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The neural, stress hormone and inflammatory correlates of childhood deprivation and threat in psychosis: a systematic review.

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Abstract

Childhood adversity increases the risk of developing psychosis, but the biological mechanisms involved are unknown. Disaggregating early adverse experiences into core dimensions of deprivation and threat may help to elucidate these mechanisms. We therefore systematically searched the literature investigating associations between deprivation and threat, and neural, immune and stress hormone systems in individuals on the psychosis spectrum. Our search yielded 74 articles, from which we extracted and synthesized relevant findings. While study designs were heterogeneous and findings inconsistent, some trends emerged. In psychosis, deprivation tended to correlate with lower global cortical volume, and some evidence supported threat-related variation in prefrontal cortex morphology. Greater threat exposure was also associated with higher C-reactive

protein, and higher and lower cortisol measures. When examined, associations in controls were less evident. Overall, findings indicate that deprivation and threat may associate with partially distinct biological mechanisms in the psychosis spectrum, and that associations may be stronger than in controls. Dimensional approaches may help disentangle the biological correlates of childhood adversity in psychosis, but more studies are needed.

Key words: Psychosis, childhood adversity, biological correlates, neuroimaging, inflammation, cortisol

1. Introduction

Childhood adversity is an established risk factor for the development of psychosis, yet the biological mechanisms underpinning this relationship remain unclear (Varese et al., 2012). As similar biological alterations have been observed in people with a history of childhood adversity, people with psychosis, and people with both (Tryon et al., 2021), it is plausible that deviations from normal biological development, brought about or contributed to by childhood adversity, confer risk for psychosis.

Research investigating this possibility has focused on several biological domains, including brain structure and function, and the body's immune and stress response. A prominent hypothesis, the neural diathesis-stress model, proposes that chronic or severe stressors such as childhood adversity, combined with pre-existing abnormalities in the hypothalamic–pituitary–adrenal (HPA) axis, result in the emergence and/or exacerbation of psychotic symptoms (Pruessner et al., 2017).

Another well-known theory is that childhood adversity represents one of two 'hits' to the immune system which ultimately result in psychosis (Feigenson et al., 2014). It is possible that adverse experiences prime the immune system early in life (1st hit) such that subsequent stressors elicit an exaggerated immune response.

Alternatively, childhood adversity may trigger an exaggerated response in an already-primed immune system (2nd hit), due, for example, to a genetic predisposition or prenatal insult, prompting the emergence of psychotic symptoms.

These mechanisms may influence the course of neurodevelopment, with research suggesting that both immune (Brenhouse et al., 2019) and cortisol (McEwen, 2012) perturbations associate with variation in brain structure and function.

Much of the research attempting to quantify the effect of adversity on biological systems in psychosis has used broad measures of adversity (e.g., "total trauma"). However, different experiences may have distinct impacts on neurodevelopment and psychopathology (Bentall et al., 2014); this approach may therefore mask effects unique to certain adversity types. To help disentangle these effects and identify both shared and distinct mechanisms through which different adversities affect development, "dimensional" models of adversity have been proposed.

One such model, the Dimensional Model of Adversity and Psychopathology (DMAP) (Sheridan and McLaughlin, 2014), proposes that two core features of experience, deprivation and threat, underlie specific adversity exposures to varying degrees, and contribute to psychopathology via at least partially distinct pathways. Deprivation is operationalized as a lack of input in social and cognitive domains and is suggested to disrupt normative development in the association cortex. Threat, operationalized as harm or risk of harm to an individual, is conversely thought to alter fronto-limbic circuits such that threats in the environment can be more rapidly identified, for example by sensitizing salience networks.

A recent systematic review by McLaughlin and colleagues (2019) found evidence consistent with the propositions made by the DMAP. While experiences characterized by deprivation were associated with altered function and reduced gray matter volume (GMV) in frontoparietal regions, those characterized by threat were associated with an elevated amygdala response to threat, and reduced GMV in the amygdala, hippocampus, and medial prefrontal cortex (PFC). Recent research has applied this model in the psychosis spectrum (LoPilato et al., 2021, 2020, 2019), revealing a level of distinction between biological correlates of deprivation and threat.

In 2019, Cancel and colleagues conducted a systematic review examining the relationship between childhood adversity and neuroimaging metrics in psychosis, and found some evidence for adversity-related alterations. While informative, the review did not focus a priori on different dimensions of adversity, and was confined to cohorts with established psychotic illness, even though psychosis is thought to lie on a continuum (van Os et al., 2009). It also omitted studies examining associations between adversity and other biological domains, despite the interactive relationship between the brain and other systems during development (e.g., the immune [Brenhouse et al., 2019] and stress response [McEwen et al., 2016]), and the involvement of these systems in the biological response to childhood adversity. The review also shed little light on the specificity of findings to psychosis; the extent to which the biological correlates of adversity differ between individuals with and without psychosis is therefore unclear.

Further insight into the neurobiological impacts of childhood adversity in psychosis may be derived by considering adversity as a dimensional framework, rather than a monolithic construct, and by considering key biological domains along the entire psychosis spectrum. To date, no attempt has been made to systematically investigate the biological correlates of adversity in psychosis parsed by broad dimensions of adversity.

Accordingly, we synthesized research investigating the biological correlates of deprivation and threat in individuals on the psychosis spectrum, with a focus on neural, immune, and stress hormone-related measures. Our focus on the immune and stress response was due both to their close relationship with functional and structural brain development, and to research supporting their disruption both in people with psychosis (Bradley and Dinan, 2010; Rodrigues-Amorim et al., 2018) and people exposed to childhood adversity (Baumeister et al., 2016; Bernard et al., 2017). While other biological systems may be relevant (such as dopamine transmission), too few studies have been conducted in these areas to warrant synthesis in this review.

Our aims were to: 1) identify biological correlates of deprivation and threat in samples consisting of people with psychosis (or psychosis symptoms); 2) determine whether relationships with deprivation and threat are partially distinct from one another and align with the predictions made by the DMAP; and 3) ascertain the extent to which such relationships are specific to the psychosis spectrum. Notwithstanding the importance of

other features of adversity (such as timing and chronicity), it was hoped that a dimensional framework could provide an alternative foundation for investigating the mechanisms linking childhood adversity to psychosis.

2. Methods

This review follows the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines (http://www.prisma-statement.org/). On conception of this review, a research protocol was written and submitted to PROSPERO (ID CRD42021227368).

2.1 Search strategy

Using OVID (https://ovidsp.ovid.com/), the online databases "PsycINFO" and "MEDLINE" were combined and searched (by MT) for articles concerning psychosis, childhood adversity and measurable biological characteristics in the domains of brain structure, brain function (including functional connectivity), the immune system and HPA axis function. Full search terms can be found in the supplementary material.

Additional OVID filters constrained our search to peer-reviewed studies carried out in humans and printed in English. We conducted our first search on the 15th of January 2021 and our final search on the 30th of June 2022. The reference lists of suitable articles were also searched and followed up manually to obtain articles missed by our OVID search.

2.2 Selection criteria and screening

To meet our inclusion criteria, studies were required to have measured the relationship between childhood adversity and either neural, stress hormone, and/or inflammatory characteristics in individuals on the psychosis spectrum. Neural characteristics could include any structural, functional or connectivity brain metric acquired via neuroimaging; inflammatory characteristics included any metric directly quantifying the immune response; stress hormone characteristics included any measure of cortisol, the most commonly studied stress hormone. Studies only measuring molecular, genetic, or epigenetic characteristics were outside the scope of our review.

As well as people diagnosed with psychotic disorders (including first episode psychosis, schizophrenia, schizoaffective disorder, schizophreniform disorder, bipolar disorder with psychotic features, major depressive

disorder with psychotic features, unspecified psychotic disorder), those at familial or clinical high-risk for psychosis were eligible, as were non-clinical individuals with psychotic-like experiences, including schizotypy.

It was required that measures of childhood adversity could be classified as either deprivation and/or threat, and experiences had to have occurred when the individual endorsing them was under the age of 18. In line with the DMAP (McLaughlin et al., 2014), we defined deprivation as "the absence of expected environmental inputs and complexity", and included experiences such as neglect, poverty, institutionalization, and neighborhood disadvantage. Threat was defined as "the presence of threats to one's physical integrity" and ranged from personal victimization such as sexual abuse or bullying, to neighborhood-level threat such as poor neighborhood safety.

