Measuring Resilience in Children and Understanding the Interaction Between Genetic Susceptibility & Environmental Risk

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GENERAL ABSTRACT

Understanding variability in developmental outcomes following exposure to early life adversity has been an area of increasing interest in psychiatry, as resilient outcomes are just as prevalent as negative ones. This dissertation attempts to contribute to the field of resiliency research and covers 3 areas of study. The first study consists of a review which examines current approaches to measuring resilience in children and reveals that studies tend to rely on self-report methods to capture resilience which poses some challenges. A multi-dimensional measure of child resilience based on cognitive and behavioral features is proposed. To better understand the developmental origins of resilient outcomes in children, a second study featuring gene-by-environment analyses is presented. In this study, polygenic scores (associated with environmental sensitivity, child global psychopathology and major depressive disorder) were interacted with exposure to maternal depressive symptoms (MDS). Specifically, positive self-evaluation, hopefulness, motivation, and overall resilience were measured in 5-year-old children using a challenging puzzle task (CPT). The majority of our findings indicate that genetic susceptibility combined with exposure to: 1) low levels of prenatal MDS elicit the best outcomes; 2) high levels of prenatal MDS elicit worse outcomes. Our findings also demonstrate that when exposed to low levels of prenatal MDS, children low in genetic susceptibility were most motivated while genetically susceptible children were least motivated. These findings lend support to the differential susceptibility, vantage sensitivity and prenatal programming of postnatal plasticity hypotheses. A third study focused on the behavioral component of the CPT and examines patterns of irritability relative to competence as a function of resilience. Videos of children performing the CPT were coded according to the Disruptive Behavior Diagnostic Observation Schedule, a structured clinic-based assessment designed to capture emotional dysregulation in young children.

Similar gene-by-environment analyses as in Study 2 were conducted, except we were predicting the probability of exhibiting external features of resilience (as opposed to internal features of resilience). A portion of our findings were explained by the vantage sensitivity hypothesis whereby significant variation in outcomes was observed at low levels of exposure to MDS. Overall, the findings from this dissertation hold promise for an ecologically-valid measure of resilience in young children that can be used in various settings.

RÉSUMÉ GÉNÉRAL

La compréhension de la variabilité des résultats du développement suite à l'exposition à l'adversité au début de la vie est un domaine d'intérêt croissant en psychiatrie, car les résultats résilients sont tout aussi prévalents que les résultats négatifs. Cette thèse tente de contribuer au domaine de la recherche sur la résilience et couvre 3 domaines d'étude. La première étude consiste en une revue qui examine les approches actuelles de la mesure de la résilience chez les enfants et révèle que les études ont tendance à s'appuyer sur des méthodes d'auto-évaluation pour saisir la résilience, ce qui pose certains défis. Une mesure multidimensionnelle de la résilience de l'enfant basée sur des caractéristiques cognitifs et comportementaux est proposée. Pour mieux comprendre les origines développementales des résultats de résilience chez les enfants, une deuxième étude comprenant des analyses gène-par-environnement est présentée. Dans cette étude, les scores polygéniques (associés à la sensibilité à l'environnement, à la psychopathologie globale de l'enfant et au trouble dépressif majeur) ont été mis en interaction avec l'exposition aux symptômes dépressifs maternels (SDM). Plus précisément, l'auto-évaluation positive, l'espoir, la motivation et la résilience globale ont été mesurés chez des enfants de 5 ans à l'aide d'une tâche de puzzle difficile (TPD). La majorité de nos résultats indiquent que la susceptibilité génétique combinée à l'exposition à : 1) de faibles niveaux de SDM prénataux donnent les meilleurs résultats ; 2) des niveaux élevés de MDS prénataux donnent de moins bons résultats. Nos résultats montrent également que, lorsqu'ils sont exposés à de faibles niveaux de SDM prénataux, les enfants ayant une faible susceptibilité génétique sont les plus motivés, tandis que les enfants génétiquement sensibles sont les moins motivés. Ces résultats appuient les hypothèses de susceptibilité différentielle, de sensibilité à la situation et la programmation prénatale de la plasticité postnatale. Une troisième étude s'est concentrée sur la composante comportementale du TPD et examine les

modèles d'irritabilité par rapport à la compétence en fonction de la résilience. Les vidéos d'enfants effectuant le TPD ont été codées selon le Disruptive Behavior Diagnostic Observation Schedule, une évaluation clinique structurée conçue pour saisir la dysrégulation émotionnelle chez les jeunes enfants. Nous avons effectué les mêmes analyses gène-par-environnement que dans l'étude 2, sauf que nous prédisions la probabilité de présenter des caractéristiques externes de résilience (au lieu de les caractéristiques internes de résilience). Une partie de nos résultats a été expliquée par l'hypothèse de la sensibilité de la position avantageuse, selon laquelle une variation significative des résultats a été observée à de faibles niveaux d'exposition au SDM. Dans l'ensemble, les résultats de cette thèse sont prometteurs pour une mesure écologiquement valide de la résilience chez les jeunes enfants qui peut être utilisée dans divers contextes.

List of Abbreviations

AIC = Akaike information criterion

AUC = area under the curve

BIC = Bayesian information criterion

CESD = Center for Epidemiologic Studies Depression Scale

CPT = Challenging Puzzle Task

DB-DOS = Disruptive Behavior Diagnostic Observation Schedule

ELA = early life adversity

G×E = gene-by-environment

GPC = global psychopathology in children

LEGIT = Latent Environmental & Genetic InTeraction

MAVAN = Maternal Adversity, Vulnerability, and Neurodevelopment

MDD = major depressive disorder

MDS = maternal depressive symptoms

PC = principal component

PGS = polygenic score

PPPP = Prenatal programing of postnatal plasticity

SUSC = susceptibility

Contribution to Original Knowledge

- The use of a measure of resilience that does not rely on an absence of psychopathology
- Taking into account the chronicity, severity, and timing of maternal depressive symptoms
- Incorporating a longitudinal design
- Using three different polygenic scores (PGSs) that have been tested in child populations (i.e., PGSs associated with global child psychopathology, MDD, and environmental susceptibility).
- An ecologically-valid measure of child resilience which captures internal and external processes of adaptation in response to a challenge.
- Tests of environmental sensitivity to confirm our gene-by-environment interaction findings
- A valid framework with which to detect differential susceptibility, vantage sensitivity and prenatal programming of postnatal plasticity effects

Contribution of Authors

- My supervisor Dr. Ashley Wazana guided my research questions, helped me to think critically about study design, fostered collaborations with other researchers, and supported me with all aspects of theory, data analyses, clinical applications and manuscript preparation. As the principal investigator on this research project, Dr. Wazana facilitated data acquisition and constructed a team of experts to manage various aspects of the project, including data collection, data analysis and dissemination.
- Dr. David Laplante assisted with manuscript preparations, revisions and the conceptualization of my data analysis plan for all 3 studies. He was instrumental in providing critical and timely feedback with particular attention on how to better streamline the presentation and interpretation of my findings.
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- Alegra Kandyoti and Marie-Elyse Lafaille Magnon both received training on how to apply the DB-DOS coding structure to the CPT for Study 3, after which they assisted with the coding of hundreds of puzzle videos and participated in consensus meetings to optimize our interrater reliability.

- Dr. Ezster Szekely assisted with the conceptualization of study design and assisted with reviewing all three manuscripts. Dr. Szekely possesses a wealth of knowledge when it comes to developmental theory. She therefore advised me on how to apply those theories to large, longitudinal data sets and in relation to my specific research questions.
- Dr. Erica Anderson provided in-person DB-DOS training to several members of our team. The training we received was applied to video coding of the CPT for Study 3. After our training, Dr. Anderson remained available to assist with coding questions and participated in consensus meetings when necessary.
- The remaining authors are principal investigators on the MAVAN project and were involved in the initial conceptualization of the project almost 20 years ago. They formulated the study design, implemented a strategy for data collection and analysis, and have been instrumental to knowledge dissemination. Each investigator has contributed their expertise to the field of developmental research and many have applied the knowledge gained in clinical settings.
- Dr. Michael Meaney was the original principal investigator who spearheaded the MAVAN project. The MAVAN project represents the first longitudinal study linking neurocognitive/ behavioural function with structural neurodevelopment through neuroimaging and genetic vulnerability in humans, in the presence or absence of maternal adversity. Without him, this research would not have been possible.

GENERAL INTRODUCTION

Substantial efforts have gone into understanding the developmental origins of psychopathology and the different pathways that lead to mental illness. In fact, most studies in psychiatry are based on a diathesis–stress model which assumes that exposure to cumulative risk predisposes an individual to develop psychiatric problems (Monroe & Simons, 1991; Rosenthal, 1963). Given this accepted view of disease onset, a significant amount of research has focused on types of medical intervention and therapeutic approaches to treat psychiatric disorders. To better recommend treatment, it could be informative to incorporate a bottom-up approach whereby we learn from individuals who have beat the odds. Studying those who have managed to flourish despite the presence of risk factors (including exposure to early life adversity) can teach us a great deal about effective ways to overcome and cope with stress. Identifying the strengths and promotive factors that can protect one against the detrimental impacts of ELA may be especially valuable to vulnerable populations whose realities consist of co-existing with risk factors and structural inequalities.

The ability to thrive in the face of adversity is known as *resilience* (Rutter, 2006). However, before resilience can be studied, it is necessary to understand how resilience is measured. And before resilience can be measured, it is important to work with a consistent and comprehensive definition of resilience so as to reduce its variability as a measurable phenotype. For example, there has been some debate about whether resilience is a process or trait (Masten, 2007). A recent review article synthesized the literature on resilience and came up with a cohesive definition that refers to resilience "*as a dynamic developmental process that encompasses an individual's capacity to adapt positively following significant adversity*" (VanMeter & Cicchetti, 2020). In this regard, understanding resilience as a process rather than a static trait implies that it encompasses

strategies, attitudes and behaviors that can be learned (King et al., 2020). Furthermore, being resilient does not imply that one does not experience negative emotions when stressed or facing a challenge. A resilient individual may react strongly to a failure, but the difference is that they can bounce back more easily (Tugade & Fredrickson, 2004). Therefore, in order to properly evaluate resilience, assessment tools that measure recovery from stress are needed.

Moving away from a deficit-based approach, the question now becomes: what are the developmental factors that lead to resilient outcomes? Many researchers have attempted to answer this question already and have discovered genetic correlates of resilience (Elbau et al., 2019; Feder et al., 2009; Stein et al., 2009) in addition to early environmental predictors of resilience, including friendship quality, opportunities for academic engagement, secure attachment relationships, and supportive parenting (Gartland et al., 2019; VanMeter & Cicchetti, 2020). Otherwise, many studies have examined how protective factors (e.g., nurturing relationships, self-esteem, living in a safe and stable environment, social support, family cohesion, etc.) can moderate the impact of risk given that positive outcomes often manifest despite exposure to significant risk factors (Cui et al., 2020; Elmore et al., 2020; Kirby et al., 2020; Rutter, 1987). This variation in outcomes led some researchers to reframe how risk is contextualized, because depending on what the supposed risk factor is interacting with, that risk may never be activated (Cicchetti & Rogosch, 2012). Based on this reasoning, perhaps absolute risk should instead be referred to as relative risk. Moving forward, in order to properly contextualize these interacting factors, it is necessary to study the other end of the spectrum – both in terms of positive environments and positive outcomes. The interaction of factors that create the conditions for psychiatric disorders at one end of the spectrum can be the same factors that build resilience at the other end of the spectrum (Boyce et al., 2021).

To illustrate this point, take the example of genetic risk. There is more research emerging which suggests that we may be misclassifying genetic risk or at the very least, not applying it in the proper context. This is likely because genetic risk has often been approached through a pathologizing lens (e.g., diathesis stress) (Assary et al., 2018; Maglione et al., 2018). When approached from an evolutionary point of view and as the developmental psychologist, Michael Pluess points out, if so-called genetic "risk" is having a negative effect, then why haven't these risk alleles been eliminated from the gene pool by process of natural selection? The fact that these risk alleles are so frequent in the population (Chang et al., 1996; Gelernter et al., 1999) suggest that there must be some fitness and reproductive advantages to having these genetic profiles (Bakermans-Kranenburg & van, 2015; Pluess, 2017). This logic is what underlies the differential susceptibility hypothesis and prompts us to reconsider genetic risk as genetic "plasticity" (Belsky et al., 2009), whereby genetic susceptibility can be advantageous if combined with a favorable environment, or disadvantageous if combined with negative environmental factors (Belsky & Pluess, 2009). Evidence of differential susceptibility effects has already emerged in the literature with susceptibility genotypes only conferring risk if combined with adverse environments; otherwise, these same genotypes proved beneficial when combined with favorable environments (Cao et al., 2022; Flasbeck et al., 2019; Lee et al., 2021; Letourneau et al., 2020; Shaw et al., 2019; van Ijzendoorn et al., 2012)

By not studying the full range of outcomes, it is not possible to determine whether certain influences which have been previously deemed risk factors are in fact inducing general vulnerability. For example, it turns out that some individuals vary in their sensitivity to the environment, whether it be good or bad – a concept known as environmental sensitivity (Pluess, 2015). The differential susceptibility hypothesis falls within the environmental sensitivity

framework as does the vantage sensitivity hypothesis (Thibodeau et al., 2016). According to vantage sensitivity, some individuals are more likely to benefit from the positive effects of supportive experiences than others as a function of inherent characteristics, including one's genetic or biological make-up (Pluess, 2017). Vantage sensitivity essentially mirrors diathesis-stress and highlights individual variation in response to positive environmental factors instead of negative ones (Bakermans-Kranenburg & van, 2015). However, contemporary models of environment sensitivity including differential susceptibility and vantage sensitivity, are not easily detected because positive outcomes are rarely measured.

These challenges also apply to conventional theories of prenatal stress exposure framed within the Developmental Origins of Health and Disease (DOHaD) approach. The DOHaD framework encompasses a range of developmental theories including the fetal programming hypothesis (aka the thrifty phenotype or Barker hypothesis) which stipulates that exposure to stress in utero programs the fetus to be susceptible to disease later in life (Barker, 1997; Wadhwa et al., 2009). Using the example of prenatal malnourishment as an indicator of prenatal stress, the fetus will divert nutrients towards the development of its essential organs (primarily the brain) in anticipation of a shortage of nutrients postnatally. This response can be advantageous in the short-term, but detrimental in the long-term since growth is impaired during this time leading to low birth weight and other associated health problems (Barker, 1997). The fetus will be especially maladapted if the postnatal environment is suddenly different from the prenatal environment (e.g., prenatal malnutrition is followed by a postnatal high-fat diet), a concept known as the environmental mismatch hypothesis (Chaby, 2016). In this case, the individual will be vulnerable to metabolic imbalances such as obesity, insulin resistance, coronary heart disease, and hypertension (Remacle et al., 2004; Vickers & Breier, 2000).

The environmental mismatch hypothesis expands upon the prenatal programming hypothesis and views exposure to prenatal stress as being detrimental to child outcomes *only* if the postnatal environment is incongruent with the prenatal environment. Otherwise, prenatal stress exposure matched with postnatal stress exposure can be advantageous (Gluckman et al., 2005). The logic being that the conditions influencing the prenatal environment are very likely to be the same conditions that shape the postnatal environment, so the fetus adapts to maternal signals in preparation for a similar postnatal environment. In other words, the environmental mismatch hypothesis highlights the adaptive value of exposure to ELA and assumes that plasticity evolved to match an individual to its predicted or expected environment (Daskalakis et al., 2013). Evidence for the environmental mismatch hypothesis comes from animal studies of neonatal stress exposure (e.g., low licking and grooming or maternal separation) resulting in an attenuated stress response in adulthood when matched with social isolation post-weaning (Daskalakis et al., 2012; Santarelli et al., 2014).

The prenatal programing of postnatal plasticity (PPPP) hypothesis explains additional variation in outcomes and is based on a similar premise as the environmental mismatch hypothesis except it does not exclude incongruent prenatal and postnatal environments as being adaptive. Rather, it assumes that prenatal stress exposure primes the fetus to be susceptible to its postnatal environment, regardless of quality (Hartman & Belsky, 2018a, 2018b; Hartman et al., 2018; Pluess & Belsky, 2011). In the context of a constantly changing world where the environment is not always predictable, postnatal plasticity allows the fetus to defer its commitment to a specific developmental trajectory until it can evaluate the postnatal context and adapt accordingly to optimize its chances for survival. Given that a mismatched prenatal-postnatal environment would be extremely costly to the developing child, it would seem more adaptive for children to vary in

their susceptibility to environmental influences (Hartman & Belsky, 2018a). Animal studies support this hypothesis demonstrating that prenatally stressed prairie voles who were cross-fostered to contexts of high parental care displayed lower stress reactivity as adults, whereas low parental care was associated with high stress reactivity (Hartman et al., 2018). In terms of human studies, preterm infants[1] exposed to a high-quality caregiving environment exhibited better social and cognitive functioning compared to preterm infants who were exposed to lower quality caregiving (Gueron-Sela et al., 2015; Landry et al., 2001).

