Psychiatry Research 340 (2024) 116107

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Genetic determinants of coping, resilience and self-esteem in schizophrenia suggest a primary role for social factors and hippocampal neurogenesis

Francesco Mazzarotto [a,b], Palmiero Monteleone [c], Alessandra Minelli [a,d], Stefania Mattevi [a], Giammarco Cascino [c], Paola Rocca [e], Alessandro Rossi [f], Alessandro Bertolino [g], Eugenio Aguglia [h], Carlo Altamura [i], Mario Amore [j], Antonello Bellomo [k], Paola Bucci [l], Enrico Collantoni [m], Liliana Dell'Osso [n], Fabio Di Fabio [o], Andrea Fagiolini [p], Luigi Giuliani [l], Carlo Marchesi [q], Giovanni Martinotti [r], Cristiana Montemagni [e], Federica Pinna [s], Maurizio Pompili [t], Antonio Rampino [g], Rita Roncone [u], Alberto Siracusano [v], Antonio Vita [w,x], Patrizia Zeppegno [y], Silvana Galderisi [l], Massimo Gennarelli [a,d,*], Mario Maj [l], Italian Network for Research on Psychoses [1]

[a] *Department of Molecular and Translational Medicine, University of Brescia, Brescia, Italy*
[b] *National Heart and Lung Institute, Imperial College London, United Kingdom*
[c] *Department of Medicine, Surgery and Dentistry "Scuola Medica Salernitana", University of Salerno, Salerno, Italy*
[d] *Genetic Unit, IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy*
[e] *Department of Neuroscience, Section of Psychiatry, University of Turin, Turin, Italy*
[f] *Section of Psychiatry, Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, L'Aquila, Italy*
[g] *Department of Neurological and Psychiatric Sciences, University of Bari, Bari, Italy*
[h] *Department of Clinical and Molecular Biomedicine, Psychiatry Unit, University of Catania, Catania, Italy*
[i] *Department of Psychiatry, University of Milan, Milan, Italy*
[j] *Section of Psychiatry, Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics and Maternal and Child Health, University of Genoa, Genoa, Italy*
[k] *Psychiatry Unit, Department of Medical Sciences, University of Foggia, Foggia, Italy*
[l] *Department of Psychiatry, University of Campania "Luigi Vanvitelli" Naples, Italy*
[m] *Psychiatric Clinic, Department of Neurosciences, University of Padua, Padua, Italy*
[n] *Section of Psychiatry, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy*
[o] *Department of Neurology and Psychiatry, Sapienza University of Rome, Rome, Italy*
[p] *Department of Molecular Medicine and Clinical Department of Mental Health, University of Siena, Siena, Italy*
[q] *Department of Neuroscience, Psychiatry Unit, University of Parma, Parma, Italy*
[r] *Department of Neuroscience and Imaging, G. D'Annunzio University, Chieti, Italy*
[s] *Section of Psychiatry, Department of Public Health, Clinical and Molecular Medicine, University of Cagliari, Cagliari, Italy*
[t] *Department of Neurosciences, Mental Health and Sensory Organs, S. Andrea Hospital, Sapienza University of Rome, Rome, Italy*
[u] *Unit of Psychiatry, Department of Life, Health and Environmental Sciences, University of L'Aquila, L'Aquila, Italy*
[v] *Department of Systems Medicine, Psychiatry and Clinical Psychology Unit, Tor Vergata University of Rome, Rome, Italy*
[w] *Psychiatric Unit, School of Medicine, University of Brescia, Brescia, Italy*
[x] *Department of Mental Health, Spedali Civili Hospital, Brescia, Italy*
[y] *Department of Translational Medicine, Psychiatric Unit, University of Eastern Piedmont, Novara, Italy*

A R T I C L E I N F O

Keywords:
Personal resources
Genome-wide association study
Micro-RNAs
Pleiotropy
Common genetic variants

A B S T R A C T

Schizophrenia is a severe psychiatric disorder, associated with a reduction in life expectancy of 15–20 years. Available treatments are at least partially effective in most affected individuals, and personal resources such as resilience (successful adaptation despite adversity) and coping abilities (strategies used to deal with stressful or threatening situations), are important determinants of disease outcomes and long-term sustained recovery. Published findings support the existence of a genetic background underlying resilience and coping, with variable

* Corresponding author at: Department of Molecular and Translational Medicine, University of Brescia, Genetic Unit, IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy.
E-mail address: massimo.gennarelli@unibs.it (M. Gennarelli).

[1] The members of the Italian Network for Research on Psychoses involved in this study are listed in the Appendix.

https://doi.org/10.1016/j.psychres.2024.116107
Received 10 May 2024; Received in revised form 18 July 2024; Accepted 24 July 2024
Available online 30 July 2024

Lipid metabolism
Neuroticism
Worry

heritability estimates. However, genome-wide analyses concerning the genetic determinants of these personal resources, especially in the context of schizophrenia, are lacking. Here, we performed a genome-wide association study coupled with accessory analyses to investigate potential genetic determinants of resilience, coping and self-esteem in 490 schizophrenia patients. Results revealed a complex genetic background partly overlapping with that of neuroticism, worry and schizophrenia itself and support the importance of social aspects in shapingthese psychological constructs. Hippocampal neurogenesis and lipid metabolism appear to be potentially relevant biological underpinnings, and specific miRNAs such as miR-124 and miR-137 may warrant further studies as potential biomarkers. In conclusion, this study represents an important first step in the identification of genetic and biological correlates shaping resilience, coping resources and self-esteem in schizophrenia.

1. Introduction

Schizophrenia (SCZ) is a disabling psychiatric disorder that may lead to severe impairment in psychosocial functioning and a reduction in life expectancy of 15–20 years (Galderisi et al., 2014; Correll et al., 2022). Personal resources, including coping abilities, individual resilience and self-esteem, have been shown to contribute to the patient's real-life psychosocial functioning, either directly or mediating the effect of other variables (Galderisi et al., 2014; Rossi et al., 2017; Hofer et al., 2023a; Zizolfi et al., 2019; Chen et al., 2019; Zizolfi et al., 2019; Chen et al., 2019).

Resilience enables functional adaptation to adverse contexts and is defined as the positive adaptation to extreme adversity (Luthar, 2006). Intrapersonal resilient factors—such as a positive perception of one's own abilities—have been shown to act as severity predictors for psychiatric symptoms, while interpersonal factors specifically related to level of social support predict psychosocial functioning in SCZ (Poloni et al., 2018). As far as social aspects are concerned more broadly, social competence (i.e. the ability to engage in meaningful interactions with others) is among the psychological constructs with the strongest overlap with resilience (Luthar, 2006; Caqueo-Urízar et al., 2021).

Coping resources encompass strategies put in place to face stressful situations and they generally mediate the relationship between psychosocial stress and health-related outcomes. These comprise many different cognitive and behavioral approaches, including, for example, positive reappraisal, seeking support and denial. Often, coping behaviors are analysed by grouping them in broader coping strategies, with a lack of consensus on an optimal grouping (Solberg et al., 2022). Among the most widely used grouping, lie the 3-factor division betweenemotion-focused, problem-focused and avoidance-focused approaches, and 2-factor ones such as adaptive vs. maladaptive approaches (Solberg et al., 2022; Folkman and Moskowitz, 2004; Aburn et al., 2016). Problem-focused coping (i.e. strategies practically targeting the cause of stress) is generally regarded as the most effective strategy, because of its association with lower stress levels and improved mental health (Penley et al., 2002). Emotion-focused coping (i.e. approaches aimed at managing the emotions caused by the source of stress) has been recently demonstrated to correlate negatively with resilience (Navrady et al., 2018). However, emotion-focused approaches may be more effective when the cause of stress is not within the person's control, as shown during the COVID-19 lockdown, in which this type of approach was associated with fewer mental health symptoms (Fluharty et al., 2021). Avoidance-focused coping encapsulates strategies that don't address the stressor but rather suppress or ignore its existence and, while these can have short-term benefits, are less beneficial in the long-term (Korem et al., 2023).

One of the conventional two-factor groupings distinguishes between adaptive and maladaptive approaches, i.e. those action-oriented strategies characterized by positive thinking, acceptance and cognitive restructuring as opposed to styles relying on suppression, rumination and withdrawal (Webb Hooper et al., 2013). Maladaptive approaches, as opposed to adaptive ones, are associated with negative outcomes (e.g. mental illness across one's lifespan) and more severe symptoms in the disease context (Wadsworth, 2015; Mian et al., 2018).

In SCZ, both resilience and coping skills have been shown to mediate the effects of negative symptoms on the patient's functioning, while variables like neurocognition, disorganization, avolition and positive symptoms, as well as family and social incentives, predict real-life functioningdirectly or through the mediation of resilience (Galderisi et al., 2014; Chen et al., 2019; Poloni et al., 2018). Overall, coping and resilience, as well as self-esteem (with low self-esteem regarded as a hurdle), are considered important outcome predictors in SCZ, with all three playing a role in long-term sustained recovery (Zizolfi et al., 2019; Torgalsbøen and Rund, 2010; Roosenschoon et al., 2019; Hofer et al., 2023b).

Penley et al. (2002); Navrady et al. (2018); Fluharty et al. (2021) resilience and coping skills are determined by biological and environmental factors. Published findings support the existence of a genetic background underlying resilience (Maul et al., 2020), with the involvement of genetic and epigenetic variations inneuroendocrine pathways and immune modulators (McEwen, 2016; Ménard et al., 2017; Binder, 2018). Heritability estimates concerning resilience and coping are extremely variable, with figures from twin studies and population cohorts ranging from approximately 10 % to >70 % and, interestingly, suggesting a higher heritability in men compared with women for resilience (Navrady et al., 2018; Hansson et al., 2008; Boardman et al., 2008; Wolf et al., 2018; Dunn and Conley, 2015).

To our knowledge, a single genome-wide association studies (GWAS) has been performed to date to analyze genetic associations with self-assessed psychological resilience measured through a dedicated scale and highlighted, a role for *DCLK2*, (involved in hippocampal plasticity) and *KLHL36* (a risk locus for late-onset Alzheimer disease) (Stein et al., 2019).

Since low resilience is associated with higher susceptibility to stress-related mental illness, such as post-traumatic stress disorder (PTSD), also GWAS on PTSD can, to a certain extent, be considered informative on the genetic background of resilience (Maul et al., 2020). These analyses identified numerous loci associated with PTSD, ranging from *RORA*, implicated in neuroprotection, to *NLGN1*, associated with autism and involved in memory and learning (Logue et al., 2013; Kilaru et al., 2016). While replication across the PTSD GWAS remained globally scarce, the association concerning specific loci such as the one comprising *MAD1L1*, thought to play a role in cell cycle control, has been robustly replicated in recent, large-scale analyses (Stein et al., 2021; Hess et al., 2021; Hess et al., 2023; He et al., 2021; Ashley-Koch et al., 2015; Melroy-Greif et al., 2017; Duncan et al., 2018).

