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PERSPECTIVE

Genomics and psychological resilience: a research agenda

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Abstract

Although exposure to adversity increases risk for poor mental health outcomes, many people exposed to adversity do not develop such outcomes. Psychological resilience, defined broadly as positive emotional and/or behavioral adaptation to adversity, may be influenced by genetic factors that have remained largely unexplored in the era of large-scale genome-wide studies. In this perspective, we provide an integrative framework for studying human genome-wide variation underlying resilience. We first outline three complementary working definitions of psychological resilience—as a capacity, process, and outcome. For each definition, we review emerging empirical evidence, including findings from positive psychology, to illustrate how a resilience-based framework can guide novel and fruitful directions for the field of psychiatric genomics, distinct from the ongoing study of psychiatric risk and related traits. Finally, we provide practical recommendations for future genomic research on resilience, highlighting a need to augment cross-sectional findings with prospective designs that include detailed measurement of adversities and outcomes. A research framework that explicitly addresses resilience could help us to probe biological mechanisms of stress adaptation, identify individuals who may benefit the most from prevention and early intervention, and ascertain modifiable protective factors that mitigate negative outcomes even for those at high genetic risk.

Introduction

Although exposure to adversity increases risk for poor mental health outcomes [1, 2], many people exposed to adversity do not develop such outcomes [3, 4]. Psychological resilience—whereby individuals maintain or regain positive mental health and/or functioning despite adversity [5–7]—has long been thought to be determined by multiple influences [8], ranging from environmental factors (e.g., community and social resources) to cognitive–behavioral patterns (e.g., problem-solving, reframing). More recently, researchers have also studied the role of heritable genetic variation in shaping resilience. The results from twin studies suggest that between 31 and 52% of observed variance in resilience phenotypes can be explained by such genetic variation [9–11]. A limited set of candidate gene studies have sought to validate genetic contributors to resilience [12–14], but have been generally criticized for a poor record of replication [15]. More recently, genomic methods such as genome-wide association studies (GWAS) [16–18] and polygenic scoring [19, 20] have proliferated along with large publicly available data resources such as the UK Biobank [21] and are now poised to enable well-powered human genetic research on psychological resilience. However, few studies have capitalized on the availability of comprehensive genotyping and large-scale data science to study this phenomenon.

This perspective aims to address this gap by proposing an integrative framework for extending genome-wide approaches to resilience. To accomplish this goal, we first outline three working definitions of psychological

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resilience, and review emerging evidence from genome-wide data for each of these definitions. Although psychological resilience is inextricably linked to the study of psychiatric risk and related traits, we discuss how a resilience-based framework can guide distinct and fruitful directions for the field of psychiatric genomics. We then summarize directions for future genomic research on resilience, highlighting a need to augment cross-sectional findings with prospective designs that include detailed measurement of adversities and outcomes. By broadening the current scope of psychiatric genomics research, we may gain additional molecular insights to guide ongoing basic and clinical research in understanding how humans adapt successfully to stress and adversity.

An integrative genomic framework for studying resilience

The first step to extending genome-wide approaches to psychological resilience requires consensus on how resilience should be defined. Theoretical definitions of resilience have been discussed in detail elsewhere [8, 22–24], typically requiring exposure to adversity and evidence of positive adaptation despite adversity. However, one debate in the field has been whether resilience can be meaningfully studied as [1] a trait-like *capacity* that precedes adversity [2]; a dynamic *process* that unfolds during and after adversity [3]; an *outcome* following adversity [7, 8, 24, 25]. We argue that genome-wide data could be used to examine resilience through each of these interrelated definitions (Fig. 1).

