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Testing the Neurodevelopmental, Trauma and Developmental Risk Factor Models of Psychosis using a naturalistic experiment

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Funding: Ms Liu has a funded PhD studentship by the Department of Psychology at the University of Warwick. BLS received funding from the German Federal Ministry of Education and Science (grants PKE24, JUG14, 01EP9504, and 01ER0801), and EPICure from Medical Research Council Programme (grant ref No.: MR/J01107X/1). Prof Marlow receives part funding from the Department of Health's NIHR Biomedical Research Centre's funding scheme at UCLH/UCL, and Prof Wolke, Prof Bartmann, Dr Mendonca and Prof Johnson from European Union's Horizon 2020 research and innovation program (RECAP-Preterm) under grant agreement: 733280.

Acknowledgement: Ms Liu and Prof Wolke had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors contributed to the interpretation of the data and critical revision of the manuscript, and Profs Johnson, Bartmann, Marlow, Wolke and Dr O'Reilly further contributed to the acquisition of data.

We would like to thank all current and former Bavarian Longitudinal Study and EPICure group members, paediatricians, psychologists and research nurses.

Word count: 4066

Abstract

Background: The Neurodevelopmental and Trauma theories are two widely cited models of psychosis. A third – the Developmental Risk Factor model – recognises the combined role of neurodevelopmental risks and trauma. Our objective was to test these theories using preterm populations as a natural experiment, given the high prevalence of neurodevelopmental deficits and exposure to trauma.

Methods: Two population-based preterm birth cohorts, the Bavarian Longitudinal Study (BLS; N=399) and EPICure Study (N=184) were included with term-born controls. Peer victimisation in childhood was assessed by parent and child report and psychotic experiences (PE) were assessed in early adulthood. Different models of psychosis were tested using regression and mediation analyses.

Results: There was support for the Trauma and Developmental Risk Factor model in the BLS. Peer victimisation increased the risk of PE for preterm and term-born participants equally (OR=4.87, 95% CI: 1.96 to 12.08). There was an indirect effect where preterm children were more likely to be victimised, which subsequently increased risk of PE ($\beta = 1.12$ (SE=0.61), 95% CI: 0.11 to 2.48). The results were replicated in EPICure.

Conclusions: Exposure to trauma which is experienced more often by neurodevelopmental risk children rather than neurodevelopmental risk per se increases the risk of psychotic experiences. The findings are consistent with the Trauma model and Developmental Risk Factor model. Interventions focused on reducing trauma may reduce the development of PE.

Introduction

A range of theories have been proposed to explain the aetiology or development of psychosis but have been difficult to test as clinically diagnosed psychosis is rare (3% across the lifetime) (van Os *et al.* 2009). While in contrast, psychotic experiences (PE) are more frequently experienced in adolescence and adulthood (Zammit *et al.* 2013) and are characterised by the same cluster of symptoms as psychotic disorders, including hallucinations, delusions and thought disorders, but do not meet the threshold for a clinical diagnosis (van Os *et al.* 2009). They are considered to be on the same continuum and the risk of psychotic disorders in adulthood has been found to be greater in those with PE in adolescence, suggesting that PE may become persistent and subsequently develop into clinical impairment (van Os *et al.* 2009; Zammit *et al.* 2013). There is increasing evidence that factors found to be associated with psychosis are similarly associated with PE supporting their use in population studies (Johns & Os 2001).

One of the most widely cited theory of psychosis is the Neurodevelopmental model (Marenco & Weinberger 2000) (NM), which explains psychosis as a consequence of early disturbed events in the development of the nervous system, creating lesions and disrupting neuronal connections in the brain of the developing foetus (Murray & Lewis 1987; Murray 1994; McNeil *et al.* 2000). The consequences of these early lesions could remain dormant until maturation of the prefrontal cortex in adolescence, leading to the use of neural networks that are not well developed and thus enabling the clinical expression of psychosis (Murray 1994; Marenco & Weinberger 2000). There is evidence from neuroimaging studies of brain abnormalities such as enlarged ventricular volumes in first-episode and chronic schizophrenia patients (Adriano *et al.* 2012; De Peri *et al.* 2012), as well as studies showing increased prevalence of psychosis in people with a history of obstetric complications (Murray & Lewis 1987). However, brain lesions are difficult to study in large population studies thus motor, cognitive and behavioural

