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Evidence, and replication thereof, that molecular-genetic and environmental risks for psychosis impact through an affective pathway

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Abstract

Background. There is evidence that environmental and genetic risk factors for schizophrenia spectrum disorders are transdiagnostic and mediated in part through a generic pathway of affective dysregulation.

Methods. We analysed to what degree the impact of schizophrenia polygenic risk (PRS-SZ) and childhood adversity (CA) on psychosis outcomes was contingent on co-presence of affective dysregulation, defined as significant depressive symptoms, in (i) NEMESIS-2 (n=6,646), a representative general population sample, interviewed four times over nine years and (ii) EUGEI (n=4,068) a sample of patients with schizophrenia spectrum disorder, the siblings of these patients and controls.

Results. The impact of PRS-SZ on psychosis showed significant dependence on co-presence of affective dysregulation in NEMESIS-2 (relative excess risk due to interaction [RERI]: 1.01, p=0.037) and in EUGEI (RERI=3.39, p=0.048). This was particularly evident for delusional ideation (NEMESIS-2: RERI=1.74, p=0.003; EUGEI: RERI=4.16, p=0.019) and not for hallucinatory experiences (NEMESIS-2: RERI=0.65, p=0.284; EUGEI: -0.37, p=0.547). A similar and stronger pattern of results was evident for CA (RERI delusions and hallucinations: NEMESIS-2: 3.02, p<0.001; EUGEI: 6.44, p<0.001; RERI delusional ideation: NEMESIS-2: 3.79, p<0.001; EUGEI: 5.43, p=0.001; RERI hallucinatory experiences: NEMESIS-2: 2.46, p<0.001; EUGEI: 0.54, p=0.465).

Conclusions. The results, and internal replication, suggest that the effects of known genetic and non-genetic risk factors for psychosis are mediated in part through an affective pathway, from which early states of delusional meaning may arise.

Introduction

Both genetic and environmental influences increase risk for psychotic disorder. One of the best replicated, non-proxy environmental effects with a relatively large effect size is childhood adversity (CA)(Varese *et al.*, 2012). Molecular genetic analysis of schizophrenia case-control data allows for estimation of a model that predicts trait values from genetic variation, expressed as a polygenic risk score (PRS-SZ), providing a direct measure of schizophrenia genetic risk for analysis (Purcell *et al.*, 2009).

The risk associated with CA and PRS is not specific for psychotic disorder. Around two thirds of genetic associations are common to schizophrenia, bipolar disorder and major depressive disorder and overlap also exists with genetic variants contributing to autism, attention-deficit/hyperactivity disorder, and intellectual disabilities (Cross-Disorder Group of the Psychiatric Genomics *et al.*, 2013, Cross-Disorder Group of the Psychiatric Genomics Consortium, 2019). Therefore, PRS of mental disorders to a large degree represent transdiagnostic risk for mental suffering, particularly the affective spectrum. The level of non-specificity seen for genetic risk also applies to environmental risk factors. CA thus is similarly broadly associated with a range of mental (affective) disorders (Green *et al.*, 2010).

The non-specificity of the most important genetic and environmental risks for psychotic disorder may indicate a shared mechanism of generic mental suffering. This is compatible with epidemiological studies on psychopathology, which have established that the earliest expression of psychosis typically arises within a transdiagnostic mix of symptoms (McGorry and van Os, 2013), particularly depression (Hafner *et al.*, 2005), and that affective dysregulation, particularly depression, is strongly associated with the prevalence and incidence of subthreshold expression of psychotic phenomena in the general population (Guloksuz *et al.*, 2020, van Os and Reininghaus, 2016) as well as with clinical psychotic syndromes (Herniman *et al.*, 2019, Wilson *et al.*, 2020). It has been suggested that affective processes are crucial in the causation of psychosis (Bebbington, 2015, Garety *et al.*, 2005, Krabbendam and van Os, 2005, Upthegrove *et al.*, 2017), as predicted by

network models of psychosis (Isvoranu *et al.*, 2016), in which genetic and environmental influences impact each other in a dynamic fashion (Guloksuz *et al.*, 2015, Isvoranu *et al.*, 2020, Isvoranu *et al.*, 2017).

These data in combination suggest that although CA and PRS-SZ are strongly associated with schizophrenia spectrum disorder, the mechanism by which they increase risk may be transdiagnostic and mediated in part by a generic pathway of affective dysregulation. If this were true, the impact of CA and PRS on psychosis outcomes would show a degree of dependence on co-occurring affective dysregulation: i.e. is higher if there is additional evidence of affective dysregulation and is lower in the absence of affective dysregulation (Fig. 1). Recent work using indirect measures of genetic risk indeed suggest that this type of relationship exists between (proxy) genetic and environmental risks on the one hand and affective dysregulation on the other in their effects on psychosis outcomes (Pries *et al.*, 2018, Radhakrishnan *et al.*, 2019). However, the hypothesis remains to be tested with direct measures of genetic risk such as PRS-SZ.

In this study, we examined, and attempted to replicate, the hypothesis that the association between PRS-SZ and CA on the one hand, and psychosis outcomes on the other, is contingent, to a degree, on co-presence of significant affective dysregulation. To this end, we examined the interacting contributions of PRS-SZ and CA on the one hand, and affective dysregulation on the other, in models of psychosis in (i) a large population-based cohort (n=6,646) that was examined four times over period of 9 years; and (ii) a large schizophrenia-spectrum case-sibling-control study of 4,068 participants.

