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Childhood Trauma and Neurocognition in Adults With Psychotic Disorders: A Systematic Review and Meta-analysis

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Background: **Characterizing the link between childhood trauma and adult neurocognitive function in psychosis is crucial for improving the fields understanding of how early environmental risk factors impact the presentation of the disorder. To date, the literature has been inconsistent: meta-analytic synthesis is lacking, and it is unclear whether specific cognitive functions are affected.** ***Methods:*** **A meta-analysis was performed on a total of 3315 subjects with a psychotic disorder. The links between childhood trauma, overall neurocognitive function, and four cognitive subdomains (working memory, executive function, verbal/visual memory, and attention/processing speed) were examined. Relevant sample characteristics and methodological moderators were tested. The strength of the association between trauma and overall neurocognition in individuals with psychotic disorders was also compared to that of healthy controls.** ***Results:*** **Among individuals with psychotic disorders, there was a significant association between overall cognition and childhood trauma, $r = -.055$; 95% CI = −0.09, −0.02, $P = .002$. There was also a modest, negative relationship between childhood trauma and working memory, $r = -.091$; 95% CI = −0.15, −0.03, $P = .002$. Moderators did not have a significant effect on these analyses. Further, the association between childhood trauma and neurocognition was significantly stronger in healthy controls compared to patients with a psychotic disorder.** ***Conclusion:*** **A small negative association was found between overall cognition and childhood trauma in individuals with psychotic disorders. Results suggest the association is less strong for individuals with a psychotic disorder compared to healthy populations. Findings are informative for prominent etiological models of psychosis.**

Key words: neurocognition/psychosis/childhood trauma/early life stress/working memory

Introduction

Childhood trauma, including exposure to physical, sexual, and emotional abuse, as well as to emotional and physical neglect,[1] has been implicated as a risk factor for development of psychotic disorders.[2–4] An increasing body of evidence suggests that exposure to early life trauma may affect the presentation of some observed symptoms as well as neurocognitive deficits in psychosis.[5] Despite this increasing recognition, the relationship between early life trauma exposure and neurocognitive function in psychosis has, until recently, been grossly understudied.[6,7] The literature is not conclusive on whether effects are uniform across all neurocognitive domains (global vs specific neurocognitive function), which would aid understanding of underlying neurodevelopmental mechanisms. Further, case–control comparisons have seldom been undertaken.

In both animal and healthy human population studies, exposure to trauma during periods of greater neurodevelopmental plasticity has been linked to lasting impairments in brain function.[8] Trauma exposure has also been strongly linked to disturbances in critical developmental skills (ie, emotion regulation, social communication) and increased levels of chronic stress, which likely contribute to the development and progression of neurocognitive dysfunction across the life span.[2,8–10] Numerous theories link the effects of trauma on affect, cognition, social, and role function to increased risk for developing psychotic symptoms.[11,12] Indeed, childhood trauma has long been observed as a psychosis risk factor, with some studies supporting a causal relationship between trauma exposure and development of the disorder.[3,13] For example, studies suggest individuals diagnosed with a psychotic disorder are more likely to report previous exposure to traumatic life events relative to healthy controls and

unaffected siblings.[10,14,15] In addition, recent studies have found that a history of trauma can predict symptom severity (ie, severity of delusions and hallucinations), as well as treatment resistance and number of hospitalizations after psychosis onset.[10,13] However, despite neurocognitive deficits being a core facet of the presentation of schizophrenia, the link between childhood trauma and neurocognitive function to this date is not fully understood. Several critical questions remain regarding potential mechanisms through which neurocognitive function could relate to childhood trauma.

Neurocognitive dysfunction is a core feature of psychosis.[16] Neurocognitive assessment can aid in predicting illness severity, social function, and occupational function, and is highly informative for understanding the etiology of the disorder.[16–18] However, research exploring the association between childhood trauma and neurocognition in psychotic populations has produced mixed results. Previous studies of these associations have measured both overall neurocognition and specific cognitive functions with mixed outcomes.[19–30] For example, Aas and colleagues[2,31,32] reported associations between childhood trauma and specific cognitive domains, such as working memory, verbal memory, and executive function (EF). However, more recent well-powered studies have reported null results with regard to overall cognition.[33,34] Given divergence in the types of neurocognition explored, many questions have yet to be answered. Moreover, little attention has been given to relevant moderators or methodological and sample characteristics that may be adding to the inconsistent findings. Furthermore, meta-analytic evidence suggests that childhood trauma has a robust effect on neurocognition in otherwise healthy individuals.[35] Measuring whether this effect is present in individuals with a psychotic disorder, and whether it is quantifiably different to the effect found in healthy populations would inform the field's understanding of the pathogenesis of psychosis.

Despite an excellent qualitative review by Aas and colleagues,[2] there are currently no meta-analytic studies evaluating general and specific neurocognitive functions in relation to trauma exposure in psychosis. As noted, extant studies have rarely contrasted diverging neurocognitive domains, or carefully considered relevant moderators such as age, gender, and type of psychotic disorder.[22,32] The present systematic review and meta-analysis sought to address these gaps by determining whether childhood trauma is associated with distinct neurocognitive domains in individuals with a psychotic disorder. In addition to examining specific neurocognitive processes, we also evaluated overall neurocognitive function. Understanding specific and global areas of dysfunction may help to shed light on mechanisms underlying the association. The review also examined whether moderating factors influence the relationship between childhood trauma and adult neurocognition. Findings may help to shed light on factors contributing to the discrepant findings in the existing literature. Finally, to supplement the review, exploratory analyses compared the strength of the association between childhood trauma and overall neurocognition in psychotic disorder patients and healthy controls. Taken together, this information will aid in developing and refining mechanism-specific theories as well as informing efforts for improving prediction, early identification, and intervention.