The genetic determinants of specific coping strategies have been investigated in one GWAS to date, in which heritability was estimated to be up to 19.5 % depending on the specific coping scale in question and variants in *FBXO45*, involved in the regulation of synapse maturation, were associated with a coping strategy based on emotional expression in a Japanese population cohort (Shimanoe et al., 2019). We are not aware of any published study investigating the genetic background of self-esteem.

Given the high heritability of SCZ and the importance of resilience, coping resources and self-esteem as outcome predictors, investigating genetic determinants these personal resources in SCZ patients may lead to the identification of particularly relevant genetic loci. For this reason,

we performed a GWAS to shed light on the genetic determinants of resilience, coping resources and self-esteem assessed on SCZ patients through dedicated scales, also aiming at the identification of potential biomarkers.

2. Methods

2.1. Study subjects and clinical assessment

Patients participating in this study were recruited in the context of a multicentric study involving 26 Italian university psychiatric clinics and/or mental health departments, comprising the Italian Network for Research on Psychoses (NIRP), with a general aim of investigating genetic and non-genetic variables affecting real-life functioning of individuals with SCZ.

Patients were enrolled if they met the following inclusion criteria: a) diagnosis of schizophrenia according to DSM-IV, confirmed with the Structured Clinical Interview for DSM-IV—Patient version (SCID-I-P); b) age range between 18 and 66 years; c) no family history of schizophrenia; d) no history of head trauma with loss of consciousness; e) no history of moderate to severe mental retardation or of neurological diseases; f) no history of alcohol and/or substance abuse in the last six months; g) no current pregnancy or lactation; h) ability to provide an informed consent; i) no treatment modification in the last three months.

Personal resources were assessed by means of the following self-administered instruments:

a) the Brief-COPE (Carver, 1997), a questionnaire including 14 subscales, each composed of two items, referring to specific coping-related behavioral strategies (self-distraction, active coping, denial, substance use, use of emotional support, use of instrumental support, behavioral disengagement, venting, positive reframing, planning, humor, acceptance, religion and self-blame). There is no total score, but subscales are grouped to form broader coping strategy-related scores with the most prevalent constructs consisting in the evaluation of 2 or 3 different coping styles (Solberg et al., 2022). Accordingly, the Brief-COPE structures evaluated in this study were a 3-factor Brief-COPE assessing problem-focused, emotion-focused and avoidance-focused coping, and a 2-factor Brief-COPE assessing adaptive and maladaptive coping. Within each subscale and coping strategy, a higher score indicates greater use of that strategy;
b) the Resilience Scale for Adults (RSA) (Friborg et al., 2003), which includes 33 items organized into 6 scales reflecting intrapersonal (perception of self, planned future, social competence and structured style) and interpersonal protective factors (family cohesion, social resources) facilitating adaptation when facing psychosocial adversities. The first two intrapersonal scales are combined to form a joint scale (personal competence);
c) the Recovery Style Questionnaire (RSQ) (Drayton et al., 1998), that is a 39-item self-report measure assessing the patient's ability in recovering from psychosis. It is composed of 13 scales (each with 3 items) referring to the concepts of continuity, belonging, responsibility, curiosity, education, search for help, guilt, cause, optimism, impact, fear, appreciation and satisfaction. A total score is computed;
d) the Self-Esteem Rating Scale (SERS) (Nugent and Thomas, 1993), conceived as a clinically oriented self-report measure of self-esteem in adults. It is composed by 40 items exploring multiple aspects of self-evaluation (overall self-worth, social competence, problem-solving abilities, intellectual abilities, self-competence and worth compared with others). A total score is computed with higher values representing stronger self-esteem.

All subjects provided written informed consent to participate after receiving a comprehensive explanation of the scope and goals of the network. The study protocol was approved by the Ethical Committee of the coordinating center (approval number 73/2012; February 9th, 2012).

2.2. Genotyping, quality control and data processing

The analyzed cohort comprised 490 patients genotyped in two batches with the Illumina Infinium PsychArray-24 BeadChip ($n = 307$) and with the Illumina Infinium Global Screening Array-24 ($n = 183$).

Genotyping data quality control (QC) was performed on the two batches separately. Initial sample-level QC was applied to exclude samples characterized by variant call rate <95 %, sex discrepancy, inferred relatedness and outlying heterozygosity rate ($n = 33$). In addition, samples with any missing phenotype record were also removed ($n = 45$), as well as outliers with respect to any of the total coping and resilience scores ($n = 2$). The 410 samples that meet all the QC goals were retained for the subsequent Principal Component Analysis (PCA). Variant-level QC involved the removal of variant sites characterized by missingness >5 %, internal minor allele frequency <1 %, significant deviation from the Hardy-Weinberg equilibrium ($p < 1E{-}6$) or non-random missingness by haplotype ($p < 1E{-}4$). These steps were performed following a SNP pruning procedure to retain only variants not in significant linkage disequilibrium with each other ($r^2 < 0.5$ within 50 bp). Prior to imputation, a further QC step on the whole set of variants was performed to check strand, variant rs IDs, position, alleles and ref/alt assignment against the Haplotype Reference Consortium (HRC) reference panel using a dedicated tool (available at https://www.well.ox.ac.uk/~wrayner/tools/). Genome-wide imputation was performed on each batch in isolation using Eagle 2.4 phasing, Minimac4 and the HRC (r1.1) panel available on the Michigan Imputation Server (v1.6.8) (Das et al., 2016). Results from the two batches were subsequently merged, and QC was repeated on the final dataset.

A genotypic PCA was performed combining all cases with the 1000 Genomes Project individuals ($n = 2504$) and, in addition to highlighting the absence of residual batch effects, allowed the identification of 3 samples of non-European origin (Fig. S1). These samples were excluded from further analysis bringing the total amount of samples undergoing the final association analysis to 407. PC selection based on consensus across 6 different approaches (performed using the findPC R library (Zhuang et al., 2022)) supported the inclusion as covariates of the first 3 PCs (explaining 84.8 % of the total variance) in the subsequent association analyses (Figs. S2 and S3).

2.3. Genome-wide association analysis

The genome-wide association analysis was performed with EMMAX (Kang et al., 2010) (v20120210) on a total of 407 patients and 1,795,556 variants. Genetic association was evaluated separately for each construct (3-factor Brief-COPE, 2-factor Brief-COPE, RSA, RSQ and SERS).

Age, sex and the first 3 PCs as per the PCA described in paragraph 2.2 were included as covariates in each model. Constructs consisting in a unique scale (i.e. RSQ and SERS) were analyzed as in the example below for RSQ (dependent variable in bold, independent variable in italics):

$$\mathbf{RSQ} \sim \textit{genotypes} + \text{age} + \text{sex} + \text{PC1} + \text{PC2} + \text{PC3}$$

Single SNP p-values $<5 \times 10^{-6}$ were considered suggestive of association throughout the study.

For scores composed by multiple scales and/or subscales (i.e. Brief-COPE and RSA), the analysis was structured in a 2-tier fashion, applying either the suggestive ($p < 5 \times 10^{-6}$) and/or the conventional genome-wide ($p < 5 \times 10^{-8}$) significance thresholds according to the tier in question, as explained in Fig. 1.

Regardless of their significance, any SNP without any other marker in LD ($r^2 > 0.6$) or with $p < 1 \times 10^{-5}$ within 50 kb was considered

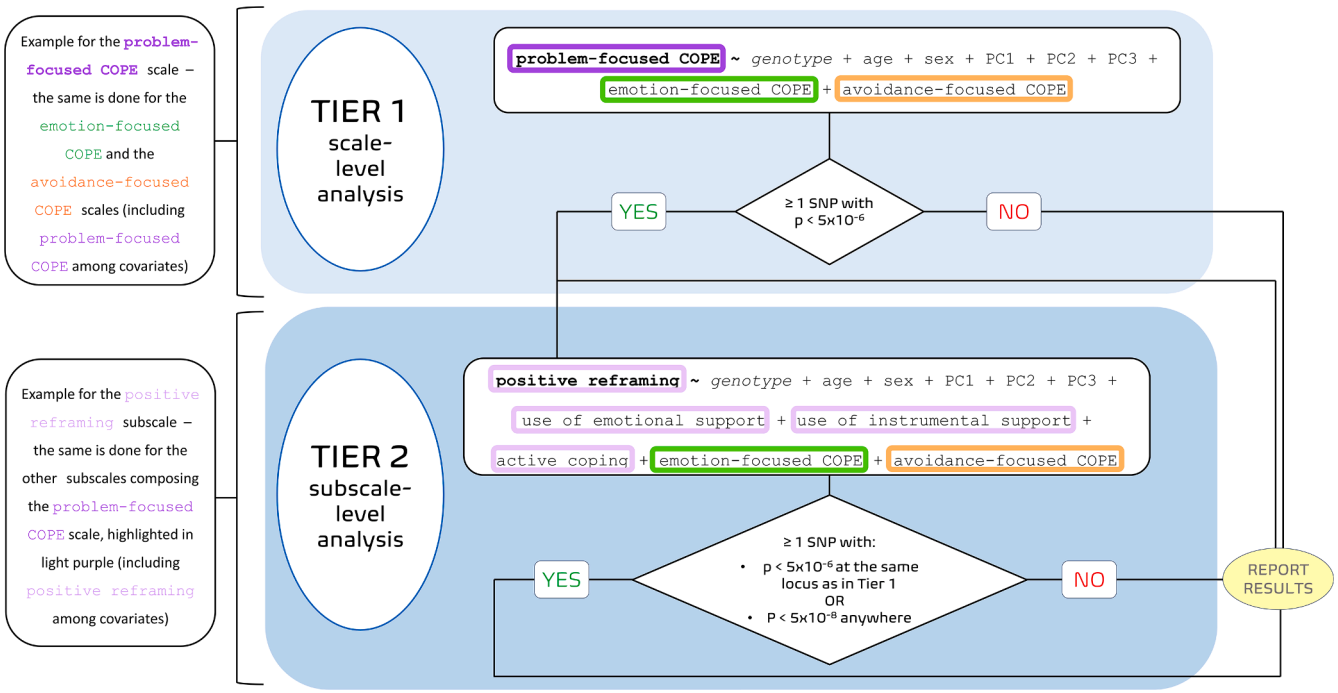

Fig. 1. analysis workflow applied on scores composed by multiple scales and/or subscales (i.e. Brief-COPE and RSA). In Tier-1, genome-wide association analysis is performed on each scale composing the score (e.g. problem-focused COPE, circled in dark purple), with other scales added as covariates (e.g. emontion-focused COPE and avoidance-focused COPE here, circled in green and orange, respectively). If significant genetic associations with a given scale are detected, genome-wide association analysis (Tier-2) is repeated on each subscale composing the scale in question (e.g. positive reframing, circled in light purple). Of note, while the main purpose of Tier-2 analysis is to investigate whether the Tier-1 association is driven by a specific subscale, additional associations not detected in the Tier-1 step may emerge. For this reason, in Tier-2 analysis two significance thresholds are applied: the suggestive significance threshold $p < 5 \times 10^{-6}$ is used for SNPs at the same loci emerged in Tier-1, while the stricter genome-wide significance threshold ($p < 5 \times 10^{-8}$) is applied for associations concerning a specific subscale emerging in other areas of the genome.

spuriously associated with the trait under analysis and not investigated further. Association results have been analyzed with FUMA (Watanabe et al., 2017), while Q-Q plots and Manhattan plots have been produced using the qqman R library (Turner, 2018).