As shown in this model, some individuals may possess pre-existing characteristics, or "resiliency factors," that increase their general *capacity* for resilience. For example, individuals with high levels of dispositional optimism or cognitive ability may be able to generally cope more flexibly and regulate difficult emotions, including in the face of adversity [26]. The genetic basis of these predisposing capacities could be studied through GWAS. Second, resilience is now thought to represent a dynamic *process* that unfolds in the aftermath of adversity [6, 7], involving an interplay between predisposing capacities, other protective factors (e.g., situational resources, such as social support), and risk factors (e.g., pre-existing vulnerabilities; situational characteristics of the adversity, such as its type, timing, duration, and severity). Studies incorporating both genomic and environmental data may shed light on this process by examining genetic influences in combination with non-genetic risk and protective factors across time. Third, resilience can be evidenced by the subsequent *outcome*, whether absence of disorder, presence of positive functioning, and/or recovery to baseline following adversity [5]. Thus, similar to psychiatric disorders, these outcomes could be studied in a GWAS context, but with several meaningful distinctions, as summarized in the following sections. Together, these definitions of resilience may provide complementary (or distinct) insights on adaptation across the continuum of exposure to adversity, reflecting shared (or unique) genetic underpinnings [27].

In the next section, we review emerging evidence for each of these definitions and discuss how novel features of a resilience framework (Fig. 2) may broaden existing efforts in psychiatric genomics. Importantly, psychiatric genomics has traditionally focused on specific disorders or vulnerability traits in cross-sectional designs, rather than strength-based factors and protective processes influencing broad adaptive outcomes across time. Through the lens of this resilience framework, we thus map out a promising territory for genomic research.

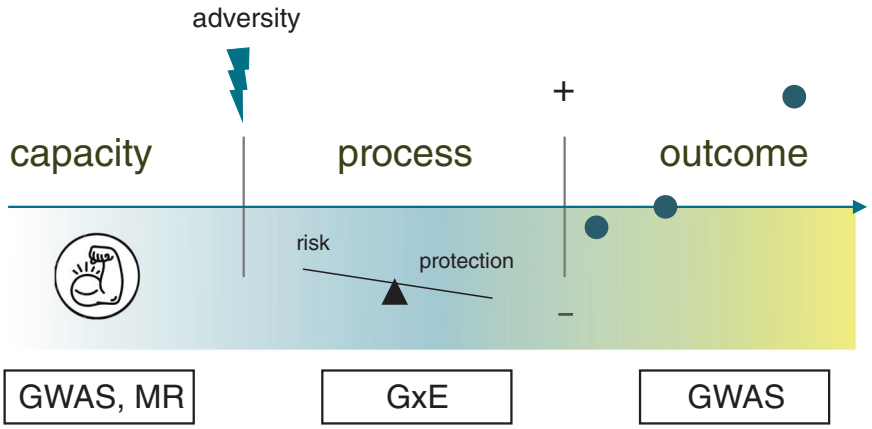

Fig. 1 Proposed integrative genomic framework for resilience. GWAS = genome-wide association studies. MR = Mendelian randomization studies. GxE = gene-by-environment studies

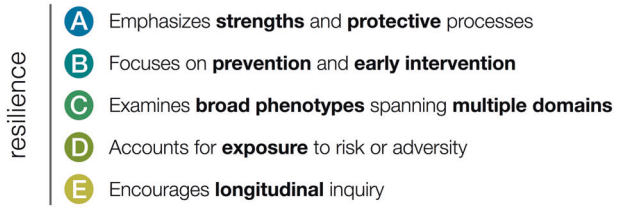

Fig. 2 Novel features of a resilience framework for psychiatric genomics

Genetic factors underlying *capacity* for resilience

Rather than focusing on vulnerability and disease, a resilience framework *directs attention to traits that index positive psychological strengths (Feature A)*. Such traits do not require adversity to be present, but could exert beneficial effects when adversity occurs. Though not explicitly studied in the context of resilience, numerous affective, personality, and cognitive phenotypes known to facilitate adaptive coping [28] and buffer against negative psychiatric outcomes following traumatic events [29] have been examined in GWAS. For example, an early GWAS identified one genome-wide significant locus associated with a positive affect, or the tendency to experience positive emotions [30], within a high-trauma sample of 2522 African-American individuals. This locus was correlated with brain and blood expression of microRNAs previously implicated in reward behavior and with activation of reward-related brain regions ($n = 55$). However, a subsequent small study ($n = 82$) of European individuals unselected for trauma exposure [31] did not fully replicate this finding. One of the earliest large-scale GWAS of subjective well-being ($n = 298{,}420$)—encompassing a positive affect and life satisfaction—identified three separate loci associated with subjective well-being [32]. A larger meta-analytic GWAS ($n = 388{,}538$) leveraging genome-wide information from correlated traits [33] identified 49 independent loci associated with subjective well-being and supported a role for genes expressed in central nervous system tissues and related to dopaminergic neurons, startle response, and exploration of new environments.