Given strong evidence that the terms making up the interactions, PRS-SZ and CA on the one hand, and affective dysregulation on the other, are associated with each other (Brainstorm *et al.*, 2018, Kessler and Magee, 1993, Nivard *et al.*, 2017), the theoretical model of how they work together to affect the outcome of psychosis was considered to be one of mediation, under the framework proposed by Kraemer and colleagues (Kraemer *et al.*, 2001). According to this framework, statistical

interaction is indicative of moderation if the terms of the interaction are not correlated with each other, and indicative of mediation if the terms of the interaction are correlated with each other. Conceptually, this means that mediation would explain values of Y (psychosis) as indirectly caused by values of X (genetic and non-genetic aetiology) over a pathway of affective dysregulation.

Method

Study Populations

NEMESIS-2

All four waves of the Netherlands Mental Health Survey and Incidence Study-2 (NEMESIS-2) were used. NEMESIS-2 was conducted to study the prevalence, incidence, course, and consequences of mental disorders in the Dutch general population. The baseline data of NEMESIS-2 were collected from 2007 to 2009, follow-up was until 2018. The study was approved by the Medical Ethics Review Committee for Institutions on Mental Health Care and written informed consent was collected from participants at each wave. To ensure representativeness of the sample in terms of age (between the ages of 18 and 65 at baseline), region, and population density, a multistage random sampling procedure was applied. Dutch illiteracy was an exclusion criterion. Non-clinician, trained interviewers applied the Composite International Diagnostic Interview (CIDI) version 3.0 (Alonso *et al.*, 2004, de Graaf *et al.*, 2008) and additional questionnaires during home visits. Details of NEMESIS-2 are provided elsewhere (de Graaf *et al.*, 2010, de Graaf *et al.*, 2012). The first wave (T0) enrolled 6,646 participants (response rate 65.1%; average interview duration: 95 minutes), who were followed up in 3 visits within 9 years: successive response rates at year 3 (T1), year 6 (T2), and year 9 (T3) were 80.4% (*n* = 5,303; excluding those who deceased; interview duration: 84 minutes), 87.8% (*n* = 4,618; interview duration: 83 minutes), and 86.8% (n = 4,007; interview duration: 102 minutes), respectively. Rates at baseline reflect lifetime occurrence; rates at T1 to T3 reflect interval (baseline-T1, T1–T2, and T2-T3) occurrence of approximately 3 years. Attrition between T_0 and T_3

was not significantly associated with any of the mental disorders at T_0, after controlling for sociodemographic characteristics (de Graaf *et al.*, 2018, Nuyen *et al.*, 2019).

EUGEI

The EUGEI project is a 25-centre, 15-country, EU-funded collaborative network studying the impact of genetic and environmental factors on the onset, course and neurobiology of psychosis spectrum disorder (European Network of National Networks studying Gene-Environment Interactions in Schizophrenia *et al.*, 2014). Workpackage 6, entitled 'Vulnerability and Severity', focussed on the psychometric expression of genetic and environmental liability in the siblings of patients, who are at higher than average genetic and environmental risk compared to healthy comparison participants. The sample in Workpackage 6 was collected in Spain (5 centres), Turkey (3 centres) and Serbia (1 centre) and consisted of 1,525 healthy comparison participants, 1,261 patients with a diagnosis of psychosis spectrum disorder (average duration of illness since age of first contact with mental health services: 9.9 years) and 1,282 siblings of these patients. Patients were diagnosed with schizophrenia spectrum disorder according to the DSM-IV-TR. This diagnosis was confirmed by the Operational Criteria Checklist for Psychotic and Affective Illness (McGuffin *et al.*, 1991). Exclusion criteria for all participants were diagnosis of psychotic disorders due to another medical condition, history of head injury with loss of consciousness, and intelligence quotient < 70.

To achieve high quality and homogeneity in clinical, experimental, and environmental assessments, standardized instruments were administered by psychiatrists, psychologists, or trained research assistants who completed mandatory on-site training sessions and online training modules including interactive interview videos and self-assessment tools (European Network of National Networks studying Gene-Environment Interactions in Schizophrenia *et al.*, 2014). Both on-site and online training sessions were repeated annually to maintain high inter-rater reliability throughout the study enrolment period (for details see: https://cordis.europa.eu/result/rcn/175696_en.html).

The EUGEI project was approved by the Medical Ethics Committees of all participating sites and conducted in accordance with the Declaration of Helsinki. All respondents provided written informed consent and, in the case of minors, such consent was also obtained from parents or legal guardian.