Methods

Search Strategy

This study was conducted according to PRISMA guidelines. PubMed, Ovid Medline, and Web of Science were searched on July 28, 2018 (see figure 1). Search terms for childhood trauma (Child* abuse OR child* neglect OR child* trauma OR child* maltreatment OR child* adversity OR early life stress OR early life trauma) were combined with search terms for cognition (cognit* OR neurocognit* OR neuropsych*) and search terms for psychosis and related disorders that could have psychotic features (psychosis OR psychotic OR schizophreni* OR schizot* OR schizo* OR delusi* OR bipolar OR depressi*) with AND commands.

Study Selection and Characteristics

The studies included for overall cognition and cognitive subdomain analyses provided quantitative, published data in adults (≥18 without overlapping samples, 23 including partially overlapping samples) with a diagnosis of a psychotic disorder. Psychotic disorder diagnoses included schizophrenia, schizoaffective disorder, schizophreniform disorder, psychosis not otherwise specified/delusional disorder, bipolar disorder with psychotic features, and/or depression with psychotic features. Diagnoses were determined by standardized, validated diagnostic assessments meeting the Diagnostic and Statistical Manual of Mental Disorders, Fourth Version (DSM-IV)[21–25,27,28,30–34,36,37] and/or the International Classification of Diseases, Tenth Revision (ICD-10) criteria.[19,20,26,29,32,38–41] To meet inclusion criteria, studies were required to provide data on (1) variables from neuropsychological testing (normed, formally validated batteries of cognitive function [see table 1]) and (2) childhood trauma, as well as data on the relationship between these two variables, such that an effect size statistic could be computed. Studies were excluded if they reported data including both control participants and psychosis groups, rather than reporting the associations of diagnostic groups separately. Two reviewers (T.V. and M.A.) independently reviewed full articles with relevant titles and abstracts with an 89.9% agreement rate, and discrepancies were resolved through discussion. When more than one published study used the same subjects,

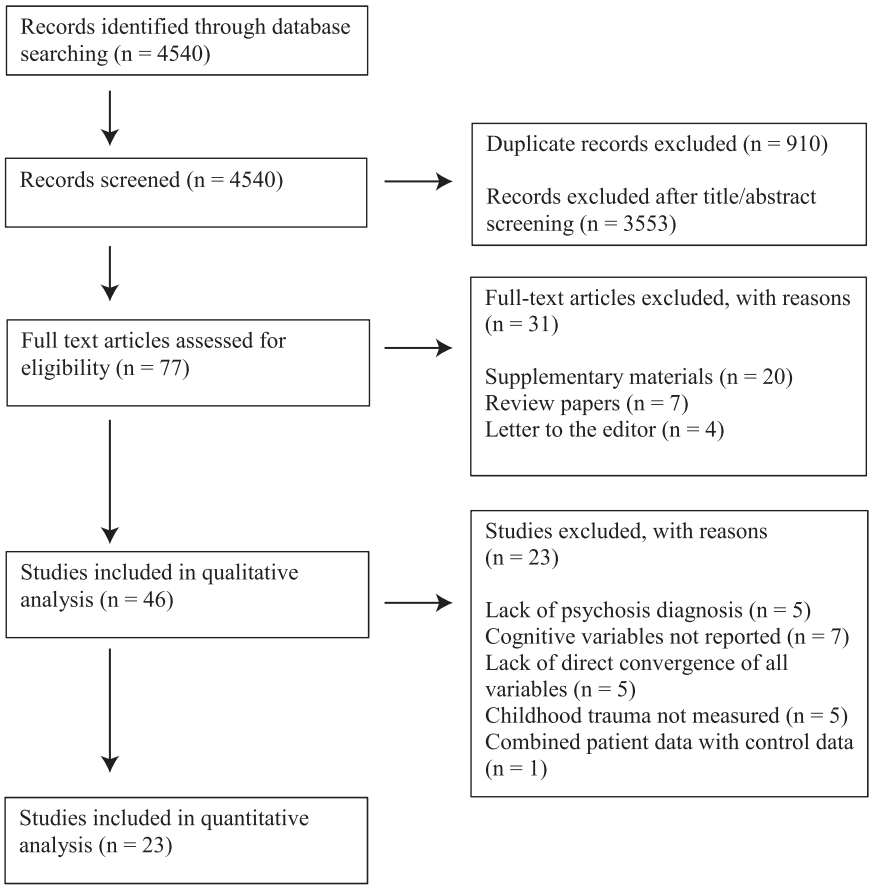

Fig. 1. Flowchart of selected studies.

the study with the larger sample size was chosen to maximize power. The included studies for overall cognition contained 3315 diagnosed participants.

Quality and Selective Reporting

The Downs and Black checklist[42] was used to assess methodological quality and risk of bias of included studies (see supplementary table S1). This can be instructive for determining implications of the current findings, and more generally for improving understanding of the social epidemiology of psychosis. Selective reporting was assessed by marking "Outcome not reported" in cases where childhood trauma types were measured but not reported with regards to cognition (see supplementary table S2).

Outcome Variable Characteristics

Childhood Trauma. For 12 studies included in main analyses, childhood trauma exposure was dichotomized, and for 11 it was measured on a continuous scale (see table 2). For studies that dichotomized childhood trauma, the effect size statistic was converted to a point-biserial *r* after correcting for potential uneven split between groups, such that increasing values indicated exposure to childhood trauma. For studies that reported childhood trauma on a continuous scale (reflecting a sum of items with more items indicating greater trauma exposure), an *r* statistic was calculated, with increasing values also indicating increased exposure to childhood trauma.