Similar to the differential susceptibility hypothesis, the PPPP theory suggests that prior risk (e.g., either genetic susceptibility or prenatal stress exposure) can be developmentally advantageous if paired with subsequent protective factors (Pluess & Belsky, 2011). However, there is a lack of empirical human studies that measure positive outcomes in relation to prenatal stress exposure, again due to the focus on adverse effects of prenatal stress. In light of an under-detection of environmental sensitivity and PPPP findings, we will contribute to this literature by first exploring valid measures of resilience since the focus will be shifted from investigating the developmental origins of psychopathology to investigating the developmental origins of *resilience*. Furthermore, examining a broader spectrum of environmental influences and child outcomes will prompt us to reconsider how risk is contextualized. Our specific research aims are as follows:

Study 1 - A review of child measures of resilience along with some recommendations for how to proceed with future resiliency research in children. The consideration of ELA and the role of genetics in the prediction of resilience is also discussed. The review highlights that studies are moving away from defining resilience as an absence of psychopathology. However, ecologically

[1] Here, preterm birth is considered a marker of prenatal stress.

valid measures of resilience are still needed as the majority of studies rely on self-report or parent-reported methods of data collection.

Study 2 - A child-friendly stress paradigm was introduced as a potential measure of resilience in children. Children's cognitive appraisals (positive self-evaluation, hopefulness and motivation) in relation to a challenging puzzle task (CPT) were measured and their response patterns were entered into a gene-by-environment model. Specifically, an additive genetic score was combined with varying levels of exposure to maternal depressive symptoms to predict resilient outcomes on the CPT. We then evaluated whether our findings were consistent with contemporary models of environmental sensitivity and/or PPPP.

Study 3 – To complement the cognitive appraisal component of the CPT, we explored the corresponding behaviors and emotions elicited by the CPT. Videos of children performing the CPT were coded according to a structured clinic-based assessment designed to capture emotional regulation in young children. Patterns of total irritability relative to total competence were entered into a gene-by-environment model, whereby the outcome in question was the probability of belonging to the resilient class. Similar to Study 2, we then evaluated whether our findings were consistent with contemporary models of environmental sensitivity and/or PPPP.

Bridge to Study 1

Because our focus was to investigate the developmental origins of resilience, the supporting literature throughout this dissertation was limited to studies with children. Despite an increase in resiliency research across a range of populations, there are few studies that measure resilience in *young* children (Gartland et al., 2019). This presents an opportunity to contribute to the literature while tapping into how children first learn about the degree to which adversity is controllable and develop strategies for how to adapt to such adversity. By identifying which children are particularly sensitive to their environments and are thus more likely to benefit from supportive resources, we can direct interventions towards these children. First and foremost, establishing a clearly defined and measurable phenotype is necessary since there is significant variation in how individuals respond to stress. Understanding the mechanisms underlying that variation will reveal the causal processes involved which can then inform intervention strategies and therapeutic tools. The study of causal processes and the developmental origins of resilience also requires a longitudinal study design framed within a gene-by-environment (G×E) interaction model since genetic influences are not always detected unless they are studied in relation to key environment factors as was revealed by the groundbreaking studies by Caspi and colleagues (Caspi et al., 2002; Caspi et al., 2003). Moreover, being able to detect significant G×E effects necessitates the consideration of variation of both genetic and environmental factors. Otherwise, the focus on negative outcomes and negative influences through the lens of a diathesis-stress framework will skew the distribution and lower the potential to detect G×E effects (Bakermans-Kranenburg & van, 2015). Given the importance of context in detecting G×E effects along with a need to capture positive influences and outcomes, we start our journey of studying the developmental origins of resilience by exploring the current landscape of child resilience measures. We then build a case

for the development of a standardized measure of child resilience that can be administered in clinical, research and educational settings.

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STUDY # 1

Measuring Resilience in Children: A Review of Recent Literature and Recommendations for Future Research

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ABSTRACT

Purpose of Review: Understanding variability in developmental outcomes following exposure to early life adversity (ELA) has been an area of increasing interest in psychiatry, as resilient outcomes are just as prevalent as negative ones. However, resilient individuals are understudied in most cohorts and even when studied, resilience is typically defined as an absence of psychopathology. This review examines current approaches to resilience and proposes more comprehensive and objective ways of defining resilience.

Recent Findings: Of the 36 studies reviewed, the most commonly used measure was the Strengths and Difficulties Questionnaire (n = 6), followed by the Child Behavior Checklist (n = 5), the Resilience Scale for Chinese Adolescents (n = 5), the Rosenberg Self-Esteem Scale (n = 4), and the Child and Youth Resilience Scale (n = 3).

Summary: This review reveals that studies tend to rely on self-report methods to capture resilience which poses some challenges. We propose a complementary measure of child resilience that relies on more proactive behavioral and observational indicators; some of our preliminary findings are presented. Additionally, concerns about the way ELA is characterized as well as the influence of genetics on resilient outcomes prompts further considerations about how to proceed with resiliency research.

INTRODUCTION

Development is marked by periods of heightened neural plasticity in which brain regions involved in the regulation of emotion and stress are particularly sensitive to the effects of early life adversity (ELA). Although ELA experienced early in life can have long-term negative impacts on the developing child, sometimes resulting in psychiatric and behavioral problems (Babenko et al., 2015; Hornung & Heim, 2014; Murgatroyd et al., 2010; Silberman et al., 2016), many children remain unaffected (Bonanno & Mancini, 2008; Peskin, 2016). In fact, as many as 50% of individuals who are exposed to stressful events do not go on to develop a stress-related psychiatric illness in later life (Bonanno & Mancini, 2008; Claessens et al., 2011). This suggests that there are important variations in how people respond to stress and traumatic events, with some individuals prone to maladaptive outcomes while others function well. As a result, the focus of recent research has been to better understand positive outcomes in addition to negative ones.

Positive adaptation or better-than-expected outcomes in the context of ELA is known as resilience (Luthar et al., 2006; Masten, 2001). Although there are varying definitions of resilience, it is best understood as a dynamic process that integrates many systems within an individual (e.g., temperament, biological predispositions) as well as in the environment of the individual, rather than a static state or trait-like attribute (Norris et al., 2009). In other words, resilience is a biopsychosocial process that involves several interacting factors including: neurobiological mechanisms, stress and emotional regulation systems, prosocial skills, coping strategies and temperament (Agnafors et al., 2016; Davydov et al., 2010; Masten, 2007; Reuben & Shaw, 2015).

Measuring Resilience in Children

How resilience is characterized and detected may vary depending on the developmental period since responses to challenges are typically content- and context-specific (Fergus & Zimmerman, 2005). It has been suggested that detecting resilient functioning in young children may be more reliable given that their vulnerability confers increased sensitivity to the environment making them more responsive to the task at hand (Bonanno & Diminich, 2013). Still, the methods by which resilience is captured and measured (whether in children or adults) poses some challenges particularly because resilience has often been characterized as an absence of psychopathology or dysfunction although the two are not synonymous. Accordingly, it is key that resiliency research captures some of the more proactive cognitive, emotional, and behavioral processes associated with resilient functioning.

The current review aims to highlight recent trends in resiliency research by reviewing studies of child resilience published in the last 18 months. Using PubMed®, a biomedical literature database, the following search parameters were entered: ((((resilience[Title] OR resilient[Title] OR resiliency[Title] OR "positive outcomes"[Title] AND (("2019/04/15"[Date - Publication] : "2020"[Date - Publication]))) AND (child[Title] OR children[Title]) AND (english[Filter])) NOT (review[Title/Abstract]). A total of 99 articles were returned. After scanning titles and abstracts for relevance, 34 studies were excluded for the following reasons: they were measuring resilience in parents, caregivers or mothers who had children with some disability, disorder or medical condition (n = 34) while the remaining studies were excluded (n = 29) because they were deemed irrelevant for other reasons (e.g., were editorials, consisted of retrospective reports of ELA or the name of the cohort had the term resilience in it). Thus, the final selection consisted of 36 articles for which the age range was birth to 19 years old.

The majority of the studies identified in the review used quantitative approaches, while 4 studies used qualitative methods (Asante, 2019; Kaiser & Sinanan, 2020; Mantovani et al., 2020; Veronese et al., 2020) and 3 studies incorporated a mixed-methods research design (Cheetham-Blake et al., 2019; Fogarty et al., 2019; Worku et al., 2019). Twenty-four of the 36 studies reviewed were cross-sectional, 7 studies used a longitudinal research design and the remaining were intervention-based (n = 5). Although measures of psychopathology were featured in the reviewed studies, unless they were used to construct a measure of resilience, they are not reported here as it was not the purpose of the review. Otherwise, resilience was featured as the outcome measure in 27 studies, another 7 studies examined resilience as a mediating factor (n = 4) (Beeckman et al., 2019; Elmore et al., 2020; Matsuyama et al., 2020; Wang et al., 2019) or as a predictor variable (n = 3) (Cheetham-Blake et al., 2019; Cohen et al., 2019; Tian et al., 2019) and 2 studies assessed the psychometric properties of resilient measures (Folayan et al., 2020; Llistosella et al., 2019). In terms of sample size, the range of participants for the qualitative studies was from 9 to 137, while for quantitative studies, the range was from 24 to 51156 participants. The majority of measures were based on child or youth self-reports, whereas 9 of the 36 studies were based on parent-reports and 1 on teacher reports (Table 1).

The most common instrument used to measure resilience in children was the Strengths and Difficulties Questionnaire (SDQ) which was used in 6 of 36 the studies. The SDQ captures both positive and negative outcomes in children and can be administered to children, parents or teachers. The 25-item SDQ (plus an optional incapacity section) measures current attention/hyperactivity problems, conduct problems, emotional problems, peer relationships, and prosocial behaviors (Goodman, 1997). In the current review, 3 of the 6 studies administered the parent-reported version of the SDQ (Fogarty et al., 2019; Miller-Graff et al., 2020; Rotheram-Borus et al., 2019) while the

child-reported version was used twice (Jefferies et al., 2019; Vreeman et al., 2019) and the teacher-reported version once (Kirby et al., 2020). Of these, 3 studies included SDQ total scores in their analyses (Fogarty et al., 2019; Kirby et al., 2020; Vreeman et al., 2019), 2 studies used both total scores and the prosocial skills subscale (Miller-Graff et al., 2020; Rotheram-Borus et al., 2019) and 1 study used only the peer relations subscale of the SDQ (Jefferies et al., 2019).

The other two most common measures of child resilience were the Resilience Scale for Chinese Adolescents (RSCA) and the Child Behavior Checklist (CBCL), each of which were used in 5 studies. The RSCA is a 27-item survey with a 5-point Likert scale that taps into seven domains: goal focus, emotion control, positive cognition, family support, interpersonal assistance, personal strength and support (Hu, 2008). The RSCA was exclusively used in studies with Chinese participants (Liu et al., 2020; Morgan et al., 2020; Tam et al., 2020; Tian et al., 2019; Xiao et al., 2019). The CBCL addresses a range of emotional and behavioral problems including internalizing and externalizing symptoms; total scores or its subscales can be used (Achenbach, 1983). The pre-school version of the CBCL contains 100 items, is intended for children aged 1.5 to 5 years and relies on parent reports. The school-age version is made up of 118 items, is designed for children aged 6 to 18 years and can be teacher- or parent-reported; otherwise if the child is 11 years or older, then the 112-item Youth Self-Report (YSR) version of the CBCL can be used (Achenbach & Rescorla, 2001). For the current review, three studies relied on parent reports (Conover, 2020; Malee et al., 2019; Rotheram-Borus et al., 2019) while two studies administered the YSR version (Cui et al., 2020; Ndetei et al., 2019). Of the studies identified in the current review, 1 study used examined CBCL total scores as well as the internalizing and externalizing subscales (Conover, 2020), another study analyzed CBCL total scores along with the aggressive subscale (Rotheram-Borus et al., 2019), 1 study used the Activities and Social subscale (Cui et al., 2020), and 2 studies

used CBCL total scores only (Malee et al., 2019; Ndetei et al., 2019). However, in two of these studies, CBCL scores were used as an indicator of behavioral and emotional problems rather than resilience (Conover, 2020; Ndetei et al., 2019). The other studies used the CBCL "activities and social" subscale as a measure of social competence (Cui et al., 2020) while the remaining two studies defined resilience as having CBCL scores in the normal range (Malee et al., 2019; Rotheram-Borus et al., 2019).

The next most commonly used instruments were the Rosenberg Self-Esteem Scale and the Child and Youth Resilience Measure (CYRM). The Rosenberg Self-Esteem Scale was administered in 4 studies (Cohen et al., 2019; Cui et al., 2020; Folayan et al., 2020; Tam et al., 2020) and the CYRM in 3 (Conover, 2020; Jefferies et al., 2019; Llistosella et al., 2019). The Rosenberg Self-Esteem scale is composed of 10 items and conforms to a 4-point Likert scale (Rosenberg, 1965). There are three versions of the CYRM, the 12-, 28- and 32-item versions all of which are based on a 5-point Likert scale (Liebenberg et al., 2013; Ungar & Liebenberg, 2011). The CYRM-12 was administered in 2 studies (Conover, 2020; Jefferies et al., 2019) while the CYRM-32 was used and validated in one study (Llistosella et al., 2019).

Another two studies (Folayan et al., 2020; Hebbani et al., 2020) administered the 25-item Connor Davidson-Resilience Scale (CD-RISC) (Connor & Davidson, 2003), although Folayan et al. (Folayan et al., 2020) utilized the reduced 10-item version (Campbell-Sills & Stein, 2007). The Ryff and Keyes Scales of Psychological Well-Being is an instrument consisting of six sub-scales: self-acceptance, positive relations with others, autonomy, environmental mastery, purpose in life and personal growth (Ryff & Keyes, 1995) and was administered in 2 studies as well (Hebbani et al., 2020; Worku et al., 2019). The remaining studies used other measures of resilience and are indicated in Table 1.

With the exception of six studies where resilience was either characterized as an absence of psychological inflexibility (Beeckman et al., 2019), having low scores on the SDQ (Kirby et al., 2020; Vreeman et al., 2019), or being in the normal range behaviorally (e.g., CBCL scores) (Malee et al., 2019; Rotheram-Borus et al., 2019), developmentally (Rotheram-Borus et al., 2019), or cognitively (Young et al., 2020), the remaining studies used actual resilient scales or measures of positive adjustment rather than relying on an absence of psychopathology to characterize resilience. This is reassuring considering that a similar review which was conducted recently (from 2004 to 2017) and examined measures resilience in children, found that 18 of the 30 identified studies characterized resilience as an absence of psychopathology, namely low levels of: externalizing and internalizing problems, anxiety, depressive symptoms, aggression, delinquency, antisocial behavior and drug use. (Gartland et al., 2019). It is possible that current research in psychiatry is starting to recognize how misleading it has been to equate an absence of psychopathology with resilience.

A significant limitation of the studies identified in the current review and of those reviewed by Gartland et al. (Gartland et al., 2019) is that none featured observable behavioral measures of resiliency in the children; rather they were all based on self-reports and parent-reports or to a lesser extent, teacher-reports. Some of the limitations of relying on self-report measures are that they introduce social-desirability and recall biases (Althubaiti, 2016) and disagreement among informants has been a long-standing issue in research (De Los Reyes, 2013; Korelitz & Garber, 2016). Observational measures of resilience such as how a child copes with a stressful task may be a more reliable means of detecting resilience in young children as it provides insight into the behavioral and cognitive processes involved. Although there was one study identified in our review which used the BEST-C (the children's version of the Trier Social Stress Test) and includes

verbal reports assessing self-reported stress and coping in response to the task, these reports were only examined in the context of a manipulation check. Furthermore, the main purpose of this study was to assess the impact of this task on salivary cortisol and heart rate (Cheetham-Blake et al., 2019). An alternative to this paradigm is the Challenging Puzzles Task (CPT), which not only captures how children deal with a stressful task, but also taps into three indicators of resilience: positive self-evaluation, hopefulness and motivation (Cicchetti, 2010; Fergus & Zimmerman, 2005; Gillespie et al., 2007; Ho et al., 2010). These constructs are detectable in children as young as 4 years old (Smiley & Dweck, 1994) and are relatively stable up to 5 years later (Ziegert et al., 2001).

Recommendations for Future Research

The Maternal Adversity, Vulnerability and Neurodevelopment (MAVAN), a community-based, prospective cohort study of pregnant mothers and their offspring, is currently using the CPT to identify the developmental pathways associated with risk and resilience. Dyads are assessed longitudinally, with multiple assessments of both mother and child in home and laboratory across from pregnancy to late adolescence. In our study, the CPT was administered to 5-year-old children by a trained experimenter in the child's home alongside other measures of child behavior. The CPT (Cole et al., 2007) is a modified version of the task used by Cole and colleagues with children of the same age (Smiley & Dweck, 1994; Ziegert et al., 2001): our adapted version consisted of five puzzle trials instead of the original seven trials. The CPT consists of a series of possible and impossible puzzles, whereby reactions to a challenge (in this case, three impossible puzzles) are captured via a rating scale. Puzzles 1 and 5 are possible to solve and can be completed with the help of the research assistant as needed while puzzles 2 to 4 are impossible and have a time limit

of 2-minutes. A picture of each puzzle is shown before the challenge begins and after each puzzle the children are asked the following questions: 1) How well do you think you did on the puzzle? (positive self-evaluation); 2) How do you think you will do on the next puzzle? (hopefulness); 3) How do you feel about doing the next puzzle? (motivation). To answer these questions, a pre-puzzle trial is conducted to ensure the child understands the accompanying rating scales (of stars and happy/sad faces) which range from 1 (negative outlook) to 5 (positive outlook; Figure 1).