Assessment of psychotic experiences

In NEMESIS-2, a psychosis add-on instrument based on the G section of previous CIDI versions was included. This add-on instrument consists of 20 psychotic symptoms corresponding to the symptoms assessed in a previous population survey in the Netherlands, NEMESIS, the precursor of NEMESIS-2 (Bijl *et al.*, 1998, de Graaf *et al.*, 2010). Detailed descriptions of the specific PE items can be found in previous work using NEMESIS (Smeets *et al.*, 2013) and NEMESIS-2 (van Nierop *et al.*, 2012). At baseline, lifetime prevalence of PE was assessed. A clinician did a follow-up telephone interview when participants reported a psychotic symptom to assess whether this symptom was a true PE using questions from the Structured Clinical Interview for DSM-IV. At baseline, a total of 1,081 participants (16.3%) endorsed at least one self-reported PE. Of these, 794 participated in clinical re-interview (73.5%), of whom 340 (42.8%) reported at least one clinically validated PE. At T1, 440 out of a total 5,303 (8.3%) participants reported that at least one self-reported PE had occurred since the previous interview. Of these, 367 (83.4%) participants were available for clinical re-interview, of whom 172 (46.9%) reported at least one clinically validated PE. At T2, 284 out of the total 4,618 (6.2%) participants reported at least one self-reported PE since the previous interview. Of these, 230 (81.0%) participants were available for clinical re-interview, of which 135 (58.7%) reported at least one clinically validate PE. At T3, 222 out of the total 4,007 (5.5%) participants reported at least one self-reported PE since the previous interview. Of these, 207 (93.2%) participants were available for clinical re-interview, of which 77 (37.2%) reported at least one clinically validate PE. Given similarities between CIDI self-reported and clinically validated PE, in

terms of associations, predictive value and outcome (Bak *et al.*, 2003, van der Steen *et al.*, 2019, van Nierop *et al.*, 2012), CIDI self-reported PE were used, thus increasing statistical power.

PE were dichotomized consistent with previous work in NEMESIS and NEMESIS-2 (Pries *et al.*, 2018, Radhakrishnan *et al.*, 2019, van Rossum *et al.*, 2011). Thus, presence of delusions was defined as having at least one delusion endorsed and presence of hallucinations was similarly defined.

In EUGEI, the Community Assessment of Psychic Experiences (Cape; www.cape42.homestead.com) was developed to rate self-reports of lifetime psychotic experiences (Konings *et al.*, 2006). The Cape includes dimensions of positive psychotic experiences, negative experiences and depressive experiences. Effect sizes for internal stability are high, as are correlations between Cape dimensions and conceptually similar dimensions of the Structured Interview for Schizotypy, Revised (Konings *et al.*, 2006, Vollema and Ormel, 2000). Items are modelled on patient experiences as contained in the Present State Examination, 9th version (Wing *et al.*, 1974), schedules assessing negative symptoms such as the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1982) and the Subjective Experience of Negative Symptoms (SENS) (Selten *et al.*, 1993), and scales assessing depressive symptoms such as the Calgary Depression Scale (Addington *et al.*, 1993). Items are scored on a 4-point scale. In the current analyses, Cape dimensions of frequency of positive experiences (20 items), and depressive experiences (8 items) were included. A total score representing the mean of all items was calculated for each dimension. For the analyses, conform previous work in this area (Heins *et al.*, 2011, van Dam *et al.*, 2015, van Os *et al.*, 2017), frequency of positive symptoms dichotomized around the 80th percentile in the control group, were used as measures for delusions and hallucinations. Similarly, the frequency score of the 17 Cape delusion items, dichotomized around the 80th percentile in the control group, was used as the delusion outcome. Any presence of hallucinations, as measured by the three Cape hallucination items, was used as the binary hallucination outcome.

Childhood adversity

In NEMESIS-2, CA was assessed at T0 using a questionnaire based on the NEMESIS trauma questionnaire (de Graaf *et al.*, 2010). Whenever a subject reported having experienced one of five types of childhood adversity before the age of 16 years [emotional neglect (not listened to, ignored, or unsupported), physical abuse (kicked, hit, bitten, or hurt with object or hot water), psychological abuse (yelled at, insulted, unjustly punished/treated, threatened, belittled, or blackmailed), peer victimization (bullying), and one time or more sexual abuse (any unwanted sexual experience)], they were asked to state how often it had occurred on a scale of 1 (once) to 5 (very often). Conforming with previous work in this area, the childhood adversity score was dichotomized at the 80th percentile (Heins *et al.*, 2011, van Dam *et al.*, 2015, van Os *et al.*, 2017).

In EUGEI, childhood adversity was assessed using the Childhood Trauma Questionnaire Short Form (CTQ) that consists of 28 items rated on a 5-point Likert scale measuring five domains of maltreatment (emotional and physical neglect along with emotional, physical, and sexual abuse) (Bernstein *et al.*, 2003). The psychometric characteristics of the translated versions (Spanish, Turkish, Dutch, and Serbian) of the CTQ have been comprehensively studied (Hernandez *et al.*, 2013, Mitkovic-Voncina *et al.*, 2014, Sar *et al.*, 2004, Thombs *et al.*, 2009). Consistent with previous work in similar samples, CTQ score was modelled as a binary variable, calculated around the 80th percentile in the control group (Heins *et al.*, 2011, van Dam *et al.*, 2015, van Os *et al.*, 2017).