In this review, we employed a standard definition for physical, sexual, and emotional abuse, as an act causing injury or trauma in the respective domains; this approach is consistent with other work in this area.[1] Emotional neglect was defined as failure by a caretaker to meet basic emotional and psychological needs, and physical neglect constituted failure to provide for a child's basic physical needs, such as food, shelter, clothing, safety, and health care (see table 2 for details on types of trauma reported).[1]

Neurocognitive Variables. Cognitive data were initially considered in 8 primary domains, including overall cognitive ability/IQ, EF, working memory, verbal/visual memory, attention/processing speed, perception/visuospatial abilities, premorbid IQ, and social cognition. To be included in analyses using a random effects model, it was determined that a domain should have at least 5 studies with reported data, as is recommended in cases when nontrivial heterogeneity is expected.[43] As a result,

Table 1. Study Characteristics

First Author (Year)	*N*	% Female	Mean Age	Dx[a] Affective or FEP	Covariates	Trauma Measure	Cognitive Domains	Cognitive Measure	Nonindependent Samples (First Author [Year])	Excluded From Main Analyses
Aas (2011a)[32]	138	47.1	30.6	FEP, including affective psychosis	Education and ethnicity	CECA.Q	Overall cognition, EF, WM, memory, attention	RAVLT, WMS-R, LNS, TMT, DS, Raven's Colored Progressive Matrices	Aas (2012a)[40]	
Aas (2011b)[39]	30	33.33	30.1	FEP	N/A	CECA.Q	Overall cognition, WM, memory, attention	WMS III, TMT, SWM, WAIS III	--	
Aas (2012a)[40]	83	37.3	27.4	FEP	N/A	CECA.Q	Overall cognition, EF, WM, memory, attention	WAIS-R, Raven's Colored Progressive Matrices, TMT	Aas (2011a)[32]	√
Aas (2012b)[31]	406	47.29	30.7	Including affective psychosis	Age and gender	CTQ	Overall cognition, EF, WM, memory	CVLT, LNS, DS, WASI	Aas (2012c)[36] Aas (2013)[37]	
Aas (2012c)[36]	118	55.1	32.2	Including affective psychosis	Age, gender, and paternal education	CTQ	Overall cognition, EF, WM, memory	WASI-III, LNS, DS, CVLT	Aas (2012a)[40] Aas (2013)[37]	√
Aas (2013)[37]	249	51	30.7	Including affective psychosis	Age, gender, diagnosis	CTQ	Overall cognition, EF, WM, memory	WASI, D-KEFS, LNS, DS, CVLT	Aas (2012a)[40] Aas (2012c)[36]	√
Campbell (2013)[29]	30	40	31.8	FEP, including affective psychosis	Premorbid IQ	TEC, PDS, TREQ	IQ, overall cognition, EF, WM, memory, attention	WASI, NART, Rey-Osterieth Complex Figure, Hayling & Brixton, Corsi Block Tapping	—	
Garcia (2016)[24]	79	36.8	25.3	Including affective psychosis	Age, gender, education status	CTQ	Overall cognition, WM, memory, attention	MCCB	—	
Green (2014)[26]	617	32.74	39.7	Including affective psychosis	COMT genotype	CAQ	Overall cognition, EF, memory, attention	COWAT, LNS, WAIS III, WTAR, RBANS	Green (2015)[41]	
Green (2015)[41]	444	32.7	39.7	Including affective psychosis	FK506 binding protein genotypes	CAQ	Overall cognition, EF, memory, attention	WTAR, LNS, COWAT, RBANS	Green (2014)[26]	√
Kelly (2016)[22]	80	30	32.5	Including affective psychosis	N/A	CTQ	Overall cognition	RBANS	—	
Killian (2017)[63]	56	25	23.8	FEP	N/A	CTQ	Overall cognition, WM, memory, attention	RBANS	—	
Li (2017)[21]	162	64.19	37.8	Including affective psychosis	N/A	CTQ-SF	Overall cognition, EF, memory, attention	RBANS	—	

Table 1. Continued

First Author (Year)	*N*	% Female	Mean Age	Dx[a] Affective or FEP	Covariates	Trauma Measure	Cognitive Domains	Cognitive Measure	Nonindependent Samples (First Author [Year])	Excluded From Main Analyses
Lysaker (2001)[28]	43	0	45	Including affective psychosis	N/A	Clinical interview	Overall cognition, EF, WM, memory, attention	WCST, LNS, WAIS	—	
Mansueto (2017)[30]	532	24.4	27.6	N/A	Age and gender	CTQ-SF	Overall cognition, EF, memory, attention	RST, WLT, CPT	—	
Quide (2017)[20]	50	56.5	37.7	Including affective psychosis	N/A	CTQ	IQ, WM	WASI, NBack	[b]Green (2014, 2015), Quide (2018)	
Quide (2018)[38]	79	43.04	42.52	Including affective psychosis	Age and gender	CTQ	Overall cognition, memory, attention, WM	RBANS, LNS, COWAT	[b]Green (2014, 2015), Quide (2017)	
Ruby (2017)[23]	17	28.57	31.5	Including affective psychosis	N/A	ETI	IQ, overall cognition, EF, memory	WMS-R, WAIS, FAS	—	
Schalinski (2017)[19]	168	33.33	27.9	Including affective psychosis	N/A	MACE	Overall cognition, WM, memory, attention	MCCB	—	
Schenkel (2005)[27]	40	37.5	41.9	Including affective psychosis	N/A	Clinical interview	IQ, overall cognition, EF	COWAT, Hayling & Brixton Tests, Shipley IQ	—	
Shannon (2011)[25]	85	21.18	41.1	N/A	IQ and current depressive symptoms	CTQ	Overall cognition, memory	WMS-III	—	
Sideli (2014)[34]	134	35.07	29.4	N/A	N/A	CECA.Q	IQ, overall cognition, EF, WM, memory, attention	NART, WAIS-III, WMS-III, TMT, DS	—	
Van Os (2017)[33]	698	23.94	27.6	N/A	Age, sex, ethnic group, education level, symptom score, and cannabis use	CTQ	IQ, overall cognition	WAIS IQ	—	

