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Article

TwinssCan — Gene-Environment Interaction in Psychotic and Depressive Intermediate Phenotypes: Risk and Protective Factors in a General Population Twin Sample

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Abstract

Meta-analyses suggest that clinical psychopathology is preceded by dimensional behavioral and cognitive phenotypes such as psychotic experiences, executive functioning, working memory and affective dysregulation that are determined by the interplay between genetic and nongenetic factors contributing to the severity of psychopathology. The liability to mental ill health can be psychometrically measured using experimental paradigms that assess neurocognitive processes such as salience attribution, sensitivity to social defeat and reward sensitivity. Here, we describe the TwinssCan, a longitudinal general population twin cohort, which comprises 1202 individuals (796 adolescent/young adult twins, 43 siblings and 363 parents) at baseline. The TwinssCan is part of the European Network of National Networks studying Gene-Environment Interactions in Schizophrenia project and recruited from the East Flanders Prospective Twin Survey. The main objective of this project is to understand psychopathology by evaluating the contribution of genetic and nongenetic factors on subclinical expressions of dimensional phenotypes at a young age before the onset of disorder and their association with neurocognitive processes, such as salience attribution, sensitivity to social defeat and reward sensitivity.

Keywords: Psychosis; depression; genetics; environment; salience attribution; social defeat; stress sensitivity; reward sensitivity; general population; twins

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The early and prodromal stages of psychopathology are marked with the expression of intermediate phenotypes, including subtle, nonclinical psychotic experiences (Dominguez et al., 2009; Guloksuz et al., 2015; Rossler et al., 2011); cognitive impairment (Ahern & Semkovska, 2017; Dominguez et al., 2010; Reichenberg et al., 2010) and affective dysregulation (Fusar-Poli et al., 2014; Häfner et al., 2005). In the general population, subclinical phenotypes may display low levels of correlation, whereas increased multidimensional psychopathology can be found at the level of psychiatric services (Goes et al., 2012; Lamers et al., 2011; van Os et al., 2010). Psychotic experiences are more severe in the presence of other dimensional phenotypes such as affective dysregulation (McGrath et al., 2016; Pries et al., 2018) and are linked to the severity of psychopathology (Guloksuz et al., 2015; Kelleher et al., 2014; Navarro-Mateu et al., 2017). Furthermore, studies show that the genetic and environmental vulnerabilities that are commonly associated with major mental disorders are also nonspecifically associated with different intermediate phenotypes (Brainstorm Consortium et al., 2018; Guloksuz et al., 2015; Misiak et al., 2017; Nivard et al., 2017; van Os et al., 2010; van Os, van der Steen et al., 2017). In addition, greater exposure to genetic and environmental risks drives greater co-occurrence of phenotypes and increased severity of psychopathology (Guloksuz et al., 2015; Pries et al., 2018). Based on this, much attention has been given to the study of nonclinical multidimensional psychopathology to understand the development of mental ill health.

Several neuropsychological processes have been proposed to index vulnerability and resilience for mental disorders. For

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example, experiences of subtle alterations in salience attribution in response to environmental information may result in paranoid ideation, hallucinatory experiences and thought interference (Catalan et al., 2014; Galdos et al., 2011). Similarly, experiences of social defeat are highly stressful for young people and increase the risk for psychopathology (Eisenberger et al., 2006; Nesdaele & Lambert, 2007; Sandstrom et al., 2003). Furthermore, stress sensitivity and reward sensitivity, that is, negative affect and positive affect in response to environmental inputs, are crucial mechanisms in both psychotic and nonpsychotic disorders (Delespaul, 1995; Lataster et al., 2009; Myin-Germeys & van Os, 2007; Wichers et al., 2007b). On the other hand, experiencing positive emotions such as reward can be protective for psychopathology (Rutten et al., 2013; Wichers et al., 2007a). Therefore, individuals who are particularly skilled in experiencing and seeking such positive experiences can be hypothesized to be less prone to develop a mental disorder than people who are less reward sensitive.

The current cohort was specifically sampled to further evaluate the mechanism of dimensional phenotypes at the early stages of psychopathology. The TwinssCan sample is a unique cohort of a young twin population. It provides deep phenotyping of subclinical symptoms, thorough assessment of putative risk factors (i.e. genetic and nongenetic) and experimental tests to evaluate underlying neuropsychological processes, for example, salience attribution, social defeat, stress sensitivity and reward sensitivity. Therefore, this project is well equipped to investigate not only cross-sectional differences of psychopathology and resilience but also dynamic moment-to-moment variations, as well as long-term trajectories. The primary objective of the project is to investigate risk and protective factors for the development of psychopathology and the role of genetic and nongenetic factors contributing to intermediate phenotypes. Further, it aims to examine whether variations of (1) salience attribution, (2) reward sensitivity, (3) stress sensitivity and (4) the level of subtle psychotic experience and affective dysregulation in daily life are associated with genetic vulnerability, exposure to environmental factors and gene-environment interactions.