2.4. miRNA target analysis

Micro-RNAs validated or predicted to regulate the nearest-to-peak genes at the associated loci were identified using the multiMiR R library, automatically querying 11 different databases of validated and predicted miRNA-gene interactions (Ru et al., 2014). Owing to the many results returned by the default query and aiming at a shortlist of robust miRNA candidates, the following filtering criteria have been applied for each gene:

- of validated gene-miRNA interactions, only those supported by strong evidence were retained.
- of predicted gene-miRNA interactions, only those within the top 5 % in terms of prediction scores within each database were retained. Of these, interactions prioritized by a minimum of 3 databases among Diana-microT, ElMMo, miRanda and miRDB were kept in the final candidate list. The other 3 databases of predicted interactions (MicroCosm, PITA and TargetScan) were not included in this filtering step due to the limited (<10) and non-overlapping entries left. Please refer to the multiMiR publication for information concerning the single databases (Ru et al., 2014).

When present, the miRNA evidence characterizing an associated gene was classified according to a 4-tier scale, as follows, with evidence strength in decreasing order:

- Class A: the gene is an experimentally validated target of ≥1 miRNA shown to influence coping- or resilience capabilities in humans or animal models.
- Class B: the gene is a high-confidence computationally predicted target of ≥1 miRNA shown to influence coping- or resilience capabilities in humans or animal models.
- Class C: the gene is an experimentally validated target of ≥1 miRNA associated with SCZ, other psychiatric conditions or traits relevant in a psychiatric disease context.
- Class D: the gene is a high-confidence computationally predicted target of ≥1 miRNA associated with SCZ, other psychiatric conditions or traits relevant in a psychiatric disease context.

The evidence concerning each miRNA in terms of its involvement in brain- or psychiatric-relevant traits or conditions was triaged from PubMed (details in the Supplementary Notes) and from the NHGRI-EBI GWAS Catalog (Sollis et al., 2023) (accessed on 7th–11th August 2023).

2.5. Genetic overlap and polygenic risk score analysis

Previously published associations between the nearest-to-peak genes highlighted by the analysis and psychiatric conditions or relevant traits were surveyed, considering those below the same significance cutoff used in this study ($p < 5 \times 10^{-6}$). Traits or conditions that appeared to be particularly recurrent (i.e. those associated with >2 of the genes emerged in this study) were tested to assess whether their recurrence was statistically significant, and therefore suggestive of a significant genetic overlap with coping/resilience. This was done by means of binomial tests, considering the total number of genes ($n = 61{,}029$ including protein-coding genes, non-protein-coding genes and pseudogenes, as from the GRCh37 Ensembl genome browser) and how many of these were associated with the trait/condition in question at least once

according to GWAS Catalog.

In addition, to further characterize genetic overlap at the single-scale level, the correlation between the polygenic risk score (PRS) for SCZ derived from the latest GWAS by the Psychiatric Genomics Consortium (Trubetskoy et al., 2022) and the COPE, RSA, RSQ and SERS scales of the 409 patients analyzed here was assessed using PRSice-2 (Choi and O'Reilly, 2019). SNPs were divided in deciles according to their association *p*-value. In case ≥1 deciles were characterized by a significant R^2 for model fit, the direction of effect of the PRS computed using the most significant SNP decile on the scale in question was assessed using the Pearson correlation coefficient.

3. Results

3.1. Clinical sample

A total of 490 patients (72.2 % ($N = 354$) males, age at recruitment: 39.7 ± 10.4 years, age of SCZ onset: 23.8 ± 6.6 years) completed all the requested assessments and agreed to provide blood samples for genetic analyses. All patients were treated with antipsychotic drugs and were clinically stable for at least three months. The 407 samples retained for the GWAS following the QC outlined in paragraph 2.2 had comparable characteristics to the full clinical sample (73.5 % ($N = 299$) males, age at recruitment: 39.8 ± 10.1 years).

3.2. Genome-wide genetic associations with coping and resilience abilities

A total of 16 SNP-based genetic associations across the analyzed coping and resilience scores emerged (Table 1 and Fig. 2). The genomic inflation factor (lambda) was in the range 0.97–1.02 for each of the analyses, ensuring the absence of significant inflation or bias (Fig. S4). Where not mentioned, MAGMA gene-based or gene-set analyses did not identify significant associations.

3.2.1. 3-factor brief—coping orientation to problems experienced (COPE)

Avoidance-focused coping emerged as associated with SNPs at the

Table 1
Details concerning genetic associations emerged in the study. In the column "Mean (SD) score per genotype (N)" the average score (and SD) concerning the scale or subscale in question is reported separately for carriers of each of the three possible genotypes, with their absolute number between brackets. These numbers don't always add up to 407 (total number of patients analyzed) due to samples with a missing genotype for the variant in question. Abbreviations: GRCh37, genomic position in GRCh37 and alleles; MAF (gnomAD_NFE), minor allele frequency in the non-Finnish European subset of gnomAD v2.1.1 genomes ($N \approx 7500$).

Score	Scale / subscale	Lead SNP	GRCh37	Nearest gene	Gene product description	P	Mean (SD) score per genotype (N)	MAF (gnomAD NFE)
COPE (3-factor)	Avoidance-focused coping	rs637963	11:100954828:T:C	*PGR*	Progesterone receptor	1.3×10^{-6}	TT: 1.8 ± 0.4 (190), TC: 2.0 ± 0.4 (161), CC:2.1 ± 0.5 (92)	0.34
	Problem-focused coping	rs73125698	3:64895087:G:A	*ADAMTS9*	ADAM Metallopeptidase	4.1×10^{-6}	GG: 2.8 ± 0.6 (319), GA: 2.4 ± 0.7 (81), AA:2.6 ± 0.2 (4)	0.08
	Use of informational support (problem-focused coping subscale)	rs59515125	3:32035619:C:T	*OSBPL10*	Oxysterol binding protein	3.8×10^{-8}	CC: 2.8 ± 0.9 (260), CT: 2.4 ± 0.9 (120), TT: 2.2 ± 0.9 (18)	0.17
COPE (2-factor)	Adaptive coping	rs1406447	2:148497676:A:G	*ACVR2A*	Activin receptor	4.4×10^{-6}	AA: 2.4 ± 0.5 (130), AG: 2.5 ± 0.5 (196), GG: 2.8 ± 0.5 (71)	0.35
	Maladaptive coping	rs11983675	7:150421377:T:A	*GIMAP1-GIMAP5*	Readthrough transcription of 2 GTPases	1.2×10^{-6}	AA: 1.9 ± 0.5 (337), AT: 2.2 ± 0.5 (67), TT: 2.4 ± 0.5 (2)	0.10
		rs12606558	18:44171827:G:A	*LOXHD1*	Protein of unclear function with 15 PLAT repeats	3.8×10^{-6}	GG: 2.0 ± 0.5 (221), GA: 1.8 ± 0.4 (165), AA: 1.8 ± 0.4 (16)	0.30
		rs12954992	18:65669512:A:C	*DSEL*	Dermatan Sulfate Epimerase	7.4×10^{-7}	AA: 1.8 ± 0.5 (192), AC: 2.0 ± 0.5 (175), CC: 2.3 ± 0.6 (32)	0.35
RSA	Personal competence	rs7069590	10:43552895:T:C	*RET*	Tyrosine kinase receptor	1.8×10^{-6}	TT: 30.4 ± 9.3 (220), TC: 28.7 ± 8.7 (149), CC: 26.3 ± 9.3 (35)	0.23
		rs1789250	18:76715856:G:A	*SALL3*	Transcription factor	3.4×10^{-6}	GG: 28.3 ± 8.9 (275), GA: 31.3 ± 9.3 (119), AA: 34.6 ± 8.8 (12)	0.24
	Social competence	rs11250166	8:11651662:G:A	*FDFT1*	Squalene synthase	2.6×10^{-6}	GG: 18.6 ± 5.3 (279), GA: 20.5 ± 5.1 (101), AA: 22.3 ± 5.9 (12)	0.18
	Social resources	rs12495100	3:29498599:A:C	*RBMS3*	RNA-binding protein	2.2×10^{-7}	AA: 26.2 ± 5.2 (228), AC: 25.5 ± 6.1 (141), CC: 22.0 ± 5.4 (33)	0.28
RSQ total score		rs7118149	11:24700545:G:A	*LUZP2*	Leucine zipper protein	5.2×10^{-7}	GG: 7.4 ± 2.1 (96) GA: 7.9 ± 2.3 (217), AA: 9.1 ± 1.8 (91)	0.51
		rs7948935	11:132019785:C:G	*NTM*	Neurotrimin	4.1×10^{-6}	CC: 7.9 ± 2.2 (340), CG: 9.2 ± 2.2 (53), GG: 11 (1)	0.04
		rs9588277	13:111485430:A:G	*ANKRD10*	Ankyrin repeat domain	3.5×10^{-6}	AA: 8.4 ± 2.1 (277), AG: 7.3 ± 2.2 (115), GG: 7.0 ± 2.1 (14)	0.20
		rs12586818	14:33787178:C:G	*NPAS3*	Transcription factor	4.2×10^{-7}	CC: 7.9 ± 2.2 (357), CG: 9.6 ± 1.8 (45), GG: 10 (1)	0.08
SERS total score		rs7087272	10:100603604:A:G	*HPSE2*	Heparanase	6.0×10^{-7}	AA: 24.1 ± 40.1 (312), AG: 0.6 ± 40.1 (79), GG: −28.8 ± 30.0 (4)	0.08

