Tapes will be kept in a locked cabinet at the University of Manchester.

- **Tasks:**
  The tasks involve listening to some stories and giving your opinion on what was happening and explaining how you would have felt and acted in the same situations. In some tasks you be asked to look at pictures of people’s faces on a laptop and choose the word that best describes how they were feeling.

Are there any risks involved in taking part and will my information be kept confidential?

There is the possibility that you may find some of the questions in this study uncomfortable or upsetting. If this is the case, you are free to leave any of these questions unanswered and you are welcome to end your participation any time. All information collected about you will be kept strictly confidential and will be anonymous. This means that any information that we collect will have your name and address removed so that you cannot be recognised. However, we will have to inform someone if you say something that makes us believe you might harm yourself or other people. After anonymising your information to ensure you cannot be identified from it, your information will be kept on a password protected file, on a password protected computer at the University of Manchester. This data will be kept for a maximum of 10 years before being deleted. Remember, you will not be identifiable from this information.

Version 1: 18.10.2013
Will anyone else know that I am taking part in this study?

Your healthcare practitioner (e.g. nurse, psychiatrist) and GP will be told you are taking part but will not be told about what answers you give in the questionnaires, interviews and tasks (unless you want this information shared). As mentioned above, we will have to inform someone if you say something that makes us believe you might harm yourself or others. This is to ensure everyone is kept safe and well.

Reimbursement for my time

You will be given £10 to reimburse you for your time taking part in this study.

What are the likely benefits of this study?

Some people enjoy completing the tasks involved in research and the opportunity to talk to someone about their experiences. If you decide to take part, we will ask whether you want us to share the information we collect with your care team (optional), which they may find useful.

What if I have questions or want to complain about this study?

You may also want to talk to your healthcare team or family about the study. If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. If they are unable to resolve your concern or you wish to make a complaint regarding the study, please contact a University Research Practice and Governance Co-ordinator on 0161 2757583 or 0161 2758093 or by email to Research.Complaints@manchester.ac.uk.

In the unlikely event that something goes wrong and you are harmed during the research you may have grounds for a legal action for compensation against the University of Manchester or the NHS Trust but you may have to pay your legal costs.

Will I be able to find out about what this study has found?

Two trainee clinical psychologists will be analysing the data collected in this project as part of their doctoral theses, supervised by Dr Katherine Berry and Dr Sandra Bacci. Hopefully, the research will also be published in a scientific journal. If requested, Jasper or Hannah can send you a copy of the final published article.

Thank you very much for reading this. Please don’t hesitate to ask if you have any questions.

Version 1: 18.10.2013
Yours sincerely,

Ms Hannah Darrell  
Email: Hannah.Darrell@postgrad.manchester.ac.uk

&

Dr Jasper Palmier-Claus  
Email: Jasper.Palmier-Claus@manchester.ac.uk  
Work Tel: 07871991406

Trainee Clinical Psychologists  
Division of Clinical Psychology  
2nd Floor Zochonis Building  
University of Manchester,  
Brunswick Street  
Manchester, M13 9PL

Supervised by:

Dr Sandra Bucci  
Academic Supervisor  
Email: Sandra.Bucci@manchester.ac.uk  
Tel:01613060400

Dr Katherine Berry  
Academic Supervisor  
Email: Katherine.Berry@manchester.ac.uk  
Tel:01613060400

Version 1: 18.10.2013
Appendix L. Participant information sheet for non-clinical participants.

The Scribe (Social Cognition Research in Bonding and Emotions) study

We would like to invite you to take part in a research study. Before you decide you need to understand why the research is being done and what it would involve for you. Please take time to read the following information carefully. Talk to others about the study if you wish. Thank you for reading this.

What is the study about?

This study looks at something called ‘social cognition’. Social cognition is a person’s ability to understand the intentions and behaviours of others. We think that a person’s social cognition abilities might have been influenced with experiences in their childhood. We are interested in looking at how a person’s childhood experiences effects their social cognition and then how social cognition effects a person’s emotions and ability to socialise.