Note: CECA.Q, childhood experience of care and abuse questionnaire; COWAT, Controlled Oral Word Association Test; CTQ, Childhood Trauma Questionnaire; CVLT, California Verbal Learning Test; DS, Digit Symbol; EF, executive function; FEP, first-episode psychosis; LNS, letter number sequencing; MACE, Maltreatment and Abuse Chronology of Exposure; MCCB, MATRICS Consensus Cognitive Battery; NART, National Adult Reading Test; PDS, Post-Traumatic Diagnostic Scale; RAVLT, Rey Auditory Verbal Learning Test; RST, response shifting tasks; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; SWM, Spatial Working Memory (from the Cambridge Neuropsychological Test Automated Battery [CANTAB[59]]); TEC, Traumatic Experiences Checklist; TMT, Trail Making Test; TREQ, troubles related experiences questionnaire; WAIS, Wechsler Adult Intelligence Scale; WM, Working Memory; WMS-R, Wechsler Memory Scale-Revised; WTAR, Wechsler Test of Adult Reading.

[a]Indicates whether authors specified that FEP was recruited, as well as whether authors specified that sample included affective psychosis Dx individuals. N/A indicates that authors did not report either of the two.

[b]Quide (2017, 2018) and Green (2014 and 2015) both recruited from Schizophrenia Research Banks, therefore samples are not independent; whereas Quide reported IQ and working memory measures, Green (2014, 2015) reported overall cognition, EF, attention/processing speed, and verbal/visual memory. Because Green and colleagues' sample size is larger, Green was chosen for overall cognition, whereas Quide et al. was designated for working memory and IQ domains.

Table 2. Trauma Sample Characteristics of Studies Included in Main Analyses

Author (year)	Trauma Binary?	Coded Trauma Type(s)
Aas (2011a)[32]	Yes	Total CTQ[1] score
Aas (2012b)[31]	No	CTQ[1] Physical abuse, sexual abuse, emotional abuse, emotional neglect, physical neglect
Aas (2011b)[39]	No	Total CECA-Q[90] score
Campbell (2013)[29]	Yes	Total trauma score from TEC,[91] PDS,[92] TREQ[93]
Garcia (2016)[24]	No	Total CTQ,[1] emotional abuse, physical abuse, sexual abuse, emotional neglect, physical neglect
Green (2014)[26]	No	CAQ[94] Physical abuse, emotional abuse, emotional neglect
Kelly (2016)[22]	Yes	CTQ[1] Physical abuse
Killian (2017)[63]	No	CTQ[1] Abuse and neglect
Li (2017)[21]	No	Total CTQ,[1] emotional abuse, physical abuse, sexual abuse, emotional neglect, physical neglect
Lysaker (2001)[28]	Yes	Sexual trauma collected from clinical interview
Mansueto (2017)[30]	Yes	CTQ[1] total
Quide (2018)[38]	Yes	CTQ[1] total
Ruby (2017)[23]	No	ETI[95] total
Schalinski (2017)[19]	No	MACE[96] abuse and neglect
Schenkel (2005)[27]	Yes	Physical abuse, sexual abuse and neglect coded from clinical interview
Shannon (2011)[25]	Yes	CTQ[1] total
Sideli (2014)[34]	Yes	CECA-Q[90] physical abuse and sexual abuse
Van Os (2017)[33]	Yes	CTQ[1] total

Note: CECA.Q, childhood experience of care and abuse questionnaire; CTQ, Childhood Trauma Questionnaire; ETI, Early Trauma Inventory; MACE, Maltreatment and Abuse Chronology of Exposure scale; PDS, Post-Traumatic Diagnostic Scale; TEC, Traumatic Experiences Checklist; TREQ, troubles related experiences questionnaire.

enough data was reported to analyze 5 of the initial cognitive domains.

Overall Cognitive Ability Overall cognitive ability (k = 17) was assessed by averaging reported Wechsler Abbreviated Scale of Intelligence (WASI) scores (k = 4),[44] Wechsler Adult Intelligence Scale (WAIS)-III scores (k = 6),[45] Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) total score (k = 2),[46] MATRICS Consensus Cognitive Battery (MCCB) total score (k = 3),[47] Shipley IQ (k = 1),[48] Wechsler Test of Adult Reading (WTAR) (k = 1),[49] and by averaging scores on the Word Learning Task (WLT), Continuous Performance Test (CPT), and response shifting tasks (RST) tests (k = 1).[50–52] In the case of 4 studies, a total WAIS estimate was derived from partial reporting of specific WAIS subtests (vocabulary and comprehension subtests, similarity and vocabulary, verbal subtest questions about geography and literature, and finally digit symbol and letter number sequencing [LNS], respectively).[45,53] To provide a more specific index of IQ, an additional separate subdomain was created to compare studies that reported a complete WASI or WAIS score (k = 6).