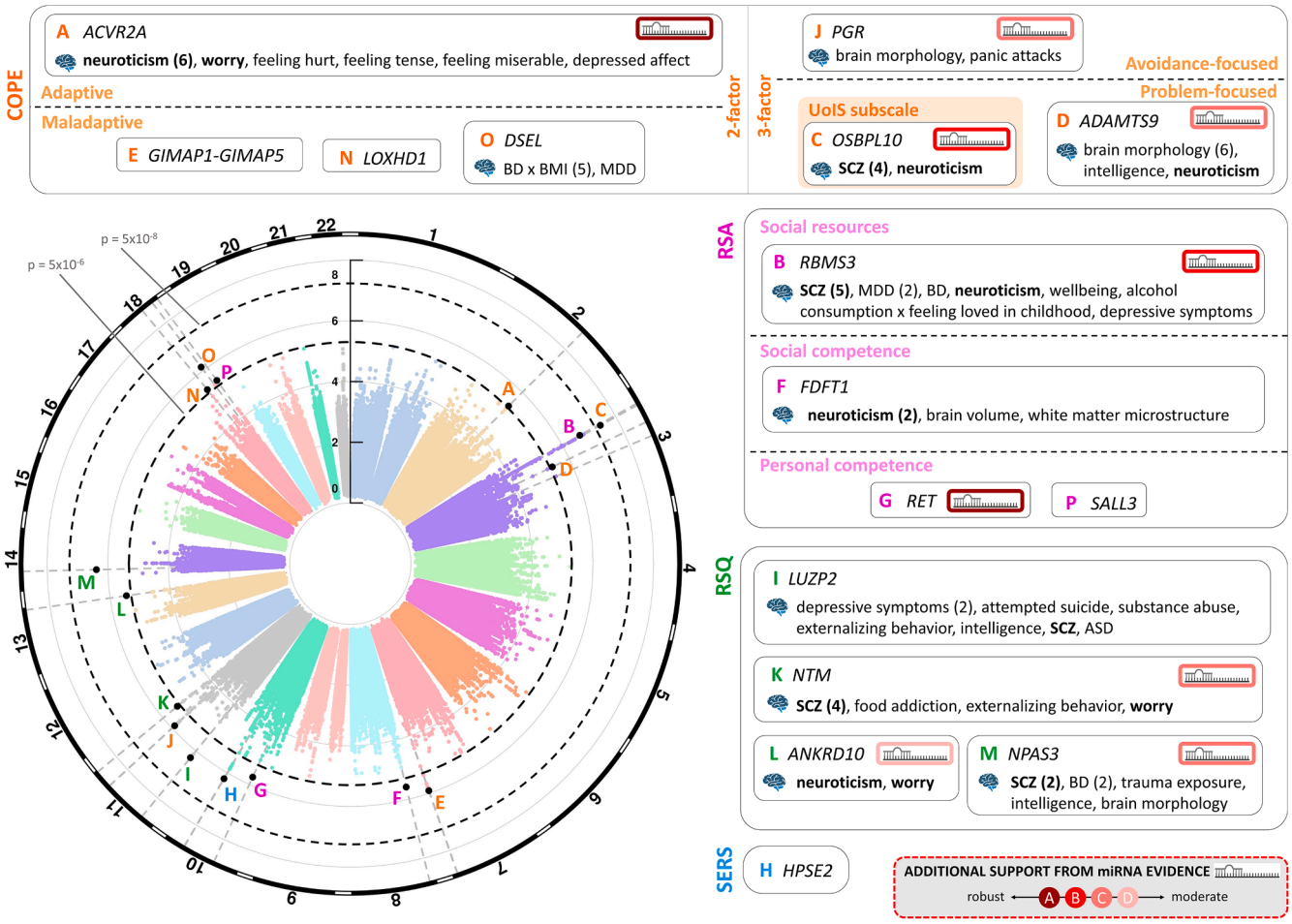

Fig. 2. Genome-wide association results across the 4 analyzed scores. The Manhattan plot shows, for each SNP, the most significant association across COPE, RSA, RSQ and SERS (orange, pink, green and blue association peaks, respectively, labeled with letters A to P starting from chromosome 1). The two black dashed lines represent significance thresholds applied in the analysis (corresponding to $p = 5 \times 10^{-6}$ and 5×10^{-8}). The brain symbols denote previously published brain- or psychiatric-relevant associations for each gene, as from GWAS Catalog (see the Supplementary Notes for details on trait nomenclature), with the exception of the association between PGR and panic attacks (not listed in the catalog) (Ho et al., 2004). In case of multiple associations for a given gene with the same trait/condition, the number of studies in which the association emerged is reported between brackets. Interactions between traits/conditions are indicated with an 'x'. The classification assigned to the additional supporting evidence from the miRNA target analysis, where available, is displayed by the color of the miRNA labels, as shown in the dashed box at the bottom. Traits/conditions tested in the genetic overlap analysis (i.e. those associated with at least 3 genes) are highlighted in bold. ASD = autism spectrum disorder, BD = bipolar disorder, BMI = body mass index, MDD = major depressive disorder, SCZ = schizophrenia.

locus comprising *PGR*, encoding the progesterone receptor, on chromosome 11 (lead SNP: rs637963, $p = 1.3 \times 10^{-6}$), while problem-focused coping was associated with variants in the region of *ADAMTS9*, encoding a metallopeptidase, on chromosome 3 (lead SNP: rs73125698, $p = 4.1 \times 10^{-6}$) (Fig. S5). Subsequent Tier-2 analyses revealed a genome-wide significant association for the subscale concerning the "use of informational support", a component of the problem-focused coping construct related to the tendency of seeking advice from others, for variants harbored by the *OSBPL10* gene, coding for an oxysterol-binding protein (Fig. 3, lead SNP: rs59515125, $p = 3.8 \times 10^{-8}$).

3.2.2. 2-factor brief-cope

A single genetic association signal was detected for adaptive coping (lead SNP: rs1406447, $p = 4.4 \times 10^{-6}$) upstream of *ACVR2A*, an activin receptor. Three distinct loci emerged as associated with a maladaptive style, with the closest protein-coding genes to the association peaks being *DSEL* (approximately 0.5 Mb upstream of the peak, coding for an epimerase), *GIMAP1-GIMAP5* (a locus where readthrough transcription occurs naturally, encoding two ATPases) and *LOXHD1* (a protein of unknown function), with the last 2 harboring the associated variants (Fig. S6). Lead SNPs were rs12954992 ($p = 7.4 \times 10^{-7}$), rs11983675 ($p = 1.2 \times 10^{-6}$) and rs12606558 ($p = 3.8 \times 10^{-6}$), respectively. Tier-2 analyses did not reveal specific sub-scales as potential drivers of these associations. MAGMA gene-set analysis (taking into account the full distribution of SNP *p*-values) identified the SNP associations with maladaptive coping to be enriched for the Gene Ontology cellular component "axon cytoplasm" (Bonferroni-corrected $p = 0.045$, 45 of 62 "axon cytoplasm" genes).

3.2.3. Resilience scale for adults

In the analysis of genetic association with RSA, associations were detected for 3 of the 5 RSA scales (Fig. S7). More specifically, variants in proximity of *RET* (lead SNP: rs7069590, $p = 1.8 \times 10^{-6}$) and *SALL3* (lead SNP: rs1789250, $p = 3.4 \times 10^{-6}$), encoding a transmembrane tyrosine kinase receptor and a transcription factor, respectively, were predictive of the personal competence scale. Subsequent tier-2 analysis did not replicate these associations, suggesting these not to be driven by a specific subscale. Social competence was associated with variants in a gene-dense region on chromosome 8, tagged by the lead SNP rs11250166 ($p = 2.6 \times 10^{-6}$) and with the nearest protein-coding gene being *FDFT1*, coding for an enzyme involved in cholesterol biosynthesis.

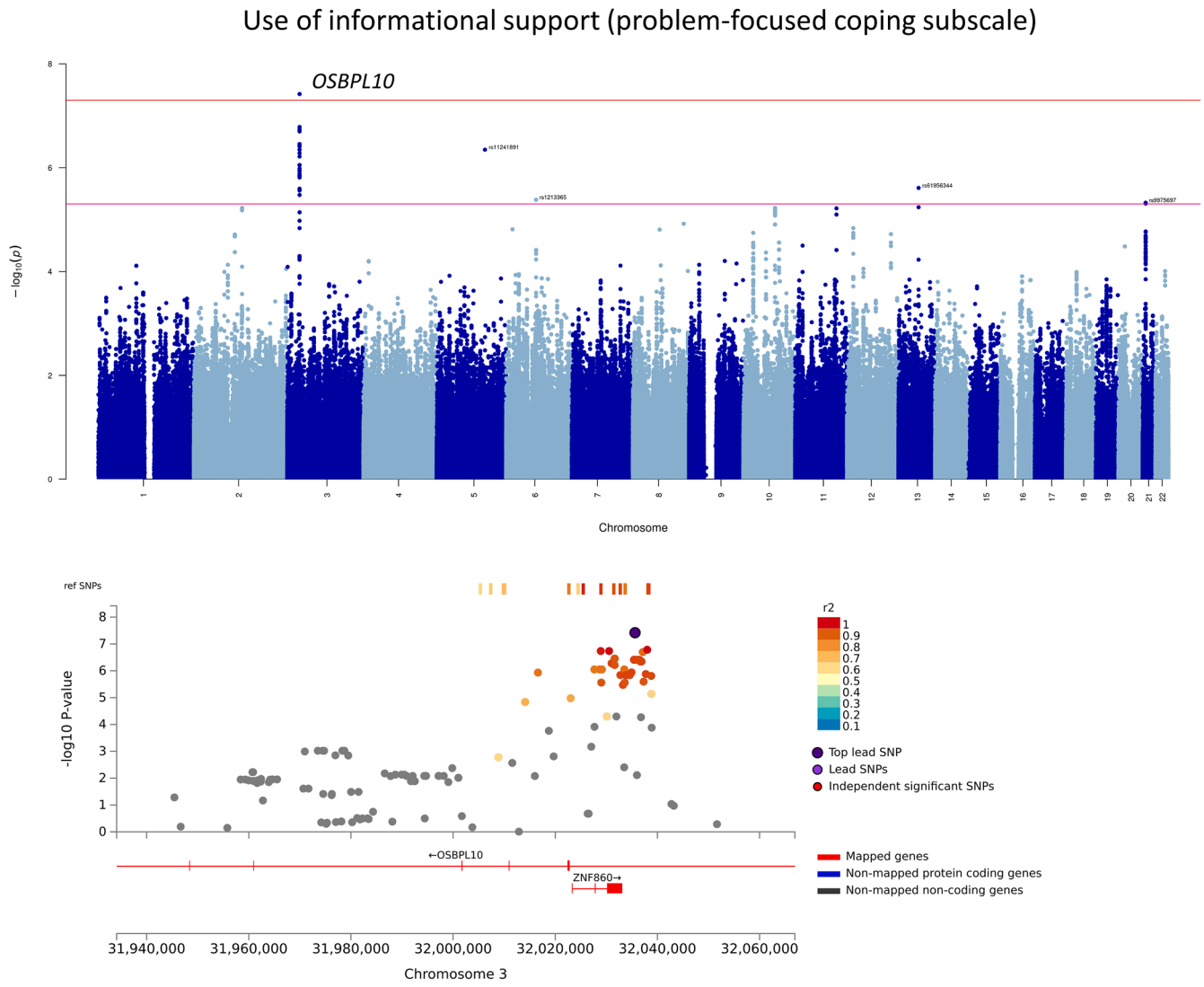

Fig. 3. Genome-wide association results for the use of informational support subscale of the problem-focused coping style score (3-factor COPE, top) and regional plot of the association peak on chromosome 3 within OSBPL10 (bottom). The horizontal pink line on the genome-wide plot represents the suggestive association threshold of $p = 5 \times 10^{-6}$, while the red line represents the genome-wide significance threshold of $p = 5 \times 10^{-8}$.