Analyses in which researchers had combined deprivation and threat measures (e.g., "total trauma") were eligible for inclusion as part of a "mixed adversity" (MA) grouping, following the methodology of McLaughlin and colleagues (2019). While additional adversity types such as parental death or separation sometimes contributed to MA scores, analyses were only included if deprivation and threat collectively made up at least half of the score weighting.

The titles and abstracts of deduplicated articles from our OVID search were imported into Covidence (www.covidence.org), where they were simultaneously screened for eligibility by two researchers (MT and DR). Full texts of remaining articles were then assessed against our inclusion and exclusion criteria. Disagreement regarding inclusion at either stage was resolved through discussion or via consensus with a third senior researcher (VC).

2.3 Data extraction and analysis

Study characteristics, methodology, and relevant results were extracted from eligible papers, and clarity sought from study authors regarding methodology and/or results when these were unclear. Subsequently, findings from relevant analyses were synthesized into those concerning brain structure/function, inflammatory markers, and cortisol, and within each type of adversity grouping (i.e., deprivation, threat, and MA).

2.4 Quality assessment

We conducted a quality assessment for each study in accordance with PRISMA guidelines. Ratings were guided by the National Institutes of Health "Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies" (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools). As studies often only partially met the 'yes' criterion for certain questions on the NIH tool, we added a 'somewhat' response category. See Table S1 for full ratings.

3. Results

3.1 Overview

Our database search yielded 1017 unique records, of which 62 were eligible. An additional 12 studies were identified through manual searching. This resulted in a total of 74 studies that were data-extracted and synthesized (see Figure S1 for screening flow diagram).

In our quality assessment, 37 studies were judged to be of "good" quality, 34 were deemed "fair" and three were "poor" (see Table S1). Common shortfalls included the absence of power analyses, no or insufficient detail regarding the amount and/or characteristics of eligible subjects who did not participate, and the predominantly retrospective (rather than prospective) measurement of childhood adversity exposure.

Methodology and relevant findings for all studies are presented in Tables S2-4 in the supplementary material. Where available, the results of equivalent analyses in controls are included in the tables alongside that of cases. Table S5 provides further detail regarding the measurement of deprivation and threat in each study, including relevant analytical considerations. Co-occurrence between the adversity dimensions was generally not reported. Where it was, co-occurrence was typically significant but rarely considered in statistical analyses.

Twenty-five studies reported findings for deprivation, 33 for threat, and 52 for mixed adversity (see Table 1 for the distribution of biological domains within each). Of studies reporting findings for deprivation and/or threat separately, most examined specific forms of abuse or neglect; only one explicitly examined the dimensions as defined by the DMAP (LoPilato et al., 2019). Seven studies assessed deprivation, threat and MA in the same participants. An additional 12 studies examined both deprivation and threat, but not MA.

Forty-eight studies examined associations between adversity dimensions and biological metrics or compared metrics between exposed and non-exposed cases (and less frequently, exposed and non-exposed controls). We refer to these as 'association studies'. The significance and direction of findings from these studies are presented in Table 2. Higher/lower biological metric units in adversity-exposed individuals are considered positive/negative associations, respectively.

Twenty-one studies examined the interaction between group and adversity on biological metrics. These are referred to as 'interaction studies'. All but two of these studies examined MA exclusively. The significance and nature of these interactions are presented in Table 3, along with (if reported) main or within group adversity effects where significant interaction effects were absent.

Findings from association and interaction studies, grouped by dimension, are provided below, followed by findings from studies with alternative designs. As a healthy control group was not a prerequisite for inclusion in our review, several studies did not conduct or report corresponding analyses in controls. As such, within each adversity section we first describe findings for which corresponding analyses were reported for controls, followed by findings where they were not. The proportion of association and interaction studies finding positive, negative, both, or no associations between adversity dimensions and biological metrics are presented as pie charts in Figure S2. These were restricted to cases given the fewer corresponding analyses in controls.

3.2. Deprivation

3.2.1 Analyses with a control group

Of 11 association studies examining deprivation in both cases and controls, six reported significant correlations with at least one biological metric in cases only (i.e., corresponding analyses in controls did not yield significant results).

Negative associations with deprivation were reported for total GMV (Cancel et al., 2015), total cortical volume (LoPilato et al., 2019; Yeo et al., 2014), GMV in widespread anterior regions concentrated in the PFC (see Table S2 for specific regions) (Yeo et al., 2014), right hippocampal volume (LoPilato et al., 2019) and left orbitofrontal cortex (OFC) H-shaped sulci volume (Wang et al., 2022). Deprivation also predicted lower fractional anisotropy

in the white matter tract connecting the left superior-medial prefrontal (SMPF) region with the hippocampus (Molina et al., 2018), and higher fractional anisotropy in the right superior longitudinal fasciculus (SLF) (Asmal et al., 2019), although notably the former study was rated “poor” in our quality assessment (Molina et al., 2018).

In contrast, one study reported a negative association between deprivation and anterior cingulate cortex (ACC) volume in controls only (i.e., absent in cases) (Rokita et al., 2020). In the remaining four association studies, deprivation did not significantly correlate with brain structure (Salokangas et al., 2021), immune (Quidé et al., 2019) or cortisol (Lange et al., 2017; Yang et al., 2021) markers in cases or controls.

Only one interaction study examined deprivation exposure with group status (Corsi-Zuelli et al., 2020). This study reported no significant interaction, nor within-group effects, of deprivation on inflammatory markers in a sample comprising first episode psychosis patients, unaffected siblings of patients, and controls.

3.2.2 Analyses without a control group

Eleven studies assessed correlations with deprivation in analyses that did not include a control group. Four of these reported a significant relationship between deprivation and at least one biological metric examined.

In a voxel-wise analysis of gray matter density (GMD), Cancel and colleagues (2015) revealed a negative association in the dorsolateral PFC. Another study reported that deprivation exposure and being a carrier of the met allele of the brain-derived neurotrophic factor (BDNF) val66met gene, collectively contributed to lower CA2-3 hippocampal subfield volume (Aas et al., 2014). Two studies reported significant relationships between deprivation and the BOLD response to emotional stimuli. Of these, one revealed increased activity to negative (relative to positive) images in the right middle temporal gyrus (mid-TG) (Aas et al., 2017a), while the other found lower functional connectivity between the amygdala and the left precuneus for negative (relative to positive) images (Cancel et al., 2017), with higher deprivation.

Seven studies reported no significant correlation of deprivation with cortical structure (Rapado-Castro et al., 2020), total GMV (Sheffield et al., 2013), pituitary volume (Bipin et al., 2021), and indicators of the stress cortisol response (Aas et al., 2020; Braehler et al., 2005; Hirt et al., 2019; Seitz et al., 2019), respectively.

3.3 Threat

3.3.1 Analyses with a control group

Thirteen studies examined the association of threat exposure with biological metrics separately in cases and controls. Six reported significant associations in cases only.

Threat exposure was reported to predict reduced total intracranial volume, GMV in the frontal lobe, white matter volume in the amygdala-hippocampus complex (Salokangas et al., 2021), pituitary gland volume (Cullen et al., 2015), and fractional anisotropy in the right inferior fronto-occipital fasciculus (IFOF), inferior longitudinal fasciculus (ILF) and forceps major (Asmal et al., 2019), and higher right OFC H-shaped sulci volume (Wang et al., 2022). In the inflammatory domain, two studies found threat-related elevations in C-reactive protein (CRP) (Hepgul et al., 2012; Quidé et al., 2019).

In contrast, one association study reported a significant negative association between threat and the right medial OFC volume that was present in both cases and controls (Vargas et al., 2019). The remaining six association studies reported no significant correlations between threat and brain structure (Cancel et al., 2015; LoPilato et al., 2019; Molina et al., 2018), inflammation (Aas et al., 2017b) and cortisol (Lange et al., 2017; Yang et al., 2021).

Two studies examined the interaction between threat exposure and group status, with both reporting a significant interaction effect. The first found higher transforming growth factor (TGF)-β in threat-exposed first episode psychosis patients, decreased TGF-β in threat-exposed controls, and no effect in siblings of patients (Corsi-Zuelli et al., 2020). The second found that cortisol awakening response with respect to ground was increased in first episode patients with a severe history of threat exposure, but reduced in severely exposed controls (Ciufolini et al., 2019).

3.3.2 Analyses without a control group

Fifteen association studies assessed correlations with threat exposure in cases but not in a corresponding control group, with 13 reporting a significant association.