Executive Function EF (k = 10) was measured through tasks measuring phonological and semantic fluency, including the WAIS-R category fluency (semantic ["body parts," "fruits," and "animals"]) and letter fluency (phonemic [F, A, and S]) tasks,[53] Controlled Word Association Test (COWAT)-FAS (the most common version of the COWAT, which uses the letters F, A, and S),[54] COWAT Animals total,[54] the COWAT,[55] the RBANS language dimension including semantic fluency,[46] the Wisconsin Card Sort Test (WCST),[56] RST,[52] and Hayling and Brixton test errors.[57]

Working Memory The working memory domain (k = 10) was derived from the LNS and/or digit span tasks, assessed via WMS, MCCB, and WAIS-III tests.[45,47,58] A study using the Nback task[20] as well as another using the Cambridge Neuropsychological Test Battery Spatial Working Memory Test[59] were also included.

Verbal/Visual Memory The verbal/visual memory domain (k = 14) comprised performance on the Rey Auditory Verbal Learning Test[60]; the visual reproduction, paired associates, recognition, and recall subtests of the Wechsler Memory Scale (WMS)-R[58]; the California Verbal Learning (CVLT)[56];WMS-III verbal and nonverbal memory and visual reproduction[58]; MCCB and RBANS verbal and visual learning[46,47]; the WLT composite[50]; and the WMS-III logical memory, word lists, and visual reproduction.[58]

Attention and Processing Speed The attention and processing speed domain (k = 9) included Trail Making Test (TMT)-A, WAIS-R, and WAIS-III digit symbol subtests[45,53]; MCCB and RBANS attention subtests[46,47]; and the CPT-HQ subtest.[51]

Moderators

Moderators examined included mean age and percentage of female, use of covariates (eg, age, gender, premorbid IQ), recruitment of samples including affective psychotic disorders, and use of first-episode psychotic populations. Mean age and gender were chosen as they have been shown to influence outcome variables.[61,62] Potentially relevant methodological moderators were chosen; these consisted of use of first-episode psychosis (FEP) populations and recruitment of samples including affective psychosis, sample size, as well as use of covariates. Variables including use of covariates, recruitment of FEP, and recruitment of affective psychosis were dummy coded. Some relevant moderators (including years of illness, race, substance use, and antipsychotics dosage) could not be directly analyzed because a majority of the studies did not provide sufficient data to examine these variables.

Healthy Control Comparisons

A recent meta-analytic review found that there was a robust association between childhood trauma and cognitive function in otherwise healthy individuals.[35] The current study sought to explore whether the association between childhood trauma and overall cognition differed between healthy individuals and those with a psychotic disorder. To this end, included studies that additionally reported control data (k = 7)[32–34,38,39,41,63] were tested for difference of effect using a Fisher's Z transformation. Within each diagnostic group, Fisher's Z was calculated by averaging the r value, and summing the total number of subjects within diagnostic categories. A z value corresponding to an alpha level of 0.05 (± 1.96) was considered to be a significantly distinct effect across diagnoses.

Meta-analytical Procedure

Analyses were run using an R script (written and published by Daniel S. Quintana) for correlational meta-analyses using the robumeta[64] and metafor[65] packages for R.[66,67] For each cognitive test, a Pearson's r estimate was calculated. In the case of 10 studies, the associations between childhood trauma and cognition were converted to a Cohen's d, and then to a point-biserial correlation estimate. A correlational approach was chosen given that converting r statistics to Cohen's d for an inherently continuous variable can result in an underestimation of the effect.[68] In the case of reported Spearman's r, values were converted to a t score and then converted to Pearson's r. Reported beta values were converted to t scores, and then converted to Pearson's r estimates. Pearson's r estimates were transformed to Fisher's Z and sample variances were estimated. A random-effects model was used.

Study heterogeneity was calculated using the I^2 test, which is not sensitive to number of studies included, with 25%, 50%, and 75% constituting low, moderate, and large amounts of heterogeneity, respectively.[69] Homogeneity of mean weighed effect sizes was assessed using the Q test. Bias was assessed through inspection of funnel plots, and through the Eggers regression test, which is well suited for smaller meta-analyses.[70] The metafor R package was used to identify potential outliers and influential cases.[71] Meta-regressions were used to assess the effects of moderator variables on observed between-group differences. Meta-regression analyses were conducted with random-effects modeling, using the restricted-information maximum likelihood method with a significance level cutoff of $P < .05$. For 5 studies, samples were not independent.[20,36,37,40,41] In this case, samples with greater sample size were chosen for inclusion as a rule for the main analyses (see table 1). Additional analyses were run including these studies using robust variance estimation, which requires less computational power and accounts for statistical dependency (k = 23 for overall cognition, see table 3).[72]

Results

Study Characteristics and Quality

Quality scores on the Downs and Black checklist ranged from 11 to 17 (out of a possible 18 for cross-sectional, nonintervention studies). The mean for included studies was 14, SD = 1.56 (see supplementary table S1 for scores for each included study). The least well-met quality criteria were (1) conducting power analyses, (2) blinding

Table 3. Comparison of Analyses Including Non-independent Samples Using Robust Variance Estimation, and Main Analyses Excluding Nonindependent Samples