Measures of resilience were captured in two ways. First, self-ratings according to the above questions were recorded and used to conduct trajectory analyses across the 5 puzzles for each indicator of resilience. Preliminary data corresponding to the trajectory analyses of the children's CPT responses revealed three distinct appraisal patterns. Whether assessing positive self-evaluation, hopefulness or motivation, three consistent response patterns emerge. One group of children remain relatively stable exhibiting positive self-appraisal throughout the puzzle task even when faced with failures (resilient group), another group shows a decrease in self-appraisal when faced with impossible puzzles followed by an improvement in self-appraisal when presented with a solvable puzzle (rebound group), while a third group of children exhibit steadily decreasing self-appraisal even when presented with a solvable puzzle post-impossible trials (discouraged group; Figure 2). Similar trajectories have been detected in other studies on resilience *(Foster et al., 2019; Park et al., 2020; Quale & Schanke, 2010), further validating our findings.

Figure 1: The Challenging Puzzles Task (CPT)

After each of the 5 puzzles, each child is asked:

1) How well do you think you did on the puzzle? (positive self-evaluation)

2) How do you think you will do on the next puzzle? (hopefulness)

3) How do you feel about doing the next puzzle? (motivation)

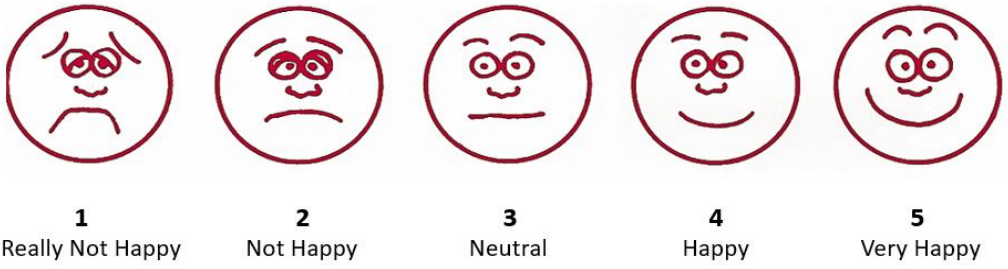
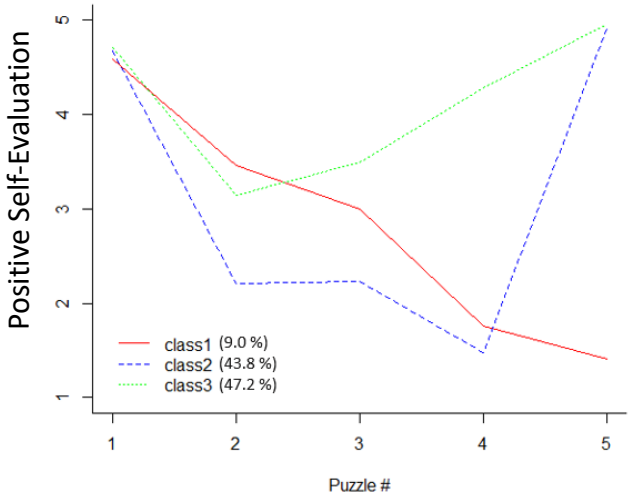


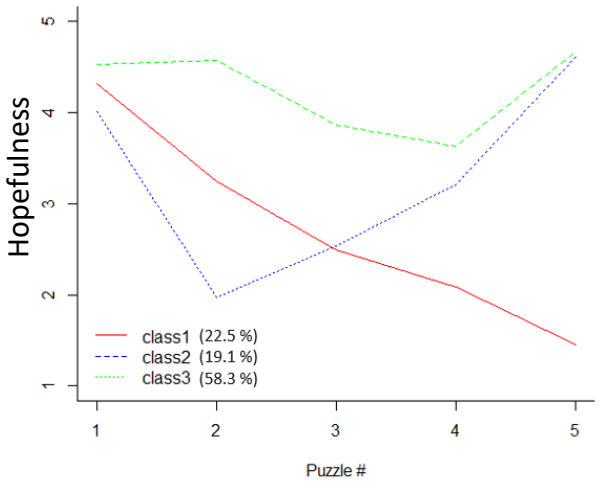
FIGURE 1. Images and examples of the Challenging Puzzles Task (CPT). Three questions corresponding to positive self-evaluation, hopefulness and motivation are asked after each puzzle and participants can respond using the child-friendly rating scales.

Figure 2: Trajectory Patterns on the Challenging Puzzles Task (CPT)

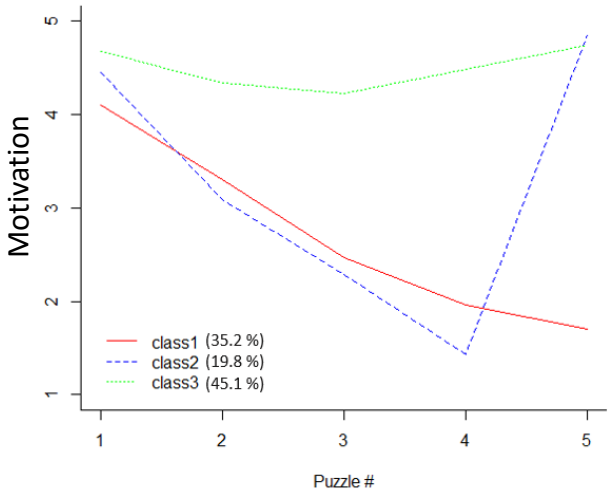
2a. Mean Patterns of Positive Self-Evaluation



2b. Mean Patterns of Hopefulness



2c. Mean Patterns of Motivation



Response patterns for the three indicators of resilience on the RCP task identifying children as discouraged (Class 1), rebound (Class 2), and resilient (Class 3).

Secondly, a video component of the CPT is currently being coded according to the Disruptive Behavior Diagnostic Observation Schedule (DB-DOS), a structured clinic-based

assessment designed to capture emotional dysregulation in young children (Wakschlag, Briggs-Gowan, et al., 2008; Wakschlag, Hill, et al., 2008). For our purposes, the DB-DOS was adapted to capture salient behaviors relevant to the CPT: anger modulation, stress reactivity, competence, prosocial skills and coping strategies. Examples of the behaviors in question are noted across all 5 puzzles with attention paid to the intensity, frequency as well as the child's verbal and physical cues (e.g., frowning, self-talk, complaints, shrugging of shoulders, crossing of arms, etc.). Codes range from 0 to 3 with 3 indicating that the behavior in question is present to a high degree and 0 indicating that the behavior is not present. The scores are then totaled across each domain. Because of the subjectivity in coding, internal reliability was set at 80% with the second coder needing to demonstrate agreeableness on 4/5 behavior codes before going on to code independently. Additionally, 12.5% of the videos were double-coded to establish interrater reliability. Essentially, this video component of the CPT will complement the self-ratings by demonstrating whether the child's ratings are consistent with their behaviors, thereby supporting this task as a valid measure of resilience. Analyses using this measure are currently underway and will be presented in the near future.

Early Life Adversity

An additional consideration that needs to be addressed when studying the influence of ELA on child resilience is the manner in which ELA is operationalized. One factor that is often overlooked and difficult to disentangle is the timing of exposure to ELA. The early life period is critical as some windows of development may be more influential than others. For example, the prenatal period has been the focus of much investigation because the fetus is forming according to incoming signals from the maternal environment (Charmandari et al., 2005). The fetus is therefore susceptible to prenatal stress and maternal mood states whose effects can be directly transmitted

via neuroendocrine signals and epigenetic programming (Charil et al., 2010; Sandman et al., 1994). On the other hand, postnatal influences have the potential to modulate or even override prenatal effects as well as genetic vulnerability effects (Buss et al., 2007; Lemaire et al., 2006; Weaver et al., 2004). Children's brains are known to be extremely plastic up until early adulthood (Dow-Edwards et al., 2019; Wierenga et al., 2018) and compelling evidence from attachment and maternal care research demonstrates the profound impact of postnatal influences on child development (Bowlby, 1982; Holt-Lunstad, 2018; Landry et al., 2006).

Other research suggests that it is not necessarily a question of timing, but whether the prenatal environment "matches" the postnatal environment, a concept known as the match-mismatch hypothesis (Daskalakis et al., 2013). If the postnatal environment is congruent with the prenatal environment, the fetus' adaptations in utero will apply outside the womb resulting in more favorable outcomes. However, if the prenatal and postnatal environments are a mismatch, the fetus will be maladapted to the postnatal environment, leading to negative outcomes. Another theory proposes that prenatal stress can promote postnatal plasticity and positive outcomes (if reared in a supportive environment) due to an increased sensitivity that develops from prenatal stress exposure (Hartman & Belsky, 2018a). Regardless of timing effects, perhaps the more important question is: does prenatal ELA extend into the postnatal period and if so, how chronic and/or severe is the ELA? To answer this question, longitudinal measures of ELA are necessary. However, the chronicity and severity of ELA is not often captured when assessing environmental risk; rather the mere presence or absence of a stressor is captured (Manly et al., 1994; Matthey & Petrovski, 2002; Reuben & Shaw, 2015). Categorizing environmental risk this way likely leads to inconsistent results as one incident of child maltreatment can have a very different impact compared to having experienced years of child maltreatment.

The Role of Genetics

None of the articles reviewed assessed the influence of genetics on resilient outcomes in children although several gene variants (namely those associated with the serotonin transporter, BDNF, CRHR1 and DRD4) have been associated with resilience due to their implication in emotional and stress regulation in previous studies (Agnafors et al., 2016; Cicchetti & Rogosch, 2012; Das et al., 2011; Nederhof et al., 2010; Polanczyk et al., 2009; Stein et al., 2009; van Winkel et al., 2014; Woody et al., 2016). Despite the general consensus that there are direct genetic influences on resilience, mixed results about genetic studies*(Belsky et al., 2009; Elbau et al., 2019; Niitsu et al., 2019) have prompted a reflection about how to capture the complexity of genetic susceptibility and its interaction with environmental factors. As a result, current research efforts are not only moving away from candidate gene studies, but they are also moving towards gene-by-environment (G×E) interaction studies to explain behavior. Emerging evidence suggests that a combination of environmental and genetic factors likely influence the relationship between stress exposure and resilient outcomes. In other words, genotype may only be a risk factor under certain environmental conditions (Claessens et al., 2011), a concept that is supported by the differential susceptibility hypothesis (Daskalakis et al., 2013). Specifically, the differential susceptibility hypothesis posits that an underlying biological vulnerability may not only render individuals more sensitive to adverse environments (resulting in worse outcomes), but equally sensitive to positive environments as well, flourishing as a result (Belsky et al., 2009). On the other hand, individuals without genetic susceptibility may be more likely to persevere regardless of environmental quality.

Despite the recognition that G×E approaches may be more appropriate, the majority of G×E studies demonstrate moderate replicability (Assary et al., 2018). One potential reason for this

is that most G×E studies focus on a restricted range of environmental factors and a limited number of genes. Thus, it is necessary to design studies that can model complex environmental and genetic factors. Furthermore, most G×E studies are based on a diathesis-stress model whereby genetic susceptibility to psychiatric disorders manifests under stressful conditions with more severe stressors increasing the chances that a disorder will develop in a dose-dependent manner (Belsky & Pluess, 2013). The problem is that the diathesis-stress model often focuses on negative environmental influences and negative outcomes; otherwise an absence of adversity and dysfunction is measured in place of positive factors (Masten, 2001; Reuben & Shaw, 2015). Measuring resilience as the absence of adversity or dysfunction may mask potential differential susceptibility findings since such approaches favor vulnerability explanations (Belsky & Pluess, 2009) which may lead to inconsistent results. The diathesis-stress model also fails to explain why susceptibility genotypes have not been selected against over the course of evolution. The significant frequency of many of these "susceptibility" genotypes *(Elbau et al., 2019) suggest some advantage to carrying "risk alleles" or at the very least, that the expression of such genes depends on variability in the environment.

Due to the longitudinal design of the MAVAN study, we have been collecting a range of behavioural, psychological and biological data (including genetics) at several time-points over the course of child development. Accordingly, we have the opportunity to examine not only the timing effects of ELA and its cumulative impact, but also complex G×E models of development (Jolicoeur-Martineau et al., 2018), including resiliency.

Conclusion

The results from this review suggest that efforts towards measuring resilience in children are moving away from operationalizing resilience merely as the absence of psychopathology

towards an understanding that resilience is a dynamic process that encompasses several interacting features including coping strategies, emotional regulation abilities, flexibility, self-esteem, a positive outlook and prosocial skills. Some of the studies identified in the review attempted to capture some of this complexity by using a mixed-methods approach or by using multiple instruments to measure resilient functioning. Also important to note is that although the majority of the reviewed studies featured resilience as an outcome variable, only 5 reported effect sizes (Herbell et al., 2020; Jefferies et al., 2019; Kirby et al., 2020; Miller-Graff et al., 2020; Worku et al., 2019). In order to determine how explanatory these child measures of resilience are, more standardized reporting of effect size estimates are needed. Despite the move towards more valid measures of resilience being used in research, relying exclusively on self-reports or parent-reports poses some challenges as resilience is a multi-dimensional construct that relies on behavioural and cognitive processes. For this reason, we propose a method of operationalizing resilience in young children that combines a behavioral task, self-ratings, and observational measures. Preliminary findings derived from this approach appear promising.

We also highlight other considerations in resiliency research and propose solutions for how to move forward with regards to: 1) how ELA is characterized and; 2) the influence of genetics on resilient outcomes. Although this review outlines measures of resilience in children, important next steps would be constructing and validating resiliency measures that would be applicable across the lifespan so that the stability of resilient functioning could be determined. This information would reveal the critical protective factors involved, including key strategies and processes that could be used in the promotion of mental wellness. The application of such intervention strategies would be most optimal early in childhood when maladaptive patterns are

not yet entrenched as children are still capable of modifying their behaviors and developing their cognitive skills.

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Table 1: Review of Studies and Measures Used

Study	Age Range (in years)	Informant	Sample Size	Study Design	Resilience Variable	Rosenberg Self-Esteem	CYRM	CBCL	Qualitative	Other Measure(s)
Asante et al., 2019	*M* age = 14	Child	16	Cross-sectional	Outcome				x	Qualitative semi-structured interviews
Beeckman et al., 2019	8-18	Child	59	Cross-sectional	Mediator					Avoidance and Fusion Questionnaire for Youth (AFQ-Y) + Chronic Pain Acceptance Questionnaire–Adolescent version (CPAQ-A)
Bethell et al., 2019	6-17	Parent	51,156	Cross-sectional	Outcome					Child Flourishing Index, Family Resilience & Connection Index and Social Engagement Index (constructed using items from the NSCH)
Cheetham-Blake et al., 2019	7-11	Child	34	Cross-sectional	Predictor				x	The Kidcope questionnaire + At-home parent–child dyadic interviews
Cohen et al., 2019	10-11	Child	167	Cross-sectional	Predictor	x				My Life Today scale + 10-item emotional regulation scale + The Brief Symptom Inventory (BSI)
Conover et al., 2020	6-10	Parent	36	Intervention	Outcome		x	x		Context of "Tell Me a Story" intervention; Ego-Resiliency Q-Sort (ER-11); Total CBCL as well as internalizing and externalizing subscales used
Cui et al., 2020	14-18	Child	1354	Longitudinal	Outcome	x		x		Future Events Questionnaire; child maltreatment was measured every two years from birth onwards
Ellersgaard et al., 2020	7	Child	522	Cross-sectional	Outcome					KIDSCREEN-27 (Quality of life measures) & Self-esteem scale 'I think I am
Elmore et al., 2020	8-17	Parent	40,302	Cross-sectional	Mediator					Using the "HOPE: Health Outcomes from Positive Experiences" framework, the following factors were constructed: Emotional Competency, Constructive Social Engagement, Safe and Stable Environment, Trusting Relationships with Adults

Study	Age Range (in years)	Informant	Sample Size	Study Design	Resilience Variable	SDQ	Rosenberg Self-Esteem	CYRM	CD-RISC	Qualitative	Other Measure(s)
Fogarty et al., 2019	10	Parent	9	Longitudinal	Outcome	x				x	Semi-structured interviews about: (a) experiences of abuse within relationships, (b) making decisions around staying or leaving relationships, (c) parenting, (d) how they and their children coped, and (e) help seeking
Folayan et al., 2020	6-16	Child	1001	Cross-sectional	Psycho-metrics		x		x		Perceived Social Support scale
Hebbani et al., 2020	*M* age = 19.7	Child	331	Cross-sectional	Outcome				x		Socio-cultural factors Questionnaire (culturally mediated factors linked to resilience) + Sherer General self-efficacy scale (SGSS) + the Ryff and Keyes Scales of Psychological Well-Being
Herbell et al., 2020	6-17	Child	1,900	Cross-sectional	Outcome						Child Flourishment Index + Family Resilience & Connection Index; parental coping and parental emotional support were also measured (constructed using items from the NSCH)
Jefferies et al., 2019	9-12	Child	227	Cross-sectional	Outcome	x		x			Other measures of physical activity and competence including PLAYfun, PLAYself, PLAYinventory, PLAYparent and PLAYpe_teacher; also the peer relations subscale of the SDQ was used
Kaiser et al., 2020	13-14	Child	12	Cross-sectional	Outcome					x	Phenomenological qualitative approach using in-depth interviews
Kirby et al., 2020	4-5	Teacher	636	Longitudinal	Outcome	x					General Health Questionnaire (GHQ-28), Kessler-6, Infant Characteristics Questionnaire, Family Resources Survey (FRS) adult deprivation questions, Early Years Foundation Stage Profile (EYFSP), maternal self-efficacy; these measures were administered either at 6, 18, 12 or 24 months in parents

