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An investigation in the relationship between Childhood Adversity and Cognitive Function in Psychosis and Individuals at Clinical High Risk of Psychosis

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Doctorate In Clinical Psychology

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Declaration

Data has been used form the existing YOUR study with full approval from PIs.

I am aware of and understand the university's policy on plagiarism and I certify that this thesis is my own work, except where indicated by referencing. The work submitted here has not been submitted in support of another degree or qualification from this or any other institute of learning.

I declare that this thesis I an original report of my research and has been written by me.

I declare that this thesis was composed by myself and that the work contained herein is my own except where explicitly stated otherwise in text

Signature ……. Date:

Acknowledgements

I would like to thank, in particular, both the participants of the Youth Mental Health and Resilience Study (YOUR) study, for participating in this study. I would also like to thank the principal investigators of the YOUR study for allowing me to contribute to this study and to utilize the database for my clinical doctorate thesis.

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Table of contents

Contents Page

Tables and figures

Tables chapter 1

Figures chapter 1

Appendixes

Thesis Portfolio Abstract

Background

An increasing body of research is suggesting that childhood trauma and adversity may be associated with various adverse mental health outcomes, including psychosis. Cognitive functioning is often compromised in psychosis, and research has shown that there may be a link between early trauma and cognitive impairment

in people with psychosis. No systematic review of the literature of this link has been undertaken, and very few studies have examined samples of individuals at high clinical risk for psychosis, to assess whether the potential link between adversity and cognitive functioning exists, without the confounding factors of length of illness, antipsychotic medication and chronicity of symptoms.

Method

The systematic review of all relevant electronic databases investigates the research to date on the association between childhood adverse experiences and cognitive ability in psychosis, and the conclusions that can be drawn from the existing literature, taking into account relevant considerations regarding sample, methodology and statistical analysis. The subsequent empirical study utilizes a sample at clinical high risk of developing psychosis, and a healthy control group to investigate whether any putative association in specific domains of cognitive functioning, or global cognitive ability and childhood adversity exist in those at clinical high risk, compared to controls.

Results

The systematic review indicated that at present, the literature looking into childhood adversity and cognitive ability in relation to psychosis is heterogeneous, with some studies finding that this association only occurs in patients, whilst others suggest it only occurs in the control groups. Some studies found it to be specific to certain cognitive domains, whilst others suggest it was a more global impairment. Methodology, samples and analysis differed considerably across studies, and likely contribute to the heterogeneity of the literature. The empirical paper showed a significant interaction effect between group (high risk versus controls) in the high childhood adversity group, in relation to global cognitive ability. Interestingly, this was not related to psychotic symptom severity or distress.

Conclusion

Several limitations of the existing studies limit the conclusions that can be drawn from the existing evidence regarding the link between childhood adversity and cognitive ability, and future research in prodromal samples is essential. The empirical study showed that there is a link between childhood adversity and cognitive ability in those at clinical high risk of developing psychosis, before disorder onset, that is not present in controls. This suggests that this may form a vulnerability in those at high risk for psychosis, rather than a more general mechanism present in the typical population.

Thesis Lay Summary

Background: Researchers have found that early traumatic experiences and stress may increase somebody's risk of developing psychosis. However, the mechanisms underlying this association are still unclear. Some investigators have suggested that early trauma may impact normal brain development negatively by affecting systems involved in generating our stress response, and psychological mechanisms involved in generating psychotic symptoms. It is unclear at present to what extent early

adversity and brain development interact in this way, and whether people that are at high risk of developing psychosis may also show these signs of altered brain development, or whether it only occurs in people that have had established psychosis for a long time.

Method: This portfolio has involved reviewing the existing literature using systematic review techniques to comprehensively assess the link between childhood adversity and mental abilities, such as memory and global estimates of mental ability, in relation to psychosis. These techniques involved searching 8 different databases and critically assessing them using narrative synthesis techniques. We then also looked at this link in people at high clinical risk of developing psychosis, in order to see if this link between trauma and cognitive ability was present in people at high risk of developing psychosis, but before disorder onset. This would reduce the risk of thepresence of confounding factors such as length of illness.

Results: We found that across the existing literature, there were so many different samples, methods, and statistics used that it is difficult to interpret any of the literature with real clarity. We found that people at clinical high risk may be particularly sensitive to the effects of high levels of trauma compared to healthy controls.

Conclusions: The systematic review found that more research into the link between childhood adversity and brain development is required, taking into account other relevant factors, such as duration of illness and medication. The experimental study reported here demonstrates that there may be some changes in global mental ability in people at high risk of developing psychosis due to elevated clinical symptoms that does not occur in those people that do not have these difficulties. Therefore there may be changes to brain development and psychological mechanisms in those at high risk in relation to early adversity.

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Investigating childhood trauma/adverse experiences and cognitive ability in psychosis: A systematic review of the literature

(Written in accordance with author guidelines for: Schizophrenia Bulletin (Appendix A)

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Systematic Review Abstract:

Background

An increasing body of research is suggesting that childhood trauma may be associated with psychosis. Cognitive functioning is often compromised in psychosis,

and research has shown that a link between early childhood trauma and cognitive functioning in people with psychosis may exist.

Method

The aim of this study is to provide a narrative systematic review of the research literature on all articles published in English that investigated the association between cognitive function and childhood trauma or adverse childhood experiences in individuals with psychosis. In total, eight databases were searched. Additional articles were identified following examination of reference lists from primary search results to ensure that all pertinent studies were included. Categories of search terms covering psychosis, childhood trauma/adversity and cognitive ability within databases was implemented where possible to ensure a comprehensive search of the available literature.

Results

Electronic database searches yielded 1051 results with 814 remaining following the exclusion of duplicates and a total of 18 meeting our criteria were included for the study. Some studies identified associations between cognitive ability and trauma, however studies varied in the cognitive domains in which associations between cognitive ability and trauma were found, and whether these occurred only in the patient groups, or also/only in the control groups.

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Conclusions

The review highlights the need for larger studies with individuals presenting with first episode psychosis or high-risk samples, and the need for more homogenous conceptualisations of childhood trauma/adversity and cognitive ability to be used across studies in order to provide more robust interpretability and generalisability. Reviewed papers highlighted the heterogeneity of participants and differing methodology, which limit the generalizability of findings.

1. Introduction

1.1 Introduction

An accumulating body of evidence is converging to suggest that an association exists between childhood trauma (CT) and psychotic disorders, such as schizophrenia.[1-4] Rates of self-reported CT are higher in individuals with psychotic disorders[5,6] compared to the typical population[7,8] and a recent meta-analysis concluded that even the broader definition encompassing adverse childhood experiences (ACEs), such as bullying by peers, parental separation and witnessing domestic abuse, strongly contribute to the risk of psychosis in adulthood, with a

cumulative dose/response relationship between number of events experienced and the likelihood of psychotic symptoms.[9]

Evidence also suggests that psychosis, and in particular schizophrenia, are related to severe cognitive impairments compared to healthy controls[10,11] , spanning several different cognitive domains, such as executive, working memory, sustained attention, episodic and verbal memory, as well as global impairments in cognition[12-16]. These have been associated with level of disability[17] occupational impairments, functional outcome[17-21] and severity of positive symptoms [22-25]. It has been suggested that CT/ACE may be associated with these impairments, by having adverse effects on the neural systems that are critical to responding to stress, such as the hypothalamic-pituitary-adrenal (HPA) and noradrenergic systems[26-29]. This may then contribute to the structural and functional brain changes that have been implicated in the pathophysiology of psychosis, such as reduced hippocampal volumes and cortical thinning[30-35].

Furthermore, psychological models of psychosis suggest that early ACEs contribute to the emergence of symptoms by triggering a change in arousal mechanisms, such as heightened anxiety, which, in the context of vulnerability to psychosis, may create a cognitive confusion causing an anomalous experience, such as thoughts being experienced as voices. These subtle cognitive changes may then trigger the cognitive abnormalities associated with psychosis, as well as be linked to specific psychotic symptoms. This model proposits that specific psychotic symptoms, such as persecutory delusions, may arise from a search for meaning that reflects an interaction between psychotic processes, pre-existing beliefs and the adverse environment[36-37]

Although the evidence suggests ACEs and the putatively affected processes may underpin the cognitive deficits in psychosis[38], to date, there is inconsistency to what extent cognitive impairments are associated with early adversity, and if so which cognitive domains are most affected, or whether the deficits present on a more global cognitive scale. Some studies also show that early adversity may have a detrimental effect on cognitive ability in the typical population too, in the absence of mental health issues, and thus it remains unclear whether CT lies on the aetiological pathway to psychosis by impacting on cognitive ability, or whether it is a more general mechanism present in the typical population as well[39-40]. Understanding the way in which adversity associates with cognitive function may have crucial implications for the way in which therapy is delivered for individuals with psychosis. Currently cognitive behavioural therapy for psychosis is recommended as a treatment option, which should be made available to everyone with a diagnosis of schizophrenia in England and Wales and Scotland [41-43.] However, if adversity affects cognitive ability, this may warrant a trauma-focused psychological treatment, which in itself may need to be revised or adapted in the context of impaired cognitive ability. Additionally, as early intervention in psychosis is associated with improved prognosis[44], understanding the way in which CT/adversity and cognitive ability is associated in psychosis, compared to the typical population may also provide a target for early intervention strategies.

Some of the inconsistencies may stem from cross-study variability in the quality of cognitive testing, differences in trauma measures, sample sizes, definition of patients and inclusion of controls. To our knowledge, no systematic review of this literature exists. Hence, the aim of this systematic review is to synthesize and assess the current evidence base that has investigated CT and how it associates with cognitive function in relation to psychosis, and to identify gaps and areas for further research. The terms CT and ACE will be used interchangeably across this systematic review, unless otherwise stated, as they are often used interchangeably across the literature. As a secondary aim, we wish to assess whether the evidence suggests

that this association is greater in individuals with psychosis, when compared to the typical population.

1.2 Methodology:

1.2.1 Search Strategy and Inclusion Criteria

An inclusive search strategy spanning all relevant databases was implemented (Appendix B). Subsequently, papers were included in the review if they met the following criteria

- They were peer reviewed original empirical work (ie not book chapters, conference abstracts, reviews) published in English
- A measure of cognitive ability using a known, standardized test was employed
- Paper must have examined the association between trauma and cognitive ability in their sample
- A sample of individuals presenting with psychosis were included
- Studies measuring CT/ACEs, defined as: (1) must have occurred before age 18 or be described as in “childhood” or “adolescence” (2) must be differentiated from adulthood trauma

A subsample of papers were at this stage also screened by an independent rater to minimize bias in selection of reviewed studies. Categories covering psychosis and cognitive ability within databases was implemented where possible to ensure a comprehensive search of the available literature, and identified using the following search terms “cognitive ability*” or cognition or neuropsychol* or “neuro* assessment*” or “cognitive assess*” AND (pathway* or associat* or or “mechanism*” mediat* or variable* or relation* or "risk *", “predictor”) AND “child abus*” “child traum*” “physical abus*” “sexual abus*” “rape*” “psychological

abus*" "emotional abus*" "neglect*" "maltreat*" "bully" "bullied" "victim*" "sexual trauma*" "psychological traum*" "physical assault*" "sexual assault*" "molest*" AND (psychos* or schiz* or hallucinat* or paranoi* or voice* or delusion* or prodrom* OR high risk)."psychological distress"

Databases searched were Pubmed/Medline, PsychArticles full text, EMBASE, EMBASE classic, Global Health, Epub ahead of print and other non-indexed citations. Web of Science and Proquest were also searched to see if any further articles emerged, however they did not. Additional articles were identified following examination of reference lists from primary search results to ensure, as much as possible, that all pertinent studies were included.

1.2.2 Data Extraction

Where available, the following data were extracted from each included article: authors, year of publication, sample characteristics (sample type/source, sample size, age, sex, recruitment source, country), cognitive variables, and trauma measure used, inclusion and exclusion criteria of participants and findings pertaining to the relationship between cognitive ability and CT.

1.2.3 Quality Assessment

As most published quality criteria checklists relate to randomised controlled trials and intervention studies, which this systematic review does not contain, new quality criteria were developed and adapted from existing sources. Fourteen quality criteria were developed (Appendix C) after consultation with colleagues: COSMIN checklist, CONSORT checklist, SIGN methodology checklists, CASP critical appraisal checklists and PRISMA statement[45-49]. These fourteen quality criteria guided the subsequent quality appraisal. A random sample of studies was reviewed by one other reviewer to increase the validity of the ratings. All disagreements were resolved by discussion between the tworeviewers. The independent reviewer, a

third-year Trainee Clinical Psychologist, applied the quality assessment to six papers, as a check of reliability. Cohen's κ suggested substantial agreement in ratings, κ=.88, p<.001. All initial disagreements were discussed and resolved collaboratively. There were no noticeable areas that disagreements were more prevalent.

1.3. Results

1.3.1 Papers included for Review

The process of identifying studies for inclusion is presented graphically in Figure 1.

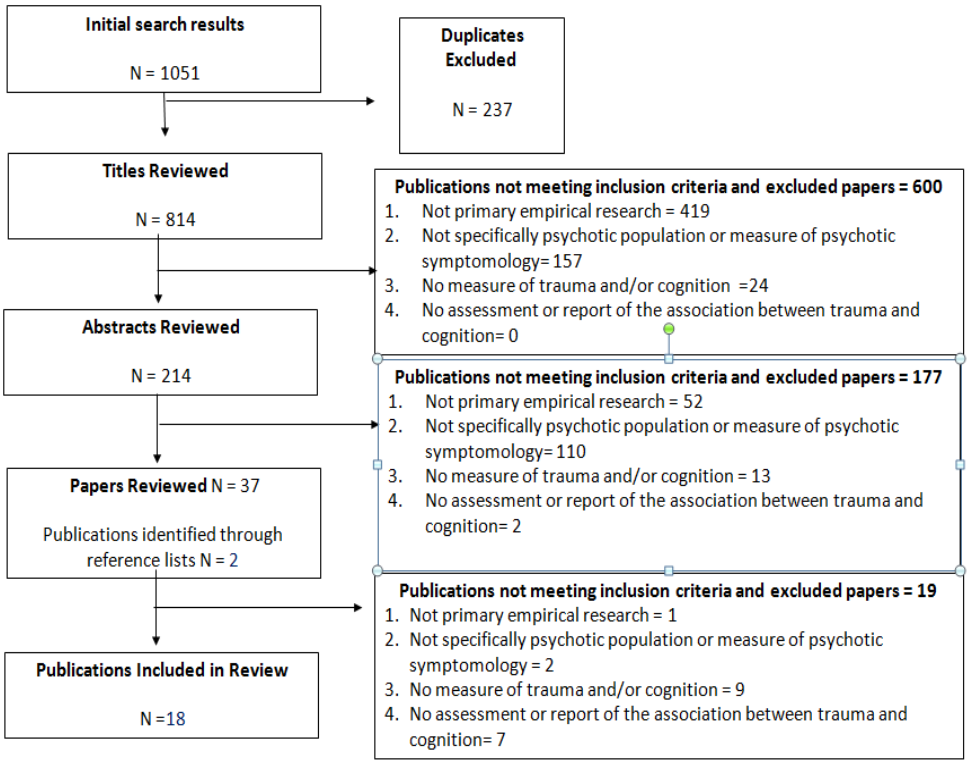

Figure 1. Search results and selection procedure illustrated in a PRISMA flowchart[47]

Electronic database searches yielded 1051 results with 814 remaining following the exclusion of duplicates. The first screening wave consisted of reviewing titles only,

and this resulted in the exclusion of 419 titles. The second wave involved reviewing abstracts too, and this excluded a further 177 references. At this point 43 papers were reviewed in more depth, and at this stage 22 further studies were excluded as they did not meet the criteria of either being primary research, no measure of psychotic symptomology, no measure of trauma and/or cognition. A further 2 studies were found by hand searching the reference lists at this stage. A Total of 18 included for the study.

1.3.2 Critical appraisal of study quality

In general, most studies found that there were associations between CT and cognitive ability, in that higher levels of abuse was associated with lower levels of cognitive functioning. However, the quality of the reviewed papers was in general confounded by poor generalizability and inadequate statistical sampling. All studies clearly set out their objectives for their investigations; namely, to investigate the link between CT/ACE and cognitive ability. However, some studies provided only partial rationale regarding why they focused on specific types of CT such as sexual abuse, or why they focused their investigation on the cognitive domains that they did[50-54]. This creates potential for bias in the literature by an inadequate sampling of all types of CT/ACE and cognitive ability. For a summary of extracted demographic variables, please see Appendix E. For the quality ratings of each reviewed paper please see Appendix F.

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1.3.4 Methodology of reviewed papers

1.3.4.1 Sample size and inclusion/exclusion criteria considerations

The reviewed studies vary considerably in their sampling methods, setting, age range, gender, and to what extent they adequately capture a representative sample

of the target population. Sample sizes ranged from as small as forty with no control group[54], to over 1000 with an inclusion of an adequate control group[55]. Only one study used a prospective power analysis to establish an appropriate sample size[56]. Interestingly, the one other study[54] that conducted a posteriori power concluded that their sample size of 134 patients, and 124 controls was inadequate to detect previously found associations between CT and cognitive domains tested. This has implications for the studies that were reviewed that included smaller samples than this[50-52, 57-59], and sheds doubt on the extent to which the reviewed papers utilize sample sizes large enough to capture the association between CT and cognitive ability, in particular if not reporting effect sizes for any resulting associations.

Variation also existed in the specifics of the inclusion and exclusion criteria for the targeted populations for each study (For a detailed summary of these in relation to each study, please see appendix E). This creates difficulty in replication, as well as limiting generalisability across studies. For example, one study[60] cited unstable medical conditions as an exclusion criterion, providing no further information regarding what these conditions were. Three studies failed to mention any exclusion criteria[49, 50,52]. Most studies also varied in the cut-off criteria for full scale IQ, meaning that some studies did not exclude based on intellectual disability or provided different values for their cut-off for included individual studies, which limits cross-study generalisability as well as obscuring interpretability of any putative associations between cognitive ability and CT/ACE in these studies.

1.3.4.2 Recruitment setting considerations

Recruitment settings ranged across studies, including inpatient, outpatient, community centre and local support groups. Some of the reviewed studies recruited patients from only one setting[50,51, 61 , 54] whilst others had a mix of inpatient and outpatient settings[,52,55,60,61-63,58,]. Including both inpatient and outpatient samples is a strength in the sense that it targets a broader population, however also creates a potential for differences in severity of illnesses, which no study adequately controls

for. No study transparently reported how many individuals that were invited actually took part in their study. Some studies mentioned drop-out rates, but failed to explain why these individuals dropped out[60]. Only one study[53] disclosed that they provided control for individuals with a tendency to give socially desirable responses, or individuals likely to produce false-negative reports, by examining items from a minimization/denial scale. Another issue limiting the representativeness of the populations across studies is that the average percentage of females across the studies ranged from 0%[50] to 64% [60].

1.3.5 Summary of findings of reviewed papers

Only two studies[51,52] reported effect sizes, with the largest being a Cohens d of 1.85[52], which is considered a large effect size. However, this was for a group comparison between patients that were abused, versus all controls (regardless of abuse), in overall cognitive ability. It is unclear why the authors report this effect size, as opposed to one that more adequately would assess those controls that were abused, versus the patients that were abused. Only one other study[51] reported effect sizes, comparing a "trauma positive" and "trauma negative" group in different cognitive domains, but quoting small effect sizes.

Findings differed across the studies. Some of the studies found that CT was associated with impaired performance in specific cognitive abilities, such as memory, working memory, attention, and language, premorbid IQ, and used only patient samples[50,51,54]. One study used both patients and controls, however only included in their CT and cognitive ability associations a subsample of 45 patients[57]. Two studies that only utilized patients found no association between measures of CT and cognitive ability[52,53] . Two studies[58,65] included both patients and controls, and found no significant associations between cognitive ability and CT in any of the tested cognitive domains. Two studies found effects in controls but not patients in full-scale IQ [55,64]. Two studies[56, 66] found impaired performance in cognitive ability in relation to higher CT in several domains such as, verbal intelligence, language, attention, and concentration. Other studies found effects in several cognitive

domains for both patients and controls[52,61,63]. The one study[59] that utilized a high risk sample but not a control group, found that the CTQ physical trauma subscale negatively associated with tests of attention and executive function. A detailed summary of the main findings of each study along with relevant considerations pertaining to their statistical analysis that will be discussed in subsequent sections, are presented in Table 1.