Sample Characteristics and Assessments

Participants were sampled from the East Flanders Prospective Twin Survey (EFPTS), a prospective, population-based registry of multiple births in the province of East Flanders, Belgium (Derom et al., 2019). The TwinssCan project was recruited across three waves (baseline and two follow-ups). Baseline data were assessed from April 2010 to April 2014 (Pries, Guloksuz, Menne-Lothmann et al., 2017), including male and female twins in the age range of 15–35 years, their singleton siblings and their parents. It included 839 participants: 292 monozygotic twins (MZ), 486 dizygotic twins (DZ), 18 triplets and 43 siblings. Furthermore, data from 363 parents were assessed. At baseline, 60% of the participants were female (MZ: 63%; DZ: 57%; triplets: 61%; siblings: 70%). The mean age was 17.4 ($SD = 3.6$) years (MZ: 18.0 [$SD = 4.2$]; DZ: 16.9 [$SD = 2.8$]; triplets: 16.8 [$SD = 2.0$]; and siblings: 20.1 [$SD = 4.7$]), and most participants had an upper secondary education (primary education: 0.1%; lower secondary education: 6%; upper secondary education: 68%; tertiary education: 26%). For the second wave, 60% of the twins and siblings were reassessed. Sequential analysis based on sex, fetal membranes, umbilical cord blood groups, placental alkaline phosphatase and DNA fingerprints was used to determine zygosity (Deromet al., 2013).

Participants were included if they clearly understood and were able to verbally assent to the study procedures and when they voluntarily agreed to participate by means of written informed consent. Signed consent of the parent(s) was required when participants were younger than 18 years. Participation was not possible if caregivers indicated the presence of a pervasive mental disorder. Participants were excluded from the sample if the instructor, study coordinator or neuropsychological tester confirmed they were not able to complete testing and gave invalid, unreliable data on questionnaires, structured interviews and experimental tests. The local ethics committee approved the study (Commissie Medische Ethiek van de Universitaire ziekenhuizen KU Leuven, Nr. B32220107766).

A broad range of variables were assessed using validated self-report questionnaires, structured interviews and experimental tests. Placenta, blood and saliva samples have been stored at −80°C in biobanks. DNA has been isolated from saliva for all subjects. DNA from placenta and blood is available for the monozygotic twins. A study battery summary of clinical, biological, social-demographics, physical, environmental exposures, cognitive, psychological and experimental measures is reported in Table 1.

Findings

Genetic and Nongenetic Risk Factors

Several studies examined how childhood adversity (CA) and genetic liability for psychopathology may affect mental ill health in the TwinssCan cohort. Lecei et al. (2019) explored whether gene-environment correlation may explain the association previously found between CA and psychopathology. In other words, they tested whether genetic liability for psychopathology made individuals also more likely to experience CA, which would result in a mechanism referred to as genetic confounding of the association between CA and psychopathology. Within-twin differences of CA were regressed on within-twin differences of psychopathology (assessed with the Symptom Checklist-90-R; SCL-90; Derogatis et al., 1976) in MZ twins. As MZ twins have identical DNA, the researchers argued that associations between within-twin differences indicate that the association between CA and psychopathology cannot be attributed only to genetic predisposition. CA in the whole sample as well as within-twin differences in CA was associated with psychopathology. These results suggest that at least part of the association between CA and psychopathology is independent from genetic predisposition and therefore genetic confounding cannot explain the association between CA and psychopathology.

Following this, Pinckaers et al. (2019) examined whether CA interacted with proxy genetic liability and affected psychopathology in the TwinssCan cohort. Genetic liability was approximated by estimating the co-twins' psychopathology scores on the SCL-90. Genetic vulnerability moderated the association between CA and the negative dimension of the Community Assessment of Psychic Experiences (CAPE; Stefanis et al., 2002). The association with the total CAPE score approached near significance, whereas neither of the other associations, that is, with the subscales positive and depression symptom dimension, showed a significant interaction effect. The results suggest that genetic vulnerability complicated by CA affects subthreshold expression of psychosis, especially in the negative symptom dimension.

While much attention is given to macro levels of psychopathological changes, which can occur over periods of years or months,

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Table 1. TwinssCan Study battery summary