Polygenic risk score for schizophrenia

For details of genotyping and calculation of PRS in NEMESIS-2 and EUGEI we refer to recent papers detailing these procedures (Guloksuz *et al.*, 2019, Pries *et al.*, 2020). We used recent GWASs of schizophrenia (Pardinas *et al.*, 2018) for PRS calculations (Choi *et al.*, 2018). PRS-SZ was created, using the same genotyping platform for EUGEI and NEMESIS-2, from best-estimate genotypes at six different *p*-thresholds (0.5, 0.1, 0.05, $5{\cdot}10^{-3}$, $5{\cdot}10^{-5}$, $5{\cdot}10^{-8}$). For our primary analyses, we used the

p-threshold of < 0.05, as this threshold explained most variation in the phenotype in the Psychiatric Genomics Consortium analysis (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). Conform previous analyses in these samples, statistical analyses were adjusted for three and 10 principal components in NEMESIS-2 and EIGEI, respectively (Guloksuz *et al.*, 2019, Pries *et al.*, 2020).

Affective dysregulation

A measure of affective dysregulation was constructed that was comparable across NEMESIS-2 and EUGEI. In NEMESIS-2, depressive symptoms were assessed with the CIDI version 3.0 (Alonso *et al.*, 2004, de Graaf *et al.*, 2008). Affective dysregulation was considered present if participants experienced at least one of the two CIDI 3.0 core symptoms of Depressive Episode, assessed at baseline (assessing lifetime occurrence) and each follow-up visit (assessing interval occurrence). The prevalence of affective dysregulation, thus defined, was 36%.

In EUGEI, Cape frequency of depressive symptoms (8 items), dichotomized around the 80th control percentile, was used as the measure for affective dysregulation, conform previous work in this area (Heins *et al.*, 2011, van Dam *et al.*, 2015, van Os *et al.*, 2017).

Statistical analyses

Risk set

NEMESIS-2

For the childhood adversity analyses, data on childhood adversity, affective dysregulation and psychotic experiences were available for the entire sample with few missing values (n=6,643 at baseline). In the PRS analysis, material for DNA analysis of sufficient quality was available for 3,104 individuals (47%) at T0 (Pries *et al.*, 2020). Excluding individuals who at interview has been assessed as member of an ethnic minority, given lack of generalizability of PRS to this group, left 3052 for analysis. These 3,052 individuals yielded 9,982 observations with data on psychosis outcomes and

affective dysregulation at least one of the four interviews. Values for important diagnostic, socio-demographic, familial and environmental risk variables were very similar in a comparison between the 9,982 included and the 9,046 non-included observations (Table 1a).

EUGEI

The EUGEI sample consisted of 4,068 individuals. For the childhood adversity analysis, there were 3,627 participants with complete data for psychosis outcomes, affective dysregulation and childhood adversity (1,491 healthy comparison participants, 1,137 relatives and 999 patients). For the PRS analysis, individuals of non-white ethnic group were excluded, as were individuals with missing GWAS information and missing data on psychosis outcomes and affective dysregulation, leaving 3,088 participants (1,186 healthy comparison participants, 1,001 relatives and 901 patients) for the current analysis. Values for important diagnostic, socio-demographic, familial and environmental risk variables were very similar in a comparison between the 3,088 included and the 934 non-included observations (Table 1b).

Analyses

All analyses were performed using Stata, version 16 (StataCorp, 2019). $P < 0.05$ (2-tailed) was considered nominally statistically significant. Given that in each person contributed multiple observations so that observations were clustered within persons (NEMESIS-2), or that participants were clustered in families (EUGEI), the Stata *cluster* option was used to take into account intra-group correlations occasioned by clustering of observations within individuals (NEMESIS-2) or families (EUGEI). Models including PRS were adjusted for three principal components (NEMESIS-2) or 10 principal components (EUGEI). Analyses using the EUGEI sample were additionally adjusted for country and for group (control, sibling, patient) using two dummies for siblings status and patient status.

Given differences between delusions and hallucinations in their patterns of association with other variables (Bartels-Velthuis *et al.*, 2012, Escher *et al.*, 2002, Smeets *et al.*, 2012), three psychosis phenotypes were examined as dependent variable in regression models: delusions and hallucinations (or: psychosis), hallucinations (with or without delusions) and delusions (with or without hallucinations).

Regression models were fitted to examine the hypothesis that the association between affective dysregulation and psychosis would be stronger if PRS-SZ was high. To test this hypothesis, interactions between affective dysregulation and PRS-SZ/CA were tested in models of psychosis phenotypes. Consistent with previous epidemiological analyses with PRS-SZ in this sample, PRS-SZ was examined as a dichotomous variable, using the 75th percentile as cut-off (hereafter: PRS_{75}), with sensitivity analyses using a range of cut-offs (50%, 60%, 70% 80% and 90% percentile cut-offs) (Guloksuz *et al.*, 2019). In NEMESIS-2, 75% cut-offs of the entire population were used; in EUGEI, 75% percentile cut-offs of the control values were used.

Logistic regression models, taking into account clustering of observations within participants as described above, were applied to test the association between binary affective dysregulation and PRS_{75} with the three psychosis phenotypes. In testing interaction, additive models were chosen over multiplicative models prior to genetic data collection (EUGEI consortium meeting, December 14, 2013).

To test the joint effects of affective dysregulation and PRS, we entered the four states occasioned by the combination of binary affective dysregulation and binary PRS_{75} as independent variables (three dummy variables with no-risk state as the reference category), and psychosis phenotype as the dependent variable, in logistic regression models.