Table 1. Table of Key findings and values on association between Childhood trauma and Cognitive Ability, and relevant sample/measure/statistical considerations. Relevant methodology has been extracted from the reviewed papers and is included in the table below. P = patients, HC = healthy controls

Authors	Sample	Childhood Measure Utilized and analysis method of CTQ measure	Key findings and values on association between Childhood trauma and Cognitive Ability	Statistical Considerations
Methods extracted from: Li et al. 2017[60]	**P=162**	CTQ, 28 item[1] Total score of CT. Dichotomized physical abuse, sexual abuse, emotional abuse, physical abuse and emotional neglect based on cut-off scores for low to moderate/severe	**<u>Correlation analysis</u>** Physical and sexual abuse significantly negatively correlated with language score ($r = -0.190, -0.216$, respectively, $p < 0.05$). Physical neglect and total score of CTQ negatively correlated with the attention score ($r = -0.17, -0.206$, $p < 0.05$, respectively) as well as the total RBANS score ($r = -0.199, -0.223$, respectively $P < 0.05$). PN negatively correlated with delayed memory ($r = -0.167$, p b 0.05). **<u>Regression analysis</u>** PN and attention, and the cognitive total score, Multiple regression: odds ration = 91.047, confidence interval, 75.037 ~ 107.063 , $p < 0.001$	No control for any factors on the correlation analysis. No control for multiple comparisons For the multiple regression: sex, living environment (rural/urban), antipsychotics (typical/atypical)
Methods extracted from: Kelly et al. 2016[53]	P = 100	CTQ, 28 Item[1]. Only utilized physical abuse using cut-off criteria for low to moderate/high	RBANS total score and found no significant differences in either men or women, or a physical abuse by sex interaction in RBANS total score.	Age, race, and level of education No mention of control for multiple comparisons

Authors	**Sample**	**Childhood Measure Utilized and analysis method of CTQ measure**	**Key findings and values on association between Childhood trauma and Cognitive Ability**	**Statistical Considerations**
Methods extracted from: Green et al. 2014[62]	**P =** 617 Only conducted in the patient group.	Childhood adversity questionnaire[2] total childhood adversity scores entered into analyses as continuous variable as well as separate categories for physical abuse, emotional neglect, emotional abuse, as continuous variables	No association total childhood cognitive measure.	No control for confounding factors in main analysis
Methods extracted from: Van Os Et al. 2017[55]	Patients with non-affective psychosis = 1119 Siblings of patients N = 1059 HC = 586	CTQ, 25 Item[3] general abuse factor from sums of all categories, as well as emotional and physical neglect, and as total CT score CT analysed as a continuous variable and a dichotomous variable	CT in controls associated with significant reduction in IQ (-4.85, 95% confidence interval 95%CI: 7.98 to -1.73 p = .002), lesser reduction in siblings, (-2.58, 95% CI = -4.69 to -0.46, p = 0.017, no significant reduction in patients (0.84, 95% CI = -2.78 to 1.10, p = .398.	Age, sex, ethnic group educational level, CAPE total score, cannabis use.

Methods extracted from: Garcia et al. 2016 [65]	79 individuals with early psychosis (P) HC = 59	CTQ, 28 item[1]. Conducted analyses separately for emotional, sexual, physical abuse and emotional and physical neglect, as well as using total CTQ score, no cut off. continuous	No significant differences found in any of the tested cognitive domains *(p ns*)	Adjusted for age, gender and education status No control for multiple comparisons in the correlations analysis Multiple linear regression analyses were adjusted for false discovery rate
Authors	**Sample**	**Childhood Measure Utilized and analysis method of CTQ measure**	**Key findings and values on association between Childhood trauma and Cognitive Ability**	**Statistical Considerations**
Methods extracted from: Aas & steen et al. 2012[67]	239 schizophrenia spectrum disorder 167 bipolar patients	CTQ 28 item[1] data dichotomized into two groups (low or high trauma) subscale for physical, sexual, emotional abuse and emotional and physical neglect.	When general cognition as measured by the WASI was added to the model, CAE and specific cognitive domains no longer reached the level of statistical significance **<u>General IQ score</u>** Coefficient 0.09, se = 0.01, t = 11.02, *p* 0.001*	Analysis controlled for performance and verbal tasks from WASI, age and gender Controlled for multiple comparisons
Methods extracted from: Aas and navari et al. 2012[57]	83 FEP, 63 HC	Childhood experience of care and abuse questionnaire[4] Defined as exposure to one or more of the following: severe physical abuse, severe sexual abuse, parental loss or separation and total score dichotomized into severe and non-severe categories	Childhood trauma was also significantly negatively correlated with performance on the following domains: executive function and working memory (p=0.02; r=−0.3); attention and concentration (p=0.01; r=−0.3); language (p=0.04; r=−0.3); verbal intelligence (p=0.02; r=−0.3).	age, sex, ethnicity, education Regression analysis Only 45 sub sample conducted the trauma measure though

Methods extracted from: Aas & Dazzan et al. 2011[66]	138 FEP, 138 HC	Childhood Experiences of Care Abuse Questionnaire[4] Defined as exposure to one or more of the following: severe physical abuse, severe sexual abuse, parental loss or separation Dichotomized into severe and non-severe categories	Trauma associated with a significant decrease in verbal intelligence domain(P=0.035), the language domain (P=0.044), and the attention, concentration and mental speed domain (P=0.047) No differences in pre-morbid IQ in the patients with and without trauma No effects of trauma were found in the controls.	Ethnicity and education
Authors	**Sample**	**Childhood Measure Utilized and analysis method of CTQ measure**	**Key findings and values on association between Childhood trauma and Cognitive Ability**	**Statistical Considerations**
Methods extracted from: Sideli et al. 2014[56]	**P =** 134 **HC** =124	Childhood physical and sexual abuse with the Childhood Experience of Care and Abuse Questionnaire[4] Analyses limited to physical abuse resulting in injuries and to penetrative sexual abuse. Dichotomized as present or not	No patient differences in general intellectual ability or cognitive function. abused controls performed worse than non-abused controls in the executive function t(1,122) 2.60, p = 0.019 and working memory domain, t (1,122) = 3.06, p = 0.003)	Gender, age, ethnicity, and education level No control for medication Bonferroni correction for multiple testing
Methods extracted from: Green et al. 2015[63]	P = 617 HC = 659	The Childhood Adversity Questionnaire[2] The CAQ comprises 20 items (scored as yes or no) that assess experiences of physical abuse, emotional abuse, sexual abuse, emotional abuse, emotional neglect, and family dysfunction. Only items pertaining to deliberate maltreatment	Patients Rbans total B = 10.35, confidence interval (2.74-74,96, t = 2.68, p = 0.01 Rbans attention B = 19,35, confidence interval = 2l65 – 21.27) RBANs language = beta (8.81, confidence interval = 1.98,	No control for confounding factors No control for multiple comparisons Regressions conducted for patient and control groups separately.

		(not adverse living circumstances) were used	15.65, t = 2.53, p 0 .01) Controls RBANS attention Beta = 11.56(2.61-20.52), t = 2.55, p = .01 WTAR beta 6.55 (0.45-12.65, t = 2.12 (0.04) LNS beta 2.23(0.31-4.14), t = 2.29(0.02)	
Authors	**Sample**	**Childhood Measure Utilized and analysis method of CTQ measure**	**Key findings and values on association between Childhood trauma and Cognitive Ability**	**Statistical Considerations**
Methods extracted from: Shannon et al. 2011[50]	P = 85,	CTQ, 28 item version[1] Participants separated into (child trauma positive and child trauma negative)	WMS-III logical memory Immediate recall , F = 2.83, p = 0.044, n2 = .099 Delayed recall = f = 2.85, P = 0.043, PARITAL ETA SQUARED = 0.1 WMS-III WORD LISTS Recognition F = 3.29, P = 0.025, partial eta squared= 0.114 WMS-III letter-number sequencing Total score F = 6, p = 0.001, partial eta squared = 0.189	Covarying for depression levels and estimates of premorbid IQ No control for multiple comparisons

Methods extracted from: Kilian et al. 2017[58]	FEP or schizophreniform disorder (n = 56) HC = 52	CTQ, 25 Item[3] CTQ scores grouped into an abuse score (sexual abuse + physical abuse + emotional abuse score) and a neglect score (physical neglect + emotional neglect score)	No type childhood abuse associated with cognitive impairments on any of the MCCB domains, p ns	Educational level and depression patient group. No control for multiple comparisons
Methods extracted from: Mccabe et al. 2012[64]	P = 408 HC = 267	modified version of the childhood adversity questionnaire[2] five or more childhood adversities, compared to zero, Factor analysis of the 19 CAQ items identified 5 factors with Eigen values >1 (see Table 2); Abusive Parenting (Factor 1); Loss, Poverty and Sexual Abuse (Factor 2); Neglectful Parenting (Factor 3); Dysfunctional Parenting (Factor 4) and Sibling Loss (Factor 5).	**<u>Effects in controls only, not patients</u>** Exerience of 5 or more childhood adversities (compared to 9 associated with significant decrease in both WTAR verbal Mmean – 106,4, SD = 10.2 vs 114, SD = 9.4, Tukey = -7.00 (SE = 1.89), p = 0.001) and WASI (mean = 112.0, SD = 12.7 vs 199.8, SD = 9.2; Tukey = -7.76 (SE = 2.52), p = 0.012) IQ scores.	age, gender and education No control for multiple comparisons
Authors	**Sample**	**Childhood Measure Utilized and analysis method of CTQ measure**	**Key findings and values on association between Childhood trauma and Cognitive Ability**	**Statistical Considerations**
Methods extracted from: Schalinski et al. 2018[52]	168 individuals with schizophrenia spectrum disorder, n = 50 non-psychotic individuals with similar age and education BUT ONLY USED A SUB SAMPLE OF 62 FOR THE ACTUAL THING??	MACE scale developed to capture 10 forms of ACE between infancy and age 18. For each of the 75 items (assigned to 10 subscales) experience was coded as yes-no. For each subscale, positively endorsed items were linearly interpolated to obtain severity scores that range from 0 to 10. Overall severity of ACE was calculated using the . Sum of all 10 subscale-severities (ranging from 0 to 100)	BminMSE= beta estimates based on the optimal lambda to find the minimum mean squared error in LASSO-penalized regression analysis. **Overall score** Abuse sum age 3 BminMSE −0.90 SD 2.53 (0.16) p = 0.0016 patient abuse versus no abuse d = 0.65 patient no abuse versus d = 1.20 patients abuse versus controls d = 1.85 **Attention** Abuse sum age 3 BminMSE= −0.77 ,SD 2.25 (0.26) p =	Years of education, and two binary variables (first/repeated admission and gender

	50 non psychotic HC from general population		0.00006 patient abuse versus no abuse d = 0.24 patient no abuse versus controls d = 0.73 patients abuse versus controls d = 0.95 **Working memory** Abuse sum age 3 BminMSE −0.04 SD = 1.31 (0.09) p = 0.0102 patient abuse versus no d = 0.57 patient no abuse versus controls d = 0.63 patients abuse versus controls d = 1.19 **Verbal learning** BminMSE = −0.50 SD = 1.61 (0.13) p = 0.0036 patient abuse versus no d = 0.67 patient no abuse versus controls d = 0.43c patients abuse versus controls d = 1.10 **Visual Learning** Abuse sum age 3 BminMSE −0.65 SD 1.77 (0.17) p = 0.006 patient abuse versus no d = 0.51 patient no abuse versus patients abuse versus controls d = 0.58 d = 1.10	
Authors	**Sample**	**Childhood Measure Utilized and analysis method of CTQ measure**	**Key findings and values on association between Childhood trauma and Cognitive Ability**	**Statistical Considerations**
Methods extracted from: Ucok et al. 2016[59]	53 UHR	CTQ, 25 item [3] This study dichotomized the sample by using cut-off scores for the presence of emotional, physical and sexual trauma and physical and emotional neglect.	CTQ-physical trauma subscale negatively associated with WCST completed categories (rho = −0.465, p = 0.002), Stroop-word reading time (rho = 0.42, p = 0.003), Stroop-color reading time (rho = 0.44, p = 0.002), CTQ-physical neglect subscale scores were correlated with the Digit Span Forward test scores (rho = −0.41, p = 0.004) P ns: emotional/sexual trauma in terms of cognitive performance, childhood emotional neglect.	Ultra high risk sample. No control for any confounding factors Bonferroni corrected for multiple comparisons
Methods extracted	P = 89 , healthy non-	CTQ, 25 item[3]	CT negatively associated with BD performance (B - 120, x = -2.29, CI 95% 223.47 to -17.47, *p* = 0.02)	Controlled for substance use and cumulative

from: Hernaus et al. 2014[61]	psychotic siblings = 95	Calculating the mean of the 25 items resulted in a general measure of CT.	CT not associated with AVLT performance *(p ns)* No significant CT by group interaction in delayed AVLT/BD performance (*P ns*)	antipsychotic medication Multiple comparisons controlled for
Methods extracted from: Schenkel et al. 2005[54]	P = 40	Structured social history interview of childhood abuse/neglect Patients with history of PA, SA, and neglect. Groups divided based on types of abuse they experienced (i.e., zero, one type, two or more).	Tests for a linear trend across groups indicated significant effects for both the premorbid (F(1,39)=6.73, p b.05) and clinical cognitive (F(1,39)=22.28, p b.001) factor scores (both tests using unweighted estimates clinical factor that represented greater symptomatology and more impaired cognitive functioning	MANOVA, no control for confounding factors.
Methods extracted from: Lysaker et al. 2001[50]	43 patients with schizophrenia or schizoaffective disorder	Sexual abuse based on unnamed questionnaire derived from Levitan et al. (1998)[5]	MANCOVA comparing neurocognitive test scores, using age and vocabulary as covariates, indicated significant group differences (f(9, 31) = 5.53, p < .001). Patients with SA abuse had impaired processing speed, working memory, and executive function compared to patients (f(9, 31) = 5.53, p < .001). reporting no abuse.	Age and premorbid IQ

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1.3.5.1 Factors influencing the quality of the conceptualisation of CT/CA across the reviewed studies

Different measures, as well as conceptualisations of CT/ACE occurred across the reviewed studies. Several studies failed to mention the reliability and validity of the measures they used [16,65-68, 49,50,51-53] . None of the studies mentioned how, or if, they attempted to contain the potentially distressing nature of the content listed in most of the CT measurements. Some studies covered reliability and validity well by covering whether the psychometric properties such as reliability and validity had also been considered for patients with psychosis[58, 59,54].

Only one study[52] looked at timing, as well as quantifying severity of the trauma. Two papers[62,63] utilized the Childhood adversity questionnaire[68] which assesses sexual trauma from the parent only, which means sexual trauma from other perpetrators may have been under reported. Many of the studies included for the review were conducted in different countries, and although some studies mention whether the CT measure is normed to their country/population[56,60] some do not[57, 66,67] and thus the potential for cross-cultural differences, such as differences in social desirability items, and full disclosure, remains a potentially confounding factor across all of the studies. It is crucial to note that all measures of the reviewed studies are retrospective in nature, and retrospective recall may critically depend on a person's cognitive ability, substance misuse, as well as diminish in accuracy when clouded by psychotic experiences and their severity, as well as affective symptoms of patients.

As is clear from Table 1, there is clear cross study variability in how the same measure of CT is subsequently used for the statistical analysis, as studies varied in what item score was considered having mild/moderate/severe exposure to CT, or whether they were included in the analysis as a continuous variable or based on median split. Studies also varied in which types of abuse and/or neglect were analysed, or whether a total sum of abuse/neglect was included. For example, two studies[62,63], that used the same sample of controls and patients and questionnaire,

used different methods of defining levels of trauma, resulting in the control group being excluded in one of their papers due to low levels of trauma, whilst the other study includes them by approaching trauma differently. This exemplifies how the inconsistency of the conceptualisation of CT across the reviewed studies creates a lack of combinability that has profound implications for the quality and accuracy of the reviewed papers.

1.3.5.2 Factors influencing the quality of the conceptualisation of cognitive ability across the reviewed studies

Most of the cognitive variables across the studies were well-known, standardized measures (For a breakdown of these and the cognitive domains tested, please see Table 2). However often studies would not mention reliability or validity for the tests utilized, test retest reliability, nor their everyday value[57-60, 66,68].

Table 2. Table of all the tests utilized across the studies, and what cognitive domain they represent. Numbers of papers are as follows: Li et al[60] = 1, Van Os et al[55] =2, Garcia et al[19] =3, Ucok et al[59] = 4, Sideli et al[56] = 5, Aas & Steen et al[67] = 6, Lysaker et al[50] =7, McCabe et al[64] = 8, Schalinski et al[52], = 9 , Kelly et al[53] = 10, Kilian et al[58] = 11, Aas, Dazzan et al[66] = 12, Shannon et al[51]= 13, Schenkel et al[54] =14, Green et al[63] =15, Green et al[62] =16, Hernaus et al[61]=17, Aas, Navari et al[57]=18

Cognitive Domain	Tests	Papers that utilized these
Immediate recall	RBANS subdomain word list 1, short story 1[1]	1, 15, 16, 10
	The California Verbal Learning Test[2]	6, 7
	Rey Auditory Verbal Learning Test[3]	18 17, 4
	Visual reproduction subtest of the Wechsler Memory Scale[4]	18
	Immediate scores of the Visual reproduction task of the Wechsler Memory Scale[4]	5
	immediate scores of the Logical memory task of the Wechsler Memory Scale[4]	5, 13
Delayed Recall	RBANS subdomain word list 2, word list recognition, story 2 , figure recall[1]	1, 10, 15, 16
	The California Verbal Learning Test[2]	6, 7
	Rey Auditory Verbal Learning Test[3]	12, 18, 4
	Visual reproduction subtest of the Wechsler Memory Scale—Revised (Wechsler, 1987)[4]	12, 18
	Delayed scores of the Visual reproduction task of the Wechsler memory scale[4]	5
	Delayed scores of the Logical memory task of the Wechsler Memory Scale	5, 13
	Auditory verbal learning task from the Wechsler adult intelligence scale 4th edition[5]	17
Visuospatial	RBANS subdomain Figure Copy, line orientation[1]	1 10, 15, 16
	Block Design from WAIS-R, block design from Wechsler adult intelligence scale 4th edition[5]	2 , 18, 17
	Brief Visuospatial Memory Test-Revised[6]	3, 11, 9
	A of Raven's Colored Progressive Matrices[7]	12, 18
	The contour integration test[8]	14
Executive Functioning	Trail Making Test Part B[9]	12, 18,4, 5
	Controlled oral word association test[10]	15, 16 , 14
	Wisconsin Card Sorting test[11]	7, 4
	Brixton spatial anticipation test[12]	14
	hayling sentence completion test from the hayling Brixton tests[12]	14
	Neuropsychological Assessment Battery mazes[13]	3, 11, 9
	Raven's Colored Progressive Matrices sets A & B[7]	12,18
	Stroop test[12]	4
Language	RBANS subdomain Picture naming, semantic fluency[1]	1, 10, 15 , 16
	Information from Wechsler adult intelligence scale 4th edition[5]	2
	Semantic fluency[5]	12,18,5
	Category fluency[5]	12, 18, 5
	Vocabulary and comprehension subtests from Wechsler adult intelligence scale-revised[15]	12
	Shipley institute of living scale vocabulary subtest[16]	14
	RBANS subdomain digit span, coding[1]	1, 10, 15, 16
	Arithmetic from WAIS[5]	2
	digit symbol subtest WAIS-R[15]	18, 5 , 2
	Continuous Performance Test-Identical Pairs[13]	3, 11 ,9, 4

Attention/working memory	Letter–Number Span Test Wechsler abbreviated intelligence scale[17]	6, 18, 12
	Digit span5	6, 18
	Digit span of the WAIS[5]	5
	Letter-number sequencing from wechsler memory scale[4]	13
	forward and backward digit span[4]	6 , 4
	Spatial span of the Wechsler memory scale[4]	5
	Stroop test[14]	4
	N-back test[13]	4
Processing speed	Brief Assessment of Cognition in Schizophrenia-Symbol Coding[13]	3, 11, 9
	Hopkins Verbal Learning Test-Revised WMS Spatial Span[4]	3, 11, 9
	University of Maryland Letter–Number Span[13]	3, 11, 9
	Trail-Making test Part A[9]	3, 11, 18, 5 ,9, 4
General Cognitive Functioning	WAIS[5]	2,5
	WASI [17]	6 , 8
	Full-scale IQ was derived from the subtests of the WAIS—R[15]	18, 12

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Some studies[53,60,62,63] utilized the Repeatable Test for the Assessment of Neuropsychological Status (RBANS)[69]. This test was originally developed as a screening measure primarily for elderly individuals and may therefore be more relevant for the types of impairment observed in patients with dementing illnesses,

as opposed to psychosis, and it may also be implicated in ceiling effects for the control groups, which was not considered across the studies.