Negative associations were reported for total GMV (Sheffield et al., 2013), cortical thickness in the bilateral mid-TG and right superior frontal gyrus (SFG) (Rapado-Castro et al., 2020), and GMV in the left middle frontal gyrus (mid-FG), left inferior frontal gyrus (IFG) and bilateral ACC (Sheffield et al., 2013). Additionally, two studies, both of which split their analyses by BDNF val66met gene allele type, found negative associations between certain threat measures and hippocampus volume in met but not homozygotic valine (val/val) carriers (specifically the bilateral hippocampus [Aas et al., 2013] and CA2/3 and CA4 DG subfields [Aas et al., 2014]). Positive associations were also reported between threat and cortical thickness in the right rostral mid-FG, and surface area in the right caudal ACC, respectively (Rapado-Castro et al., 2020).

Threat-related alterations to brain function were also reported. One study used functional magnetic resonance imaging (fMRI) during an emotion task to reveal heightened activity to negative (relative to positive) stimuli in the bilateral superior temporal gyrus (STG), angular gyrus, Heschl's gyrus, insula, pre and postcentral gyrus, and right precentral gyrus, putamen, central opercular cortex and intracalcarine gyrus, in cases exposed to threat (Aas et al., 2017a). A further study found that threat predicted decreased functional connectivity between the amygdala and clusters in the left precuneus, left posterior cingulate/precuneus, and the right calcarine sulcus during negative (relative to positive) images (Cancel et al., 2017).

In the inflammatory domain, one study found higher tumor necrosis factor (TNF)-α levels (but not other cytokines) in threat-exposed cases (Dennison et al., 2012). For cortisol, one study reported threat-related elevations in cortisol awakening response (Mondelli et al., 2010). Two studies examined morning cortisol (levels 30 or 60 minutes after waking) and found positive (in males only) (Ruby et al., 2017) and negative (almost entirely male sample) (Braehler et al., 2005) associations with threat respectively. However, both studies received a "poor" rating in our quality assessment.

Two hair cortisol concentration studies reported significant threat-related findings. The first reported a positive association between hair cortisol concentration and threat (Aas et al., 2019), whereas the second reported a negative association for threat exposures under age 11 (Hirt et al., 2019). A further study found a positive association between threat and 5β reductase, a proxy measure of cortisol metabolism (Aas et al., 2020).

The remaining two studies reporting no significant associations with threat examined pituitary volume (Bipin et al., 2021) and cortisol response (Seitz et al., 2019).

3.4 Mixed adversity (MA)

3.4.1 Analyses with a control group

Of 13 studies investigating associations between MA and biological metrics in cases and controls, six reported one or more significant effects in cases alone.

MA was negatively associated with amygdala lateral nucleus volume (Armio et al., 2020) and left OFC H-shaped sulci volume (Wang et al., 2022), and positively associated with resting state functional connectivity between the medial PFC and cerebellum (Dauvermann et al., 2021). For the inflammatory and cortisol domains, MA predicted higher levels of TNF-α, monocyte chemoattractant protein (MCP)-1 (Di Nicola et al., 2013) and morning cortisol (Faravelli et al., 2017), but had a blunting effect on cortisol awakening response (Pruessner et al., 2013).

In contrast, one association study found a control-specific association between MA and reduced ACC volume (Rokita et al., 2020). In both cases and controls, Benedetti and colleagues (2011) reported positive associations of MA with GMV in the SFG and anterior cingulate, and both positive (SFG) and negative (amygdala) associations with BOLD response to an emotion face-matching task.

The five remaining association studies investigated brain structure (Asmal et al., 2019; LoPilato et al., 2019) and cortisol (Cullen et al., 2020; Mondelli et al., 2010; Phassouliotis et al., 2013) respectively, reporting null associations with MA for all metrics examined in cases and controls.

Twenty studies examined two-way interactions between group status and MA, or three-way interactions including a third predictor variable, for biological metrics. Nine of these yielded at least one significant interaction effect.

In the neural domain, one study found a negative association between MA and total GMV in psychosis patients, with no effect in siblings or controls (Frissen et al., 2018). Another found that MA predicted lower average

cortical thickness in schizophrenia patients, no association in controls, and higher thickness in siblings, although the latter did not significantly differ from the relationship in controls (Habets et al., 2011). Additionally, Du Plessis and colleagues (2020) reported a sex-by-group-by-MA interaction effect for hippocampal fissure size, driven by a positive MA-fissure size association in female psychosis patients, but not male patients or male or female controls.

A further study examined global alterations in white matter integrity, finding MA-related fractional anisotropy reductions in psychosis patients (at follow-up but not baseline) but no effect in controls or siblings (Domen et al., 2019). The authors also found greater MA-related fractional anisotropy decline from baseline to follow-up in patients than in the other two groups. For neural function, one study found a group by MA interaction effect on activation in the bilateral cuneus, calcarine sulcus and lingual gyrus during a visuo-spatial working memory task (Quidé et al., 2017a). Follow up analyses revealed that in patients, stronger activation was associated with MA, while in controls, MA predicted weaker activation.

In the inflammatory domain, Corsi-Zuelli and colleagues (2020) found positive associations between MA and TGF-β in first episode patients and siblings, in contrast to a negative association in controls. Another study found an interaction effect between psychosis liability (recent-onset psychosis and clinically high-risk vs siblings and controls) and MA on T helper 17 (Th17) cell counts (Counotte et al., 2018). The effect was driven by elevated Th17 cell numbers in MA-exposed subjects in those with high but not low psychosis liability.

Two additional studies found 3-way interaction effects, where the third variable (in addition to group and MA) was a metric from a second biological domain. The first found a group by MA by inflammation (CRP, TNF-α, and interleukin [IL]-6 composite score) interaction effect, whereby inflammation predicted both decreased gray matter covariation (GMC) in the bilateral posterior cingulate cortex (PCC)/precuneus, inferior/superior parietal lobule and postcentral gyrus, and increased GMC in the left mid-TG, in cases with low MA and controls with high MA (Quidé et al., 2021a). The second found group by MA by cortisol interaction effects for both neural activity and functional connectivity during an emotion task (see Table S4 for full details) (Quidé et al., 2020).

Of the 11 remaining studies finding no interaction between MA and group status, four examined brain structure (Begemann et al., 2021; Hernaus et al., 2014; Hoffmann et al., 2018; Poletti et al., 2016), three

examined brain function (Peeters et al., 2015a, 2015b; Quidé et al., 2018) two examined immune markers (Counotte et al., 2019; Misiak et al., 2020), and two investigated cortisol (Labad et al., 2020; Söder et al., 2019).

In the absence of significant interactions, one of these studies found within group associations between MA and lower frontal GMV in bipolar disorder patients and controls, but not in patients with schizophrenia spectrum disorder (Begemann et al., 2021). Two instead found main effects of MA, indicating that associations did not depend on group status. Using fMRI during a response inhibition task, Quidé et al (2018) found that MA predicted stronger left IFG activation, and stronger functional connectivity between the left IFG and both the left cerebellum/fusiform gyrus and the right calcarine sulcus, across the whole sample. Söder and colleagues (2019) found that while no group (familial high-risk for psychosis and controls) by MA interaction effect was present for hair cortisol concentration, MA predicted higher hair cortisol concentration in the wider sample (which also included clinically high-risk subjects).

3.4.2. Analyses without a control group

Sixteen studies investigated the relationship between MA and biological metrics in cases but not controls, of which 14 reported significant effects.

Negative associations were reported for total brain volume in males only ('poor' study quality) (Ruby et al., 2017), total GMV (Sheffield et al., 2013), total cortical surface area (Barker et al., 2016a), hippocampal volume (right hemisphere [Barker et al., 2016b]; left hemisphere [Alameda et al., 2018; Hoy et al., 2012]), and amygdala volume (bilateral [Hoy et al., 2012]; left hemisphere [Barker et al., 2016b]). One of these studies (Ruby et al., 2017) also found a positive association with amygdala to whole-brain ratio in males ('poor' study quality). Further, Aas and colleagues (2012) found that a greater number of adversity types predicted lower bilateral amygdala volumes, and the same team later found that met genotype (BDNF val66met gene) and exposure to MA collectively contributed to reduced CA2-3 hippocampal subfield volumes (Aas et al., 2014). A further study found widespread MA-related reductions to white matter integrity (see Table S4 for specific regions) (Poletti et al., 2015).