Why have I been invited?

You have been invited to take part in this study because you do not have a history of mental illness and are aged 16 or older. We hope to recruit 120 individuals to take part in this study.

Do I have to take part?

No, it is your decision whether you take part or not. If you do decide to take part, you will be given this information sheet to keep and asked to sign a consent form saying you agree to take part. If you decide to take part, you are still free to withdraw at any time, without giving a reason.

What will participation involve?

If you choose to take part, a researcher will arrange to meet with you at a room at the University of Manchester. The study will take no longer than 1 hour and 15 minutes and will involve completing some questionnaires, short interviews and tasks. Additionally,

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you will be asked for some personal details (e.g. age, ethnicity, diagnosis, medication, months since first contact with services and number of criminal convictions).

- **Questionnaires:**
  The questionnaires in this study look at a number of different things, such as difficult experiences that you may (or may not) have had during childhood and how you tend to feel and act. There are no right or wrong answers. Some examples of the things that you will be asked to rate on the questionnaires are 'I believe that I was emotionally abused' and 'when I get mad I say nasty things'.

- **Short interviews:**
  The interviews will help the researchers learn a little about how you feel and experiences you may (or may not) have. Some examples of the questions that you will be asked are 'how do you see the future for yourself?' and 'do you feel inferior or even worthless'. We may wish to record the interviews in order to go over it at a later date, but this is optional and completely up to you. We may wish to audio record the interviews in order to go over it at a later date, but this is optional and completely up to you. If you are audio recorded, tapes will be kept for a maximum of 6 months before being wiped clean. Tapes will be kept in a locked cabinet at the University of Manchester.

- **Tasks:**
  The tasks involve listening to some stories and giving your opinion on what was happening and explaining how you would have felt and acted in the same situations. In some tasks you be asked to look at pictures of people’s faces on a laptop and choose the word that best describes how they were feeling.

**Are there any risks involved in taking part and will my information be kept confidential?**

There is the possibility that you may find some of the questions in this study uncomfortable or upsetting. If this is the case, you are free to leave any of these questions unanswered and you are welcome to end your participation any time. All information collected about you will be kept strictly confidential and will be anonymous. This means that any information that we collect will have your name and address removed so that you cannot be recognised. However, we will have to inform someone if you say something that makes us believe you might harm yourself or other people.

**Will anyone else know I am taking part?**

We will inform your GP that you are taking part in the study. In the unlikely event that during the course of the study it becomes apparent that you have been having experiences of psychosis then with your permission we will put you in touch with the appropriate clinical service. With your permission we will also inform your GP.

Version 1: 18.10.2013
Reimbursement for my time

Whilst there will be no financial reimbursement, if you are a psychology student, we are able to provide you with 10 research participation credits.

What are the likely benefits of this study?

Some people enjoy completing the tasks involved in research and the opportunity to talk to someone about their experiences.

What if I have questions or want to complain about this study?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. You may also want to talk to your healthcare team or family about the study. If they are unable to resolve your concern or you wish to make a complaint regarding the study, please contact a University Research Practice and Governance Co-ordinator on 0161 2757583 or 0161 2758093 or by email to Research.Complaints@manchester.ac.uk.

In the unlikely event that something does go wrong and you are harmed during the research you may have grounds for a legal action for compensation against the University of Manchester but you may have to pay your legal costs.

Will I be able to find out about what this study has found?

Two undergraduate students and two trainee clinical psychologists will be analysing the data collected in this project as part of their theses, supervised by Dr Katherine Berry and Dr Sandra Bucci. Hopefully, the research will also be published in a scientific journal. If requested, the researchers can send you a copy of the final published article.

Thank you very much for reading this. Please don’t hesitate to ask if you have any questions.