Another important issue when including individuals with psychosis is considering the increased risk of fatigue, severity of psychotic symptoms, lack of attention all contributing to floor effects[70] which may affect the test validity, sensitivity and/or specificity of the cognitive testing. No study adequately explained how they controlled for issues of fatigue, or ensuring that the individual sustained attention during the assessment. Studies also varied in their inclusion of premorbid IQ, and whether this was included in subsequent statistical analysis. This is a crucial point to consider if other aspects of the psychotic disorder, such as symptom severity were not accounted for.

Studies also varied in their age ranges. Across the reviewed studies, average age for patients ranged from 23.8[58] to 45[50], with one study[60] reporting that the range of individuals approached was between 16 to 75. Crucially, length of illness, chronicity of symptoms and medication use, have all been highly associated with cognitive impairments in psychosis[67-73]. Thus any reported associations between the measures of CT/ACE and cognitive ability may be critically confounded, unless these factors are appropriately controlled for. Only 5 studies used samples of individuals in the early stages of their psychotic disorder[56-58 65,66,], two of which use subsamples drawn from the same participant pool[57,66]. Only one of the reviewed studies[59] uses a clinical high risk sample, which to a certain extent provides more information regarding the target population without the confounds of length of illness/antipsychotic medication, however this study did not include a control group, which limits the conclusions we can make regarding the specificity of their results to psychosis.

1.3.5.3.1 Control for confounding variables affecting quality of cognitive ability and CT/ACE utilized across studies

As cognitive ability has been associated with education and full scale IQ[74] estimates of years in education and a measure of premorbid IQ would be crucial. However, as is clear from Table 1, studies varied in the extent to which these were included. As antipsychotic medication has been highly correlated with cognitive function in studies of patients with psychosis[75] this would have been an imperative confounding factor to include. Crucially, only a small minority of reviewed studies controlled for antipsychotic medication exposure. For example, one study[60] found that patients undergoing treatment with atypical antipsychotics had significantly higher delayed memory and RBANS total scores compared to patients treated with first-generation antipsychotics, yet failed to include this variable in their analysis.

1.3.5.3.1 Adequate inclusion of controlling for multiple comparisons across reviewed studies

Some studies were found to control for multiple comparisons well throughout, by using by stringent Bonferroni corrections on the p values obtained for each test[60,64,65] or at least indicating which tests remained significant after bonferroni testing. However, other studies did not report any control for multiple comparisons, or adjust their regression analysis for false discovery rate, yet conducted several correlations between different cognitive tests and different types of abuse, providing high risk of Type 1 errors. Two studies[50,54] used a multivariate analysis of variance (MANOVA) which is a method by which the risk of Type 1 errors is minimised. However, often significant effects are followed up by subsequent ANOVAs. However, the original MANOVA protects only the dependent variable for which group differences genuinely exist[76] and thus some authors suggest that these subsequent ANOVAS should also be controlled for multiple comparisons[77], which the authors do not do. Other studies did not need to control for multiple comparisons to the same extent [55], as they looked at full scale IQ. The studies that utilize sibling/case designs control for the family effect well, by using family

structure[55,61] in their random intercept multilevel regression models, protecting against the potential effect of individuals from the same family scoring more similarly.

1.4 Discussion

1.4.1 Summary of reviewed papers

To summarise, this review identified 18 studies that have looked at the association between CT/ACE and cognitive variables in individuals with psychosis. In brief, study findings are diverse, and no clear conclusion can be drawn on whether patients or controls show more impaired cognitive ability in association with adversity. However, the systematic review of the literature highlights that adverse events may have an effect on both localised and globalcognitive domains, suggesting that further more rigorous and well-controlled studies are required.

However, a lack of transparent reporting of effect sizes across reviewed studies, and differences across group comparisons limit the generalisability of the existing evidence. Furthermore, the different conceptualisations of CT/adversity and cognitive ability, combined with a general lack of inclusion of appropriate confounding factors and adequate control of multiple comparisons, critically limit any robust interpretation of the reviewed evidence base. Although ten of the studies reported including control groups, there was clear cross-study variability in their inclusion in subsequent analysis, which further limits the conclusions that can be drawn from the reviewed evidence-base.

In order for any reported association between ACE and cognitive ability to be considered robust and generalizable across studies, the quality of the included cognitive variables is imperative. However, the chronicity of samples across the reviewed papers, along with inadequate control for medication, length of illness,

and symptom severity, critically limit the quality of the cognitive variables tested. Furthermore, as many studies include several tests spanning several cognitive domains without use of appropriate control for multiple comparisons, the risk of Type 1 error remains rife across the present studies.

Several issues with the conceptualisation of CT/ACE limit the quality of the reviewed papers. Evidence has emerged that both the timing and cumulative nature of adversity may be important, especially if contributing to subsequent brain development[78] and thus this limits some of the conclusions that can be made regarding the way in which the reviewed studies conceptualise trauma. In brief, some of the studies separated their measures for sexual, physical and emotional abuse/neglect and differed in their subsequent inclusion in analysis, and/or summing the total score into one generic "trauma" score. Furthermore, no study considered how the socio-economic status or mental health and/or intelligence of household may have affected upon the results.

1.5.2 Implications for research

Our review highlights that across the reviewed studies, the measurement of childhood adversities has been heterogeneously conceptualised, and that there is a lack of detail on the severity for the individual as well as timing of the trauma. Adversities rarely occur in isolation, and therefore studies considering the cumulative effect of trauma on cognitive ability are required. Furthermore, most studies investigated CT in a more narrow definition, and future studies looking at the cumulative effect of ACEs are required, such as household dysfunction, mental health of parents and poverty are also required, as evidence suggests these may be equally implicated in psychosis[78].

Some of the heterogeneity in the findings may be attributed also to the way in which the patient groups were defined, and control of patient characteristic confounding variables. Future studies may wish to examine severity of psychotic

symptomology, or medication, in relation to the link between early adversity and cognitive ability, rather than solely considering diagnosis, as this may provide more in depth information on the putative link. Furthermore, future studies of early psychosis samples are also required in order to minimize the confounding effect of antipsychotic medication, length of illness and other confounding characteristics mentioned above.

1.5.3 Limitations of this review

One limitation of the present study is that the literature regarding genetic predispositions to psychosis was not investigated or reviewed, in the context of potential interaction with ACE and cognitive ability. There is some evidence indicating an abnormal HPA axis in patients with psychotic disorders irrespective of early trauma and evidence of systemic cortisol metabolism[79] with links to genetic markers in psychosis[80,81]. Future studies should aim to also review the evidence relating to this how it may interact with ACE We did not assess other important variables, such as psychotic symptom severity, interpersonal factors, attachment and PTSD symptomology/comorbidity, which may moderate or mediate the relationship between CT and cognitive ability in psychosis.

1.5.4 Conclusions

In conclusion, the differences in sampling methods, statistical analysis, and the quality of the trauma and cognitive variables included, limit the conclusions on the extent to which ACEsimpacts on cognitive ability, and whether it occurs only in individuals with psychosis, or is a more general risk mechanism for impaired cognitive ability in the typical population too. Crucially, many reviewed studies did not control for length of illness, antipsychotic/antidepressant medication, and future studies utilizing early psychosis/high risk samples are essential. This review underscores the importance of more extensive research utilizing more detailed assessments of exposure to adversities throughout childhood and adolescence, and a more theoretically informed selection of cognitive variables. The evidence

remains in the early stages, and future research in this area is necessary before any more firm conclusions can be made.

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Doctorate in Clinical Psychology
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Childhood adversity and cognitive ability in a sample of individuals at high clinical risk of developing psychosis and healthy controls

Written in Accordance with author guidelines:

Schizophrenia Bulletin Please see Appendix A for a full outline of these guidelines)

Keywords: Psychosis, childhood adversity, clinical high risk, cognitive ability, schizophrenia, symptom severity

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Abstract: Empirical paper

Background

The aim of this study was to investigate the relationship between cumulative levels of adverse childhood experiences (ACEs) and both global and specific cognitive functioning in individuals at high clinical risk (CHR) of developing psychosis.

Methods

85 individuals at CHR and 79 similarly matched healthy controls were evaluated on ACEs and cognitive function. Two way MANOVAs were conducted to assess the interactionbetween specific domains of cognitive functioning and group membership, whilst two way ANOVAS were run to assess the interaction between global cognitive ability and group membership.

Doctorate in Clinical Psychology
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Results

We found a significant interaction between group (CHR and healthy controls) and ACEs in the BACS composite score, $F(2,143) = 7.27$, $p = .001$. Post hoc tests indicated that healthy controls with high levels of ACEs performed significantly better than the CHR group $F(1,143) = 7.95$, $p < .001$ partial eta squared = 0.053

Conclusions

Our results indicate that in individuals at CHR who have experienced high levels of ACEs score significantly lower on a global estimate of cognitive ability, compared to healthy controls. These findings indicate that those at CHR for psychosis may be particularly vulnerable to the impact of ACEs on global cognitive ability, compared to healthy controls, and support the importance of future investigations into traumatological models of psychosis

2.1 Introduction

A history of adverse childhood experiences (ACEs) is reportedly more common in people with established psychosis, and has been linked to an increased risk of developing psychosis[1,,2].It has been associated with the severity of positive psychotic symptoms, such as hallucinations and delusions[3-7] and earlier first admissions and more frequent hospitalisations[8]. It is an extensive concept that encompasses exposure to a range of difficult and/or unpleasant situations or experiences, usually before the age of 16/18[9,10]. The adversities typically considered in studies of psychosis include household poverty, separation from a parent (i.e., family breakdown), death of a parent, neglect, abuse (including physical, sexual, and emotional), peer bullying, and parental psychopathology[11-14]

One proposed mechanism for the relationship between ACE and psychosis is through early stress operating on key neurobiological systems involved in generating the human stress response, such as the hypothalamic pituitary adrenal (HPA) axis [15,16] . Furthermore, other theories suggest that early stress affects key psychological mechanisms which are involved in the emergence of specific psychotic symptoms, such as persucatory delusions, which create an anamolous cognitive experienceEmerging evidence has investigated the association between ACEs and cognitive function in psychosis samples; however, the evidence-base is diverse and heterogeneous[18-20]. One issue of contention is whether ACE associates with global or specific cognitive deficits[21-23], and whether this association is more prevalent in psychosis, compared to the typical population. At present it is unclear to what extent ACEs affects cognitive ability in psychosis compared to the typical population, as there is also evidence to suggest that it is associated with impaired cognitive capacity in the general population[24,25]

A recent systematic review assessing the link between early adversity and cognitive ability in relation to psychosis found several limitations in the evidence that curtails the generalisability of conclusions that can be drawn regarding the above. In brief, most samples utilized patients that had had the disorder for several years; however, cognitive deficits have been linked to antipsychotic medication length of illness, chronicity of psychotic symptoms, institutionalization, prolonged substance use and medication, and poor physical health[26-30] . Thus, it remains highly likely that some, if not all, existing literature is heavily confounded by these factors, which may explain some of the inconsistencies across studies regarding associations between cognitive domains and ACEs in psychosis, ability compared to controls[31,32].

Most of the existing literature assessing the link between cognitive ability and ACEs has not investigated the cumulative effect of ACEs. However, adversities tend to co-occur and persist over time, often in worsening cycles of vulnerability[9,33] and evidence is converging to suggest that multiple adversities may have an additive

effect on risk of developing psychosis, as well as severity of symptoms[34-36]. Understanding this link further may help elucidate information regarding resilience[37] to psychosis, as not everyone that experiences early trauma goes on to develop psychosis.

In order to provide a more robust understanding regarding the link between ACEs and cognitive ability in relation to psychosis, as opposed to confounding factors, studies of individuals at clinical high risk (CHR) for developing psychosis can be studied, without the potential confounds of antipsychotic medication, chronicity of symptoms and length of illness mentioned above. In brief, CHR individuals can be identified when they present with "attenuated" psychotic symptoms, full-blown psychotic symptoms that are brief and self-limiting, or a significant decrease in functioning in the context of a family history of schizophrenia[38] . Studies of cognitive function in these populations have suggested that individuals at CHR for psychosis may have more cognitive deficits compared to controls, and that these are associated with the severity of their psychotic symptoms [39-41]. Only one study has used a clinical high risk sample to look at this association[42], however this study did not include a control group. Assessing the link between CA and cognitive ability in those at CHR has profound clinical implications, as this may provide optimal targets for early intervention strategies. Based on the existing literature, it is predicted that those at high risk would be more sensitive to the effects of ACE, compared to controls, in that higher levels of ACE's will be associated with lower levels of cognitive functioning in those at high risk. It is also predicted that this may be present on a global scale, as opposed to specific cognitive domains.

2.2 Materials and Methods

2.2.1 The Youth Mental Health Risk and Resilience Study (YouR-study)

The present study draws its sample from a larger ongoing and established study: the Youth Mental Health Risk and Resilience Study (YOUR-Study) individuals between the ages of 16 to 35 were recruited, that were deemed either at high clinical risk of developing psychosis or to be a healthy control. Inclusion criteria for the high-risk sample were high risk-criteria according to the Comprehensive assessment of at-risk mental states (CAARMS)[43] or Schizophrenia Proneness instrument (SPI-A)[44], or SPI-A only, male or non-pregnant female >16, <35 years of age, written informed Consent, normal to corrected vision. Exclusion criteria for the high risk sample were suicidal ideation, pregnancy, > 16, <35 years of age, metal implants in body parts, or an existing neurological disorder. For the controls, the inclusion and exclusion criteria were the same as above, without the CAARMS/SPI-A criteria, and the added on exclusion criteria that they did not have a 1st degree relative with a diagnosis of schizophrenia.

The controls were recruited from a pre-existing database of Psychology students, or through flyers distributed at university settings and a specific webpage set up for the purposes of this study. The recruitment of high risk individuals also involved individuals from a pre-existing database of Psychology students, or through flyers distributed at university settings and the same specific webpage used for controls. NHS patient services in NHS Greater Glasgow and Clyde and NHS Lothian, NHS First Episode Psychosis Services, Community Mental Health Teams (CMHTs), Primary Care Mental Health Teams (PCMHTs), Clinical Psychology Services, Community Adolescent Mental Health Services (CAMHS), student counselling services, and the general population. Informed consent will be obtained either online through the website or on site by a member of the research team. Following informed consent, a screening questionnaire will be administered and basic demographic information will be obtained. If the participant endorses more than 6 items on the PQ or 3 or more perceptual/cognitive items, participants will be contacted per telephone/email by a member of research team. A first visit will then be scheduled. After informed consent is obtained during which the positive scale of the

CAARMS/SIPS-Interview will be administered to establish ultra high risk criteria. In addition, information about family history, drug abuse and demographic information will be obtained.

Thus, the present study utilized a total of 85 individuals that met high risk criteria, and 79 controls that had a full neuropsychological profile and measures of adverse childhood experiences. All measures were administered by trained research assistants, receiving supervision by senior medical professionals. If anybody was distressed or suicidal during the assessments, the questions were discontinued and appropriate referrals to crisis services or referrers made.

2.2.2 Ethical Procedure

The YouR-Study was performed according to the Research Governance Framework for Health and Community Care (Second edition, 2006) and the study has appropriate REC approval from the west of Scotland research ethics committee and then has local R&D approval from NHS Lothian and NHS greater Glasgow and Clyde, and informed consent was gathered from all participating individuals.

2.3 Instruments

2.3.1 Neuropsychological assessments

The brief assessment of cognition in schizophrenia (BACS) is an instrument that was specifically developed with the intention to assess aspects of cognition that have been found to be the most impaired and strongly correlated to outcome in schizophrenia[31]. It assesses five different domains of cognitive function with six tests, which can also be combined to provide a more general, “composite” score of cognitive ability, which has been previously highly linked to functional outcome in psychosis[45]. The BACS takes approximately 30-35 minutes to complete in patients with schizophrenia and is a well-validated and portable instrument with high

reliability, and has been shown to be as sensitive to cognitive impairment in patients as a standard battery of tests that required over 2 hours to administer[45-47]. The following tests were administered as noted in the BACs manual from where the test explanations are extracted[45]:

2.3.1.1 Verbal Memory

Assessed with 5 trials of list learning, whereby individuals are presented with 15 words and then asked to recall as many as possible, with the main measure being the number of words recalled per trial, in any order (range 0-75).

2.3.1.2 Working Memory

Individuals were presented with clusters of numbers that increased in length, and required to tell the numbers in order, from lowest to highest, with the main measure being the number of correct responses (range 0-28).

2.3.1.3 Motor Speed

This was assessed with a token motor task, whereby individuals were given plastic tokens and asked to place them two at a time into a container as quickly as possible. A 60 second time limit was imposed, and the number of tokens correctly placed into the container was the main measure.

2.3.1.4 Verbal Fluency

Category Instances

Patients were given 60 seconds to name as many words as possible within a given category. Version A: supermarket items; Version B: tools.

Controlled oral word association test

In two separate trials, patients were given 60 seconds to generate as many words as possible that begin with a given letter. Version A: F, S; Version B: P, R Measure: number of words generated per trial.

2.3.1.5 Attention and speed of information processing

Symbol coding. As quickly as possible, patients wrote numerals 1 –9 as matches to symbols on a response sheet for 90 seconds. Measure: number of correct numerals (range: 0 –110)

2.3.1.6 Executive Function

Tower of London adapted task in which the main outcome measure: number of correct responses (range: 0 – 22).

2.3.2 Adverse Childhood Experiences Measures

The method for assessing childhood adversity experiences was adapted from a previously validated method[48]. For the exact questions included in this inventory, please see Appendix H. In brief, it is a scale that is adapted from several pre-existing scales: Conflict Tactics Scale[49], the Wyatt questions on sexual abuse[50] and the Child trauma questionnaire [51]. The ACEs questionnaire demonstrates excellent test–retest reliability, internal consistency (Cronbach's a = .95), and construct validity[52, 53]. All questions relate to the individuals eighteen first years of life. The questions pertain to any experiences of: physical, sexual, emotional abuse, emotional and physical neglect. Five types of dysfunction of household are also assessed: mental illness, domestic violence, parental separation or divorce, substance abuse, and criminal behaviour in the household. Participants rated their exposure to ACEs as "never, once or twice, sometimes, often, or very often". If they answered that the type of ACE occurred at least once, then they were considered to have been exposed to that ACE.

2.3.3 Assessment of Psychosis/At Risk Mental States

The CAARMS is a semi-structured interview schedule to be used by qualified mental health professionals[43]. It has been used reliably in several clinical high risk studies[55-57] .It includes assessment of subthreshold positive symptoms such as: disorders of thought content (such as overvalued ideas and delusions), perceptual abnormalities (such as hallucinations), conceptual disorganization (such as objective assessment of formal thought disorder).

2.4 Statistical Analysis

2.4.1 Analysis Regarding Group Effects on Cognitive Ability in Relation to Number of ACEs experienced

All statistical analysis was conducted with SPSS (version 23). As in Dube[48] the total number of exposures (range: 0–10) was summed to create a cumulative AC experience score for each participant. ACE scores of 3 or more were combined into one category reflecting a high level of ACE in accordance with previous studies[48,50], and a factor with three levels was created: no ACE's reported, low levels of ACE's reported, and high levels of ACE's reported.

The primary scores for each BACS subtest were transformed into z-scores whereby the mean for healthy control subjects was set to 0 and the standard deviation (SD) to 1. Composite score for global cognition was generated by transforming the mean of all six BACS z-scores to standardized values, with reference to the normative mean for the healthy control subjects as 0 and the SD as 1[43].

Firstly, a two-way ANOVA with the interaction between Group (High Risk and Controls) and number of ACEs (none, low, high) as the independent variable, and the standardized BACs score composite as the independent variable were run, with relevant confounding factors entered and removed if they did not significantly improve the model's fit. A two-way MANOVA with the interaction between Group (High Risk and Controls) and number of ACEs (none, low, high) as the independent variable, and the z-scores of the six sub tests of the BACS entered as our dependent variables was conducted (verbal memory, working memory, motor speed, verbal fluency, attention and speed of information processing, executive function). All underlying assumptions for the ANOVA and MANOVA were checked before

proceeding, and any necessary transformations conducted. Any significant interaction effects were followed up with simple main effects analysis and post-hoc testing, Bonferroni corrected for multiple comparisons throughout.