	Variable/purpose	Instruments
Clinical and biological	Positive, negative and depressive symptoms	Community Assessment of Psychic Experiences (CAPE)[a] (Stefanis et al., 2002)
	Somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, psychoticism	The Symptom Checklist-90-R (SCL-90)[a] (Derogatis et al., 1976)
	Schizotypy	Structured Interview for Schizotypy – Revised (SIS-R; Vollema & Ormel, 2000)
	Depression, psychosis, mania and PTSD	Composite International Diagnostic Interview (CIDI-12)[a] (World Health Organization, 1990)
	Autism spectrum	Autism-spectrum Quotient (AQ)[a] (Hoekstra et al., 2008)
	Hearing impairment	Short questionnaire
	DNA and epigenetic	Blood sample, placenta and cheek swabs
	Cortisol	Salivary cortisol (within the protocol of the digi-SPEE; Menne-Lothmann et al., 2017)
Social-demographics	Date of birth, gender, marital state, housing, income, job, education, number of siblings, mother tongue, native country of (grand)parents, age of parents, education of parents, marital status of parents, ethnicity, grade of urbanicity, religion/ spirituality	The General Demographic Questionnaire
Environmental exposures	Substance-use and alcohol-use	Composite International Diagnostic Interview (CIDI-12)[a] (World Health Organization, 1990)
	Cannabis-use	Urine drug screen
	Obstetric complications	Obstetric complications
	Childhood adversity	Childhood Trauma Questionnaire – short form (JTV-SV; Bernstein et al., 2003)
	Bullying	Retrospective Bullying Questionnaire (RBQ)[a] (Schäfer et al., 2004)
	Stressful life events	Life Events Questionnaire[a] (Paykel, 1997)
	Differential sibling experiences	The Sibling Inventory of Differential Experiences (SIDE; Daniels & Plomin, 1985)
	Self-perception of social rank	Social Comparison Scale (SCS; Allan & Gilbert, 1995)
Physical	Habitual physical activity	Baecke questionnaire on physical activity (Baecke et al., 1982)[a]
Cognitive and psychological	Neuroticism and extraversion	Eysenck Personality Questionnaire (EPQ-RSS)[a] (Sanderman et al., 1995)
	Prosocial behavior	Prosocial Tendencies Measure (PTM)[a] (Carlo & Randall, 2002)
	Wellbeing	Amsterdamse Psychological Well Being (AWB)[a] (Ryff, 1989)
	Coping	Utrecht Coping list (UCL)[a] (Schreurs et al., 1993)
	Self-esteem	Rosenberg Self-esteem Scale (RSE)[a] (Rosenberg, 1965)
	Positive and negative affect	Positive and Negative Affect Scales (PANAS; Watson et al., 1988; within the protocol of the digi-SPEE)
	Perceived parenting	Parental Bonding Instrument (PBI; Parker et al., 1979)
	IQ	WAIS – Verbal Fluency, Letter Number Sequencing, Visual Memory Span/Spatial Span (Krabbendam et al., 2005; Wechsler, 1997)

(*Continued*)

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Table 1. (*Continued*)

	Variable/purpose	Instruments
Experimental tasks	Salience attribution	White Noise Test (Pries, Guloksuz, Menne-Lothmann et al., 2017)
	Salience attribution	Psycho-babble (Hoffman et al., 2007)
	Daily variations of thoughts, feelings, symptoms, the current context and appraisal of that context	Experience Sampling Methodology (ESM; Delespaul, 1995; van Os, Verhagen et al., 2017)
	Implicit self-esteem	Single Target — Implicit Association Task (ST-IAT) for self-esteem (Rudolph et al., 2008)
	Virtual social defeat	Digital Social Peer Evaluation Experiment (digi-SPEE; Menne-Lothmann et al., 2017)
	Reward sensitivity	Signal Detection Task and reversal with reward (adapted version; Pizzagalli et al., 2005)
	Positive or negative interpretations of ambiguous situations	Ambiguous Situations (adapted assessment part; Mathews & Mackintosh, 2000)

[a]Reassessed during wave 2 and wave 3.

recent concepts of psychopathology acknowledge that the development of mental disorders is best understood when also looking at micro, complex, moment-to-moment dynamic changes (van Os, Verhagen et al., 2017). Therefore, Pries, Klingenberg et al. (2019) investigated whether molecular genetic risk for schizophrenia interacted with CA and daily life stressors to influence moment-to-moment variations of mental states (i.e., negative affect, positive affect and subtle psychosis expression) and stress sensitivity. Molecular genetic vulnerability was expressed through polygenic risk score (PRS) for schizophrenia, which was calculated by summing weighted trait-alleles (EUGEI investigators, 2014; Purcell et al., 2009; Ripke et al., 2014). Momentary mental states were assessed using a structured diary technique, the experience sampling methodology (ESM; Delespaul, 1995; van Os, Verhagen et al., 2017). The results were that exposure to early life events showed a statistical interaction with PRS for schizophrenia, leading to increased psychosis expressions, negative affect, stress-sensitivity and decreased positive affect. However, daily life stressors did not significantly interact with genetic markings for the same outcome variables.

In another study on momentary mental states, Vaessen et al. (2017) used the TwinssCan cohort to evaluate whether sensitivity to daily life stress predicts onset or persistence of psychopathology. The authors used ESM data at baseline to assess affective responses to daily life stress (i.e., stress sensitivity) and found, contrary to previous work, that stress sensitivity was associated with neither persistence nor onset of psychopathology.

Finally, using the network approach, Hasmi et al. (2017) investigated whether CA and proxy genetic liability for psychopathology (measured through co-twin scores on the SCL-90) were associated with network structures of affective regulation in daily life. The researchers compared regression coefficients, density and centrality indices of different networks and found that individuals with low genetic liability showed higher overall and negative affect density between network elements, whereas CA was associated with increased positive affect density and overall density.

