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The extraordinary "ordinary magic" of resilience

Elena L. Grigorenko
University of Houston, Houston, TX, USA

Abstract

In this essay, I will briefly sample different instances of the utilization of the concept of resilience, attempting to complement a comprehensive representation of the field in the special issue of Development and Psychopathology inspired by the 42nd Minnesota Symposium on Child Psychology, hosted by the Institute of Child Development at the University of Minnesota and held in October of 2022. Having established the general context of the field, I will zoom in on some of its features, which I consider "low-hanging fruit" and which can be harvested in a systematic way to advance the study of resilience in the context of the future of developmental psychopathology.

Keywords: Adverse childhood experience; developmental neuroscience; developmental psychopathology; early life stress; molecular genetics; resilience

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Introduction

In its early and, perhaps, the broadest definition, resilience was equated with the capacity to cope with and overcome adversity. The origin of this now vast field of research and practice is typically attributed, at least partially (Masten, 2007; Masten & Tellegen, 2012), to the work of Norman Garmezy who was concerned with issues related to primary prevention of psychiatric disorders and proposed and propelled the investigation of children who are at risk for the manifestation of psychopathology later in life because they were born to parents (mothers, fathers, or both) with psychiatric disorders (Garmezy, 1985, 1992). In particular, he focused on families of individuals with schizophrenia, stressing that both the very origin of these children and their family environment form a system of risk factors for the development of psychopathology. In his earlier writings, Garmezy (1971) juxtaposed vulnerable (whose unfavorable prognosis follows the expectations generated by their familial risk factors) and invulnerable (whose unfavorable prognosis upsets "our prediction tables" and bears "the visible indices that are hallmarks of competence," p. 114) children underlying the importance of developing not only prevention models aimed at curtailing the incidence of susceptibility to psychopathology in vulnerable children, but also enhancement models leading invulnerable children to survival and adaptation.

Although this early work laid the foundation for the science of resilience and offered the first broad notion of the concept, the evolution and crystallization of both the definition and the field of resilience have emerged through the contributions of multiple researchers and multiple studies (Cicchetti & Garmezy, 1993; Masten & Tellegen, 2012; Masten et al., 2023). As eloquently put, "Resilience research co-emerged with developmental psychopathology from the same nexus of influences (Cicchetti, 2006; Masten, 2007)" (Masten & Tellegen, 2012, p. 346). Cicchetti's work was fundamental to this nexus as he has contributed to the understanding of the phenomenon by interrogating it at different levels of analyses (Cicchetti, 2010), approaching it from different domains and contexts (Cicchetti & Rogosch, 2007; Curtis & Cicchetti, 2007; Denckla et al., 2020), and developing and evaluating the much-needed interventions for children and adolescents who have lived through adverse experiences (Luthar & Cicchetti, 2000). In this essay, I will briefly sample different instances of the utilization of the concept of resilience, attempting to complement a comprehensive representation of the field in the special issue of *Development and Psychopathology* inspired by the 42nd Minnesota Symposium on Child Psychology, hosted by the Institute of Child Development at the University of Minnesota and held in October of 2022 (Masten et al., 2023). Having established the general context of the field, I will zoom in on some of its features, which I consider particularly promising to focus on to advance the study of resilience in the context of the future of developmental psychopathology.

Definitions, definitions, definitions

Garmezy's (1974) initial broad interpretation of resilience as the capacity to maintain normative development and demonstrate adaptive outcomes in the presence of adversity has been reflected in the definition of resilience as presented by the American Psychological Association, APA: "Resilience is the process and outcome of successfully adapting to difficult or challenging life experiences, especially through mental, emotional, and behavioral flexibility and adjustment to external and internal demands" (2024). Alternatively, paraphrasing, resilience is the physical and mental (or behavioral and psychological) capacity to confront and manage adversity generating stress, adjust to change, recoup,

Corresponding author: Elena L. Grigorenko; Email: elena.grigorenko@yale.edu
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regain composure, and rise from holdups and setbacks. So . . . . resilience is life itself!

Yet, although defined through broad strokes, such definitions were marked (Denckla et al., 2020) as difficult to translate into research language constrained by verifiable theories, falsifiable hypotheses, and interpretable data. Correspondingly, there is an ongoing quest for the definition of resilience through developing theoretical interpretations that generate specific testable hypotheses addressable with collectible and explainable data. Given the range of existing definitions, can constant features of the concept of resilience be noted? It seems so!

First, resilience assumes the presence of exogenous risk in response to which it arises. Thus, it has been defined as having a lower vulnerability to the presentation of such risk and maintaining the overall normative developmental trajectory in the face of the need to overcome or to continue facing adversity (Rutter, 2006). This notion of resilience stresses its "relative" nature (Holz et al., 2020), as it arises in response to outer factors of various types (from wars and natural catastrophes to school bullying). Yet, it is important to stress that resilience is a dynamic developmental process (Rutter, 2012), endogenous to the individual, and, therefore, characterized by person-specific characteristics at multiple levels of functioning (e.g., genome, brain, behavior). This facet of resilience stresses the consistency of positive outcomes for resilient individuals in the context of various adversities, alluding to "true (or overall)" resilience (Kaufman et al., 1994). To capture this juxtaposition, resilience has been discussed to have both state (in response to adverse exogenous impacts) and trait (an ever-present endogenous denominator) presentations and manifest as both domain-specific (e.g., in response to physical stress) and domain-general (e.g., in response to any stress) adaptation to the changed environment. However, Denckla et al. (2020, p. 7) objects to the view of resilience as a trait: "Resilience is multidimensional; it is not static or trait-like."

Second, similarly to the need for the vision system to be exposed to light to trigger its maturation or for the ontogenetic emergence of language to be surrounded by language-producing talking heads, resilience emerges in response to stress; in essence, it is the other side of the story of stress reactivity. Therefore, resilience is often studied explicitly and implicitly in the literature on stress (McEwen, 1998). Yet, "While research is beginning to demonstrate the link from social adversity to negative outcomes via altered neural mechanisms, which is in line with the vulnerability perspective, the resilience perspective has only recently become a focus within neuroscience." (Holz et al., 2020, p. 380). Thus, the field knows much more about the neuroscience of adversity than about the neuroscience of resilience. Yet, these systems are interconnected, as adversity needs to be encountered, and stress needs to be experienced to develop resilience, which, in turn, modulates the response to stress and adversity. This interactive nature of resilience has been identified as the capability of a complex system to endure and/or rebound from disturbance; this notion of resilience has been used in ecology (Holling, 1973), economics (Rose, 2007), and sociology (McKeown et al., 2022). Correspondingly, resilience is one of the characteristics of a complex system capturing its dynamics sampled through the system's adaptive cycles; specifically, resilience refers to the capacity of a system to successfully adapt to challenges that threaten the function, survival, or development of that system (Masten et al., 2021).