abnormalities in childhood prior to the onset of psychosis are often considered as intermediate phenotypes, with evidence of these abnormalities reported in previous studies (Jones *et al.* 1994; Pantelis *et al.* 2003; Dean *et al.* 2018). These neurodevelopmental impairments are frequent after low birth weight and premature birth and have been found to increase the risk of psychosis in adulthood (Byrne *et al.* 2007; Nosarti *et al.* 2012). However, these neurodevelopmental impairments have also been associated with exposure to early childhood deprivation and adversities (Sonuga-Barke *et al.* 2017); therefore, caution is needed to interpret these as support purely for the NM.

In contrast, another well-known theory of psychosis is the Trauma model (TM), which places emphasis on the role of childhood adversity (Read 1997). Increased exposure to stressful events in childhood can bias cognitive processes and lead to hostile interpretations of anomalous experiences, as well as disrupt the chemical balance of the dopamine system which are found to be abnormal at psychosis onset (Read *et al.* 2014; Guy *et al.* 2017). Some studies have found that exposure to any trauma from caregivers (e.g. abuse) or peers (e.g. bullying) can increase the risk of psychotic disorders in later life (Varese *et al.* 2012; Croft *et al.* 2018), and others found increased risk of psychotic experiences with only certain types of trauma (Bell *et al.* 2019). The effects of childhood abuse may be partly due to gene-environment correlation, as abusive behaviour may originate from intergenerational transmission of violence (Hines & Saudino 2002). Bullying does not have this gene-environment correlation and has similar effect sizes as other types of trauma on psychosis (Fisher *et al.* 2013; Wolke *et al.* 2014), even when controlling for genetic risks (Croft *et al.* 2018).

The third theory – the Developmental Risk Factor model (DRFM) – proposes an indirect or moderated pathway from neurodevelopmental risks to psychosis, through childhood trauma (Murray & Fearon 1999). Early neurodevelopmental deficits can lead to social and behavioural

problems, which in turn increase the likelihood of exposure to traumatic events (Murray *et al.* 2017). There are two mechanisms of how neurodevelopmental risks and exposure to trauma may relate to psychosis. Firstly, children with neurodevelopmental deficits may be disproportionately more affected when exposed to trauma (i.e. more vulnerable to the effects of trauma; moderation effect). The alternative model proposes that children with neurodevelopmental deficits are simply more often exposed to trauma rather than being more vulnerable to its effects, i.e. mediation effect.

A test of these models requires the prospective study of children at risk of neurodevelopmental problems, whose exposure to trauma in childhood and psychotic experiences in adulthood are assessed. Children born very preterm (VP; <32 weeks gestational age) or with very low birth weight (VLBW; <1500 gram) provide a natural experiment as they have widespread brain abnormalities persisting into adulthood (de Kieviet *et al.* 2012) making the whole population at risk for neurodevelopmental difficulties (Volpe 2009). Furthermore, they have more cognitive, motor, social and behavioural difficulties (Allotey *et al.* 2018), considered as intermediate phenotypes in the Neurodevelopmental model. Finally, VP/VLBW children are also more likely to be exposed to peer inflicted trauma such as being bullied (Wolke *et al.* 2015). Thus they represent an ideal naturalistic sample as a proxy to test the NM against the TM and DRFM of psychosis.

It is surprising that there are no studies examining the relationships between trauma and psychotic disorders in adulthood in VP/VLBW populations. One problem, as raised above, is that psychotic disorders are of low prevalence in the general population and VP/VLBW only make up 1-2% of all births, therefore large sample sizes are required in prospective studies. Psychotic experiences (PE) on the other hand are on the extended psychosis phenotype and more prevalent, and have been shown to be a significant risk factor for transitioning into

psychotic disorders (Zammit *et al.* 2013). Only one study (Thomas *et al.* 2009) found a significant effect of VP/VLBW on PE, although PE were only assessed at 12 years and childhood trauma was not examined.