Experimental Tests

Three studies used the TwinssCan cohort to validate experimental tasks: the digital social peer evaluation experiment (digi-SPEE) and the white noise test. Menne-Lothmann et al. (2017) used the digi-SPEE to investigate how negative virtual social evaluation of peers impacts on participants' implicit self-esteem, cortisol levels and positive and negative affects. For this experimental study, participants were assessed twice. During the first session, baseline assessments were collected. Furthermore, participants were told that they would be coupled with other twins for the next session, based on a rating system. They were instructed to rate other participants' profiles on intelligence, appearance and congeniality and were told their profile would be rated as well. During the second session, participants were informed that they were rated too low to be allocated to a group, after which follow-up measures were collected. The findings showed that negative affect and cortisol levels were increased after mild negative evaluations, and positive affect as well as self-esteem were reduced. The findings indicate that the digi-SPEE can be used to study important mechanisms of psychopathology and manipulate biological and implicit as well as explicit mental changes.

Following this, Klippel et al. (2018) evaluated the influence of environmental (i.e., prenatal stress, CA, bullying, and subjective social status) and proxy genetic factors on sensitivity to peer evaluation on the digi-SPEE. Genetic factors and gene-environment interaction did not significantly influence implicit self-esteem, negative affect and positive affect after negative peer evaluation. However, bullying was associated with increased negative affect, and low subjective social status was associated with decreased self-esteem as well as positive affect after peer evaluation.

Pries, Guloksuz, Menne-Lothmann et al. (2017) tested whether subclinical expression of psychotic symptoms was associated with experiencing speech illusions that were assessed using the white noise speech illusion task. To detect speech illusions, participants were exposed to white noise and instructed to indicate whether they heard voices and speech fragments. Subtle expressions of psychotic symptoms were measured through the Structured Interview for Schizotypy — Revised (SIS-R; Vollema & Ormel, 2000) and the CAPE. For this purpose, two methodological approaches, as published previously in the literature (Catalan et al., 2014; Galdos et al., 2011), were applied. However, neither method revealed an association between speech illusions and subclinical psychosis expressions in the general population. The findings indicate that contrary to findings in clinical populations, white noise speech illusion may not be associated with psychosis proneness in the adolescent/young adult general population.

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Future Directions

Over recent years, the TwinssCan project resulted in important findings on the effects of genetic and nongenetic exposures on psychopathology. Additionally, researchers evaluated the applicability of the digi-SPEE task (Klippel et al., 2018; Menne-Lothmann et al., 2017) and the white noise speech illusion task (Pries, Guloksuz, Menne-Lothmann et al., 2017) measuring social defeat and salient attribution, respectively. These studies add valuable knowledge that contributes to our current understanding of the complexity of subclinical multidimensional psychopathology, as well as the nonspecific effects of exposures. They highlight the role of gene-environmental interaction focusing both on macro and micro levels of psychopathological changes, that is, changes occurring over month and years (Lecei et al., 2019; Pinckaers et al., 2019; Vaessen et al., 2017) and from moment to moment (Hasmi et al., 2017; Pries, Klingenberg et al., 2019; Vaessen et al., 2017), respectively.

It is increasingly acknowledged that the development of pleiotropic psychopathology depends on a complex network of environmental exposures, that is, the exposome (Guloksuz et al., 2018; Pries, Lage Castellanos et al., 2019), and polygenic vulnerability (Guloksuz et al., 2019), which affect individuals throughout their life. Similarly, resilience is thought to dynamically change and can only be understood by prospectively evaluating different biological and psychological processes (Kalisch et al., 2017; Rutten et al., 2013; Snijders et al., 2018). By benefitting from these recent developments, we recently calculated the exposome score (Pries, Lage-Castellanos et al., 2019), which we aim to apply to the TwinssCan population. Further, new features are under way. The third wave of the TwinssCan project will soon be processed and provided to the researchers. Future work will include evaluation of epigenetic information in combination with genome-wide molecular data. As the multiples are recruited from the EFPTS, stored placenta samples will be used to compare early life epigenetic variations to markings later in life. As the literature highlights the role of epigenetic variations for psychopathology (Pries, Gülöksüz, & Kenis, 2017; Rutten & Mill, 2009) as well as resilience (Rutten et al., 2018; Snijders et al., 2018), these approaches are valuable future targets for investigations aiming to better understand factors and processes underlying mental ill health.

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Conflict of interest. None.

References

Ahern, E., & Semkovska, M. (2017). Cognitive functioning in the first-episode of major depressive disorder: A systematic review and meta-analysis. *Neuropsychology*, *31*, 52–72.

Allan, S., & Gilbert, P. (1995). A social comparison scale: Psychometric properties and relationship to psychopathology. *Personality and Individual Differences*, *19*, 293–299.