Two studies reported alterations in task-based fMRI response. One found that, during an emotion task, MA predicted a larger response to negative (relative to positive) images in the right angular gyrus, supramarginal gyrus, mid-TG and lateral occipital cortex (Aas et al., 2017a). The other found increased activation in the PCC/precuneus and dorsomedial PFC, and decreased activation in the right anterior temporoparietal junction, during a theory of mind task, in MA-exposed cases (Quidé et al., 2017b). Another study, via measurement of resting cerebral blood flow (rCBF), found an association between MA and heightened blood flow in the right hippocampus/subiculum and left parahippocampal gyrus, and diminished blood flow in the left IFG and superior/medial PFC (Allen et al., 2018).

Several significant associations were found between MA and cortisol measures. One study found MA-related reductions in morning cortisol in a mostly male sample ('poor' quality study) (Braehler et al., 2005), another found lower afternoon cortisol in males but not females ('poor' quality study) (Ruby et al., 2017), and a third found a lower hair cortisol concentration when only MA under age 11 was considered (Hirt et al., 2019).

Conversely, the two remaining studies found no association between MA and hippocampal structure (Mondelli et al., 2011) and cortisol levels (Seidenfaden et al., 2017), respectively.

3.5 Other study designs

Five studies conducted analyses which, while including adversity dimensions and biological metrics as variables, did not use either of the aforementioned study designs.

Karcher and colleagues (2021) investigated whether several brain structural metrics mediated positive associations between measures of deprivation and threat, and psychotic-like experiences, in non-clinical youth in the Adolescent Brain Cognitive Development (ABCD) study (N>10,000). They found that lower total intracranial volume, total subcortex volume, and total cortical volume, thickness, and surface area each explained a significant portion of the variance between threat (one of two measures) and deprivation (two of two measures), and psychotic-like experiences. Follow-up regional analyses revealed that all significant mediation effects for cortical volume were particularly concentrated in the lateral orbitofrontal, middle temporal and post-central cortex. Effect sizes were similar between the two adversity dimensions.

Popovic and colleagues (2020) harnessed a large dataset comprising recent-onset psychosis, recent-onset depression, clinically high-risk for psychosis subjects and controls, to derive multivariate patterns of covariation between whole-brain GMV and phenotypic traits consisting of childhood adversity exposures, age, sex and diagnosis. Recent-onset psychosis loaded positively (albeit of small magnitude) onto one of the five latent variables identified. This latent variable linked psychosis, older age, male sex, and select deprivation and threat exposures, with alterations to GMV in the frontal, temporal, parietal, occipital and subcortical regions (negative weightings) and to GMV in the thalamus (positive weighting).

Two additional studies examined interaction effects but not between group and adversity. First, Hou and colleagues (2020) examined the interaction between adversity and cortical gyrification on group status (clinically high-risk vs controls), reporting that MA and one deprivation measure (but no threat measures) weakened the group difference in left STG gyrification. Second, in a sample of community controls, Quidé and colleagues (2021b) found an interaction between schizotypy (measured as a continuous variable) and MA on GMC in the left and right caudate, putamen, lentiform nuclei and thalami, extending to the hippocampal and parahippocampal gyri insulae. This effect was driven by a negative association between schizotypy and GMC in these regions in subjects without a history of MA, and no association in subjects with a history of MA.

Lastly, Trotta and colleagues (2021) reported that individuals with psychotic-like experiences and MA exposure had three times higher odds of belonging to a group with elevated CRP, IL-6 and suPAR levels (inflammation groups derived using latent component analysis) than did those with no psychotic-like experiences and no MA, while those with psychotic-like experiences or MA alone did not differ from the latter.

4. Discussion

4.1 Overview of results

This review aimed to synthesize the available literature examining relationships between childhood adversity and measures of neurobiology across neural, inflammatory and stress response systems in the psychosis spectrum. We aimed to identify biological correlates of childhood adversity in these domains, evaluate whether they differed to some degree by dimension of adversity (specifically, deprivation or threat), and determine the

extent to which they were specific to psychosis. A primary outcome of our review was inconsistency in findings, in large part due to variability in the biological measures investigated which resulted in a small number of analyses for specific metrics within adversity groupings. High heterogeneity among studies should thus be kept in mind when interpreting our discussion of the findings.

4.2 Do early life experiences of deprivation and threat associate with variation in neurobiology in the psychosis spectrum?

The majority of studies reported at least some evidence to support adversity-related variation in neurobiology. Of the 48 association studies included, 38 reported one or more significant relationships between deprivation, threat, and/or MA, and biological metrics, in individuals on the psychosis spectrum (9/21 deprivation studies; 20/28 threat studies; 21/29 MA studies). Of the 21 studies examining interactions between adversity and group (psychosis spectrum vs controls), 13 reported either an interaction, a main effect of adversity in the total sample, or a within group effect in individuals on the psychosis spectrum specifically, for one or more biological metric (0/1 deprivation studies; 2/2 threat studies; 12/20 MA studies). Furthermore, all five studies with alternative study designs (i.e., not association or interaction studies) found some evidence to support a relationship between adversity, neurobiology and psychosis.

However, studies often included multiple analyses across several biological metrics, of which a significant proportion yielded null findings (see Tables 2 and 3, and Figure S2). Moreover, findings relating to specific metrics were often inconsistent between studies. Nevertheless, we highlight some of the most consistent patterns within each adversity grouping.

For deprivation, evidence was strongest for an association with lower cortical gray matter globally, possibly concentrated in prefrontal regions. While studies examining this relationship were limited in number, all showed this general pattern, and were predominantly of good quality with large sample sizes (Karcher et al., 2021; LoPilato et al., 2019; Popovic et al., 2020; Yeo et al., 2014).

The most consistent associations with threat exposure were with higher CRP, reported in two of three studies examining this relationship, with the third showing the same prior to adjustment for body mass index (Aas et

al., 2017b). Preliminary evidence for higher TGF-β and TNF-α levels with threat exposure was also observed (Corsi-Zuelli et al., 2020; Dennison et al., 2012). Threat also tended to associate with variation in cortisol, with most studies examining this relationship yielding positive or negative associations for certain metrics (cortisol awakening response, morning and afternoon cortisol, hair cortisol concentration and cortisol metabolism [5β reductase]). Investigations of diurnal/basal cortisol levels and cortisol response to a psychosocial or pharmacological stress test conversely revealed no effect of threat, or indeed any adversity grouping.

MA tended to yield multidirectional associations with task-related neural activation across a range of paradigms, and (less consistently) volumetric reductions in the amygdala and hippocampus. While some studies also found associations between hippocampal morphology and deprivation and threat, these tended to be contingent on carrying the met variant of the val66met gene (associated with low BDNF release [Egan et al., 2003]). Moderate support for adversity-related associations with total GMV, white matter integrity and brain function was found for all three adversity groupings (i.e., deprivation, threat and MA).

Despite these tentative patterns, a significant proportion of analyses in our review did not reveal an association between childhood adversity and neural, immune and stress-response systems in the psychosis spectrum. Given more consistent support for significant associations in the wider literature however (e.g., Baumeister et al., 2016; Bernard et al., 2017; McLaughlin et al., 2019), it is possible that several methodological factors contributed to some of these null results. In addition to small sample sizes and retrospective reporting of adversity, biological assessments were generally performed decades after adversity exposure; alterations may thus have normalized in the intervening period (Ellwood-Lowe et al., 2018; Rakesh et al., 2021a). Furthermore, illness-related factors, or treatment with antipsychotics (which was often not controlled for), might have obscured the effects of adversity on biological measures. Although this review was unable to group findings across illness stage or developmental period, it is noteworthy that a number of large studies (all with > 100 cases) examining people at the earliest stage or least symptomatic end of the psychosis spectrum (e.g., those at clinical or familial high-risk), found associations between adversity and biological domains (Barker et al., 2016a, 2016b; LoPilato et al., 2019; Salokangas et al., 2021), sometimes in the absence of effects in participants with established illness (Salokangas et al., 2021).

4.3 Do deprivation and threat have partially distinct biological correlates, and do these align with predictions of the DMAP?

Although some overlap was expected, we aimed to evaluate whether the literature indicated a level of distinction between the biological correlates of deprivation and threat, suggesting partially different mechanisms.