The aim of this prospective longitudinal study from birth into adulthood was to simultaneously test which of the three models – the NM, the TM or the DRFM – best explains the development of PE. This was investigated in two prospective population-based cohort studies of preterm-born children: the German Bavarian Longitudinal Study (BLS), a regionally defined cohort study of VP/VLBW infants followed from birth until 26 years of age, and the EPICure study, a cohort of extremely preterm (EP; <26 weeks' gestation) children born in the United Kingdom (UK) and Ireland and followed up until 19 years of age. The BLS was the discovery sample, and the EPICure cohort the replication sample. The assessment of PE was identical in both samples.

Methods

Design and participants

BLS

The BLS is a prospective whole population study of children born in Southern Bavaria (Germany) between January 1985 and March 1986, who required admission from obstetric wards to neonatal special care within the first 10 days after birth (Wolke & Meyer 1999). The sample has been described in detail previously (Madzwamuse *et al.* 2015). In short, 202 (49%) VP/VLBW and 197 (64%) term-born adults matched on sex and socioeconomic status (SES) who were also recruited at birth had completed PE assessment at 26 years (Fig. 1).

Ethical approval was obtained from the University of Munich Children's Hospital, the Bavarian Health Council and the Ethical Board of the University Hospital Bonn. Parents gave informed

written consent and all participants gave informed written consent for the assessment in adulthood.

EPICure

The EPICure cohort included EP infants born before 26 weeks' gestation in the UK and Ireland from March through December 1995. The sample has been described in detail previously (Johnson *et al.* 2009). In summary, 120 (39%) EP and 64 (42%) term-born adults matched on sex and ethnic group completed PE assessment at 19 years (Fig. 1). EP participants were recruited at birth whereas term-born participants were recruited at 6 years. Ethical approval was given by the South Central Hampshire A Research Ethics Committee (Ref: 13/SC/0514). Parents gave informed written consent and all participants gave informed written consent for the assessment in adulthood.

Measures

Peer Victimisation

BLS:

Victimisation experiences at age 6 and 8 were assessed prospectively via a structured parent interview which has been reported previously (Wolke *et al.* 2015). The child was considered a victim if they were bullied "1-3 days per month" to "everyday". Victimisation at age 6 and 8 was combined so that victimisation at either age represented peer victimisation in childhood.

Victimisation at age 13 was self-assessed prospectively by children using one item of the Strengths and Difficulties Questionnaire (SDQ) (Goodman 2001): "other children pick on or bully me". Responses were on a 3-point scale and children who answered "certainly true" or "somewhat true" were considered victims in adolescence. The following victimisation variables were constructed: (1) non-victimised children; (2) victim at one time period (childhood or adolescence) and (3) victim at two time periods (childhood and adolescence).

EPICure

Victimisation was reported by parents prospectively at age 6 and 11 using the same item of the SDQ as the BLS at age 13 (Wolke *et al.* 2015). The same coding procedure was used as the BLS to produce the following variables: (1) non-victimised children; (2) victim at one time period (either 6 or 11 years) and (3) victim at two time periods (both 6 and 11 years).

Cognition

Both BLS and EPICure used the same assessment of IQ (Kaufman Assessment Battery for Children; K-ABC) (Kaufman & Kaufman 1983). The K-ABC is a standardised test with an average score of 100 and standard deviation of 15. IQ was taken at age 6, but substituted by IQ data at age 8 (in the BLS sample, N=1356, $r=0.83$) or age 11 (in the EPICure sample, N=306, $r=0.89$) if scores were missing at age 6. In total, 12 cases were substituted for BLS and 15 for EPICure.

Motor impairment

Children's motor impairment was assessed using the Test of Motor Impairment (TOMI) (Stott *et al.* 1968) at age 6 and 8 in BLS, and items from the Movement Assessment Battery for Children (M-ABC) (Henderson & Sudgen 1992) at age 6 in EPICure, which is derived from the TOMI. Scores range from 0 to 16 in the TOMI and 0 to 5 in the M-ABC, with higher scores indicating more motor problems. For 33 participants in the BLS who did not have TOMI data at age 6, data were substituted by those taken at age 8 as there was a strong positive correlation between them (N=1204, $r=0.63$).

