Childhood adversities and psychosis: evidence, challenges, implications

Craig Morgan, Charlotte Gayer-Anderson

Society and Mental Health Research Group, Centre for Epidemiology and Public Health, Health Service and Population Research Department, Institute of Psychiatry, King's College London, London, UK; National Institute for Health Research (NIHR) Mental Health Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London, London, UK

There is a substantial body of research reporting evidence of associations between various forms of childhood adversity and psychosis, across the spectrum from experiences to disorder. This has been extended, more recently, to include studies of cumulative effects, of interactions with other factors, of specific effects, and of putative biological and psychological mechanisms. In this paper we evaluate this research and highlight the remaining methodological issues and gaps that temper, but do not dismiss, conclusions about the causal role of childhood adversity. We also consider the emerging work on cumulative, synergistic, and specific effects and on mechanisms; and discuss the broader implications of this line of research for our understanding of psychosis. We conclude that the current balance of evidence is that childhood adversities – particularly exposure to multiple adversities involving hostility and threat – do, in some people, contribute to the onset of psychotic experiences and psychotic disorders.

Key words: Childhood adversity, childhood abuse, psychotic experiences, psychotic disorders, cumulative effects, gene-environment interaction, protective factors

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There has been a flurry of research on the relationship between childhood adversity and psychosis over the past ten years. This has extended, more recently, to studies that have sought to elaborate on the nature of the relationship, by examining cumulative effects, interactions with other risk factors (e.g., genes), specificity of effects, and putative mechanisms.

For some authors, the accumulated evidence unequivocally establishes that difficult and unpleasant experiences in childhood contribute to the development of psychoses[1]. For others, the evidence is not so clear cut[2]. At issue, in part at least, are fundamental questions about the nature and aetiology of psychosis. Much, then, is at stake and a further appraisal of the evidence is warranted.

In this paper, we first summarize and critically evaluate research on the association between childhood adversities and psychosis (including low-level experiences, at risk states, and disorders). In doing this, we focus particularly on remaining methodological issues and gaps in the literature, and on research that has further investigated the nature of the association. We then reflect on the broader implications of this work for our understanding of psychosis.

CHILDHOOD ADVERSITY

Childhood adversity is a broad term that denotes exposure to a range of difficult or unpleasant situations or experiences, usually before the age of 16. The adversities typically considered in studies of psychoses include household poverty, separation from a parent (i.e., family breakdown), death of a parent, neglect, abuse (including emotional, psychological, physical, and sexual), and peer bullying.

Estimates suggest that large numbers of children are exposed to such situations and experiences. In the UK, for example, according to estimates, over 3 million children (~28%) live in poverty (defined as less than 60% of the average household income)[3], over 3 million children (~23% of those living in families) live in lone parent households[4], around 6% of those aged 0-10 years and around 19% of those aged 11-17 years experience some form of severe maltreatment, and around 30% to 40% experience some form of bullying (including name calling, social exclusion, threats, and – increasingly – cyber bullying) in a given year[5].

More broadly, the World Health Organization (WHO) World Mental Health Surveys estimate that – across all countries, irrespective of level of economic development – the prevalence of exposure to at least one childhood adversity (including loss, maltreatment, economic adversity, and illness) is around 40%[6]. What is more, adversities tend to co-occur and persist over time, often in worsening cycles of disadvantage and vulnerability, in which one difficulty leads to and compounds others. As a consequence, many children are exposed to multiple adversities that persist and become entrenched throughout childhood and adolescence, often with lifelong consequences. For example, the WHO World Mental Health Surveys found that most adversities were highly correlated: of those reporting any, around 60% reported exposure to multiple adversities[6].

PSYCHOSIS

In recent years, substantial evidence has accrued that sporadic and non-distressing psychotic experiences (e.g., fleeting hallucinations, suspiciousness and paranoia, magical thinking) are common in the general population (the most recent meta-analysis suggests a lifetime prevalence of around 7%[7]) and are associated with the later development of psychotic and other disorders[8,9].