Study	Age Range (in years)	Informant	Sample Size	Study Design	Resilience Variable	SDQ	RSCA	CYRM	CBCL	Qualitative	Other Measure(s)
Liu, et al., 2020	12-14	Child	646	Cross-sectional	Outcome		x				Also measured parent-child relations
Llistosella, et al., 2019	12-19	Child	270 + 15 + 432	Cross-sectional	Psycho-metrics			x			Study I = CRYM-28; Study II = semi-structured interviews with 6 youth aged 17 to 19, 4 participants from Study I and 5 resilient experts; Study III = validation of the CYRM-32; convergent and discriminant validity was compared to the Brief Resilient Coping Scale (BRCS), Coping Strategies for Adolescents (ACS) and Self-Concept Form 5 (AF5)
Malee, et al., 2019	6-14	Parent	448	Longitudinal	Outcome				x		Completed every 6 months; resilience was defined as having CBCL T-scores within the normal range (T-score <60)
Mantovani, et al., 2020	14-18	Child	9	Intervention	Outcome					x	Semi-structured, one-to-one interviews in relation to a 1-year peer-mentoring relationship
Matsuyama, et al., 2020	6-10	Parent	2,712	Longitudinal	Mediator						Children's Resilient Coping Scale (CRCS); resilience as a mediator between parent-child interactions and dental caries incidence
Mayr, et al., 2020	9-15	Child	24	Intervention	Outcome						Lifestyle intervention; cardiorespiratory fitness and Piers-Harris 2 children's self-concept scale was assessed at baseline and at 12 weeks
Miller-Graff, et al., 2020	4-17	Parent	385	Cross-sectional	Outcome	x					SDQ = Total and prosocial skills subscale; other parental measures included: the Family Adaptability and Cohesion Scale (FACES-IV), the Parent Behavior Scale (PBS) and the Resilience Research Centre-Adult Resilience Measure (RRC-ARM)
Morgan, et al., 2020	9-16	Child	252	Cross-sectional	Outcome		x				Also administered the Perceived Parental Rearing Patterns Scale (Egna Minnen av barndoms uppfostran, EMBU), Chinese version

Study	Age Range (in years)	Informant	Sample Size	Study Design	Resilience Variable	SDQ	RSCA	Rosenberg Self-Esteem	CBCL	Qualitative	Other Measure(s)
Ndetei et al., 2019	11-18	Child	1883	Cross-sectional	Outcome				x		Resilience scale (ER-89) + the Youth Self Report (YSR)
Rotheram-Borus et al., 2019	0-5	Parent	1073	Longitudinal	Outcome	x			x		Resilience was defined as being within the normal range for growth, cognitive functioning, and behavior; measures include: the Bayley Scale of Infant Development, the Peabody Picture Vocabulary Test, the Kaufman Assessment Battery for Children (KABC)
Shaw et al., 2019	11, 13, 15	Child	5286	Cross-sectional	Outcome						5-item World Health Organization Wellbeing index + 3 promotive factors: frequency of eating family meals together, classmate support and teacher support
Tam et al., 2020	9-10	Child	276	Intervention	Outcome		x	x			Resilience-based intervention; also administered: Making Sense of Adversity Scale (MSAS) and the Cultural Self-Efficacy Scale for Children and Adolescents (CSES-A)
Tian et al., 2019	10-17	Child	2898	Cross-sectional	Predictor		x				Also assessed self-harm and depressive symptoms
Veronese et al., 2020	7-13	Child	29	Cross-sectional	Outcome					x	Participatory approach based on children's drawings of maps representing safe and unsafe places followed by a guided walk (n = 10) through those places
Vreeman et al., 2019	10-14	Child	253	Intervention	Outcome	x					Context of RCT; depression symptoms were measured using the Patient Health Questionnaire (PHQ-9); resilience was defined as having low scores on SDQ Total and PHQ-9
Wang et al., 2019	0.5-6	Parent	2397	Cross-sectional	Mediator						Devereux Early Childhood Assessment (DECA) + 'Infant-Junior Middle School Student's Ability of Social Life Scale; having a score of 60 or more on DECA was defined as resilience
Worku et al., 2019	≥ 13	Child	137	Cross-sectional	Outcome					x	Conducted interviews and focus groups + the Ryff and Keyes Scales of Psychological Well-Being

Study	Age Range (in years)	Informant	Sample Size	Study Design	Resilience Variable	Other Measure(s)
Wu et al., 2020	8-14	Child	816	Longitudinal	Outcome	Self-rating Scale of Psychological Resilience; the preliminary questionnaire was validated in a pre-sample of 269 children
Xiao et al., 2019	10-17	Child	2898	Cross-sectional	Outcome	RSCA = Resilience Scale for Chinese Adolescents
Young et al., 2020	4	Child	64	Longitudinal	Outcome	Different types of intelligence were assessed using the Wechsler Preschool and Primary Scales of Intelligence 3rd Ed (WPPSI-III); language ability was determined using the Clinical Evaluation of Language Fundamentals—Preschool, 2nd Ed (CELF-Pre-2); visual ability and motor coordination was assessed using the Beery-Buktenica Test of Visual Motor Integration (VMI); cortical thickness, surface area and brain volume were assessed using MRI scans; resilient was defined as having good neurodevelopmental outcomes and cognitive abilities

CBCL = Child Behavior Checklist; CD-RISC = Connor Davidson-Resilience Scale; CYRM = Child and Youth Resilience Measure; NSCH = National Survey of Children's Health; RSCA = Resilience Scale for Chinese Adolescents; SDQ = Strengths and Difficulties Questionnaire.

Bridge to Study 2

This review demonstrates that although resiliency research is moving away from measuring resilience as an absence of psychopathology, most resilience scales are not necessarily capturing positive behaviors and attitudes in relation to stress. Resilience refers to more than just social competence or positive mental health (Rutter, 2006). Moreover, relying on questionnaire methods to detect resilience offers a rather narrow scope since resilience does not represent a single quality or trait. Not to mention, a questionnaire format may not be realistic for young children. It would instead be more informative to measure resilience as an observed behavior (Rutter, 2006). In Study 1, we introduce a child-friendly stress paradigm, the challenging puzzle task (CPT), which is a more ecologically valid measure of resilience. The CPT elicits a range of reactions and permits the measurement of several cognitive indicators of resilience, namely: positive self-evaluation, hopefulness and motivation. In Study 2, we incorporate the CPT into practice and conduct data-driven trajectory analyses to determine children's response patterns on the CPT. To evaluate some of the developmental and interacting factors that could be influencing resilient outcomes, we tested children's response patterns within a gene-by-environment (G×E) context where varying levels of genetic susceptibility and exposure to maternal depressive symptoms (MDS) were entered as model predictors. By integrating a more ecologically-valid measure of resilience along with a full range of MDS exposure, we will be better positioned to detect G×E effects given that genetics alone do not predict psychopathology, nor resilience (Rutter, 2006). Assuming that G×E effects will be detected, tests of environmental sensitivity will be applied to determine whether our findings are consistent with the differential susceptibility and vantage sensitivity hypotheses. Furthermore, in order to capture effects of prenatal programming of postnatal plasticity (PPPP), we will conduct simultaneous analyses to examine the separate and combined influences of

exposure to prenatal and postnatal MDS. The strengths of this study are that it moves beyond a diathesis-stress framework, is grounded in evolutionary theory, incorporates a longitudinal design, uses an ecologically-valid measure of resilience, applies complex G×E modeling, and considers the full range of exposure to one type of ELA, MDS.

Study # 2

Resilience in the face of an impossible task: the joint role of genetic susceptibility and early life adversity

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ABSTRACT

To better understand the developmental origins of resilience, gene-by-environment (G×E) analyses were conducted by interacting genetic susceptibility with exposure to maternal depressive symptoms (MDS) to predict resilient outcomes in 5-year-old children. Positive self-evaluation, hopefulness, motivation, and overall resilience were measured using a challenging puzzle task. Three different G×E models corresponding to exposure to prenatal, postnatal and cumulative MDS were tested in relation to genetic susceptibility (as measured by three polygenic scores). The majority of our findings indicate that for positive self-evaluation, hopefulness and overall resilience, genetic susceptibility combined with exposure to: 1) low levels of prenatal MDS elicit the best outcomes; while 2) high levels of prenatal MDS elicit worse outcomes. Our results also demonstrate that children low in genetic susceptibility are most motivated while genetically susceptible children are least motivated. Our findings lend support to the differential susceptibility and vantage sensitivity hypotheses. Furthermore, the significant association between prenatal MDS and postnatal environmental sensitivity provides evidence for prenatal programming of postnatal plasticity.

INTRODUCTION

Resilience

Development is marked by periods of heightened neural plasticity in which brain regions involved in the regulation of emotion and stress are particularly sensitive to the effects of early life adversity (ELA). Although stress experienced early in life can lead to altered neural circuits, maladaptive behaviors, and psychopathology (Hornung & Heim, 2014), many children remain unaffected (Bonanno & Mancini, 2008; Peskin, 2016). In fact, some children exhibit positive outcomes in the face of ELA and can bounce back after a challenging event, demonstrating resilience (Davydov et al., 2010; Reuben & Shaw, 2015). Although there are many ways to define and characterize resilience, it is best understood as a dynamic process rather than a static state or trait-like attribute (Earvolino-Ramirez, 2007). Flourishing in the context of a stressful event depends on many complex inter-related factors. Several cognitive, emotional and behavioral features, namely the appraisal of the challenge, such as the tendency to not take failures personally; the coping strategies used; the motivation to withstand challenges; hopeful thinking such as optimism; and an ability to adapt (Agnafors et al., 2016; Bonanno & Diminich, 2013; Masten, 2007; Snyder et al., 2002). Underlying some of these processes are neural mechanisms linked to stress regulation. For example, when faced with a challenge, resilient individuals have an attenuated stress response and tend to return to homeostasis more quickly. These processes along with the tendency to not overgeneralize fears during a stressful event make effective emotional regulation more possible (Charney, 2004; Feder et al., 2009). Overall, a biopsychosocial perspective best reflects how adaptation to stress involves interacting neurobiological mechanisms, genetic factors, psychological influences and behaviors (Cicchetti, 2010; Kent et al., 2015).

Measuring Resilience in Children

The methods by which resilience is measured (whether in children or adults) pose some challenges because resilience has often been characterized as an absence of psychopathology or dysfunction, even though the two are not synonymous (Bell et al., 2013; Halevi et al., 2016; Lansford et al., 2006; Wingo et al., 2010). An effective (or optimal) assessment of resilience would benefit from capturing some of the positive and adaptive processes involved. Although a recent review shows that more studies are moving towards measuring resilience in children using actual resilience scales and measures of positive adjustment, these studies were exclusively based on self-report or parent-reported measures (King et al., 2021). However, because resilience relates to one's reaction to adversity, it should be measured in relation to stressful or challenging circumstances.

To date, four different types of stressful or challenging lab-based tasks have been administered in children. The first task, originally designed to predict anger, avoidant behaviors, and self-worth, consists of a series of impossible and possible puzzles (Smiley et al., 2016; Smiley et al., 2010) based on geometrical block designs of the Weschler Intelligence Scale for Children, third edition (WISC-III (Wechsler, 1991)). Task preference as well as self-ratings of contingent self-worth were measured and the strategies used during each task were also documented. The second is the "find-a-word" puzzle task (Hoza et al., 2001) which features nonsense words that are either impossible or possible to find. Children are then asked a series of performance-evaluation questions as well as attribution questions. This task has been used among children aged 8 to 13 as a measure of physiological stress reactivity and features a manipulation check to verify perceptions of success or failure and the level of difficulty (Breaux et al., 2018; McQuade & Breaux, 2017). The third challenging task, the Bath Experimental Stress Test for Children (BEST-C), is a public-speaking task and math challenge that assesses social stress (Cheetham & Turner-Cobb, 2016).

The BEST-C is used in conjunction with a physiological measure of stress (e.g., salivary cortisol and/or heart rate), so the protocol features a manipulation check to verify whether the subjective reporting matches that of the physiological responses measured (Cheetham-Blake et al., 2019). Finally, the Challenging Puzzles Task (CPT), appropriate for children as young as 4 years of age, consists of several impossible and possible puzzle trials with corresponding and ecologically valid self-rating questions intended to assess learned helplessness (Cole et al., 2007).

Although the tasks mentioned above elicited a range of behaviors, analyses only focused on one end of the spectrum – maladaptive behaviors. The CPT, however, has the potential to measure positive adaptation given that it also captures several features of resilient functioning via the self-appraisal component, which assesses positive self-evaluation, hopefulness, and motivation.

The Role of Early Life Adversity (ELA)

Consistent with the focus on studying psychopathology and maladaptive behaviors, there is extensive research documenting the effects of ELA on the developing child (Maglione et al., 2018; Nugent et al., 2011; Silberman et al., 2016). Evidence suggests that ELA can have an additive effect whereby the more chronic or severe a stressor is, the higher the likelihood of developing psychiatric symptoms (Belsky & Beaver, 2011; Manly et al., 1994). However, many studies tend to capture the mere presence or absence of a stressor and do not necessarily consider the chronicity and severity of ELA when assessing environmental risk (Manly et al., 1994; Matthey & Petrovski, 2002; Reuben & Shaw, 2015; Ungar, 2019). One type of ELA that is a cause for concern is exposure to parental psychopathology, particularly maternal depression (depressive symptoms experienced during pregnancy and/or the postpartum period), given that worldwide

prevalence rates are around 12% (Woody et al., 2017). Exposure to MDS and the circumstances that contribute to it can directly impact maternal care as depressed mothers sometimes exhibit reduced parental capacity which can lead to difficulty in bonding with their child as well as responding to their needs (Campbell et al., 2007). The timing with which exposure to ELA occurs is also critical, with some developmental periods being more influential than others (Abbott et al., 2018; Heim & Binder, 2012). We discuss various theories of prenatal programming in a previous paper (King et al., 2021) and conclude that although prenatal stress can be directly passed on to the fetus via neuroendocrine signals and epigenetic programming (Charil et al., 2010; Sandman et al., 1994), genetic susceptibility and postnatal influences can moderate prenatal effects (Abbott et al., 2018; Weaver et al., 2004). In some cases, exposure to prenatal stress can even be advantageous when combined with positive postnatal influences, a concept known as prenatal programming of postnatal plasticity (PPPP) (Hartman & Belsky, 2018a). Going forward, longitudinal measures of ELA are necessary to better understand timing effects and the extent to which prenatal ELA extends into the postnatal period.

The Role of Genetics

Although, there are several gene variants known to be associated with resilience due to their implication in emotional and stress regulation (Agnafors et al., 2016; Cicchetti & Rogosch, 2012; Das et al., 2011; Feder et al., 2009; van Winkel et al., 2014; Woody et al., 2016), limited success with candidate gene models have led to polygenic approaches to better understand how common genetic variants influence complex traits (Dudbridge, 2013; Martin et al., 2019). Furthermore, individual SNPs may not be detected by genome-wide association studies (GWAS) or reach genome-wide significance on their own, but that does not necessarily mean that their

combined effect will not have an influence on the phenotype in question (Dudbridge, 2013). In fact, GWAS-derived polygenic scores (PGSs) can explain more trait heritability (yield bigger effect sizes) because a larger portion of genotyped variants and loci of smaller effect can be included due to the use of a more lenient significance threshold (Evans et al., 2009; Ho et al., 2019). PGSs are essentially an aggregate of GWAS hits for a particular phenotype. They are calculated by multiplying the number of risk alleles a person carries for a specific target outcome by the effect size (or weight) of each genetic variant associated with that outcome based on previous studies and then summing each of these products across all risk loci to create an additive effect score for each individual. Summing the contribution of many variants into one score also reduces the burden of multiple testing and increases statistical power (Martin et al., 2019).

Several PGSs have been constructed to identify the genetic etiology underlying psychiatric disorders in children and youth, namely autism spectrum disorders (Rai et al., 2018; Takahashi et al., 2020), ADHD (Hamshere et al., 2013; Martin et al., 2014), and major depressive disorder (MDD) (Halldorsdottir et al., 2019; Lussier et al., 2021). Additionally, the EArly Genetics and Lifecourse Epidemiology consortium developed a PGS associated with general childhood psychopathology (Neumann et al., 2022) while the Twins Early Development Study constructed a PGS associated with environmental sensitivity (Keers et al., 2016). These PGSs can add to the emerging literature investigating genetic influences of resilience and stress, especially given that the results to date are mixed.

Gene-by-Environment Interactions

Mixed findings about the direct influence of genotype on resilience suggests the role of other factors in gene function (Belsky et al., 2009; Elbau et al., 2019; Niitsu et al., 2019). Evidence suggests that genetic factors interact with environmental factors to influence the relationship

between stress exposure and resilient outcomes, with genotype sometimes conferring risk when combined with certain environmental factors (Claessens et al., 2011). Such gene-by-environment (G×E) interactions imply that environmental factors can moderate genetic effects and vice versa. However, most G×E studies in psychiatry are guided by diathesis-stress thinking whereby genetic susceptibility to psychiatric disorders manifests under stressful conditions with more severe stressors and risk factors increasing the chances that a disorder will develop (Bebbington, 1987; Monroe & Simons, 1991). The limitations of the diathesis-stress model are that it focuses exclusively on negative environmental influences and outcomes (Masten, 2001; Reuben & Shaw, 2015). Measuring positivity as a lack of negative factors overlooks other models of environmental sensitivity while over-representing vulnerability findings (Belsky & Pluess, 2009).

