

Original Article

*Denotes equal contribution of the authors.

Cite this article: Antonucci LA *et al* (2024). Personality changes during adolescence predict young adult psychosis proneness and mediate gene–environment interplays of schizophrenia risk. *Psychological Medicine* **54**, 3838–3848. <https://doi.org/10.1017/S0033291724002198>

Received: 12 January 2024

Revised: 7 August 2024

Accepted: 16 August 2024

First published online: 28 October 2024

Keywords:


bullying victimization; gene–environment correlations; latent growth curve models; personality; psychosis proneness

Corresponding author:

Giulio Pergola;

Email: giulio.pergola@uniba.it

Personality changes during adolescence predict young adult psychosis proneness and mediate gene–environment interplays of schizophrenia risk

Linda A. Antonucci^{1,*}, Alessandra Raio^{1,*}, Gianluca Christos Kikidis¹, Alessandro Bertolino^{1,2}, Antonio Rampino^{1,2}, Tobias Banaschewski³, Arun L.W. Bokde⁴, Sylvane Desrivieres⁵, Herta Flor^{6,7}, Antoine Grigis⁸, Hugh Garavan⁹, Andreas Heinz¹⁰, Jean-Luc Martinot^{11,12}, Marie-Laure Paillère Martinot^{11,12,13}, Eric Artiges^{11,12,14}, Frauke Nees^{3,6,15}, Dimitri Papadopoulos Orfanos⁸, Luise Poustka¹⁶, Sarah Hohmann¹⁷, Juliane H. Fröhner¹⁸, Michael N. Smolka¹⁸, Nilakshi Vaidya¹⁹, Henrik Walter¹⁰, Robert Whelan²⁰, Gunter Schumann^{19,21}, Catharina A. Hartman²², Giulio Pergola^{1,23,24}  and the IMAGEN Consortium

Abstract

Background. Psychotic symptoms in adolescence are associated with social adversity and genetic risk for schizophrenia. This gene–environment interplay may be mediated by personality, which also develops during adolescence. We hypothesized that (i) personality development predicts later Psychosis Proneness Signs (PPS), and (ii) personality traits mediate the association between genetic risk for schizophrenia, social adversities, and psychosis.

Methods. A total of 784 individuals were selected within the IMAGEN cohort (Discovery Sample-DS: 526; Validation Sample-VS: 258); personality was assessed at baseline (13–15 years), follow-up-1 (FU1, 16–17 years), and FU2 (18–20 years). Latent growth curve models served to compute coefficients of individual change across 14 personality variables. A support vector machine algorithm employed these coefficients to predict PPS at FU3 (21–24 years). We computed mediation analyses, including personality-based predictions and self-reported bullying victimization as serial mediators along the pathway between polygenic risk score (PRS) for schizophrenia and FU3 PPS. We replicated the main findings also on 1132 adolescents recruited within the TRAILS cohort.

Results. Growth scores in neuroticism and openness predicted PPS with 65.6% balanced accuracy in the DS, and 69.5% in the VS. Mediations revealed a significant positive direct effect of PRS on PPS (confidence interval [CI] 0.01–0.15), and an indirect effect, serially mediated by personality-based predictions and victimization (CI 0.006–0.01), replicated in the TRAILS cohort (CI 0.0004–0.004).

Conclusions. Adolescent personality changes may predate future experiences associated with psychosis susceptibility. PPS personality-based predictions mediate the relationship between PRS and victimization toward adult PPS, suggesting that gene–environment correlations proposed for psychosis are partly mediated by personality.

Introduction

Current research refers to psychosis proneness signs (PPS) as unusual psychotic-like experiences (PLEs), like perceptual abnormalities or persecutory ideation (Bourgin *et al.*, 2020). PPS occur in both at-psychosis-risk (Bonnett, Varese, Smith, Flores, & Yung, 2019) and non-clinical populations (Loch *et al.*, 2011): up to 26.7% of the general population reports at least one PPS (Bourgin *et al.*, 2020), without seeking psychiatric help (Yung *et al.*, 2009). Interestingly, PPS occur more frequently among young individuals (McGrath *et al.*, 2015) until young adulthood. This age stage also represents the typical onset period for psychosis-spectrum disorders, including schizophrenia (Solmi *et al.*, 2022). Although PPS do not meet the threshold for full-blown psychosis (Mark & Touloupoulou, 2016), their occurrence during adolescence may precede later psychotic onset (Nuevo, Van Os, Arango, Chatterji, & Ayuso-Mateos, 2013). When PPS persist into young adulthood, the individual risk for full-blown psychosis increases (McGrath *et al.*, 2016). Thus, PPS represent an early target to

© The Author(s), 2024. Published by Cambridge University Press. This is an Open Access article, distributed under the terms of the Creative Commons Attribution licence (<http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted re-use, distribution and reproduction, provided the original article is properly cited.



investigate how psychosis susceptibility develops over time (Howes & Murray, 2014). Investigating PPS may refine early identification and prediction of individual risk.

In the context of the high schizophrenia heritability, estimated up to 80% (Lichtenstein et al., 2009), exposure to adverse environmental factors contributes to the risk of developing schizophrenia and other psychoses (van Os, Kenis, & Rutten, 2010). For schizophrenia, the gap between the genetic risk explainable in terms of genetic variants and the heritability estimates in twins is remarkable. Thus, disentangling different types of gene-environment interplay (Zwicker, Denovan-Wright, & Uher, 2018) is important for early identification and primary prevention (Pergola, Penzel, Sportelli, & Bertolino, 2023; Plomin, DeFries, & Loehlin, 1977; Uher & Zwicker, 2017): indeed, gene-environment relations require the environment to enact genetic risk; the environment may, in turn, be modulated by early intervention programs.

Notably, schizophrenia genetic risk loci have previously been associated with 'neuroticism' and 'openness' personality traits (Smeland et al., 2017). Personality traits are heritable (Vukasović & Bratko, 2015), and they develop during adolescence (Roberts, Caspi, & Moffitt, 2001). Late adolescence is also the period in which PPS typically emerge. Adolescent PPS have been associated with personality characteristics, especially with schizotypal traits (Barrantes-Vidal, Racioppi, & Kwapił, 2020; Fonseca-Pedrero, Ortuno-Sierra, Inchausti, Rodríguez-Testal, & Debbane, 2019). However, prior research did not examine the identified relationships in the frame of gene-environment interplay models to explain psychopathology development. We reasoned that static (e.g. genetics) and dynamic (e.g. personality) *intrinsic* factors might be modulated by *extrinsic* factors (e.g. social adversities) when contributing to PPS. Pergola et al. (2019) already reported evidence of an evocative gene-environment correlation in schizophrenia. In that study, the polygenic risk score (PRS) for schizophrenia (PGC2 wave), cumulating the effects of many risk variants, was associated with the subsequent frequency of sub-clinical psychotic symptoms. This effect was *mediated* by peer and teacher reports of an established schizophrenia environmental factor, i.e. bullying victimization (Armitage et al., 2022; Woolway et al., 2022). However, it is still unexplained how genetic factors could act on the social environment; one hypothesis considers evocative gene-environment correlations (Lella, Antonucci, & Pergola, 2023). Peer victimization is not necessary or sufficient *per se* for a diagnosis of schizophrenia; it may represent an environmental risk factor potentially correlated with genetic risk for schizophrenia (Woolway et al., 2022). We hypothesized that adolescent personality evolution may interact with such exposure in predicting psychosis vulnerability, and potentially be associated with genetic susceptibility, as well (Millan et al., 2016). Importantly, genetics, social challenges, and personality evolution are intertwined, and their relationship may be non-linear, e.g. detectable only in the presence of high genetic risk (Pergola et al., 2019). Non-linear interactions between multiple variables are best captured by machine learning approaches when aiming to achieve individual-level predictions (Dwyer, Falkai, & Koutsouleris, 2018). Therefore, we aimed to deliver longitudinal calculators of psychosis risk that quantify the predictive potential of individual personality trajectories by combining multivariate and change-tracking techniques (i.e. Latent Growth Curve Models-LGCM).

Here, we aimed to investigate whether personality development during adolescence plays a role in gene-environment interplays predicting subsequent PPS. We analyzed a naturalistic population recruited within the IMAGEN consortium, generating a

multivariate risk calculator based on adolescent patterns of personality change aimed at predicting PPS severity in adulthood. Next, we associated our algorithm predictions with the risk of developing emotional and behavioral disorders to explore the wider clinical relevance of our personality-based risk calculator. Finally, we investigated the association of polygenic risk for schizophrenia with subsequent PPS severity. We hypothesized that this relationship was mediated by personality-based multivariate predictions and bullying. To test our findings' generalizability, we replicated the main results on another independent cohort of young individuals (TRAILS). The study is outlined in Fig. 1.

Methods

Sample and assessment

We selected 784 individuals recruited within the IMAGEN study (Schumann et al., 2010), from a wider naturalistic cohort of 13-years-old adolescents undergoing four assessment waves, at Baseline (BL) and at two, four, and six years after BL completion (i.e. follow up 1, 2, 3 – FU1, FU2, FU3) (see online Supplementary Information–SI, Section 1). Parents and adolescents gave written consent and verbal assent, respectively. We selected participants based on the full availability of the individual total score for the Community Assessment of Psychic Experiences – 42 (CAPE-42) (Stefanis et al., 2002), used to assess PPS at FU3 as the last available time point (see online SI, Section 2). The IMAGEN cohort was randomly split (2:1 ratio) into a discovery sample ($N = 526$; Table 1A) and a validation sample ($N = 258$; Table 1B). To test our findings generalizability, we replicated IMAGEN models on an external cohort of 1546 adolescents (Table 1C), selected from the Tracking Adolescents' Individual Lives Survey (TRAILS) study (see online SI, Section 12.1), based on CAPE-42 full data availability at the last accessible time point (wave 3-w3). Details about subsequent steps of participant retention in both cohorts are depicted in a Consort Chart (online Supplementary Figure 1).