Psychotic experiences (PE)

Psychotic experiences were assessed by trained interviewers using a semi-structured psychotic-like symptoms interview (Zammit *et al.* 2013) in the BLS at age 26 and EPICure at age 19. The interview consists of 12 core questions covering hallucinations, delusions and thought

disorders occurring in the past 6 months. Participants who answered “yes” or “maybe” were cross-questioned and probed to establish whether the experience was psychotic by the interviewer. Coding of PE followed definitions and rating rules for the Schedules for Clinical Assessment in Neuropsychiatry (SCAN; (World Health Organization 1994) and unclear responses were rated down and only marked as definite when an example met SCAN rating rules. Detailed description of the interview has been reported previously (Zammit *et al.* 2013). Interviewers rated each experience as not present, suspected or definitely present. In this study, PE was dichotomised into either no symptom or any suspected/definite psychotic symptoms if one or more symptoms were rated as suspected or definitely present. Previous studies reported good inter-rater and test-retest reliability ($\kappa = 0.83$ and 0.86 respectively) in childhood and early adulthood (Horwood *et al.* 2008; Zammit *et al.* 2013).

Covariates

Potential covariates included in both cohorts were sex and SES at birth, grouped as low, middle and high, and computed as a weighted composite score of parents’ education and occupation in the BLS (Wolke & Meyer 1999). In EPICure it was classified based on parental occupation using Social Class based on Occupation (formerly Registrar General’s Classification) (Office for National Statistics 2005) . Male and upper social class served as reference groups.

Statistical analysis

Analysis was conducted using R version 3.5.0. Differences between VP/VLBW/EP and term-born controls were reported, with differences in IQ and motor impairment computed to determine whether the VP/VLBW/EP group have more neurodevelopmental deficits as per design as a naturalistic experiment.

Four different models were specified: first, VP/VLBW/EP was specified as a predictor of PE to test the NM (Fig. 2a path 1). Second, peer victimisation, as an index of trauma, was specified

as predictor of PE to test the TM (Fig. 2a path 2). Finally, two alternative models to test the DRFM were proposed. Peer victimisation was specified as predictor, with VP/VLBW/EP as a risk factor for either (a) being more exposed to and disproportionately affected by victimisation (interaction effect; Fig. 2a path 3), or (b) being exposed more often to peer victimisation but not more vulnerable to the effects (mediation effect; Fig. 2a path 4).

Simple and multiple logistic regression models (controlling for sex and SES) were computed to assess the first two models (NM and TM; Fig. 2a path 1 and path 2). Additionally, interaction effects between VP/VLBW/EP and victimisation were also assessed to test the third model (DRFM; moderation effect, Fig. 2a path 3), with the Firth-type penalised likelihood approach used in EPICure due to small data sets (Heinze 2009). Finally, RMediation package was used to test the mediation interpretation of the DRFM (Fig. 2a path 4).

Missing data

The prevalence of missing data was 9.8% in the BLS and 19% in EPICure. Multiple imputation was carried out in R using multivariate imputation by chained equations (MICE), with 40 iterations as recommended to improve power (Graham *et al.* 2007). Results from the imputed dataset are presented here and results from the complete case analysis are reported as a sensitivity analysis.

Results

Sample characteristics

Drop-out analyses have been described previously, with those dropping out more likely to be from lower SES, to have had more behavioural problems and neurodevelopmental impairment (Madzwamuse *et al.* 2015; Linsell 2017).

Descriptive statistics for variables in both samples are shown in Table 1. Both BLS and EPICure cohorts had similar distribution of male and female participants. However, the BLS preterm-born children were more likely to be of lower SES (29.4%) than term born controls (22.8%). Both VP/VLBW children and EP children were more likely to be victimised in both childhood and adolescence (23.8%, 17.9%) compared to term born controls (14.3%, 9.3%). The rates of PE were 13.8% for BLS and 9.8% for EPICure, with no significant differences between VP/VLBW/EP and controls in either cohort.

In both cohorts, VP/VLBW/EP children had more neurodevelopmental deficits at age 6, as demonstrated by lower scores on IQ and motor tests than term-born controls (Table 1).

Model Testing

VP/VLBW/EP and PE (NM)

Pooled results from logistic regression models after imputation are shown in Table 2. VP/VLBW/EP was not a significant predictor of PE in either cohort.