Cognitive abilities, including intelligence (IQ), have also been widely conceptualized as a protective factor across development [34] and associated with the absence of psychopathology in at-risk populations [35]. Based on prospective evidence that lower IQ predicts later risk for psychiatric disorders in trauma-exposed individuals [36], IQ has been posited to be a marker of cognitive reserve that could buffer individuals from psychopathology following adversity [37]. IQ and cognitive ability, as well as highly correlated phenotypes, such as educational attainment, have been the subject of several large-scale GWAS [38–41], including a recent meta-analytic GWAS in 269,867 individuals that identified 205 independent genome-wide significant loci for intelligence [40], and a meta-analytic GWAS of educational attainment in over 1.1 million individuals that identified 1271 genome-wide significant loci, yielding polygenic scores explaining 7–10% of variation in cognitive performance [41]. Consistent with a potential role in resilience, these cognitive phenotypes have also been found to be inversely correlated genetically with psychopathology ($r = -0.10$ to -0.27) [39, 40], though the causal nature of these relationships is not well understood.

Personality traits, such as conscientiousness and extraversion, have also been known to account for substantial variance in positive functioning and psychological adjustment [11, 42]. A GWAS of these traits ($n = 123{,}132$–$260{,}861$) identified a total of six genome-wide significant loci that were subsequently associated in external databases with gene expression in brain tissues [43]. Genome-wide variation associated with conscientiousness and agreeableness has also been inversely correlated with psychiatric disorders such as depression [43]. Elsewhere, polygenic scores for extraversion, constructed by combining GWAS-estimated effects of loci across the genome into a single score, have been associated with several dimensions of psychosocial well-being, though still explain <1% of variation in these dimensions [44].

Emerging work has begun to more directly study capacity for resilience, including trait resilience [45, 46]—a dispositional ability to cope effectively and "bounce back" from stress—which has been shown to protect against psychiatric disorders in the context of adversity [47]. Despite twin studies estimating heritability around 40% [9, 11], only one GWAS of trait resilience to our knowledge has been conducted [48]. This GWAS of trait resilience (defined as perceived coping ability) was performed in a sample of US Army soldiers ($n = 11{,}492$) and identified one independent genome-wide significant locus (rs4260523) located upstream of a gene (*DCLK2*) previously implicated in neuron survival and preferentially expressed in brain areas, including the frontal cortex and hippocampus. Studies could extend this work by investigating the genomic basis of trait resilience in larger, population-based samples, as well as other heritable traits associated with stress adaptability such as emotion regulation, cardiovascular flexibility, and social affiliation [49–51].

Rather than motivating further GWAS of individual traits, a resilience framework is expected to *prioritize inquiry spanning multiple traits (Feature B)*. Individual traits, like positive affect or intelligence, should not be taken to constitute resiliency per se, but rather represent components—or ingredients—of resiliency. Given a wide array of traits likely associated with a capacity for resilience, future efforts may benefit from integrating GWAS results to assess

genetic variation shared by these traits and conduct functional follow-ups, providing clues to the underlying adaptive molecular mechanisms. A multivariate genome-wide association meta-analysis [52] recently identified 304 independent loci linked to a well-being "spectrum" encompassing positive affect/life satisfaction and neuroticism/depression traits ($n = 2{,}370{,}390$), pointing to gene expression in the prefrontal cortex and hippocampus, particularly the subiculum, and enrichment for GABA-related interneurons in these areas. Finally, a resilience framework *focuses on identifying opportunities to prevent psychiatric morbidity (Feature C)*, rather than solely addressing established disease. While GWAS literature has already suggested that traits, such as positive affect, may be inversely related to psychiatric risk at a genetic level [32, 40, 43], it remains unclear whether such inverse associations reflect true protective effects that could be targeted through preventive efforts. Such questions can be interrogated using causal inference methods such as Mendelian randomization, which leverages the properties of genetic data—i.e., independent and random assignment of alleles prior to life events—to bypass typical limitations of observational studies, such as confounding and reverse causation [53]. We recently applied this method to validate causal protective influences of educational attainment for PTSD [54] and physical activity for depression [55]. Other heritable and putatively malleable resiliency factors could be tested in a similar framework to probe protective mechanisms and prioritize prevention strategies.