Relevant demographic variables were also compared between those at high risk and the control group, as well as across the different levels of the ACE variable, with X^2 tests for categorical variables and one-way ANOVAs for relevant continuous variables.

2.5 Results

2.5.1 Demographics

Sample Demographics are shown in Table 1 and 2. A significant difference emerged between high risk and controls in number of years in education, $F(1,149) = 5.40$, $p = .021$ and medication, $F(1,161) = 22.8$, $p <. 000$. No other demographic variables differed significantly between the groupings (Appendix I).

Table 1. Relevant Demographics for the different groups (controls versus high risk), levels of ACE (none,low,high).

	Controls (n = 78)	**High Risk (n = 85)**
Sociodemographic		
Age (years), mean (SD)	23.1(4.24)	22.1(4.34)
Education (years), mean (SD)	16.4(3.07)	15.2(3.20)
Gender (M/F)	(28/50)	(21/64)
Premorbid IQ (NART)	112(8.76)	113(10.5)

Table 2. Relevant Demographics for levels of ACE (none,low,high).

	None (n = 55)	Low (n = 64)	High (n = 35)
Sociodemographic			
Age (years), mean (SD)	22.4(3.83)	22.4(4.19)	23.1(5.32)
Education (years), mean (SD)	16.0(3.09)	15.8(3.15)	15.5(3.47)
Gender (M/F)	(18/42)	(23/45)	(8/27)
Premorbid IQ (NART)	112(8.28)	114(10.8)	110(9.36)

2.5.2 Relationship between level of ACEs and specific cognitive domains in Controls versus CHR

All parametric assumptions of a two way MANOVA were checked and appropriate transformations applied (Appendix J).. There was no significant main effect of either group (p = .335), nor level of ACE (p =.499) on the combined effect of all different BACS domain scores. There was no significant interaction effect between group and level of ACES on the combined effect of all different BACS domain scores, F(6,278) = 1.49,, Wilks' Λ = 1.49, p = .128, partial η^2 = .061. Breakdown of prevalence rates of the different ACEs across the different groupings and ACE levels are summarised in Table 3. Raw mean scores of the different cognitive domains and the total BACS score are presented in table 4.

Table 3. Prevalence rates of the different ACEs in the CHR and control groups

	Prevalence(yes)		
	Controls(n =79)	**High Risk Sample total (n = 88)**	**Total (n =67)**

Abuse (yes)			
▪ **Emotional**	**8 (10.1%)**	**21(24%)**	**29(17%)**
▪ **Physical**	**3(3.8%)**	**5(6%)**	**8(5%)**
▪ **Sexual**	**6(7.6%)**	**11(13%)**	**17(10%)**
Neglect (yes/no)			
▪ **Emotional**	**6(7.6%)**	**16(18%)**	**22(13%)**
▪ **Physical**	**0(0%)**	**10(11%)**	**10(6%)**
Household dysfunction yes/no)			
▪ **Battered mother**	**2(2.5%)**	**10(11%)**	**12(7%)**
▪ **Parental separation or divorce**	**19(24.1%)**	**32(36%)**	**51(31%)**
▪ **Mental illness in household**	**20(25.3%)**	**41(47%)**	**61(37%)**
▪ **Household substance abuse**	**11(13.9%)**	**23(26%)**	**34(20%)**
▪ **Incarcerated household member**	**1(1.3%)**	**6(7%)**	**7(4%)**
ACE score			
▪ **0**	**38(48%)**	**23(26%)**	**61(36.5%)**
▪ **1**	**20(25%)**	**26(30%)**	**46(28%)**
▪ **2**	**12(15%)**	**12(14%)**	**24(14%)**
▪ **3**	**4(5%)**	**8(9%)**	**12(7%)**
▪ **4**	**4(5%)**	**6(7%)**	**10(6%)**
▪ **>5**	**1(1%)**	**13(15%)**	**14(8%)**

Table 4. Raw mean scores of the different cognitive domains and the total BACS score are presented in

	None	**Low**	**High**	**Total**
Verbal Memory total score				

(verbal memory & learning)				
Controls	**51.9(1.65)**	**50.1(1.79)**	**57.4(3.39)**	**51.8(9.67)**
High Risk	**48.7(2.12)**	**54.2(1.65)**	**47.2(1.2)**	**50.6(11.0)**
Digit Sequencing (working memory)				
Controls	**21.3(3.33)**	**20.9(3.14)**	**22.6(2.00)**	**21.28(3.14)**
High Risk	**20.4(3.70)**	**21.5(4.79)**	**19.4(2.82)**	**20.6(4.04)**
Token Motor (motor function)				
Controls	**80.5(15.5)**	**76.9(18.7)**	**76.3(15.1)**	**78.6(16.8)**
High Risk	**76(15.9)**	**71.3(18.1)**	**65.0(16.5)**	**70.6(17.4)**
Semantic Fluency (verbal fluency)				
Controls	**56.3(12.4)**	**55.3(12.4)**	**63.3(10.9)**	**56.7(12.3)**
High Risk	**54.8(13.9)**	**60.2(12.2)**	**54.9(11.4)**	**57.2(12.5)**
Symbol coding (speed of processing)				
Controls	**75.9(12.8)**	**70.2(12.9)**	**73.3(9.99)**	**73.3(12.7)**
High Risk	**69.0(15.9)**	**69.5(13.6)**	**62.2(11.4)**	**67.2(13.9)**
Tower of London (executive function)				
Controls	**18.8(1.7)**	**18.0(2.20)**	**18.7(2.96)**	**18.5(2.01)**
High Risk	**18.04(2.79)**	**18.8(1.83)**	**17.5(2.42)**	**18.2(2.34)**
Mean Total BACS score				

(mean/sd)				
Controls	**303(28.7)**	**289(31.2)**	**305(19.8)**	**297(2.5)**
High Risk	**281(44.8)**	**295(32.8)**	**263(33.3)**	**281(38.5)**

2.5.3 Relationship between level of ACEs and BACS total composite score in Controls versus CHR

All assumptions required for two-way ANOVA were checked and upheld (Appendix K). There was a significant effect of group on the BACS composite score,(F (1,157) = 8.21, Wilks' Λ = 1.92, η^2= 0.050, p = 0.005, and analysis of means showed that this was because those at high risk (m = -.160, sd = .844) had significantly lower BACS composite scores compared to controls (m = .175, sd = .845). There was no significant main effect of ACE (p = .795) on BACS composite score. A significant interaction effect emerged between group and level of ACES in the composite BACS score, F(2,143) = 7.27, p = .001, Wilks' Λ = 1.98 partial η^2 = .092. This interaction effect was followed up by analysis of simple main effects and post-hoc testing, controlled for multiple comparisons, (Bonferroni), which showed that when controls and those at high clinical risk with a high level of ACEs were compared, mean composite BACS scores was 1.098 points higher in controls, compared to the CHR group (95% CI = ,-1.65 - .422)), F(1,143) = 7.95, p <.001 partial eta squared = 0.053. This is illustrated in Figure 2.

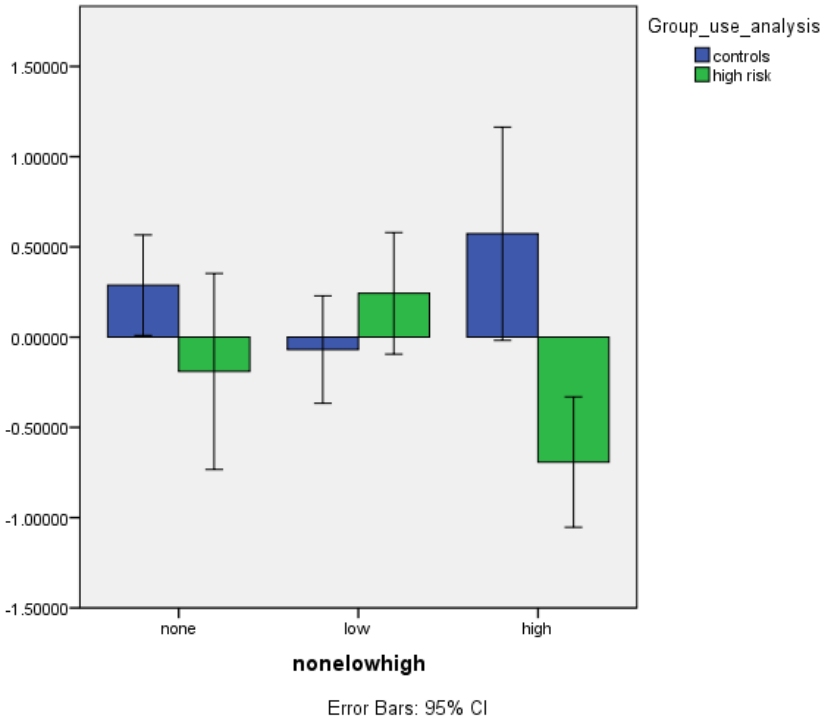

Figure 2. Clustered bar chart showing differences in standardized z scores for BACS composite score (y-axis) between controls (blue) and the clinical high risk group (green) (x axis). Errors bars reflect the 95% confidence intervals.

2.6 Discussion

2.6.1 Summary of Main Findings

To summarise, we investigated whether there was any association between the number of ACEs experienced and group membership (clinical high risk versus control) in any of the BACS subdomains, as well as the composite score, indicative of global cognitive ability. We found higher levels of ACEs in the high-risk sample, which is consistent with previous research[59,60]. We found that although there was no significant interaction effect between levels of ACEs and group membership in relation to the specific cognitive domains, there was a significant interaction effect in relation to the BACS composite score, in that those at high risk had significantly

lower BACs composite scores, compared to healthy controls, when having experienced a high level of ACEs.

Intriguingly, we did not find that the relationship between number of ACEs and symptom severity/distress as measured by the CAARMS was mediated by the BACS composite cognitive score in the high risk sample. To our knowledge, the present study is the first to investigate the cumulative effect of number of ACEs on global cognition in a sample of high risk individuals, as well as assess to what extent this relationship was also present in a healthy control group.

2.6.2 Clinical Implications

Increasingly, evidence is pointing towards the heterogeneity of psychosis and the lack of one underlying causal factor. In particular, evidence is pointing towards the underlying brain pathology being widespread in nature, rather than linked to isolated brain regions[61-63]. Thus, the research indicating that global estimates of cognitive ability are affected may better able to capture these widespread perturbations, and this study indicates the importance to continue to assess more general cognitive ability, as opposed to just specific domains in relation to the high-risk state, in order to not obscure important global effects in cognitive ability.

Our findings suggest that an increased level of ACES in those at high risk of developing psychosis is associated with a lower cognitive score compared to healthy controls. This has important clinical implications, as understanding the developmental trajectory of the high risk state, compared to typical development, can grant us unique insight into developing psychopathology and individual differences in risk and resilience. As early intervention has been consistently associated with improved prognosis in psychosis [64-66] our results indicate that efforts aimed at ameliorating early ACEs may have a critical impact on those who subsequently go on to have attenuated psychotic symptoms, by potentially

protecting estimates of global cognitive ability, thus potentially offering a target for resilience strategies. Our results should provide evidence for the importance of lobbying for childhood adversity prevention programmes, or attempting to reduce the number of ACEs by early identification of children exposed to early adversities. Previous studies that have used environment enrichment programme for children between the age of 3 to 5 showed that this was associated with a reduced number of schizotypal traits in early adulthood.[67,68]

Clinically, our results are important, as there remains reluctance on the part of mental health services to routinely inquire about trauma, potentially due to concerns about offending, or distressing the individual concerned[69-73]. Furthermore, cognitive therapy based on the understanding of early ACEs may provide a further key intervention strategy aimed at preventing transition to psychosis in high-risk samples, as time since the trauma is not a predictor of treatment outcome in trauma-focused approaches[73-76]. We may also be able to reduce the impact of the psychological sequelea of ACEs and the impact they may subsequently have on symptoms by formulating on trauma, as opposed to just distress. As individuals with psychosis that have a background of adversity also have greater health care utilization and poorer psychosocial outcomes[79,80] future research may benefit from looking at how these outcomes combine with ACE an cognitive ability, rather than just estimates of symptom distress or severity and assess the relationship between ACEs and cognitive ability.

2.6.3 Limitations

One limitation of present study is that the childhood adversity measure we utilized did not assess the impact of the trauma on the individual in terms of asking how traumatic it was for the individual**.** For example, early adversity such as sexual abuse, seems to be particularly implicated in auditory verbal hallucinations but less so in paranoid delusions[85,86]. It has been suggested that trauma may link with

cognitive vulnerability to psychosis by contributing to negative cognitive schema, whereby individuals perceive themselves as powerless and others as threatening and subsequently the world as unsafe[85,86], and this may be important for future studies to consider.

Another limitation of this study is that we did not look into the specificity of psychotic symptoms as opposed to other symptoms, such as PTSD/comorbidity, interpersonal factors, and/or attachment, which may moderate or mediate the relationship between CT and cognitive ability in psychosis[87]. Psychological mediators such as emotional intelligence, shame, and alienation will be crucial for future investigations to assess. Additionally, it is important to note also that the BACS total score may have limited validity and reduce important individual variability across sub-domains of cognitive functioning. Furthermore, we did not assess to what extent early adversity was confounded by socio-economic status or low intelligence of parents/household members, which future studies may want to do.

Another limitation is our measure of cumulative ACEs, which assumes a linear effect of ACEs. By simply adding the number of exposures, we are assuming that each has an equivalent effect, which is unlikely to be the case, and the possibility that there are threshold effects has not been considered[88]. Some studies of abnormal HPA axis in patients with psychotic disorders irrespective of early trauma and evidence of systemic cortisol metabolism with links to genetic markers in psychosis[89,90] also exist, and we did not assess the extent to which this may interact or influence our cumulative measure of adversity. Indeed, recent research has utilized a threshold model whereby both genetic and environmental factors such as childhood adversity, cannabis use, urbanicity, foreign born, hearing impairment, and family history of affective disorders, interact and indicated an additive effect of these in that the greater the number of risk factors, the greater the odds of psychotic experiences[91].

Furthermore, although we showed a different effect of high levels of adversity in those at high risk compared to psychosis, we did not include other controls, such as first episode psychosis, or include individuals with other mental health conditions, such as depression. As many children are exposed to adversity and do not develop psychotic disorders or experiences, future research is required to assess the link to other negative mental health outcomes, such as depression and substance abuse. Furthermore, our controls consisted of mostly university students, and both of our groups indicated a relatively high premorbid IQ and years of education, and future studies with perhaps more representative samples of the population may be required to generalize our finding.

2.6.4 Summary and Conclusions

Our findings suggest that the impact of high levels of ACEs on global cognitive ability may be particularly associated in those at clinical high risk of developing psychosis, compared to healthy controls, and that this may be mediated by another aspect of vulnerability to psychosis as opposed to psychotic symptom distress/severity. Our findings have important clinical implications and indicate the importance of adversity informed approaches to assessing those at clinical high risk of developing psychosis.

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Provide a summary of **no more than 250 words** describing why and how the study, analysis, or review was done, a summary of the essential results, and what the authors have concluded from the data. The abstract should not contain unexplained abbreviations. Up to six key words that do not appear as part of the title should be provided at the end of the abstract.

Main Text

Unsolicited original manuscripts reporting novel experimental findings should be comprised of these sections, in this order: Abstract, Introduction, Methods, Results, Discussion, Acknowledgments, References, and Figure Legends. Review articles must contain an abstract; however, the body of the text can be organized in a less structured format. Authors of review articles are encouraged to use section headers to improve the readability of their manuscript.

Number pages consecutively beginning with the title page. Spelling should conform to that used in *Merriam-Webster's Collegiate Dictionary* , eleventh edition. Clinical laboratory data may be expressed in conventional rather than Système International (SI) units.

Acknowledgments

These should be as brief as possible but include the names of sources of logistical support.

Authors are encouraged to be circumspect in compiling the reference section of their manuscripts.
Please note: references to other articles appearing in the same issue of the journal must be cited fully in the reference list.

Each reference should be cited in consecutive numerical order using superscript arabic numerals, and reference style should follow the recommendations in the *American Medical Association Manual of Style* , 10th edition, with one exception: in the reference list, the name of all authors should be given unless there are more than 6, in which case the names of the first 3 authors are used, followed by "et al."

Book: Talairach J, Tournoux P. *Co-planar stereotaxic atlas of the human brain* . New York, NY: Thieme Medical Publishers; 1998.

Book chapter: Goldberg TE, David A, Gold JM. Neurocognitive deficits in schizophrenia. In: Hirsch SR, Weinberger DR, eds. *Schizophrenia* . Oxford, England: Blackwell Science; 2003:168-184.

Journal article: Thaker GK, Carpenter WT. Advances in schizophrenia. *Nat Med* 2001;7:667-671.

Journal article with more than 6 authors: Egan MF, Straub RE, Goldberg TE, et al. Variation in GRM3 affects cognition, prefrontal gluatamate, and risk for schizophrenia. *Proc Natl Acad Sci USA* 2004;101:12604-12609.

Article published on Advance Access only: Gilad, Y. and Lancet, D. March 5, 2003. Population Differences in the Human Functional Olfactory Repertoire. *Mol Biol Evol*

Figures and Tables

Full length manuscripts including regular and invited theme articles should contain no more than a combined total of 5 tables and figures. Theme introductions and special features are limited to 2 tables or figures (total). Figures and tables must be referred to using arabic numbers in order of their appearance in the text (e.g., Figure 1, Figure 2, Table 1, Table 2, etc.).

Tables should be created with the table function of a word processing program; spreadsheets are not acceptable. Include only essential data, and format the table in a manner in which it should appear in the text. Each table must fit on a single manuscript page and have a short title that is self-explanatory without reference to the text. Footnotes can be used to explain any symbols or abbreviations appearing in the table. Do not duplicate data in tables and figures.

Please be aware that the figure requirements for initial online submission (peer review) and for reproduction in the journal are different. Initially, it is preferred to embed your figures within the word processing file or upload them separately as low-resolution images (.jpg, .tif, or .gif files). However, upon submission of a revised manuscript, you will be required to supply high-resolution .tif files for reproduction in the journal (1200 d.p.i. for line drawings and 300 d.p.i. for color and half-tone artwork). It is advisable to create high-resolution images first as these can be easily converted into low-

Supplementary Material

Supporting material that is not essential for inclusion in the full text of the manuscript, but would nevertheless benefit the reader, can be made available by the publisher as online-only content, linked to the online manuscript. The material should not be essential to understanding the conclusions of the paper, but should contain data that is additional or complementary and directly relevant to the article content. Such information might include more detailed methods, extended data sets/data analysis, or additional figures (including color). It is standard practice for appendices to be made available online-only as supplementary material. All text and figures must be provided **in separate files from the manuscript files labeled as supplementary material** in suitable electronic formats (instructions for the preparation of supplementary material can be viewed here).

All material to be considered as supplementary material must be submitted at the same time as the main manuscript for peer review. It cannot be altered or replaced after the paper has been accepted for publication. Please indicate clearly the material intended as supplementary material upon submission. Also ensure that the supplementary material is referred to in the main manuscript where necessary.

Appendix B. Search strategy and databases covered for systematic review

Electronic database searches yielded 1051 results with 814 remaining following the exclusion of duplicates. The first screening wave consisted of reviewing titles only, and this resulted in the exclusion of 419 titles. The second wave involved reviewing abstracts too, and this excluded a further 177 references. At this point 43 papers were reviewed in more depth, and at this stage 22 further studies were excluded as they did not meet the criteria of either being primary research, no measure of psychotic symptomology, no measure of trauma and/or cognition. A further 2 studies were found by hand searching the reference lists at this stage. Total of 18 included for the study.

Categories covering psychosis and cognitive ability within databases was implemented where possible to ensure a comprehensive search of the available literature, and identified using the following search terms "cognitive ability*" or cognition or neuropsychol* or "neuro* assessment*" or "cognitive assess*" AND (pathway* or associat* or or "mechanism*" mediat* or variable* or relation* or "risk *", "predictor") AND "child abus*" "child traum*" "physical abus*" "sexual abus*" "rape*" "psychological abus*" "emotional abus*" "neglect*" "maltreat*" "bully" "bullied" "victim*" "sexual trauma*" "psychological traum*" "physical assault*" "sexual assault*" "molest*" AND (psychos* or schiz* or hallucinat* or paranoi* or voice* or delusion* or prodrom* OR high risk)."psychological distress"

Databases searched were Pubmed/Medline, PsychArticles full text, EMBASE, EMBASE classic, Global Health, Epub ahead of print and other non-indexed citations. Web of Science and Proquest were also searched to see if any further articles emerged, however they did not. Additional articles were identified following examination of reference lists from primary search results to ensure, as much as possible, that all pertinent studies were included.