Third, as resilience is a systemic characteristic, it requires the amalgamation of numerous signals from peripheral and central sources, extending from short-range signaling of local circuits of the nervous to long-range signaling of humoral immunity factors of the immune system (Cathomas et al., 2019). The appreciation of and appeal to the multilevel investigation of resilience was made 30 years ago (Cicchetti & Garmezy, 1993). These multiple interdependent levels have been conceptualized as allostatic load, stress inoculation, developmental trajectories, epigenetic factors, and transgenerational effects, among others (Southwick & Charney, 2012). Yet, despite the conceptual and practical appearance of finding psychological, biological, and biopsychological protective markers characteristic of resilience, the field still lacks an understanding of what these markers are, especially when sampled at the individual levels. Although still not numerous and mostly correlational in nature, there are studies sampling resilience as a complex collection of systemic indicators at multiple levels of individual functioning (Holz et al., 2020).

Fourth, although initially discussed as a rather rare positive outcome in the high-risk context of familial risk for schizophrenia, resilience has been reconceptualized as a common phenomenon (Masten, 2001). A superficial analogy here is a differentiation of big C and little c creativity (Runco, 2019), indicating both the commonality (or not) of the process and the magnitude of the product (small everyday creative moments or highly impactful creative products). As per this analogy, Resilience (big R) pertains to rare remarkable demonstrations of strength in the face of adversity (e.g., Nelson Mandela and Aleksei Navalny), whereas resilience (little r) is a quantitative trait measurable in the general population. With regard to the latter, research has identified a number of factors differently associated with resilience, such as positively correlated strong social support, both through family and the wider social network (Herrman et al., 2011) and negatively associated social isolation (Tost et al., 2015); and such as positively correlated active coping responses intended to gain actual or perceived control of a stressor by minimizing its physical, psychological, or social harm (Russo et al., 2012) and negatively correlated passive coping, such as avoidance and helplessness (Southwick et al., 2004; Wood & Bhatnagar, 2015). Relatedly, there is accumulating evidence to differentiate passive and active (or more active) resilience (Rakesh et al., 2019). There is an open task of cross-mapping these various concepts onto a single "quilt" of resilience.

This "quilt" of definitions makes studying resilience a challenge, which necessitates an introduction of a specific definition used prior to a study-based specification and operationalization of the concept. So, what is the one for this essay? Here, resilience is defined as an integral over an interval, where performance is sampled behaviorally and biologically repeatedly (continuously) as a process and cross-sectionally (categorically) as an outcome (see the APA definition above) in the face of adversity and under stress. This definition seems to reflect the four common features of the multitude of conceptualizations of resilience, namely: (1) the manifestation of resilience is substantiated by the presence of adversity and stress; (2) resilience is a dynamic systemic characteristic; (3) resilience is characterized by a complex collection of systemic indicators at multiple levels of individual functioning; and (4) resilience is a common feature of the general population (i.e., a source of individual differences).

This endorsement of the definition in this essay is three-fold. First, the current literature on the neuroscience of resilience has established numerous targets that serve both as the (neuro) physiological substrates and biomarkers of resilience. The analysis of this literature presents the "hot spots" of resilience as a source of

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individual differences in the general population. Second, this definition permits a description of resilience at multiple levels of human performance and through the characterization of a changing complex system as it interacts with adverse challenges. Third, the availability of portable wearable and carriable devices today permits the collection of the needed data to substantiate and interrogate the notion of resilience as dynamic readiness characterized as a continuum of (neuro)physiological states integrated over numerous contexts, situations, and tasks.

(Neuro)physiological substrates and markers of resilience

To restate, resilience has been referred to as the capacity to face adversity and manage stress within the normal range of psychological and physiological functioning (Wu et al., 2013). This definition assumes that there is a notion of what that normal baseline is and what deviations from the baseline are acceptable for readiness to perform optimally with and without different sources of stress. Importantly, there is evidence (Ledford et al., 2020) that self-reported appraisal of resilience (that calls for the awareness of both the amount of stress and the individual's readiness) appears to be as accurate as the capture of resilience through various biomarkers (that do not call for any awareness and are easily recordable) in predicting outcomes (9.6% vs. 10.8%, respectively). Yet, the predictive power of their combination is almost additive (17.2%), indicating that only a partial and small amount of predictive information contributed through these different types of assessments overlap. Hence, although it is well-known that, among others, both psychological and (neuro)physiological factors contribute to resilience, it is important to focus on the latter, as many relevant indicators can be collected noninvasively and continuously.

It is accepted that the neurophysiological mechanisms of resilience are remarkably intricate (Murrough & Russo, 2019). Importantly, most of the data have been derived from studies of stress reactivity (see juxtaposition above), and the hypothesized apparatus has linked modifications in immune, hormonal, and microbiota-related pathways substantiated by specific neuro-circuits and genetic and epigenetic events and processes. Notably, the general assumption is that salient features of resilience are likely to rely on the active engagement of key (neuro)physiological systems whose critical function is to maintain homeostasis rather than on the absence of maladaptive alterations that are expected to be generated by stress (Russo et al., 2012). To describe the systemic adaptive response of the brain and body to stress, Bruce McEwen coined the term "allostasis" (McEwen, 1998, 2012), which is a state of the multilevel activation of the hormonal and cytokine signaling, the sympathetic nervous system and hypothalamic-pituitary-adrenal (HPA) axis, which have the capacity to calm down and recover adequately (Osório et al., 2017). Thus, resilience can be seen as derived from the specific (neuro)physiological allostatic reactions that are produced in response to stress (Murrough & Russo, 2019). These responses are "sufficient but not excessive" and indicative of "rapid and efficient psychobiological recovery" (Feder et al., 2019, p. 444). Importantly, for this discussion, these responses are assumed to be replicable, although modulated by the characteristics of stress.

Resilience in the brain

As the capacity to regulate emotions is a recognized aspect of resilience, it has been hypothesized that the function of the (neuro) physiological systems substantiating the cognitive restraint of emotion (Kong et al., 2015; Takeuchi et al., 2014; Urry et al., 2004) and reward circuitry might be relevant for the understanding of the (neuro)physiological bases of resilience. Behaviorally, resilience in such studies is typically defined through indicators such as inhibitory control (Maier & Watkins, 2010; Ochsner & Gross, 2005) and emotional appraisal and regulation (Hänsel & von Känel, 2008; Maier & Watkins, 2010), and flexibility (Waugh et al., 2008). Specifically, it has been demonstrated that individual differences in these processes substantiated by the related capability to employ prefrontal cortical (PF, or PF cortex, PFC) control systems that control affective processing by the amygdala and related structures mediate a response to adversity (Rodman et al., 2019). Additionally, it has been hypothesized that the parietal lobe (PL) might play a role in resilience due to its centrality in the evaluation of the emotional relevance of the external stimuli in particular and emotion regulation in general (Bisley & Goldberg, 2010; Bzdok et al., 2016). Particularly, the primary somatosensory cortex is responsible for initiating the processing of sensory inputs, and the secondary somatosensory cortex engages cognitive processes to complete their processing. Both areas are located in PL, and, therefore, the lobe orchestrates a complex interplay between incoming stimuli and pre-existing somatosensory representations, generating fresh memory traces (Wagner et al., 2005). Hence, it is sensible to wonder whether children who experience early life stress (ELS) but exhibit enhanced parietal functioning (i.e., children with, presumably, stronger resilience) are less susceptible to the impact of the novel external stimuli when they are somehow related to, reminiscent of, or can trigger their past neglected experiences (Luo et al., 2023).