Contemporary models of environmental sensitivity include the differential susceptibility, vantage sensitivity and PPPP hypotheses. The differential susceptibility model asserts that genetically susceptible individuals are more sensitive to adverse environments (resulting in worse outcomes), but equally sensitive to positive environments as well, thereby flourishing in such scenarios (Belsky & Pluess, 2009). Whereas, the vantage sensitivity hypothesis assumes that individual variation in susceptibility emerges in contexts of positive environmental exposure (Pluess, 2017). In both cases, these theories prompt us to reconsider susceptibility genes as plasticity genes (Belsky et al., 2009). This line of thinking also underlies the PPPP theory and claims that prenatal stress can prime the fetus to be more receptive to its postnatal environment, for better or for worse (Pluess & Belsky, 2011).

Objectives

Given the under-detection of resilient outcomes and of environmental sensitivity effects, the current study aims to investigate how genetic susceptibility and MDS interact to predict cognitive features of resilience (positive self-evaluation, hopefulness, and motivation) in response to a CPT. We ask two questions:

1) Is there a differential impact of prenatal, postnatal, or cumulative MDS on resilient outcomes in children?
2) Does genetic susceptibility modify the impact of MDS on resilient outcomes in children?
3) Will our findings provide evidence for the differential susceptibility, vantage sensitivity and PPPP hypotheses?

Our analyses are strengthened by: 1) the use of an ecologically-valid measure of resilience; 2) taking into account the chronicity, severity, and timing of exposure to MDS; 3) incorporating a longitudinal design; 4) considering the full spectrum of an environmental predictor and an outcome variable; and 5) using three PGSs that have been tested in child populations (i.e., global child psychopathology, MDD, and environmental susceptibility). We hypothesize that genetic susceptibility (higher PGSs) combined with cumulative environmental risk (exposure to chronic MDS) will be associated with lower resilience in children. We also expect genetically susceptible children to be more resilient when exposed to low levels of MDS compared to those who are not genetically susceptible.

METHODS

Design

This study is part of the Maternal Adversity, Vulnerability and Neurodevelopment (MAVAN) cohort: a longitudinal, community-based, prospective study of pregnant mothers and their children (O'Donnell et al., 2014). Starting in 2003, pregnant mothers were recruited from obstetric clinics in Montreal, Quebec and Hamilton, Ontario, with a subsample of high-risk women recruited from a mental health clinic in Hamilton. Measures of maternal adversity were collected once prenatally and 5 times postnatally. Genetic data were collected at 36 months, while resilient outcomes were assessed when the children were 60 months (5 years of age).

Sample

Pregnant women were enrolled in the study if they were 18 years of age and older, and fluent in either English or French. Exclusion criteria included serious obstetric complications during the pregnancy or delivery, extremely low birth weight, prematurity (<36 weeks' gestation), or any congenital diseases. Mothers were, on average, 30.75 years old at recruitment (SD = 4.9; range = 18 to 44 years) and their pregnancies lasted, on average, 39.2 weeks (SD = 1.19; range = 36 to 42). Because this was a longitudinal study, the sample size decreased over time partly due to attrition. The sample size further decreased because not all participants completed each measure. Consequently, analyses for this study were reduced from a total sample size of 590 to a sub-sample of 205 mother-child dyads (Table 1).

Table 1: Adjusted Sample Size

	N
Total sample size	590
Completed the challenging puzzle task (CPT)	323
Available genetic data (polygenic scores)	260
Maternal depressive symptoms data (CESD scores)	343
Sub-sample size *	205

Notes: CESD = Center for Epidemiologic Studies Depression Scale;

* = Participants were included if they had completed the CPT and if genetic and CESD data were available.

Most mothers were partnered (95.5%) and white (87%). About half the sample (54.1%) were from the Montreal region and were university-educated (54.1%). The mean household income of the sample at the time of recruitment was $62,287 CAN (SD = $30,288) which is slightly higher than the national median after-tax income of $56,000 at the time (Statistics Canada, 2005). There were roughly an equal number of males (50.2%) and females (49.8%) in the sample and the average age of children was 5.07 years (SD = 0.10; range = 4.84 to 5.53). Ethical approval for this study was obtained from the Douglas Mental Health University Institute (Montreal) and St-Joseph's Hospital (Hamilton).

Measures

Environmental Predictor: Maternal Depressive Symptoms (MDS). MDS were measured using the 20-item self-report Center for Epidemiologic Studies Depression Scale (CESD) (Radloff, 1977) during pregnancy (26^{th} week of gestation) and at 6, 12, 24, 36 and 48 months postnatally. Mothers endorsed depressive symptoms using a 4-point Likert scale ranging from 0 (rarely or none of the time) to 3 (all of the time).

For the current study, three measures of child exposure to MDS were calculated (prenatal, postnatal, and cumulative). Prenatal exposure to MDS was measured during the second trimester, while postnatal and cumulative exposure to MDS was calculated using area under the curve with respect to ground (AUC_G) estimates. AUC_G calculations return a value for each participant which represents overall exposure across two dimensions: the *x-axis* which corresponds to chronicity (MDS across the various time-points) and the *y-axis* which corresponds to severity (the range of CESD scores). Postnatal AUC_G estimates were computed using the 5 postnatal time-points while

cumulative AUC_G was computed using all six time-points. Higher AUC_G values signify more chronic and/or severe MDS. Based on the subsample, mean depression scores ranged from 10.03 (6 months postpartum; SD = 8.7) to 11.67 (prenatal (SD = 9.4) and 24 months postpartum (SD = 8.8)).

Moderator: Genetic Susceptibility. Complete method descriptions including information about genotyping and PGS construction can be found in previous publications (Chen et al., 2018; Silveira et al., 2017). Genetic susceptibility was captured using three PGSs associated with: global psychopathology in children (GPC), susceptibility (SUSC) and major depressive disorder (MDD). These PGSs were selected because the outcome variables in question fall within the spectrum of psychological and cognitive pathways associated with hopelessness, susceptibility, and possibly broad psychopathology. The SUSC PGS was of particular interest because it is the first PGS of its kind to not be based on a negative phenotype, but rather environmental sensitivity. It is therefore a better genetic predictor of differential susceptibility effects (Zhang & Belsky, 2022).

Construction of the MDD PGS were based on genetic loci associated with the detection of lifetime MDD among adults (Major Depressive Disorder Working Group of the Psychiatric et al., 2013). Whereas, the GPC PGS has been tested in children as young as 5 years old (Neumann et al., 2022) and is derived from several measures of child behavior and functioning including externalizing, internalizing, attention problems (Achenbach & Rescorla, 2001; Goodman, 1997; Hansson et al., 2005; Pulkkinen et al., 1999; Rutter, 1967; Wells, 1980). Construction of the SUSC PGS was based on discordance in emotional problems (Goodman, 1997) between members of a twin pair. Emotional problems were measured in the discovery and validation samples at age 12 using the emotional symptoms subscale of the Strengths and Difficulties Questionnaire. Higher

PGS scores are thus related to more emotional problems in children and represent genetic loci associated with sensitivity to the environment (Keers et al., 2016).

Outcome Variable: Resilience. A modified version of the Challenging Puzzles Task (CPT; (Cole et al., 2007; O'Donnell, 2011; Smiley & Dweck, 1994; Ziegert et al., 2001) was administered by a trained experimenter alongside other measures of child behavior at age 5. In the current study, the number of puzzle trials was reduced from seven to five. The CPT consists of a series of possible and impossible puzzles, whereby reactions to a challenge (in this case, three impossible puzzles) are captured via an ecologically valid rating scale. Specifically, puzzles 1 and 5 were possible to solve and can be completed with the help of the research assistant as needed while puzzles 2 to 4 were impossible and had a time limit of 2-minutes. After each puzzle, the children were asked the following questions: 1) How well do you think you did on the puzzle? (positive self-evaluation); 2) How do you think you will do on the next puzzle? (hopefulness); 3) How do you feel about doing the next puzzle (motivation)? Answers to these questions range from 1 (negative outlook) to 5 (positive outlook). Higher scores corresponding to positive self-evaluation, hopefulness and motivation over the five puzzles served as indicators of resilience. Images of the puzzle along with the rating scales can be found in a recent review published by our team (King et al., 2021; O'Donnell, 2011).

Analysis

Puzzle Response Patterns: Data-driven response patterns across the five puzzles were fitted with *Extended Mixed Models Using Latent Classes and Latent Processes* (LCMM) (Proust-Lima C, 2020), a package available in R. We experimented with fitting our data into 2, 3 and 4 class structures; however, due to limited power, we restricted our analyses to 2 classes. Response patterns were fitted individually for each indicator of resilience: positive self-evaluation,

hopefulness and motivation. Logistic regression analyses were conducted to predict the probability of belonging to the resilient class for each of the three indicators of resilience. Analyses were also conducted for the overall pattern across all 3 indicators of resilience (model 4), with a dichotomous outcome (resilience across all three indicators vs. resilient on none, 1 or 2 of the indicators). This dichotomized outcome variable is subsequently referred to as "Overall Resilience".

G×E Analyses: Using alternating optimization (Jolicoeur-Martineau et al., 2018), LEGIT (Latent Environmental & Genetic InTeraction) constructs a generalized linear model based on G×E interactions, where G is a weighted sum of genetic variants and E is a weighted sum of the environment. For the current study, G consisted of all three polygenic scores (PGS), while E consisted of maternal depressive symptoms (MDS). Due to timing effects and their differential impact on the developing child, the separate and combined contributions of prenatal and postpartum depressive symptoms were assessed (e.g., prenatal depressive symptoms only, postnatal depressive symptoms only, and cumulative MDS (prenatal + postnatal depressive symptoms)). Because different indicators of resilience were tested (positive self-evaluation, hopefulness, motivation and overall), G×E analyses were conducted with each indicator as a separate outcome. Overall, three separate models were tested (prenatal, postnatal and cumulative MDS) for each of the four outcomes. Consequently, we applied corrections for multiple testing to all of our analyses using an eigenvalue-based method (Galwey, 2009) where eigenvalues were derived from a correlation matrix composed of the outcome variables in question. After applying the "galwey" method, it was determined that the number of independent tests to correct for was three.

When modeling genetic susceptibility using PGSs, different sets of SNPs based on significance thresholds can be selected with more liberal thresholds permitting the inclusion of

significantly more SNPs. Prior to conducting the G×E analyses, the different significance thresholds (ranging from 1e08 to 1.0) were regressed with each outcome measure; the best threshold was determined based on model fit indices (AIC) and used in all subsequent analyses. Finally, where there were significant G×E interactions, post-hoc tests of environmental sensitivity were applied. These tests determined whether differential susceptibility, diathesis-stress, or vantage sensitivity were the best fitting in terms of the outcome in question (Jolicoeur-Martineau et al., 2020).

Covariates: All models were adjusted for child sex, child age and maternal education (e.g., having a university education or higher) since these variables can influence child outcomes. For example, sex effects have been reported in other studies that use a challenging task, with girls exhibiting better recovery and naming more strategies compared to boys (Gentzler et al., 2013; River et al., 2018). Child age was controlled for because there are cognitive features to the CPT which may elicit better performance by older children. Finally, maternal education is an indicator of socioeconomic status and may thus confound the association between ELA and child outcomes (Bohnert & Breslau, 2008; Laplante et al., 2008). Prenatal and postnatal MDS were also controlled for in our postnatal and prenatal analyses respectively given that postnatal MDS could be influencing prenatal effects and vice versa. Lastly, genetic ancestry was accounted for by including the three principal components that were the most informative of population structure in this cohort (Silveira et al., 2017).

Imputation: The package Multivariate Imputation by Chained Equations available in R (van Buuren, 2021) was used to estimate missing values and generate 50 imputed datasets. Since PGS construction is derived from GWAS where genotypes have already undergone imputation (using information based on haplotypes) (McCarthy et al., 2016), it was not advised to further

impute genetic data. So we limited the analyses to 260 as this was the total number of children for whom we had genetic data. Demographic data, puzzle scores, covariates as well as the predictor variables were all entered to inform the imputed values. The final imputed datasets consisted of estimated values corresponding to the outcome variable in question (e.g., responses on the CPT) as well as CESD scores (e.g., MDS) across the various time-points. These analyses were conducted in parallel to validate our findings and are featured in the Supplementary section of this paper.

RESULTS

Identifying Response Patterns in Children

The pattern of responses for the three indicators (positive self-evaluation, hopefulness and motivation) can be classified into two classes: discouraged and resilient (Figure 1).

1) Class 1 - Discouraged: Steadily decreasing self-appraisal even when presented with a solvable puzzle post-impossible trials.
2) Class 2 – Bounce-back: A slight decrease in self-appraisal when faced with three impossible puzzles followed by an improvement in self-appraisal when presented with a solvable puzzle.

Across the five puzzle trials, 90.4% of children were classified as being in the bounce-back group (class 2) for positive self-evaluation (Figure 1a), 76.5% for hopefulness (Figure 1b), and 63.8% for motivation (Figure 1c). Just over half of the sample (57.5%) were in the bounce-back group for all three indicators of resilience. The models testing prenatal MDS were the best fitting for the analyses corresponding to positive self-evaluation, hopefulness and overall resilience. The only exception was for motivation, in which case, the model including postnatal MDS was the best fitting one. Only the plots corresponding to the best fitting models are shown and discussed.

Figure 1: Response Patterns on the Challenging Puzzles Task (CPT)

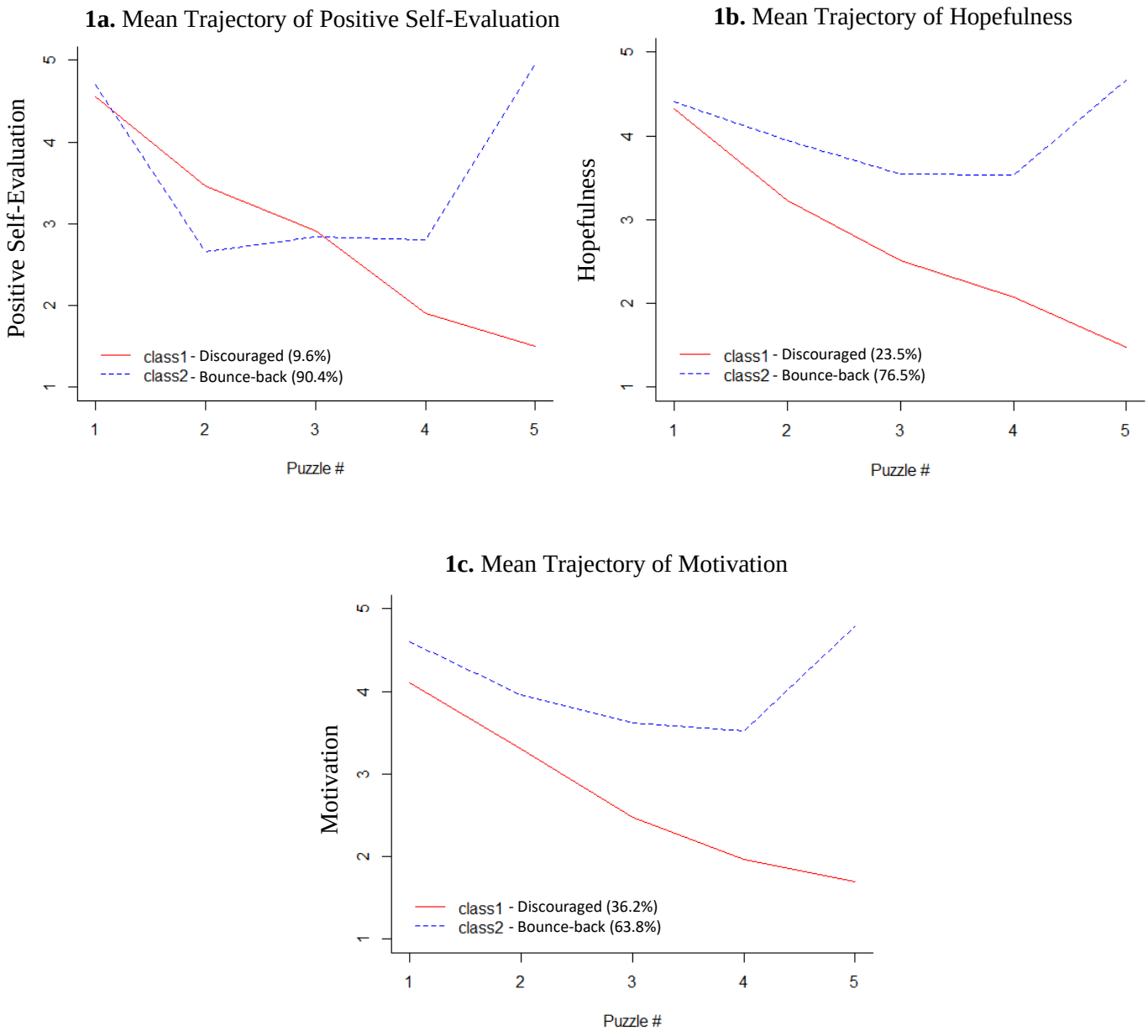


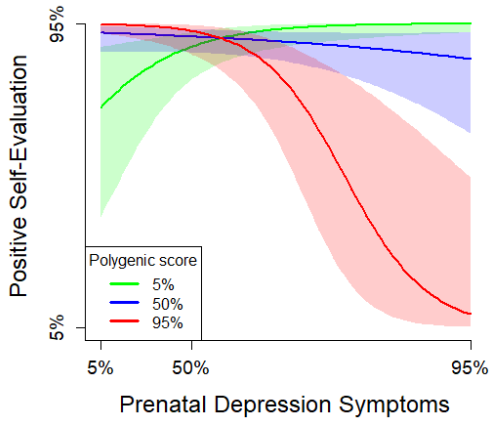
Figure 1*:* Puzzles 1 and 5 are possible to solve, while puzzles 2 through 4 are impossible to solve.