<u>Appendix C</u> Table of 14 quality criteria used to grade each paper

Gradings allocated 2 points if deemed well-covered , 1 point if partially addressed , and 0 points if "poorly addressed", "not addressed", "not reported", "not applicable".

Quality Criteria	Criteria Description	Grading
1	**Is the previous relevant background literature discussed (rationale?)**	**2** Well covered relevant background literature discussed and rationale for present study clearly understood **1** Partially covered and rationale explained **0** Background literature not clearly stated
2	**Does the study question address a clear and appropriate question with appropriate hypotheses?**	**2** clearly stated and directional if appropriate **1** partially stated/not directional **0** not stated at all
3	**Population-clearly described and justified? Eg adequate inclusion/exclusion criteria**	**2** Well-covered inclusion and exclusion criteria stated **1** Partially covered **0** Inclusion criteria/exclusion criteria not mentioned, inadequately mentioned
4	**Was the sample representative of the population? E.g. sampling methods, setting, age range, gender, consider how many invited took part.**	**2** Well-covered confident in generalizability, multiple setting recruitment, good balance of age, gender etc **1** Somewhat representative but not optimal **0** very specific population
5	**Power calculation for sample included?**	**2** Power calculation provided **1** Power calculation provided from other paper **0** No power calculation reported

6	**Were standardised measures of childhood trauma mentioning validity and reliability mentioned?**	**2** Well covered validity and reliability mentioned as appropriate for different measures (eg childhood trauma) **1** Partial: covered validity and reliability mentioned for some measures **0** no mention of validity and reliability
7	**Were the cognitive variables measures reliable and valid?**	**2** Present: Standardised and well-normed measures, good reliability and validity **1** Partial: Compromised in any area above **0** Absent: No standardised measure specific to cognitive variable(s) used
8	**Were known confounding factors measured and accounted for in the analysis? Eg gender, iq, length of illness, antipsychotic medication, substance use) in particular antipsychotic medication**	**2** Present: Thoroughly measured and accounted for **1** Partial: Some mentioned and somewhat accounted for **0** Absent: Not measured. Or measured but not accounted for in analysis
9	**Are the analysis methods appropriate? In particular, multiple comparisons adequately controlled for**	**2** Present: The analysis is appropriate for the study design and the collected data **1** Partial: Could be better **0** Absent: The analysis used is inappropriate for the study design and/or data
10	**Were effect sizes and confidence intervals cited for reported associations cited?**	**2** Present **1** Partially present **0** Not mentioned at all, not covered at all
11	**Overall results-clearly and logically explained?**	**2** well covered **1** partially covered **0** poorly covered, not covered at all
12	**Wider implications discussed**	**2** well covered

		1 partially covered **0** poorly covered, not covered at all
13	**Findings compared to other studies and discrepancies addressed**	**2** well covered **1** partially covered **0** poorly covered, not covered at all
14	**Limitations addressed**	**2** well covered **1** partially covered: but some essential limitations not mentioned **0** poorly covered, not covered at all

Appendix E Table of extracted demographics from relevant studies, adapted from the reviewed studies

Authors and Year	Sample (N)	Relevant Demographics of Sample	Exclusion & Inclusion Criteria	Trauma Measure	Setting	Study design
Li, X-B., et al. 2017	**P=162**	**Age** (Mean/sd): (37.82/10.16) **Percentage Female**: 64% **Country:** China	**Inclusion criteria:** diagnosis of schizophrenia based on the criteria of the Structured Clinical Interview for DSM-IV (SCID) ,in a stable clinical condition, age between 16 and 65 years, ability to sign the consent form, IQ above 80 on the WASI **Exclusion criteria:** Patients were excluded if they had unstable medical conditions.	CTQ, 28 item	Inpatients or outpatients	Cross-sectional
Green et al. 2014	**P =** 617 **HC =** 659	**Age** (Mean/sd): P=(39.65/10.82) HC=(42.48/13.58) **Percentage Female:** P =33% HC =56% Country: Australia	**Inclusion criteria:** control participants had no personal history of DSM-IV Axis 1 disorder, and no history of psychotic disorder in their first-degree biological relatives. **Exclusion criteria** : inability to converse fluently in English, organic brain disorder, brain injury with greater than 24 h post-traumatic amnesia, (IQ < 70), movement disorders, current diagnosis of substance dependence, and/or electroconvulsive therapy received in the last 6 months.	CAQ (Childhood adversity questionnaire	Inpatient and outpatient services as well as community and support group	Cross-sectional
Authors and Year	**Sample (N)**	**Relevant Demographics of Sample**	**Exclusion & Inclusion Criteria**	**Trauma Measure**	**Setting**	**Study design**

Van Os et al. 2017	**Patients with non-affective psychosis = 1119** **Siblings of patients N = 1059** **HC = 586**	**Age**(Mean/sd): HC = 30.42(10.58) P = 27.57(7.95) Siblings = 27.83(8.27) Mean whole sample = 28.28(8.76) **Percentage Female:** HC = 54% Siblings = 24% Patients= 42% **Country:** Netherlands & parts of Dutch-speaking Belgium	**Inclusion criteria** patients: age range 16-50 (extremes included), diagnosis of non-affective psychotic disorder according to DSM-IV. For siblings: same as above. For controls: same as above but also no lifetime psychotic disorder, no first degree family member with a lifetime psychotic disorder. Co morbidity in patients and siblings was not an exclusion criteria. When siblings had a lifetime psychotic disorder they were included in the patient group.	CTQ, 25 Item	Outpatients or inpatients	Longitudinal
Authors and Year	**Sample (N)**	**Relevant Demographics of Sample**	**Exclusion & Inclusion Criteria**	**Trauma Measure**	**Setting**	**Study design**

Garcia et al. 2016	79 individuals with early psychosis (P) HC = 59	**Age**(Mean/sd): HC = 24(4.8) P =28.8(5.9) **Percentage Female:** P = 39% HC =47% **Country:** Spain	**Inclusion Criteria:** Early psychosis patients were subjects with a PD less than 3 years from the onset of the illness. **Exclusion criteria:** Pregnancy, learning disaiblity, severe head injury or neurological disease, active glucocorticoid treatment, active substance dependence (other than tobacco or cannabis), language difficulties or visual impairment that limited the administration of the cognitive battery. **Doesn't state for control group, except screened for psychiatric disorder**	CTQ, 28 item	Early Intervention Service. HC = recruited from the community through advertisements	Cross-sectional
Aas & Steen tal. 2012	239 schizophrenia spectrum disorder 167 bipolar patients	**Age**(Mean/sd): 30.07(3) **Percentage Female**: 47% **Country:** Norway	None stated but says part of larger TOP study in Norway, not referenced however	CTQ, 28 Item	From psychiatric units (outpatient and inpatient	Cross-sectional
Authors and Year	**Sample (N)**	**Relevant Demographics of Sample**	**Exclusion & Inclusion Criteria**	**Trauma Measure**	**Setting**	**Study design**

Kelly et al. 2016	P = 100	**Age(Mean/sd):** Male CPA+ = 31.6(9.8) Male CPA- = 30.9(7.7) Women CPA+ = 37.8(10.8) Women CPA- = 32.6(11.9) **Percentage Female:** 47% **Country:** Norway	Not clearly stated.	CTQ, 28 Item	Inpatient and outpatient	Cross-sectional
Lysaker et al. 2001	43 patients with schizophrenia or schizaffective disorder	**Age:** Mean = 45 yrs, sd not stated **Percentage female**: 0 % **Country**: USA	**None stated, except for:** **Inclusion criteria** SCID confirmed DSM IV diagnoses of schizophrenia (n = 31) or schizoaffective disorder (n = 12)	Childhood abuse was assessed with the use of a self-report questionnaire developed specifically for the Mental Health Supplement (29).	Outpatient	Cross-sectional
Authors and Year	**Sample (N)**	**Relevant Demographics of Sample**	**Exclusion & Inclusion Criteria**	**Trauma Measure**	**Setting**	**Study design**

Aas & Navari 2012	83 FEP, 63 HC Only 45 sub sample conducted the trauma measure though	**Age(mean/sd)** P = (27.4/7.9) (28.0/ 7.7) **Percentage Female:** P = 31% HC= 59% **Country: USA**	**Inclusion criteria:** presented for the first time to the local psychiatric services with a functional psychotic illness (ICD-10 F10–19, over a 3-year period. **Exclusion criteria** were (a) history of head trauma resulting in loss of consciousness for over 1 h; (b) presence of a disease of the central nervous system; (c) moderate or severe learning disabilities as defined by ICD-10 (World Health Organisation, 1992a); (d) poor fluency in English language; and (e) transient psychotic symptoms resulting from acute intoxication as defined by ICD-10	Childhood experience ofcare and abuse questionnare but only on a subsample of 45 patients	General population and FEPS presenting for first time at psychiatric services	Cross-sectional
Authors and Year	**Sample (N)**	**Relevant Demographics of Sample**	**Exclusion & Inclusion Criteria**	**Trauma Measure**	**Setting**	**Study design**

Hernaus et al. 2014	89 patients with psychotic disorder, Patient diagnoses were: schizophrenia (n = 69), brief psychotic disorder (n = 2), psychotic disorder not otherwise specified (n = 18). 95 healthy non-psychotic siblings	**Age(mean/sd)** Siblings =26.66(8.79) P =28.08(7.04) **Percentage Female** Siblings = 47% P =33% **Country:** Netherlands	**Inclusion criteria:** Diagnoses were based on DSM-IV criteria, using the Comprehensive Assessment of Symptoms and History (CASH) interview The CASH was additionally used to confirm the absence of non-affective psychosis in siblings **Exclusion criteria** brain injury with loss of consciousness >1 hour, meningitis/other neurological diseases, cardiac arrhythmia, severe claustrophobia, Vmetal corpora aliena (including intrauterine devices) VI) ,pregnancy.	CTQ, 25 item	Outpatient and general population	Longitudinal but not for the measures used in the present study
Schalinski et al. 2018	168 individuals with schizophrenia spectrum disorder, 50 non psychotic HC from general population	**(Mean(SD)** P=27.9(8.4) HC = 26.8(7.9) **Percentage Female:** P = 33% HC =44% **Country**: Germany	**None clearly stated, exclusion criteria** Expert psychiatrists/psychotherapist made diagnosis upon admission: participants met criteria of a diagnosis of schizophrenia 76.2%, schizoaffective disorder 10.7%, and acute polymorphic psychotic disorder 13.1%. Ninety-five individuals with psychosis were admitted for the first time	Subsample f 62, MACE scale developed to capture 10 forms of ACE	Unclear as says admitted for first time?? Outpatients, local centre of psychiatry, and general population	Cross-sectional
Authors and Year	**Sample (N)**	**Relevant Demographics of Sample**	**Exclusion & Inclusion Criteria**	**Trauma Measure**	**Setting**	**Study design**

Shenkel et al. 2005	P = 40	Mean(SD) = 41.9(10.7) (range 20-62) 38% USA	**None clearly stated, exclusion criteria.** All subjects met DSM-IV (American Psychiatric Association, 1994) criteria for schizophrenia (n = 21) or schizoaffective disorder (n = 19) and gave informed consent to participate in the research study.	Structured social history interview of childhood abuse/ neglect	Inpatient psychiatric rehabilitation research unit at a state psychiatric hospital	Cross-sectional
Mccabe et al. 2012	P = 408 HC = 267	P Mean(SD) = 40.72(11.07) HC Mean(SD) = 39.27(13.70) P = 34% HC = 57% **Country:** Australia	**Inclusion criteria:** aged 18 – 65 years. **Exclusion criteria:** Participants are English speaking (required for neuropsychological assessments) and **Exclusion criteria** are organic brain disorder, brain injury with greater than 24 hours post-traumatic amnesia, (IQ <70 70), movement disorders, current diagnosis of substance dependence, electroconvulsive therapy received in the last 6 months and, for controls, a personal or family history of psychosis or bipolar disorder.	Modified version of the childhood adversity questionnaire (CAQ)	Inpatient, outpatient, community, general population	Cross-sectional
Authors and Year	**Sample (N)**	**Relevant Demographics of Sample**	**Exclusion & Inclusion Criteria**	**Trauma Measure**	**Setting**	**Study design**

Ukok et al. 2016	53 UHR	**Mean(SD) = 21.1(4.8)** 26% Country: Turkey	**Inclusion criteria:** criteria to identify individuals at UHR (Yung et al., 1998). **Exclusion criteria:** Unwillingness to participate, illiteracy, mental retardation, prior antipsychotic treatment, severe medical condition, prior history of psychosis that lasted more than a week, and present alcohol and substance abuse.	CTQ, 25 item	Comprised help-seeking persons who came directly or were referred to our university clinic by other psychiatrists for further evaluation	Cross-sectional
Shannon et al. 2011	P = 85,	Mean(SD) = 41.1(11.7) 21% Country: Ireland	**None Clearly stated.** *SM-IV* diagnoses were reached by consensus after case note review and discussion between the responsible psychiatrist and his colleagues. A total of 90 patients fulfilling diagnostic criteria were approached and 85 people gave written consent to participate after a complete description of the study was provided. Of those 85, 67 were male and 18 were female.	CTQ, 28 item version	Community outpatients	Cross-sectional
Authors and Year	**Sample (N)**	**Relevant Demographics of Sample**	**Exclusion & Inclusion Criteria**	**Trauma Measure**	**Setting**	**Study design**

Kilian et al. 2017	FEP or schizophreniform disorder (n = 56) HC = 52	P Mean(SD) = 23.8(6.2) HC Mean(SD) = 25.1(6.8) P = 25%, HC = 65% **Country:** South Africa	**Inclusion criteria:** aged 16–45 years; experiencing a first psychotic episode; and meeting DSM-IV TR (Diagnostic and Statistical Manual of Mental Diseases, Fourth Edition, Text Revisions) We assessed patients with the Structured Clinical Interview for DSM-IV [SCID] (First et al. 2002). **Exclusion criteria** : a lifetime exposure to antipsychotic medication for longer than 4 weeks; any serious general medical condition; obvious current substance abuse; and an educational level of lower than Grade 7. A group of healthy controls, matched for age, gender and ethnicity were recruited from the same catchment area as the patient group through personal contacts and advertisements. Controls were excluded if they had an educational level of lower than Grade 7 and if they had a psychiatric disorder as identified with the SCID, Non-Patient-Edition.	CTQ, 25 Item	Patients were recruited from first admissions to Tygerberg and Stikland hospitals, and from community clinics	Cross-sectional
Authors and Year	**Sample (N)**	**Relevant Demographics of Sample**	**Exclusion & Inclusion Criteria**	**Trauma Measure**	**Setting**	**Study design**

Green et al. 2015	P = 617 HC = 659 617 clinical cases with an ICD-10 diagnosis of schizophrenia (n ¼ 526) or schizoaffective disorder (n ¼ 91), to be referred to collectively as 'SZ', and 659 healthy controls (HC).	P Mean(SD) = 39.65(10.82) , HC Mean(SD) - 42.48(13.58)	**Same as Green et al. (2014)**	The Childhood Adversity Questionnaire (CAQ)	Inpatient and outpatient services as well as community and support group	Data is longitudinal but this study cross-sectional
Authors and Year	**Sample (N)**	**Relevant Demographics of Sample**	**Exclusion & Inclusion Criteria**	**Trauma Measure**	**Setting**	**Study design**

SIdeli et al. 2014	**P =** 134 **HC** =124		Cases were individuals aged 18 to 65 at their first admission fulfilling ICD-10 criteria for psychosis (F20-29 or F30-34); subjects with severe learning disability (IQ < 50), poor English fluency, or a known organic cause for their psychosis were excluded. Controls were recruited from the same catchment area as cases and screened for current or past psychotic disorders using the Psychosis Screening Questionnaire, PSQ [4]	Childhood Experience of Care and Abuse Questionnaire	First admission Controls were recruited from the same catchment area as cases and screened for current or past psychotic disorders using the Psychosis Screening Questionnaire, PSQ	Cross-sectional
Authors and Year	**Sample (N)**	**Relevant Demographics of Sample**	**Exclusion & Inclusion Criteria**	**Trauma Measure**	**Setting**	**Study design**

Aas & Dazzan et al. 2011	138 FEP, 138 HC	P = 47% HC = 54% UK	**Inclusion criteria:** Diagnoses were made according to ICD-10 criteria individuals aged 16–65 years were approached, who consecutively presented for the first time to the local psychiatric services of South-East London for a functional psychotic illness (ICD-10 F10-19, (excluding coding F1x.0 for Acute intoxication; F20-29 and F30-39, psychotic codings; over a 3-year period **Exclusion criteria**: History of head trauma resulting in loss of consciousness for over 1 h, the presence of a disease of the central nervous system, moderate or severe learning disabilities as defined by ICD-10 ,poor fluency in English language; transient psychotic symptoms resulting from acute intoxication as defined by ICD-10). As the focus of the current study was on cognitive function in schizophrenia and affective psychoses (bipolar and affective depression), patients with brief and transient psychosis were excluded. Controls were screened using the Psychosis Screening Questionnaire, exclude if present or past psychotic disorder or any of listed criteria above	Childhood Experiences of Care Abuse Questionnaire (CECA.Q)	Subjects aged 16–65 years were approached, who consecutively presented for the first time to the local psychiatric services of South-East London A random sample of controls was recruited from the same catchment areas as the patients using a procedure adapted from that used by the Office of Population and Census Statistics Psychiatric Morbidity Survey	Cross-sectional

Appendix F Quality ratings utilizing the quality criteria for each reviewed paper

	Quality Criteria	**Overall**

Authors	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Score
Li et al. 2017	1	0	1	1	0	2	2	0	1	1	1	1	1	0	**11**
Van Os et al. 2017	1	2	1	2	0	0	1	2	2	2	2	2	1	0	**18**
Garcia et al. 2016	1	1	2	1	0	1	1	1	1	0	2	2	2	2	**17**
Ukok et al. 2016	1	2	2	1	0	2	1	1	1	0	1	1	1	1	**15**
Sideli et al. 2014	2	2	1	1	0	1	1	0	1	0	2	2	2	1	**16**
Aas & Steen et al. 2012	2	1	1	1	0	2	1	1	2	0	2	2	2	2	**19**
Lysaker et al. 2001	1	2	0	1	0	0	1	1	2	0	2	1	0	1	**12**
McCabe et al. 2012	2	2	1	1	0	0	2	2	2	0	2	1	2	2	**19**
Schalinski et al. 2018	1	1	1	1	0	2	2	2	2	2	2	2	1	1	**20**
Kelly et al. 2016	2	1	0	1	0	2	1	1	2	0	1	2	1	2	**16**
Kilian et al. 2017	2	1	2	1	0	2	2	1	1	0	2	1	1	2	**18**
Aas & Dazzan et al. 2011	2	2	2	1	0	2	2	1	1	0	2	2	2	2	**21**

Shannon et al. 2011	1	1	0	1	0	0	1	1	2	2	2	2	2	2	**17**
Schenkel et al. 2005	2	2	1	1	0	0	1	0	1	0	2	2	2	2	**16**
Green et al. 2015	2	1	2	2	0	1	1	1	1	1	2	1	2	2	**19**
Green et al. 2014	2	2	2	2	0	1	2	0	1	0	2	1	1	2	**18**
Hernaus et al. 201	2	1	2	1	0	0	1	2	2	1	2	2	1	2	**19**
Aas & Navari et al. 2012	2	2	2	2	0	0	1	1	1	1	2	2	2	2	**20**

Appendix G. Full Youth and Mental Health Study Resilience Protocol

Youth Mental Health Risk and Resilience

Study (YouR-Study)

Running title:	YouR-Study
Protocol Version:	**4.0**
Date:	**19.122015**
REC Reference Number:	**14-WS-0099 Sponsor's Protocol Number:GN13CP220**
Sponsor:	**NHS Greater Glasgow & Clyde**
Funder:	**Medical Research Council**

Amendment number	Date	Protocol version
Amendment 01	05 August 2014	Version 2.0
Amendment 02	24 October 2014	Version 3.0
Amendment 03	19 January 2015	Version 4.0

This study will be performed according to the Research Governance Framework for Health and Community Care (Second edition, 2006) and WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI Ethical Principles for Medical Research Involving Human Subjects 1964 (as amended).