As the number of empirical studies has grown (Dedovic et al., 2009; Pitman et al., 2012; Shin & Liberzon, 2010; van der Werff et al., 2013), numerous brain structures have been implicated as substantiations of resilience, including the anterior cingulate cortex (ACC), hippocampus, insula, orbitofrontal cortex (OFC), and ventro-medial and dorsolateral prefrontal cortical (vmPFC). An early comprehensive review of the literature on the (neuro) physiological bases of resilience has demonstrated that it arises from a sophisticated orchestra of tuned-up structures connected by the interchange between distributed brain systems, including the amygdala, ACC, and PFC, which are neuromodulated (Feder et al., 2019). A later review (Holz et al., 2020) fine-tuned the "convergent resilience circuit," still stressing its reliance on frontal regions, particularly the perigenual anterior cingulate cortex (adjacent to OFC), numerous regions of the PFC, and key limbic structures such as the ventral striatum (VS). To illustrate, a concurrent stimulation of the dorsolateral prefrontal cortical and OFC leads to enhanced resilience (Salehinejad et al., 2017). In addition, there is evidence of a positive association between resilience and a larger hippocampal structure (Moreno-López et al., 2020).

Special attention has been given to findings of altered hippocampus dentate gyrus (DG) development, as it has been previously related to stress reactivity (Anacker et al., 2018; Boldrini et al., 2019; Roddy et al., 2019) and depression and suicidal behavior (Boldrini et al., 2019; Boldrini et al., 2013; Huang et al., 2013; Roddy et al., 2019; Wang et al., 2010), and contains structures involved in adult neurogenesis (Toni & Schinder, 2016). Experimental manipulations of the ventral DG in model organisms have been related to resilience to chronic stress and depressive-like behaviors, suggesting a substantive and even causal role for the DG in resilience (Anacker et al., 2018; Boldrini et al., 2019; Hill et al., 2015; Tunc-Ozcan et al., 2019; Veena et al., 2009). Specifically, DG neurogenesis made adult mice in the experimental group more

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resilient to chronic stress compared to control rodents (Anacker et al., 2018). Contrary to this, inhibiting immature neurons increased susceptibility to stress (Bagot et al., 2015; Jimenez et al., 2018; Padilla-Coreano et al., 2016). Relatedly, antidepressant treatments, exercise, and environmental enrichment have been reported to enhance DG structure and function (Boldrini et al., 2013; Erickson et al., 2011; Nuninga et al., 2020; Van Praag et al., 1999; Veena et al., 2009). Antidepressants have been stated to cause neurogenesis increase in mice (Malberg et al., 2000; Wang et al., 2008), rats (Lyons et al., 2011), nonhuman primates (Perera et al., 2011), and perhaps patients with depression (Boldrini et al., 2013; Boldrini et al., 2009). It is well established that successful recovery and adaptation after ELS (Charney, 2004) is marked by active coping style, effective and efficient emotional regulation, and adequate cognitive functioning, which might either result from or lead to brain circuit remodeling, such as alterations in DG cellular plasticity, encoding of emotion-related memories, and strengthening the amygdala–PFC connectivity (Boldrini et al., 2019). Given this pattern of these findings, a possible translational outcome might be related to the potential causal function of the DG in the manifestation of depressive symptomatology after exposure to maternal stress, as it can open pathways to novel interventions.

In substantiating the involvement of different brain structures and networks, the literature cited illustrations of not only resilience itself but also related behaviors. Specifically, positive coping has been associated with an increased volume of perigenual anterior cingulate cortex (Holz, Boecker, Jennen-Steinmetz, et al., 2016), and the neighboring OFC has been labeled a neural marker of optimism (Nes & Segerstrom, 2006). The latter, in turn, has been linked to resilience (Feder et al., 2009; Ozbay et al., 2008), especially in adulthood and older age (Feder et al., 2019), and reported to mediate the connection between anxiety and lateral OFC (Dolcos et al., 2016). Relatedly, the enlarged vmPFC was observed to foster resilient functioning and safeguard against internalizing disorders (Morey et al., 2016). There was also a report of the dynamic changes in the mobilization of vmPFC in response to stress, with prolonged stress exposure increasing engagement in this area (Sinha et al., 2016). Additionally, various elements of this circuitry have been implemented in research capturing the role of social support in pain-related adversity (Coan et al., 2006; Eisenberger et al., 2011; Eisenberger et al., 2007; Younger et al., 2010).

The major chunk of this literature pertains to group studies utilizing structural and functional MRI (e.g., Amico et al., 2011; Fischer et al., 2019; Hopper et al., 2007; Peres et al., 2011; Phan et al., 2005; Rauch et al., 2003; Rauch et al., 2000; Rodman et al., 2019; Shin et al., 2011; Sun et al., 2019; van Dijk et al., 2024), where individuals who experienced ELS are compared to typically developing individuals or to themselves when stratified by such variables as absence or presence of a particular disorder (e.g., PTSD, anxiety, or depression) or high-risk clinical groups are compared to low-risk controls. Thus, post-ELS, in non-PTSD, compared to PTSD, functional connectivity was decreased between the insula and the right amygdala (Etkin & Wager, 2007) but increased between the thalamus and the right medial frontal or the left rostral ACC, rACC (Yin et al., 2011).

There also have been studies of healthy individuals investigating the neural correlates of resilience (Burt et al., 2016; Gupta et al., 2017; Kong et al., 2015; Reynaud et al., 2013; Salehinejad et al., 2017; Waugh et al., 2008). Similarly to the research in clinical samples, the generated findings are also quite mosaic, demonstrating both convergence and divergence with the findings from studies focusing on clinical diagnoses. Of interest is the differential engagement of the insula by low- (nonspecific activation to both the neutral and aversive stimuli) and high- (specific activation only to aversive stimuli) resilient people (Waugh et al., 2008), indicative of the capacity to use brain resources adequately under threat. Similarly, the salience network (i.e., the bilateral insula, dorsal ACC, dACC, and rACC) demonstrated less spontaneous activation in healthy young adults (Kong et al., 2015), indicating, perhaps, higher capacity for emotional regulation (Etkin et al., 2011). There are also studies linking resilience to brain morphology (i.e., cortical thickness and surface area) of cortical-limbic regions engaged with the inhibition systems (Gupta et al., 2017). A large sample study has documented that those adolescents who experienced ELS and demonstrated positive life outcomes had larger volumes of gray matter in the right middle and superior frontal gyrus (Burt et al., 2016). Later, the resilience-higher gray matter volumes were reported to be differentiated by sex so that the sex-by-resilience interaction differentiated the role of the enlarged gray matter in different areas of the brain for males and females (Cornwell et al., 2023). Moreover, in a sample from a healthy population with ELS (Luo et al., 2023), the engagement of PL was reported to be characteristic of resilience. Yet, there are some contradictory results on the involvement of PL (Barzilay et al., 2020; Grieder et al., 2020), suggesting that it may have a complex and context-dependent role in resilience. Healthy samples have also been used to study functional connectivity, resulting in a complex map of positive and negative correlations with various brain regions and connectivity between them (Shi et al., 2019). There are studies where resilience is defined as a continuous indicator (e.g., adaptive psychosocial functioning adjusted for the severity of childhood adversity; González-García et al., 2023) that can be correlated with different characteristics of brain functioning, such as the nodal degree, which indexes the number of associations that various brain regions form in a given network (González-García et al., 2023).