Baecke, J. A., Burema, J., & Frijters, J. E. (1982). A short questionnaire for the measurement of habitual physical activity in epidemiological studies. *American Journal of Clinical Nutrition*, *36*, 936–942.

Bernstein, D. P., Stein, J. A., Newcomb, M. D., Walker, E., Pogge, D., Ahluvalia, T., … Zule, W. (2003). Development and validation of a brief screening version of the Childhood Trauma Questionnaire. *Child Abuse & Neglect*, *27*, 169–190.

Brainstorm Consortium, Anttila, V., Bulik-Sullivan, B., Finucane, H. K., Walters, R. K., Bras, J., … Murray, R. (2018). Analysis of shared heritability in common disorders of the brain. *Science*, *360*, eaap8757.

Carlo, G., & Randall, B. A. (2002). The development of a measure of prosocial behaviors for late adolescents. *Journal of Youth and Adolescence*, *31*, 31–44.

Catalan, A., Simons, C. J., Bustamante, S., Drukker, M., Madrazo, A., de Artaza, M. G., … Gonzalez-Torres, M. A. (2014). Novel evidence that attributing affectively salient signal to random noise is associated with psychosis. *PLoS One*, *9*, e102520.

Daniels, D., & Plomin, R. (1985). Differential experience of siblings in the same family. *Developmental Psychology*, *21*, 747–760.

Delespaul, P. A. E. G. (1995). *Assessing schizophrenia in daily life: The experience sampling method*. Maastricht: Maastricht University Press.

Derogatis, L. R., Rickels, K., & Rock, A. F. (1976). The SCL-90 and the MMPI: A step in the validation of a new self-report scale. *British Journal of Psychiatry*, *128*, 280–289.

Derom, C., Thiery, E., Peeters, H., Vlietinck, R., Defoort, P., & Frijns, J. P. (2013). The East Flanders Prospective Twin Survey (EFPTS): An actual perception. *Twin Research and Human Genetics*, *16*, 58–63.

Derom, C., Thiery, E., Rutten, B. P. F., Peeters, H., Gielen, M., Bijnens, E., … Weyers, S. (2019). The East Flanders Prospective Twin Survey (EFPTS): 55 years late. *Twin Research and Human Genetics*, 1–6. doi: 10.1017/thg.2019.64.

Dominguez, M. D., Saka, M. C., Lieb, R., Wittchen, H. U., & van Os, J. (2010). Early expression of negative/disorganized symptoms predicting psychotic experiences and subsequent clinical psychosis: A 10-year study. *American Journal of Psychiatry*, *167*, 1075–1082.

Dominguez, M. D., Wichers, M., Lieb, R., Wittchen, H.-U., & van Os, J. (2009). Evidence that onset of clinical psychosis is an outcome of progressively more persistent subclinical psychotic experiences: An 8-year cohort study. *Schizophrenia Research*, *37*, 84–93.

Eisenberger, N. I., Jarcho, J. M., Liebermann, M. D., & Naliboff, B. D. (2006). An experimental study of shared sensitivity to physical pain and social rejection. *Pain*, *126*, 132–138.

EUGEI Investigators. (2014). Identifying gene-environment interactions in schizophrenia: Contemporary challenges for integrated, large-scale investigations. *Schizophrenia Bulletin*, *40*, 729–736.

Fusar-Poli, P., Nelson, B., Valmaggia, L., Yung, A. R., & McGuire, P. K. (2014). Comorbid depressive and anxiety disorders in 509 individuals with an at-risk mental state: Impact on psychopathology and transition to psychosis. *Schizophrenia Bulletin*, *40*, 120–131.

Galdos, M., Simons, C., Fernandez-Rivas, A., Wichers, M., Peralta, C., Lataster, T., … van Os, J. (2011). Affectively salient meaning in random noise: A task sensitive to psychosis liability. *Schizophrenia Bulletin*, *37*, 1179–1186.

Goes, F. S., McCusker, M. G., Bienvenu, O. J., Mackinnon, D. F., Mondimore, F. M., Schweizer, B., … Potash, J. B. (2012). Co-morbid anxiety disorders in bipolar disorder and major depression: Familial aggregation and clinical characteristics of co-morbid panic disorder, social phobia, specific phobia and obsessive-compulsive disorder. *Psychological Medicine*, *42*, 1449–1459.

Guloksuz, S., Pries, L. K., Delespaul, P., Kenis, G., Luykx, J. J., Lin, B. C. D., … van Os, J. (2019). Examining the independent and joint effects of molecular genetic liability and environmental exposures in schizophrenia: Results from the EUGEI study. *World Psychiatry*, *18*, 173–182.

Guloksuz, S., van Nierop, M., Lieb, R., van Winkel, R., Wittchen, H. U., & van Os, J. (2015). Evidence that the presence of psychosis in non-psychotic disorder is environment-dependent and mediated by severity of non-psychotic psychopathology. *Psychological Medicine*, *45*, 2389–2401.