	Exclude Nonindependent Samples	Include Nonindependent Samples	Extra Samples Included
Overall cognition	−0.055, CI_{95}[−0.09, −0.02]	−0.06, CI_{95}[−0.11, −0.01]	Aas, 2012a,[40] Aas, 2012c,[36] Aas, 2013[37]; Green, 2015[41] Quide, 2017[20]; Quide, 2018[38]
Executive functioning	−0.07, CI_{95}[−0.13, 0]	−0.07, CI_{95}[−0.17, 0.02]	
Working memory	−0.09, CI_{95}[−0.15, −0.03]	−0.12, CI_{95}[−0.18, −0.05]	
Attention and processing speed	−0.07, CI_{95}[−0.15, 0]	−0.08, CI_{95}[−0.18, 0.03]	
Verbal/visual memory	−0.05, CI_{95}[−0.09, 0]	−0.04, CI_{95}[−0.11, 0.03]	

interviewers involved in collection of outcome data, (3) reporting time period of recruitment, and (4) reporting proportion of approached subjects that declined to participate. All studies contained an adequate measure of childhood trauma exposure, including sexual and physical abuse, emotional abuse, and physical and emotional neglect. However, selective reporting was common with regard to reporting all measured specific trauma types. For instance, only 22.7% of selected studies reported outcomes with regard to all trauma types indicated (ie, physical, sexual and emotional abuse as well as emotional and physical neglect), with 36.3% having reported outcomes for 2 or more trauma types (see supplementary table S2).

Meta-analysis of Childhood Trauma, Overall Cognition, and Cognitive Subdomains

We observed an overall significant result for the association between childhood trauma and overall cognitive ability, $r = -.055$; 95% CI =−0.09, −0.02, $P = .002$; See figure 2. Heterogeneity was low ($I^2 = 0\%$, CI 0= .00, 68.01, $P = .47$). Egger's coefficient bias test was not significant, suggesting an absence of small-study bias ($P = .48$). There were no significant moderating effects ($P = .09$–.71). Interestingly, although overall cognitive ability analyses were significant, analyses of studies using a WASI/WAIS complete IQ measure (k = 6) were not, $r = -.008$; 95% CI = −0.07, 0.06, $P = .81$; However, this may be due to limited power due to the substantially decreased number of included studies. Heterogeneity was low ($I^2 = 0\%$, $P = .93$), and no evidence of small-study bias (Egger's coefficient bias test) was detected ($P = .58$).

Analyses of the EF domain yielded significant results, $r = -.065$; 95% CI = −0.13, 0.00, $P = .045$. Heterogeneity was low to moderate ($I^2 = 39.06\%$, CI = 0.00, 90.03, $P = .10$). Egger's coefficient bias test was not significant, suggesting an absence of small-study bias ($P = .75$). There were no significant moderating effects ($P = .36$–.67), asides from an effect on the border of statistical significance for the proportion of female subjects in the sample [$Q(1) = 3.72$, $P = .05$].

Of note, a modest significant negative relationship between childhood trauma exposure and working memory function was observed [$r = -.091$; 95% CI = −0.15, −0.03, $P = .002$; See figure 3]. Heterogeneity was low ($I^2 = 0.05\%$, CI = 0.00, 81.88, $P = .35$). Egger's coefficient bias test was not significant, suggesting an absence of small-study bias ($P = .55$). There were no significant moderating effects ($P = .36$–.97).

In contrast, analyses of the verbal/visual memory domain yielded less strong, though significant results, $r = -.047$; 95% CI = −0.09, −0.00), $P = .03$. Heterogeneity was low ($I^2 = 7.61\%$, CI = 0.00, 76.30, $P = .38$). Egger's coefficient bias test was not significant, suggesting an absence of small-study bias ($P = .75$). There were no significant moderating effects ($P = .19$–.99). Finally, analyses of the attention domain yielded significant results,

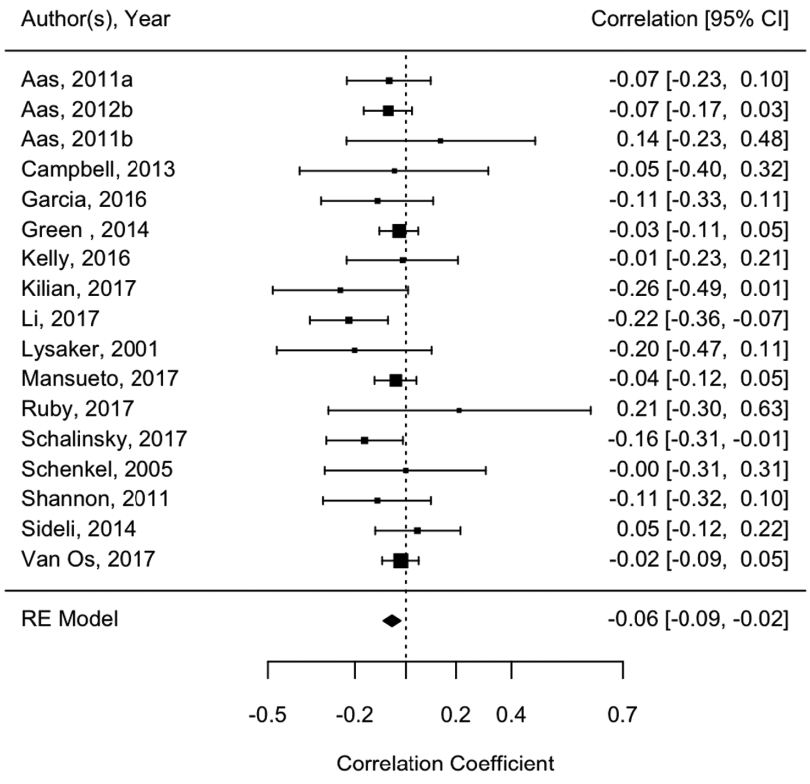

Fig. 2. Forest plot showing the relationship between childhood trauma and overall cognitive performance.