The strongest evidence for divergent associations came from studies examining multiple adversity groupings (of at least deprivation and threat) in the same participants. These studies arguably enable more accurate comparisons due to minimization of methodological variability. In studies that examined deprivation, threat and MA (see Table S6), all but one found distinct associations for deprivation and threat for at least one biological metric, with corresponding associations with MA either absent or in the same direction as one or the other dimension. Contrasting associations were also reported in seven of 12 studies examining both deprivation and threat (but not MA).

4.3.1 Biological domains showing evidence for partially distinct patterns of association with deprivation and threat

The biological domains with the strongest evidence for distinct patterns were global and cortical brain morphology, and the immune and stress response.

Whereas deprivation exposure correlated with lower cortical volume globally, threat exposure tended to associate with variation in specific frontal cortical regions. Evidence for MA-related cortical variation was weak overall. These distinct effects were particularly apparent in two large studies which found deprivation-specific reductions in total cortical volume (LoPilato et al., 2019), and threat-specific reductions in frontal gray matter (Salokangas et al., 2021), despite controlling for experiences in the opposing dimension.

These patterns align somewhat with the predictions of the DMAP, which posits deprivation-related reductions in parts of the association cortex involved with processing complex cognitive and social inputs, and threat-related alterations to the development of circuits involved in emotion processing and regulation, including the ventromedial PFC (McLaughlin et al., 2014). Nevertheless, caveats are warranted; we were unable to infer, for

example, which specific regions were responsible for global associations with deprivation. Moreover, certain threat-related associations were noted in regions typically involved in the deprivation pathway (Rapado-Castro et al., 2020).

While moderate support linked threat exposure to variation in inflammation, there was little to no evidence for deprivation-related associations with these metrics. While the DMAP makes no specific predictions regarding an immune-related pathway by either deprivation or threat, it does propose that chronic threat alters the development of fronto-amygdala circuits involved in threat-detection, which are thought to work closely with the immune system (Brenhouse et al., 2019). Nevertheless, the only study in our review to examine the effect of threat exposure on amygdala response to threatening stimuli found no association (Aas et al., 2017a).

Associations with cortisol also appeared to be threat-specific, with null associations found in all deprivation analyses, and mixed support for MA. This pattern is consistent with the predictions of the DMAP, which posits that early threat-related stress gives rise to long-term changes (chronic activation and/or blunting) in HPA axis function. Multidirectional associations between childhood adversity and cortisol are common in the broader literature (Bernard et al., 2017), and it is thought that blunted cortisol release results from over-regulation of the HPA axis, as an adaptive reaction to sustained cortisol hypersecretion (Fries et al., 2005).

4.3.2 Biological domains showing little evidence for partially distinct patterns of association with deprivation and threat

In contrast, there was little evidence for differential associations of deprivation and threat with subcortical morphology, white matter integrity or brain function.

Studies investigating subcortical morphology were mostly limited to the hippocampus and/or amygdala. For hippocampal volume, associations were (inconsistently) found across deprivation, threat and MA, although the only study examining all three reported volume reductions specific to deprivation (LoPilato et al., 2019). The DMAP proposes that chronic HPA axis activation brought about by early threat exposure upregulates corticotropin releasing hormone expression in the hippocampus, leading to changes in hippocampal morphology and function. Despite some evidence linking threat to HPA function at the cortisol level, these

effects did not extend to hippocampal morphology in our review. Rather, our findings suggest that the association of childhood adversity with hippocampal morphology, if present, occurs irrespective of adversity dimension, at least in psychosis.

While the DMAP makes no specific predictions regarding amygdala structure, a central tenet of the model is that threat preferentially impacts the structural and functional development of the amygdala-medial PFC circuit and salience network. Consistent with this, in McLaughlin and colleagues' (2019) systematic review, threat, but not deprivation, correlated with lower amygdala volume. However, no associations were reported between amygdala volume and threat or deprivation in the studies in our review, although almost half of MA studies found at least one association, mostly negative in direction.

Our findings suggest that both dimensions of adversity may exert subtle structural effects on the hippocampus and amygdala. Several factors may explain this dimensional overlap. First, some deprivation exposures (such as deprivation of resources necessary for survival), may be particularly stressful, and thus trigger mechanisms typically associated with threat that impact stress-sensitive regions. Second, the development of emotion circuits including the hippocampus and amygdala may accelerate with both forms of adversity (i.e., parental absence and abuse) as a compensatory evolutionary mechanism to bring forward the acquisition of skills needed for self-sufficiency (e.g., fear learning) (Callaghan and Tottenham, 2016). Third, deprivation and threat may have divergent impacts on these regions under specific conditions, but the lack of consideration of features such as sex and adversity timing in the relevant studies could have obscured these distinctions. For example, a study in the broader literature by Teicher et al (2018) found sex and timing-specific effects of abuse and neglect on hippocampal volume, which the authors speculated may have been driven by interactions with distinct sex hormone processes at various points in development.

Associations with white matter integrity were observed for deprivation, threat, and MA, largely in tracts connecting the prefrontal cortex with other regions. However, the limited number of studies and varied regions examined rendered insufficient evidence to support distinct regional patterns in each dimension. Similarly, in addition to heterogeneity in study tasks, too few studies examined associations of the dimensions separately with brain function to draw strong conclusions. Of the two studies examining deprivation and threat (Aas et al.,

2017a; Cancel et al., 2017), both found similar associations for each dimension with brain function or connectivity, although associations were spatially more widespread for threat than deprivation.

4.4 Are the biological correlates of early life adversity specific to, or different in, the psychosis spectrum?

As demonstrated in Tables 2 and 3, correlates were often found in individuals on the psychosis spectrum but not controls, although there were exceptions to this pattern (e.g., threat-related associations with frontal cortex structure and MA-related associations in brain function were reported in both groups). Of the 24 association studies reporting analyses in controls, only three reported significant relationships in these subjects (1/11 deprivation studies; 1/13 threat studies; 2/13 MA studies). Similarly, when analyses of interactions between adversity and group were significant, post hoc analyses generally indicated significant associations in the psychosis spectrum alongside null effects in controls.

The absence of effects in controls conflicts with findings in healthy community samples. For example, systematic review and meta-analytic evidence has supported associations between childhood deprivation and cortical volume reductions (McLaughlin et al., 2019), and between several forms of adversity and both elevated inflammation (Baumeister et al., 2016) and an altered cortisol response (Bernard et al., 2017; Bunea et al., 2017). It is possible that in our review, associations were present in controls but were more subtle than in the psychosis spectrum, and thus difficult to detect in the small samples used by many studies.

While this could be due to lower levels of adversity exposure in controls relative to individuals with psychosis (as was typically reported in the studies within this review), it is also possible that certain individuals are more 'sensitive' to the neurobiological effects of adversity than others, increasing the formers' risk for psychosis and other psychopathology. Such heightened sensitivity has been attributed to the possession of certain genetic characteristics, such as the COMT gene (Green et al., 2014), BDNF val66met polymorphism (Alemany et al., 2011), a high psychosis polygenic risk score (Guloksuz et al., 2019), and a combination of genetic and other environmental risk factors (Heurich et al., 2022). For certain types of adversity, it may be that genetic variants involved in developmental synaptic refinement play a role. For example, the DMAP proposes that deprivation-related cortical reductions occur partly via experience-dependent synaptic mechanisms during development, including reduced synaptogenesis/dendritic branching, and earlier or heightened synaptic pruning. Similar

mechanisms have been proposed to explain the etiology of psychosis (Glantz and Lewis, 2000) with contemporary models implicating the immune system in this process (Johnson and Stevens, 2018).

Stronger findings in people with psychosis are also consistent with both the two-hit hypothesis (Feigenson et al., 2014), and the neural stress-diathesis model (Pruessner et al., 2017) of psychosis. Both of these models propose that a predisposed immune system or stress response, respectively, are more likely to become dysregulated upon exposure to environmental stress. Such dysregulation may then contribute to the development or progression of psychotic symptoms; a theory supported by findings of cortisol and immune marker differences between clinically high-risk converters and non-converters to psychosis (Perkins et al., 2015; Walker et al., 2013).

Finally, it is possible that other psychopathologies contributed to the stronger relationships in the psychosis spectrum, as psychosis is often accompanied by other disorders (Plana-Ripoll et al., 2019) for which adversity-related biological alterations to these measures have been reported (e.g., depression [Tozzi et al., 2020; Miller and Cole, 2012]).