Thus, the understanding of the brain foundation of resilience is only emerging, and as of today, the relevant literature lacks consistency (Eaton et al., 2022; Méndez Leal & Silvers, 2021; Zhang et al., 2023). As the literature grows, there is hope for convergence on the definition of resilience, which, in turn, should aim to converge the findings on its brain bases. However, at this point, the bottom line is that the prefrontal and subcortical structure, function, and functional connectivity are engaged with and relevant to the manifestation of resilience (Zhang et al., 2023). Therefore, these systems, together or separately, depending on the instrumentation, should be consistently sampled while brain readiness to perform is recorded under different stressogenic situations.

Resilience in the genome

Whereas there has been much research and progress in mapping out the genetic bases of stress reactivity, far less is understood regarding the genetic endowment of resilience. It has been argued (Elbau et al., 2019; Murrough & Russo, 2019) that identifying genetic variation that differentiated disease risk in the face of adversity should enhance the understanding of mechanisms that trigger and advance resilience, thus detecting new pharmacological targets. Genetic variation, which has already been associated with signaling systems that modulate the structure and function of the relevant neural substrates in response to stress, has been deemed to be a good starting point as candidate genes for resilience (Elbau et al., 2019; Holz et al., 2020; Niitsu et al., 2018). Of no surprise is

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that most of these genes have a role in the central nervous system functioning. Thus, the serotonergic pathway (Kiser et al., 2012) is known to substantiate emotional processing (Cao et al., 2018). Increased serotonin turnover in the amygdala, hypothalamus, PFC, and VS has been reported under stress (Feder et al., 2009). Similarly, the dopaminergic pathway, substantiating motivation (Dreher et al., 2008), operates in the PFC and gets inhibited in the VS (Charney, 2004) following stress. It has been observed that levels of dopamine are amended in depression and PTSD (Charney, 2004; Dunlop & Nemeroff, 2007); heightened dopamine turnover has been stated to substantiate exaggerated fear response to stress (Hoexter et al., 2012). Given these associations, it is plausible that genetic variation in serotonergic and dopaminergic signaling might also be relevant to substantiating individual differences in resilience. Similarly, a genetic variation known to alter stress responsivity (Matosin et al., 2018) might play an important part in resilience. In addition to the involvement of the neurotransmitter systems, the literature on stress reactivity emphasizes the importance of hormonal signaling, engaging systems such as corticotropin (corticotropin-releasing hormone, CRH, a central regulator of the HPA axis) and oxytocin (a natural hormone managing reproductive system and engaged with many aspects of social behavior). There are now "classic" genetic variants that are both functional and common, which have been analyzed with regard to their association with resilience (Niitsu et al., 2018): the serotonin-transporter-linked polymorphic region (5-HTTLPR) in the serotonin transporter gene (*SLC6A4*), and repeats and single-nucleotide polymorphisms, SNP, in dopamine receptor D4 (*DRD4*), corticotropin-releasing hormone receptor 1 (*CRHR1*), and oxytocin receptor (*OXTR*) genes.

A variable-number tandem repeat polymorphism in the promoter region of the *SLC6A4* gene is a well-studied variant. The region 5-HTTLPR consists of a 14-repeat short variant, S-allele, and a 16-repeat long variant, L-allele (Heils et al., 1996; Lesch et al., 1996). Of note also is a single-base substitution (A > G) in the L type of 5-HTTLPR known as rs25531 (Hu et al., 2006). A large corpus of research has registered an association between the 5-HTTLPR L-allele and decreased activation of the amygdala (Munafò et al., 2008). Moreover, carriers of the L-allele demonstrated heightened functional coupling between the PFC and the amygdala (Pezawas et al., 2005). It has also been reported (Holz, Zohsel, et al., 2018) that environmental adversity moderated the impact of 5-HTTLPR on amygdala activation and connectivity in a number of studies (Alexander et al., 2012; Canli et al., 2006). Additionally, certain genotypes of 5-HTTLPR/rs25531 were associated with resilience in children/adolescents, while others were connected to resilience in adults (Niitsu et al., 2018). The variation in the promoter region of *SLC6A4* has been featured in genetic association studies of a number of psychiatric conditions, stressing a lack of specificity of its action. Moreover, it was featured in several interaction studies (known as G × E or gene by environment), where it was treated as a genetic liability to a particular (similarly nonspecific) adverse environmental impact. Importantly, the field does not converge on the specific role of this variation but acknowledges its relevance for understanding the genetic underpinning of both susceptibility and resistance to the manifestation of negative outcomes in the face of adversity.

Another well-studied source of genetic variation is a variable number of tandem repeats in a 30-base repeat sequence (VNTR) polymorphism in the monoamine oxidase A (*MAO-A*) gene. MAO-A is an enzyme that is central to the catabolism of a number of neurotransmitters, including serotonin. The activity of MAO-A influences serotonin levels: high levels of MAO-A activity can lead to decreased serotonin availability, and low MAO-A activity can result in increased serotonin levels. High levels of MAO-A are controlled by the MAO-A-H genotype, which has been stated to partially differentiate resilience in men (Holz et al., 2020). Specifically, a lower emotional sensitivity in the amygdala (Alia-Klein et al., 2009; Lee & Ham, 2008; Meyer-Lindenberg et al., 2006), along with increased recruitment of PFC-based (ACC, vmPFC) cognitive control networks, was reported in individuals with the MAO-A-H genotype (Fan et al., 2003; Meyer-Lindenberg et al., 2006; Passamonti et al., 2008; Passamonti et al., 2006). Furthermore, it has been observed that the unfavorable genotype (i.e., 3 versus 4 repeats, with 3R variant resulting in lower MAO-A activity) and environmental adversity can co-act, substantiating the manifestation of negative outcomes such as reactive aggression; importantly, these effects appear to be sex-specific (Byrd & Manuck, 2014; Caspi et al., 2002). Thus, genetic variants associated with stress reactivity and resilience might exert sex-specific effects (Holz, Boecker, Buchmann, et al., 2016), substantiating well-known sex differences in response to adversity.