Yours sincerely,

Ms Hannah Darrell (trainee clinical psychologist)
Email: Hannah.Darrell@postgrad.manchester.ac.uk

Dr Jasper Palmier-Clau (trainee clinical psychologist)
Email: Jasper.Palmier-Clau@manchester.ac.uk
Work Tel: 07871991406

Version 1: 18.10.2013
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Academic Supervisor  
Email: Sandra.Bucci@manchester.ac.uk  
Tel:01613060400  

Dr Katherine Berry  
Academic Supervisor  
Email: Katherine.Berry@manchester.ac.uk  
Tel:01613060400  

Version 1: 18.10.2013
Appendix M. Participant information sheet for ultra-high risk participants.

Participant Information Sheet (Group 3)

The SCRiBE (Social Cognition Research in Bonding and Emotions) study

We would like to invite you to take part in a research study. Before you decide you need to understand why the research is being done and what it would involve for you. Please take time to read the following information carefully. Talk to others about the study if you wish. Thank you for reading this.

What is the study about?

This study looks at something called ‘social cognition’. Social cognition is a person’s ability to understand the intentions and behaviours of others. We think that a person’s social cognition abilities might have been influenced with experiences in their childhood. We are interested in looking at how a person’s childhood experiences effects their social cognition and then how social cognition effects a person’s emotions and ability to socialise.

Why have I been invited to take part?

You have been invited to take part in this study because you have been having or have had unusual experiences (e.g. hearing strange sounds) and/or suspicious thoughts. You will also be aged 16 or older. We hope to recruit 120 people to take part in this study.

Do I have to take part?

No, it is your decision whether you take part or not. If you do decide to take part, you will be given this information sheet to keep and asked to sign a consent form saying you agree to take part. If you decide to take part, you are still free to withdraw at any time, without giving a reason. This would not affect the standard of care that you receive.

What will participation involve?

If you choose to take part, a researcher will arrange to meet with you at a place that is convenient for you (e.g. your home or a health centre). The study will involve completing some questionnaires, interviews and tasks. Additionally, you will be asked for

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some personal details (e.g. age, ethnicity, diagnosis, medication, months since first
contact with services and number of criminal convictions), which with your permission
we will also access through your healthcare case-notes. You may have already completed
one of the interviews recently as part of your routine clinical care. If this is the case then
we will be asking you to sign a form allowing us access to this information. With the
interview this study should take 1 hour and 55 minutes. Without the interview it should
take 1 hour and 15 minutes.

- **Questionnaires:**
The questionnaires in this study look at a number of different things, such as
difficult experiences that you may (or may not) have had during childhood and
how you tend to feel and act. There are no right or wrong answers. Some
examples of the things that you will be asked to rate on the questionnaires are ‘I
believe that I was emotionally abused’ and ‘when I get mad I say nasty things’.

- **Short interviews:**
The interviews will help the researchers learn a little about how you feel and
experiences you may (or may not) have. Some examples of the questions that you
will be asked are ‘has anybody been giving you a hard time or trying to hurt you?’
and ‘is there a change in the way things look to you?’ We may wish to audio
record the interviews in order to go over it at a later date, but this is optional and
completely up to you. If you are audio recorded, tapes will be kept for a
maximum of 6 months before being wiped clean. Tapes will be kept in a locked
cabinet at the University of Manchester.

- **Tasks:**
The tasks involve listening to some stories and giving your opinion on what was
happening and explaining how you would have felt and acted in the same
situations. In some tasks you be asked to look at pictures of people’s faces on a
laptop and choose the word that best describes how they were feeling.

*Are there any risks involved in taking part and will my information be kept
confidential?*

There is the possibility that you may find some of the questions in this study
uncomfortable or upsetting. If this is the case, you are free to leave any of these
questions unanswered and you are welcome to end your participation any time. All
information collected about you will be kept strictly confidential and will be anonymous.
This means that any information that we collect will have your name and address
removed so that you cannot be recognised. However, we will have to inform someone if
you say something that makes us believe you might harm yourself or other people. After
anonymising your information to ensure you cannot be identified from it, your
information will be kept on a password protected file, on a password protected computer
at the University of Manchester. This data will be kept for a maximum of 10 years before
being deleted. Remember, you will not be identifiable from this information.