Peer Victimization and PE (TM)

Being victimised at both time periods was a significant predictor of PE in both BLS and EPICure cohorts and remained significant after adjustment for sex and SES. Being victimised at one time period also predicted PE but only in BLS, which showed an increased risk of PE with increased exposure (4.55 odds if victimised at both time periods vs 3.01 odds if victimised at one time period only) (Table 2).

VP/VLBW/EP, Peer Victimization and PE (DRFM)

Interaction

No interaction effect between VP/VLBW/EP and victimisation was found in predicting PE in either cohort (Table 2).

Mediation

In the BLS cohort, being born VP/VLBW increased risk of being victimised even after controlling for covariates in the ordinal logistic regression model (Table 3). Victimization explained 8% of the variance in PE. A significant mediation path was found between VP/VLBW and PE via victimisation: $\beta=0.41$, 95%CI: 0.04 to 0.92, but no significant direct effect was found: $\beta=0.27$, 95%CI: -0.33 to 0.87. See Fig 2b.

In the EPICure cohort, EP predicted victimisation in the adjusted ordinal logistic regression model. (Table 3). Victimization explained 21% of the variance in PE. A significant mediation path was also found: $\beta=1.09$, 95%CI: 0.13 to 2.46. No significant direct effect was found: $\beta=0.58$, 95%CI: -0.82 to 1.98. See Fig 2b.

Sensitivity analysis

The analyses were repeated using complete cases from both cohorts. There were no differences in the pattern or magnitude of effects reported above. Detailed outputs are presented in [supplementary materials \(Table S1-S2, Fig S1\)](#).

Discussion

This analysis of two birth cohorts found that peer victimisation in middle childhood – regardless of birth weight or gestational age –increased the risk of psychotic experiences in adulthood, at both 19 years and 26 years. Preterm birth and associated neurodevelopmental risk did not have a direct effect on PE in either cohort. Test of mediation according to current statistical recommendations (Rucker *et al.* 2011; Kenny & Judd 2014; Jaekel *et al.* 2018) did show an indirect effect of VP/VLBW/EP on PE through increasing children’s risk of being victimised more often by peers. This was shown in both the BLS and EPICure sample. Preterm children were not more vulnerable to the effects of victimisation; rather, they were more likely

to be victimised. In sum, these findings support both the Trauma and Developmental Risk Factor model, but no support was found for the Neurodevelopmental model.

The effect of peer victimisation on PE is consistent with previous research (Fisher *et al.* 2013; Wolke *et al.* 2014; Croft *et al.* 2018) with bullying at two time periods, or chronic bullying, having almost twice as much impact as bullying at one time period only. Although chronic bullying increased risk of PE in both cohorts, only the BLS study showed a risk of PE with victimisation at one time only. One explanation could be that the prevalence of PE at 26 years was higher than in EPICure at 19 years, which combined with the smaller sample size and higher dropout rates, may have contributed to the sample not having enough power to detect the effect of victimisation at one time period.

It is surprising that no support was found for the Neurodevelopmental model, which proposes a direct effect of neurodevelopmental risks on psychosis. The prevalence of PE was not significantly raised in the VP/VLBW/EP group – a population with a high prevalence of neurodevelopmental deficits as shown previously (de Kieviet *et al.* 2012) and in this study (e.g. IQ and motor deficits in childhood). It contradicts a previous large registry study which found prematurity as a risk factor for psychosis. The prevalence of psychosis in the preterm population may be an overestimate in registry studies, as they are more often in contact with professionals due to pre-existing health conditions and may thus be diagnosed more often (Nosarti *et al.* 2012). Another explanation could be that previous studies examined psychotic disorders rather than PE, and the majority of people with PE do not go on to develop schizophrenia (Zammit *et al.* 2013). However, we still found support for the Trauma model, and we would have expected to find support for NM given the VP/VLBW/EP population represents an extreme group with widespread neurodevelopmental impairment.