The scale pertaining to social resources was predicted by variants within *RBMS3*, encoding an RNA-binding protein (lead SNP: rs12495100, $p = 2.2 \times 10^{-7}$).

3.2.4. *Recovery style questionnaire*

The RSQ score was predicted by genotypes at 4 different loci, tagged by SNPs rs7118149 ($p = 5.2 \times 10^{-7}$), rs7948935 ($p = 4.1 \times 10^{-6}$), rs9588277 ($p = 3.5 \times 10^{-6}$) and rs12586818 ($p = 4.2 \times 10^{-7}$). The closest genes to these SNPs are *LUZP2* (a leucine zipper protein), *NTM* (a protein involved in cell adhesion), *ANKRD10* (an ankyrin repeat containing protein) and *NPAS3* (a transcription factor), respectively (Fig. S8).

3.2.5. *Self-Esteem rating scale*

The SERS score resulted associated with variants within *HPSE2* (Fig. S8, lead SNP: rs7087272, $p = 6.0 \times 10^{-7}$), encoding an inactive heparanase.

3.3. *miRNAs targeting genes at associated loci*

In total, 22 miRNAs previously implicated in psychiatric-relevant traits or diseases were experimentally validated or confidently predicted to target 9 of the 16 genes emerged from the association analysis (Table 2). In terms of strength of evidence, *ACVR2A* and *RET* were characterized by experimentally validated interactions with miRNAs directly involved in resilience/coping capabilities (class A miRNA evidence) whereas *OSBPL10* and *RBMS3* were supported by high confidence, computationally predicted evidence of the same type (class B). The 5 remaining genes were characterized by experimentally validated interactions with miRNAs implicated in psychiatric disease or other relevant traits (class C: *PGR, ADAMTS9, NTM* and *NPAS3*) or by computationally predicted evidence of the same type (class D: *ANKRD10*; see Methods, Table 2 and Fig. 2). A detailed summary of the published evidence concerning each identified gene-miRNA interactions is available in the Supplementary Notes.

3.4. *Genetic overlap and polygenic risk score analysis*

Among the previously published GWAS associations concerning the 16 genes identified in this study, those with neuroticism, SCZ and worry were particularly recurrent (having emerged as associated at least once with 6, 5 and 3 genes, respectively). Taking into account the total number of genes ($n = 61{,}029$, including pseudogenes and non-protein-coding genes (source: Ensembl genome browser)) and how many of

Table 2
Results of the miRNA target analysis performed with the multiMiR R library on the 16 nearest-to-peak genes. For each coping/resilience (sub)scale, miRNAs experimentally validated or computationally predicted (with high confidence) to target the associated genes are listed, as are relevant traits or conditions in which the miRNA has been implicated in the literature and the relative references. The strength of the miRNA evidence in support of a causal role for the gene in question is represented by the miRNA evidence class, as described in the Materials and Methods section. In cases in which published brain- or psychiatric-relevant implications concerned the miRNA from the complementary strand (5p vs. 3p or vice versa) or a paralogue (e.g. miR-9 vs. miR-9-2), these are reported with the indication of the strand/paralogue between brackets. Detailed evidence summaries and additional references are available in the Supplementary Notes. Additional miRNAs ($n = 12$) prioritized by multiMiR but with no published evidence of relevant associations are also listed in the Supplementary Notes. ASD = autism spectrum disorder, BD = bipolar disorder, MDD = major depressive disorder, PTSD = post-traumatic stress disorder, SCZ = schizophrenia.

Scale	Subscale	miRNA	Targeted gene(s)	Relevant traits, conditions or processes in which the miRNA is involved	Supplementary References	miRNA evidence class
COPE	Adaptive coping (2-factor COPE)	miR-16-5p	ACVR2A	SCZ, resilience toward stress in mice, psychological stress, MDD, resilience toward MDD	16, 25–30	A
	Problem-focused coping (3-factor COPE)	miR-29a-3p	ADAMTS9	SCZ, BD, ASD, response to psychotherapy in TRD. Expression changes during psychotherapy in TRD	1, 7–11	C
	(Use of Informational Support subscale for OSBPL10 associations)	miR-124a-3p	OSBPL10	SCZ, MDD, BD, resilience toward stress in mice, shared SCZ/BD risk, neuronal fate determination, neuroticism, cognitive function	7, 12–20	B
		miR-182-5p	OSBPL10	SCZ severity, MDD, response to mood stabilizers in BD. Expression changes during pharmacological treatment in MDD	21–24	
	Avoidance-focused coping (3-factor COPE)	miR-126-3p	PGR	Expression changes during psychotherapy in TRD	1	C
		miR-181a-5p	PGR	SCZ, methamphetamine use disorder, contextual fear memory formation	2–7	
		miR-378a-3p	PGR	(5p): BD	8	
RSA	Social resources	let-7a-2-3p	RBMS3	(5p): inflammation in PTSD, psychological stress, synaptic development and function. Expression changes during treatment in SCZ	8, 38, 49–51	B
		let-7 g-3p	RBMS3	(5p): SCZ, psychological stress, coping behaviour in pigs	38, 40, 52	
		miR-7-5p	RBMS3	SCZ, coping behavior in pigs	41, 52–54	
		miR-9-5p	RBMS3	Dopamine receptor density, SCZ, psychiatric disorders (miR-9-2)	9, 55–60	
		miR-129-5p	RBMS3	SCZ. Of note, *GRIN2A* and *GRIN2B* (SCZ genes) are experimentally validated targets	19, 35, 36	
		miR-137-3p	RBMS3	SCZ, phenotype heterogeneity in SCZ, SCZ-associated behavioral deficits in mice, brain/corpus callosum volumes, gray matter structure, hyppocampal functional connectivity, synaptogenesis, neural transmission. Its targets are enriched in SCZ risk loci.	19, 35, 56, 61–81	
		miR-155-5p	RBMS3	MDD severity, response to lithium in BD, resilience toward stress in mice	82–84	
		miR-335-3p	RBMS3	(5p): SCZ, psychiatric disease	85, 86	
		miR-607	RBMS3	Response to lithium in BD	87	
	Personal competence	miR-15a-5p	RET	PTSD in mice, psychological stress, stress-related diseases. Expression changes during psychotherapy in TRD	1, 37, 38	A
		miR-128-3p	RET	Behavioral disorders, behavioral sensitization, neurite outgrowth/migration/excitability	31–34	
		miR-195-5p	RET	SCZ, SCZ severity, treatment resistance in SCZ. Expression changes during psychotherapy in TRD.	1, 39–44	
		miR-218-5p	RET	Resilience toward stress in mice, treatment resistance in SCZ	45–48	
		miR-129-5p	RET	See above (the same miRNA targets also RBMS3)		
RSQ	—	miR-182-5p	NTM	See above (the same miRNA targets also OSBPL10)		C
		miR-1283	ANKRD10	Borderline personality disorder	88	D
		miR-17-5p	NPAS3	SCZ	7, 20, 40, 89, 90	C

these have ever been associated with neuroticism ($N = 1230$), SCZ ($n = 2209$) and worry ($n = 213$) (source: GWAS Catalog, search date: August 24th 2023), all 3 conditions were highlighted by binomial testing as significantly over-represented ($p = 1.4 \times 10^{-6}$ for neuroticism, $p = 6.9 \times 10^{-5}$ for schizophrenia, $p = 5.7 \times 10^{-4}$ for worry). Bonferroni correction was applied, adjusting for the testing of 3 traits/conditions.

The PRS for SCZ resulted as being significantly correlated with maladaptive coping (SNP p-value threshold=0.027, $R^2 = 0.02$, $p = 0.004$; Fig. S9), avoidance-focused coping (SNP p-value threshold=0.009, $R^2 = 0.018$, $p = 0.004$; Fig. S10) and self-esteem assessed with SERS (SNP p-value threshold=0.00015, $R^2 = 0.024$, $p = 0.002$; Fig. S11). The correlation of the SCZ PRS with maladaptive and avoidance-focused coping was positive (Pearson's correlation coefficient = 0.15 and 0.12, respectively), while the correlation with self-esteem assessed with the SERS scale was negative (Pearson's correlation coefficient = −0.15).

4. Discussion

4.1. Discussion and interpretation of findings

To our knowledge, this is the first GWAS to investigate the genetic

determinants of resilience, coping abilities and self-esteem in SCZ. As expected, results highlight a complex genetic background, with associated variants tagging genes coding for proteins with diverse molecular functions. Variation at 16 loci emerged as associated with resilience and coping abilities, with several nearest-to-peak genes previously associated with either the risk of psychiatric disease or with one or more traits or conditions of psychiatric relevance. Variants within *OSBPL10*, encoding oxysterol-binding protein like 10, reached genome-wide significance for their association with the "use of informational support" subscale of Brief-COPE, a component of problem-focused coping related to the tendency of seeking advice from other individuals. This was observed after correction for all other components of the Brief-COPE scale and supports an important role for social factors in influencing coping strategies of SCZ patients. Of note, *OSBPL10* was repeatedly identified as a SCZ risk locus in recent large-scale GWASs (Trubetskoy et al., 2022; Ikeda et al., 2019; Lam et al., 2019; Li et al., 2017), suggesting variants in this gene to act not only as risk factors for SCZ, but also as potential determinants of disease severity by contributing to shape the patients' coping abilities. Altered levels of circulating oxysterols (i.e. the oxidized forms of cholesterol, able to cross the blood-brain barrier) were previously associated with several psychiatric disorders including SCZ, and the ratio between 24- and 27-hydroxycholesterol (the main brain-specific and peripheral oxysterol, respectively) was recently proposed as a biomarker for SCZ risk and symptom severity (Sun et al., 2021; Guidara et al., 2022). In this respect, it would be important to clarify whether the Osbpl10 protein binds these specific oxysterols, as that would provide insights into the mechanisms through which *OSBPL10* influences the SCZ phenotype.