Version 1: 18.10.2013
Will anyone else know that I am taking part in this study?

Your healthcare practitioner (e.g. clinical psychologist) and GP will be told you are taking part but will not be told about what answers you give in the questionnaires, interviews and tasks (unless you want this information shared). As mentioned above, we will have to inform someone if you say something that makes us believe you might harm yourself or others. This is to ensure everyone is kept safe and well.

Reimbursement for my time

You will be given £10 to reimburse you for your time taking part in this study.

What are the likely benefits of this study?

Some people enjoy completing the tasks involved in research and the opportunity to talk to someone about their experiences. If you decide to take part, we will ask whether you want us to share the information we collect with your care team (optional), which they may find useful.

What if I have questions or want to complain about this study?

You may also want to talk to your healthcare team or family about the study. If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. If they are unable to resolve your concern or you wish to make a complaint regarding the study, please contact a University Research Practice and Governance Co-ordinator on 0161 2757583 or 0161 2758093 or by email to Research.Complaints@manchester.ac.uk.

In the unlikely event that something does go wrong and you are harmed during the research you may have grounds for a legal action for compensation against the University of Manchester or the NHS Trust but you may have to pay your legal costs.

Will I be able to find out about what this study has found?

Two trainee clinical psychologists will be analysing the data collected in this project as part of their doctoral theses, supervised by Dr Katherine Berry and Dr Sandra Bucci. Hopefully, the research will also be published in a scientific journal. If requested, Jasper or Hannah can send you a copy of the final published article.

Thank you very much for reading this. Please don’t hesitate to ask if you have any questions.
Yours sincerely,

Ms Hannah Darrell
Email: Hannah.Darrell@postgrad.manchester.ac.uk

&

Dr Jasper Palmier-Claus
Email: Jasper.Palmier-Claus@manchester.ac.uk
Work Tel: 07871991406

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Dr Sandra Bucci
Academic Supervisor
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Dr Katherine Berry
Academic Supervisor
Email: Katherine.Berry@manchester.ac.uk
Tel: 01613060400

Version 1: 18.10.2013
Appendix N. Consent form for non-clinical participants.

<table>
<thead>
<tr>
<th>Study no:</th>
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<tbody>
<tr>
<td>Participant identification no:</td>
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<tr>
<td>Consent Form (Group 1)</td>
</tr>
<tr>
<td>The SCRIBE (Social Cognition Research in Bonding and Emotion) study</td>
</tr>
<tr>
<td>Please initial by the following statements:</td>
</tr>
<tr>
<td>1) I confirm that I have read and understand the information sheet dated [date] for the above study. I have had the opportunity to consider the information, ask any questions and have had these answered satisfactorily.</td>
</tr>
<tr>
<td>2) I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.</td>
</tr>
<tr>
<td>3) I understand that data collected during the study, may be looked at by individuals from the University of Manchester, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my data.</td>
</tr>
<tr>
<td>4) I agree to my GP being informed of my participation in this study.</td>
</tr>
<tr>
<td>5) I give permission for the interviews to be recorded so that the research team can listen back to them at a later date.</td>
</tr>
<tr>
<td>6) I agree to take part in the study.</td>
</tr>
</tbody>
</table>

Version 1: 18.10.2013
Name and date of participant:

Name (PRINT) ........................................
Signed............................................ Date.............................................

Name and date of person taking consent:

Name (PRINT) ........................................
Signed............................................ Date.............................................
Appendix O. Consent form for clinical participants.

The SCriBE (Social Cognition Research in Bonding and Emotion) study

Please initial by the following statements:

1) I confirm that I have read and understand the information sheet dated ________________ for the above study. I have had the opportunity to consider the information, ask any questions and have had these answered satisfactorily.

2) I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.