Guloksuz, S., van Os, J., & Rutten, B. P. F. (2018). The exposome paradigm and the complexities of environmental research in psychiatry. *JAMA Psychiatry*, *75*, 985–986.

Häfner, H., Maurer, K., Trendler, G., an der Heiden, W., Schmidt, M., & Könnecke, R. (2005). Schizophrenia and depression: Challenging the paradigm of two separate diseases — A controlled study of schizophrenia, depression and healthy controls. *Schizophrenia Research*, *77*, 11–24.

https://doi.org/10.1017/thg.2019.96 Published online by Cambridge University Press

Hasmi, L., Drukker, M., Guloksuz, S., Menne-Lothmann, C., Decoster, J., van Winkel, R., … van Os, J. (2017). Network approach to understanding emotion dynamics in relation to childhood trauma and genetic liability to psychopathology: Replication of a prospective experience sampling analysis. *Frontiers in Psychology*, *8*, 1908.

Hoekstra, R. A., Bartels, M., Cath, D. C., & Boomsma, D. I. (2008). Factor structure, reliability and criterion validity of the Autism-Spectrum Quotient (AQ): A study in Dutch population and patient groups. *Journal of Autism and Developmental Disorders*, *38*, 1555–1566.

Hoffman, R. E., Woods, S. W., Hawkins, K. A., Pittman, B., Tohen, M., Preda, A., … McGlashan, T. H. (2007). Extracting spurious messages from noise and risk of schizophrenia-spectrum disorders in a prodromal population. *British Journal of Psychiatryy*, *191*, 355–356.

Kalisch, R., Baker, D. G., Basten, U., Boks, M. P., Bonanno, G. A., Brummelman, E., … Kleim, B. (2017). The resilience framework as a strategy to combat stress-related disorders. *Nature Human Behaviour*, *1*, 784–790.

Kelleher, I., Devlin, N., Wigman, J. T., Kehoe, A., Murtagh, A., Fitzpatrick, C., & Cannon, M. (2014). Psychotic experiences in a mental health clinic sample: Implications for suicidality, multimorbidity and functioning. *Psychological Medicine*, *44*, 1615–1624.

Klippel, A., Reininghaus, U., Viechtbauer, W., Decoster, J., Delespaul, P., Derom, C., … Wichers, M. (2018). Sensitivity to peer evaluation and its genetic and environmental determinants: Findings from a population-based twin study. *Child Psychiatry & Human Development*, *49*, 766–778.

Krabbendam, L., Myin-Germeys, I., Hanssen, M., & van Os, J. (2005). Familial covariation of the subclinical psychosis phenotype and verbal fluency in the general population. *Schizophrenia Research*, *74*, 37–41.

Lamers, F., van Oppen, P., Comijs, H. C., Smit, J. H., Spinhoven, P., van Balkom, A. J., … Penninx, B. W. (2011). Comorbidity patterns of anxiety and depressive disorders in a large cohort study: The Netherlands Study of Depression and Anxiety (NESDA). *Journal of Clinical Psychiatry*, *72*, 341–348.

Lataster, T., Wichers, M., Jacobs, N., Mengelers, R., Derom, C., Thiery, E., … Myin-Germeys, I. (2009). Does reactivity to stress cosegregate with subclinical psychosis? Findings from a general population twin sample. *Acta Psychiatrica Scandinavica*, *119*, 45–53.

Lecei, A., Decoster, J., De Hert, M., Derom, C., Jacobs, N., Menne-Lothmann, C., … Wichers, M. (2019). Evidence that the association of childhood trauma with psychosis and related psychopathology is not explained by gene-environment correlation: A monozygotic twin differences approach. *Schizophrenia Research*, *205*, 58–62.

Mathews, A., & Mackintosh, B. (2000). Induced emotional interpretation bias and anxiety. *Journal of Abnormal Psychology*, *109*, 602–615.

McGrath, J. J., Saha, S., Al-Hamzawi, A., Andrade, L., Benjet, C., Bromet, E. J., & Kessler, R. C. (2016). The bidirectional associations between psychotic experiences and DSM-IV mental disorders. *American Journal of Psychiatry*, *173*, 997–1006.

Menne-Lothmann, C., Decoster, J., van Winkel, R., Collip, D., Rutten, B. P. F., Delespaul, P., & Wichers, M. (2017). Psychological and biological validation of a novel digital social peer evaluation experiment (digi-SPEE). *Noro Psikiyatri Arsivi*, *54*, 3–10.

Misiak, B., Krefft, M., Bielawski, T., Moustafa, A. A., Sasiadek, M. M., & Frydecka, D. (2017). Toward a unified theory of childhood trauma and psychosis: A comprehensive review of epidemiological, clinical, neuropsychological and biological findings. *Neuroscience & Biobehavioral Reviews*, *75*, 393–406.

Myin-Germeys, I., & van Os, J. (2007). Stress-reactivity in psychosis: Evidence for an affective pathway to psychosis. *Clinical Psychology Review*, *27*, 409–424.