In both cohorts, each individual was assigned to a higher- or lower-PPS group, based on the median of the FU3 CAPE-42 total score distribution, which for the IMAGEN cohort was calculated in the Discovery sample and used as a cut-off also in the Validation sample (so that data remained independent of cut-off determination). Two-sample t tests and χ^2 tests assessed differences between Higher-PPS and Lower-PPS (IMAGEN Discovery/Validation samples: Table 1A/1B; TRAILS replication cohort: Table 1C; $\alpha = 0.05$).

For each IMAGEN participant, a total of 14 personality scores (listed in online Supplementary Table 1) were computed at BL, FU1, and FU2 based on the items from the following self-report questionnaires (see online SI, Section 3 for details):

- the NEO Five-Factor Inventory (Costa & McCrae, 1992), which assesses personality on five main dimensions (Neuroticism, Extraversion, Openness, Agreeableness, and Conscientiousness), i.e. the so-called Big Five traits (Raad & Perugini, 2002);
- the Temperament and Character Inventory–Revised (Farmer & Goldberg, 2008), based on the Cloninger comprehensive model of temperament and character (Cloninger, Svrakic, & Przybeck, 1993). The IMAGEN version provided measures for Novelty Seeking and its four temperamental subcomponents (exploratory excitability, impulsiveness, extravagance, and disorderliness);

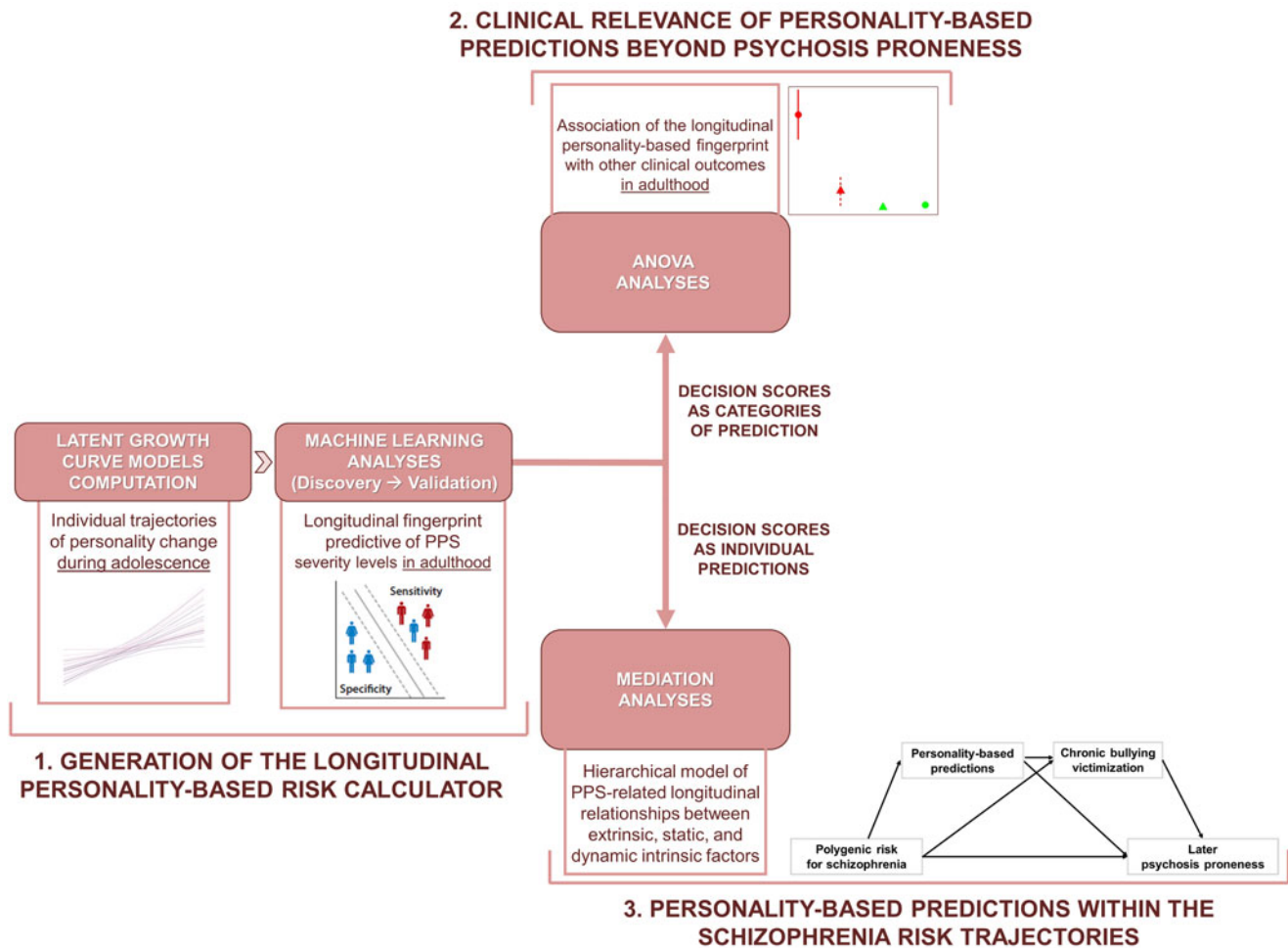


Figure 1. The outline of the study. (1) Individual trajectories of change during adolescence based on personality traits were estimated via latent growth curve models. The two derived trait-related coefficients of change per participant fed a machine learning algorithm as longitudinal predictors of psychosis proneness signs (PPS) in young adulthood. Longitudinal decision scores extracted from the generated models were used: (2) to predict clinical outcomes other than PPS in adulthood; (3) as a longitudinal interface between individual polygenic risk for schizophrenia and bullying victimization across the pathway toward final PPS. (Figure representing machine learning analyses adapted from Dwyer et al., 2018). PPS, Psychosis Proneness Signs.

– the substance use risk profile scale (Woicik, Stewart, Pihl, & Conrod, 2009), investigating the role of our main personality traits (Hopelessness, Anxiety Sensitivity, Impulsivity, Sensation Seeking) as potential risk factors for addictive behaviors and co-morbid psychopathology development.

Descriptive statistics and between-group comparisons, performed via two-sample *t* tests ($\alpha = 0.05$), are reported for each selected score at each time point in online Supplementary Table 2.

The three IMAGEN waves of personality data collection were used as input variables to estimate individual trajectories of change in both the discovery and validation samples (see Methods, Section ‘Latent Growth Curve Models pipeline’).

In the TRAILS cohort, a total of 12 personality variables (listed in online Supplementary Table 13), including both w3 cross-sectional and w3-w1 longitudinal scores (see online SI, Section 12.2), were analyzed through the very same machine learning pipeline implemented on IMAGEN data (see Methods, Section ‘Machine learning pipeline’).

Generation of the longitudinal personality-based risk calculator

Latent growth curve models pipeline

To compute personality-based trajectories of individual change over time, we implemented LGCMs (Burant, 2016) via the R statistics (<https://cran.r-project.org/>) ‘lavaan’ package. A total of 14 LGCMs were computed separately in both Discovery and Validation samples, one for each personality variable assessed at BL, FU1, and FU2 (listed in online Supplementary Table 1). Incomplete personality information at FU1 (missing data proportion: 7.03–9.33%) was handled via full information maximum likelihood (Allison, 1987; Felt, Depaoli, & Tiemensma, 2017). FU3 personality information was excluded from LGCMs computation so that PPS outcomes were solely predicted based on prior time points.

LGCMs computation details are reported in online SI, Section 4.1. Details about goodness-of-fit indices and metrics are reported in online SI, Section 4.2.