Variations in several genes participating in the turnover of dopamine have also been investigated. The catechol-o-methyl-transferase Val158Met polymorphism (rs4680) regulates the extra-synaptic dopamine degradation due to its impact on the catechol-o-methyltransferase enzyme (Holz et al., 2020). There are numerous studies of the association between this polymorphism and various relevant brain structures, although the results are somewhat difficult to interpret. The literature reports the polymorphism's associations, specifically with the Val allele, with lower punishment-related VS activity (Schmack et al., 2008); alleviated activation during reward anticipation (Dreher et al., 2009; Yacubian et al., 2007); potentiated activity of the nucleus accumbens, the ACC and the right inferior PL during reward receipt (Camara et al., 2010); as well as and null findings (Forbes et al., 2009). The polymorphism has also been reported to differentiate the impact of ELS in the reward circuit, with lower activity in the VS and ACC with increasing levels of childhood adversity in Val carriers and the opposite effect for Met homozygotes (Boecker-Schlier et al., 2016). Variations in the dopamine receptor DRD4, specifically, its D4 version (Van Tol et al., 1992) and a VNTR containing 3 to 11 repeats in the dopamine transporter *DAT* (also known as *SLC6A3*) gene has been associated with individual differences in reward processing, ostensibly by acting on VS ventral striatal activity (Aarts et al., 2010; Dreher et al., 2009; Filbey et al., 2008; Forbes et al., 2009; Hahn et al., 2011; McClernon et al., 2007; Nikolova et al., 2011; Paloyelis et al., 2012; Wittmann et al., 2013), although there are some contradictory findings (Hoogman et al., 2013). Moreover, in DRD4 resilience scores were associated with the CC and CT genotypes of rs1800955 (Cicchetti & Rogosch, 2012) and the 7r7r and 4r7r genotypes of the VNTR (Das et al., 2011).

Variants in *CRHR1* and *OXTR* genes have received less attention, although both have been associated with resilience scores. The relevant variation in *CRHR1* was captured not with a single polymorphism but with a combination of them, suggesting that the TAT haplotype might contribute to the biological foundation of resilience (Cicchetti & Rogosch, 2012). The *OXTR* polymorphism rs53576 has also been associated with resilience, although there is a disagreement on what particular genotype, GG (Cicchetti & Rogosch, 2012) or AA (Bradley et al., 2013), carried the signal.

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Other candidate genes, selected due to their specific biological function, have been considered. Among them are genes coding for brain-derived neurotrophic factor (BDNF), FK506 binding protein 5 (FKBP5), and regulator of G-protein signaling 2. BDNF confirms the survival of existing neurons and supports the growth and differentiation of new neurons and synapses, being especially active in the areas of the brain, substantiating learning, memory, and higher thinking. It has been reported that the GG genotype of its rs6265 polymorphism contributed to resilience (Nederhof et al., 2010; van Winkel et al., 2014), but perhaps only in Caucasians (Niitsu et al., 2018). The *FKBP5* gene encodes a protein FKBP51, a member of the immunophilin protein family and known for its role in immunoregulation and basic cellular processes involving protein folding and trafficking. The protein binds to the immunosuppressants FK506 and rapamycin, mediates calcineurin inhibition, and regulates the affinity of the glucocorticoid receptor (GR) for cortisol (Binder, 2009; Denny et al., 2000; Wochnik et al., 2005). In fact, FKBP51 co-chaperones to GR directly affect its sensitivity to circulating glucocorticoids; thus, an important role of the FKBP51 protein is the regulation of stress responsivity. Loss of FKBP51 in gamma-aminobutyric-acid or glutamate neurons leads to negative outcomes, especially under high-risk environments (van Doeselaar et al., 2023). The rs1360780 polymorphism in this gene appears to differentiate glucocorticoid resistance of the GR in the CC genotype (Binder et al., 2008), generating a more effective negative feedback loop thought to be stimulated by glucocorticoid, coupled with a more rapid stress adaptation in the face of adversity (Matosin et al., 2018; Zannas et al., 2016) and a blunted threat-induced amygdala activity in the context ELS (Holz et al., 2015; VanZomeren-Dohm et al., 2015; White et al., 2012). Finally, the regulator of G-protein signaling 2 gene encodes the Regulator of G-protein Signaling 2 protein, which modulates the activity of G proteins, where the GG genotype of the rs4606 polymorphism has been reported to contribute to resilience in Black parents (Dunn et al., 2014).

Of note is that, to date, seemingly only two genome-wide association studies (GWAS) have been conducted. The first one featured resilience conceptualized through a self-report of perceived resilience collected on almost 15,000 US Army soldiers of European descent (Stein et al., 2019). There were three results at the genome-wide level of significance. The first signal was within a locus on an intergenic region on chromosome 4 upstream from the *DCLK2* (Doublecortin-Like Kinase 2) gene (4 SNPs in linkage disequilibrium; top SNP: rs4260523 [$p = 5.65 \times 10^{-9}$] is an eQTL in frontal cortex), which is a member of the doublecortin family of kinases that promote survival and regeneration of injured neurons. The second signal was in the gene *KLHL36* (Kelch-Like Family Member 36) at $p = 1.89 \times 10^{-6}$. A polygenic risk score (PGS, a weighted additive score of all alleles that demonstrated associations with a trait in the framework of GWAS, reflecting a substantial amount of the trait-associated variance with a single measure) derived from the self-assessed resilience GWAS was not significantly associated with outcome-based resilience. In addition, when a subsample of soldiers ($N = 581$) exposed to the highest level of deployment stress was extracted, genome-wide significant association with outcome-based resilience was registered for one locus (top SNP: rs12580015 [$p = 2.37 \times 10^{-8}$]) on chromosome 12 downstream from *SLC15A5* (solute carrier family 15 member 5). Notably, the estimate for the heritability of resilience was 16%. The second study (Cusack, Aliev, et al., 2023) used a previously utilized (Amstadter et al., 2016; Cusack, Bountress, et al., 2023) discrepancy-based indicator of resilience, calculated based on the information on trauma exposure and a checklist of psychiatric symptoms (depression and anxiety). Heritability estimates for resilience did not differ from zero. Zero variants met genome-wide level of significance, but nine passed the suggestive association threshold and mapped onto three genes: *SEZ6L* (a protein-coding gene that contributes to specialized endoplasmic reticulum functions in neurons), *LINC02112* (Long Intergenic Non-Protein Coding RNA 2112), and *FRK* (fyn related Src family tyrosine kinase), and one cluster of genes (*NKAIN3, GGH, TTPA, YTHDF3-AS1*) on chromosome 8 related to metabolization and transport of various vitamins and minerals. Whereas for *SEZ6L* and the chromosome 8 cluster, the associations presented meaningful interpretations, but these were not obvious for the two other genes. Importantly, none of these candidates have been implicated in resilience earlier. Finally, researchers utilized PGS previously established for alcohol dependency, alcohol consumption, and PTSD. They demonstrated genetic overlap between resilience and AD, as well as resilience and PTSD.