Genetic and environmental factors that contribute to resilience *processes*

A resilience framework by definition *implies the presence of challenge or adversity (Feature D)*. A growing number of studies in psychiatric genomics have incorporated measures of adversity. These studies have examined, for example, whether polygenic risk scores for psychopathology interact with life adversities (e.g., trauma exposure, stressful life events) to influence conditions such as depression [56–58], typically detecting the main effects of both polygenic risk and these adversities, while evidence for interaction effects has been mixed [58]. Similarly, genome-wide gene-environment studies have revealed inconsistent, though likely underpowered, interaction effects between adversities and variants across the genome [59, 60].

Beyond the need for larger samples and detailed measurements of adversity to strengthen such efforts, a resilience framework again *shifts attention from risk to protective processes (Feature A)*. Studies incorporating genomic and environmental data are well suited to examine resilience processes in which genetic influences combine with other protective and risk factors to influence adaptive outcomes following adversity. A handful of studies have reported protective interactions between candidate gene profiles and early adversity on depression [61, 62], though candidate approaches have now been criticized [15]. Polygenic approaches that incorporate genome-wide variation are more robust, though inquiry with respect to resilience remains limited [63]. High polygenic loading for a protective trait and/or low polygenic loading for a vulnerability trait may buffer against the negative effects of adversity. One study [64] demonstrating this approach examined whether polygenic scores for subjective well-being constructed from the large GWAS described earlier [32] could buffer the negative effect of spousal loss on depressive symptoms in a longitudinal cohort of aging individuals in the United States. This study found that while these individuals generally experienced a spike in depressive symptoms following the death of a spouse, those with higher well-being polygenic scores showed significantly smaller increases in depression compared with those with lower well-being scores.

A resilience framework also motivates efforts to identify modifiable factors that could offset genetic risk. Such efforts have been demonstrated in other fields, with studies reporting that protective lifestyle factors can decrease risk for negative outcomes, such as cardiovascular disease, even among individuals at high genetic vulnerability indexed by polygenic risk [65]. In the realm of psychiatry, studies have begun to adopt this approach. In a prospective cohort of US Army soldiers ($n = 3900$), we found that unit cohesion—support and respect between peers and with group leaders—was associated with reduced risk for new-onset depression following combat exposure, even for individuals with high polygenic risk for depression [66]. Another study in a population-based cohort ($n = 4166$) found that personal coping abilities (indexed by self-reported trait resilience) attenuated associations between polygenic risk for depression and actual depression, even when adjusting for vulnerability factors like neuroticism [67]. These studies highlight novel opportunities to validate modifiable factors (e.g., mindsets, behaviors, and environments) with protective effects in the face of genetic risk. A study of such factors may guide the design of targeted interventions to promote resilience in vulnerable populations.

Finally, a resilience framework *prioritizes longitudinal inquiry with implications for early intervention and prevention (Features B and E)*. It has been long theorized that resilience as a dynamic *process* is best understood via prospective studies that assess the effects of risk and protective factors across time [7, 8]. Cross-sectional studies of resilience are limited by potential confounding from contemporaneous reports of both outcomes and modifying factors. With richer longitudinal data before and after