Table 1 Reviews (with quantified summaries) and meta-analyses of childhood adversity and psychosis since 2005

Review	Year	Number of papers	Target population	Exposure(s)	Overall summary effect, OR (95% CI) unless otherwise specified	% exposed
Read et al[10]	2005	66	In- and out-patients, at least 50% with psychosis (no comparison group)	Sexual abuse Physical abuse Either Both		48% F, 28% M 48% F, 50% M 69% F, 59% M 36% F, 19% M
Morgan and Fisher[11]	2007	20	In- and out-patients with psychosis (no comparison group)	Sexual abuse Physical abuse Either Both		42% F, 28% M 35% F, 38% M 50% F, 50% M 26% F, 18% M
van Dam et al[12]	2012	7	Psychotic experiences	Bullying	2.70 (2.00-3.60)	
Varese et al[1]	2012	41	Any psychosis (including experiences and disorder)	Any adversity Sexual abuse Physical abuse Emotional abuse Neglect Parent death Bullying	2.78 (2.34-3.31)(population attributable risk: 33%) 2.38 (1.98-2.87) 2.95 (2.25-3.88) 3.40 (2.06-5.62) 2.90 (1.71-4.92) 1.70 (0.82-3.53) when an outlier was excluded: 2.30 (1.63-3.24) 2.39 (1.83-3.11)	
Bonoldi et al[13]	2013	23	Psychotic disorder (no comparison group)	Sexual abuse Physical abuse Emotional abuse		26% 39% 34%
de Sousa et al[14]	2013	20	Psychotic disorder	Parent communication deviance	Hedge's g: 0.97 (0.76-1.18)	
Matheson et al[21]	2013	25	Schizophrenia	Any adversity (including abuse, neglect, loss, witness domestic violence, life events)	3.60 (2.08-6.23) vs. controls 1.23 (0.77-1.97) vs. affective psychoses 2.54 (1.29-5.01) vs. anxiety 1.37 (0.53-3.49) vs. depression 0.03 (0.01-0.15) vs. post-traumatic stress disorder/dissociation 0.69 (0.29-1.68) vs. other psychoses 0.65 (0.09-4.71) vs. personality disorder	
Cunningham et al[15]	2015	7	Any psychosis (including experiences and disorder)	Bullying	2.15 (1.14-4.04)	
Kraan et al[16]	2015	6	Ultra high risk (for psychosis)	Trauma (including abuse and neglect)	Hedge's g: 1.09, $Z=4.60$, $p<0.01$ (confidence intervals not given)	
Trotta et al[17]	2015	9	Persistence of psychotic experiences or symptoms	Any adversity (including abuse, neglect, parent death or separation, bullying, being in care)	1.73 (1.26-2.32) non-clinical samples: 1.76 (1.19-2.32) clinical samples: 1.55 (0.32-2.77)	
Velikonja et al[18]	2015	25	Schizotypal traits	Trauma (including abuse, neglect, bullying, parent death or separation, or other traumatic experiences, such as household discord, a life- or injury-threatening event)	OR range: 2.01 to 4.15	

This evidence has led to a rapid growth of research investigating risk factors for these experiences, on the basis that they may tell us something about the putative causes of psychotic disorders. This is part of a broader trend for research to focus on earlier (e.g., at risk mental states) and both broader (i.e., all psychotic disorders) and more specific (i.e., psychotic symptoms or complaints) psychosis phenotypes. These trends reflect ongoing debates and disputes about the very nature of psychoses (e.g., continuum vs. categorical models). Research on childhood adversity extends across the spectrum of psychosis outcomes.

EVIDENCE

Since Read et al[10] published their review of studies of physical and sexual abuse and psychosis in 2005, there have been at least thirteen narrative or systematic reviews (including at least eight meta-analyses) on one form or other of childhood adversity and psychosis[1,11-22]. Those that report either summary proportions exposed to adversity or summary effects of adversity on psychosis are detailed in Table 1.

The evidence that has emerged is consistent. Most indicators or forms of adversity that have been considered are associated with around a 2 to 4-fold increased risk or odds of psychosis. For example, Varese et al[1], in the most comprehensive meta-analysis to date, identified 36 studies and found that, irrespective of study design, childhood adversity was overall associated with a 2.78 increased odds of psychosis (95% CI: 2.34-3.31). Considering the specific forms of adversity, the odds ratios were 2.38 (95% CI: 1.98-2.87) for sexual abuse; 2.95 (95% CI: 2.25-3.88) for physical abuse; 3.40 (95% CI: 2.06-5.62) for emotional abuse; 2.39 (95% CI: 1.83-3.11) for bullying; and 2.90 (95% CI: 1.71-4.92) for neglect. Only parental death was not strongly associated with psychosis (OR = 1.70, 95% CI: 0.82-3.53).