The interactive notion of resilience is well suited for genome-wide G × E studies (Genome Environment Wide Interactions Studies [GEWIS]) to identify gene variants that are able to differentiate individual responses to adverse environmental stimuli. Although there are some GEWIS primarily with negative outcomes (e.g., depression) and adverse life events, their results are difficult to interpret (Arnau-Soler et al., 2019; Coleman et al., 2020; Dunn et al., 2016; Ikeda et al., 2016; Otowa et al., 2016; Suppli et al., 2022). By virtue of their design, GEWIS requires large sample sizes and documented stressful life events. To thwart power issue, the field put forward the usage of PGS, which are constructed separately for different outcomes, for example, depression (Halldorsdottir et al., 2019; Mullins et al., 2016; Peyrot et al., 2018) and schizophrenia (Hess et al., 2024). Unfortunately, the results are mixed. Specifically, studies on depression do not support the presence of interaction between depression PGS and the environment (Elbau et al., 2019). On the contrary, the outlook for schizophrenia appears to be promising. There has also been an attempt to consider trauma exposure as a ubiquitous trans-diagnostic risk factor for multiple negative outcomes.

In the spirit of Garmezy's work with families with high-risk individuals who do not manifest the disorder, researchers (Hess et al., 2024; Hess et al., 2021) developed a framework to hoard GWAS data and then excavate them for common genetic variants that protect high-risk individuals from schizophrenia; this work resulted in the derivation of the first-ever "polygenic resilience score" for schizophrenia. This reinforces the assumption that common variants that are not in linkage disequilibrium with known schizophrenia risk alleles might exert a protective effect. If so, this work can turn the table for genetic researchers who, instead of searching for and investigating risk alleles, will do so for protective alleles (Hess et al., 2021). This, in turn, can inspire new approaches to intervention.

Importantly, there are additional indicators of engagement at the molecular level, specifically through the human methylome, which reflects the dynamic response of the genome to the environment. Recent research has pinpointed genetic impacts on DNA methylation, shedding light on the regulatory processes underlying gene expression and disease risk. Importantly, approximately 34.2% of CpGs, the foundational unit of the methylome, are affected by SNPs. These genetic variants act either directly (cis-acting) or within 1 megabase of the tested CpG (Villicaña et al., 2023). Importantly, it has been demonstrated that it is possible to construct a risk resilience score based on epigenetic

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markers (Magwai et al., 2021). Thus, specific CpG sites exhibited significant correlations with resilience and were predominantly enriched in genes pivotal to neural plasticity, stress response, and immune function. Alterations in the methylation patterns of these genes potentially impact an individual's coping mechanisms in the face of stressors. Moreover, the constructed methylation risk resilience score demonstrated efficacy in distinguishing between low- and high-resilience individuals, indicating that methylation signatures can be used for such differentiation (Lu et al., 2023). Interestingly, the final model included three methylation probes (cg18565204, cg17682313, and cg07167608) in the genes (*AARS, FBXW7*, and *LINC01107*, respectively) that have not been flagged in any other study as candidate genes for resilience before. Yet, similar to the research on structural variance described above, there are candidate genes featured in numerous epigenetic studies. DNA methylation of the *MHC, DNMT3A, DNMT3B, NR3C1*, and *FKBP5* genes has been reported to be significantly associated with posttraumatic stress disorder and resilience (Mehta et al., 2020; Miller et al., 2020). It has also been hypothesized that epigenetic mechanisms that substantiate the etiology of anxiety disorders and, possibly, conference to resilience, can be either shared or overlapping (Schiele & Domschke, 2018). Nonetheless, unlike the case with research into the structural variation associated with resilience that can be investigated with any source of DNA, there is a serious concern regarding the source of DNA for epigenetic studies. To explain, as specialized cells respond to physiological and environmental stimuli differently, the modulation experienced and exerted by neurons can be specific to brain function (Moore et al., 2013) and, thus, not generalizable to other cell types (e.g., blood and saliva). Although there is a correlation between methylation profiles of different cell types, its value is far from one (Braun et al., 2019; Chen et al., 2017; Magwai et al., 2021; Thompson et al., 2013). The degree to which altered methylation in the peripheral blood or saliva may reflect biomarkers of resilience is still an open question.

Finally, although still preliminary, the extant research provides the foundation for further exploration of such targets as neuropeptide Y (see below), glutamate and gamma-amino-butyric-acid (as mentioned above), and a class of potassium channels family Q (KCNQ channels), which are responsible for the muscarinic currents in neurons (Tan et al., 2020).

Thus, given the profile of the results so far, it seems plausible that there are specific sources of individual differences in the genome that substantiate, either through structural or through functional variation, individual differences in resilience. Yet, the pattern results for the genome are even more "quilt-ish" than it is for the brain. Thus, the ensemble of candidate genes, although reasonable in theory, does not get consistently implicated in practice, questioning the robustness of individual results. The completed GWAS do not engage the hypothesized candidate genes and do not replicate each other's findings. The only gene that has been independently implicated in genetic and epigenetic studies of resilience is *FKBP5*, but, as discussed above, its encoded protein lacks brain or behavior specificity as it has a generic role in immunoregulation and basic cellular processes involving protein folding and trafficking. To conclude, in general, more data are needed to clarify the current footprint of the involvement of the genome in the emergence and manifestation of resilience. As a practical consideration, it is recommended to sample wholistically, both through the variation in the genome and methylome, to generate the needed unbiased data while readiness to perform is documented under different stressogenic situations.

Resilience in the body

The large body of literature associating various physiological indicators of bodily functioning and circulating biomarkers (e.g., hormones, neuropeptides, neurotransmitters) with resilience vs. vulnerability to psychological distress has already been discussed in a number of reviews of different types (Charney, 2004; McEwen, 2016; Osório et al., 2017; Watanabe & Takeda, 2022); the review of this literature is outside of the range of the present essay. Here, only selected indicators and biomarkers are mentioned in the context of the discussion above.

Peripheral biomarkers

There are numerous physiological indicators that are used to understand how individuals respond to stress and gauge their resilience (Chen et al., 2015; Daskalakis et al., 2016; Palmfeldt et al., 2016; Walker et al., 2017). The main indicators are autonomic measures, like heart rate variability (HRV), which reflects the body's stress adaptation by showing how the vagal control of heart rate changes in response to environmental changes. Vagally mediated HRV is employed as an index used to evaluate the extent of top-down appraisals, mediated by cortical-subcortical pathways, shape brainstem activity and autonomic responses in the periphery of the organism (Gillie & Thayer, 2014; Thayer et al., 2012). Higher scores on trait resilience psychometric scales have been observed in individuals with high vagally mediated HRV at rest (Souza et al., 2013). Conversely, chronic reductions in vagal activity, as indicated by HRV, have been consistently associated with psychopathology (Clamor et al., 2016; Gillie & Thayer, 2014). It is worth noting that HRV has been connected to individual differences in brain morphology, particularly ACC (Carnevali et al., 2018). Moreover, there have been reports on the associations between regional brain morphometric characteristics, specifically cortical thickness, and resting state vagally mediated HRV (Winkelmann et al., 2017). Some studies have used the dexamethasone suppression test (DST), where the DST suppression rate indicated stress resilience (Ma et al., 2016). The DST serves to assess the activation of the HPA axis, an integral system in physiological arousal and physiological stress (Fink, 2017). However, there is a lack of compelling evidence that supports the DST as a distinct measure of resilience rather than simply physiological arousal (O'Donohue et al., 2021).