The second most significant association observed in this study—between variants inside *RBMS3* and the "social resources" subscale of the RSA—further underscores the potential relevance of social aspects (in this case in the determination of resilience), which have long been recognized as key, for example, in increasing resilience to stress (Ozbay et al., 2008). *RBMS3* encodes an RNA-binding protein most likely exerting a cytoplasmic function possibly involved with the maturation, transport and stability of RNA, rather than acting as a transcription factor (Penkov et al., 2000). Specific RNA targets of Rbms3 have not been identified, but the fact that the Rbms3 protein was observed to bind poly-A and poly-U oligonucleotides suggests that it is likely to interact with a large variety of RNAs. Besides playing a crucial role in embryonic development and being an important determinant of the progression of different types of cancers, *RBMS3* has also been associated with several psychiatric traits and has emerged multiple times as a SCZ risk locus (Trubetskoy et al., 2022; Ikeda et al., 2019; Lam et al., 2019; Li et al., 2017; Goes et al., 2015; Górnicki et al., 2022). In addition, it interacts directly with the calmodulin-binding protein neurogranin (encoded by *NRGN*), which is an established risk locus for SCZ and has a crucial role in modulating synaptic plasticity (Huttlin et al., 2021; Hwang et al., 2021).

A third association supporting the involvement of social factors in the determination of personal resilience emerged between the "social competence" subscale of the RSA and rs11250166, located approximately 1.5 kb upstream of *FDFT1*, encoding squalene synthase and positioned within a risk locus for neuroticism (Hill et al., 2020; Baselmans et al., 2019). This gene is associated with squalene synthase deficiency, and behavioral assessment for anxiety and other psychiatric traits is recommended in patients affected by this disorder (Coman et al., 2020). Squalene is a precursor of cholesterol, and metabolic syndrome (as well as, more specifically, lipid disorder) is known to be associated with schizophrenia (Vancampfort et al., 2015; Vancampfort et al., 2013). Although the link with cholesterol biosynthesis may be, at least in part, one of the underlying reasons also behind the association of *OSBPL10* with the use of informational support subscale, it is difficult to speculate on a specific role of *FDFT1*. However, the present finding may stimulate further research to check for potential correlations between polymorphisms in this gene and squalene levels in people with SCZ. It must be noted that rs11250166 is in a gene-dense region, with the *NEIL2* gene encoding a DNA glycosylase, located also in the vicinity of the variant (6.8 kb downstream) and demonstrated to modulate anxiety and learning in mice (Hildrestrand et al., 2021).

The association between variants at the *PGR* locus and avoidance-focused coping strategies may constitute an interesting hint into genetic factors that potentially contribute to the determination of coping approaches in a sex-specific manner. A common variant in the 5′-UTR of *PGR*, which codes for the progesterone receptor, was indeed associated with panic attacks in females but not in males in a small cohort of patients (Ho et al., 2004). While we didn't perform sex-specific association analyses because of the limited number of females in our cohort, these results may support the idea that specific progesterone-related factors may play a role in the determination of individual coping abilities.

The association of variants at the *NTM* and *NPAS3* loci with the RSQ score may involve neuronal formation and developmental processes. Neurotrimin, encoded by *NTM* is thought to regulate neurite sprouting, while *NPAS3*, encoding Neuronal PAS Domain Protein 3, is a transcription factor demonstrated to act as a master regulator of hippocampal neurogenesis. Such regulation is, in turn, exerted through the regulation of the expression of an ensemble of genes that are themselves crucial in determining neuropsychiatric traits, including *FMR1* (associated with fragile X syndrome) and *UBE3A* (associated with Angelman syndrome) (Michaelson et al., 2017; Singh et al., 2018). The association between the *NPAS3* locus and RSQ is particularly intriguing considering that, at least in mice, hippocampal neurogenesis is at the basis of individual resilience toward psychological stress (Planchez et al., 2021; Anacker et al., 2018).

The genetic overlap analyses highlighted potential, general overlap between the genetic milieu underlying resilience, coping and self-esteem with that of schizophrenia, neuroticism and worry. While further and more specific analyses are warranted, the PRS analysis yielded more specific findings. The genetic risk of schizophrenia interestingly emerged as positively correlated with higher levels of maladaptive and avoidance-focused coping, and with lower self-esteem. These findings support the idea that the association of less beneficial coping strategies and lower self-esteem with mental illness may, at least in part, also be due to a shared genetic basis. It is worth noting, however, that the proportion of variance explained by the PRS itself is low (1.8–2.4 %), and that similar analyses on larger cohorts and/or utilizing augmented versions of the PRS should be performed to draw definitive conclusions.

Micro-RNAs controlling the expression of the genes identified in this analysis comprise specific miRNAs recurrently associated with psychiatric disorders or related traits, such as miR-137 and miR-124 (predicted to target *RBMS3* and *OSBPL10*, respectively). As indicated in Table 2 and described in detail in the Supplementary Notes, both these miRNAs have been associated with SCZ in several studies and have been implicated in the determination of neuronal fate and synaptic transmission (Trubetskoy et al., 2022; Goes et al., 2015; Xu et al., 2016; Fu et al., 2022; Xie et al., 2022; Sabaie et al., 2022; Wendt et al., 2021; Ripke et al., 2011; Autism Spectrum Disorders Working Group of The Psychiatric Genomics Consortium, 2017; Pardiñas et al., 2018; Yao et al., 2021; Peyrot and Price, 2021). Variants inside the miR-137 host gene (*MIR137HG*) were identified as being predictive of phenotypic heterogeneity in SCZ as well as to affect hippocampal volume and functional connectivity (Kelly et al., 2014; Liu et al., 2014), and both these miRNAs were observed to be enriched for target genes in SCZ risk loci (Hauberg et al., 2016; Ying et al., 2022). While direct links between miR-137 and coping or resilience have not been identified to date, this miRNA has been recently shown to act as an important regulator of emotion processing (Pergola et al., 2023). MiR-124 has instead been proposed to be a mediator of resilience levels in mice (reason why miRNA evidence concerning *OSBPL10* was classified as level B) (Pan-Vazquez et al., 2015; Higuchi et al., 2016). Overall, these pieces of evidence suggest these miRNAs as potential candidate biomarkers for resilience and coping abilities in SCZ, although the level of evidence provided by the miRNA analysis

conducted here is not sufficient to draw definitive conclusions.

The same study in which miR-124 was proposed as a biomarker of resilience had also identified miR-16, experimentally proven to target *ACVR2A* (supported by class A miRNA evidence) (Pan-Vazquez et al., 2015). *ACVR2A* encodes Activin A Receptor Type 2A and has emerged as suggestively associated with an adaptive coping strategy in this study. Activin is a hormone of the transforming growth factor-β superfamily, and activin signaling has been demonstrated to enhance adult neurogenesis in the hippocampus and to modulate anxiety (Link et al., 2016; Ageta et al., 2008). Furthermore, *ACVR2A* was identified as a risk locus for neuroticism or worry in 7 different studies (Hill et al., 2020; Luciano et al., 2018; Nagel et al., 2018a; 2018b; Kichaev et al., 2019; Hindley et al., 2023; Wendt et al., 2023).

The remaining genes that we found associated with coping or resilience scales are generally supported by less abundant evidence concerning a potential role. However, *ADAMTS9, LUZP2* and *ANKRD10* have been identified as risk loci for relevant traits, such as neuroticism, worry or SCZ itself (Table 1 and Fig. 2). Finally, miRNA evidence concerning the tyrosine kinase receptor gene *RET* (not associated with relevant traits in the literature) was classified as class A, by virtue of being a validated target of miR-15, identified as a biomarker of resilience in mice (Maurel et al., 2021).

This study failed to replicate the main genetic associations emerged in the two previously published GWAS on resilience and coping directly assessed through dedicated scales (Stein et al., 2019; Shimanoe et al., 2019). However, of note, variation in *NLGN1* (encoding Neuroligin 1), previously associated with PTSD (Kilaru et al., 2016), achieved nominal significance at the gene level ($0.01 < p < 0.05$) for association with maladaptive and avoidance-focused coping, as well as for SERS. There may be multiple reasons for this lack of replication, including (but not limited to) differences in the study design and in the analyzed cohort.

4.2. Limitations

This study suffers from some important limitations. First, the size of the analyzed cohort confers limited statistical power in the context of a genome-wide investigation, and this forced us to use a suggestive association threshold besides the conventional genome-wide significance threshold. A direct consequence of this is the need to interpret results of this work (including those of accessory analyses) with caution. However, most of the associated loci are supported by orthogonal evidence for what concerns a potential role in psychiatric conditions, and we believe these results to represent important pilot findings. Second, while the evidence from the miRNA target analysis has solely been used as supportive where present, its classification is based on somewhat arbitrary parameters. Third, exclusion criteria comprise history of alcohol and/or substance abuse in the last six months and, while this is common in studies on psychiatric disease, it may introduce a bias against patients with higher "substance use" Brief-COPE subscale scores.

4.3. Conclusions

This is the first GWAS investigating the genetic determinants of coping, resilience and self-esteem in SCZ patients. Results confirm a complex genetic background partly shared with SCZ itself and highlight a pronounced genetic overlap with neuroticism and worry. Social factors appear to be of primary importance in the determination of resilience and coping abilities, given the multiple social correlates predicted by variation at the loci identified in this analysis. From the biological point of view, hippocampal neurogenesis and transmission, possibly as well as lipid metabolism, emerged as potentially important determinants of personal resources. Of note, several genes and miRNAs highlighted by this study (e.g. *OSBPL10, NPAS3, ACVR2A, FDFT1* and miR-137) have been reported to play an important role in those processes.

Data availability

The GWAS summary statistics of each of the scales analyzed here are available in the Figshare repository, with the following doi:10.6084/m9.figshare.26413000.

CRediT authorship contribution statement

Francesco Mazzarotto: Writing – review & editing, Writing – original draft, Visualization, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Palmiero Monteleone:** Writing – review & editing, Resources, Project administration, Data curation. **Alessandra Minelli:** Writing – original draft, Methodology, Investigation, Funding acquisition, Data curation. **Stefania Mattevi:** Software, Formal analysis. **Giammarco Cascino:** Resources, Methodology, Data curation. **Paola Rocca:** Resources, Methodology, Data curation. **Alessandro Rossi:** Resources, Methodology, Data curation. **Alessandro Bertolino:** Resources, Methodology, Data curation. **Eugenio Aguglia:** Resources, Methodology, Data curation. **Carlo Altamura:** Resources, Methodology, Data curation. **Mario Amore:** Resources, Methodology, Data curation. **Antonello Bellomo:** Resources, Methodology, Data curation. **Paola Bucci:** Resources, Methodology, Data curation. **Enrico Collantoni:** Resources, Methodology, Data curation. **Liliana Dell'Osso:** Data curation, Methodology, Resources. **Fabio Di Fabio:** Resources, Methodology, Data curation. **Andrea Fagiolini:** Resources, Methodology, Data curation. **Luigi Giuliani:** Resources, Methodology, Data curation. **Carlo Marchesi:** Resources, Methodology, Data curation. **Giovanni Martinotti:** Resources, Methodology, Data curation. **Cristiana Montemagni:** Resources, Methodology, Data curation. **Federica Pinna:** Resources, Methodology, Data curation. **Maurizio Pompili:** Resources, Methodology, Data curation. **Antonio Rampino:** Resources, Methodology, Data curation. **Rita Roncone:** Resources, Methodology, Data curation. **Alberto Siracusano:** Resources, Methodology, Data curation. **Antonio Vita:** Resources, Methodology, Data curation. **Patrizia Zeppegno:** Resources, Methodology, Data curation. **Silvana Galderisi:** Resources, Methodology, Investigation, Data curation. **Massimo Gennarelli:** Supervision, Resources, Project administration, Methodology, Funding acquisition, Data curation. **Mario Maj:** Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The network performed recruitment and clinical evaluation thanks to funds by the Italian Society of Psychopathology (SOPSI). SOPSI had no role in conceiving the study design, collecting or analysing samples, interpretating results, writing the manuscript or deciding to submit the paper for publication. Genotyping costs were supported by the grant "Ricerca Corrente" from the Italian Ministry of Health.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2024.116107.