From each of the 14 general LGCMs implemented in both the discovery and validation samples, two individual latent

Table 1. Demographic characteristics of: (A) IMAGEN Discovery Sample; (B) IMAGEN Validation Sample; (C) TRAILS Replication cohort

A. IMAGEN Discovery sample	All subjects (mean ± SD)	High-PPS (mean ± SD)	L-PPS (mean ± SD)	H-PPS v. L-PPS T/ χ^2 (<i>p</i> -value)
<i>N</i>	526	261	265	n.a.
<i>Gender ratio (M/F)</i>	235/291	103/158	132/133	5.28 (0.02)*
<i>Age in years</i>				
<i>BL</i>	13.94 ± 0.39	13.96 ± 1.9	13.91 ± 0.35	1.41 (0.16)
<i>FU1</i>	15.99 ± 0.6	15.98 ± 0.62	16.01 ± 0.58	−0.50 (0.61)
<i>FU2</i>	18.35 ± 0.6	18.39 ± 0.62	18.32 ± 0.58	1.47 (0.14)
<i>FU3</i>	22.04 ± 0.6	22.08 ± 0.67	21.99 ± 0.57	1.76 (0.08)
B. IMAGEN Validation sample	All subjects (mean ± SD)	H-PPS (mean ± SD)	L-PPS (mean ± SD)	H-PPS v. L-PPS T/ χ^2 (<i>p</i> -value)
<i>N</i>	258	142	116	n.a.
<i>Gender ratio (M/F)</i>	126/132	63/79	63/53	2.14 (0.14)
<i>Age</i>				
<i>BL</i>	13.96 ± 0.38	13.94 ± 0.35	13.97 ± 0.38	−0.66 (0.51)
<i>FU1</i>	16 ± 0.58	16.01 ± 0.57	16 ± 0.58	0.09 (0.92)
<i>FU2</i>	18.37 ± 0.65	18.44 ± 0.68	18.28 ± 0.58	2 (0.046)*
<i>FU3</i>	22.02 ± 0.7	22.11 ± 0.64	21.91 ± 0.67	2.45 (0.15)*
C. TRAILS Replication cohort	All subjects (mean ± SD)	H-PPS (mean ± SD)	L-PPS (mean ± SD)	H-PPS v. L-PPS T/ χ^2 (<i>p</i> -value)
<i>N</i>	1546	750	796	n.a.
<i>Gender ratio (M/F)</i>	846/700	458/292	388/408	23.17 (<0.001***)
<i>Age in years</i>				
<i>Wave 1</i>	11.09 ± 0.56	11.08 ± 0.55	11.09 ± 0.56	0.51 (0.61)
<i>Wave 3</i>	16.24 ± 0.68	16.21 ± 0.67	16.26 ± 0.70	1.49 (0.13)

BL, Baseline; FU1/FU2/FU3, Follow-Up 1/2/3; H-PPS, Higher-Psychosis Proneness Signs; L-PPS, Lower-Psychosis Proneness Signs; M/F, Male/Female; n.a., not assessed; SD, Standard Deviation. (*) marks $p < 0.05$, (**) marks $p < 0.01$, (***) marks $p < 0.001$.

coefficients of change (i.e. an intercept factor and a slope factor for each participant) were derived. The 28 personality-based coefficients of change estimated per participant fed a supervised machine learning algorithm built to predict PPS severity levels at FU3 (see Methods, 2.2.2).

Machine learning pipeline

We carried out our machine learning analytic strategy via NeuroMiner, version 1.05 (www.pronia.eu/neurominer/) (Antonucci et al., 2020; Koutsouleris et al., 2016). The 28 individual personality-based coefficients of change computed via LGCMs (see Methods, Section 'Latent Growth Curve Models pipeline') fed a Support Vector Machine algorithm aimed at predicting Higher- v. Lower-PPS at FU3 in our Discovery sample. We adopted a repeated nested cross-validation design (Antonucci et al., 2021; Koutsouleris et al., 2021) (see online SI, Section 5 for details) to generate a multivariate personality-based longitudinal risk calculator of psychosis proneness. Permutation analyses served to assign statistical significance to both PPS and extra labels prediction performance (Golland & Fischl, 2003; Koutsouleris et al., 2016) (see online SI, Section 6), measured through balanced accuracy (BAC). To assess the generalizability of our personality-based risk calculator, we applied the discovery prediction model to our independent validation sample via out-of-sample cross-validation (OOCV) (Antonucci et al., 2021; Haas et al., 2021).

To verify that generated predictions were not affected by potential confounds, we correlated individual prediction scores

extracted from the discovery risk calculator with BL measures for cognitive performance and substance use (see online SI, Section 5.1. for details). All significant p values were < 0.05 , false discovery rate (FDR)-corrected (Benjamini & Hochberg, 1995).

Personality-based predictions beyond psychosis proneness symptoms

To investigate whether the predictive performance of our personality-based risk calculator was associated with clinical read-outs outside PPS, we used ANOVAs on four different categories of prediction (i.e. two groups of correctly predicted v. two groups of misclassified individuals for higher- or lower-PPS) and the risk to develop emotional, conduct, hyperactivity and any other disorders at FU3. Such risk was estimated for individuals included in both the discovery and validation samples through the Development and Well-being Assessment Algorithm (Goodman, Ford, Richards, Gatward, & Meltzer, 2000) from the Strength and Difficulties Questionnaire items (Goodman, 1997). For details, see online SI, Sections 7,8.

Personality-based predictions within the schizophrenia risk trajectories

To assess the total effect between predictor and outcome, we preliminarily tested the association between polygenic liability for several psychiatric conditions and psychosis proneness via correlation

analyses (see online SI, Section 11); then, we investigated how putative relationships between polygenic risk for schizophrenia, exposure to victimization, and personality-based predictions may influence PPS. To this aim, we carried out a serial mediation analysis and two moderated mediation analyses via R statistics, using PROCESS Macro v. 4 (Hayes, 2017) (see online SI, Section 11 for details). All the models, depicted in online Supplementary Figure 2, were implemented only on 653 individuals with available genetic data out of the 784 included participants (see online Supplementary Table 3 for descriptive statistics). Individual genetic risk for schizophrenia was estimated using genetic data to calculate a PRS for schizophrenia (Purcell *et al.*, 2009; Pergola *et al.*, 2019) (see online SI, Section 9). To stratify individuals for chronic victimization, we computed the rank product of victimization total scores at BL, FU1, and FU2 (listed in online Supplementary Table 1, descriptive statistics in online Supplementary Table 4), collected through the Bully Questionnaire (details in online SI, Section 10). This score entered in our mediation framework as a second-order mediator or a moderator factor.

To test the modeled pathway generalizability, the very same serial mediation design was implemented on 1132 TRAILS individuals with available genetic data out of the 1546 included participants (online Supplementary Table 15). We generated two different models, respectively including the rank product of victimization scores at w2 and w3 as reported:

- by children via the Youth Self Report (Achenbach & Rescorla, 2006);
- by parents via the Child Behaviour Checklist (Achenbach & Rescorla, 2006).

Complete details are reported in online SI, Section 12.2 and 12.3.

Results

Demographic differences between samples

Demographic characteristics are separately reported for IMAGEN discovery and validation samples and for TRAILS replication cohort. The discovery sample featured a higher proportion of females in H-PPS than in L-PPS ($\chi^2 = 5.28$; $p = 0.02$) (Table 1A), whereas the TRAILS replication cohort featured a lower proportion ($\chi^2 = 23.17$; $p < 0.001$) (Table 1C). The validation sample included slightly older individuals in H-PPS than in L-PPS at FU2 ($t = 2$; $p = 0.046$) and at FU3 ($t = 2.45$; $p = 0.015$) (Table 1B).

Machine learning results

In the discovery sample, the risk calculator based on the 28 individual personality coefficients of change predicted higher-PPS *v.* lower-PPS at FU3 with a cross-validated BAC of 65.6% ($p = 0.01$) (detailed metrics in Table 2). Only PPS predictions showed a significant permuted p -value ($p < 0.05$). Features with the highest probability of being selected for prediction included individual intercept coefficients for neuroticism, followed by individual slope and intercept coefficients for openness (online Supplementary Figure 3). Figure 2 shows raw trajectories of change over time for neuroticism and openness for the first 10 individuals from the upper ≥ 0.95 and the lower ≤ 0.05 limits of the ensemble prediction probability scores distribution: the most prototypical individuals from, respectively, the higher-PPS and

the lower-PPS prediction class, showed opposite longitudinal patterns (*i.e.* increasing *v.* decreasing) for neuroticism, whereas they showed only mean differences between higher *v.* lower openness levels over time.

OOCV results (Methods, Section ‘Machine learning pipeline’) revealed that the discovery risk calculator showed high personality-based prediction performance also when applied to validation unseen individuals (BAC: 69.5%; detailed metrics in Table 2). Neither the discovery nor the validation predictions demonstrated inflation due to information leakage (see online SI, Section 5.2. for details). No significant association between prediction scores from the discovery risk calculator and scores at BL for cognitive performance (online Supplementary Table 8) and substance use (online Supplementary Table 9) emerged, suggesting that predictions were not affected by neuropsychological or substance use-related variables.

Personality-based predictions beyond psychosis proneness symptoms

In both discovery and validation samples, ANOVAs revealed a significant main effect of the prediction rate on scores for emotional and hyperactivity disorders risk at FU3 (all $p < 0.001$, specific F -statistics reported in online Supplementary Figure 4). Only individuals correctly predicted by the algorithm as Higher-PPS at FU3 also showed significantly higher risk scores at the same time point: specifically, this pattern occurred only for emotional disorders risk in the Discovery sample (online Supplementary Figure 4A) and for both emotional and hyperactivity disorders risk in the Validation sample (online Supplementary Figure 4C and 4D) (all $p < 0.001$). Only in the Discovery sample, correctly predicted and misclassified Higher-PPS individuals did not differ from each other in terms of estimated risk for hyperactivity disorders, both showing significantly higher scores at FU3 (online Supplementary Figure 4B) (all $p < 0.05$). No significant effect of the prediction index on scores of estimated risk for conduct (Discovery $F = 0.68$; $p = 0.56$; Validation $F = 0.21$; $p = 0.88$) or other disorders (Discovery $F = 0.84$; $p = 0.72$; Validation $F = 0.32$; $p = 0.61$) emerged at FU3.