In the short time since the publication of that review, over twenty additional studies have been published, most of which provide further evidence that childhood adversities are more common among those with psychosis, again across the spectrum[23-44]. Perhaps most notably, in a prospective study of 1,112 adolescents, Kelleher et al[31] found that cessation of trauma was associated with subsequent cessation of psychotic experiences.

Other meta-analyses that have focused on specific adversities (e.g., bullying[12]) or specific psychosis outcomes (e.g., schizophrenia[21], at risk mental states[16], schizotypy[18]) report similar findings, i.e., a 2 to 4-fold increased risk or odds (Table 1). Further, another recent meta-analysis suggests that childhood adversity is associated with a persistence of psychotic experiences over time, a finding that is of particular interest as it is persistence of low-level experiences that most strongly predicts later development of psychotic disorder[17].

On the face of it, then, there is a remarkably consistent convergence of evidence that various forms of childhood adversity are associated, perhaps in linear fashion (see below), with psychosis outcomes across the spectrum. Further, those studies that have adjusted for potential confounders do not find evidence that associations can be accounted for by genetic or other established risk factors[1,37,45].

CHALLENGES

However, there remain several caveats and gaps. First, a majority of the studies are of low-level psychotic experiences in general population samples. This is important for at least three reasons. One, measurement of these experiences is often limited, e.g. to single questions, and measurement error is no doubt high (i.e., misclassification of experiences as psychotic that are not). We include our own work in this[46]. Two, low-level psychotic experiences very often co-occur with, and may not be easy to distinguish from, symptoms of depression, anxiety, and post-traumatic stress disorder – all of which are strongly associated with adversity and trauma. Three, it does not necessarily follow that experiences associated with endorsement of psychosis-related items on questionnaires will be associated with psychotic disorder or vice versa. For example, recent studies have failed to find any association between psychotic experiences and polygenic risk scores for schizophrenia[47]. Consequently, the extent to which associations between childhood adversities and psychotic experiences hold for psychotic disorders – which are characterized by multiple severe and distressing psychotic symptoms and functional impairment – is far from clear.

Second, studies of psychotic disorder are fewer and – with some notable exceptions[48-50] – of poor methodological quality, often comprising small convenience samples of prevalent cases (including some restricted to subgroups, e.g. late onset[51,52], women[53]) and of controls. Associations in these studies could arise due to selection biases if, for example, those with a more severe and/or long-standing disorder are more likely to have experienced adversities. This noted, the small number of larger and more robust studies do, overall, suggest associations with childhood adversities, but with important nuances. For example, in the AESOP study of first-episode cases and randomly sampled controls, we found, first, some evidence of associations with parental loss and with separation from a parent[54] and, second, some evidence of associations between physical and, more tentatively, sexual abuse among women, but not men[49] (incidentally, gender differences remain underexplored). Further, Cutajar et al[50], in a study of 2,759 individuals known to have been sexually abused in childhood and a matched control group, found evidence for an association specifically with sexual abuse involving penetration that occurred between age 12 and 17 years. More studies of disorder are evidently needed to further clarify these associations.

Third, most studies have relied on retrospective recall of exposure to abuse and other adversities in childhood. How-