Table 1 Operationalizing resilience outcomes for GWAS

Resilience outcome	Advantages	Disadvantages
Absence of psychiatric disorder	Large sample sizes, similar to existing GWAS data sets	Inverse of GWAS for disorder, and thus limited new insights
Absence of psychiatric disorder in high adversity-exposed individuals	Available in existing data sets; may reveal unique signals distinct from the full sample GWAS	Reduced sample size and statistical power for GWAS
Residual-based (i.e., of psychiatric symptoms and/or functioning regressed on adversity exposure)	Preserves larger sample size for GWAS; more fine-grained phenotype of relative resilience conditioned on adversity	Empirical derivation of resilience scores; requires adequate measurement of adversity; regression assumptions about the influence of adversity exposure
Positive functioning (e.g., post-traumatic growth)	Focuses on potentially overlooked positive domains of resilience following adversity	Not yet widely collected in genomic studies
Resilient trajectories	Captures the dynamic nature of resilience by studying recovery after exposure to adversity	Requires longitudinal data; trajectory assignment resulting in multinomial outcomes, limiting sample size and power

adversity, we may be able to ascertain sensitive periods where genetically vulnerable individuals are most susceptible to the effects of protective factors following adversity exposure, to inform the optimal timing of interventions.

Genetic factors associated with resilient *outcomes*

To date, few genome-wide studies have examined resilient outcomes following adversity. Resilient outcomes could be operationalized in several ways (Table 1). One definition consistent with current GWAS designs is the absence of psychiatric disorder. However, a major criticism of this approach would be effective equivalence to a GWAS of the disorder (i.e., switching case–control status, such that variants positively associated with disorder are simply those negatively associated with absence of disorder). As mentioned, a resilience framework *implies exposure to adversity (Feature D)*. Earlier GWAS work ($n = 9599$) has suggested that genetic contributions to psychiatric disorders like depression differ in groups exposed and unexposed to adversity [68]. Thus, a more appropriate way to study resilient outcomes may be to restrict GWAS analyses only to those individuals exposed to risk or adversity. An existing corollary of this approach is GWAS of post-traumatic stress disorder, where trauma exposure has typically been incorporated as an inclusion criteria [69, 70]. We have further demonstrated this approach in a GWAS where the absence of new-onset psychiatric disorders (i.e., MDD, GAD, PTSD, and panic disorder) was operationalized as outcome-based resilience in US Army soldiers who experienced high levels of deployment-related trauma exposure [48]. While the resulting high-exposure subset was small ($n = 581$), a genome-wide significant locus was identified downstream of *SLC15A5*, whereas no genome-wide signal was detected using the full sample of deployed soldiers ($n = 1939$). Although this work relies on necessarily smaller samples, statistical power could be enhanced by leveraging larger consortia, where individual studies have data on adversity (for further considerations, see Table 1). Examining the absence of disorder in individuals exposed to especially high levels of adversity may allow us to identify genetic variants related to resilience, rather than those associated with disorder or adversity exposure that would have otherwise been detected in the full sample.

Resilient outcomes could also be operationalized as quantitative traits conditioned on adversity exposure. A twin study using this approach [10] examined stressful life events as predictors of current internalizing symptom scores. The residuals of this regression model—i.e., individual deviations from average symptom scores predicted by stressful life events—were taken to represent relative resilience, where negative residual values indicated fewer internalizing symptoms than predicted by adversity. This resilience phenotype was found to be heritable at over 50% after adjusting for measurement error and situational influences from the environment [10]. Genetic variants associated with this relative resilience may be those that enable individuals to adapt more or less efficiently than predicted by the level of adversity they have experienced—though remain to be identified. However, residuals usually remain correlated with the outcome itself, which raises caution for interpreting genetic signals for relative resilience as fully independent from disorder (for further considerations, see Table 1).

In addition, a resilience framework ideally *includes multiple domains of psychological functioning (Feature C)*. According to the dual-factor model of mental health, the absence of disorder and the presence of psychological well-being represent somewhat unique dimensions of mental