The discussion regarding the correlation between these biomarkers and stress resilience is limited, particularly in studies that incorporate multiple biomarkers without a defined total stress resilience score or an examination of the individual relationship between each marker and resilience (Carlson et al., 2012; Hoge et al., 2018; Schneider et al., 2013; Smeets, 2010). Importantly, many psychobiological factors interact to promote resilience (Feder et al., 2009). Because of this interaction, it is unclear whether a few of these indicators, analyzed separately in response to one stressor, can cumulatively quantify resilience. Similarly, it is unclear whether, when sampled across multiple contexts, situations, and tasks, they provide a convergent indicator of resilience.

Circulating biomarkers

Circulating biomarkers (CB) are biomarkers that circulate cell-free in plasma/serum and include nucleic acids, extracellular vesicles, proteins, and metabolites. CB may provide early indicators of maladaptive responses to external and internal stressors and can be used to monitor (neuro)physiological status

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ongoingly. Specifically, there are four types of CB, which are essential in understanding the dynamic response to stress and resilience. Recent reviews have provided a comprehensive account of the role of CB in resilience (Beckner et al., 2022; Charney, 2004; O'Donohue et al., 2021); here, the main points of these reviews are summarized and expanded to include the most recent data.

Neuroendocrine biomarkers are key to both stress adaptation – cortisol, epinephrine, and norepinephrine – and to countering stress-induced effects of the HPA axis and regulation of synaptic plasticity – neuropeptide Y and BDNF. These markers can be sampled through a variety of cell types. For example, cortisol can be sampled through blood, saliva, urine, and hair, among other cells. It has been demonstrated that serum cortisol concentrations can increase by more than 250% under severe stress, both physical (Morgan, Wang, Southwick, et al., 2000) and psychological (Morgan, Wang, Mason, et al., 2000) duress. Higher cortisol concentration while under stress was associated with poorer cognitive performance (Lieberman et al., 2005). Similarly, higher cortisol concentration at baseline was a significant predictor of dropout from short survival training (Vaara et al., 2020). However, higher baseline cortisol was predictive of successful selection for performance in a long, high-demand selection course and positively correlated with self-reported grit and resilience (Farina et al., 2019). Salivary cortisol also has been shown to be a useful biomarker of resilience (Nishimi et al., 2022). It is important to note that both blood and saliva cortisol are marked by significant variability between and within people (Hruschka et al., 2005), across and within studies (Kudielka et al., 2009), and across time (Kudielka et al., 2009) limiting the interpretability and generalizability of results (Hayes et al., 2016). This massive variability potentially limits the utilization of cortisol both cross-sectionally and longitudinally. Importantly, research has reported the modulating role of physical fitness, where individuals with higher, compared to lower, fitness exhibited lower norepinephrine and higher neuropeptide Y 24-hr post-stress (Szivak et al., 2018). In addition, stress has been reported to exert a negative impact on circulating BDNF, decreasing its amount (Beckner et al., 2021; Henning et al., 2014; Suzuki et al., 2014) and dampening cognitive performance (Beckner et al., 2021; Gepner et al., 2018).

Inflammatory cytokines are soluble protein messenger molecules secreted by immune cells, adipose tissue, and a number of other organs. Pro-inflammatory cytokines (interleukin 6 – IL-6, IL-1β, and tumor necrosis factor TNF-α) trigger or heighten inflammation by relaying messages coordinating an immune response. Anti-inflammatory cytokines (IL-4 and IL-10) stop or lessen inflammation by relaying messages that prevent an excessive immune response that can lead to tissue damage. Previous research has indicated that prolonged exercise, inadequate training recovery, or excessive training stress can lead to an increase in circulating levels of IL-6 and TNF-α (Jürimäe et al., 2011; Main et al., 2010). They are commonly observed in conjunction with exercise-induced muscle damage (Smith, 2000) and have a detrimental effect on mood state (Booth et al., 2006). As such, modifications in circulating inflammatory levels could potentially offer a means of tracking physiological and psychological pressure and indirectly evaluating physiological resilience. Moreover, the profile of the inflammatory response, as reviewed recently, at least at this point, is inconsistent (Chester et al., 2013; Li et al., 2014) and indicates the sensitivity of the response not only to external stressogenic characteristics but also to individual characteristics. This inconsistency calls for more research (Beckner et al., 2022).

Furthermore, as summarized by Beckner et al. (2022), stress influences the biological activity of hormones. Importantly, it has been observed that both strenuous physical effort and caloric deficit can lead to alterations in IGF-I binding proteins and sex-hormone binding globulin. These proteins are essential to regulate the bioavailability of IGF-I and testosterone, respectively (Hamarsland et al., 2018; Henning et al., 2014). A 70% decline in testosterone concentration coupled with a 46% increase in sex-hormone binding globulin was observed during strenuous training (Henning et al., 2014). Dehydroepiandrosterone (DHEA) is an endogenous hormone and a precursor to testosterone. DHEA's role is to modulate the adverse effects of elevated cortisol, thereby providing beneficial behavioral and neurotrophic effects (Morgan et al., 2009; Morgan et al., 2004; Taylor et al., 2007). The adrenal cortex secretes DHEA, which can be converted into dehydroepiandrosterone sulfate (DHEA-S) by sulfotransferase in the adrenals, liver, and small intestine, which accounts for the majority of DHEA in circulation as a result of its longer biological half-life (15–30 mins vs. 7–10 h, respectively) (Morgan et al., 2009). These hormones are commonly known as DHEA(s) collectively, unless otherwise specified, due to their ability to produce similar physiological effects (Morgan et al., 2009). Given that DHEA-S can counter some of the catabolic effects of cortisol, examining the ratio of these two hormones rather than absolute abundance has been used as an assessment of hormonal imbalance or vulnerability to stress (Wu et al., 2013). It has been demonstrated that baseline DHEA concentration was a predictor of human performance (Morgan et al., 2009). Additionally, Morgan et al. (2004) reported a substantial elevation in DHEA and DHEA-S concentrations from baseline in response to survival training, which remained elevated at 24-h post-training. Trainees exhibiting higher DHEA(S)-salivary cortisol ratios during stress achieved higher performance scores (Morgan et al., 2009).

Similarly to the assortment of physiological indicators tied to resilience, there is a multiplicity of circulating biomarkers relevant for measuring resilience. It is crucial to comprehend this multitude and apply appropriate data reduction measures. For example, Handley et al. (2023) demonstrated the practicality of using latent profile analysis to capture heterogeneity in diurnal cortisol and diurnal DHEA, potentially as a protective mechanism against cortisol levels (Charney, 2004). Additionally, research has demonstrated that a childhood neuroendocrine profile characterized by high diurnal cortisol alongside low diurnal DHEA was specifically linked to improved adaptive functioning during the transition to adulthood (Handley et al., 2024).