Positive Self-Evaluation: A significant G×E interaction emerged for positive self-evaluation, with all three PGSs driving the genetic effect, although the only PGS to survive

correction and be validated by the imputed data set was the SUSC PGS. Genetically susceptible children reported high positive self-evaluation when exposed to low levels of MDS. However, in contexts of exposure to high levels of MDS, genetically susceptible children were least inclined to report positive self-evaluation. When exposed to high levels of MDS, children with lower genetic susceptibility reported the highest positive self-evaluation compared to children with high genetic susceptibility. Children with moderate genetic susceptibility reported high positive self-evaluation regardless of their level of exposure to MDS (Table 1). Tests of environmental sensitivity confirmed that the differential susceptibility model best fit the G×E interaction (BIC = 155.28).

Table 1: Logistic Regression Analyses - Positive Self-Evaluation

Q1 – Prenatal MDS (AIC: 116.52)	
Intercept	β = -7.538521, *p* = 0.614286
Genetic	β = -0.293068, *p* = 0.550070
Environment	β = -0.206708, *p* = 0.581473
Postnatal MDS	β = -0.001582, *p* = 0.081501 .
Sex_male	β = 0.3042886, *p* = 0.600046
Maternal Education	β = 0.6759941, *p* = 0.310801
Child Age	β = 2.1368158, *p* = 0.470418
PC1	β = 2.5923148, *p* = 0.614052
PC2	β = -12.680865, *p* = 0.335504
PC3	β = -6.8455318, *p* = 0.156381
G×E	β = -2.69915, *p* = 0.00045 ***
GPC PGS	β = 0.2384, *p* = 0.04677 * **x**
SUSC PGS	β = 0.4374, *p* = 0.00002 ***
MDD PGS	β = -0.3242 , *p* = 0.00347 **



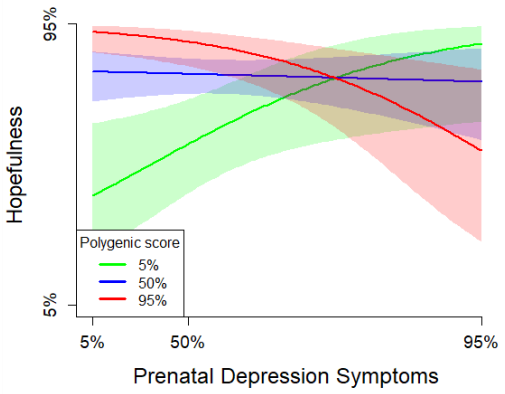
Notes: MDS = maternal depressive symptoms; PC = principal component; G×E = Gene-by-Environment interaction; GPC PGS = polygenic score corresponding to global psychopathology in children; SUSC PGS = polygenic score corresponding to susceptibility; MDD PGS = polygenic score corresponding to major depressive disorder; **x** = did not survive correction for multiple testing.

Hopefulness: A similar G×E interaction was found for hopefulness whereby the most hopeful children were those who were genetically susceptible and were exposed to low levels of MDS. The overlapping confidence interval bands does not allow us to conclude whether those

children who had a combination of low PGS and exposure to high levels of MDS were as hopeful as those of the other genetic groups. The pattern for children with moderate genetic susceptibility was similar to positive self-evaluation – they remained hopeful regardless of their level of exposure to MDS. Vantage sensitivity was confirmed to best fit the G×E interaction when tested for type of environmental sensitivity (BIC = 257.93). This is likely because there is a clear distinction between the levels of genetic susceptibility where exposure to MDS is lowest (as can be seen by the non-overlapping confidence interval bands; Table 2). For these analyses, only the GPC PGS survived correction.

Table 2: Logistic Regression Analyses – Hopefulness

Q2 – Prenatal MDS (AIC: 219.9)	
Intercept	β = -3.278536, *p* = 0.73073
Genetic	β = 0.87887, *p* = 0.01305 *
Environment	β = -0.12006, *p* = 0.56142
Postnatal MDS	β = -0.001225, *p* = 0.06588.
Sex_male	β = -0.228262, *p* = 0.53534
Maternal Education	β = 0.257133, *p* = 0.51074
Child Age	β = 1.055593, *p* = 0.57458
PC1	β = -0.782796, *p* = 0.81229
PC2	β = -1.884314, *p* = 0.61985
PC3	β = -0.171642, *p* = 0.95778
G×E	β = -0.99436, *p* = 0.00132 **
GPC PGS	β = 0.3901, *p* = 0.00736 **
SUSC PGS	β = 0.3253, *p* = 0.01784 * **x**
MDD PGS	β = 0.2846, *p* = 0.03198 * **x**



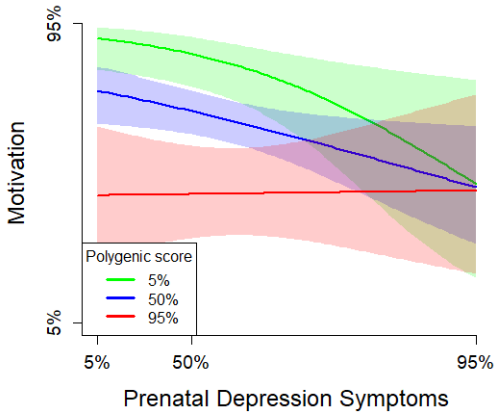
Notes: MDS = maternal depressive symptoms; PC = principal component; G×E = Gene-by-Environment interaction; GPC PGS = polygenic score corresponding to global psychopathology in children; SUSC PGS = polygenic score corresponding to susceptibility; MDD PGS = polygenic score corresponding to major depressive disorder; **x** = did not survive correction for multiple testing.

Motivation: Main effects of genetics and environment were found for this indicator of resilience. Differential genetic susceptibility was more apparent among those children who were exposed to low MDS, with children low in genetic susceptibility reporting the highest motivation

on the CPT, followed by children with moderate, then high genetic susceptibility. When exposed to high levels of MDS, all children, regardless of their PGS, report moderate levels of motivation. However, given that a significant G×E interaction was not detected, we cannot test for type of environmental sensitivity. In this model, the GPC and SUSC PGSs were driving the genetic effects (Table 3). Even though model fit statistics suggested that the postnatal MDS model was the best fitting, the effect of prenatal MDS exposure on outcomes did not survive test correction. Therefore, the results presented correspond to the next best-fitting model: prenatal exposure to MDS.

Table 3: Logistic Regression Analyses – Motivation

Q3-Prenatal MDS (AIC: 263.04)	
Intercept	β = -0.159330, *p* = 0.984173
Genetic	β = -1.06206, *p* = 0.00052 ***
Environment	β = -0.45943, *p* = 0.013567 *
Postnatal MDS	β = 0.000338, *p* = 0.576648
Sex_male	β = -0.08759, *p* = 0.784468
Maternal Education	β = 0.025036, *p* = 0.941066
Child Age	β = 0.166624, *p* = 0.916154
PC1	β = 6.150605, *p* = 0.062510 .
PC2	β = -1.88431, *p* = 0.086907 .
PC3	β = 0.3602248, *p* = 0.896755
G×E	β = 0.47637, *p* = 0.084224 .
GPC PGS	β = 0.3728, *p* = 0.014540 *
SUSC PGS	β = -0.5081, *p* = 0.000683 ***
MDD PGS	β = 0.1190, *p* = 0.367723



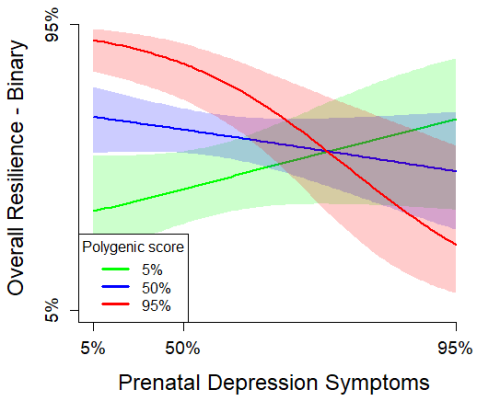
Notes: MDS = maternal depressive symptoms; PC = principal component; G×E = Gene-by-Environment interaction; GPC PGS = polygenic score corresponding to global psychopathology in children; SUSC PGS = polygenic score corresponding to susceptibility; MDD PGS = polygenic score corresponding to major depressive disorder.

Overall Resilience: For the model predicting resilience across all 3 indicators, a significant G×E interaction effect was found with the GPC and SUSC PGSs driving the genetic effects. Genetically susceptible children who were exposed to low levels of MDS appear to be the group

that is most resilient overall. Whereas, a combination of high genetic susceptibility and exposure to high levels of MDS are least likely to exhibit overall resilience. The opposite is true for children with low genetic susceptibility; when exposed to low levels of MDS, they are least likely to be consistently resilient and when exposed to high levels of MDS, they are more likely to display overall resilience compared to the other genetic groups (Table 4). When tests of environmental sensitivity were applied, vantage sensitivity seemed to best fit the data (BIC = 313.96) and this is again evident by the distinct confidence interval bands present at low levels of exposure to MDS.

Table 4: Logistic Regression Analyses – Overall Resilience

Overall Resilience – Prenatal MDS (AIC: 272.07)	
Intercept	β = 1.3420105, *p* = 0.86694
Genetic	β = 0.89110, *p* = 0.00259 **
Environment	β = -0.37192, *p* = 0.05168
Postnatal MDS	β = -0.000188, *p* = 0.75071
Sex_male	β = 0.211401, *p* = 0.49685
Maternal Education	β = 0.262399, *p* = 0.42390
Child Age	β = -0.182915, *p* = 0.90791
PC1	β = 0.452805, *p* = 0.87474
PC2	β = -6.58015, *p* = 0.06420 .
PC3	β = -0.782833, *p* = 0.77853
G×E	β = -0.93624, *p* = 0.00123 **
GPC PGS	β = -0.3594, *p* = 0.00906 **
SUSC PGS	β = 0.4840, *p* = 0.00022 ***
MDD PGS	β = 0.1566, *p* = 0.168605



Notes: MDS = maternal depressive symptoms; PC = principal component; G×E = Gene-by-Environment interaction; GPC PGS = polygenic score corresponding to global psychopathology in children; SUSC PGS = polygenic score corresponding to susceptibility; MDD PGS = polygenic score corresponding to major depressive disorder.

Model Validation & Test Correction

The majority of our findings survived corrections for multiple testing and were validated when compared to the imputed analyses. The only exceptions were concerning the individual

PGSs. The imputed data sets corresponding to the prenatal MDS models revealed that in the prediction of positive self-evaluation, motivation and overall resilience, only the SUSC PRS was validated and survived correction (Supplementary Tables 1, 3 and 4). Whereas, in the prediction of hopefulness, only the GPC PRS survived correction (Supplementary Table 2). Across all analyses, neither child sex, maternal education, child age, nor genetic ancestry emerged as significant confounding factors.

DISCUSSION

The current study examined the effects of polygenic scores (associated with emotional sensitivity, global child psychopathology and major depressive disorder) and exposure to prenatal, postnatal or cumulative MDS on resiliency outcomes in 5-year-old children. To go beyond characterizing ELA as the mere presence or absence of stress, MDS was measured in terms of its chronicity, intensity and timing (the development window(s) in which exposure occurred). Our outcome measure of resilience was constructed as a positive measure in response to a structured stressful task with corresponding ecologically valid questions, rather than being defined as an absence of psychopathology, a self-report questionnaire or parent reports of child resilience (King et al., 2021). We also examined interactions between genetic and environmental factors to be able to detect environmental sensitivity effects.

Measuring Indicators of Resilience in Young Children Using a Challenging Puzzle Task

Given that resilience is best understood as a process rather than a static response to stress, we chose to conduct data-driven trajectory analyses using the CPT which permits the measurement of reactions to a challenge over several trials (Norris et al., 2009). These analyses revealed that

when children are faced with failure, the majority of children became discouraged during the stressful trials, but then recovered during the final possible trial (bounce-back group) and a second, smaller group of children became increasingly distressed never recovering (discouraged group). In addition, more than half of the sample (57.5%) sustained a positive outlook across all three resiliency indicators (positive self-evaluation, hopefulness, and motivation) implying that overcoming a challenge is not uncommon for 5-year-old children. These dynamic measures of response pattern provide robust indicators of strength and resilience.

Differential Impact of Exposure to Prenatal, Postnatal and Cumulative MDS

The prenatal MDS models were generally most parsimonious (according to model fit statistics) and most likely led to significant findings. The fact that the models testing exposure to prenatal MDS were consistently driving an effect on outcomes suggests that there may be something about exposure to MDS during the prenatal period which renders genetically susceptible children not only more vulnerable to stress, but more sensitive to favorable environments as well – a concept that is consistent with prenatal programming of postnatal plasticity (Hartman & Belsky, 2018b; Pluess & Belsky, 2011). The prenatal programming of postnatal plasticity theory is based on the notion that the environment is uncertain and as a result, it would be advantageous for the prenatally stressed fetus to curb its resources until the postnatal environment becomes more predictable. In doing so, the fetus is primed to be especially receptive to life outside the womb (for better or for worse) before committing to a developmental trajectory (Frankenhuis & Del Giudice, 2012).

How Does Genetic Susceptibility Contribute to Resilient Outcomes?

With the exception of the model predicting motivation, our analyses revealed that genetically susceptible children are more likely to flourish and recover from a challenging task when exposed to low levels of MDS. However, when exposed to high levels of MDS, this effect is reversed with genetically susceptible children demonstrating the worst recovery following failure, a finding that is consistent with the differential susceptibility hypothesis. The findings corresponding to hopefulness and overall resilience were indicative of the vantage sensitivity hypothesis whereby differences in resilient outcomes were only apparent in the context of a favorable environment (e.g., exposure to low levels of MDS). Specifically, children low in genetic susceptibility were least likely to be overall resilient when exposed to low levels of MDS, compared to those with moderate or high genetic susceptibility. When it comes to motivation, being genetically susceptible did not appear advantageous, even when the environment is favorable. It is possible that there is a stronger genetic component to motivation which is less prone to being shaped by the environment. For example, of the three indicators of resilience studied (e.g., positive self-evaluation, hopefulness and motivation), there is substantial evidence demonstrating that motivation is controlled by the dopaminergic system (Nunes et al., 2022; Salamone et al., 2022). It is therefore likely that a more established genetic architecture is underlying this indicator of resilience. Finally, across all analyses, it appears that children with moderate genetic susceptibility are more stable and consistently recover from failure regardless of their level of exposure to MDS.

Although our analyses were examining the combined influence of all three PGSs, the SUSC PGS appeared to be driving most, if not all of the genetic effects. Given that all of our findings were reflective of either differential susceptibility or vantage sensitivity, it seems appropriate that the SUSC PGS would be the genetic driver of these effects. Previous applications

of this PGS demonstrated that genetically susceptible children tend be more sensitive to adverse environments, but are also more likely to benefit from treatment (Keers et al., 2016).

Limitations

Also, although our AUC_G measure of MDS captures the chronicity and/or severity of postnatal and cumulative MDS, it was not possible to parse out the separate effects of severity and chronicity on our outcome measures. Even though the CPT is dynamic, non-static measure, it is still a brief, lab-based measure that does not fully capture all aspects of resilience and it is very context-specific. Finally, although most of our findings were generally consistent, it is likely that some of the variability in results could be attributed to different PGS thresholds being used. For example, depending on the outcome, the GPC PGS threshold ranged from $p < 1e06$ to 0.05 while the MDD PGS threshold ranged from $p < 1e08$ to 0.2. With the exception of positive self-evaluation for which analyses were conducted using a SUSC PGS threshold of $p < 0.0001$, the remaining outcomes used a SUSC PGS threshold of $p < 1e05$.

Future Directions

One recommendation going forward would be to construct a PGS based on regulatory gene variants associated with resilience rather than linking variants to psychopathology. A recent study by the Schizophrenia Working Group of the Psychiatric Genomics Consortium has constructed a polygenic resilience score which appears to moderate the risk for schizophrenia (Hess et al., 2021). Otherwise, the SUSC PGS used in the current study is a strong candidate and can be used independently if validated in larger samples. Also, important to note is that the construction of PGSs fails to capture gene-by-gene interactions and genes/variants which may be working together

as a network. Often the variants that are detected have no direct biological relevance to the outcome in question. When constructing PGSs, variants high in linkage disequilibrium (LD) are pruned, removing highly correlated SNPs and retaining those with the highest signals. This is done to reduce the redundancy of overlapping signals in regions with highly correlated SNPs, which would otherwise inflate effect sizes. The drawback of LD pruning is that biologically meaningful information about gene "networks" is lost and an independent contribution of otherwise associated alleles is assumed. By not accounting for the effects of LD and haplotype structure, the predictive accuracy of PGSs is limited as a result (De La Vega & Bustamante, 2018; Vilhjalmsson et al., 2015). Accordingly, when investigating genetic vulnerability to disease, it would be worthwhile to consider both PGSs and variants in LD, including haplotypes and gene networks.