ever, memory of past experiences is dependent, to some extent, on cognitive ability and is clouded and shaped by subsequent experiences, fluctuating moods, and re-tellings. This may be especially true for traumatic events and could bias findings if there is differential recall by those with and those without psychosis: for example, greater recall among those with psychosis due to the influence of current mental state (e.g., more paranoia) or effort after meaning (i.e., searching past experiences to explain current problems). As Susser and Widom[2] note in their commentary on Varese et al[1], this is not a problem that can be addressed with meta-analyses: "Pulling together many studies that share a similar bias will produce a biased result". This noted, it seems unlikely that recall bias alone could explain the repeated findings. In fact, there is some evidence that reports of abuse among those with psychosis are stable over time and not influenced by current mental state[55]. Furthermore, studies that have established exposure to adversities before measurement of psychotic experiences or onset of psychotic disorder have also reported associations[37,45,50]. For example, in the E-Risk Study of 2,232 twins, Arseneault et al[45] found that parent reports of maltreatment and of bullying by age 7 were associated with, respectively, a 3.48 (95% CI: 1.93-6.27) and a 2.19 (95% CI: 1.25-3.83) increased odds of psychotic experiences at age 12. Moreover, the study by Cutajar et al[50] established exposure prior to onset of disorder.

Fourth, the measurement of childhood adversities has been relatively crude, with most studies considering presence or absence of exposure at any point during childhood, with only limited consideration of the type, timing, severity, or duration of exposure. We noted this limitation in an early paper[11], and data addressing this have been slow to emerge. What available data (e.g., those by Cutajar et al[50] mentioned above) do suggest is that these dimensions matter and further underscore the importance of more extensive research utilizing more detailed assessments of exposure to adversities throughout childhood and adolescence.

To be clear, these methodological issues do not invalidate the current evidence. What they do is to add caveats, urge some caution, and highlight areas to be considered in future research.

EXPLORING THE NATURE OF THE ASSOCIATION

Research has begun to further elaborate on the nature of the association between childhood adversity and psychosis (although many of the limitations highlighted above also apply to this work). This is driven by three observations. First, and as noted at the outset, specific adversities rarely occur in isolation. Second, many children are exposed but only a minority develop psychotic experiences, fewer still a psychotic disorder. Third, childhood adversity is associated with a range of negative mental health and other outcomes (e.g., substance use).

If childhood adversity is indeed involved in the development of psychosis, these observations raise further questions about the cumulative effect of exposure to multiple adversities, about other factors that may amplify or minimize effects (i.e., causal partners), about whether there is any specificity for psychosis, and – ultimately – about the mechanisms through which risk is increased.

CUMULATIVE EFFECTS

There is evidence that the effect of multiple adversities on risk or odds of psychosis is cumulative[27,31,33,48,56,57]. For example, Wicks et al[57], in their study of Swedish population register data, found that there was a modest linear increase in risk of psychotic disorder for each additional indicator of childhood adversity. Further, while not part of the meta-analysis, Varese et al[1] report that 9 of 10 studies that examined multiple adversities found some evidence of a linear effect, i.e. greater risk or odds with each additional adversity.

There are, however, some limitations to these findings. For example, simply adding the number of exposures assumes that each has an equivalent effect, which is unlikely to be the case. Further, analyses assume that effects are linear; this is rarely formally tested and the possibility that there are threshold effects has not been considered. Finally, alternative approaches may yield additional insights (e.g., using latent class analyses to identify groups of individuals characterized by exposure to varying clusters of adversities).

CAUSAL PARTNERS

Childhood adversities are neither sufficient nor necessary for the onset of psychosis. This means that their impact must be dependent on the presence of other factors or causal partners. Reflecting this, there is a developing body of research examining the combined (synergistic) effects of childhood adversity and both genetic and other environmental factors.

Gene-environment interaction

Studies of gene-childhood adversity interaction have produced mixed results. Some have used indirect proxy markers for genetic risk, usually a history of psychosis in a first-degree relative. For example, Tienari et al[58] examined whether the effect of family communication on risk of schizophrenia was dependent on genetic risk, using an adoption study design. They, first, assessed family communication patterns (dichotomized into low-dysfunction and high-dysfunction) in a sample of adoptees of mothers with a diagnosis of a schizophrenia spectrum disorder (high genetic risk group; N=145) and a sample of adoptees of mothers without a diagnosis of a schizophrenia spectrum disorder (low genetic risk group; N=158) and, second, followed the adoptees – up to 21 years later – to determine who developed a schizophrenia spectrum disorder.

They found strong evidence that the effect of dysfunctional family communication patterns on odds of disorder at follow-up was dependent on level of genetic risk. In the high genetic risk group, odds of disorder were ten times greater in the high-dysfunction than in the low-dysfunction group (OR=10.00, 95% CI: 3.26-30.69); in the low genetic risk group, the odds of disorder for each level of family dysfunction were roughly the same (OR=1.11, 95% CI: 0.37-3.39).