4.5 Considerations and future directions

Our review highlights the reliance of research in this area on cross-sectional designs with small sample sizes and retrospective self-reporting of early life adversity. Such designs are prone to bias and may be insufficiently powered to detect subtle effects on neurobiology (Baldwin et al., 2019; Button et al., 2013). The timing, frequency, and chronicity of, and duration since, adversity exposure, were also rarely considered in analyses, except in instances where severity and frequency were combined to create a single exposure metric. Given evidence that the biological (Gee and Casey, 2015; Smith and Pollack, 2021) and clinical (Morgan et al., 2020; Croft et al., 2019) impacts of adversity vary depending on these factors, it is vital they be considered moving forward. Further, few studies examined interactions between biological metrics in relation to adversity, which may be integral to complex pathways linking adversity with psychosis.

Large longitudinal studies with prospective and comprehensive measures of adversity are difficult to conduct in the psychosis spectrum, in part due to recruitment and retention challenges (Furimsky et al., 2008). Consortia

including PRONIA (www.pronia.eu), NAPLS (napls.ucsf.edu), and the ABCD study (abcdstudy.org), are attempting to overcome such challenges by streamlining processes of recruitment, data collection and analysis, and pooling data across multiple sites. Projects like these may be key to isolating the developmental periods most sensitive to adversity, understanding the independent and interacting effects of different adversity attributes on biological systems, and ultimately developing interventions to mitigate the risk of psychosis.

We note that while we focused on deprivation and threat in this review, research suggests that other types of experience confer risk for psychosis as well. For example, greater residential mobility (Price et al., 2018) and living in socially fragmented communities (Ku et al., 2021) during development, are associated with higher rates of psychosis, even after accounting for other risk factors like deprivation and urbanicity (Allardyce et al., 2005; Zammit et al., 2010). Residential mobility has been described as characteristic of the "unpredictability" dimension (e.g., (Belsky et al., 2012), and social fragmentation the "discrepancy" dimension (Vargas et al., 2020), described in other work. Unpredictability is thought to affect connectivity in emotional circuits, while discrepancy may involve changes to the oxytocinergic system and neural regions associated with social rejection, such as the ACC. Researchers should consider adopting a dimensional approach to investigate the effects of other known environmental risk factors for psychosis.

The field may also benefit from investigating the effects of adversity at different levels of proximity to the individual (e.g., family vs neighborhood-level exposures) in parallel, as well as their interactions. For example, while associations have been reported between neighborhood adversity and neurobiology (e.g., in cortical and subcortical morphology [Hackman et al., 2021] and inflammation [Broyles et al., 2012]), findings from several recent studies, including one in the psychosis spectrum (Ku et al., 2022), have suggested that positive experiences in the caregiving (Brody et al., 2019; Miller et al., 2014; Rakesh et al., 2021b), school (Rakesh et al., 2021b), and community (Ku et al., 2022) environment, may offset some of these effects. Insight from such findings could facilitate the development of psychosocial interventions targeted at multiple levels of youth experience, which may help to mitigate the risk of poor mental health outcomes such as psychosis (Blair and Raver, 2016; Carroll-Scott et al., 2013).

4.6 Limitations

Our review has several limitations. First, as demonstrated in Table S5, adversity exposures tend to cooccur between (as well as within) adversity dimensions, and few studies examining one or both separately took methodological steps to address this overlap. Effects may thus have been influenced by variance from the opposing dimension. It should also be noted that our approach of grouping exposures into one or the other dimension, although common in the literature, is not a perfect depiction of a dimensional framework, as dimensions are intended to represent features of experience rather than discrete adversity types (McLaughlin et al., 2021). As tools informed by dimensional adversity models are developed and validated (see Cohodes et al., 2023), the field will become less reliant on measures designed to quantify specific exposure types.

Second, our search strategy aimed to target a broad range of experiences, including macro-level exposures such as neighborhood poverty or crime. Although research suggests that features of the broader ecological context associate with biological (Gard et al., 2021; Rakesh et al., 2022) and psychosis-related (Pedersen et al., 2022; Solmi et al., 2020) outcomes, the extent to which these measures correlate with individual or family-level experiences of deprivation and/or threat will vary, and it is currently unclear how closely the biological mechanisms associated with exposures at different levels overlap (Ellis et al., 2022). Nevertheless, most studies included in our review focused on abuse and (to a lesser extent) neglect; the generalizability of our findings may thus be somewhat limited to adversities experienced at the individual level.

Finally, while the effects of adversity may differ across the psychosis spectrum, due to study heterogeneity we were unable to stratify results by age or illness severity/stage. Similarly, while we were interested in evaluating sex-specific effects, only five studies considered these in analyses, despite established sex differences in the incidence and illness course of psychosis, as well as sexual dimorphisms in brain (Kaczkurkin et al., 2019), immune (Brenhouse et al., 2019), and HPA axis development (Bale and Epperson, 2015). This is an ongoing problem in neuroscience and biological research more broadly (Garcia-Sifuentes and Maney, 2021).

4.7 Conclusion

In summary, this review synthesized the findings from 74 studies examining the relationship between early life experiences of deprivation and/or threat, and markers of neural (brain structure/function), immune and stress response systems in the psychosis spectrum. We found some evidence for partially distinct correlates in brain

morphology and the immune and cortisol response between dimensions; most notably, lower levels of cortical gray matter related to deprivation, and higher inflammation and cortisol alterations related to threat. We found little evidence for dimension-specific relationships with subcortical (particularly limbic) brain structures, white matter integrity or regional brain function. Stronger relationships were generally found in the psychosis spectrum relative to controls. As study designs were heterogeneous and findings inconsistent, conclusions should be treated as preliminary.

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Table 1.

Number of studies examining each dimension and biological metric category (N=74 independent studies)

	Deprivation	Threat	Mixed adversity
Neural	17	18	33
Inflammatory	2	5	6
Stress hormone	6	9	10
Multiple domains	0	1	3

Table 2.

Associations between biological metrics and dimensions of adversity

	Cases			
	Association with deprivation	**Association with threat**	**Association with MA**	**Association with deprivation**
Brain structure				
Total brain volume				
Ruby et al., 2017	-	no sig associations	negative (males)	-
Cerebrospinal fluid volume				
Hoy et al., 2012	-	-	no sig associations	-
Sheffield et al., 2013	-	no sig associations	no sig associations	-
Intracranial volume				
Alameda et al., 2018	-	-	no sig associations	-
Hoy et al., 2012	-	-	no sig associations	-
Salokangas et al., 2021	no sig associations	negative	-	no sig associations
Ventricular volume				
Aas et al., 2013	-	no sig associations	-	-
Total gray matter volume				
Cancel et al., 2015	negative	no sig associations	-	no sig association
Hoy et al., 2012	-	-	no sig associations	-
Sheffield et al., 2013	no sig associations	negative	negative	-

Total cortical volume				
LoPilato et al., 2019	negative	no sig associations	no sig associations	no sig association
Yeo et al., 2014	negative	-	-	no sig association
Total cortical thickness				
Barker et al., 2016a	-	-	no sig associations	-
LoPilato et al., 2019	no sig associations	no sig associations	no sig associations	no sig association
Total cortical surface area				
Barker et al., 2016a	-	-	negative	-
Frontal lobe volume				
Salokangas et al., 2021	no sig associations	negative	-	no sig associations
Cortical region of interest				
Benedetti et al., 2011	-	-	positive	-
Rapado-Castro et al., 2020	no sig associations	negative; positive	-	-
Salokangas et al., 2021	no sig associations	negative	-	no sig associations
Vargas et al., 2019	-	negative	-	-
Wang et al., 2022	negative	positive	negative	no sig association
Whole-brain structure				
Cancel et al., 2015	negative	-	-	-
Sheffield et al., 2013	-	negative	-	-
Vargas et al., 2019	-	no sig associations	-	-
Yeo et al., 2014	negative	-	-	no sig association
Hippocampus				
Aas et al., 2012	-	-	no sig associations[b]	-
Aas et al., 2013	-	negative (met carriers)	-	-
Aas et al., 2014	negative[c]	negative (met carriers)	negative[c]	-
Alameda et al., 2018	-	-	negative	-
Barker et al., 2016b	-	-	negative	-
Hoy et al., 2012	-	-	negative	-
LoPilato et al., 2019	negative	no sig associations	no sig associations	no sig association
Mondelli et al., 2011	-	-	no sig associations[b]	-
Rokita et al., 2020	no sig associations	-	no sig associations	no sig association
Ruby et al., 2017	-	-	no sig associations	-
Vargas et al., 2019	-	no sig associations	-	-
Amygdala				
Aas et al., 2012	-	-	negative[b]	-
Alameda et al., 2018	-	-	no sig associations	-
Armio et al., 2020	-	-	negative	-
Barker et al., 2016b	-	-	negative	-
Hoy et al., 2012	-	-	negative	-
LoPilato et al., 2019	no sig associations	no sig associations	no sig associations	no sig association
Rokita et al., 2020	no sig associations	-	no sig associations	no sig association
Ruby et al., 2017	-	-	positive (males)	-
Vargas et al., 2019	-	no sig associations	-	-
Amygdala/hippocampus				
Salokangas et al., 2021	no sig associations	no sig associations	-	no sig associations
Amygdala/hippocampus (GM)				
Salokangas et al., 2021	no sig associations	no sig associations	-	no sig associations
Parahippocampus				
Vargas et al., 2019	-	no sig associations	-	-
Insula				
LoPilato et al., 2019	no sig associations	no sig associations	no sig associations	no sig association
Thalamus				
LoPilato et al., 2019	no sig associations	no sig associations	no sig associations	no sig association
Anterior cingulate cortex				
Rokita et al., 2020	no sig associations	-	no sig associations	negative
Pituitary gland volume				
Bipin et al., 2021	no sig associations	no sig associations	-	-
Cullen et al., 2015	-	negative	-	-