In terms of resilience research where an interplay of multiple factors is involved, it would be informative to consider the types of coping strategies utilized, temperament style (including stress reactivity) and emotional regulation abilities. A follow-up study already in progress will examine the behavioral component of the CPT used in this study, whereby the above-mentioned factors will be examined. Specifically, videos of children performing the CPT will be coded according to the Disruptive Behavior Diagnostic Observation Schedule (DB-DOS), a structured clinic-based assessment designed to capture emotional dysregulation in young children (Wakschlag et al., 2008). Moreover, it will be possible to assess how well the behavioral measures of resilience captured by the DB-DOS complement the self-reported indicators of resilience measured in the current study. Finally, it would be very informative to validate the CPT as a potential measure of resilience with other non-CPT measures.

Conclusion

Our findings lend support to the differential susceptibility, vantage sensitivity and PPPP hypotheses with genetic susceptibility only being a risk factor when combined with exposure to high levels of prenatal MDS; otherwise, genetic susceptibility appears advantageous when combined with exposure to low levels of prenatal MDS. Having longitudinal measures of ELA as well as an ecologically-valid measure of resilience provides insight into how MDS interacts with genetic susceptibility to predict resilient functioning in young children. Understanding the source of such outcome variability could aid in identifying vulnerability and strengths whereby targeted prevention strategies, including early interventions during critical periods of development, could prevent problematic behaviors from becoming entrenched in adulthood. This study contributes to our understanding of the developmental origins of resilience and highlights the possibility of positive outcomes despite risk exposure.

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Supplementary Table 1: Logistic Regression Analyses - Positive Self-Evaluation

		Non-Imputed	Imputed
Q1 – Prenatal MDS (AIC: 116.52)	**Intercept**	β = -7.538521, *p* = 0.614286	β = -2.476153, *p* = 0.85689
	Genetic	β = -0.293068, *p* = 0.550070	β = -0.23342, *p* = 0.585823
	Environment	β = -0.206708, *p* = 0.581473	β = 0.037684, *p* = 0.917483
	Postnatal MDS	β = -0.001582, *p* = 0.081501 .	β = -0.00101, *p* = 0.22297
	Sex_male	β = 0.3042886, *p* = 0.600046	β = -0.121761, *p* = 0.81055
	Maternal Education	β = 0.6759941, *p* = 0.310801	β = 0.678828, *p* = 0.21336
	Child Age	β = 2.1368158, *p* = 0.470418	β = 1.1176113, *p* = 0.679389
	PC1	β = 2.5923148, *p* = 0.614052	β = 2.76647, *p* = 0.500974
	PC2	β = -12.680865, *p* = 0.335504	β = -10.951383, *p* = 0.222311
	PC3	β = -6.8455318, *p* = 0.156381	β = -3.183864, *p* = 0.426329
	G×E	β = -2.69915, *p* = 0.00045 ***	β = -2.15534, *p* = 0.00025 ***
	GPC PGS	β = 0.2384, *p* = 0.04677 * **x**	β = 0.236467, *p* = 0.076684
	SUSC PGS	β = 0.4374, *p* = 0.00002 ***	β = 0.47641, *p* = 0.00002 ***
	MDD PGS	β = -0.3242 , *p* = 0.00347 **	β = -0.28713, *p* = 0.02424 * **x**
Q1 – Postnatal MDS (AIC: 126.78)	**Intercept**	β = -8.530844, p = 0.59562	β = 10.21271, *p* = 0.47382
	Genetic	β = 3.008315, p = 0.00237 **	β = -2.61756, *p* = 0.00257 **
	Environment	β = -0.001714, p = 0.08735 .	β = 0.00151, *p* = 0.11502
	Prenatal MDS	β = -0.320330, p = 0.25377	β = 0.18130, *p* = 0.51606
	Sex_male	β = 0.383098, p = 0.48999	β = -0.18260, *p* = 0.72797
	Maternal Education	β = 0.414448, p = 0.50146	β = -0.51011, *p* = 0.37445
	Child Age	β = 2.327285, p = 0.46589	β = -2.67481, *p* = 0.34362
	PC1	β = -5.074790, *p* = 0.19454	β = 2.57859, *p* = 0.43574
	PC2	β = -3.703129, *p* = 0.52709	β = 2.94087, *p* = 0.58996
	PC3	β = -3.302848, *p* = 0.49141	β = -0.52799, *p* = 0.91133
	G×E	β = -0.004939, *p* = 0.00256 **	β = 0.00449, *p* = 0.00294 **
	GPC PGS	β = 0.3664, *p* = 0.0177 * **x**	β = 0.33423, *p* = 0.05078 .
	SUSC PGS	β = 0.3646, *p* = 0.0153 *	β = 0.47275, *p* = 0.00324 **
	MDD PGS	β = -0.2689 , *p* = 0.1234	β = -0.19302, *p* = 0.26400
Q1 – Cumulative MDS (AIC: 123.72)	**Intercept**	β = -5.597589, *p* = 0.70265	β = 7.40858, *p* = 0.59292
	Genetic	β = 2.289474, *p* = 0.02189 * **x**	β = -2.06407, *p* = 0.02035 * **x**
	Environment	β = -0.001759, *p* = 0.04537 * **x**	β = 0.00126, *p* = 0.13034
	Sex_male	β = 0.532860, *p* = 0.35084	β = -0.38553, *p* = 0.47508
	Maternal Education	β = 0.319633, *p* = 0.60613	β = -0.38137, *p* = 0.51313
	Child Age	β = 1.745577, *p* = 0.54862	β = -2.08899, *p* = 0.44585
	PC1	β = 0.631863, *p* = 0.90195	β = -1.47018, *p* = 0.71678
	PC2	β = -9.947065, *p* = 0.17422	β = 6.67066, *p* = 0.32422
	PC3	β = -1.575139, *p* = 0.73861	β = 0.78521, *p* = 0.86155
	G×E	β = -0.005013, *p* = 0.00353 **	β = 0.00459, *p* = 0.00242 **
	GPC PGS	β = 0.2588, *p* = 0.03159 * **x**	β = 0. 28353, *p* = 0.01751 *
	SUSC PGS	β = 0.4063, *p* = 0.00878 **	β = 0.43822, *p* = 0.00495 **
	MDD PGS	β = -0.3349 , *p* = 0.06900 .	β = -0. 27825, *p* = 0.09374 .

Notes: MDS = maternal depressive symptoms; PC = principal component; G×E = Gene-by-Environment interaction; GPC PGS = polygenic score corresponding to global psychopathology in children; SUSC PGS = polygenic score corresponding to environmental sensitivity; MDD PGS = polygenic score corresponding to major depressive disorder; **x** = did not survive correction for multiple testing.

Supplementary Table 2: Logistic Regression Analyses – Hopefulness

		Non-Imputed	Imputed
Q2 – Prenatal MDS (AIC: 219.9)	**Intercept**	β = -3.27854, *p* = 0.73073	β = -0.066605, *p* = 0.9936558
	Genetic	β = 0.87887, *p* = 0.01305 *	β = 0.890181, *p* = 0.0056954 **
	Environment	β = -0.12006, *p* = 0.56142	β = 0.024243, *p* = 0.9023758
	Postnatal MDS	β = -0.001225, *p* = 0.06588 .	β = -0.001344, *p* = 0.025757 * **x**
	Sex_male	β = -0.228262, *p* = 0.53534	β = -0.116782, *p* = 0.7228401
	Maternal Education	β = 0.257133, *p* = 0.51074	β = 0.334017, *p* = 0.3318883
	Child Age	β = 1.055593, *p* = 0.57458	β = 0.427059, *p* = 0.7959146
	PC1	β = -0.782796, *p* = 0.81229	β = 0.263267, *p* = 0.9286653
	PC2	β = -1.884314, *p* = 0.61985	β = -1.999855, *p* = 0.5567342
	PC3	β = -0.171642, *p* = 0.95778	β = -0.258652, *p* = 0.9203118
	G×E	β = -0.99436, *p* = 0.00132 **	β = -0.937595, *p* = 0.001066 ***
	GPC PGS	β = 0.3901, *p* = 0.00736 **	β = 0.395602, *p* = 0.0036384 **
	SUSC PGS	β = 0.3253, *p* = 0.01784 * **x**	β = 0.314325, *p* = 0.0170812 * **x**
	MDD PGS	β = 0.2846, *p* = 0.03198 * **x**	β = 0.290073, *p* = 0.0212316 * **x**
Q2-Postnatal MDS (AIC: 225.81)	**Intercept**	β = -4.420104, *p* = 0.63959	β = -1.8545008, *p* = 0.826118
	Genetic	β = 1.767324, *p* = 0.00135 **	β = 1.734118, *p* = 0.000615 ***
	Environment	β = -0.000674, *p* = 0.30068	β = -0.000881, *p* = 0.1418414
	Prenatal MDS	β = -0.190949, *p* = 0.34439	β = -0.0497878, *p* = 0.798151
	Sex_male	β = -0.248969, *p* = 0.48965	β = -0.1573611, *p* = 0.6275763
	Maternal Education	β = 0.391738, *p* = 0.30602	β = 0.3813600, *p* = 0.259180
	Child Age	β = 1.203188, *p* = 0.51905	β = 0.7244657, *p* = 0.663955
	PC1	β = -0.431568, *p* = 0.89676	β = 1.3347358, *p* = 0.661122
	PC2	β = -0.697402, *p* = 0.84515	β = -1.0434236, *p* = 0.763814
	PC3	β = -1.411065, *p* = 0.65529	β = -1.2526229, *p* = 0.622373
	G×E	β = -0.002087, *p* = 0.02038 * **x**	β = -0.002000, *p* = 0.014109 *
	GPC PGS	β = 0.5348, *p* = 0.00387 **	β = 0.556468, *p* = 0.0012850 **
	SUSC PGS	β = 0.2830, *p* = 0.11505	β = 0.287297, *p* = 0.0930533 .
	MDD PGS	β = 0.1822, *p* = 0.29109	β = 0.156236, *p* = 0.3328167
Q2 – Cumulative MDS (AIC: 221.82)	**Intercept**	β = -4.625486, *p* = 0.62642	β = -2.5787869, *p* = 0.759107
	Genetic	β = 2.009720, *p* = 0.00206 **	β = 1.903660, *p* = 0.000808 ***
	Environment	β = -0.001049, *p* = 0.04765 * **x**	β = -0.000965, *p* = 0.044066 * **x**
	Sex_male	β = -0.249203, *p* = 0.48797	β = -0.1685173, *p* = 0.602691
	Maternal Education	β = 0.272764, *p* = 0.47533	β = 0.3163855, *p* = 0.348384
	Child Age	β = 1.301577, *p* = 0.48876	β = 0.8864892, *p* = 0.594052
	PC1	β = 0.355858, *p* = 0.90812	β = 2.2542362, *p* = 0.417461
	PC2	β = -1.416827, *p* = 0.68109	β = -1.5513825, *p* = 0.649757
	PC3	β = -0.859993, *p* = 0.78895	β = -0.8372414, *p* = 0.740858
	G×E	β = -0.001657, *p* = 0.07352 .	β = -0.001772, *p* = 0.028311 * **x**
	GPC PGS	β = 0.4981, *p* = 0.00101 **	β = 0.520878, *p* = 0.000546 ***
	SUSC PGS	β = 0.2473, *p* = 0.09470 .	β = 0.261608, *p* = 0.084151 .
	MDD PGS	β = -0.2546, *p* = 0.08279 .	β = -0.21751, *p* = 0.150546

Notes: MDS = maternal depressive symptoms; PC = principal component; G×E = Gene-by-Environment interaction; GPC PGS = polygenic score corresponding to global psychopathology in children; SUSC PGS = polygenic score corresponding to environmental sensitivity; MDD PGS = polygenic score corresponding to major depressive disorder; **x** = did not survive correction for multiple testing.

Supplementary Table 3: Logistic Regression Analyses – Motivation

		Non-Imputed	Imputed
Q3-Prenatal MDS (AIC: 263.04)	**Intercept**	β = -0.159330, *p* = 0.984173	β = -5.661861, *p* = 0.442239
	Genetic	β = -1.062062, *p* = 0.000522 ***	β = 0.781336, *p* = 0.000847 ***
	Environment	β = -0.459430, *p* = 0.013567 *	β = -0.332598, *p* = 0.051697
	Postnatal MDS	β = 0.000338, *p* = 0.576648	β = -0.000037, *p* = 0.946197
	Sex_male	β = -0.087590, *p* = 0.784468	β = 0.089384, *p* = 0.754422
	Maternal Education	β = 0.025036, *p* = 0.941066	β = -0.064003, *p* = 0.827795
	Child Age	β = 0.166624, *p* = 0.916154	β = 1.292093, *p* = 0.374340
	PC1	β = 6.150605, *p* = 0.062510 .	β = 4.259577, *p* = 0.096371
	PC2	β = -5.448959, *p* = 0.086907 .	β = -5.583876, *p* = 0.074496
	PC3	β = 0.360225, *p* = 0.896755	β = -0.480762, *p* = 0.827908
	G×E	β = 0.476366, *p* = 0.084224 .	β = -0.462335, *p* = 0.032034 * **x**
	GPC PGS	β = 0.3728, *p* = 0.014540 *	β = -0.366523, *p* = 0.042062 * **x**
	SUSC PGS	β = -0.5081, *p* = 0.000683 ***	β = 0.605390, *p* = 0.000680 ***
	MDD PGS	β = 0.1190, *p* = 0.367723	β = -0.028088, *p* = 0.8561172
Q3-Postnatal MDS (AIC: 261 .75)	**Intercept**	β = 1.031800, *p* = 0.8989	β = -1.88026, *p* = 0.77468
	Genetic	β = -0.431299, *p* = 0.4242	β = 0.34277, *p* = 0.46763
	Environment	β = 0.000685, *p* = 0.2942	β = -0.00020, *p* = 0.71674
	Prenatal MDS	β = -0.400357, *p* = 0.0321 * **x**	β = 0.28266, *p* = 0.08639 .
	Sex_male	β = -0.152370, *p* = 0.6374	β = 0.22370, *p* = 0.43468
	Maternal Education	β = 0.102331, *p* = 0.7630	β = 0.00090, *p* = 0.99754
	Child Age	β = -0.097618, *p* = 0.9514	β = 0.18871, *p* = 0.88405
	PC1	β = 9.357391, *p* = 0.0122 *	β = -8.05305, *p* = 0.01102 *
	PC2	β = -5.811400, *p* = 0.0791 .	β = 4.89539, *p* = 0.10850
	PC3	β = -0.420284, *p* = 0.8797	β = 1.47079, *p* = 0.50626
	G×E	β = -0.001823, *p* = 0.0876 .	β = 0.00102, *p* = 0.22644
	GPC PGS	β = 0.3720, *p* = 0.00152 **	β = 0.44691, *p* = 0.00686 **
	SUSC PGS	β = -0.3189, *p* = 0.01673 * **x**	β = -0.29095, *p* = 0.09879 .
	MDD PGS	β = 0.3091, *p* = 0.01054 *	β = 0.26213, *p* = 0.10999
Q3-Cumulative MDS (AIC: 264.81)	**Intercept**	β = 1.1242733, *p* = 0.8896	β = -1.71317, *p* = 0.79369
	Genetic	β = -0.5534910, *p* = 0.2947	β = 0.40538, *p* = 0.38272
	Environment	β = 0.0000061, *p* = 0.9906	β = 0.00027, *p* = 0.53475
	Sex_male	β = -0.1682028, *p* = 0.5983	β = 0.23876, *p* = 0.40193
	Maternal Education	β = 0.0732366, *p* = 0.8273	β = 0.02095, *p* = 0.94274
	Child Age	β = -0.0477322, *p* = 0.9762	β = 0.10575, *p* = 0.93467
	PC1	β = 8.9809306, *p* = 0.0147 *	β = -7.94028, *p* = 0.01203 *
	PC2	β = -5.4916117, *p* = 0.0869 .	β = 4.60928, *p* = 0.12690
	PC3	β = -0.1534719, *p* = 0.9553	β = 1.26696, *p* = 0.56500
	G×E	β =-0.0014476, *p* = 0.1339	β = 0.00087, *p* = 0.26247
	GPC PGS	β = 0.3782, *p* = 0.00143 **	β = 0.45511, *p* = 0.00535 **
	SUSC PGS	β = -0.2995, *p* = 0.02206 * **x**	β = -0.27765, *p* = 0.10671
	MDD PGS	β = 0.3223, *p* = 0.00843 **	β = 0.26725, *p* = 0.09871 .

Notes: MDS = maternal depressive symptoms; PC = principal component; G×E = Gene-by-Environment interaction; GPC PGS = polygenic score corresponding to global psychopathology in children; SUSC PGS = polygenic score corresponding to environmental sensitivity; MDD PGS = polygenic score corresponding to major depressive disorder; **x** = did not survive correction for multiple testing.