Doctorate in Clinical Psychology
Catherine Bois
2018

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PROTOCOL APPROVAL

Youth Mental Health Risk and Resilience Study (YouR-Study)

Chief Investigator **Dr. Peter J. Uhlhaas**

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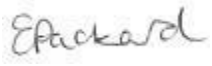
Signature: 

Date: 2310/2014

TABLE OF CONTENTS

ABBREVIATIONS

AE	Adverse event
BACS	Brief Assessment of Cognition in Schizophrenia Battery
BLIPS	Brief Limited Intermittent Psychotic Symptoms
CAARMS	Comprehensive Assessment of At-Risk Mental State
CANTAB	Cambridge Neuropsychological Test Automated Battery
CCNi	Centre for Cognitive Neuroimaging
CI	Chief Investigator
EHRS	Edinburgh High Risk Study
EEG	Electroencephalography
FEP	First-Episode Psychosis
fMRI	Functional Magnetic Resonance Imaging
GABA	Gamma-Aminobutyric Acid
GAF	Global Assessment of Functioning
MEG	Magnetoencephalography
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Spectroscopy
PANSS	Positive and Negative Syndrome Scale
PQ	Prodromal Questionnaire
R&D	Research and Development
REC	Research Ethics Committee
SAE	Serious Adverse Event
SCID	Structured Clinical Interview for DSM-IV
SIPS	Structured Interview for Prodromal Syndromes
SPI-A	Schizophrenia Proneness Instrument, Adult Version
ScZ	Schizophrenia
UHR	Ultra-High-Risk

STUDY SYNOPSIS

Title of Study:	Youth Mental Health Risk and Resilience Study
Study Centres:	NHS Greater Glasgow and Clyde University of Glasgow NHS Lothian University of Edinburgh
Duration of Study:	48 Months
Primary Objective:	To Develop a Biomarker for the Early Diagnosis of Psychosis
Secondary Objective:	To Examine the Psychological Processes Underlying the UHR-State and Identify Changes during the Transition to Psychosis
Primary Endpoint:	Neural Synchrony Parameters in MEG-Data
Rationale:	The presence of changes in neural synchrony in UHR-participants and FEP has not been comprehensively investigated
Methodology:	Longitudinal
Sample Size:	100 UHR-participants, 25 FE-ScZ patients and 50 age-matched healthy controls
Screening:	PQ/Basic Symptom-Questionnaire, CAARMS/SIPS/SPI-A Scales
Registration/Randomisation:	N/A
Main Inclusion Criteria:	Inclusion criteria UHR: Written informed consent Male or non-pregnant female ≥16 years of age UHR-criteria according to CAARMS/SIPS or SPI-A normal to corrected vision Inclusion criteria FEP: Written informed consent Male or non-pregnant female ≥16 years of age Diagnosis of FEP (DSM-IV 295.0) normal to corrected vision Inclusion criteria (controls) Written informed consent Male or non-pregnant female ≥16 years of age normal to corrected vision

Main Exclusion Criteria:	Exclusion criteria (UHR) An existing neurological disorder > 35 years of age Metal implants in body parts Pregnancy suicidal ideation Exclusion criteria (FEP) An existing neurological disorder > 35 years of age Metal implants in body parts Pregnancy suicidal ideation Exclusion criteria (controls) An existing neurological disorder > 35 years of age Metal implants in body parts Pregnancy 1st degree relative with a diagnosis of ScZ suicidal ideation
Statistical Analysis:	Time-Frequency Analysis, Cluster-based test statistics for MEG-Signals, Information theoretical analysis

SCHEDULE OF ASSESSMENTS: UHR-GROUP

Study Procedure	Screening I	Visit 1: Screening Interview	Visit 2: Debriefing	Visit 3 Psychol. Assessment I	Visit 4 Psychol. Assessment III	Visit 5 MEG/ MR	Follow-UP (every 3 months for up to 2 years)
Timeline		1 month (+/- 2 weeks)	1 month (+/- 2 weeks)	1 month (+/- 2 weeks)	2 months (+/- 2 weeks)		
Obtain Informed Consent	√	√					
Review Inclusion/Exclusion Criteria		√	√				
Screening Questionnaire	√						
Demographic Information	√	√					
Visual Acuity					√		
CAARMS		√		√			√
SPI-A		√		√			
SIPS		√		√			√
Mini-SKID				√			
SCID-Interview							√
Questionnaires				√	√	√	√
Neuropsychology					√		
MEG-Measurement						√	
MR-Measurement						√	
Blood-Samples						√	
Urine-Samples						√	

SCHEDULE OF ASSESSMENTS: FEP-GROUP

Study Procedure	Screening I	Visit 1: Screening Interview	Visit 2: Debriefing	Visit 3 Psychol. Assessment I	Visit 4 MEG/MR	Follow-UP
Timeline		1 month (+/- 2 weeks)	1 month (+/- 2 weeks)	1 month (+/- 2 weeks)	1 month (+/- 2 weeks)	3 months (+/- 2 weeks)
Obtain Informed Consent	√	√				
Review Inclusion/Exclusion Criteria		√	√			
Screening Questionnaire	√					
Demographic Information	√	√				
Visual Acuity				√		
CAARMS		√				
SPI-A		√				
SIPS		√				
Mini-SKID						
PANSS				√		√
SCID-Interview				√		
Questionnaires						
Neuropsychology						√
MEG-Measurement					√	√
MR-Measurement					√	
Blood-Samples					√	
Urine-Samples					√	

SCHEDULE OF ASSESSMENTS: Control-GROUP

Study Procedure	Visit 1: Screening Interview	Visit 2 Psychol. Assessment I	Neuroimaging I	Visit 3: Psychological Assessment	Neuroimaging II
Timeline	1 month (+/- 2 weeks)	1 month (+/- 2 weeks)	1 month (+/- 2 weeks)	2 months (+/- 2 weeks)	2 months (+/- 2 weeks)
Obtain Informed Consent	√				
Review Inclusion/Exclusion Criteria		√			
Screening Questionnaire	√				
Demographic Information	√				
Visual Acuity	√				
CAARMS	√				
SPI-A	√				
SIPS	√				
Mini-SKID	√				
PANSS					
Questionnaires	√	√			
Neuropsychology		√		√	
MEG-Measurement			√		√
MR-Measurement			√		
Blood-Samples			√		
Urine-Samples			√		

GLOSSARY OF TERMS

Gray-Matter: is a major component of the central nervous system, consisting of neuronal cell bodies, neuropil (dendrites and myelinated as well as unmyelinated axons), glial cells (astroglia and oligodendrocytes) and capillaries. Grey matter is distinguished from white matter, in that grey matter contains numerous cell bodies and relatively few myelinated axons, while white matter is composed chiefly of long-range myelinated axon tracts and contains relatively very few cell bodies.

Diffusion Tensor Imaging (DTI): allows the mapping of the diffusion process of molecules, mainly water, in biological tissues, in vivo and non-invasively. Molecular diffusion in tissues is not free, but reflects interactions with many obstacles, such as macromolecules, fibers, membranes, etc. Water molecule diffusion patterns can therefore reveal microscopic details about tissue architecture, either normal or in a diseased state.

Magnetic Resonance Imaging (MRI): is a medical imaging technique used in radiology to investigate the anatomy and function of the body in both health and disease. MRI scanners use strong magnetic fields and radiowaves to form images of the body. The technique is widely used in hospitals for medical diagnosis, staging of disease and for follow-up without exposure to ionizing radiation.

Magnetic Resonance Spectroscopy (MRS): is a specialised technique associated with magnetic resonance imaging (MRI). MRS is a non-invasive ionizing radiation free analytical technique that has been used to study metabolic changes.

Neural Synchrony: A neuronal synchrony measure is a number that quantifies the level of synchrony of a large population of neurons

within a network. It is usually normalized to be between 0 and 1. It is equal to 0 when the neurons in the population fire in an asynchronized manner, it is equal to 1 when all those neurons fire in full synchrony, exactly at the same times, and it is between 0 and 1 for partially synchronized states, i.e., states in which the firing times of the neurons are related (synchronized) but not identical (fully synchronized).

Magnetoencephalography (MEG): a functional neuroimaging technique for mapping brain activity by recording magnetic fields produced by electrical currents occurring naturally in the brain, using very sensitive magnetometers. Arrays of SQUIDs (superconducting quantum interference devices) are currently the most common magnetometer, and SERF being investigated for future machines. Applications of MEG include basic research into perceptual and cognitive brain processes, localizing regions affected by pathology before surgical removal, determining the function of various parts of the brain, and neurofeedback.

Neural Oscillations: Neural oscillation is rhythmic or repetitive neural activity in the central nervous system. Neural tissue can generate oscillatory activity in many ways, driven either by mechanisms localized within individual neurons or by interactions between neurons. In individual neurons, oscillations can appear either as oscillations in membrane potential or as rhythmic patterns of action potentials, which then produce oscillatory activation of post- synaptic neurons. At the level of neural ensembles, synchronized activity of large numbers of neurons can give rise to macroscopic oscillations, which can be observed in the electroencephalogram (EEG). Oscillatory activity in groups of neurons generally arises from feedback connections between the neurons that result in the synchronization of their firing patterns. The interaction between neurons can give rise to oscillations at a

different frequency than the firing frequency of individual neurons.

White Matter (WM): White matter is one of the two components of the central nervous system and consists mostly of glial cells and myelinated axons that transmit signals from one region of the cerebrum to another and between the cerebrum and lower brain centers. White matter tissue of the freshly cut brain appears pinkish white to the naked eye because myelin is composed largely of lipid tissue veined with capillaries. Its white color is due to its usual preservation in formaldehyde.

1. INTRODUCTION

1.1 Background

Schizophrenia (ScZ) is the most severe manifestation of psychosis and is recognised as a debilitating mental illness with a lifetime prevalence of approximately 1% which leads to enormous economical and social costs (20 billion € in 2005 in EU) [1]. This is due to the fact that the pathophysiology is still unclear and the existing treatments are largely ineffective in targeting the pronounced cognitive and physiological dysfunctions.

One critical factor in potentially improving the outcome would be the identification of individuals at ultra high-risk (UHR) for the development of First Episode Psychosis (FEP) to allow the possibility to intervene prior to the full manifestation of the syndrome [2]. Evidence suggests that FEP is preceded by a prodromal early phase involving attenuated subthreshold, psychotic symptoms of up to 5 years [3] which are associated with a reduction in brain tissue and cognitive deficits [4]. Accordingly, one central goal of current research is the characterization of the underlying pathophysiological processes in UHR-participants and the development of biomarkers, which would allow prediction of the illness-trajectory, as well as the identification of psychological and neurobiological mechanisms which confer resilience in at-risk individuals.

The search for biomarkers for early diagnosis identification of psychosis has focused on brain imaging techniques with an excellent spatial but limited temporal resolution for neural events, such as functional and anatomical magnetic resonance imaging (fMRI) [4]. This issue may be important because normal brain functioning and the associated cognitive processes are fundamentally depended upon fast (millisecond) and transient synchronization of neural oscillations [5] which are ideally captured with Electro/Magnetoencephalography (EEG/MEG) approaches.

Emerging evidence suggests that ScZ is associated with aberrant neural oscillations and their synchronization (neural synchrony), in particular at gamma-band frequencies (30-200 Hz), during a wide range of cognitive and perceptual processes, including working memory [6] and visual perception [7]. Brain oscillations have been shown to occur during normal brain functioning and are closely linked to the ability to perceive, memorize and attend to information. Thus, it appears that brain

oscillations could be a key to understanding the prediction of those who develop FEP and ScZ.

Importantly, the impairments in neural synchrony are ideally suited for translational research because of evidence linking gamma-band oscillations during normal brain functioning to the integrity of GABAergic interneurons [8] and glutamatergic neurotransmission [9]. Supporting this hypothesis, the diagnosis of ScZ is associated with pronounced abnormalities in levels of GABA and Glutamate measured by magnetic resonance spectroscopy (MRS) [10].

Rationale

ScZ remains one of the most challenging and urgent problems in science and medical research because of the severe disability associated with the disorder and the lack of progress in identifying the underlying causes. One critical factor in potentially improving the outcome of ScZ would be the identification of individuals at high-risk for the development of the disorder, to allow the possibility to intervene prior to the full manifestation of the syndrome.

In the proposed project, we will employ for the first time a state-of-the-art MEG approach to investigate neural synchrony in UHR-participants for the development of FEP with the aim of improving the prediction of progression. Despite the fundamental role of neural oscillations and their synchronization in the pathophysiology of ScZ [11], neural synchrony in UHR- participants has not been systematically explored. In addition, we will employ MRS to establish links between aberrant GABAergic and Glutamategic neurotransmission and neural synchrony parameters in prodromal ScZ.

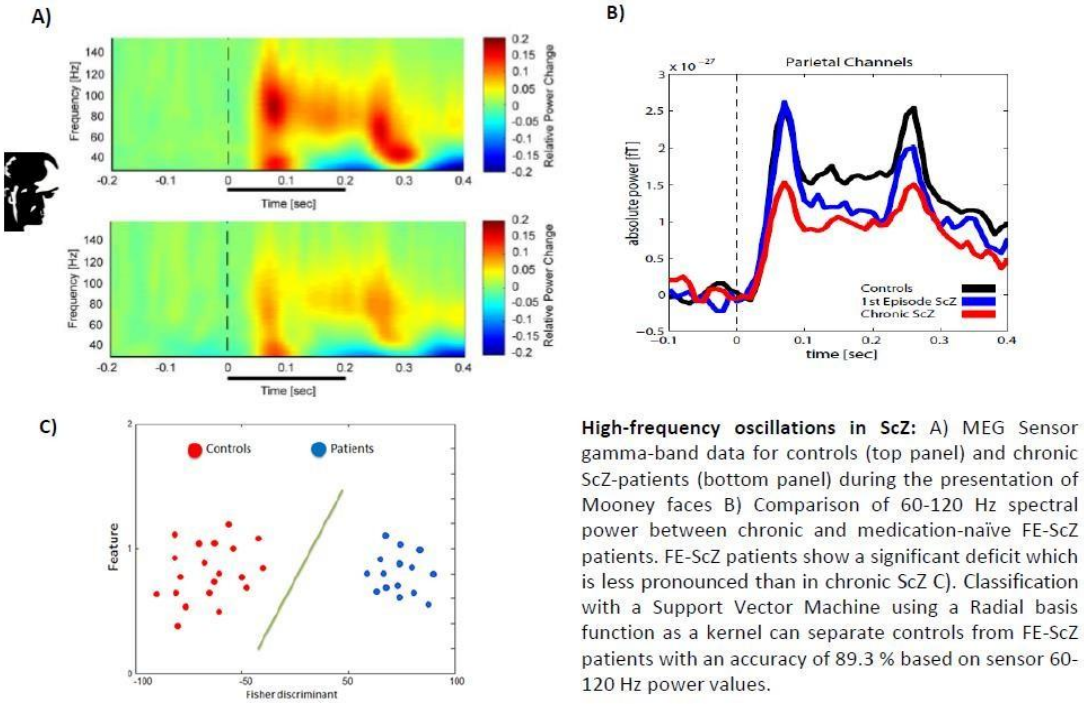
In essence, the impact of this research will target the physiological and psychological mechanisms that predispose and protect individuals from developing psychosis. Firstly, we will gain an unprecedented amount of insight into the contribution of neural synchrony to the onset and cognitive dysfunctions amongst young people at risk of FEP through the reconstruction of large-scale oscillatory networks during resting-state and cognitive processes. This will give rise to new explanatory theories and specific models of pathophysiological processes. Secondly, we will develop a

prognostic model based on MEG- data that will allow the early detection of participants with an elevated risk for the development of FEP which can be used for the prediction of the illness course, thus leading eventually to more targeted therapeutic approaches and possibly reducing the incidence of FEP. Thirdly, we will establish links with core dysfunctions in GABAergic and Glutamatergic neurotransmission through correlations with MRS-data which will be crucial for links with translational research and the development of novel, evidence-based interventions for UHR- participants.

In addition to UHR-participants, we expect that we will also detect participants who are already experiencing FEP-symptoms. Recruitment of this group will allow comparisons of brain activity patterns with UHR-participants. Finally, we will identify the contribution of core psychological variables, such as trauma, interpersonal functioning and affect regulation, towards transition to FEP which will could potentially lead to an improved understanding of onset-mechanisms of psychosis.

Furthermore, we will carry out comprehensive psychiatric and psychological assessments which will provide clinically-relevant information which could be potentially be relevant for treatment planning in FEP- and UHR-participants.

Figure 1. MEG gamma-band oscillations in chronic and first-episode ScZ



High-frequency oscillations in ScZ: A) MEG Sensor gamma-band data for controls (top panel) and chronic ScZ-patients (bottom panel) during the presentation of Mooney faces B) Comparison of 60-120 Hz spectral power between chronic and medication-naïve FE-ScZ patients. FE-ScZ patients show a significant deficit which is less pronounced than in chronic ScZ C). Classification with a Support Vector Machine using a Radial basis function as a kernel can separate controls from FE-ScZ patients with an accuracy of 89.3 % based on sensor 60-120 Hz power values.

1.2 Prior experience of intervention in ScZ/UHR-participants

Previous work by the Chief Investigator (CI) with MEG has demonstrated pronounced impairments in high-frequency oscillations in chronically, medicated ScZ patients [12] as well as in medication-naïve FEP patients [13]. With a particular relevance for the present proposal, fluctuations in 60-120 Hz power could be used to differentiate participants with FEP from controls with a discrimination accuracy of 90 % through a linear classifier (Figure 1).

Recruitment of UHR-participants will be supported by Prof. Andrew Gumley, Professor of Psychological Therapy, University of Glasgow and NHS Greater Glasgow & Clyde. In a previous study funded by the Medical Research Council (MRC), a sample of 61 participants meeting UHR-criteria was obtained over a 30-months period from the clinical services associated with NHS Greater Glasgow and Clyde, demonstrating the feasibility of recruitment [14]. Much was learned regarding the pathways into care for this population and this learning will be applied in devising recruitment strategies for the proposed project.

In addition to NHS-Greater Glasgow and Clyde, recruitment of UHR-participants will also involve NHS Lothian and the Departments of Psychiatry and Clinical Psychology at Edinburgh University. Recruitment will be supported by Matthias Schwannauer who is Professor of Clinical Psychology and Head of Clinical & Health Psychology at the University of Edinburgh. He is also Consultant Clinical Psychologist at the Early Psychosis Support Service in NH Lothian. Professor Stephen Lawrie is Head of the Division of Psychiatry in Edinburgh and Director of the Scottish Mental Health Research Network. He supervised the MRC funded structural and functional MRI components of the Edinburgh High Risk Study.

1.3 Study hypothesis

1) We expect significant impairment in neural synchrony parameters in UHR-participants as well as in the FEP-group

2) Impairments in neural synchrony will be significantly more pronounced in those UHR- participants who will make a transition to FEP.

3) We expect increased GABA/Glutamate levels as assessed through

MRS-measurements in UHR- and FEP groups

4) In addition, UHR- and FEP groups will be characterized by reduced gray-matter volume in cortical and subcortical regions as well as reduced organization and volume of white-matter

5) We expect significant correlations between impaired neural synchrony parameters, altered GABA/Glutamate levels and anatomical variables (MRI, DTI)

6) We will explore correlations with psychological measures of attachment, affect regulation and trauma in order to inform the developing understanding of important psychological measures and their relationship with pathophysiology

1.4 Risks

The neuroimaging-measurements employed (MEG, MR) are safe and non-invasive techniques which have no known risks or side effects. Participants will be carefully screened at study entry whether they fulfil exclusion criteria, such as metal implants, for participating in neuroimaging experiment (see MR-Checklist). A mental health research nurse (RN) will attend all MEG- and MR-measurements of participants meeting UHR/FEP-criteria. If a participant becomes distressed during an assessment, the measurement will be discontinued.