Navarro-Mateu, F., Alonso, J., Lim, C. C. W., Saha, S., Aguilar-Gaxiola, S., Al-Hamzawi, A., … WHO World Mental Health Survey Collaborators. (2017). The association between psychotic experiences and disability: Results from the WHO World Mental Health Surveys. *Acta Psychiatrica Scandinavica*, *136*, 74–84.

Nesdaele, D., & Lambert, A. (2007). Effects of experimentally manipulated peer rejection on children's negative affect, self-esteem and maladaptive social behavior. *International Journal of Behavioral Development*, *31*, 115–122.

Nivard, M. G., Gage, S. H., Hottenga, J. J., van Beijsterveldt, C. E. M., Abdellaoui, A., Bartels, M., … Middeldorp, C. M. (2017). Genetic overlap between schizophrenia and developmental psychopathology: Longitudinal and multivariate polygenic risk prediction of common psychiatric traits during development. *Schizophrenia Bulletin*, *43*, 1197–1207

Parker, G., Tupling, H., & Brown, L. (1979). A parental bonding instrument. *British Journal of Medical Psychology*, *52*, 1–10.

Paykel, E. S. (1997). The interview for recent life events. *Psychological Medicine*, *27*, 301–310.

Pinckaers, F. M. E., Rotee, I. L. M., Krolinski, P., Nwosu, V., Smeets, A. P. W., Gülöksüz, S., … Drukker, M. (2019). Evidence for interaction between genetic liability and childhood trauma in the development of psychotic symptoms. *Social Psychiatry and Psychiatric Epidemiology*, *54*, 1045–1054. doi: 10.1007/s00127-019-01711-z.

Pizzagalli, D. A., Jahn, A. L., & O'Shea, J. P. (2005). Toward an objective characterization of an anhedonic phenotype: A signal-detection approach. *Biological Psychiatry*, *57*, 319–327.

Pries, L.-K., Gülöksüz, S., & Kenis, G. (2017). DNA methylation in schizophrenia. In R. Delgardo-Morales (Ed.), *Neuroepigenomics in Aging and Disease* (pp. 211–236). New York, NY: Springer.

Pries, L.-K., Guloksuz, S., Menne-Lothmann, C., Decoster, J., van Winkel, R., Collip, D., … van Os, J. (2017). White noise speech illusion and psychosis expression: An experimental investigation of psychosis liability. *PLoS One*, *12*, e0183695. doi: 10.1371/journal.pone.0183695.

Pries, L.-K., Guloksuz, S., ten Have, M., de Graaf, R., van Dorsselaer, S., Gunther, N., … van Os, J. (2018). Evidence that environmental and familial risks for psychosis additively impact a multidimensional subthreshold psychosis syndrome. *Schizophrenia Bulletin*, *44*, 710–719.

Pries, L.-K., Klingenberg, B., Menne-Lothmann, C., Decoster, J., van Winkel, R., Collip, D., … Guloksuv, S. (2019). Interaction between polygenic liability for schizophrenia and childhood adversity influences daily-life emotional dysregulation and subtle psychosis expression. *bioRxiv*, 1–22. doi: 10.1101/778761.

Pries, L.-K., Lage Castellanos, A., Delespaul, P., Kenis, G., Luykx, J. J., Lin, B. D., … Guloksuz, S. (2019). Estimating exposome score for schizophrenia using predictive modeling approach in two independent samples: The results from the EUGEI study. *Schizophrenia Bulletin*, *45*, 960–965.

Purcell, S. M., Wray, N. R., Stone, J. L., Visscher, P. M., O'Donovan, M. C., Sullivan, P. F., & Sklar, P. (2009). Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature*, *460*, 748–752.

Reichenberg, A., Caspi, A., Harrington, H., Houts, R., Keefe, R. S., Murray, R. M., … Moffitt, T. E. (2010). Static and dynamic cognitive deficits in childhood preceding adult schizophrenia: A 30-year study. *American Journal of Psychiatry*, *167*, 160–169.

Ripke, S., Neale, B. M., Corvin, A., Walters, J. T. R., Farh, K. H., Holmans, P. A., … O'Donovan, M. C. (2014). Biological insights from 108 schizophrenia-associated genetic loci. *Nature*, *511*, 421–427.

Rosenberg, M. (1965). *Society and the adolescent self-image*. Princeton, NJ: Princeton University Press.

Rossler, W., Hengartner, M. P., Ajdacic-Gross, V., Haker, H., Gamma, A., & Angst, J. (2011). Sub-clinical psychosis symptoms in young adults are risk factors for subsequent common mental disorders. *Schizophrenia Research*, *131*, 18–23.

Rudolph, A., Schröder-Abé, M., Schütz, A., Gregg, A. P., & Sedikides, C. (2008). Through a glass, less darkly? Reassessing convergent and discriminant validity in measures of implicit self-esteem. *European Journal of Psychological Assessment*, *24*, 273–281.