In a more recent analysis of data from the AESOP study, we used family history of psychotic disorder in a parent as a proxy for genetic risk to examine interaction between genetic risk and physical abuse in childhood in 172 cases with a first-episode psychosis and 246 controls[59]. We found no evidence that the combined effect of abuse and family history was greater than the effect of each alone (i.e., no evidence of interaction). This study, however, was not designed to examine gene-environment effects and the sample was no doubt underpowered to detect anything other than a large interaction effect. This noted, others have also failed to find any evidence of interaction using indirect proxy measures of genetic risk[60,61], including Arseneault et al[45] in their analyses of data from the E-Risk Study.

Other studies have used direct measures of genetic variation to examine interactions with candidate genes, i.e., genes either implicated in psychoses or in exposure-relevant systems, e.g. hypothalamic-pituitary-adrenal (HPA) axis or dopamine systems. Collip et al[62], for example, examined interactions between polymorphisms in the FKBP5 gene (a modulator of the feedback loop determining glucocorticoid receptor sensitivity, for which there is evidence of interaction with childhood trauma in post-traumatic stress disorder and depression) and childhood trauma (i.e., mean trauma scores from the Childhood Trauma Questionnaire) in a series of analyses of data from samples with expressions of psychosis across the spectrum. There was some evidence of interactions between trauma and two FKBP5 single nucleotide polymorphisms on psychotic symptoms, but these were not consistent across samples.

In another study of FKBP5 and maltreatment, in a sample of 444 cases with schizophrenia and 292 controls, Green et al[63] found some evidence that a FKBP5 single nucleotide polymorphism (not one of those implicated in Collip et al's study[62]) and maltreatment combined to affect cognition (specifically attention) in both cases and controls.

Other genes studied include those coding for brain-derived neurotrophic factor (BDNF), involved in neuronal development and cell survival in response to stress, and catechol-O-methyltransferase (COMT), involved in metabolism of catecholamines, including dopamine, in the central nervous system. Some studies found evidence of interactions (e.g., COMT[64,65], BDNF[66]) and others did not (e.g., BDNF[64]).

The evidence, then, is at present limited, with little consistency in methods and measures used. Further investigations are ongoing[67]. These are likely to make use of emerging findings from molecular genetic studies to move beyond crude proxy markers of genetic risk or pain-staking analyses of one candidate gene at a time. That is, these new studies will almost certainly make use of direct measures of total (or pathway specific) genetic risk, derived from genome wide association studies (i.e., polygenic risk scores, which provide weighted summaries of effects of multiple risk genes[68]), to model gene-childhood adversity interaction. Such research is, however, time consuming and it is likely that relevant findings will be slow to emerge and to replicate.

Environment-environment interaction

A small number of studies have examined interactions between childhood adversity and other environmental factors, notably cannabis use and adult life events and adversities. So far, these studies have been fairly consistent in finding evidence that childhood adversities do combine with subsequent cannabis use and adult adversities in psychoses.

With regard to cannabis use, there are six studies that we are aware of[69-74], only one of which did not find at least suggestive evidence of interaction[73]. To illustrate this, in our analyses of data from a household survey of around 1,700 individuals, we found that odds of psychotic experiences were increased five-fold in those who both reported abuse in childhood and cannabis use in the preceding year (compared with around a two-fold increased odds for those reporting only abuse or only cannabis use)[74].

As for adult adversity, there are four studies that we are aware of, all of which found evidence of interaction[74-77]. In our analyses of data from the household survey, for example, we found strong evidence that abuse and life events combined synergistically to increase odds of low-level psychotic experiences, over and above the effects of each alone[74]. Lataster et al[75] similarly found evidence that early and recent adversity combined synergistically to increase risk of low-level psychotic experiences in their analyses of data from the Early Developmental Stages of Psychosis study (N=1,722). The other studies suggest that these combined effects extend to psychotic disorder[76,77]. For example, Bebbington et al[76], using data from the 2007 UK Adult Psychiatric Morbidity Survey, found some evidence that sexual abuse combined with re-victimization in adulthood amplified risk of probable psychotic disorder.