2. STUDY OBJECTIVES

1) The recruitment of a large sample 100 UHR-participants and 50 healthy controls over a 4- year period as well as a follow-up to detect transition to FEP in the UHR-group

2) To recruit a sample of n = 25 FEP-participants

2) MEG-measurements during resting-state and task-related activity in combination with a novel methodological approach to comprehensively characterize neural synchrony in UHR-and participants and FEP

3) To establish links between aberrant neural synchrony parameters and proton MRS measured GABA/Glutamatergic signalling

4) To identify the relationships between MEG-parameters and cognitive dysfunctions in UHR- participants and FEP

5) To develop a MEG biomarker for predicting transition to FEP

6) To identify the contributions of attachment, affect regulation and trauma for transition to FEP

This study aims to comprehensively characterize neural circuit dysfunctions in UHR-participants using a multi-modal imaging approach and their relationship to core psychological variables. Specifically, we will investigate patterns of neural oscillations in MEG-data that shall lead to a prognostic index to allow early detection of participants with an elevated risk for the development of FEP

- Primary Endpoint
  - *Neural Oscillations in MEG-Data*
- **Secondary endpoints**
  - *MRS measurements of GABA and Glutamatelevels*
  - *fMRI-resting state activity*
  - *Conversion to Psychosis*
  - *Neuropsychological functioning*
  - *Social and Role Functioning*
  - *Affect Regulation*
  - *Stress Levels*

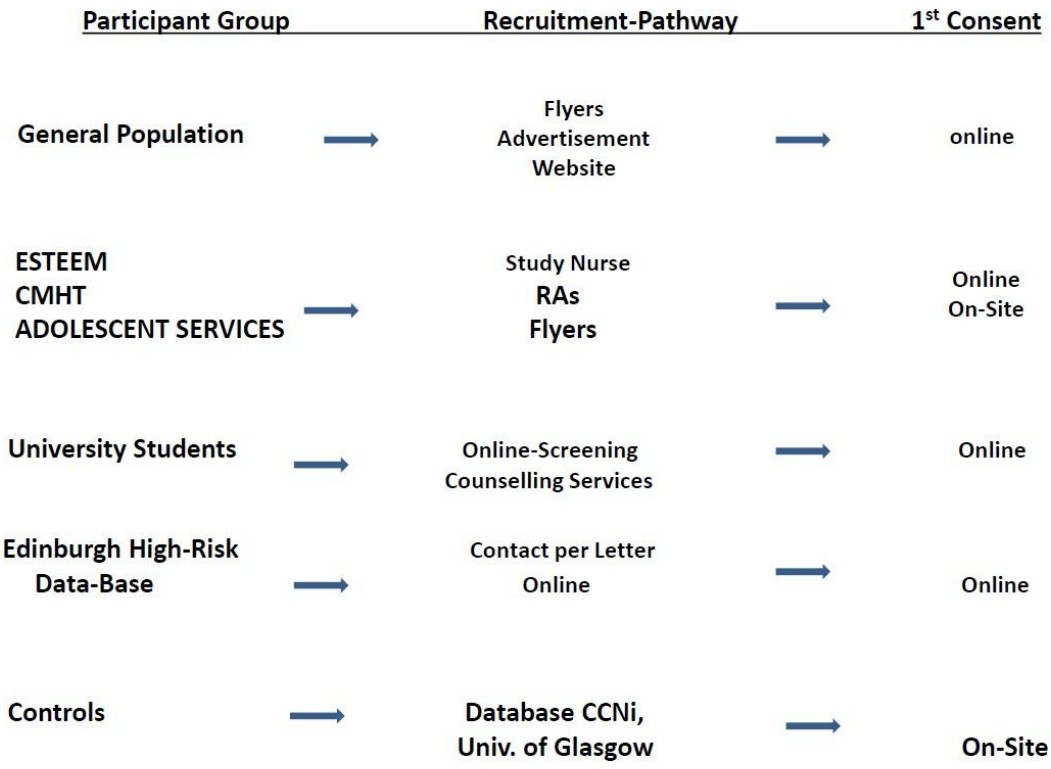
3. STUDY DESIGN

The study will be a longitudinal cohort design in UHR-participants and FEP using neuroimaging to investigate brain activity in young people at UHR. The YouR-Study will be performed according to the Research Governance Framework for Health and Community Care (Second edition, 2006).

3.1 Study Population

We aim to recruit up to 100 participants meeting UHR-criteria (see Table 1, Appendix A) and we expect to identify from this participant group an additional n = 25 participants who meet criteria for FEP over a four-year period. 50 controls will also be recruited. The recruitment of the UHR- and FEP-groups will involve NHS-patients services in NHS Greater Glasgow and Clyde, NHS Lothian, student counselling services, and the general population (see Figure 2).

Figure 2. Study Flow Chart



3.2 Inclusion criteria (UHR)

- Written informed consent
- Male or non-pregnant female ≥16 years of age
- UHR-criteria according to CAARMS/SIPS or SPI-A
- normal to corrected vision

3.3 Exclusion criteria (UHR)

- An existing neurological disorder
- > 35 years of age
- Metal implants in body parts
- Pregnancy
- suicidal ideation

3.4 Inclusion criteria (FEP)

- Written informed consent
- Male or non-pregnant female ≥16 years of age
- Diagnosis of FEP (DSM-IV 295.0)
- normal to corrected vision

3.5 Exclusion criteria (FEP)

- An existing neurological disorder
- > 35 years of age
- Metal implants in body parts
- Pregnancy
- suicidal ideation

3.6 Inclusion criteria (controls)

- Written informed consent
- Male or non-pregnant female ≥16 years of age
- normal to corrected vision

3.7 Exclusion criteria (controls)

- An existing neurological disorder

- > 35 years of age
- Metal implants in body parts
- Pregnancy
- 1st degree relative with a diagnosis of ScZ
- suicidal ideation

3.7 Identification of participants and consent

The YouR-study comprises of 2 phases: initial screening and a further assessment phases. Consent will be taken following the initial screening phase for those meeting the initial screening criteria. Only those participants that are confirmed to be UHR or FEP will be invited for further neuroimaging and psychological assessments.

General population: We will recruit potential participants from the general population through a website and flyers (see Attachment). Informed consent for the 1st screening stage will be obtained online after the purposes and aims of the screening are explained.

NHS-Patients Greater Glasgow and Clyde and NHS-Lothian: We will develop close relationships with psychiatrists, primary care and secondary mental health services including ESTEEM First Episode Psychosis Service (Glasgow), the Early Psychosis Support Service (Lothian), Community Mental Health Teams (CMHTs), Primary Care Mental Health Teams (PCMHTs), Clinical Psychology Services, Community Adolescent Mental Health Services (CAMHS), and non-statutory (third sector) mental health services.
Potential participants will be initially informed of the study by a member of their direct care team and can then either obtain information through leaflets or will be approached through a member

of the research team once the potential participant has provided verbal consent that their contact details can be shared. A member of the research team will then explain the purpose of the study. Following this, informed consent will either be obtained on-site after a period of 24 hrs or a participant can register online for the study.

Edinburgh High-Risk Data base: Participants from the Edinburgh High-Risk Study (EHRS) will be approached. The EHRS was a longitudinal prospective study of the development of ScZ, involving repeated clinical, neuropsychological and neuroimaging assessments in almost 200 individuals at high genetic risk of ScZ. This study was conducted at the Department of Psychiatry, University of Edinburgh. The custodian of the database study will approach potential participants after contacting their GP.

Recruitment through Universities and Student Counselling Services: We will approach University counselling services for potential referrals. A referral sheet will allow counsellors to assess the potential appropriateness of a referral (Appendix). The student will verbally confirm that their details can be passed to the research team. The first screening assessment will then either be carried out online or on-site. In addition, students will be invited through an email to take part online in the study.

3.8 Withdrawal of participants

Participants will be informed that they can withdraw at any point during the study and that this will not affect the care or treatment that they receive. This will be explained to the participant during the informed consent process. Identifiable data collected up to the point of withdrawal will be retained, no further data will be collected once the participant has withdrawn.

In addition, participation who have completed the screening

questionnaire but who do not fulfill criteria for either UHR-status or FEP, will not be invited to participate in phase 2 of the study. The ineligible participants will a debrief session with the CI and if required will be notified of a referral process to NHS services.

4. TRIAL PROCEDURES

4.1 Study schedule

The initial screening and psychological assessments for patients recruited through NHS Greater Glasgow & Clyde will be conducted at the University of Glasgow, University of Edinburgh, or participants homes. Neuroimaging assessments for all groups of participants will be conducted at the Centre for Cognitive Neuroimaging (CCNi), University of Glasgow.

Screening Questionnaire

- Informed consent will be obtained either online through the website or on site by a member of the research team. Following informed consent, the screening questionnaire will be administered (Appendix) and basic demographic information will be obtained. If participant score below 6 items on the PQ or endorse less than 3 perceptual and cognitive items, the participant will not proceed further and the data will be deleted.

- All participants who fill-out the questionnaire will informed of the opportunity to take part in a prize-draw for an I-pad. If the participant agrees to entry in the prize-draw, the email-address of participants will be stored.

Screening Interview (Visit I)

- If participants endorse more then 6 items on the PQ or 3 or more perceptual/cognitive items, participants will be contacted per telephone/email by a member of research team. Basic demographic information will be confirmed as well as data concerning and suicidality will be obtained. If participants are currently suicidal, appropriate referrals will be made and the participant will not continue in the study.
- A first visit will then be scheduled. After informed consent is obtained during which the positive scale of the CAARMS/SIPS-Interview [15, 16] and the COGDIS/COPER items for the SPI-A [17] are administered to establish UHR-criteria. In addition, information about family history, drug abuse and demographic information will be obtained (see Appendix). (Duration 90-120 Min)

Following the screening stage, participants who have completed the screening-questionnaire and screening-interview will be discussed in a weekly team-meeting to confirm potential UHR or FEP-criteria.

Debriefing (Visit II)

- All participants who have completed the screening stage will be invited for a debrief visit. If participants do not meet criteria for UHR or FEP, they will be debriefed about the study and if a referral for further psychiatric evaluation and treatment is required, appropriate referrals will be made.

- Participants who were found to potentially be FEP during phase 1 (screening) will be referred to the appropriate NHS service and if appropriate invited to continue participation in the study to Phase 2.
- Participants who meet UHR criteria will be invited take part in phase 2 (assessments).

Phase 2 (assessments) will differ between UHR and FEP participants.

UHR-participants

Psychological Assessment I (Visit III)

The positive scale of the CAARMS/SIPS-Interview [15, 16], the COGDIS/COPER items for the SPI-A [17] and M.I.N.I. International Neuropsychiatric Interview (M.I.N.I. 6.0)

[19] as well as the scales for premorbid adjustment and social and functional role scale will be administered. (Duration 90-120 Min)

Psychological Assessment III (Visit IV)

UHR-participants will receive further neuropsychological assessments and questionnaires which assess global and social functioning.

- The neuropsychological assessment consists of the Brief Assessment of Cognition in Schizophrenia Battery (BACS) [18] as well the following tasks from the University of Pennsylvania Computerized Neuropsychological Testing Battery (PennCNP): a) Continuous Performance Test b) N-Back Task and c) Emotion Identification Task. In addition, the Edinburgh Handedness Inventory, the National Adult Reading Test and visual acuity test will be administered.
- Several psychological measures will be used in order to identify

mechanisms of change and predictors of outcome. All are brief self-report scales, which have good psychometric properties. We have successfully used all of these measures in several large studies including CBT trials. These include:

1) The Beliefs About Paranoia Scale (BAPS) 2) The Brief Core Schema Scale (BCSS)

3) The Psychosis Attachment Measure (PAM-SR) 4) Adverse childhood experience scale (ASES) and 5) The Rust Inventory of Schizotypal Cognitions (RISC) (duration: 2 hours)

FEP-group

Psychological Assessment I (Visit III)

- Participants who may have a FEP will receive the SCID and the PANSS to establish the likelihood of an existing DSM 295.9 diagnosis. If this is confirmed, an immediate referral to FEP-services will be initiated where further diagnostic assessments will be conducted and treatment is initiated. (Duration 90-120 Min)

Controls

Screening and Psychological Assessment I (Visit I)

- Informed consent will be obtained and the positive scale of the CAARMS/SIPS- Interview [15, 16], the COGDIS/COPER items for the SPI-A [17] and M.I.N.I. International Neuropsychiatric Interview (M.I.N.I. 6.0) [19] will be administered. In addition, the scales for premorbid adjustment and social and functional role scales (Cornblatt et al.) will be used as well as a visual acuity test. (Duration 90-120 Min)

Screening and Psychological Assessment I (Visit II)

Neuropsychological assessments and questionnaires will be administered during Visit II.

- The neuropsychological assessment consists of the Brief Assessment of Cognition in Schizophrenia Battery (BACS) as well the following tasks from the University of Pennsylvania Computerized Neuropsychological Testing Battery (PennCNP): a) Continuous Performance Test b) N-Back Task and c) Emotion Identification Task. In addition, the Edinburgh Handedness Inventory and the National Adult Reading Test will be administered.
- In addition, the following questionnaires will be administered: 1) The Beliefs About Paranoia Scale (BAPS) 2) The Brief Core Schema Scale (BCSS) 3) The Psychosis Attachment Measure (PAM-SR) 4) Adverse childhood experience scale 5) The Rust Inventory of Schizotypal Cognitions (RISC) 6) Inventory of interpersonal problems – 32 item Version 7) The Significant Others Scale and 8) The International Positive and Negative Affect Schedule, short-form (I-PANAS-SF) and 9) Social Interaction Anxiety Scale (SIAS) (duration: 2 hours)

Neuroimaging for UHR/FEP/Controls

All participants will receive the same neuroimaging protocol following the psychological assessments. For participants in the FEP-group if feasible for acutely psychotic patients, the neuroimaging will be conducted before or shortly after the initiation of appropriate pharmacological treatment. MEG and MR-measurements will be conducted at the Centre for Cognitive Neuroimaging (CCNi), University of Glasgow.

The MRI- and MEG-protocols consist of the

following measurements. MRI:

a) a resting-state fMRI-measurement
b) an anatomical scan
c) a DTI-sequence
d) a MRS-measurement to obtain information on GABA and Glutamate levels Total duration: 60 min

MEG:

a) Resting-State activity during an eyes-closed and eyes-open
b) Moving-Grating Task: The task requires participants to fixate a sine-wave grating which accelerates at an unpredictable moment (Figure 1a)
c)
d) An auditory steady-state (ASS) paradigm: Participants are passively presented auditory stimuli consisting of 1500-msec broadband noise bursts at 5 and 80 Hz (100 trials per frequency) presented through plastic tubes at 76 dB sound pressure level. On other trials, participants will initiate the same auditory stimuli through button press which allows for a comparison between auditory responses during a self-initiated sensory processing vs. passive stimulation.
e) A variant of a mismatch-negativity (MNN) paradigm which involves the manipulation of local and global predictions [29] (see Figure 2). In this task, a series of tones are presented. When a rare sound is introduced within a sequence of repeated frequent sounds, it elicits a novelty response in the event- related potential, which has been termed the “mismatch negativity”
(MMN) (Figure 2b).
Total duration: 90 minutes

Figure 2.

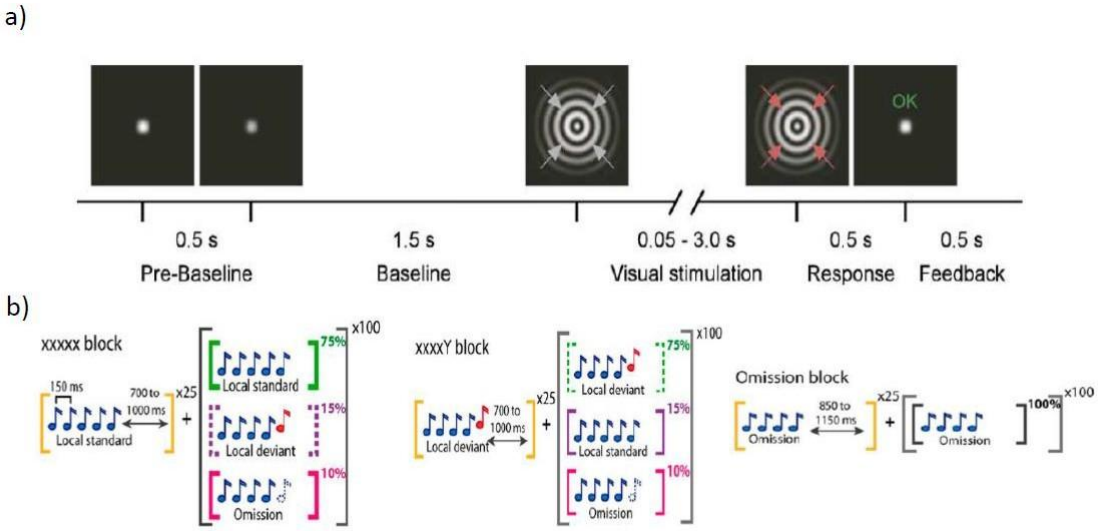


Figure 2. a) Moving-Grating task: Participants are required to fixate a circular sine-wave grating which accelerates at an unpredictable moment and button press whether an acceleration occurs. b) MMN-Paradigm: Three auditory stimuli could be presented: local standards (a series of five identical tones, denoted xxxxx), local deviants (four identical tones followed by a different tone; denoted xxxxY), and omissions (four identical tones; denoted xxxx). These stimuli were presented in three types of blocks in which one series was presented with a high frequency (initially 100%, then 75%) and the other series were rare. This design thus separated the local deviancy of the fifth sound from the global deviance of the entire sequence and also allowed to probe whether the omission effect differed when a standard or a deviant tone was expected.

Blood und Urine Samples: In addition, a blood and urine sample may be taken prior to the MRI-measurement for potential genetic testing and analysis of proteins and metabolites. Blood/urine samples will be stored at the biorepository of the NHS Greater Glasgow and Clyde health board.

UHR-participants: Before/after the MRI/MEG-assessments, the following questionnaires will be administered 1) Inventory of interpersonal problems – 32 item Version 2) The Significant Others Scale and 3) The International Positive and Negative Affect Schedule, short-form (I- PANAS-SF) and 4) Social Interaction Anxiety Scale

All participants: 1) questionnaire for the assessment of musicality and 2) the assessment of video gaming

UHR- follow up

- Follow-up interviews via telephone will be conducted every 2-3 months with UHR- participants. This will include subscales of the SIPS/CAARMS as well as the following questionnaires to examine stress-levels, interpersonal functioning and affect regulation. 1) Inventory of interpersonal problems – 32 item Version 2) The Significant Others Scale and 3) The International Positive and Negative Affect Schedule, short-form (I-PANAS-SF) (Total duration: 90 minutes)
- In addition to the SIPS/CAARMS and questionnaires, the SCID I and II interview and the social and functional role scales will be added at follow-up appointments at 6, 12 and 24 months.

FEP follow-up

- After a 3-month period initiation of appropriate clinical interventions, a follow-up measurement will be scheduled. These include MEG-measurements with MEG, neuropsychological tests as well as a PANSS-interview. In addition, the Edinburgh Handedness Inventory and the National Adult Reading Test will be administered.

Control Follow-Up

- a psychophysical assessment to examine elementary visual and auditory functions will be scheduled to allow for correlations between MEG-parameters and sensory processes in controls

4.2 a second MEG-measurement will be scheduled in which the resting-state protocol and MMN-paradigm will be recorded. These measurements shall establish the test-retest reliability of these parameters.

Study Outcome Measures

4.2.1 Primary Outcome Measure

The primary outcome measures are MEG-recorded neural oscillations.

4.2.2 Secondary Outcome Measure

Secondary outcome measures are:

a) conversion to psychosis in UHR-subjects
b) MRS-Spectroscopy
c) Resting-State fMRI
d) neuropsychology
e) trauma-, stress- and affect-levels

5. ASSESSMENT OF SAFETY

Following obtaining consent, participants will be screened for potential metal implants and other exlusion criteria for MEG and MR-measurements.

6. PHARMACOVIGILANCE

6.1 Definitions of adverse events

Adverse Event (AE) – Any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.

6.2 Serious Adverse Event (SAE)

Any adverse event or adverse reaction that:

a. results in death
b. is life threatening
c. requires hospitalisation or prolongation of existing hospitalisation
d. results in persistent or significant disability or incapacity
e. consists of a congenital anomaly or birth defect
f. is otherwise considered medically significant by the investigator
g. Important adverse events/ reactions that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above.

6.3 Reporting

Any SAE occurring to a research participant will be reported to the Sponsor and the Research Ethics Committee (REC) where in the opinion of the Chief Investigator (CI), the event was

- Related **and**
- Unexpected

7. STATISTICS AND DATA ANALYSIS

7.1 Statistical analysis plan

The proposed project aims to establish a biomarker for the early identification of FEP in UHR- participants. For the analysis of MEG-signals, advanced statistical methods to estimate task- related effects and to control for multiple comparisons will be employed, such as cluster- based test statistics, that have been employed by the CI's research group. In addition, we will systematically explore relationships between neural synchrony variables (task and resting- state) and GABA/Glutamate levels with psychopathological and psychological variables in the UHR-group. Specifically, we will identify those MEG (sensor, frequency and source-regions) and MRS-parameters with the largest effect size and perform information theoretical analysis to identify linear and non-linear dependencies.

7.2 Software for statistical analysis

Statistical analysis will be performed in open-software platforms for the analysis of MEG-data, such as fieldtrip: http://fieldtrip.fcdonders.nl/, and customized, in-house scripts.