In lieu of conclusion

As exemplified at the opening of this section, the field has not yet converged on the definition of resilience. So, why not offer one more? This proposed definition might open additional opportunities to study resilience, in Cicchetti's words (2020, p. 7), "as multidimensional spanning psychosocial and neurobiological factors." To remind the reader where this essay started, resilience is viewed here as an integration over a dynamic sampling of readiness. For clarification, readiness is the state of being physically, cognitively, emotionally, and behaviorally ready to perform optimally during a task. During development, a child encounters various tasks, gains experience in dealing with various situations, and trains to perform in different contexts, albeit environments, events, and circumstances are never wholly predictable. Resilience is then the capacity to exhibit readiness

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near-continuously across multiple contexts, situations, and tasks by withstanding or quickly recovering from physical and cognitive challenges. As readiness can be sampled through a variety of different indicators for a given task, in a given situation, and in a particular context, observing and assessing readiness throughout development (naturalistically or as repeatedly simulated experimentally) via integration over these repeated samplings can generate an index of resilience, which, in turn, can dynamically fluctuate and impact readiness as dictated by the notion of the adaptive cycle model describing the dynamics of complex systems (Holling, 1986).

The proposed definition of resilience through readiness allows the establishment of a paradigm for hypothesis generation and data collection and interpretation. The proposed paradigm emerges from the availability of wearable and portable devices that permit registering readiness online, in real-time, across multiple contexts, situations, and tasks. Correspondingly, this review intended to restate, from a slightly different perspective, what Cicchetti and colleagues repeatedly stated (Cicchetti, 2013), namely that a multidisciplinary approach integrating genetic, brain-imaging, physiological, and behavioral sampling could offer novel insights into and robust predictions of pathways to resilience to psychological stress in the face of adversity.

First, with regard to the brain, neuroimaging studies indicate that neural markers of readiness and resilience can be obtained with EEG and/or fNIRS. Currently, the number of such studies in the field of resilience is limited (Jauny et al., 2022; Lawler et al., 2021). To illustrate, elements of readiness, such as alertness, can be detected in near real-time through EEG, potentially utilizing a small number of sensors (Jagannathan et al., 2018; Jung et al., 1997). Furthermore, EEG researchers have discovered readiness potentials, which encompass changes in EEG data that transpire roughly 2 seconds prior to a voluntary action. Variations in cognitive load give rise to differences in readiness potentials (Baker et al., 2011), making them a potential neural indicator to monitor a participant's approach to their peak cognitive performance capacity. Moreover, using fNIRS has facilitated the exploration of neural correlates associated with alertness. Notably, this investigation primarily examined distinctions between task conditions post-task instead of real-time identification of alertness (Herrmann et al., 2008). Studies on resilience using EEG exist, but they are limited in both scope and number (LaGoy et al., 2022; Polusny et al., 2021; Watanabe & Takeda, 2022). Combining EEG and fNIRS in wearable devices, which have or are about to become commercially available, to capture both time and localization of the brain activities, recording in natural and staged experimental situations will generate discrete data sets across which the emergence of resilience can be derived.

Second, with regard to the genome, the indicators of low heritability of resilience, the quilt-like nature of the obtained findings on the role of structural genetic variation as opposed to the evidence that the emergence of resilience is substantiated by epigenetic mechanisms, also necessitates repeated and dynamic acquisition of the genetic data. Such data acquisition is now possible with Oxford Nanopore Technologies, ONT (Lin et al., 2021), which has revolutionized DNA sequencing with their very compact long-read sequencers, offering access to longer DNA fragments compared to previous generations of sequencers. ONT's nanopore sequencing technology enhances epigenetic methylation profiling in several ways. Firstly, it allows for the direct detection of modifications, eliminating the need for specialized library preparation steps like bisulfite conversion. Modifications such as 5mC, 5hmC, 6mA, BrdU in DNA, and m6A in RNA can be directly identified at single-nucleotide resolution. Moreover, training base-calling algorithms enable the detection of other natural or synthetic epigenetic modifications. Secondly, nanopore sequencing excels in 5mC detection, offering gold-standard calling with more even genomic coverage, less GC bias, and shorter analysis runtimes compared to traditional bisulfite sequencing. Lastly, the long reads and direct modification detection capabilities of nanopore sequencing enable the characterization of methylation in repeat-rich regions, including large repetitive arrays in the human genome previously unexplored with short-read sequencing. In summary, ONT's nanopore sequencers empower researchers to delve deeper into epigenetic modifications with unprecedented accuracy, longer reads, and streamlined sample processing. Thus, each of these devices can contribute valuable data separately in understanding the (neuro)physiological bases of readiness and resilience.

Finally, although reviewed in this essay only briefly, multiple studies indicate that peripheral physiological markers of response to stimuli may be predictive of individual resilience. Hence, resilience is closely linked to particular physiological indicators that serve as mediators during periods of stress (Maier et al., 2006). As an example, (Tutunji et al., 2023) have shown that HRV and other metrics derived from wearable devices, including Empatica E4 and other biosensors, possess the capability to accurately predict long-term stress levels. This discovery underscores the significance of these markers in resilience studies. In addition, a "readiness score" has been established by leveraging the predictive power of physiological markers such as HRV, skin temperature (ST), and accelerometry (Carper et al., 2020). The significance of these markers in evaluating individual readiness is highlighted by this score, which is calculated based on body stress, sleep quality, and physical activity (Oura Team, 2024). Likewise, the study conducted by Lee and Chun (2021) found associations between ST and skin conductivity, as measured by the Empatica E4 device, and individual alertness levels, specifically among office workers who were drowsy compared to those who were not. The assessment of cognitive states, particularly in safety-critical scenarios like driving, greatly benefits from the use of physiological markers, such as blood volume pulse, skin conductivity, ST, and respiration. These markers were found to be instrumental in predicting states of alertness, emphasizing their importance (Riani et al., 2020). Additionally, they also possess the ability to generalize across various situations, generating a comprehensive resilience index by sampling alertness and readiness.

Such an approach to resilience as a process that integrates readiness to everything, including adversity, across multiple contexts, situations, and tasks appears to be instrumental for a rapid generation of relevant data and now, at least instrumentation-wide, appears to be realistic. In addition to these dynamic studies, it is important to consider and implement longitudinal studies, which are greatly warranted as a possible window into temporal causality so it could be established whether resilience traits arise when the necessary neurobiological foundation is assembled, whether the needed biological system arises to follow the emergence of resilience, or whether these are coupled processes (Holz, Boecker-Schlier, et al., 2018; Laucht et al., 2000; Moreno-López et al., 2020; Morgan et al., 2014).

Finally, citing (again!) Denckla et al. (2020, p. 7), "Research on resilience is rooted in the field of developmental psychopathology. Scientists adhering to a developmental psychopathology framework emphasize the importance of incorporating multiple levels of analysis into their research. This approach states that different

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systems contribute to development and that these systems bidirectionally influence each other to contribute to outcomes." In many ways, the future of research on resilience is tightly connected to the future of developmental psychopathology. Both are relatively young concepts representing relatively young fields (or a unified field) of research. In their acceleration into the future, hand-in-hand, the "ordinary magic" (Masten, 2001) of resilience will be, no doubt, better understood but never trivialized.

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