Protective factors

What has not yet been considered to any great extent is whether there are protective factors that can offset the effects of childhood adversity. In general, there is strong evidence that social support, in particular the support of an adult, can limit the negative consequences of abuse and other adversities in childhood. In a secondary analysis of data from the AESOP study, we found some evidence – albeit among women only – that the effect of severe physical abuse on odds of psychosis was lower among those with more extensive networks[78].

Beyond this, we are not aware of any other studies that have examined the modifying effect of protective factors in relation to childhood adversity and psychosis. This, then, is an important avenue for future research. Investigating why some people are resilient in the face of often extensive adversities in childhood is of direct relevance to understanding how we can intervene at early stages to minimize risk and maximize resilience.

SPECIFICITY

At a broad level, most forms of childhood adversity are associated with a range of negative mental health and other outcomes. This raises the question of whether effects, if causal, are non-specific (with the particular forms that distress and disorder take being shaped by other factors, e.g. genes) or whether any types of adversity particularly increase risk of psychosis or, indeed, certain psychotic experiences.

There are good reasons to expect both non-specific and specific effects[79]. It may be, for example, that most forms of adversity – in activating a stress response – exert general effects on processes involved in many outcomes. Non-specific effects, then, are likely. What is more, identifying specific effects is difficult, because not only adversities but also symptoms frequently co-occur (and indeed many symptoms may be sequentially and causally related). Disentangling effects is far from straightforward. This noted, some specificity is likely. Different types of experiences may impact on different psychological and, perhaps, biological processes, e.g. on attributions about self and the world, on threat anticipation, on activation of brain regions regulating perception of and response to stress, which in turn may underpin specific experiences. As Bentall et al[79] argue, we might expect partial specificity.

It is perhaps no surprise, then, that there is evidence for both non-specific and specific effects. To begin with, at the broad level of any childhood adversity and mental disorder, there is limited evidence of specificity. In their meta-analysis, Matheson et al[21] found no evidence that the magnitude of the association between childhood adversity and schizophrenia was different from that for other psychoses, depression, or personality disorders. There was some evidence that the effect was greater than for anxiety and, not surprisingly, lower than for post-traumatic stress disorder or dissociation, but childhood adversities, broadly defined, were associated with an increased risk of all these disorders.

When research moves from this broad level to consider particular types of adversity, there is some evidence for specificity. For example, in a further analysis of AESOP data[80], we found some tentative evidence that physical abuse (but not sexual abuse) – particularly by mother before age 12 years – was specifically associated with psychotic disorder, a finding that mirrors what has been found in relation to other disorders when researchers have carefully separated the effects of each. In this context, it is relevant to note again that Cutajar et al[50] found an effect for sexual abuse only at the most extreme and violent level.

Others have found similar evidence for specific effects of adversities involving threat and hostility, most notably Arseneault et al[45] in their analyses of data from the E-Risk Study. When the specific effects of three negative events or experiences – a serious accident, bullying, and maltreatment – were considered, bullying and maltreatment, but not a serious accident, were associated with an increased risk of psychotic experiences. The authors speculated that negative experiences involving intention to harm may be particularly important for psychotic experiences. In an analysis of data from the Dutch NEMESIS studies, van Nierop et al[81] found further evidence for a specific effect of events involving intent to harm. This mirrors some earlier findings (e.g., Bebbington et al[82]) and ties in with evidence from studies of adults which tentatively suggest that intrusive life events (e.g., physical assault) may be specifically associated with psychoses[46,83].

Intriguingly, in one of the few studies to directly investigate associations between racial discrimination and psychosis, Karlsen et al[84] found that the strongest effect was for discrimination involving physical assault. The high rates of psychosis in some migrant and minority ethnic groups may, then, in part be a consequence of greater exposure to hostility, threat, and violence in the context of wider social disadvantage and discrimination – not social defeat (a misnomer anyway), as has been proposed[85]. In general, it may be that these experiences are particularly linked to the development of suspiciousness, paranoia, and ultimately delusions of persecution and reference, which are the most common symptoms in schizophrenia and other psychoses.