Sample size

We are confident that the MEG-approach employed in the proposed project will yield reliable and robust effects in UHR-participants as well as allow the development of a biomarker for prediction of psychosis in UHR-participants. Our current research with MEG has demonstrated large effect sizes for deficits in high-frequency oscillations in chronically medicated ScZ- patients as well as in medication-naïve FE-ScZ patients (chronic ScZ: d= 1.26; FE-ScZ d= 1.0)
[13] [12]. Because of novel and more advanced analyses approaches for the proposed project, we will maximise the possibility to detect dysfunctions in UHR-participants that will be in the range and above of effect sizes currently available for prodromal ScZ-research.

Previous studies with a variety of methods, such MR, fMRI as well as event-related potentials (ERPs), have demonstrated anatomical and physiological impairments in UHR-cohorts with medium to large effect sizes compared to healthy participants [1,5,6]. For example, Atkinson et al. [19] demonstrated an impairment in mismatch negativity (MMN) in UHR-participants vs. controls of d = .75. Given a sample of n = 50 controls and 100 UHR-participants and an estimated effect size of .75 for the current study, the power to detect significant differences in MEG-parameters between controls and UHR-participants is 97%.

In regards to the ability to distinguish between UHR-participants who will convert to psychosis vs. UHR-participants without transition, previous published effect sizes have reported medium [4] but also large effect sizes [20] for differences on anatomical and functional parameters. For the current study, a conservative, medium effect-size of d = .5 for a sample of n = 30 converted UHR-participants vs. n = 70 non-converted UHR-participants will yield a statistical power to detect significant differences between these groups of 82%. The sample of n = 30 converted UHR-participants is consistent with a meta-analysis on conversion rates in UHR-participants over a two year period [21]. Should UHR-participants be lost in the follow-up period, we will recruit additional participants during the course of the project.

8. STUDY CLOSURE / DEFINITION OF END OF TRIAL

The study will end when the steering committee agrees that one or more of the following situations applies:

i. The planned sample size has been achieved;
ii. There is insufficient funding to support further recruitment, and no reasonable prospect of additional

support being obtained;

iii. Recruitment is so poor that completion of the trial cannot reasonably be anticipated.

9. DATA HANDLING

9.1 Case Report Forms / Electronic Data Record

All data and paper questionnaires will be anonymized with a unique identifier and stored securely in locked filing cabinets and secure, password protected servers. Appropriate access controls will be in place to ensure that access to confidential research information is restricted to authorised members of the research team. Neuroimaging-data will be archived on servers of the CCNi which are passport protected. Access will be chiefly administered through the CI, to members of the research team.

9.2 Record Retention

Neuroimaging as well as clinical data will be retained at the CCNi in secure serves and file- cabinets for a minimum of 5 years.

10. STUDY MONITORING/AUDITING

Study site file will be provided to research team by Sponsor. Sponsor will perform study set- up visit and study may be selected randomly for audit from Research & Development (R&D) database.

11. PROTOCOL AMENDMENTS

Any change in the study protocol will require an amendment. Any proposed protocol amendments will be initiated by the CI following discussion with the Sponsor and amendment forms will be submitted to the REC and Research and Development (R&D). The CI will liaise with Sponsor to determine whether an amendment is non-substantial or substantial. All amended versions of the protocol will be signed by the CI and Sponsor representative. Before the amended protocol can be implemented favourable opinion/approval must be sought from the original reviewing REC and R&D office.

ETHICAL CONSIDERATIONS

11.1 Ethical conduct of the study

The study will be carried out in accordance with the World Medical Association Declaration of Helsinki (1964) and its revisions (Tokyo [1975], Venice [1983], Hong Kong [1989], South
Africa [1996] and Edinburgh [2000]).
Favourable ethical opinion will be sought from an appropriate REC before patients are entered into this clinical trial. Patients will only be allowed to enter the study once either they have provided written informed consent.

The CI will be responsible for updating the REC of any new information related to the study.

11.2 Informed consent

Written informed consent should be obtained from each trial participant prior to participation in each phase. Consent may be provided on-line or at a visit with a member of the research team prior to screening phase. Consent will be provided at a

visit prior to assessment phase (phase 2). A member of the research will explain the exact nature of the study in writing, provision of patient information sheet, and verbally. Study participants will be informed that they are free to withdraw their consent from the study or study treatment at any time.

12. INSURANCE AND INDEMNITY

The Youth Mental Mental Health Risk and Resilience Study is sponsored by NHS Greater Glasgow & Clyde. The sponsor will be liable for negligent harm caused by the design of the trial. NHS indemnity is provided under the Clinical Negligence and Other Risks Indemnity Scheme (CNORIS).

The NHS has a duty of care to patients treated, whether or not the patient is taking part in a clinical trial, and the NHS remains liable for clinical negligence and other negligent harm to patients under its duty of care.

Participants will attend study visits at CCNi, University of Glasgow. Appropriate insurance cover for negligence to participants at this non-NHS research site will be provided by University of Glasgow.

FUNDING

The study is supported by a grant from the Medical Research Council “Using Magnetoencephalography to Investigate Aberrant Neural Synchrony in Prodromal Schizophrenia: A Translational Biomarker Approach” (MR/L011689/1 64069/1). The grant has a total volume of £ ~ 800.000 over a three-year period.

13. ANNUAL REPORTS

Annual progress reports will be submitted to REC on the

anniversary of the ethics favourable opinion. A copy of this report will also be sent to the Sponsor.

14. DISSEMINATION OF FINDINGS

We will organise a study launch conference to develop a clinical network for staff across NHS Greater Glasgow & Clyde and NHS Lothian. We will enhance engagement with mental health services by offering subsequent training in the identification of young people at UHR. We will provide mental health staff with Continuing Professional Development (CPD) certificates. We will apply to be adopted by the Scottish Mental Health Research Network in order to enhance recruitment and engagement mental health staff and young people at UHR. We will periodically organise Knowledge Exchange and Impact events to enhance stakeholder engagement. We will systematically identify key stakeholders including groups who represent the needs and views of young people.

The academic community will be reached via its standard ways of dissemination at conferences and in high impact journals aiming not only at researchers of ScZ, but at the wider academic audience interested clinically or generally in neural synchrony and the application of MEG. The wider public will be informed in an appropriate manner via internet, radio, television, and specific publications in outlets aimed at such an audience. Sufferers of ScZ and their relatives will be reached via appropriate organisations and charities by providing information for use on their websites and the offer to give oral presentations to their members. Finally, we will specifically target potential users of our research maximising the chances of immediate impact. Via established networks within the Institute of Neuroscience and Psychology (INP) we will widely disseminate our findings to users in clinics and the pharmaceutical industry using their feedback to identify potential attendees for a dedicated workshop to disseminate our findings in concentrated form and to identify potential synergies for the future.

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Table 1. UHR-criteria

1) A Global Rating Scale score of 6 on Unusual Thought Content, Non-bizarre Ideas, or
BLIPS

	Disorganized Speech; or 5–6 on Perceptual Abnormalities 2) A Frequency Scale score of 4–6 on the relevant symptom scale 3) Symptoms are present for less than one week 4) Symptoms resolve without medication 5) Symptoms occurred during the past year
Attenuated symptoms	<u>A. Subthreshold intensity</u> 1) A Global Rating Scale score of 3–5 on Unusual Thought Content or Non-Bizarre Ideas; or 3–4 on Perceptual Abnormalities; or 4–5 on Disorganized Speech 2) A Frequency Scale score of 3–6 on the relevant symptom scale 3) Symptoms are present for more than one week 4) Symptoms occurred during the past year <u>B. Subthreshold frequency:</u> 1) A Global Rating Scale score of 6 on Unusual Thought Content, Non-Bizarre Ideas, or Disorganized Speech; or 5–6 on Perceptual Abnormalities 2) A Frequency Scale score of 3 on the relevant symptom scale 3) Symptoms occurred during the past year
State-plus-trait	1) History of psychosis in a first-degree relative or identification of Schizotypal Personality Disorder 2) 30% drop in GAF score from pre-morbid level, sustained for at least one month, within the past year or a GAF score of 50 or less for at least the past year

BLIPS, Brief Limited Intermittent Psychotic Symptoms; GAF, Global Assessment of Functioning

Appendix H Example of the Adverse Childhood Experiences questionnaire

Adverse Childhood Experiences Study Questionnaires

PT's Initials: _____ PT's ID: _____ Interviewer: _____ Time: _____
Date: _____

1.) Sometimes parents or adults hurt children. While you were growing up, that is during your first 18 years of life, how often did a parent, step-parent or other adult in your home swear at you, insult you or put you down?

Never once, twice sometimes often very often

2.) While you were growing up, that is during your first 18 years of life, how often did a parent, step-parent or other adult in your home act in a way that made you afraid that you might be physically hurt?

Never once, twice sometimes often very often

3.) While you were growing up, that is during your first 18 years of life, how often did a parent, step-parent or other adult in your home actually push, grab, shove, slap or throw something at you?

Never once, twice sometimes often very often

4.) While you were growing up, that is during your first 18 years of life, how often did a parent, step-parent or other adult in your home hit you so hard that you had marks or were injured?

Never once, twice sometimes often very often

5.) Some people, while growing up in their first 18 years of life, had a sexual experience with an adult or someone at least five years older than themselves. These experiences may have involved a relative, family friend, or stranger. During the first 18 years of life, did an adult or older relative, family friend, or stranger ever touch or fondle your body in a sexual way?

Yes no

6.) Have you touch their body in a sexual way?

Yes no

7.) Actually have any type of sexual intercourse (oral, anal, vaginal) with you?

Yes no

(skip Question 8, if answered “Yes” to question 7)

8.) Attempt to have any type of sexual intercourse (oral, anal, vaginal) with you?

Yes no

9.) During your first 18 years of life did you ever live with anyone who was a problem drinker or alcoholic?

Yes no

And who was that? _____

10.) During your first 18 years of life did you ever live with anyone who used street drugs?

Yes no

And who was that? _____

11.) During your first 18 years of life was anyone in your household depressed or mentally ill?

Yes no

And who was that? _____

12.) During your first 18 years of life did anyone in your household attempt to commit suicide?

Yes no

And who was that? _____

13.) Sometimes physical blows occur between parents. While you were growing up in your first 18 years of life, how often did your father (or stepfather) or mother’s boyfriend do any of these things to your mother (or stepmother)? Push, grab, slap or throw things at her?

Never once, twice sometimes often very often

14.) Kick, bite, hit her with a fist, or hit her with something hard?

Never once, twice sometimes often very often

15.) Repeatedly hit her for over at least a few minutes?

Never once, twice sometimes often very often

16.) Threaten her with a knife or gun, or use a knife or gun to hurt her?

Never once, twice sometimes often very often

17.) During your first 18 years of life did anyone in your household ever go to prison?

Never once, twice sometimes often very often

And who was that? _____

18.) During your first 18 years of life were your parents ever separated or divorced?

Yes no

(Note if parents were never together, mark as "Yes")

19.) While you were growing up, during your first 18 years of life, how true were each of the following statements? You didn't have enough to eat.

Never once, twice sometimes often very often

20.) You had to wear dirty clothes.

Never once, twice sometimes often very often

21.) There was someone to take you to the doctor if you needed it.

Never once, twice sometimes often very often

22.) Your parents were too drunk or high to take care of the family.

Never once, twice sometimes often very often

23.) You knew there was someone to take care of you and protect you.

Never once, twice sometimes often very often

And who was that? _____

24.) There was someone in your family who helped you feel special or important.

Never once, twice sometimes often very often

And who was that? _____

25.) You felt loved.

Never once, twice sometimes often very often

And who was that? _____

Appendix I Demographic variables that were non-significant between group)CHR and controls) and levels of ACES (none, low, high)

	Comparisons
Age compared across those at high risk and controls	No significant differences emerged between high risk sample and controls in age, F(1,161), =2.34, p = .128
Gender compared between those at high risk and controls	No significant differences in gender, X^2 = 2.43), p = .120.
Premorbid IQ compared between controls and those at high risk	No significant differences between controls and those at high risk in premorbid IQ as derived from the NART full scale, F(1,152) = .843, p = .360
Years of education compared between levels of ACEs	No significant differences between level of ACES in years of education, F(1,151) = .344, p = .709.
Gender compared across levels of ACEs	No significant differences between levels of ACES in gender, F(1,151) = .654, p = .521.
Medication compared against levels of ACEs	No significant differences between levels of ACES in medication, F (1,151) = 1.903, p = .153.
Age Compared between levels of ACEs.	No significant differences between level of ACEs in age, F (1,151) = .416, p = .660.

Appendix J Checking the parametric assumptions of a two way MANOVA

Assumption #4

There should be a linear relationship between the dependent variables for each group of the independent variable.

There was a linear relationship between the dependent variables, as assessed by scatterplot.

Assumption #5

There should be no multicollinearity

There was no evidence of multicollinearity, as assessed by Pearson correlation ($|r| < 0.9$).

Assumption #6

There should be no univariate or multivariate outliers

There were no univariate outliers in the data, as assessed by inspection of a boxplot for values greater than 1.5 box-lengths from the edge of the box.

Assumption #7

There needs to be multivariate normality

There were no multivariate outliers in the data, as assessed by Mahalanobis distance ($p > .001$).

Assumption #8

You should have an adequate sample size

In order to run a two-way MANOVA, each cell of the design must have at least as many cases as there are dependent variables. In this example, there are two dependent variables. Therefore, there needs to be two or more cases per cell of the design. You can confirm whether this is the case by inspecting the "**N**" column in the **Descriptive Statistics** table, as highlighted below:

Assumption #9

There should be homogeneity of variance-covariance matrices

Box's Test of Equality of Covariance Matrices[a]

Box's M	138.098
F	1.112
df1	105
df2	5935.221
Sig.	.206

Tests the null

Assumption #10

There should be homogeneity of variances

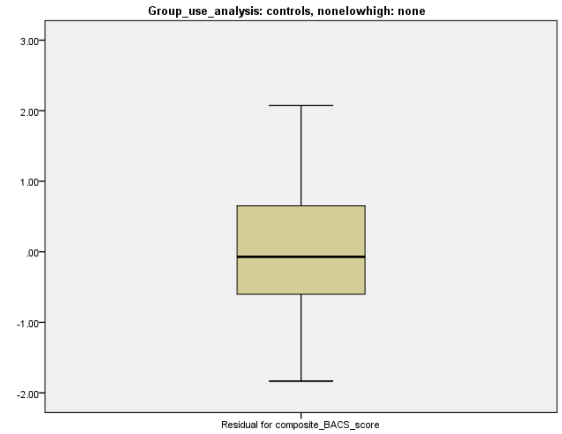
Levene's Test of Equality of Error Variances[a]

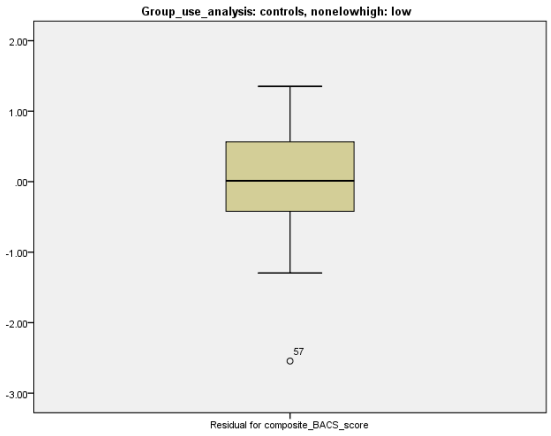
	F	df1	df2	Sig.
Zscore: Baseline: BACS Verbal memory task - total score	1.458	5	145	.207
Zscore: Baseline: BACS Total number of tokens placed in container	.466	5	145	.801
Zscore: Baseline: BACS Symbol coding score	1.340	5	145	.251
Zscore: Baseline: BACS Tower of London total score	1.309	5	145	.263
Zscore: Baseline: BACS Total digit sequencing score	2.091	5	145	.070
Zscore (overall_verbal_fluency_final)	.274	5	145	.927

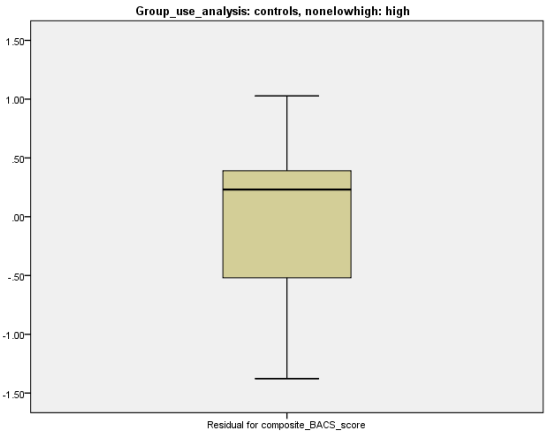
Tests the null hypothesis that the error variance of the dependent variable is equal across groups.

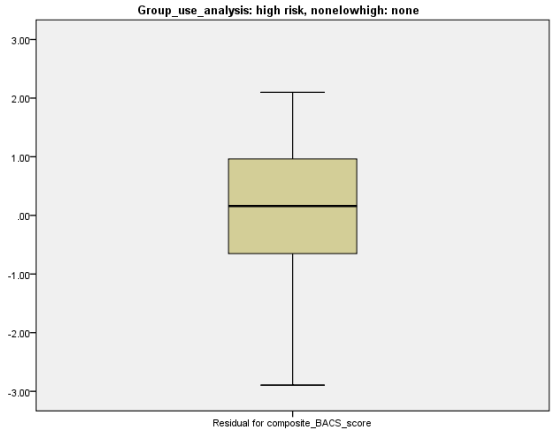
<u>Appendix K</u> Checking the assumptions for the univariate ANOVA

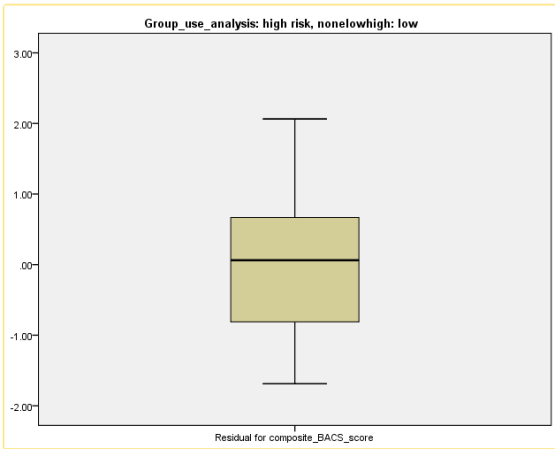
Outliers

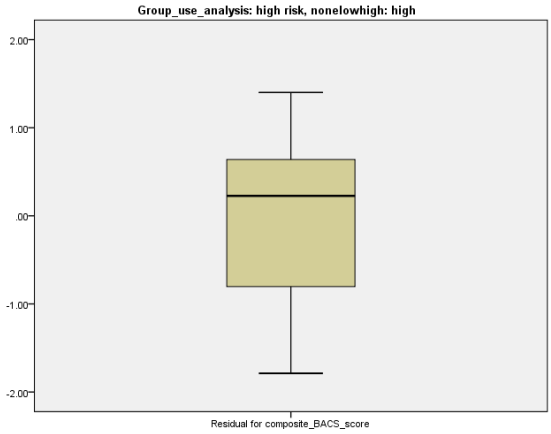












Data was normally distributed, as assessed by Shapiro-Wilk's test ($p > .05$).

Tests of Normality

Group_use_analysis	nonelowhigh		Kolmogorov-Smirnov[a] Statistic	df	Sig.	Shapiro-Wilk Statistic	df	Sig.
controls	none	Residual for composite_BACS_score	.091	37	.200*	.986	37	.905
	low	Residual for composite_BACS_score	.114	32	.200*	.954	32	.184
	high	Residual for composite_BACS_score	.174	9	.200*	.966	9	.862
high risk	none	Residual for composite_BACS_score	.073	23	.200*	.977	23	.844
	low	Residual for composite_BACS_score	.122	36	.194	.971	36	.450
	high	Residual for composite_BACS_score	.142	26	.188	.943	26	.155

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

There was homogeneity of variances, as assessed by Levene's test for equality of variances, $p > 0.05$

Levene's Test of Equality of Error Variances[a]

Dependent Variable: Zscore(average_of_z_scores)

F	df1	df2	Sig.
1.676	5	157	.143

Tests the null hypothesis that the error variance of the dependent variable is equal across groups.

a. Design: Intercept + nonelowhigh + group_use_study + nonelowhigh * group_use_study

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