We tested for departure from additivity using the interaction contrast ratio, also called the relative excess risk due to interaction (RERI). The RERI is considered the standard measure for interaction on

the additive scale in case-control studies (Knol and VanderWeele, 2012). The RERI was estimated as ($OR_{affective\ dysregulation\&PRS_{75}} - OR_{affective\ dysregulation} - OR_{PRS_{75}} + 1$)(VanderWeele and Vansteelandt, 2014). A RERI greater than zero was defined as a positive deviation from additivity, and considered significant when the 95% CI did not contain zero. Using the ORs derived from each model, the RERIs for each model were calculated using the delta method (Hosmer and Lemeshow, 1992).

Results

Distribution of demographic and risk variables are shown in Table 1a (NEMESIS-2) and Table 1b (EUGEI). In both NEMESIS and EUGEI, the terms making up the interactions in the models of psychosis outcomes were positively associated with each other (NEMESIS: PRS and affective dysregulation: p=0.030; CA and affective dysregulation: p<0.001; EUGEI: PRS and affective dysregulation: p=0.025; CA and affective dysregulation: p<0.001).

In NEMESIS-2, there was evidence that the association between affective dysregulation and psychosis phenotypes was moderated by PRS. This was apparent for the phenotype of delusions and hallucinations (RERI=1.01; 95% CI: 0.06, 1.97), and evident for the phenotype of delusions (RERI=1.74, 95% CI: 0.58, 2.91) but not for hallucinations (RERI=0.65, 95% CI: -0.54, 1.85)(Table 2, Fig. 2). Similar results were apparent in the EUGEI sample (RERI delusions and hallucinations: 3.39, 95% CI: 0.03, 6.75; RERI delusions: 4.16, 95% CI: 0.69, 7.63; RERI hallucinations: -0.37, 95% CI: -1.57, 0.83)(Table 3, Fig. 3).

There was similar and stronger evidence that the association between affective dysregulation and psychosis phenotypes was moderated by CA. In NEMESIS-2, this was evident for all psychosis outcomes (RERI delusions and hallucinations: 3.02, 95% CI: 2.04, 4.01; RERI delusions: 3.79, 95% CI: 2.59, 5.00; RERI hallucinations: 2.46, 95% CI: 1.21, 3.71)(Table 4, Fig. 4). Similar results were apparent in EUGEI (RERI delusions and hallucinations: 6.44, 95% CI: 3.10, 9.78; RERI delusions: 5.43, 95% CI: 2.25, 8.61; RERI hallucinations: 0.54, 95% CI: -0.90, 1.97)(Table 5, Fig. 5)

Sensitivity analyses showed results with binary PRS measures were consistent across the different cut-off values (supplemental figures 6 and 7).

Discussion

Findings

We found, and replicated, that the association between PRS-SZ and childhood adversity on the one hand and psychosis outcomes on the other was contingent on the co-presence of affective dysregulation, which suggests that these risks may be mediated by an affective pathway, through which particularly delusional ideation may arise (Freeman *et al.*, 2013, Garety *et al.*, 2005, Krabbendam and van Os, 2005, Upthegrove *et al.*, 2017). These findings may help explain the non-specific, transdiagnostic nature of the risk associated with PRS-SZ and CA and the strong connections between affective dysregulation and psychosis across the spectrum of psychotic disorders and the expression of subthreshold psychotic experiences (Hafner *et al.*, 2005, Upthegrove *et al.*, 2017, van Os and Reininghaus, 2016). The findings lend credence to the suggestion by Upthegrove and colleagues, that depression may be "more than comorbidity, and that increased effective therapeutic attention to mood symptoms will be needed to improve outcomes and to support prevention"(Upthegrove *et al.*, 2017). This suggestion concurs with a growing body of literature showing that psychosis arises as a result of worsening non-psychotic affective psychopathology (Guloksuz *et al.*, 2016, Guloksuz *et al.*, 2015, van Rossum *et al.*, 2011) and that the pathway from environmental risk to psychosis involves affective processes (Pries *et al.*, 2018, Radhakrishnan *et al.*, 2019, Reininghaus *et al.*, 2016a, Reininghaus *et al.*, 2016b). Recent research has confirmed that high rates of affective symptoms in early psychosis requires focussed attention on specific therapeutic options for these (Wilson *et al.*, 2020). Potential therapeutic targets may be found in constructs that research suggest may lie at the interface of the dynamics between mood and psychosis such as emotion dysregulation (Liu *et al.*, 2019), level of anticipatory pleasure for future experiences

(Hallford and Sharma, 2019) and cognitive styles shaping response to early symptoms of affective dysregulation (Rauschenberg *et al.*, 2020, Reininghaus *et al.*, 2019).