Personality-based predictions within the schizophrenia risk trajectories

Our preliminary correlation analyses indicated that only the PRS for schizophrenia was significantly associated with PPS ($\rho = 0.12$; $p = 0.008$, FDR-corrected). Thus, we included it as the only predictor in our mediation models. As shown in Fig. 3A, for the IMAGEN serial mediation model, the total effect of the schizophrenia PRS on FU3 PPS severity levels was significant ($\beta = 0.14$; $p < 0.001$; bootstrapped 95% CI 0.06–0.22). Moreover, the direct effect of the schizophrenia PRS on FU3 PPS severity levels was significant when both the mediators were taken into account ($\beta = 0.08$; $p = 0.02$; bootstrapped 95% CI 0.01–0.15; 57.1% of the total effect explained (Fairchild, Mackinnon, Taborga, & Taylor, 2009; VanderWeele, 2013)). The remaining 42.9% of the total effect of the schizophrenia PRS on PPS was funneled in an indirect effect. As shown in online Supplementary Table 10, a significant indirect effect emerged within the serial mediation pathway including both personality-based predictions and victimization ($\beta = 0.004$, bootstrapped 95% CI 0.0006–0.01; 2.8% of effect explained). Also the pathway including only personality-based predictions showed a significant indirect effect,

Table 2. Validated performance of the personality-based risk calculator predicting Higher- v. Lower Psychosis Proneness Signs (PPS) in both Discovery and Validation samples

	True negatives	True positives	False negatives	False positives	Sensitivity	Specificity	Balanced accuracy (%)	Area under the curve	Positive Predictive Value	Negative Predictive Value	Positive Likelihood Ratio	Permuted p-value
Higher-PPS v. lower-PPS	159	186	79	102	70.2	60.9	65.6	0.71	64.6	66.8	1.8	0.01
Discovery sample												
Validation sample	93	85	31	49	73.3	65.5	69.4	0.72	63.4	75	2.1	n.a.

confirming the association discovered via machine learning ($\beta = 0.05$, bootstrapped 95% CI 0.02–0.09; 35.7% of effect explained). Instead, no significant indirect effect emerged when victimization was considered as the only mediator across the PRS-PPS pathway ($\beta = -0.002$, bootstrapped 95% CI 0.004–0.01), suggesting the relevance of personality scores in the serial mediation. No moderation effects from victimization emerged on the pathways toward final PPS (see online SI, Section 11 for detailed results).

In the replication on TRAILS data, as shown in online Supplementary Table 17 and 18, we found a significant indirect effect within the serial mediation pathway including both personality-based predictions and victimization, independently of the informants (Fig. 3B model: $\beta = 0.002$, bootstrapped 95% CI 0.0004–0.004; 20% of variance explained; Figure 3C model: $\beta = 0.001$, bootstrapped 95% CI 0.0002–0.003; 10% of variance explained). Moreover, the pathway including only personality-based predictions showed a significant indirect effect in both serial mediation models (Fig. 3B model: $\beta = 0.022$, bootstrapped 95% CI 0.005–0.04; Figure 3C model: $\beta = 0.02$, bootstrapped 95% CI 0.006–0.04). On the other hand, no significant indirect effect emerged when victimization was considered as the only mediator across the PRS-PPS pathway (Fig. 3B model: $\beta = -0.003$, bootstrapped 95% CI -0.01 to -0.003 ; Figure 3C model: $\beta = 0.002$, bootstrapped 95% CI -0.003 to -0.008).

Discussion

This study aimed to investigate whether patterns of neurodevelopmental changes in dynamic intrinsic factors like personality may predict adult PPS and whether this prediction ability has a role in gene-environment interplays relevant to schizophrenia. After separating our population based on PPS severity levels, significant between-group differences for raw personality features emerged already at the cross-sectional level. However, findings from our longitudinal risk calculator showed that, in the Discovery sample, higher and lower PPS levels in young adulthood can be accurately predicted through personality and temperament trajectories of change across adolescence. Interestingly, these factors, traditionally considered relatively stable (Hampson & Goldberg, 2006), have been recently reconceptualized as sensitive to change and adaptation, especially throughout adolescence (Caspi, Roberts, & Shiner, 2005; Durbin et al., 2016; Zohar, Zwir, Wang, Cloninger, & Anokhin, 2019). Our longitudinal fingerprint supports this notion and, providing individual predictions, complements group-level cross-sectional evidence of associations between PPS in healthy adolescents and personality (Wiltink et al., 2015) or temperament (Nitzburg et al., 2016). The good validation performance of our risk calculator, when applied to unseen individuals, corroborates its generalizability potential. Indeed, the validation BAC of 69.5% is consistent with the standards reported in previous meta-analyses on machine learning prognostic models built on at-risk individuals (Sanfelici, Dwyer, Antonucci, & Koutsouleris, 2020).

Neuroticism (i.e. the vulnerability to emotional instability and negative emotionality (Begemann, Boyette, Kwast, & Sommer, 2020)) and openness (i.e. the availability to new ideas and experiences (Begemann et al., 2020)) emerged as the two personality traits most contributing to longitudinal predictions of PPS levels. Their prominent role in our algorithm is consistent with large-scale studies identifying genetic risk loci shared between schizophrenia and these two personality traits (Lo et al., 2017; Smeland et al., 2017). Accordingly, these traits are associated with psychosis-related manifestations (i.e. symptoms or

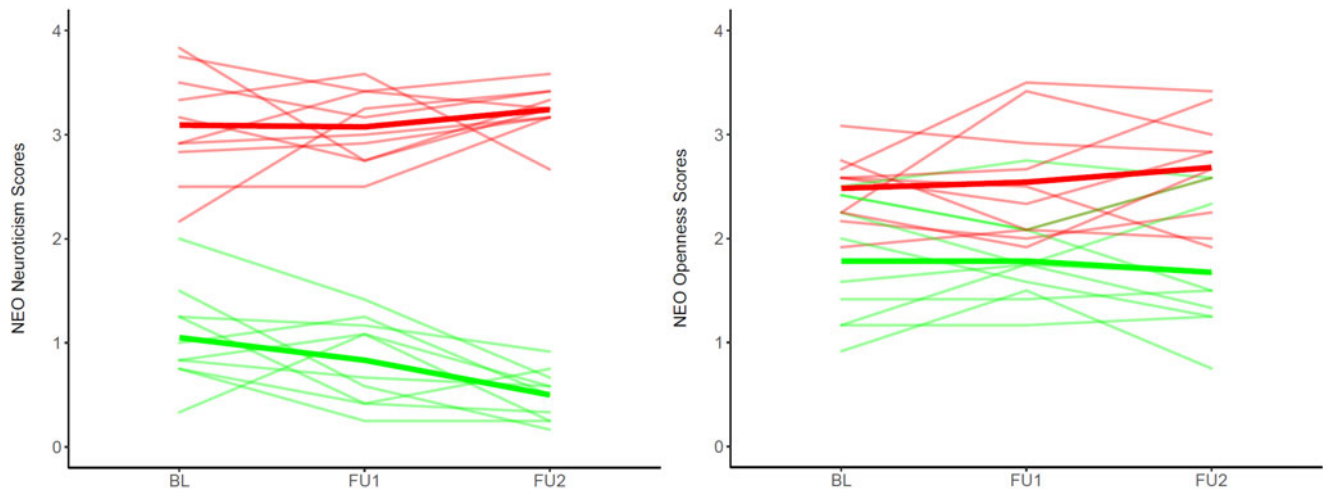


Figure 2. Raw trajectories of change over time for NEO neuroticism scores (left panel) and NEO openness scores (right panel) for the first ten individuals from the upper and the lower limits of the Ensemble Probability Prediction (EPP) scores distribution: notably, as an EPP score from 0.95 above estimated a probability to be assigned to the Higher-Psychosis Proneness Signs (PPS) class in the 95% of the generated models, we considered such individuals as highly prototypical for such severity class (red lines; the red line in bold depicts the group mean trajectory); as an EPP score from 0.5 below estimated a probability to be assigned to the Higher-PPS class in the 5% of the generated models, we considered such individuals as highly prototypical of the Lower-PPS severity class (green lines; the green line in bold depicts the group mean trajectory) BL, Baseline; FU1, Follow-Up 1; FU2, Follow-Up 2; NEO, NEO Five Factor Inventory.