At the level of symptoms, there is some evidence for a specific association between sexual abuse and hallucinations, disrupted early attachments or victimization experiences and paranoia, and parental communication deviance and thought disorder[79].

MECHANISMS

Biological

There are a number of connected biological mechanisms through which exposure to childhood adversities may increase risk for psychoses, including via effects on the HPA axis, dopamine systems, and neurocognition.

The plausibility of these hypothesized mechanisms derives from studies demonstrating dysfunctions and deficits in these biological systems among those exposed to childhood adversities, especially trauma, and among those with psychoses. First, there is strong evidence that childhood adversities are associated with hyperactivation and sensitization of the HPA axis[86,87] and, in recent years, there has been an accumulation of evidence of dysregulation of the HPA axis in those with psychoses[86,88]. For example, a number of studies have found

differences in basal cortisol levels between those with a psychotic disorder and those without, with a majority reporting elevated cortisol levels at different points during the day[86,89]. There is also some evidence that the pituitary gland may be enlarged among those with a psychotic disorder[90]. Further, overactivity of the HPA axis increases dopamine release.

Second, there is evidence that hippocampal volume is decreased both among those exposed to childhood adversity[87] and those with a psychotic disorder[86]. For example, meta-analyses suggest that hippocampal volume is reduced bilaterally in those with a first episode and in those with a long-standing disorder[91,92]. This is relevant because the hippocampus is involved in regulating the HPA axis stress response, and there is some direct evidence that smaller hippocampal volume at first psychotic episode is partly explained by stress-related processes, measured by cortisol secretion[93].

Third, there are studies that show reduced levels of BDNF – which is necessary for hippocampal neurogenesis – following exposure to stress[86] and in those with psychosis[94].

Finally, there is evidence that dopamine release is elevated following exposure to stress (albeit mainly in animal models[95]) and in those with psychosis, across the spectrum[96-98]. This has led to speculation that prolonged exposure to stress may, in combination with other factors including genes (e.g., FKBP5) and early neurodevelopmental insults, contribute to dysregulation of connected biological systems that converge on increased dopamine release, leading to the development of (positive) symptoms of psychosis[97-99]. Studies are beginning to emerge that provide some direct evidence consistent with this model[88,100,101]. At present, however, direct evidence that these mechanisms do mediate the association between childhood adversities and psychoses is limited.

This caveat accepted, it may be that childhood adversities and associated neurobiological processes underpin, in part, the neurocognitive deficits often seen among those with a psychotic disorder, particularly schizophrenia. There is evidence, for example, that childhood adversities are associated with cognitive impairments among people with psychosis, and that the neurobiological abnormalities sketched above (e.g., dysfunction of the HPA axis, reduced hippocampal volume) are associated with cognitive deficits in a number of domains, including verbal and non-verbal memory, attention, and processing speed[102-106]. What is more, these cognitive deficits may then compound risk by impacting on the capacity of individuals to cope with further stressors.

Psychological

There are also a number of psychological processes through which exposure to childhood adversities may increase risk for psychoses, including via effects on reasoning, cognitive schemas, and affect.

Research on psychological mechanisms has tended to focus on links between specific processes and specific experiences or symptoms. For example, consideration of psychological mediators of the association between childhood abuse, especially sexual abuse, and auditory hallucinations has centred on source monitoring biases (i.e., the tendency to attribute internal thoughts to external sources) and dissociation, both of which are implicated in the development of those hallucinations. The evidence, however, is limited and mixed[79]. For example, in a study of patients with current and with past hallucinations and controls, Varese et al[107] found no evidence that performance on source monitoring tasks was associated with childhood abuse. There is, however, some suggestive evidence from a small number of cross-sectional studies that dissociation may mediate the relationship between childhood abuse and psychosis[79].