Affective dysregulation as a core feature of psychosis

Much of the focus of research in clinical psychosis syndromes is on the 30% of patients with a relatively unfavourable prognosis, captured under the diagnosis of 'schizophrenia', of which cognitive dysfunction is considered a core feature (Guloksuz and van Os, 2018, Perala *et al.*, 2007). However, like most measures of psychopathology, cognitive alterations are transdiagnostic (Millan *et al.*, 2012), and cognition in patients with schizophrenia is more strongly associated with polygenic risk that indexes cognitive traits in the general population than polygenic risk from mental disorders (Richards et al., 2019). In other words, lower cognitive ability, distributed in the general population, may predict poorer outcome across mental disorders, which is why it would feature –somewhat tautologically– relatively prominently in the 30% of patients in the psychosis spectrum presenting with the poorest prognosis. Traditionally, affective dysregulation has received much less attention in research on diagnostic categories like schizophrenia (Garety *et al.*, 2001) even though it has a similar unfavourable effect on outcome (McGinty and Upthegrove, 2020). Review of treatment guidelines indicates a dearth of approaches other than prescription of antidepressant medications (Donde *et al.*, 2018). The current results concur with previous suggestions that affective dysregulation, in particular depression, may be a fundamental feature of psychosis rather than a comorbidity phenomenon (Upthegrove *et al.*, 2017). Indeed, the findings suggest that psychosis spectrum may be best framed as an outcome of developmental vulnerability that can become associated with need for care through an affective pathway. Although this may not be the only pathway, a more formal acknowledgment of the role of affective dysregulation in psychosis it would help to reposition diagnostic framing, treatment focus and research.

The findings also have implications for research, as the association between PRS-SZ and psychosis outcomes may be more productively investigated if stratified by evidence of affective dysregulation.

Similarly, it is possible that other genetic influences may be more productively uncovered if analyses are stratified by other possible pathways, for example those involving cognitive and motivational factors, that research suggest may also moderate the impact of genetic risk on psychosis outcomes (Pries *et al.*, 2018).

Delusions, Hallucinations and differential mediation by affective dysregulation

The results suggest that if psychosis aetiology in part depends on an affective pathway, this may apply to delusional ideation more than to hallucinatory experiences, particularly as regards genetic aetiology. Main effects were observed for affective dysregulation and CA for all three psychosis outcomes, but not for PRS. In addition, evidence for CA mediation by affective dysregulation was evident for both delusions and hallucinations (although not replicated across both samples), whereas for PRS this was only evident for delusions. These findings suggest a degree of dissociation between genetic and non-genetic aetiological factors in the degree of mediation by affective dysregulation, showing as divergence in results for hallucinations and delusions. It has been suggested that hallucinations may represent the 'primary' experience of aberrant salience that some suggest may be associated with underlying biological mechanisms (Howes and Murray, 2014). Delusional ideation may, to a degree, be secondary to hallucinatory experiences (Krabbendam *et al.*, 2004, Maher, 2006), depending, amongst others, on the level of genetic and non-genetic-induced affective dysregulation (Howes and Murray, 2014, Smeets *et al.*, 2010, Smeets *et al.*, 2015). This may explain why for PRS, in the absence of a main effect on psychosis outcomes, mediation by affective dysregulation was limited to delusions, given the role of emotional biases in the onset of secondary delusions. For CA, the main effect on all psychosis outcomes may either depend more on affective dysregulation, or depend on it in a different fashion, causing it to differ from the pattern of results seen for PRS. However, more work is necessary to verify to what degree the level of affective mediation of genetic aetiology in models of psychosis truly differs between delusions and hallucinations, and what the possible underlying mechanisms of this divergence may be.

It could also be argued that hallucinations are less prevalent than delusions, resulting in lower power to detect association and thus explaining the divergent findings. However, both in NEMESIS-2 as in EUGEI, the prevalence of delusions and hallucinations as defined for these analyses was approximately similar (NEMESIS-2: 6% and 5%, respectively; EUGEI: 25% and 20%, respectively). In addition, if lack of power was an issue, effect sizes for hallucinations might still be similar to those observed for delusions, which was not the case.

Methodological issues

Power was low for the analyses with PRS-SZ. The findings suggest that PRS-SZ effect sizes differ as a function of co-presence of affective dysregulation, but this effect was only significant for delusional ideation and effect sizes of PRS-SZ were low. Further replication is therefore required.

Our measure of affective dysregulation was limited to measures of depression. Arguably measures of mania and/or anxiety could have been included, or examined separately for similar interactive effects in the models presented here. Future analyses may address this issue.

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Conflict of interest. None.

Table 1a. NEMESIS-2 Sample characteristics, stratified by polygenic risk score risk set included for analysis (n=9,982 observations) or excluded from analysis (n=9,046 observations)

Status	Del/Hal	Del	Hal	Affective dysregulation	Family history	Adversity score	Cannabis use	Urbanicity	Life events	Living alone	Married/Widowed	Unemployed	Income	Edu-cation	Age	% Female
	%	%	%	mean	%	%	%	mean	Mean	%	%	%	mean	mean	mean	%
Excluded	0.1	0.06	0.05	0.37	0.52	0.54	0.02	2.98	0.72	0.22	0.63	0.13	6.9	2.99	49.15	0.54
Sd				0.48				1.35	0.92				2.48	0.9	12.91	
N	9,046	8,963	9,032	9,046	9,046	9,046	8,785	9,026	8,949	9,046	9,045	9,046	8,597	9,046	9,046	9,046
Included	0.09	0.06	0.05	0.35	0.52	0.52	0.02	3	0.7	0.19	0.64	0.11	7.03	3.06	48.43	0.56
Sd				0.48				1.34	0.9				2.42	0.89	12.92	
N	9,982	9,924	9,965	9,982	9,982	9,982	9,706	9,981	9,961	9,982	9,982	9,982	9,668	9,982	9,982	9,982
Total	0.09	0.06	0.05	0.36	0.52	0.53	0.02	2.99	0.71	0.2	0.63	0.12	6.97	3.03	48.77	0.55
Sd				0.48				1.34	0.91				2.45	0.89	12.92	
N	19,028	18,887	18,997	19,028	19,028	19,028	18,491	19,007	18,910	19,028	19,027	19,028	18,265	19,028	19,028	19,028