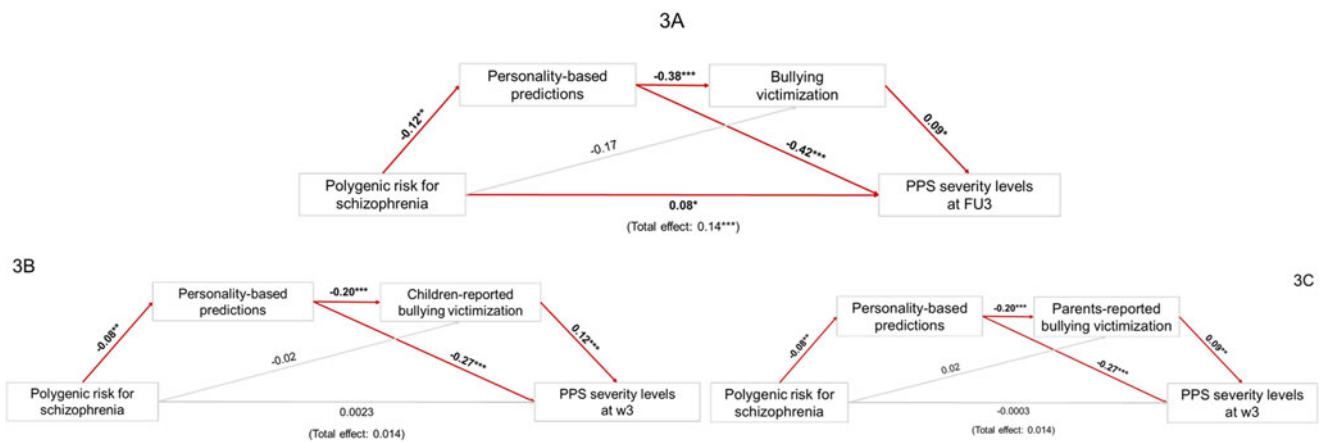


Figure 3. Findings from the serial mediation models, investigating the role of personality-based machine learning predictions and the rank product of Bullying Victimization (BV) within the pathway between polygenic risk for schizophrenia and final Psychosis Proneness Signs. **Figure 3A** depicted the model generated on IMAGEN data, **Fig. 3B** and **3C** depicted replication models generated on TRAILS data, respectively including children-reported and parents-reported BV information. Direct effects (standardized coefficients) are shown. Red arrows represent relationships returning significant direct effects. The grey arrows represent not significant direct effects. Indirect effects for each model are reported in online Supplementary Table 10 (IMAGEN model), 17, and 18 (TRAILS replication models). FU3, Follow-Up 3; PPS, Psychosis Proneness Signs; w3, wave 3. *marks $p < 0.05$; **marks $p < 0.01$; ***marks $p < 0.001$.

subclinical PPS severity, and perceived quality of life) in clinical (Franquillo et al., 2021) and healthy populations (Wiltink et al., 2015). Notably, the evolution of these traits over adolescence contributed to the predictions, suggesting that tracking these traits over time enhances early identification. When we compared the most prototypical Higher-PPS and Lower-PPS individuals, the strict separation of longitudinal neuroticism trajectories between the two groups suggested that individuals with higher starting neuroticism scores, and consistently high scores over time, have higher future risk for psychosis. Higher neuroticism is frequently self-reported by individuals prone to negative emotionality and distress (Boyette et al., 2013). This trait may represent a transdiagnostic risk factor for future psychopathology. High scores on openness have been associated with positive schizotypy and

magical thinking (Wiltink et al., 2015) in non-clinical samples (Larøi, DeFruyt, van Os, Aleman, & Van der Linden, 2005; Ross, Lutz, & Bailey, 2002). High openness characterized Higher-PPS individuals in our study but evolved in more heterogeneous within- and between-group trajectories over time. In summary, our findings suggest that the evolution of specific personality traits during adolescence might contribute to future PPS. From a clinical perspective, self-reported neuroticism correlates with maladaptive strategies of emotion regulation (e.g. rumination, self-blaming, suppression (Ludwig, Werner, & Lincoln, 2019)). The same phenomena are reported at different stages of psychosis (Chapman et al., 2020; Vines et al., 2022) and associated with delusion severity in psychotic patients (Garety et al., 2005). It follows that psychoeducational skills training, promoting

effective management of negative emotions in such individuals, might contribute to delaying or softening the negative consequences of PPS.

Interestingly, although our algorithm was specific for PPS predictions, neuroticism and openness changes showed potential clinical relevance also for other risk conditions potentially associated with PPS. Indeed, individuals correctly classified as Higher-PPS based on personality changes consistently showed a significantly higher estimated risk of developing emotional and hyperactivity disorders in young adulthood, as also reported previously (Christiansen et al., 2019; Fox, Sheffield, & Woodward, 2021).

Finally, we integrated our longitudinal personality-based predictions in a serial mediation framework including both genetic and environmental features. We found that PPS predictions based on adolescent personality changes were associated with self-reported victimization, and both prediction and victimization serially mediated the relationship between schizophrenia PRS and adult PPS severity. The schizophrenia PRS was also the only one significantly associated with PPS. We cannot exclude that the large sample size of the latest schizophrenia GWAS and the high heritability of this disorder played a role in such a significant effect. Interestingly, the serial mediation effect also emerged when the same mediation design was replicated on the data collected within the external TRAILS cohort, regardless of the different victimization informants (e.g. children or their parents) (Lella et al., 2023) and further methodological differences, confirming the association discovered via machine learning. It is noteworthy that Pergola et al. (2019) described a similar gene-environment correlation without including personality. That study found a victimization-mediated effect of schizophrenia PRS on the frequency of PPS developed at the last accessible time point, including a correlation between PRS and bullying victimization. The PRS-bullying association in TRAILS was not significant when considering personality as a mediator. This evidence suggests that the mechanism of translating genetic risk into environmental risk involves personality traits and their development during adolescence. The lack of a direct PRS-PPS association in TRAILS, whereas it was significant in IMAGEN, is of interest to future research on the assessment of potential critical periods: indeed, demographic differences between the two cohorts (IMAGEN BL-FU3 age: 13.9–22 y.o.; TRAILS w1-w3 age: 11.1–16.2 y.o.; Table 1) overlap with the mixed results on genetic associations obtained in the ALSPAC cohort when data from 13-year olds were included (Schoeler et al., 2019) or not (Riglin et al., 2019). Genetic effects on social patterns characteristic of adolescence may still be too small for detection with the sample sizes employed here in very young individuals. This age specificity would be consistent with other evidence of effects emerging in functional brain imaging only in later adolescence (Passiatore et al., 2023; Zalesky et al., 2015). Nonetheless, the successful replication of the rest of the pathways within the model speaks in favor of its validity and generalizability.

In summary, our results explain the previously reported link (Pergola et al., 2019) between victimization and genetic risk to develop later PPS as a mechanism based on personality. While the PRS of the risk carriers cannot influence the behavior of other individuals, it can influence personality traits and thus the behavioral manifestation of risk, hence explaining the significant associations with victimization. Personality appears as a privileged interface between the polygenic risk for schizophrenia and social adversities. Genetic risk carriers express personality traits

predictive of PPS and also suffer a greater environmental burden. This hypothesis was further corroborated by the peer victimization significance as mediator and not moderator, tested on the main IMAGEN cohort data, at variance with previous evidence (Guloksuz et al., 2019). Thus, the environment in this model amplifies genetic risk as in an evocative gene-environment correlation framework, whereby the reactions of the peers to heritable traits expressed by the carrier enhance risk. The small indirect effect on final PPS captured by the risk pathway, including personality and victimization, suggests that the measures of social environment employed picked up only a very modest portion of the environmental contribution to PPS. Thus, while victimization accounts only for a minor proportion of PPS risk, other gene-environment correlation mechanisms may contribute to reduce the heritability gap, identify pathways of genetic risk to environmental exposure, and devise personalized interventions to foster resilience.

Limitations

To the best of our knowledge, our model of gene-environment correlation informed by personality is the first of its kind. Thus, despite the stringent cross-validation strategy employed and the external replication of our results implemented on TRAILS data, validations in wider naturalistic populations are needed to fulfill generalizability requirements and findings translation into clinical practice (Sanfelici et al., 2020). As bullying is not the only social stressor potentially contributing to psychosis risk, future replications might model PPS vulnerability pathways including additional core factors of social adversity, such as childhood trauma, discrimination, and exclusion (Varchmin, Montag, Treusch, Kaminski, & Heinz, 2021). Additional replications are also recommended for data collections that provide (i) more than three time points to model nonlinear personality change (Durbin et al., 2016), and (ii) a more extensive personality assessment, tapping into traits based on different personality theories.

Conclusions

Our findings outline a dynamic model of PPS risk development based on a 'personality-enriched' gene-environment correlation pathway: genetic factors may act on PPS through an effect on adolescent personality changes, which in turn could modulate the exposure to negative social interactions. For this reason, our findings highlight the importance of monitoring the evolution of personality traits over time. We found that the increase or stability of high neuroticism and openness across adolescence are relevant to future psychosis proneness. Personality development is strictly entangled with environmental challenges. Thus, we envision that real-world programs aimed at softening the downstream effects of an increased genetic risk for psychosis might be oriented toward (i) early identification and management of maladaptive social environments during adolescence and (ii) promoting adaptation to social adversities in subjects with high neuroticism and openness, particularly when victimized by peers.

Disclosures

Prof Pergola received lecture fees from Lundbeck. Prof. Bertolino received consulting fees from Biogen and lecture fees from Otsuka, Janssen, and Lundbeck. Prof. Rampino received travel fees from Lundbeck. Dr Banaschewski served in an advisory or

consultancy role for eye level, Infectopharm, Lundbeck, Medice, Neurim Pharmaceuticals, Oberberg GmbH, Roche, and Takeda. He received conference support or speaker's fee by Janssen, Medice and Takeda. He received royalties from Hogrefe, Kohlhammer, CIP Medien, and Oxford University Press; the present work is unrelated to these relationships. Dr Poustka served in an advisory or consultancy role for Roche and Viforpharm and received speaker's fee by Shire. She received royalties from Hogrefe, Kohlhammer and Schattauer. The present work is unrelated to the above grants and relationships. The other authors report no biomedical financial interests or potential conflicts of interest.

Supplementary material. The supplementary material for this article can be found at <https://doi.org/10.1017/S0033291724002198>.

Funding statement. This work received support from the funding initiative FAIR-Future Artificial Intelligence Research (PNRR 'Partenariati Estesi') for the project H97G22000210007 to GP and LAA, Horizon Europe Seeds 2021 (Next Generation EU - MUR D.M. 737/2021) for the project H99J21017550006 to GP, LAA, AR and AB, EXPRIVIA for the research program: 'Artificial intelligence, genetics and transcriptomics' to GP, and the Apulian regional government for the project: 'Early Identification of Psychosis Risk' to AB.