Further, childhood adversities may influence psychological processes implicated in the development of paranoia and delusions of persecution and reference. Freeman and Garety[108] identified six psychological processes that may be involved in the emergence of paranoid ideas and for which there is some evidence: worry, negative beliefs about self, interpersonal sensitivity, sleep disturbance, anomalous internal experiences, and reasoning biases. Experiences of adversity, particularly during childhood and adolescence, when thinking styles and beliefs about the self and the world crystallize, may impact on each of these. Repeated experiences of threat, for example, may contribute to the development of a worrying thinking style, to negative beliefs about self, and to reasoning biases (i.e., a tendency to jump to conclusions or anticipate threat on the basis of limited information)[108]. These processes, moreover, may be interlinked (e.g., excessive worry leading to insomnia). Once again, however, the direct evidence that these processes mediate the association between childhood adversities and psychosis is limited, and more work is needed[108].

Finally, childhood adversities may increase risk for psychoses via an impact on affect. There is some evidence, including from longitudinal studies, that the association between childhood adversities and psychotic experiences is mediated via self-esteem and symptoms of depression and anxiety[109,110]. In an analysis of data from the Avon Longitudinal Study of Parents and Children, Fisher et al[110] found that self-esteem and affective symptoms substantially mediated the association between abuse and psychotic experiences.

The above-mentioned putative biological and psychological mechanisms represent different and complementary levels of explanation. For example, the dysfunctions and deficits observed in biological systems (e.g., stress sensitivity, increased dopamine release) may be the neurological substrata that underpin the relevant psychological processes (e.g., worry, reasoning biases). This is acknowledged in a number of integrated models of psychoses[98,101,111].

SOME IMPLICATIONS

The research summarized in this paper highlights several points. First, exposure to adversity in childhood – even

multiple adversities – is neither sufficient nor necessary to cause psychoses. This is true of all risk factors for psychoses. Other causal partners must be involved, including genetic and both non-social and other social environmental factors. The evidence, broadly, supports this. Second, many difficult and unpleasant situations and experiences in childhood may have general and lasting effects on biological systems and on cognitive abilities and schemas that predispose to a range of poor mental health outcomes, including psychoses. Third, certain types of situations and experiences may particularly increase risk for specific disorders or symptoms. On the basis of the evidence sketched in this review, exposure to contexts and events involving high levels of interpersonal hostility, threat, and violence – especially if severe and prolonged – may specifically increase risk for psychotic experiences and disorders.

These observations prompt a number of reflections on their implications for our understanding of psychosis more broadly. First, psychotic experiences and disorders, for most people, probably emerge from patchworks of causal factors – some general, some specific – that are woven over the course of development. To paraphrase Kagan[112], risk factors for psychosis form a seamless and complex tapestry that is not easily unwound. The current balance of evidence is that childhood adversities, for some people, form part of this tapestry.

Second, the precise clusters of genetic and environmental factors that together push each individual along a developmental path to psychosis may be highly idiosyncratic. That is, the causal partners involved and their relative contribution will vary from person to person.

Third, this may explain both the varied manifestations of psychotic disorders and the overlaps (comorbidities) with other disorders. If some risk factors or indicators – particularly those measured at a broad level, e.g. social class – are generic to a number of disorders, then comorbidity would be expected. If specific risk factors – to some extent at least – underpin different symptoms and features of disorder, then variations (e.g., in age of onset, in mode of onset, in the balance of positive and negative symptoms, in prognosis) would be expected according to particular clusters of causes. There is some evidence for this (e.g., genetic risk and neurodevelopmental markers associated with earlier age of onset; social adversities associated with positive symptoms; sexual abuse associated with hallucinations).

Finally, this leads to the proposition that, broadly, there will be some individuals for whom the aetiology is predominantly genetic and neurodevelopmental and others for whom the aetiology is predominantly socio-environmental, e.g. a product of repeated exposure to severe interpersonal hostility and threat in the context of enduring social adversity and isolation. Taken one step further, it may be that psychoses rooted in adversity and trauma share more in common with post-traumatic stress disorder and other trauma-related distress than with psychoses rooted in neurodevelopment[113].

CONCLUSIONS

To sum up, the current balance of evidence suggests that childhood adversities – particularly exposure to multiple adversities involving hostility and threat – do, in some people, contribute to the onset of psychotic experiences and psychotic disorders.

There remain weaknesses and gaps in the evidence, and this means that some caution is still warranted. However, addressing these weaknesses and filling in the gaps may tell us much about the very nature of psychoses and – perhaps more importantly – about how we can most effectively reduce risk, minimize distress, and improve outcomes.

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