The finding that preterm born children at high risk for neurodevelopmental impairments were bullied more often is consistent with previous longitudinal studies (Wolke *et al.* 2015) and supports the DRFM of psychosis, which proposes an indirect effect of neurodevelopmental risks on psychosis (Murray & Fearon 1999). However, these children were not more vulnerable to the effects of trauma, contradicting previous research that showed extremely low birth weight born adults to be more vulnerable to childhood adversities in the development of depression and anxiety (Van Lieshout *et al.* 2018). This study found that peer victimisation increases the risk of PE equally for all children – however those with neurodevelopmental difficulties such as the preterm population are at increased risk of being exposed to peer bullying more often. Bullying is seen as a strategic way of achieving social dominance and those who are seen as vulnerable or are socially marginalised are likely targets of bullies (Juvonen *et al.* 2003). Preterm-born children have worse physical health, poorer cognitive and social skills, and have fewer friends to defend them (Allotey *et al.* 2018). Thus they are easy targets for bullies with low risk of retaliation.

Strengths and limitations

This is the first study to test three different theories of psychosis using four clearly defined models in two cohorts from two countries (Germany and UK). Peer victimisation was assessed repeatedly in both studies and the same measure for PE was used. Both studies also used the same measures of IQ and similar measures of motor impairment. Furthermore, the inclusion of VP/VLBW/EP children provided a naturalistic experiment to study the different models of psychosis as they are at high risk of neurodevelopmental deficits; thus this population acted as a proxy for testing the neurodevelopmental model.

There are some limitations as well. First, it is inevitable in studies over 26 years that there is drop-out; those who dropped out were more likely to be socially disadvantaged and have

neurodevelopmental deficits (Madzwamuse *et al.* 2015; Linsell 2017). However, there is some evidence from simulations of the effects of selective dropout that loss to follow up may not reduce the validity of predicting outcomes in longitudinal studies (Wolke *et al.* 2009). Although there might still be a possibility of bias from reduced power due to a loss in follow-up, and there may be an association between social disadvantages and PE (Morgan *et al.* 2009). Attempts to mitigate bias was made by using multiple imputation, and a sensitivity analysis was carried out comparing results after imputation with complete case analyses. Nonetheless, the wide confidence interval in the EPICure cohort when testing interaction suggest the sample may have been underpowered to robustly test this pathway. Second, victimisation experiences were assessed by just one item from the SDQ in EPICure. Despite this, there was still a strong effect of victimisation on PE in both samples, which adds to the generalisability of the finding that peer victimisation is consistently associated with PE despite differences in measures (Day *et al.* 2016). Thirdly, we did not examine other childhood adversities apart from bullying. There is evidence that trauma from caregivers (physical and sexual abuse, neglect) are also associated with increased risk of psychosis (Varese *et al.* 2012; Croft *et al.* 2018). Lastly, genetic factors were not examined. However, a previous study which controlled for genetic risks for schizophrenia found no change in the effects of victimisation on psychosis (Croft *et al.* 2018). Furthermore, the VP/VLBW/EP population was used as a proxy for a range of neurodevelopmental deficits as a whole, as they are more likely to have had intrauterine infections (Kemp 2014) as well as specific deficits in IQ, behavioural problems and brain abnormalities.

Conclusion

When testing the three developmental models against each other, the data consistently support the Trauma and the Developmental Risk Factor Model in explaining the development of

psychotic experiences. The study provides further evidence that peer victimisation is a risk factor for PE in adulthood, and this risk is the same for children with or without neurodevelopmental deficits. Those with increased neurodevelopmental risk are not more vulnerable to the impact of bullying, but they are more likely to be bullied (Øksendal *et al.* 2019), which increases their risk of PE. One plausible mechanism is that persistent bullying can lead to feelings of social defeat, which has been shown to disrupt cortisol levels, inflammatory response and the hypothalamic–pituitary–adrenal axis in both animal and human studies (Selten *et al.* 2013). Furthermore, prolonged social defeat from victimisation can also lead to biased and hostile interpretation of social situations and the intention of others (Guy *et al.* 2017). We do not suggest there is a unified theory of psychosis, or that these models are mutually exclusive, as there are other theories of psychosis such as the stress-diathesis model which have received support. However, the study suggests that the risk of PE may be partially modifiable in childhood through effective anti-bullying strategies. Preterm-born children are more likely to be targets of bullying and this could be prevented. Furthermore, mental health services should routinely ask about histories of childhood trauma, particularly for people with psychosis, as it is a significant risk factor but is also one that is not frequently identified by health care professionals (Read *et al.* 2018a, 2018b).

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