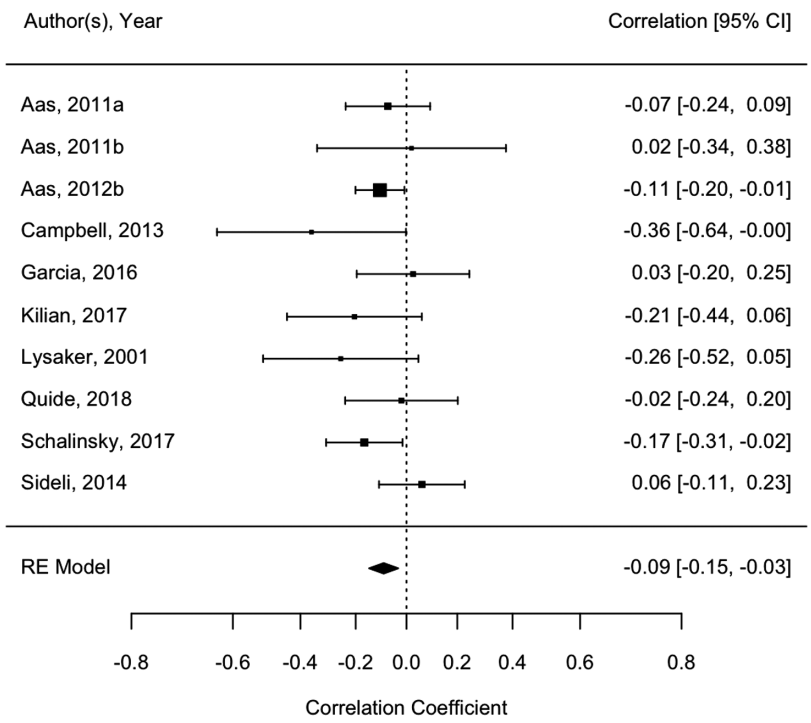

Fig. 3. Forest plot showing the relationship between childhood trauma and working memory performance.

$r = -0.075$; 95% CI =−0.15, 0.00, $P = .04$. Heterogeneity was moderate ($I^2 = 48.25\%$, CI = 0.00, 85.28, $P = .08$). Egger's coefficient bias test was not significant, suggesting an absence of small-study bias ($P = .92$). There were no significant moderating effects ($P = .13$–$.97$). Finally, additional analyses using cluster-robust variance estimation (including studies with nonindependent samples) yielded results similar in magnitude to those in the main analyses (see table 3).

Case–control Comparisons

Across the 7 studies used for comparison, the average r across 1193 subjects for the healthy control comparison group was −.131. The average r across 1579 subjects for the psychotic disorders group was −.025. The calculated Fisher's Z value was −2.77, which indicates a significant difference of effect between the two diagnostic groups ($P = .006$).

Discussion

This meta-analytic review detected an effect of childhood trauma on overall neurocognitive function, such that trauma exposure was associated with lower overall performance. The small effect may aid in explaining discrepancies in the literature.[33,34] There are two possible interpretations. First, though sample size was not found to moderate findings, larger studies tended toward smaller effect sizes. Thus, perhaps some studies with smaller samples yielded inflated effect sizes. Second, the effect may be present, but small, and only detectable through pooling together currently available samples. Regardless, this effect size supports the broader conception that mechanisms of neurocognitive dysfunction in psychosis are complex and multifaceted, with numerous putative factors contributing in parallel to varying degrees.[2,17,73–76] Notably, exploratory analyses found the association between childhood trauma and overall cognition was significantly stronger in healthy individuals compared to patients with psychotic disorders. The following sections discuss these findings in the context of the broader literature and highlight future directions and applications.

Although the effect size of the relationship between overall cognition and childhood trauma was fairly small, low heterogeneity and lack of evidence for bias lend support to the robustness of the findings (ie, "small but meaningful"). Nonetheless, a critical future direction will be to determine whether this effect is clinically meaningful. It is noteworthy that exploratory analyses yielded a significantly stronger effect of childhood trauma and neurocognition in healthy individuals in comparison to individuals with psychotic disorders. This finding is consistent with a stronger association previously observed in healthy populations,[33,34,77,78] including one previous meta-analytic review.[35] One possibility is that the effect of trauma is being "overpowered," or masked, by factors intrinsic to a psychotic disorder diagnosis, such as genetic effects, current adversity, and medication use.[33] However, given the vast evidence that childhood trauma increases likelihood of developing psychosis,[10] and given that neurocognitive deficits are a core component of the disorder, it is also possible that a larger effect is being constrained

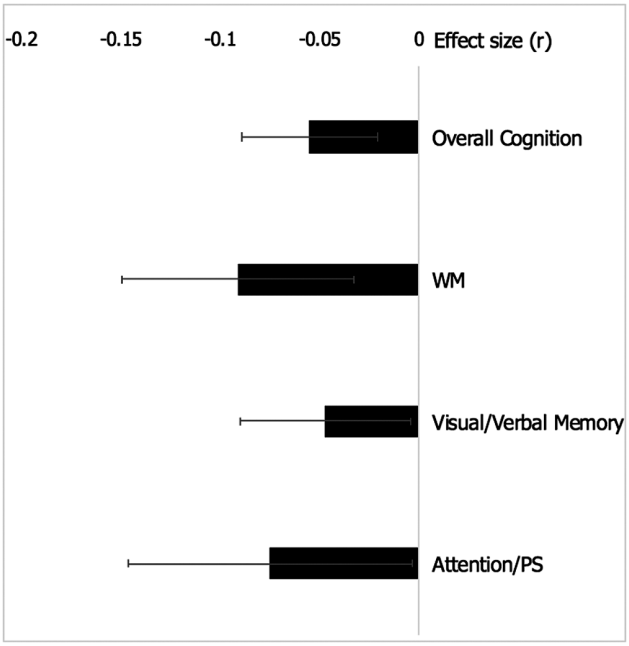

Fig. 4. Effect sizes and 95% confidence intervals across cognitive domains.

by methodological limitations in the literature. In the present investigation, however, there was no evidence of methodological moderator effects.