Total white matter volume				
Hoy et al., 2012	-	-	no sig associations	-
Sheffield et al., 2013	-	no sig associations	no sig associations	-
Frontal lobe volume (WM)				
Salokangas et al., 2021	no sig associations	no sig associations	-	no sig associations
Amygdala/hippocampus (WM)				
Salokangas et al., 2021	no sig associations	negative	-	no sig associations
Fractional anisotropy				
Asmal et al., 2019	positive	negative	no sig associations	no sig association
Molina et al., 2018	negative	no sig associations	-	no sig association
Poletti et al., 2015	-	-	negative	-
Mean diffusivity				
Poletti et al., 2015	-	-	positive	-
Brain function				
BOLD/rCBF (rest)				
Allen et al., 2018	-	-	negative; positive	-
BOLD (task)				
Aas et al., 2017a	positive[d]	positive[d]	positive[d]	-
Benedetti et al., 2011	-	-	negative; positive	-
Quidé et al., 2017b	-	-	negative; positive	-
Functional connectivity (rest)				
Dauvermann et al., 2021	-	-	positive	-
Functional connectivity (task)				
Cancel et al., 2017	negative	negative	-	-
Immune response				
C-Reactive protein				
Aas et al., 2017b	-	no sig associations[b]	-	-
Hepgul et al., 2012	-	positive	-	-
Quidé et al., 2019	no sig associations	positive	-	no sig association
Tumor necrosis factor-α				
Dennison et al., 2012	-	positive	-	-
Di Nicola et al., 2013	-	-	positive	-
Quidé et al., 2019	no sig associations	no sig associations	-	no sig association
Interleukin-2				
Di Nicola et al., 2013	-	-	no sig associations	-
Interleukin-4				
Di Nicola et al., 2013	-	-	no sig associations	-
Interleukin-6				
Dennison et al., 2012	-	no sig associations	-	-
Di Nicola et al., 2013	-	-	no sig associations	-
Quidé et al., 2019	no sig associations	no sig associations	-	no sig association
Interleukin-8				
Dennison et al., 2012	-	no sig associations	-	-
Di Nicola et al., 2013	-	-	no sig associations	-
Interleukin-10				
Di Nicola et al., 2013	-	-	no sig associations	-
Interleukin-1α				
Di Nicola et al., 2013	-	-	no sig associations	-
Interleukin-1β				
Dennison et al., 2012	-	no sig associations	-	-
Di Nicola et al., 2013	-	-	no sig associations	-
Interferon-c				
Di Nicola et al., 2013	-	-	no sig associations	-
MCP-1				
Di Nicola et al., 2013	-	-	positive	-
Cortisol				
Cortisol awakening response				
Mondelli et al., 2010	-	positive	no sig associations[b]	-

Pruessner et al., 2013	-	-	negative	-
Morning cortisol				
Braehler et al., 2005	no sig associations	negative	negative	-
Faravelli et al., 2017	-	-	positive	-
Ruby et al., 2017	-	positive (males)	-	-
Seidenfaden et al., 2017	-	-	no sig associations	-
Afternoon cortisol				
Ruby et al., 2017	-	-	negative (males)	-
Evening cortisol				
Faravelli et al., 2017	-	-	no sig associations	-
Diurnal/basal cortisol				
Braehler et al., 2005	-	-	no sig associations	-
Cullen et al., 2020	-	-	no sig associations	-
Mondelli et al., 2010	-	-	no sig associations	-
Seidenfaden et al., 2017	-	-	no sig associations	-
Hair cortisol concentration				
Aas et al., 2019	-	positive	-	-
Hirt et al., 2019	no sig associations	negative	negative	-
Yang et al., 2021	no sig associations	no sig associations	-	no sig association
Cortisol response (DST)				
Phassouliotis et al., 2013	-	-	no sig associations	-
Cortisol response (TSST)				
Lange et al., 2017	no sig associations	no sig associations	-	no sig association
Seitz et al., 2019	no sig associations	no sig associations	-	-
5α or 5β reductase				
Aas et al., 2020	no sig associations	positive	-	-

Abbreviations: BOLD=blood oxygenation level dependent; CTQ=Childhood Trauma Questionnaire; DST=dexamethasone suppression test; GM=gray matter; MA=mixed adversity; MCP=monocyte chemotactic protein; rCBF=resting cerebral blood flow; TSST=trier social stress test; WM=white matter

"positive" = at least 1 positive association; "negative" = at least 1 negative association; "no sig associations" = no significant associations; "-" = not examined/reported (sometimes more than one association was assessed for specific dimension/biological metric combinations, e.g., when associations for several different deprivation/threat measures or cortical regions of interest were analyzed separately).

[a] controls = recent onset depression subjects

[b] MA measure = number of adversity types

[c] association refers to dose effect of risk factors (met genotype + adversity dimension)

[d] biological measure = differentiation in neural response to negative>positive images

Table 3

Group by adversity dimension interaction effects

Biological metrics & authors	Groups in interaction analyses	Group*adversity dimension interaction effect(s)	Drivers of sig interaction(s) no interaction (-)	Where no interactions, main or within group effects of adversity sig interaction or not examined/reported (-)
Deprivation				
Tumor necrosis factor-α				
Corsi-Zuelli et al., 2020	FEP, sibs, Ctrl	no sig interactions	-	no effects within groups
Transforming growth factor-β				
Corsi-Zuelli et al., 2020	FEP, sibs, Ctrl	no sig interactions	-	no effects within groups
Interleukin-6				
Corsi-Zuelli et al., 2020	FEP, sibs, Ctrl	no sig interactions	-	no effects within groups
Interleukin-10				
Corsi-Zuelli et al., 2020	FEP, sibs, Ctrl	no sig interactions	-	no effects within groups
Interleukin-1β				
Corsi-Zuelli et al., 2020	FEP, sibs, Ctrl	no sig interactions	-	no effects within groups
Threat				
Tumor necrosis factor-α				
Corsi-Zuelli et al., 2020	FEP, sibs, Ctrl	no sig interactions	-	no effects within groups
Transforming growth factor-β				
Corsi-Zuelli et al., 2020	FEP, sibs, Ctrl	sig interaction	Threat → ↑ TGF-β in FEP; Threat → ↓ TGF-β in Ctrl; no association in sibs	-
Interleukin-6				
Corsi-Zuelli et al., 2020	FEP, sibs, Ctrl	no sig interactions	-	no effects within groups
Interleukin-10				
Corsi-Zuelli et al., 2020	FEP, sibs, Ctrl	no sig interactions	-	no effects within groups
Interleukin-1β				
Corsi-Zuelli et al., 2020	FEP, sibs, Ctrl	no sig interactions	-	no effects within groups
Cortisol awakening response				
Ciufolini et al., 2019	FEP, Ctrl	sig interaction	Inverted U-shaped association between CARg & threat severity in FEP; U-shaped in Ctrl	-
Diurnal/basal cortisol				
Ciufolini et al., 2019	FEP, Ctrl	no sig interactions	-	no effects in total sample
Mixed adversity (MA)				
Total gray matter volume				
Frissen et al., 2018	PP, sibs, Ctrl	sig interaction	MA → ↓GMV in PP; no association in sibs or Ctrl	-
Total cortical thickness				