Del/Hal: CIDI rating delusions or hallucinations
Del: CIDI rating delusions
Hal: CIDI rating hallucinations
Affective dysregulation: at least one of the CIDI 3.0 core symptoms of Depressive Episode
Family history: For participants who screened positive for the following psychiatric diagnoses, presence of the disorder in direct relatives was assessed: alcohol/drugs misuse, depression, mania, and anxiety disorders (panic disorder, social phobia, agoraphobia, generalized anxiety disorder).
Adversity score: total score NEMESIS-2 trauma questionnaire
Cannabis use: use of once or more per week during the lifetime period of most frequent use.
Urbanicity: five levels based on the Dutch classification of increasing population density
Life events: Total score on whether participants had experienced one of 9 life events within the last 12 months (T0) or since the last interview (T1 to T3).
Income: net annual household income, rated on a scale from 1 (lowest) to 14 (highest)
Education: 4-level continuous variable (higher level = higher educational level)

Table 1b. EUGEI sample characteristics, stratified by polygenic risk score risk set included for analysis (n=3,088 participants) or excluded from analysis (n=934 participants)

Status	Cape positive	Cape delusions	Cape any hallucination	Cape depression	CTQ score	% Controls	% Siblings	% Patients	Cognitive score	Cannabis use	Years education	In a relationship	Age	% Female
	Mean	Mean	%	Mean	Mean	%	%	%	Mean	%	Mean	%	Mean	%
Excluded	0.35	0.4	0.16	0.63	1.48	0.35	0.28	0.37	46.86	0.11	11.25	0.64	33.56	0.45
sd	0.38	0.42	0.36	0.48	0.44				8.7		4.27		9.41	
N	563	588	573	573	623	934	934	934	789	811	884	895	934	931
Included	0.36	0.39	0.2	0.66	1.49	0.38	0.32	0.29	49.01	0.12	12.19	0.69	34	0.46
Sd	0.39	0.41	0.4	0.49	0.45				7.99		4.29		9.63	
N	3,088	3,088	3,085	3,088	3,038	3,088	3,088	3,088	2,886	2,884	3,014	3,035	3,088	3,085
Total	0.36	0.39	0.2	0.66	1.49	0.38	0.31	0.31	48.55	0.12	11.98	0.68	33.9	0.46
sd	0.39	0.41	0.4	0.49	0.45				8.19		4.3		9.58	
N	3,651	3,676	3,658	3,661	3,661	4,022	4,022	4,022	3,675	3,695	3,898	3,930	4,022	4,016

Cape positive: Cape frequency score positive symptoms
Cape delusions: Cape frequency score delusion items
Cape any hallucination: Any positive rating Cape hallucinations items
Cape depression: Cape depression frequency dimension
CTQ score: CTQ total score
Cognitive score: Z-score, expressed as T-score, of Short version of the WAIS-III short form (Digit Symbol Coding subtest, uneven items of the Arithmetic subtest, uneven items of the Block Design subtest, every third item of the Information subtest (Blyler *et al.*, 2000, Velthorst *et al.*, 2013, Wechsler, 1997).
Cannabis use: use of once or more per week during the lifetime period of most frequent use

Table 2. NEMESIS-2: Risk of psychosis admixture as a function of combinations of binary schizophrenia polygenic risk (75th percentile cut-off) and binary affective dysregulation.

Phenotype	Risk	OR	95% CI		P	N
Delusions and hallucinations	PRS_{75} only	0.87	0.65	1.18	0.369	9,982
	AD only	3.45	2.91	4.09	0.000	
	PRS_{75}+AD	4.34	3.40	5.54	0.000	
	RERI	1.01	0.06	1.97	0.037	
Hallucinations	PRS_{75} only	0.94	0.63	1.41	0.778	9,965
	AD only	3.35	2.67	4.20	0.000	
	PRS_{75}+AD	3.95	2.81	5.53	0.000	
	RERI	0.65	-0.54	1.85	0.284	
Delusions	PRS_{75} only	0.74	0.50	1.08	0.123	9,924
	AD only	3.48	2.82	4.30	0.000	
	PRS_{75}+AD	4.96	3.78	6.51	0.000	
	RERI	1.74	0.58	2.91	0.003	

OR: odds ratio
95% CI: 95% confidence interval
N: number of observations in analysis
PRS_{75}: polygenic risk score 75th percentile cut-off
AD: Affective dysregulation (at least one of the two CIDI 3.0 core symptoms of Depressive Episode)
RERI: relative excess risk due to interaction

Table 3. NEMESIS-2: Risk of psychosis admixture as a function of combinations of binary affective dysregulation and binary childhood adversity (80th percentile cut-of)