This work also received funding from the European Union through the FP6 Integrated Project IMAGEN (Reinforcement-related behaviour in normal brain function and psychopathology) (LSHM-CT- 2007-037286), the Horizon 2020 funded ERC Advanced Grant 'STRATIFY' (Brain network based stratification of reinforcement-related disorders) (695313), Human Brain Project (HBP SGA 2, 785907, and HBP SGA 3, 945539), the Medical Research Council Grant 'c-VEDA' (Consortium on Vulnerability to Externalizing Disorders and Addictions) (MR/N000390/1), the National Institute of Health (NIH) (R01DA049238, A decentralized macro and micro gene-by-environment interaction analysis of substance use behavior and its brain biomarkers), the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London, the Bundesministerium für Bildung und Forschung (BMBF grants 01GS08152; 01EV0711; Forschungsnetz AERIAL 01EE1406A, 01EE1406B; Forschungsnetz IMAC-Mind 01GL1745B), the Deutsche Forschungsgemeinschaft (DFG grants SM 80/7-2, SFB 940, TRR 265, NE 1383/14-1), the Medical Research Foundation and Medical Research Council (grants MR/R00465X/1 and MR/S020306/1), the National Institutes of Health (NIH) funded ENIGMA (grants 5U54EB020403-05 and 1R56AG058854-01), NSFC grant 82150710554 and European Union funded project 'enviROMENTAL', grant no: 101057429. Further support was provided by grants from: - the ANR (ANR-12-SAMA-0004, AAPG2019 - GeBra), the Erantet Neuron (AF12-NEUR0008-01 - WM2NA; and ANR-18-NEUR0002-01 - ADORé), the Fondation de France (00081242), the Fondation pour la Recherche Médicale (DPA20140629802), the Mission Interministérielle de Lutte-contre-les-Drogues-et-les-Conduites-Addictives (MILDECA), the Assistance-Publique-Hôpitaux-de-Paris and INSERM (interface grant), Paris Sud University IDEX 2012, the Fondation de l'Avenir (grant AP-RM-17-013), the Fédération pour la Recherche sur le Cerveau; the National Institutes of Health, Science Foundation Ireland (16/ERC/3797), U.S.A. (Axon, Testosterone and Mental Health during Adolescence; RO1 MH085772-01A1) and by NIH Consortium grant U54 EB020403, supported by a cross-NIH alliance that funds Big Data to Knowledge Centres of Excellence. ImagenPathways 'Understanding the Interplay between Cultural, Biological and Subjective Factors in Drug Use Pathways' is a collaborative project supported by the European Research Area Network on Illicit Drugs (ERANID). This paper is based on independent research commissioned and funded in England by the National Institute for Health Research (NIHR) Policy Research Programme (project ref. PR-ST-0416-10001). The views expressed in this article are those of the authors and not necessarily those of the national funding agencies or ERANID.

This research is also part of the project 'Tracking Adolescents' Individual Lives Survey (TRAILS). Participating centers of TRAILS include various departments of the University Medical Center and University of Groningen, the University of Utrecht, the Radboud University Medical Center, and the Parnassia Psychiatric Institute, all in the Netherlands. TRAILS has been

financially supported by various grants from the Netherlands Organization for Scientific Research (NWO), ZonMW, GB-MaGW, the Dutch Ministry of Justice, the European Science Foundation, the European Research Council, BMMRI-NL, and the participating universities. We are grateful to everyone who participated in this research or worked on this project to make it possible.

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

¹Department of Translational Biomedicine and Neuroscience – University of Bari Aldo Moro, Bari, Italy; ²Psychiatry Unit – Policlinico di Bari, Bari, Italy; ³Department of Child and Adolescent Psychiatry and Psychotherapy, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany; ⁴Discipline of Psychiatry, School of Medicine and Trinity College Institute of Neuroscience, Trinity College Duin, Dublin, Ireland; ⁵Centre for Population Neuroscience and Precision Medicine (PONS), Institute of Psychiatry, Psychology & Neuroscience, SGDP Centre, King's College London, UK; ⁶Institute of Cognitive and Clinical Neuroscience, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany; ⁷Department of Psychology, School of Social Sciences, University of Mannheim, Mannheim, Germany; ⁸NeuroSpin, CEA, Université Paris-Saclay, Gif-sur-Yvette, France; ⁹Departments of Psychiatry and Psychology, University of Vermont, Burlington, Vermont, USA; ¹⁰Department of Psychiatry and Psychotherapy CCM, Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany; ¹¹Institut National de la Santé et de la Recherche Médicale, INSERM U 1299 "Trajectoires développementales & psychiatrie", University Paris-Saclay, CNRS, France; ¹²Ecole Normale Supérieure Paris-Saclay, Centre Borelli; Gif-sur-Yvette, France; ¹³Sorbonne University, Department of Child and Adolescent Psychiatry, Pitié-Salpêtrière Hospital, Paris; France; ¹⁴Psychiatry Department, EPS Barthélémy Durand, Etampes; France; ¹⁵Institute of Medical Psychology and Medical Sociology, University Medical Center Schleswig Holstein, Kiel University, Kiel, Germany; ¹⁶Department of Child and Adolescent Psychiatry and Psychotherapy, University Medical Centre Göttingen, Göttingen, Germany; ¹⁷Department of Child and Adolescent Psychiatry, Psychotherapy and Psychosomatics, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; ¹⁸Department of Psychiatry and Neuroimaging Center, Technische Universität Dresden, Dresden, Germany; ¹⁹Centre for Population Neuroscience and Stratified Medicine (PONS), Department of Psychiatry and Neuroscience, Charité Universitätsmedizin Berlin, Germany; ²⁰School of Psychology and Global Brain Health Institute, Trinity College Dublin, Ireland; ²¹Centre for Population Neuroscience and Precision Medicine (PONS), Institute for Science and Technology of Brain-inspired Intelligence (ISTBI), Fudan University, Shanghai, China; ²²Interdisciplinary Center Psychopathology and Emotion regulation, Department of Psychiatry, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; ²³Lieber Institute for Brain Development, Johns Hopkins Medical Campus, Baltimore, MD, USA and ²⁴Department of Psychiatry and Behavioral Science – John Hopkins University, Baltimore, MD, USA

References

- Achenbach, T. M., & Rescorla, L. A. (2006). The Achenbach System of Empirically Based Assessment. In R. P. Archer (Ed.), **Forensic uses of clinical assessment instruments** (pp. 229–262). Mahwah, New Jersey, US: Lawrence Erlbaum Associates Publishers.
- Allison, P. D. (1987). Estimation of linear models with incomplete data. *Sociological Methodology*, 17, 71–103.
- Antonucci, L. A., Pergola, G., Pigoni, A., Dwyer, D., Kambeitz-Ilanovic, L., Penzel, N., ... Bertolino, A. (2020). A pattern of cognitive deficits stratified for genetic and environmental risk reliably classifies patients with schizophrenia with healthy control subjects. *Biological Psychiatry*, 87(8), 697–707. doi:10.1016/j.biopsych.2019.11.007
- Antonucci, L. A., Raio, A., Pergola, G., Gelao, B., Papalino, M., Rampino, A., ... Bertolino, A. (2021). Machine learning-based ability to classify psychosis