In interpreting the small effect size, another factor to consider is the perennial issue of heterogeneity of psychotic disorders. While exploring global neurocognitive function, signal may be lost with regard to specific cognitive mechanisms that may be differentially affected by childhood trauma. In the current study, the effect size for the negative association between childhood trauma and working memory, though modest, was larger than that of overall cognition (see figure 4). This is notable especially in light of the fact that working memory has long been considered a critical endophenotype for psychosis.[73,79] Analyses of additional cognitive domains (EF, verbal/visual memory, and attention/processing speed) also yielded small effects in the expected direction for each respective domain. The current evidence does not allow for directly observing the mechanisms associated with these relationships. However, this is an important first step for future examinations that may allow a stronger understanding of the distinct domains and neural correlates underlying the observed associations. In addition, a marked limitation is that there were not enough studies available to examine social cognition. Given strong evidence that social cognition is critical for predicting functional outcomes in psychosis,[80] and that it may be impacted by childhood trauma,[38] this is an important future direction for the field going forward.

Although the literature has not often focused on specific cognitive domains, an emphasis on isolating the effects of distinct sorts of trauma has also been sorely lacking. Neural and theoretical models of early life stress and adversity suggest that different types of exposure may negatively impact some of the same biological systems.[81] Nonetheless, studying whether particular types of trauma are more impactful than others is a promising direction for research in this domain. Future investigations undertaking this aim should carefully consider the large possibility of overlap in exposure to multiple types of trauma (ie, exposure to a specific trauma may increase the likelihood that an individual will be exposed to multiple types of trauma simultaneously). Carefully mapping out various forms of trauma, timing of trauma, and severity of exposure to trauma in samples powered for modeling effects of covariation and interaction would be beneficial. This could aid in elucidating who is at greatest risk for experiencing negative outcomes due to trauma exposure. In this study, due to the limited data available, this was not possible. However, these questions will be critical to address as the literature develops further.

A better understanding of neurocognitive domain specificity may uniquely inform models of underlying mechanisms. However, the use of correlational data precluded examining causal relationships, which limited our ability to make causal inferences. Despite numerous animal models and human studies suggesting there are serious and lasting effects of stress and trauma on neurodevelopment,[9,82–86] this meta-analysis was limited to cross-sectional studies and therefore cannot fully address this question. In fact, a recent prospective study on healthy populations found that cognitive deficits in victimized individuals were largely explained by childhood socioeconomic disadvantage and cognitive deficits predating childhood victimization.[87] This study underscores the necessity of considering an aggregate of environmental and genetic risks when framing theoretical models of environmental effects on neurodevelopment across the life span. The present review focused on childhood trauma; however, it will be essential for future studies to create more sophisticated models of cumulative risk exposure spanning across different types of environmental risk. Incorporating risk exposure throughout the lifetime, including peri- and prenatal periods, may also yield important clues.

Furthermore, it will be important for future research to incorporate multiple types of childhood adversity beyond trauma, as well as different increments of severity. There is some promising emerging evidence that less severe exposure to childhood adversity may be associated with cognitive deficits in psychosis.[88] Exploring several types of childhood adversity will further aid the field in understanding the mechanistically distinct effects of trauma and other environmental risk exposures (such as bullying, household instability, low socioeconomic status, and exposure to environments with high crime rates). Incorporating multiple types of adversity at the individual (eg, bullying) and structural (eg, exposure to poverty or low socioeconomic status) level will also be useful in

gaining a more holistic understanding of how cumulative risk exposure affects global functioning in an individual and how it contributes to developing psychopathology.

This study benefitted from the wide range of pooled subjects, which constitutes a highly geographically diverse sample with low heterogeneity and absent evidence of bias. Nonetheless, there are multiple concerns that limit the generalizability of the results. Although all but two of the included studies used standardized, validated, childhood trauma batteries, there was some variability in which scales were used, and in some cases, which types of trauma were reported (see table 2). This may have introduced unexplained variance into the measurement of childhood trauma. There was also considerable variability in choice of cognitive battery used and although this study tried to introduce more homogeneity by compiling batteries into traditional cognitive subdomains, ideally there would be less heterogeneity with regard to cognitive measures used. This is especially true in the case of estimates of overall cognitive ability (see table 1 for descriptive information on cognitive measures). However, measured estimates of heterogeneity between studies were low for all major analyses. Nonetheless, it will be important for future studies to reduce the heterogeneity in cognitive batteries used once more published data becomes available. It is also critical to note that although a larger effect size was observed for working memory, the studies included in this analysis had smaller sample sizes on average than those included in the overall cognitive domain estimate. This difference in average sample size may have affected the observed effect size. However, sample size did not have a moderating effect in any analyses. The extent of the effects of these limitations will become evident as more studies examining these questions become available.

Future investigations would also benefit from preregistering studies in order to reduce the possibility of unconscious reporting and analytical biases. Illness duration and neuroleptic dosage should also be more fully considered as mediators of the strength of the observed association between childhood trauma and neurocognitive function. Despite neurodevelopmental models informing us that the timing of exposure to trauma is critically important,[9] the current study was not able to explore or control for these questions, and this is an essential future direction. Finally, it is important to note the methodological limitations of retrospective life event inventories. As we gain a greater understanding of the ways in which early life trauma interacts with biology and development, the need to develop reliable and valid measures of early life event exposure will increase further.[89]

Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin* online.

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