3) I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the University of Manchester, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.

4) I understand that the research team will look at relevant sections of my medical notes. I give permission for these individuals to have access to my records.

5) I agree to my healthcare team and GP being informed of my participation in this study.

6) I give permission for the interviews to be audio recorded so that the research team can listen back to them at a later date. These recordings will not be written up and quotes will not be used from the recordings. This recording is optional and completely up to you.

Version 1: 18.10.2013
6) I agree to take part in this study.

Name and date of participant:

Name (PRINT) ........................................

Signed: ........................................ Date: ........................................

Name and date of person taking consent:

Name (PRINT) .................................

Signed: ................................. Date: .................................

Optional:

6) I give permission for the information I provide in this study to be shared with my healthcare team.

Name (PRINT) .................................

Signed: ................................. Date: .................................
Appendix P. Ethics approval letter.

Health Research Authority
National Research Ethics Service
NRES Committee North West - Greater Manchester Central
HRA NRES Centre - Manchester
3rd Floor
Barlow House
4 Minshull Street
Manchester
M1 3DZ

Telephone: 0161 626 7826
Facsimile: 0161 626 7299

16 December 2013

Dr J Palmier-Claus
Trainee Clinical Psychologist
The University of Manchester
The Division of Clinical Psychology
2nd Floor, Zochonis Building
Brunswick Street
Manchester
M13 9PL

Dear Dr Palmier-Claus

Study title: The Scribe (Social Cognition Research in Bonding and Emotions) study
REC reference: 13/NW/0823
Protocol number: 1
IRAS project ID: 139239

The Research Ethics Committee reviewed the above application at the meeting held on 09 December 2013. Thank you for attending to discuss the application.

We plan to publish your research summary wording for the above study on the NRES website, together with your contact details, unless you expressly withhold permission to do so. Publication will be no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to withhold permission to publish, please contact the Co-ordinator Mrs Kath Osborne, nrescommittee.northwest-gmcentral@nhs.net.

After the Committee’s initial discussions, you were invited to join the meeting to clarify the following issues:

1. The Committee thanked you for attending the meeting and advised that it was happy with the application as submitted. From an ethical point of view the Committee’s main concerns would be the safety of participants and the issue of informed consent and both these points had been addressed to the satisfaction of the Committee.

A Research Ethics Committee established by the Health Research Authority
The Committee asked you whether you had any questions to which you replied no and then left the meeting.

Ethical opinion

The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, 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.rfforum.nhs.uk](http://www.rfforum.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 R&D office on the information it requires to give permission for this activity.

Sponsors are not required to notify the Committee of approvals from host organisations

It is responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The documents reviewed and approved at the meeting were:

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<tr>
<th>Document</th>
<th>Version</th>
<th>Date</th>
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<tbody>
<tr>
<td>Advertisement</td>
<td>1</td>
<td>10 October 2013</td>
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<tr>
<td>Covering Letter</td>
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<td>16 November 2013</td>
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<td>Evidence of insurance or indemnity</td>
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<td>15 November 2013</td>
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<td>GP/Consultant Information Sheets</td>
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<td>10 October 2013</td>
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A Research Ethics Committee established by the Health Research Authority
Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

A Research Ethics Committee established by the Health Research Authority
After ethical review

Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review

13/NW/0823 Please quote this number on all correspondence

We are pleased to welcome researchers and R & D staff at our NRES committee members’ training days – see details at http://www.hra.nhs.uk/hra-training/

With the Committee’s best wishes for the success of this project.

Yours sincerely

Signed on behalf of
Professor S J Mitchell
Chair

Email: nrescommittee.northwest-gmcentral@nhs.net

Enclosures: List of names and professions of members who were present at the meeting and those who submitted written comments

"After ethical review – guidance for researchers"

Copy to: Ms L Macrae, University of Manchester

Dr A Mee, Manchester Mental Health & Social Care Trust

A Research Ethics Committee established by the Health Research Authority