- and early stages of disease through parenting and attachment-related variables is associated with social cognition. *BMC Psychology*, 9(1), 47. doi:10.1186/s40359-021-00552-3
- Armitage, J. M., Morneau-Vaillancourt, G., Pingault, J. B., Andlauer, T. F. M., Paquin, S., Langevin, S., ... Boivin, M. (2022). A multi-informant and multi-polygenic approach to understanding predictors of peer victimisation in childhood and adolescence. *Journal of Child Psychiatry & Psychology Advances*, 2(1), e12063. doi:10.1002/jcv2.12063
- Barrantes-Vidal, N., Racioppi, A., & Kwapił, T. R. (2020). Schizotypy, schizotypal personality, and psychosis risk. In A. D. Thompson & M. R. Broome (Eds.), *Risk factors for psychosis* (pp. 81–99). San Diego, CA: Elsevier Academic Press.
- Begemann, M.J.H., Boyette, L.-L., Kwast, A.K., & Sommer, I.E.C. (2020). Personality across the psychosis continuum: A fine-grained perspective. *Schizophrenia Bulletin Open*, 1(1), sgaa064.
- Benjamini, Y., & Hochberg, Y. (1995). Controlling the false discovery rate: A practical and powerful approach to multiple testing. *Journal of the Royal Statistical Society: Series B (Methodological)*, 57(1), 289–300.
- Bonnett, L. J., Varese, F., Smith, C. T., Flores, A., & Yung, A. R. (2019). Individualised prediction of psychosis in individuals meeting at-risk mental state (ARMS) criteria: Protocol for a systematic review of clinical prediction models. *Diagnostic and Prognostic Research*, 3, 21. doi:10.1186/s41512-019-0066-5
- Bourgin, J., Tebeka, S., Mallet, J., Mazer, N., Dubertret, C., & Le Strat, Y. (2020). Prevalence and correlates of psychotic-like experiences in the general population. *Schizophrenia Research*, 215, 371–377. doi:10.1016/j.schres.2019.08.024
- Boyette, L.-L., Korver-Nieberg, N., Verweij, K., Meijer, C., Dingemans, P., Cahn, W., & de Haan, L. (2013). Associations between the Five-Factor Model personality traits and psychotic experiences in patients with psychotic disorders, their siblings and controls. *Psychiatry Research*, 210(2), 491–497.
- Burant, C. J. (2016). Latent growth curve models: Tracking changes over time. *International Journal of Aging & Human Development*, 82(4), 336–350. doi:10.1177/0091415016641692
- Caspi, A., Roberts, B. W., & Shiner, R. L. (2005). Personality development: Stability and change. *Annual Review of Psychology*, 56, 453–484. doi:10.1146/annurev.psych.55.090902.141913
- Chapman, H. C., Visser, K. F., Mittal, V. A., Gibb, B. E., Coles, M. E., & Strauss, G. P. (2020). Emotion regulation across the psychosis continuum. *Development and Psychopathology*, 32(1), 219–227. doi:10.1017/S0954579418001682
- Christiansen, L., Beck, M. M., Bilenberg, N., Wienecke, J., Astrup, A., & Lundbye-Jensen, J. (2019). Effects of exercise on cognitive performance in children and adolescents with ADHD: Potential mechanisms and evidence-based recommendations. *Journal of Clinical Medicine*, 8(6), 841. doi:10.3390/jcm8060841
- Cloninger, C. R., Svrakic, D. M., & Przybeck, T. R. (1993). A psychobiological model of temperament and character. *Archives of General Psychiatry*, 50(12), 975–990. doi:10.1001/archpsyc.1993.01820240059008
- Costa, P.T., & McCrae, R.R. (1992). Normal personality assessment in clinical practice: The NEO Personality Inventory. *Psychological Assessment*, 4(1), 5.
- Durbin, C. E., Hicks, B. M., Blonigen, D. M., Johnson, W., Iacono, W. G., & McGue, M. (2016). Personality trait change across late childhood to young adulthood: Evidence for nonlinearity and sex differences in change. *European Journal of Personality*, 30(1), 31–44. doi:10.1002/per.2013
- Dwyer, D. B., Falkai, P., & Koutsouleris, N. (2018). Machine learning approaches for clinical psychology and psychiatry. *Annual Review of Clinical Psychology*, 14, 91–118. doi:10.1146/annurev-clinpsy-032816-045037
- Fairchild, A. J., Mackinnon, D. P., Taborga, M. P., & Taylor, A. B. (2009). R2 effect-size measures for mediation analysis. *Behavior Research Methods*, 41(2), 486–498. doi:10.3758/BRM.41.2.486
- Farmer, R.F., & Goldberg, L.R. (2008). A psychometric evaluation of the revised Temperament and Character Inventory (TCI-R) and the TCI-140. *Psychological Assessment*, 20(3), 281.
- Felt, J. M., Depaoli, S., & Tiemensma, J. (2017). Latent growth curve models for biomarkers of the stress response. *Frontiers in Neuroscience*, 11, 315. doi:10.3389/fnins.2017.00315
- Fonseca-Pedrero, E., Ortuno-Sierra, J., Inchausti, F., Rodriguez-Testal, J. F., & Debbane, M. (2019). Beyond clinical high-risk state for psychosis: The network structure of multidimensional psychosis liability in adolescents. *Frontiers in Psychiatry*, 10, 967. doi:10.3389/fpsyt.2019.00967
- Fox, V., Sheffield, J. M., & Woodward, N. D. (2021). Attention-deficit/hyperactivity disorder in youth with psychosis spectrum symptoms. *Schizophrenia Research*, 237, 141–147. doi:10.1016/j.schres.2021.08.027
- Franquillo, A. C., Guccione, C., Angelini, G., Carpentieri, R., Ducci, G., & Caretti, V. (2021). The role of personality in schizophrenia and psychosis: A systematic review. *Clinical Neuropsychiatry*, 18(1), 28–40. doi:10.36131/cnforiteditore20210103
- Garety, P. A., Freeman, D., Jolley, S., Dunn, G., Bebbington, P. E., Fowler, D. G., ... Dudley, R. (2005). Reasoning, emotions, and delusional conviction in psychosis. *Journal of Abnormal Psychology*, 114(3), 373–384. doi:10.1037/0021-843X.114.3.373
- Golland, P., & Fischl, B. (2003). Permutation tests for classification: Towards statistical significance in image-based studies. *Information Processing in Medical Imaging*, 18, 330–341. doi:10.1007/978-3-540-45087-0_28
- Goodman, R. (1997). The strengths and difficulties questionnaire: A research note. *Journal of Child Psychology and Psychiatry*, 38(5), 581–586. doi:10.1111/j.1469-7610.1997.tb01545.x
- Goodman, R., Ford, T., Richards, H., Gatward, R., & Meltzer, H. (2000). The Development and Well-Being Assessment: Description and initial validation of an integrated assessment of child and adolescent psychopathology. *Journal of Child Psychology and Psychiatry*, 41(5), 645–655.
- Guloksuz, S., Pries, L. K., Delespaul, P., Kenis, G., Luyckx, J. J., Lin, B. 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(2), 173–182. doi:10.1002/wps.20629
- Haas, S. S., Antonucci, L. A., Wenzel, J., Ruef, A., Biagianti, B., Paolini, M., ... Kambeitz-Illankovic, L. (2021). A multivariate neuromonitoring approach to neuroplasticity-based computerized cognitive training in recent onset psychosis. *Neuropsychopharmacology*, 46(4), 828–835. doi:10.1038/s41386-020-00877-4
- Hampson, S. E., & Goldberg, L. R. (2006). A first large cohort study of personality trait stability over the 40 years between elementary school and midlife. *Journal of Personality and Social Psychology*, 91(4), 763–779. doi:10.1037/0022-3514.91.4.763
- Hayes, A. F. (2017). *Introduction to mediation, moderation, and conditional process analysis: A regression-based approach*. New York: Guilford publications.
- Howes, O. D., & Murray, R. M. (2014). Schizophrenia: An integrated sociodevelopmental-cognitive model. *Lancet (London, England)*, 383(9929), 1677–1687. doi:10.1016/S0140-6736(13)62036-X
- International Schizophrenia Consortium, Purcell, S. M., Wray, N. R., Stone, J. L., Visscher, P. M., O'Donovan, M. C., ... Sklar, P. (2009). Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature*, 460(7256), 748–752. doi:10.1038/nature08185
- Koutsouleris, N., Dwyer, D. B., Degenhardt, F., Maj, C., Urquijo-Castro, M. F., Sanfelici, R., ... the PRONIA Consortium. (2021). Multimodal machine learning workflows for prediction of psychosis in patients with clinical high-risk syndromes and recent-onset depression. *JAMA Psychiatry*, 78(2), 195–209. doi:10.1001/jamapsychiatry.2020.3604
- Koutsouleris, N., Kahn, R. S., Chekroud, A. M., Leucht, S., Falkai, P., Wobrock, T., ... Hasan, A. (2016). Multisite prediction of 4-week and 52-week treatment outcomes in patients with first-episode psychosis: A machine learning approach. *The Lancet. Psychiatry*, 3(10), 935–946. doi:10.1016/S2215-0366(16)30171-7
- Larøi, F., DeFruyt, F., van Os, J., Aleman, A., & Van der Linden, M. (2005). Associations between hallucinations and personality structure in a non-clinical sample: Comparison between young and elderly samples. *Personality and Individual Differences*, 39(1), 189–200.
- Lella, A., Antonucci, L.A., Pergola, G. (2023). The interpretation of discrepancies between peer victimization experiences reported by different informants in capturing victimization-related genetic liability. A commentary on Armitage et al. (2022). *Journal of Child Psychology and Psychiatry Advances*, 3(1), e12137.
- Lichtenstein, P., Yip, B. H., Bjork, C., Pawitan, Y., Cannon, T. D., Sullivan, P. F., & Hultman, C. M. (2009). Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: A population-based study. *Lancet (London, England)*, 373(9659), 234–239. doi:10.1016/S0140-6736(09)60072-6