health at both phenotypic and genetic levels [71, 72]. Consistent with this model, a recent GWAS of two phenotypes—resilience defined as absence of psychiatric symptoms following trauma exposure, and resilience defined as a trait reflecting adaptive coping abilities—indicated sizeable but incomplete genetic correlations between these phenotypes ($r_g = 0.66$) [48]. Thus, fully assessing resilience may involve integrating information across domains. Resilience should be expected to manifest across multiple domains, since positive functioning solely in one domain (e.g., absence of PTSD) may mask costs or disabilities in others [24, 73]. Approaches that statistically combine information from both negative (e.g., symptom) and positive (e.g., well-being) domains of mental health may augment our ability to detect genetic influences on broad-based resilience, as one recent twin study has suggested [74]. Furthermore, it is known that individuals with ongoing psychopathology can exhibit functional resilience, building meaningful and productive lives [27]. GWAS may thus be applied to investigate adaptive functional outcomes following exposure to stress or trauma [75]. These include traits of positive functioning in adversity-exposed populations, such as post-traumatic growth following exposure to a natural disaster, which have been explored in relation to candidate genes [76] but not with genome-wide approaches.

Finally, a resilience framework *motivates a longitudinal perspective (Feature E)*. Longitudinal trajectories have been posited as the gold standard for assessing resilient outcomes [4]. Trajectories incorporate dynamic temporal information around adversity exposure to distinguish between stable absence of negative symptoms across time (i.e., "minimal impact" resilience) versus initial declines in mental health followed by recovery (i.e., "emergent" resilience) [77]—each linked to different factors and consequences [4] but easily conflated in cross-sectional assessments. Trajectories can be derived from longitudinal data with repeated measures of mental health following an adversity exposure, though such data are difficult to collect at large scale. For this, it may be possible to draw on naturalistic databases with longitudinal data, such as population registries or electronic health records. In addition, standard trajectory analyses involve probabilistically classifying individuals into one of several trajectory groups, leading to multinomial outcomes that remain challenging to model statistically in existing GWAS frameworks (for further considerations, see Table 1).

Conclusions and recommendations for future research

Large-scale, genome-wide studies of psychological resilience show great promise for expanding foundational information on mechanisms underlying adaptation to stress and trauma, which could be taken forward into molecular, translational, and clinical studies. To fulfill this promise, we recommend that future studies (a) *clearly define resilience, whether as a capacity, process, or outcome*. Different definitions may tap into complementary manifestations of psychological resilience and provide cumulative insights into human adaptation. Explicitly defining the phenotype(s) under study, as well as the domains and time frames in which these phenotypes are manifesting, will enable replication and interpretation. For example, the absence of PTSD 6 months following acute trauma may be a different form of "resilience" than the broad presence of positive functioning, despite a cumulative lifetime burden of traumatic events, though both may be of public health relevance. Second, we recommend that studies (b) *capitalize on more nuanced approaches for studying resilience* (Fig. 2)—by explicitly accounting for adversity exposure, shifting attention to protective traits and processes, and emphasizing cross-domain and longitudinal inquiry for broad-based prevention. While resilience as an outcome or process could be approximated in cross-sectional studies with retrospective data, prospective studies with detailed measurement of adversities and outcomes provide the most rigorous design. Genomic studies are often limited in their longitudinal follow-ups and/or phenotyping. In the absence of ideal data, one practical way to study resilience at scale is to (c) *use insights from observational prospective literature to select targets for genomic discovery in large cross-sectional studies* (e.g., conducting a GWAS on trait optimism based on its known protective associations with mental health), *then validate discoveries in smaller but more richly phenotyped studies* (e.g., testing polygenic risk scores for optimism in relation to adaptive processes or outcomes). Over the long term, it will be critical to (d) *develop genomic consortia for longitudinal cohorts with well-characterized adversity exposures and outcomes*, where genome-wide data can be pooled using harmonized resilience phenotypes, and possibly (e) *integrate dynamic signatures (e.g., epigenetic markers) of adaptive processes across time*, which were beyond the scope of this perspective.

A focus on resilience aligns with efforts to identify protective genomic factors in health and disease [78, 79] and emerging research in precision psychiatry to guide targeted and effective approaches to prevention and early intervention [80]. Such efforts may help us better understand genetic sources of stress adaptation in the search for biological mechanisms. In turn, this work may allow us to distinguish individuals at relatively higher genetic propensity for adaptive traits and those who may benefit from further intervention, and to identify modifiable factors that could mitigate negative outcomes even for those at high genetic risk.

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Compliance with ethical standards

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