Appendix

Members of the Italian Network for Research on Psychoses involved in this study include: Chiara Caulo, Giulia D'Agostino (University of Salerno), Giulio Corrivetti (Department of Mental Health, Salerno);

Pierluigi Selvaggi, Enrico D'Ambrosio, Piergiuseppe Di Palo (University of Bari); Anna Rita Atti (University of Bologna); Stefano Barlati, Anna Ceraso, Gabriele Nibbio (University of Brescia); Pasquale Paribello, Luca Marras, Bernardo Carpiniello (University of Cagliari); Giuseppe Piegari, Giulia Maria Giordano, Pasquale Pezzella, Antonio Melillo (University of Campania "Luigi Vanvitelli", Naples); Carmen Concerto, Ludovico Mineo (University of Catania); Mauro Pettorruso, Stefania Chiappini, Francesco Di Carlo (University of Chieti); Mario Altamura, Ivana Leccisotti, Laura De Masi (University of Foggia); Pietro Calcagno, Gianluca Serafini, Costanza Arzani (University of Genoa); Ramona Di Stefano, Francesca Pacitti, Rodolfo Rossi, Laura Giusti, Silvia Mammarella, Sasha Del Vecchio (University of L'Aquila); Matteo Marcatili, Oscar Fusi (University of Milan); Carla Gramaglia, Debora Marangon, Lucia Bestagini (University of Eastern Piedmont, Novara); Paolo Meneguzzo, Elena Tenconi, Angela Favaro (University of Padua); Maria Lidia Gerra, Davide Fausto Borelli, Francesca Magnani (University of Parma); Barbara Carpita, Ivan Mirko Cremone, Giulia Amatori (University of Pisa); Antonino Buzzanca, Marianna Frascarelli, Tommaso Accinni, Isabella Berardelli, Denise Erbuto, Anna Comparelli (Sapienza University of Rome); Alessandro Cuomo, Arianna Goracci, Simone Bolognesi (University of Siena); Cinzia Niolu, Giorgio Di Lorenzo, Tommaso Jannini (Tor Vergata University of Rome); Claudio Brasso, Vincenzo Villari, Rodolfo Sgro (University of Turin).

References

Aburn, G., Gott, M., Hoare, K., 2016. What is resilience? An integrative review of the empirical literature. J. Adv. Nurs. 72, 980–1000.

Ageta, H., et al., 2008. Activin in the brain modulates anxiety-related behavior and adult neurogenesis. PLoS One 3, e1869.

Anacker, C., et al., 2018. Hippocampal neurogenesis confers stress resilience by inhibiting the ventral dentate gyrus. Nature 559 (7712), 98–102.

Ashley-Koch, A.E., et al., 2015. Genome-wide association study of posttraumatic stress disorder in a cohort of Iraq–Afghanistan era veterans. J. Affect. Disord. 184, 225.

Autism Spectrum Disorders Working Group of The Psychiatric Genomics Consortium, 2017. Meta-analysis of GWAS of over 16,000 individuals with autism spectrum disorder highlights a novel locus at 10q24.32 and a significant overlap with schizophrenia. Mol. Autism 8, 21.

Baselmans, B.M.L., et al., 2019. Multivariate genome-wide analyses of the well-being spectrum. Nat. Genet. 51, 445–451.

Binder, E.B., 2018. Dissecting the molecular mechanisms of gene x environment interactions: implications for diagnosis and treatment of stress-related psychiatric disorders. Eur. J. Psychotraumatol. 8, 1412745.

Boardman, J.D., Blalock, C.L., Button, T.M.M, 2008. Sex differences in the heritability of resilience. Twin. Res. Hum. Genet. 11, 12–27.

Caqueo-Urízar, A., et al., 2021. Effects of resilience and acculturation stress on integration and social competence of migrant children and adolescents in Northern Chile. Int. J. Environ. Res. Public Health 18, 1–13.

Carver, C.S., 1997. You want to measure coping but your protocol's too long: consider the brief COPE. Int. J. Behav. Med. 4, 92–100.

Chen, H., et al., 2019. Positive coping and resilience as mediators between negative symptoms and disability among patients with schizophrenia. Front. Psychiatry 10.

Choi, S.W., O'Reilly, P.F, 2019. PRSice-2: polygenic risk Score software for biobank-scale data. Gigascience 8 (7).

Coman, D., et al., 2020. Squalene synthase deficiency. In: Adam, MP, Feldman, J, Mirzaa, GM, et al. (Eds.), GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle, pp. 1993–2024.

Correll, C.U., et al., 2022. Mortality in people with schizophrenia: a systematic review and meta-analysis of relative risk and aggravating or attenuating factors. World Psychiatry 21, 248.

Das, S., et al., 2016. Next-generation genotype imputation service and methods. Nat. Genet. 48, 1284–1287.

Drayton, M., Birchwood, M., Trower, P., 1998. Early attachment experience and recovery from psychosis. Br. J. Clin. Psychol. 37, 269–284.

Duncan, L.E., et al., 2018. Largest GWAS of PTSD ($N = 20\ 070$) yields genetic overlap with schizophrenia and sex differences in heritability. Mol. Psychiatry 23, 666.

Dunn, S.H., Conley, Y.P., 2015. A systematic review of genetic influences on coping. Biol. Res. Nurs. 17, 87.

Fluharty, M., Bu, F., Steptoe, A., Fancourt, D., 2021. Coping strategies and mental health trajectories during the first 21 weeks of COVID-19 lockdown in the United Kingdom. Soc. Sci. Med. 279.

Folkman, S., Moskowitz, J.T., 2004. Coping: pitfalls and promise. Annu. Rev. Psychol. 55, 745–774.

Friborg, O., Hjemdal, O., Rosenvinge, J.H., Martinussen, M., 2003. A new rating scale for adult resilience: what are the central protective resources behind healthy adjustment? Int. J. Methods Psychiatr. Res. 12, 65–76.

Fu, X., Liu, Y., Baranova, A., Zhang, F., 2022. Deregulatory miRNA-BDNF network inferred from dynamic expression changes in schizophrenia. Brain Sci. 12 (2).

Galderisi, S., et al., 2014. The influence of illness-related variables, personal resources and context-related factors on real-life functioning of people with schizophrenia. World Psychiatry 13, 275–287.

Goes, F.S., et al., 2015. Genome-wide association study of schizophrenia in Ashkenazi Jews. Am. J. Med. Genet. B 168, 649–659.

Górnicki, T., et al., 2022. Role of RBMS3 novel potential regulator of the EMT phenomenon in physiological and pathological processes. Int. J. Mol. Sci. 23, 23.

Guidara, W., et al., 2022. Plasma oxysterols in drug-free patients with schizophrenia. J. Steroid. Biochem. Mol. Biol. 221, 106123.

Hansson, K., et al., 2008. Individual resiliency factors from a genetic perspective: results from a twin study. Fam. Process 47, 537–551.

Hauberg, M.E., Roussos, P., Grove, J., Børglum, A.D., Mattheisen, M., 2016. Analyzing the role of MicroRNAs in schizophrenia in the context of common genetic risk variants. JAMA Psychiatry 73, 369–377.

He, Q., et al., 2021. Influence of polygenic risk scores for schizophrenia and resilience on the cognition of individuals at-risk for psychosis. Transl. Psychiatry 11.

Hess, J.L., et al., 2021. A polygenic resilience score moderates the genetic risk for schizophrenia. Mol. Psychiatry 26, 800.

Hess, J.L., et al., 2023. A polygenic resilience score moderates the genetic risk for schizophrenia: replication in 18,090 cases and 28,114 controls from the psychiatric genomics consortium. Am. J. Med. Genet. Part B. https://doi.org/10.1002/AJMG.B.32957.

Higuchi, F., et al., 2016. Hippocampal microRNA-124 enhances chronic stress resilience in mice. J. Neurosci. 36, 7253–7267.

Hildrestrand, G.A., et al., 2021. NEIL1 and NEIL2 DNA glycosylases modulate anxiety and learning in a cooperative manner in mice. Commun. Biol. 4 (1).

Hill, W.D., et al., 2020. Genetic contributions to two special factors of neuroticism are associated with affluence, higher intelligence, better health, and longer life. Mol. Psychiatry 25, 3034–3052.

Hindley, G., et al., 2023. Multivariate genetic analysis of personality and cognitive traits reveals abundant pleiotropy. Nat. Hum. Behav. 7 (9).

Ho, H.P., et al., 2004. Association between a functional polymorphism in the progesterone receptor gene and panic disorder in women. Psychoneuroendocrinology 29, 1138–1141.

Hofer, A., et al., 2023a. Self-esteem in stabilized individuals with chronic schizophrenia: association with residual symptoms and cognitive functioning. Eur. Arch. Psychiatry Clin. Neurosci. 273, 1737–1746.

Hofer, A., et al., 2023b. Self-esteem in stabilized individuals with chronic schizophrenia: association with residual symptoms and cognitive functioning. Eur. Arch. Psychiatry Clin. Neurosci. 273, 1737.

Huttlin, E.L., et al., 2021. Dual proteome-scale networks reveal cell-specific remodeling of the human interactome. Cell 184, 3022–3040 e28.

Hwang, H., et al., 2021. Neurogranin, encoded by the schizophrenia risk gene NRGN, bidirectionally modulates synaptic plasticity via calmodulin-dependent regulation of the neuronal phosphoproteome. Biol. Psychiatry 89, 256–269.

Ikeda, M., et al., 2019. Genome-wide association study detected novel susceptibility genes for schizophrenia and shared trans-populations/diseases genetic effect. Schizophr. Bull. 45, 824–834.

Kang, H.M., et al., 2010. Variance component model to account for sample structure in genome-wide association studies. Nat. Genet. 42, 348–354.

Kelly, S., et al., 2014. Genome-wide schizophrenia variant at MIR137 does not impact white matter microstructure in healthy participants. Neurosci. Lett. 574, 6–10.

Kichaev, G., et al., 2019. Leveraging polygenic functional enrichment to improve GWAS power. Am. J. Hum. Genet. 104, 65–75.