Habets et al., 2011	SZ, sibs, Ctrl	sig interaction	MA → ↓cortical thickness in SZ; MA → ↑cortical thickness in sibs; no association in Ctrl	-
Cortical region of interest				
Hoffmann et al., 2018	SZ/SZA, Ctrl	no sig interactions	-	no effects in total sample
Begemann et al., 2021	SSD, BD, Ctrl	no sig interactions	-	within group effects: MA → ↓frontal GMV in BD & Ctrl; no effects in SSD
Whole brain analysis				
Poletti et al., 2016	SZ, Ctrl	no sig interactions	-	-
Quidé et al., 2021a	SZ/SZA, BD WPF, Ctrl	sig inflammation* group*MA interaction	See Table S4 for details	-
Hippocampus				
Begemann et al., 2021	SSD, BD, Ctrl	no sig interactions	-	no effects in total sample
du Plessis et al., 2020	FES, Ctrl	sig sex*group*MA interaction	MA → ↑hippocampal fissure size in female PP; no association in male PP or Ctrl	
Hernaus et al., 2014	PP, sibs	no sig interactions	-	no effects in total sample
Hoffmann et al., 2018	SZ/SZA, Ctrl	no sig interactions	-	no effects in total sample
Amygdala				
Begemann et al., 2021	SSD, BD, Ctrl	no sig interactions	-	no effects in total sample
Insula/cingulate				
Begemann et al., 2021	SSD, BD, Ctrl	no sig interactions	-	no effects in total sample
Total subcortex				
Begemann et al., 2021	SSD, BD, Ctrl	no sig interactions	-	no effects in total sample
Caudate				
Hoffmann et al., 2018	SZ/SZA, Ctrl	no sig interactions	-	no effects in total sample
Nucleus accumbens				
Hoffmann et al., 2018	SZ/SZA, Ctrl	no sig interactions	-	no effects in total sample
Putamen				
Hoffmann et al., 2018	SZ/SZA, Ctrl	no sig interactions	-	no effects in total sample
Fractional anisotropy				
Domen et al., 2019	PP, sibs, Ctrl	sig interaction	1. MA → ↓FA in SSD but not sibs or Ctrl at follow up 2. MA → greater decline in FA from baseline to follow up in SSD than sibs & Ctrl	-
BOLD (task)				
Quidé et al., 2017a	SZ/SZA/BD (cases), Ctrl	sig interaction	MA → ↑activation in cases; MA → ↓activation in Ctrl (see Table S4 for regions)	-
Quidé et al., 2018	SZ/SZA/BD WPF, Ctrl	no sig interactions	-	MA → ↑ left IFG activity in the total sample

Quidé et al., 2020	SZ/SZA, BD WPF, Ctrl	sig cortisol*group*MA interaction	See Table S4 for details	-
Functional connectivity (rest)				
Peeters et al., 2015a	PP, sibs, Ctrl	no sig interactions	-	no effects in total sample
Peeters et al., 2015b	PP, sibs, Ctrl	no sig interactions	-	no effects in total sample
Functional connectivity (task)				
Quidé et al., 2018	SZ/SZA/BD WPF, Ctrl	no sig interactions	-	MA → ↑FC between the left IFG & 1) left cerebellum/ fusiform gyrus & 2) the right calcarine sulcus in the total sample
Quidé et al., 2020	SZ/SZA, BD WPF, Ctrl	sig cortisol*group*MA interaction	See Table S4 for details	-
C-reactive protein				
Counotte et al., 2019	ROP/CHR, sibs/Ctrl	no sig interactions	-	no effects in total sample
Misiak et al., 2020	SSD, Ctrl	no sig interactions	-	no effects in total sample
Tumor necrosis factor-α				
Corsi-Zuelli et al., 2020	FEP, sibs, Ctrl	no sig interactions	-	no effects within groups
Counotte et al., 2019	ROP/CHR, sibs/Ctrl	no sig interactions	-	no effects in total sample
Transforming growth factor-β				
Corsi-Zuelli et al., 2020	FEP, sibs, Ctrl	sig interaction	Higher TGF-β in MA-exposed FEP & sibs than Ctrl; MA → ↓ TGF-β in Ctrl	-
Interleukin-6				
Corsi-Zuelli et al., 2020	FEP, sibs, Ctrl	no sig interactions	-	no effects within groups
Counotte et al., 2019	ROP/CHR, sibs/Ctrl	no sig interactions	-	no effects in total sample
Interleukin-10				
Corsi-Zuelli et al., 2020	FEP, sibs, Ctrl	no sig interactions	-	no effects within groups
Interleukin-1β				
Corsi-Zuelli et al., 2020	FEP, sibs, Ctrl	no sig interactions	-	no effects within groups
Interferon-γ				
Counotte et al., 2019	ROP/CHR, sibs/Ctrl	no sig interactions	-	no effects in total sample
CCL-2				
Counotte et al., 2019	ROP/CHR, sibs/Ctrl	no sig interactions	-	no effects in total sample
Stem cell factor				
Counotte et al., 2019	ROP/CHR, sibs/Ctrl	no sig interactions	-	no effects in total sample
T helper 1 cell numbers				
Counotte et al., 2018	ROP/CHR, sibs/Ctrl	no sig interactions	-	no effects in total sample

T helper-2 cell numbers				
Counotte et al., 2018	ROP/CHR, sibs/Ctrl	no sig interactions	-	no effects in total sample
T helper-17 cell numbers				
Counotte et al., 2018	ROP/CHR, sibs/Ctrl	sig interaction	MA → ↑Th17 cell count in ROP/CHR; no association in sibs/Ctrl	-
T regulator cell numbers				
Counotte et al., 2018	ROP/CHR, sibs/Ctrl	no sig interactions	-	no effects in total sample
Natural killer cell numbers				
Counotte et al., 2018	ROP/CHR, sibs/Ctrl	no sig interactions	-	no effects in total sample
Cortisol awakening response				
Labad et al., 2020	ROP, Ctrl	no sig interactions	-	no effects in total sample
Diurnal/basal cortisol				
Labad et al., 2020	ROP, Ctrl	no sig interactions	-	no effects in total sample
Hair cortisol concentration				
Söder et al., 2019	fHR, Ctrl	no sig interactions	-	MA → ↑ HCC in total sample (which also included CHR)
Cortisol response (DST)				
Labad et al., 2020	ROP, Ctrl	no sig interactions	-	no effects in total sample

Abbreviations: BD=Bipolar Disorder; BOLD=blood oxygenation level dependent; CARg=cortisol awakening response with respect to ground; CCL=chemokine (c-c motif) ligand; CHR=Clinically High Risk for Psychosis; Ctrl=control; DST=dexamethasone suppression test; FA=fractional anisotropy; FC=functional connectivity; FEP=First Episode Psychosis; GM=gray matter; GMV=gray matter volume; HCC=hair cortisol concentration; IFG=inferior frontal gyrus; MCP=monocyte chemotactic protein; PP=Psychosis Patients; rCBF=resting cerebral blood flow; ROP=Recent-Onset Psychosis; sibs=siblings; SSD=Schizophrenia Spectrum Disorder; SZ=Schizophrenia; SZA=Schizoaffective Disorder; TGF-β=transforming growth factor-β; Th17=T helper-17; TSST=trier social stress test; WM=white matter; WPF=with psychotic features

"sig interaction" = at least 1 significant interaction reported; "no sig interactions" = no significant interactions reported (sometimes more than one interaction was assessed for specific dimension/biological metric combinations, e.g., when interactions for several different deprivation/threat measures or cortical regions of interest were analyzed separately).

Declaration of interests

RU reports speaker fees from Sunovion, Springer Healthcare and Vitaris outside the submitted work. RU holds unpaid officership with the British Association for Pharmacology - Honorary General Secretary 2021-2024 and is Deputy Editor, The British Journal of Psychiatry.

Highlights:

- This review investigated the biological correlates of childhood deprivation and threat in psychosis.
- A systematic search of the literature produced 74 articles, mostly examining associations between various forms of adversity and brain structure and function.
- Findings were inconsistent, but deprivation tended to predict reductions in cortical volume, and threat predicted alterations to inflammation and cortisol.
- Results provide tentative support for the use of dimensional models of adversity in psychosis research.