- Lo, M. T., Hinds, D. A., Tung, J. Y., Franz, C., Fan, C. C., Wang, Y., ... Chen, C. H. (2017). Genome-wide analyses for personality traits identify six genomic loci and show correlations with psychiatric disorders. *Nature Genetics*, 49(1), 152–156. doi:10.1038/ng.3736
- Loch, A. A., Wang, Y. P., Rossler, W., Tofoli, L. F., Silveira, C. M., & Andrade, L. H. (2011). The psychosis continuum in the general population: Findings from the Sao Paulo Epidemiologic Catchment Area Study. *European Archives of Psychiatry and Clinical Neuroscience*, 261(7), 519–527. doi:10.1007/s00406-011-0204-8
- Ludwig, L., Werner, D., & Lincoln, T. M. (2019). The relevance of cognitive emotion regulation to psychotic symptoms—A systematic review and meta-analysis. *Clinical Psychology Review*, 72, 101746. doi:10.1016/j.cpr.2019.101746
- Mark, W., & Touloupoulou, T. (2016). Psychometric properties of “community assessment of psychic experiences”: Review and meta-analyses. *Schizophrenia Bulletin*, 42(1), 34–44. doi:10.1093/schbul/sbv088
- McGrath, J. J., Saha, S., Al-Hamzawi, A., Alonso, J., Bromet, E. J., Bruffaerts, R., ... Kessler, R. C. (2015). Psychotic experiences in the general population: A Cross-National analysis based on 31261 respondents from 18 countries. *JAMA Psychiatry*, 72(7), 697–705. doi:10.1001/jamapsychiatry.2015.0575
- McGrath, J. J., Saha, S., Al-Hamzawi, A. O., Alonso, J., Andrade, L., Borges, G., ... Kessler, R. C. (2016). Age of onset and lifetime projected risk of psychotic experiences: Cross-national data from the world mental health survey. *Schizophrenia Bulletin*, 42(4), 933–941. doi:10.1093/schbul/sbw011
- Millan, M. J., Andreux, A., Bartzokis, G., Cadenhead, K., Dazzan, P., Fusar-Poli, P., ... Weinberger, D. (2016). Altering the course of schizophrenia: Progress and perspectives. *Nature Reviews. Drug Discovery*, 15(7), 485–515. doi:10.1038/nrd.2016.28
- Nitzburg, G.C., Gopin, C.B., Peters, B.D., Karlsgodt, K.H., Malhotra, A.K., & DeRosse, P. (2016). The relationship between temperament and character and psychotic-like experiences in healthy children and adolescents. *European Psychiatry: the Journal of the Association of European Psychiatrists*, 31, 60–65.
- Nuevo, R., Van Os, J., Arango, C., Chatterji, S., & Ayuso-Mateos, J. L. (2013). Evidence for the early clinical relevance of hallucinatory-delusional states in the general population. *Acta psychiatrica Scandinavica*, 127(6), 482–493. doi:10.1111/acps.12010
- Passioure, R., Antonucci, L. A., DeRamus, T. P., Fazio, L., Stolfi, G., Sportelli, L., ... Pergola, G. (2023). Changes in patterns of age-related network connectivity are associated with risk for schizophrenia. *Proceedings of the National Academy of Sciences of the United States of America*, 120(32), e2221533120. doi:10.1073/pnas.2221533120
- Pergola, G., Papalino, M., Gelao, B., Sportelli, L., Vollerbergh, W., Grattagliano, I., & Bertolino, A. (2019). Evocative gene-environment correlation between genetic risk for schizophrenia and bullying victimization. *World Psychiatry*, 18(3), 366–367. doi:10.1002/wps.20685
- Pergola, G., Penzel, N., Sportelli, L., & Bertolino, A. (2023). Lessons learned from parsing genetic risk for schizophrenia into biological pathways. *Biological Psychiatry*, 94(2), 121–130. doi:10.1016/j.biopsych.2022.10.009
- Plomin, R., DeFries, J. C., & Loehlin, J. C. (1977). Genotype-environment interaction and correlation in the analysis of human behavior. *Psychological Bulletin*, 84(2), 309–322.
- Raad, B. d., & Perugini, M. (Eds.). (2002). Big five factor assessment: Introduction. In *Big five assessment* (pp. 1–18). Cambridge, MA: Hogrefe & Huber Publishers.
- Riglin, L., Hammerton, G., Heron, J., Collishaw, S., Arseneault, L., Thapar, A. K., ... Thapar, A. (2019). Developmental contributions of schizophrenia risk alleles and childhood peer victimization to early-onset mental health trajectories. *American Journal of Psychiatry*, 176(1), 36–43. doi:10.1176/appi.ajp.2018.18010075
- Roberts, B. W., Caspi, A., & Moffitt, T. E. (2001). The kids are alright: Growth and stability in personality development from adolescence to adulthood. *Journal of Personality and Social Psychology*, 81(4), 670–683.
- Ross, S. R., Lutz, C. J., & Bailey, S. E. (2002). Positive and negative symptoms of schizotypy and the Five-factor model: A domain and facet level analysis. *Journal of Personality Assessment*, 79(1), 53–72. doi:10.1207/S15327752JPA7901_04
- Sanfelici, R., Dwyer, D. B., Antonucci, L. A., & Koutsouleris, N. (2020). Individualized diagnostic and prognostic models for patients with psychosis risk syndromes: A meta-analytic view on the state of the art. *Biological Psychiatry*, 88(4), 349–360. doi:10.1016/j.biopsych.2020.02.009
- Schoeler, T., Choi, S. W., Dudbridge, F., Baldwin, J., Duncan, L., Cecil, C. M., ... Pingault, J. B. (2019). Multi-Polygenic score approach to identifying individual vulnerabilities associated with the risk of exposure to bullying. *JAMA Psychiatry*, 76(7), 730–738. doi:10.1001/jamapsychiatry.2019.0310
- Schumann, G., Loth, E., Banaschewski, T., Barbot, A., Barker, G., Buchel, C., ... the IMAGEN consortium. (2010). The IMAGEN study: Reinforcement-related behaviour in normal brain function and psychopathology. *Molecular Psychiatry*, 15(12), 1128–1139. doi:10.1038/mp.2010.4
- Smeland, O. B., Wang, Y., Lo, M. T., Li, W., Frei, O., Witoelar, A., ... Andreassen, O. A. (2017). Identification of genetic loci shared between schizophrenia and the Big Five personality traits. *Scientific Reports*, 7(1), 2222. doi:10.1038/s41598-017-02346-3
- Solmi, M., Radua, J., Olivola, M., Croce, E., Soardo, L., Salazar de Pablo, G., ... Fusar-Poli, P. (2022). Age at onset of mental disorders worldwide: Large-scale meta-analysis of 192 epidemiological studies. *Molecular Psychiatry*, 27(1), 281–295. doi:10.1038/s41380-021-01161-7
- Stefanis, N. C., Hanssen, M., Smirnis, N. K., Avramopoulos, D. A., Evdokimidis, I. K., Stefanis, C. N., ... Van Os, J. (2002). Evidence that three dimensions of psychosis have a distribution in the general population. *Psychological Medicine*, 32(2), 347–358. doi:10.1017/s0033291701005141
- Uher, R., & Zwickler, A. (2017). Etiology in psychiatry: Embracing the reality of poly-gene-environmental causation of mental illness. *World Psychiatry*, 16(2), 121–129. doi:10.1002/wps.20436
- VanderWeele, T. J. (2013). Policy-relevant proportions for direct effects. *Epidemiology (Cambridge, Mass.)*, 24(1), 175–176. doi:10.1097/EDE.0b013e3182781410
- van Os, J., Kenis, G., & Rutten, B. P. (2010). The environment and schizophrenia. *Nature*, 468(7321), 203–212. doi:10.1038/nature09563
- Varchmin, L., Montag, C., Treusch, Y., Kaminski, J., & Heinz, A. (2021). Traumatic events, social adversity and discrimination as risk factors for psychosis - an umbrella review. *Frontiers in Psychiatry*, 12, 665957. doi:10.3389/fpsy.2021.665957
- Vines, L., Bridgwater, M., Bachman, P., Hayes, R., Catalano, S., & Jalbrzikowski, M. (2022). Elevated emotion reactivity and emotion regulation in individuals at clinical high risk for developing psychosis and those diagnosed with a psychotic disorder. *Early Intervention in Psychiatry*, 16(7), 724–735. doi:10.1111/eip.13212
- Vukasović, T., & Bratko, D. (2015). Heritability of personality: A meta-analysis of behavior genetic studies. *Psychological Bulletin*, 141(4), 769–785. doi:10.1037/bul0000017
- Wiltink, S., Nelson, B., Velthorst, E., Wigman, J. T. W., Lin, A., Baksheev, G., ... Yung, A. R. (2015). The relationship between personality traits and psychotic like experiences in a large non-clinical adolescent sample. *Personality and Individual Differences*, 73, 92–97.
- Woicik, P. A., Stewart, S. H., Pihl, R. O., & Conrod, P. J. (2009). The Substance Use Risk Profile Scale: A scale measuring traits linked to reinforcement-specific substance use profiles. *Addictive Behaviors*, 34(12), 1042–1055. doi:10.1016/j.addbeh.2009.07.001
- Woolway, G. E., Smart, S. E., Lynham, A. J., Lloyd, J. L., Owen, M. J., Jones, I. R., ... Legge, S. E. (2022). Schizophrenia polygenic risk and experiences of childhood adversity: A systematic review and meta-analysis. *Schizophrenia Bulletin*, 48(5), 967–980. doi:10.1093/schbul/sbac049
- Yung, A. R., Nelson, B., Baker, K., Buckby, J. A., Baksheev, G., & Cosgrave, E. M. (2009). Psychotic-like experiences in a community sample of adolescents: Implications for the continuum model of psychosis and prediction of schizophrenia. *The Australian and New Zealand Journal of Psychiatry*, 43(2), 118–128. doi:10.1080/00048670802607188
- Zalesky, A., Pantelis, C., Cropley, V., Fornito, A., Cocchi, L., McAdams, H., ... Gogtay, N. (2015). Delayed development of brain connectivity in adolescents with schizophrenia and their unaffected siblings. *JAMA Psychiatry*, 72(9), 900–908. doi:10.1001/jamapsychiatry.2015.0226
- Zohar, A. H., Zwir, I., Wang, J., Cloninger, C. R., & Anokhin, A. P. (2019). The development of temperament and character during adolescence: The processes and phases of change. *Development and Psychopathology*, 31(2), 601–617. doi:10.1017/S0954579418000159
- Zwickler, A., Denovan-Wright, E. M., & Uher, R. (2018). Gene-environment interplay in the etiology of psychosis. *Psychological Medicine*, 48(12), 1925–1936. doi:10.1017/S003329171700383X