Kilaru, V., et al., 2016. Genome-wide gene-based analysis suggests an association between Neuroligin 1 (NLGN1) and post-traumatic stress disorder. Transl. Psychiatry 6, e820.

Korem, N., et al., 2023. Correlates of avoidance coping in trauma-exposed U.S. military veterans: results from the national health and resilience in veterans study. J. Affect. Disord. 339, 89–97.

Lam, M., et al., 2019. Comparative genetic architectures of schizophrenia in East Asian and European populations. Nat. Genet. 51, 1670–1678.

Li, Z., et al., 2017. Genome-wide association analysis identifies 30 new susceptibility loci for schizophrenia. Nat. Genet. 49, 1576–1583.

Link, A.S., Zheng, F., Alzheimer, C., 2016. Activin signaling in the pathogenesis and therapy of neuropsychiatric diseases. Front. Mol. Neurosci. 9 (32).

Liu, B., et al., 2014. The impact of MIR137 on dorsolateral prefrontal-hippocampal functional connectivity in healthy subjects. Neuropsychopharmacology 39, 2153–2160.

Logue, M.W., et al., 2013. A genome-wide association study of posttraumatic stress disorder identifies the retinoid-related orphan receptor alpha (RORA) gene as a significant risk locus. Mol. Psychiatry 18, 937.

Luciano, M., et al., 2018. Association analysis in over 329,000 individuals identifies 116 independent variants influencing neuroticism. Nat. Genet. 50, 6–11.

Luthar, S.S., 2006. Resilience in development: a synthesis of research across five decades. Dev. Psychopathol. 3, 739–795.

Maul, S., et al., 2020. Genetics of resilience: implications from genome-wide association studies and candidate genes of the stress response system in posttraumatic stress disorder and depression. Am. J. Med. Genet. B 183, 77–94.

Maurel, O.M., et al., 2021. Dysregulation of miR-15a-5p, miR-497a-5p and miR-511-5p is associated with modulation of BDNF and FKBP5 in brain areas of PTSD-related susceptible and resilient mice. Int. J. Mol. Sci. 22 (10).

McEwen, B.S., 2016. pursuit of resilience: stress, epigenetics, and brain plasticity. Ann. N. Y. Acad. Sci. 1373, 56–64.

Melroy-Greif, W.E., Wilhelmsen, K.C., Yehuda, R., Ehlers, C.L., 2017. Genome-wide association study of post-traumatic stress disorder in two high-risk populations. Twin. Res. Hum. Genet. 20, 197.
Ménard, C., Pfau, M.L., Hodes, G.E., Russo, S.J., 2017. Immune and Neuroendocrine Mechanisms of Stress Vulnerability and Resilience. Neuropsychopharmacology 42, 62–80.
Mian, L., Lattanzi, G.M., Tognin, S., 2018. Coping strategies in individuals at ultra-high risk of psychosis: a systematic review. Early Interv. Psychiatry 12, 525–534.
Michaelson, J.J., et al., 2017. Neuronal PAS domain proteins 1 and 3 are master regulators of neuropsychiatric risk genes. Biol. Psychiatry 82, 213–223.
Nagel, M., et al., 2018b. Meta-analysis of genome-wide association studies for neuroticism in 449,484 individuals identifies novel genetic loci and pathways. Nat. Genet. 50, 920–927.
Nagel, M., Watanabe, K., Stringer, S., Posthuma, D., Van Der Sluis, S, 2018a. Item-level analyses reveal genetic heterogeneity in neuroticism. Nat. Commun. 9 (1).
Navrady, L.B., et al., 2018. Genetic and environmental contributions to psychological resilience and coping. Wellcome Open Res. 3.
Nugent, W.R. & Thomas, J.W. Validation of a clinical measure of self-esteem. https://doi.org/10.1177/104973159300300205 3, 191–207 (1993).
Ozbay, F., Fitterling, H., Charney, D., Southwick, S., 2008. Social support and resilience to stress across the life span: a neurobiologic framework. Curr. Psychiatry Rep. 10, 304–310.
Pan-Vazquez, A., et al., 2015. Impact of voluntary exercise and housing conditions on hippocampal glucocorticoid receptor, miR-124 and anxiety. Mol. Brain 8 (1).
Pardiñas, A.F., et al., 2018. Common schizophrenia alleles are enriched in mutation-intolerant genes and in regions under strong background selection. Nat. Genet. 50, 381–389.
Penkov, D., et al., 2000. Cloning of a human gene closely related to the genes coding for the c-myc single-strand binding proteins. Gene 243, 27–36.
Penley, J.A., Tomaka, J., Wiebe, J.S., 2002. The association of coping to physical and psychological health outcomes: a meta-analytic review. J. Behav. Med. 25, 551–603.
Pergola, G., et al., 2023. A miR-137-related biological pathway of risk for schizophrenia is associated with human brain emotion processing. Biol. Psychiatry Cogn. Neurosci. NeuroimAging. https://doi.org/10.1016/J.BPSC.2023.11.001.
Peyrot, W.J., Price, A.L, 2021. Identifying loci with different allele frequencies among cases of eight psychiatric disorders using CC-GWAS. Nat. Genet. 53, 445–454.
Planchez, B., et al., 2021. Increasing adult hippocampal neurogenesis promotes resilience in a mouse model of depression. Cells 10 (5).
Poloni, N., et al., 2018. A naturalistic study on the relationship among resilient factors, psychiatric symptoms, and psychosocial functioning in a sample of residential patients with psychosis. Psychol. Res. Behav. Manag. 11, 123–131.
Ripke, S., et al., 2011. Genome-wide association study identifies five new schizophrenia loci. Nat. Genet. 43, 969–978.
Roosenschoon, B.J., Kamperman, A.M., Deen, M.L., Van Weeghel, J., Mulder, C.L., 2019. Determinants of clinical, functional and personal recovery for people with schizophrenia and other severe mental illnesses: a cross-sectional analysis. PLoS One 14.
Rossi, A., et al., 2017. The relationships of personal resources with symptom severity and psychosocial functioning in persons with schizophrenia: results from the Italian Network for Research on Psychoses study. Eur. Arch. Psychiatry Clin. Neurosci. 267, 285–294.
Ru, Y., et al., 2014. The multiMiR R package and database: integration of microRNA–target interactions along with their disease and drug associations. Nucleic Acids Res. 42, e133.
Sabaie, H., et al., 2022. Identification of key long non-coding RNA-associated competing endogenous RNA axes in Brodmann area 10 brain region of schizophrenia patients. Front. Psychiatry 13, 1010977.
Shimanoe, C., et al., 2019. A genome-wide association study of coping behaviors suggests FBXO45 is associated with emotional expression. Genes. Brain Behav. 18 (2).
Singh, K., et al., 2018. The combined impact of IgLON family proteins Lsamp and Neurotrimin on developing neurons and behavioral profiles in mouse. Brain Res. Bull. 140, 5–18.
Solberg, M.A., Gridley, M.K., Peters, R.M., 2022. The factor structure of the brief cope: a systematic review. West J. Nurs. Res. 44, 612–627.
Sollis, E., et al., 2023. The NHGRI-EBI GWAS Catalog: knowledgebase and deposition resource. Nucleic Acids Res. 51, D977–D985.
Stein, M.B., et al., 2019. Genomewide analyses of psychological resilience in US army soldiers. Am. J. Med. Genet. B 180, 310.
Stein, M.B., et al., 2021. Genome-wide association analyses of posttraumatic stress disorder and its symptom subdomains in the million veteran program. Nat. Genet. 53, 174.
Sun, Z., et al., 2021. Brain-specific oxysterols and risk of schizophrenia in clinical high-risk subjects and patients with schizophrenia. Front. Psychiatry 12, 711734.
Torgalsbøen, A.K., Rund, B.R., 2010. Maintenance of recovery from schizophrenia at 20-year follow-up: what happened? Psychiatry 73, 70–83.
Trubetskoy, V., et al., 2022. Mapping genomic loci implicates genes and synaptic biology in schizophrenia. Nature 604, 502–508.
Turner, S.D., 2018. qqman: an R package for visualizing GWAS results using Q-Q and manhattan plots. J. Open Source Softw. 3, 731.
Vancampfort, D., et al., 2013. A meta-analysis of cardio-metabolic abnormalities in drug naïve, first-episode and multi-episode patients with schizophrenia versus general population controls. World Psychiatry 12, 240–250.
Vancampfort, D., et al., 2015. Risk of metabolic syndrome and its components in people with schizophrenia and related psychotic disorders, bipolar disorder and major depressive disorder: a systematic review and meta-analysis. World Psychiatry 14, 339–347.
Wadsworth, M.E., 2015. Development of maladaptive coping: a functional adaptation to chronic, uncontrollable stress. Child Dev. Perspect. 9, 96–100.
Watanabe, K., Taskesen, E., van Bochoven, A., Posthuma, D., 2017. Functional mapping and annotation of genetic associations with FUMA. Nat. Commun. 8 (1), 1–11.
Webb Hooper, M., Baker, E.A., McNutt, M.D, 2013. Associations between coping, affect, and social support among low-income African American smokers. Addict. Behav. 38, 2736–2740.
Wendt, F.R., et al., 2021. Multivariate genome-wide analysis of education, socioeconomic status and brain phenome. Nat. Hum. Behav. 5, 482–496.
Wendt, F.R., et al., 2023. Sex-Specific genetic and transcriptomic liability to neuroticism. Biol. Psychiatry 93, 243–252.
Wolf, E.J., et al., 2018. A classical twin study of PTSD symptoms and resilience: evidence for a single spectrum of vulnerability to traumatic stress. Depress. Anxiety 35, 132.
Xie, M., et al., 2022. Identifying crucial biomarkers in peripheral blood of schizophrenia and screening therapeutic agents by comprehensive bioinformatics analysis. J. Psychiatr. Res. 152, 86–96.
Xu, Y., et al., 2016. Exploring transcription factors-microRNAs co-regulation networks in schizophrenia. Schizophr. Bull. 42, 1037–1045.
Yao, X., et al., 2021. Integrative analysis of genome-wide association studies identifies novel loci associated with neuropsychiatric disorders. Transl. Psychiatry 11.
Ying, S., Heung, T., Zhang, Z., Yuen, R.K.C., Bassett, A.S., 2022. Schizophrenia risk mediated by microRNA target genes overlapped by genome-wide rare copy number variation in 22q11.2 deletion syndrome. Front. Genet. 13, 812183.
Zhuang, H., Wang, H., Ji, Z., 2022. findPC: an R package to automatically select the number of principal components in single-cell analysis. Bioinformatics 38, 2949–2951.
Zizolfi, D., et al., 2019. Resilience and recovery style: a retrospective study on associations among personal resources, symptoms, neurocognition, quality of life and psychosocial functioning in psychotic patients. Psychol. Res. Behav. Manag. 12, 385–395.