Rutten, B. P., Hammels, C., Geschwind, N., Menne-Lothmann, C., Pishva, E., Schruers, K., … Wichers, M. (2013). Resilience in mental health: Linking psychological and neurobiological perspectives. *Acta Psychiatrica Scandinavica*, *128*, 3–20.

Rutten, B. P., & Mill, J. (2009). Epigenetic mediation of environmental influences in major psychotic disorders. *Schizophrenia Bulletin*, *35*, 1045–1056.

Rutten, B. P. F., Vermetten, E., Vinkers, C. H., Ursini, G., Daskalakis, N. P., Pishva, E., & Boks, M. P. M. (2018). Longitudinal analyses of the DNA methylome in deployed military servicemen identify susceptibility loci for post-traumatic stress disorder. *Molecular Psychiatry*, *23*, 1145–1156.

Ryff, C. D. (1989). Happiness is everything, or is it? Explorations on the meaning of psychological well-being. *Journal of Personality and Social Psychology*, *57*, 1069.

https://doi.org/10.1017/thg.2019.96 Published online by Cambridge University Press

Sanderman, R., Arrindell, W., & Ranchor, A. (1995). *Het meten van persoonlijkheidskenmerken met de Eysenck Personality Questionnaire (EPQ): een handleiding*. Groningen, the Netherlands: Noordelijk Centrum voor Gezondheidsvraagstukken.

Sandstrom, M. J., Cillessen, A. H. N., & Eisenhower, A. (2003). Children's appraisal of peer rejection experiences: Impact on social and emotional adjustment. *Social Development*, *12*, 530–550.

Schäfer, M., Korn, S., Smith, P. K., Hunter, S. C., Mora-Merchán, J. A., Singer, M. M., & Van der Meulen, K. (2004). Lonely in the crowd: Recollections of bullying. *Developmental Psychology*, *22*, 379–394.

Schreurs, P. J. G., Willige, G., Van De, J. F., Tellegen, B., & Graus, G. M. H. (1993). *De Utrechtse coping lijst: UCL: omgaan met problemen en gebeurtenissen: herziene handleiding 1993*. Lisse, Netherlands: Swets & Zeitlinger.

Snijders, C., Pries, L. K., Sgammeglia, N., Al Jowf, G., Youssef, N. A., de Nijs, L., … **Rutten, B. P. F.** (2018). Resilience against traumatic stress: Current developments and future directions. *Frontiers of Psychiatry*, *9*, 676.

Stefanis, N., Hanssen, M., Smirnis, N., Avramopoulos, D., Evdokimidis, I., Stefanis, C., … **Van Os, J.** (2002). Evidence that three dimensions of psychosis have a distribution in the general population. *Psychological Medicine*, *32*, 347–358.

Vaessen, T., van Nierop, M., Decoster, J., Delespaul, P., Derom, C., de Hert, M., … **Myin-Germeys, I.** (2017). Is sensitivity to daily stress predictive of onset or persistence of psychopathology? *European Psychiatry*, *45*, 167–173.

van Os, J., Kenis, G., & Rutten, B. P. (2010). The environment and schizophrenia. *Nature*, *468*, 203–212.

van Os, J., van der Steen, Y., Islam, M. A., Guloksuz, S., Rutten, B. P., Simons, C. J., & **Group Investigators**. (2017). Evidence that polygenic risk for psychotic disorder is expressed in the domain of neurodevelopment, emotion regulation and attribution of salience. *Psychological Medicine*, *47*, 2421–2437.

van Os, J., Verhagen, S., Marsman, A., Peeters, F., Bak, M., Marcelis, M., … **Lataster, T.** (2017). The experience sampling method as an mHealth tool to support self-monitoring, self-insight, and personalized health care in clinical practice. *Depression and Anxiety*, *34*, 481–493.

Vollema, M. G., & Ormel, J. (2000). The reliability of the structured interview for schizotypy-revised. *Schizophrenia Bulletin*, *26*, 619–629.

Watson, D., Clark, L. A., & Tellegen, A. (1988). Development and validation of brief measures of positive and negative affect: The PANAS scales. *Journal of Personality and Social Psychology*, *54*, 1063–1070.

Wechsler, D. (1997). *Wechsler Memory Scale* (3rd ed.). San Antonio, TX: The Psychological Corporation.

Wichers, M., Myin-Germeys, I., Jacobs, N., Peeters, F., Kenis, G., Derom, C., … **van Os, J.** (2007a). Evidence that moment-to-moment variation in positive emotions buffer genetic risk for depression: A momentary assessment twin study. *Acta Psychiatrica Scandinavica*, *115*, 451–457.

Wichers, M., Myin-Germeys, I., Jacobs, N., Peeters, F., Kenis, G., Derom, C., … **van Os, J.** (2007b). Genetic risk of depression and stress-induced negative affect in the flow of daily life. *British Journal of Psychiatry*, *191*, 1–6.

World Health Organization. (1990). Composite International Diagnostic Interview. Geneva, Switzerland: World Health Organization.

https://doi.org/10.1017/thg.2019.96 Published online by Cambridge University Press