Phenotype	Risk	OR	95% CI		P	N
Delusions and hallucinations	CA only	2.20	1.79	2.71	0.000	20,574
	AD only	3.36	2.97	3.80	0.000	
	CA+AD	7.58	6.51	8.83	0.000	
	RERI	3.02	2.04	4.01	0.000	
Hallucinations	CA only	2.76	2.11	3.60	0.000	20,537
	AD only	3.38	2.84	4.01	0.000	
	CA+AD	7.59	6.20	9.30	0.000	
	RERI	2.46	1.21	3.71	0.000	
Delusions	CA only	1.91	1.47	2.48	0.000	20,409
	AD only	3.54	3.04	4.12	0.000	
	CA+AD	8.24	6.92	9.80	0.000	
	RERI	3.79	2.59	5.00	0.000	

OR: odds ratio
95% CI: 95% confidence interval
N: number of observations in analysis
CA: childhood adversity
AD: Affective dysregulation (at least one of the two CIDI 3.0 core symptoms of Depressive Episode)
RERI: relative excess risk due to interaction

Table 4. EUGEI: Risk of psychosis admixture as a function of combinations of binary schizophrenia polygenic risk (75th percentile cut-off) and binary affective dysregulation (Cape depression 80th percentile)

Phenotype	Risk	OR	95% CI		p	N
Delusions and hallucinations#	PRS_{75} only	0.95	0.71	1.27	0.714	3,088
	AD only	7.34	5.70	9.45	0.000	
	PRS_{75}+AD	10.67	7.68	14.84	0.000	
	RERI	3.39	0.03	6.75	0.048	
Hallucinations#	PRS_{75} only	0.85	0.62	1.18	0.335	3,085
	AD only	3.53	2.68	4.65	0.000	
	PRS_{75}+AD	3.01	2.10	4.32	0.000	
	RERI	-0.37	-1.57	0.83	0.547	
Delusions#	PRS_{75} only	0.97	0.71	1.31	0.838	3,088
	AD only	7.32	5.67	9.46	0.000	
	PRS_{75}+AD	11.45	8.27	15.85	0.000	
	RERI	4.16	0.69	7.63	0.019	

#: Delusions and hallucinations: Cape positive dimension 80% control cut-off; Delusions: Cape delusions 80% control cut-off; Hallucinations: any rating of Cape hallucinations.
OR: odds ratio
95% CI: 95% confidence interval
N: number of observations in analysis
PRS_{75}: polygenic risk score 75th percentile cut-off
AD: Affective dysregulation (Cape depression dimension 80% control cut-off)
RERI: relative excess risk due to interaction

Table 5. EUGEI: Risk of psychosis admixture as a function of combinations of binary affective dysregulation (Cape depression 80th percentile) and childhood adversity (80th percentile cut-off)

Phenotype	Risk	OR	95% CI		P	N
Delusions and hallucinations#	CA only	2.29	1.77	2.96	0.000	3,627
	AD only	6.95	5.44	8.87	0.000	
	CA+AD	14.67	11.38	18.92	0.000	
	RERI	6.44	3.10	9.78	0.000	
Hallucinations#	CA only	1.87	1.38	2.52	0.000	3,624
	AD only	3.83	2.93	5.02	0.000	
	CA+AD	5.24	3.97	6.90	0.000	
	RERI	0.54	-0.90	1.97	0.465	
Delusions#	CA only	2.30	1.77	2.99	0.000	3,627
	AD only	7.40	5.78	9.46	0.000	
	CA+AD	14.13	10.96	18.21	0.000	
	RERI	5.43	2.25	8.61	0.001	

#: Delusions and hallucinations: Cape positive dimension 80% control cut-off; Delusions: Cape delusions 80% control cut-off; Hallucinations: any rating of Cape hallucinations.
OR: odds ratio
95% CI: 95% confidence interval
N: number of observations in analysis
CA: childhood adversity
AD: Affective dysregulation (Cape depression dimension 80% control cut-off)
RERI: relative excess risk due to interaction

Fig. 1. Evidence that genetic and environmental risks for psychosis are mediated by an affective pathway: effect sizes will be low if the psychosis outcome is not accompanied by affective dysregulation (left) and effect sizes will be high if affective dysregulation is co-present with the psychosis outcome

Fig. 2. NEMESIS-2: Additive interaction effects of affective dysregulation (AD) and polygenic risk score for schizophrenia (PRS; 75% cut-off) in models of psychosis phenotypes; RERI – relative excess risk due to interaction

Fig. 3. NEMESIS-2: Additive interaction effects of affective dysregulation (AD) and childhood adversity (CA) in models of psychosis phenotypes; RERI – relative excess risk due to interaction

Fig. 4. EUGEI: Additive interaction effects of affective dysregulation (AD; 80% cut-off) and polygenic risk score for schizophrenia (PRS; 75% cut-off) in models of psychosis phenotypes; RERI – relative excess risk due to interaction

Fig. 5. EUGEI: Additive interaction effects of affective dysregulation (AD; 80th percentile cut-off) and childhood adversity (CA, 80th percentile cut-off) in models of psychosis phenotypes; RERI – relative excess risk due to interaction

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