Supplementary Table 4: Logistic Regression Analyses – Overall Resilience

		Non-Imputed	Imputed
Overall Resilience -Prenatal MDS (AIC: 272.07)	**Intercept**	β = 1.342011, *p* = 0.86694	β = -1.687974, *p* = 0.812438
	Genetic	β = 0.891096, *p* = 0.00259 **	β = 0.844253, *p* = 0.000905 ***
	Environment	β = -0.371917, *p* = 0.05168 .	β = -0.213424, *p* = 0.205817
	Postnatal MDS	β = -0.000188, *p* = 0.75071	β = -0.000409, *p* = 0.437237
	Sex_male	β = 0.211401, *p* = 0.49685	β = 0.328201, *p* = 0.237761
	Maternal Education	β = 0.262399, *p* = 0.42390	β = 0.110559, *p* = 0.698138
	Child Age	β = -0.182915, *p* = 0.90791	β = 0.464158, *p* = 0.741044
	PC1	β = 0.452805, *p* = 0.87474	β = 1.154823, *p* = 0.641193
	PC2	β = -6.580152, *p* = 0.06420 .	β = -1.950950, *p* = 0.407743
	PC3	β = -0.782833, *p* = 0.77853	β = -0.474914, *p* = 0.831702
	G×E	β = -0.936243, *p* = 0.00123 **	β = -0.726420, *p* = 0.001807 **
	GPC PGS	β = -0.3594, *p* = 0.009061 **	β = -0.25330, *p* = 0.064660 .
	SUSC PGS	β = 0.4840, *p* = 0.000224 ***	β = 0.51502, *p* = 0.000228 ***
	MDD PGS	β = 0.1566, *p* = 0.168605	β = 0.23168, *p* = 0.057212
Overall Resilience – Postnatal MDS (AIC: 277.77)	**Intercept**	β = 0.5990377, *p* = 0.9381	β = -2.289342, *p* = 0.741204
	Genetic	β = -0.2710237, *p* = 0.6035	β = 0.666107, *p* = 0.109780
	Environment	β = 0.0000263, *p* = 0.9659	β = -0.000368, *p* = 0.477529
	Prenatal MDS	β = -0.2805138, *p* = 0.1224	β = -0.163655, *p* = 0.317604
	Sex_male	β = 0.0175765, *p* = 0.9546	β = 0.201440, *p* = 0.459151
	Maternal Education	β = 0.2656956, *p* = 0.4118	β = 0.080714, *p* = 0.772433
	Child Age	β = -0.0520611, *p* = 0.9727	β = 0.578713, *p* = 0.672377
	PC1	β = 7.5633001, *p* = 0.0254 * **x**	β = 5.463847, *p* = 0.034346 * **x**
	PC2	β = -7.4637002, *p* = 0.0283 * **x**	β = -3.087207, *p* = 0.192970
	PC3	β = -1.5947028, *p* = 0.5512	β = -0.677018, *p* = 0.751108
	G×E	β = -0.0017368, *p* = 0.0828 .	β = 0.000122, *p* = 0.869573
	GPC PGS	β = 0.4190, *p* = 0.00166 **	β = -0.44699, *p* = 0.019734 * **x**
	SUSC PGS	β = -0.3539, *p* = 0.01738 * **x**	β = 0.52145, *p* = 0.008743 **
	MDD PGS	β = 0.2271, *p* = 0.08773 .	β = 0.03156, *p* = 0.865688
Overall Resilience - Cumulative MDS (AIC: 276.56)	**Intercept**	β = 0.840132, *p* = 0.9133	β = -1.850068, *p* = 0.789358
	Genetic	β = -0.347943, *p* = 0.5000	β = 0.686556, *p* = 0.092540
	Environment	β = -0.000433, *p* = 0.3787	β = -0.000590, *p* = 0.154058
	Sex_male	β = 0.009847, *p* = 0.9744	β = 0.184873, *p* = 0.495045
	Maternal Education	β = 0.242908, *p* = 0.4504	β = 0.062896, *p* = 0.821493
	Child Age	β = -0.049222, *p* = 0.9742	β = 0.521201, *p* = 0.703245
	PC1	β = 7.384334, *p* = 0.0284 * **x**	β = 5.493760, *p* = 0.033370 * **x**
	PC2	β = -7.313044, *p* = 0.0279 * **x**	β = -2.935554, *p* = 0.215463
	PC3	β = -1.358629, *p* = 0.6110	β = -0.532565, *p* = 0.802861
	G×E	β = -0.001479, *p* = 0.1082	β = 0.000078, *p* = 0.906922
	GPC PGS	β = 0.4200, *p* = 0.00151 **	β = -0.467874, *p* = 0.014494 * **x**
	SUSC PGS	β = -0.3421, *p* = 0.01927 * **x**	β = 0.511952, *p* = 0.009785 **
	MDD PGS	β = 0.2379, *p* = 0.07661 .	β = 0.020174, *p* = 0.913562

Notes: MDS = maternal depressive symptoms; PC = principal component; G×E = Gene-by-Environment interaction; GPC PGS = polygenic score corresponding to global psychopathology in children; SUSC PGS = polygenic score corresponding to environmental sensitivity; MDD PGS = polygenic score corresponding to major depressive disorder; **x** = did not survive correction for multiple testing.

Bridge to Study 3

In Study 2, we examined cognitive features of resilience, namely positive self-evaluation, hopefulness and motivation in relation to a challenging puzzle task (CPT) among 5-year-old children. Across each of the three resilient indicators, two distinct patterns emerged: one class of children who bounced back after failure and a smaller group of children who never recovered post-challenge. Moreover, a combination of genetic susceptibility and exposure to low levels of prenatal maternal depressive symptoms (MDS) were predictive of resilient outcomes across most of our analyses. Otherwise, worse outcomes were observed in contexts of genetic susceptibility and exposure to high levels of prenatal MDS. These results suggest that genetic susceptibility is not inherently disadvantageous; rather it appears to be programming children's sensitivity to their environment, an effect that is consistent with the differential susceptibility hypothesis. In attempt to replicate and complement these findings, Study 3 is based on the same set of analyses except it explores external processes of resilience, instead of internal processes. For example, external processes of resilience include help-seeking behaviors, emotional regulation abilities, problem-solving skills, and coping strategies to name a few (Gartland et al., 2019; Panagou & MacBeth, 2022). More specifically, a range of behaviors and emotions elicited by the CPT were coded according to a structured clinic-based assessment and patterns of total irritability relative to total competence as a function of resilience were entered into a gene-by-environment model. Compared to Study 2 where two distinct patterns emerged, Study 3 revealed three classes of children: one group who was highly emotional (exhibiting very high irritability along with high competence), another group who displayed more competence than irritability (the resilient group) and a third group who displayed flat affect on both scales (very low irritability and competence scores). Given that our research focus was on resilient outcomes, our G×E analyses were predicting the

probability of belonging to the resilient class relative to the two other groups. Similar to Study 2, exposure to prenatal, postnatal and cumulative MDS was assessed in 3 separate models, each of which was interacted with genetic susceptibility. The strength of this study is that the outcome measure was based on coded observations, rather than children's self-rating scores on the CPT. Combining two types of measurement on the CPT (e.g., self-rating scores and coded observations) holds promise for future studies as a comprehensive measure of resilience.

STUDY 3

Applying the Disruptive Behavior Diagnostic Observation Schedule as a Measure of Resilience in Young Children in a G×E Context

[Manuscript in preparation. To be submitted to the *Journal of Development & Psychopathology*]

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ABSTRACT: 200 word-limit

Despite the emerging resilience literature, there is still a lack of ecologically valid measures in children that can capture positive adaptation in relation to challenge. We build upon existing research by adapting a child-friendly stress-paradigm (the Challenging Puzzle Task) to measure positive outcomes in 5-year-old children. Seeing as the CPT elicits a range of emotions and behaviors relevant to resilient functioning, we applied an observational clinical research tool (the Disruptive Behavior Diagnostic Observation Schedule) to assess overall irritability and competence. We derived a three-class structure from our sample based on total irritability scores relative to total competence scores: class 1 - emotionally dysregulated; class 2 – resilient; and class 3 - flat affect. Gene-by-environment analyses were conducted with the resilient class being the predicted outcome. Classes 1 and 3 were compared to the resilient class (class 2). Significant G×E interactions were detected for both comparisons, with the first comparison reflecting vantage sensitivity and due to insufficient power, tests of environmental sensitivity for the second comparison were inconclusive. Our findings nonetheless contribute to the field of resiliency research and provide evidence for the vantage sensitivity hypothesis.

INTRODUCTION

Resiliency research has grown in recent years and as a result, there is more of a consensus on how resilience is defined. Despite competing definitions of resilience, a recent review has come up with a comprehensive definition based on the literature and conceptualizes resilience "*as a dynamic developmental process that encompasses an individual's capacity to adapt positively following significant adversity*" (VanMeter & Cicchetti, 2020). The challenge going forward is developing a standardized measure of resilience. There are currently a range of resilience scales that rely on self-reports or parent-reports (King et al., 2021). The types of positive child outcomes typically measured using these scales include: cognitive competence, academic achievement, self-esteem, and the absence of mental disorders (Fergus & Zimmerman, 2005; Gartland et al., 2019; Tiet, 2002). Not only do these proxy measures fail to capture resilience as a process, but they are missing a key component of resilience which is positive adaptation in the presence of a challenge or stressor. The detection of resilience implies the overcoming of some type of adversity. Therefore, in addition to measuring positive outcomes, it is important to consider how a child copes with and recovers from a challenge. Observing a child's behavior while they are faced with a challenge may be the best means of capturing resilient functioning. This is entirely feasible since at the age of 5, one can already start to see how children manage and respond to stress (Cole et al., 2007).

In a previous paper (King et al., 2022), we discuss the few studies which have attempted to incorporate ecologically valid measures of stress reactivity and emotional regulation in young children. We discovered that emphasis is placed on detecting problematic behaviors, even though these same stress paradigms elicit both negative and positive behaviors. By focusing on one end of the spectrum, there is a lost opportunity to study resilience, especially because resilience features

both positive and negative aspects. To clarify, it is not to say that resilient individuals do not experience negative emotions in the face of a challenge. They may. The difference is that resilient individuals can bounce back from the stressor more easily. They may also possess effective strategies for managing stress among other internal resources, like positive thinking, problem solving skills, and help-seeking behavior (Panagou & MacBeth, 2022; Tugade & Fredrickson, 2004). For this reason, it is important to consider both internal and external processes of resilience when measuring positive functioning in relation to negative circumstances.

One task that elicits a range of positive and negative emotions is the Challenging Puzzle Task (CPT). The CPT uses a series of age-appropriate successes and failures while collecting information about cognitive appraisals. A previous paper focused on positive cognitive appraisals associated with the CPT discovered that certain indicators of resilience, namely positive self-evaluation, hopefulness and motivation, were very common in 5-year-old children (Charney, 2004; Ho et al., 2010; Tugade & Fredrickson, 2004). In fact, 57% of the children displayed all 3 features across the CPT. One interesting finding is that even children who were genetically susceptible recovered from failure, at least when the environmental conditions were favorable (e.g., when exposed to low levels of maternal depressive symptoms (MDS)) (King et al., 2022). In fact, these findings lend support to the differential susceptibility and vantage sensitivity hypotheses. Given that there are a lack of studies that measure positive outcomes and positive environments, it is difficult to detect differential susceptibility and vantage sensitivity effects. The same is true of resiliency research – there are a lack of ecologically valid measures of resilience. Fortunately, the CPT yielded very rich data, so there is an opportunity to not only tap into a range of measurable behaviors and emotions elicited by the CPT, but it will also be possible to test whether our previous findings generalize to external processes of resilience.

To address these aims, we have incorporated the Disruptive Behavior Diagnostic Observation Schedule (DB-DOS), an observational clinical research tool initially designed to capture disruptive behavior in preschool-aged children (Wakschlag et al., 2005) into our CPT assessment protocol. The DB-DOS includes structured tasks that elicit a range of emotions and behaviors so as to increase the likelihood that clinically salient behaviors will be observed. For example, some tasks are rigged so as to elicit frustration while other tasks are designed to test compliance. Similar diagnostic observation schedules have been used successfully in other contexts, such as in the detection of symptoms related to autism-spectrum disorders (e.g., the Autism Diagnostic Observation Schedule; (Lord et al., 2000)). Under the umbrella of disruptive behavior, the DB-DOS taps into three specific domains: behavioral regulation, anger modulation, and competence. These domains are further divided into sub-categories (Wakschlag et al., 2005) with attention paid to the intensity and frequency of the behavior in question as well as the child's verbal and physical cues (e.g., frowning, self-talk, complaining, shrugging of shoulders, crossing of arms). Another aspect of the DB-DOS paradigm is that it is composed of 3 interactional scenarios: one with the parent and the other two scenarios take place with the examiner (examiner engaged and examiner busy). The purpose of having 3 contexts is to determine whether the behaviors in question generalize across various contexts because if they do, the behaviors will carry more clinical significance. When assessing the behaviors evoked by the DB-DOS, qualitative data which reflect global, integrated judgements are first collected, then behavioral codes are assigned a range from 0 to 3, with 3 indicating that the behavior in question is present to a high degree and 0 indicating that the behavior is not present.

Several studies have implemented the DB-DOS, whereby negative outcomes are typically measured. These include: oppositional-defiant behavior, relationship-specific impairment

(Petitclerc et al., 2015), irritability, noncompliance (Massey et al., 2020), anger dysregulation (Frost et al., 2018), inattention, hyperactivity, impulsivity (Bunte et al., 2013), disruptive behavior (Gray et al., 2012; Sabol et al., 2022; Wakschlag et al., 2007), and emotion and behavior problems (Tseng et al., 2015; Yarger et al., 2021). Another variation of the DB-DOS intended to measure neural synchrony (DB-DOS: BioSync) (Quiñones-Camacho et al., 2021) incorporates functional near-infrared spectroscopy (fNIRS) which collects data corresponding to noninvasive optical imaging. In other cases, the DB-DOS is used to validate diagnoses (Bunte et al., 2013; Hampton et al., 2021). Despite the DB-DOS having a scale devoted to competence, only one study examined this scale (Lind et al., 2020).

Building upon our previous work, we believe it would be a significant contribution to the literature if we can replicate our G×E findings, particularly as it relates to differential susceptibility, vantage sensitivity and prenatal programming of postnatal plasticity (PPPP) effects. More specifically, we would like to test whether the same combination of genetic and environmental conditions apply to external processes of resilience. We do not expect the cognitive and behavioral features of resilience to completely overlap. Rather, we expect that these complementary measures will provide a global view of resilience and its interacting processes.

METHODS

Sample

The sample for this study was drawn from the Maternal Adversity, Vulnerability and Neurodevelopment (MAVAN) cohort: a longitudinal, community-based, prospective study of pregnant mothers and their children based in Montreal, Quebec and Hamilton, Ontario. Sample descriptives, including exclusion criteria are reported elsewhere (King et al., 2022; O'Donnell et

al., 2014). Due to attrition and gaps in data collection, the analyses for the current study are based on a sub-sample of 205 participants.

Table 1: Adjusted Sample Size

	N
Total sample size	590
Completed the challenging puzzle task (CPT)	323
Videos of the CPT available for coding	305
Available genetic data (polygenic scores)	260
Maternal depressive symptoms data (CESD scores)	343
Sub-sample size *	205

Notes: CESD = Center for Epidemiologic Studies Depression Scale;
* = Participants were included if they had completed the CPT and if genetic and CESD data were available.

Measures

Environmental Predictor: Maternal Depressive Symptoms (MDS). MDS was measured using the 20-item self-report Center for Epidemiologic Studies Depression Scale (CESD) (Radloff, 1977) during pregnancy (26^{th} week of gestation) and at 6, 12, 24, 36 and 48 months postnatally. Mothers endorsed depressive symptoms using a 4-point Likert scale ranging from 0 (rarely or none of the time) to 3 (all of the time). For the current study, three measures of child exposure to MDS were calculated (prenatal, postnatal, and cumulative). Prenatal exposure to MDS was measured during the second trimester, while postnatal and cumulative exposure to MDS was calculated using area under the curve with respect to ground (AUC_G) estimates. AUC_G calculations return a value for each participant which represents overall exposure across two dimensions: the *x-axis* which corresponds to chronicity (MDS across the various time-points) and the *y-axis* which corresponds to severity (the range of CESD scores). Postnatal AUC_G estimates were computed using the 5 postnatal time-points while cumulative AUC_G was computed using all six time-points. Higher AUC_G values signify more chronic and/or severe MDS.

Moderator: Genetic Susceptibility. Complete method descriptions including information about genotyping and PGS construction can be found in previous publications (Chen et al., 2018; Silveira et al., 2017). Genetic susceptibility was captured using a combination of three PGSs associated with: global psychopathology in children (GPC) (Neumann et al., 2022), susceptibility (SUSC) (Keers et al., 2016) and major depressive disorder (MDD) (Major Depressive Disorder Working Group of the Psychiatric et al., 2013). One of the rationales for using a combined PGS are that psychiatric symptoms are not as differentiated in childhood (Finsaas et al., 2018). Therefore, limiting our analyses to a PGS associated with one specific phenotype may overlook possible genetic contributions.

Outcome Variable: Resilience. A modified version of the Challenging Puzzles Task (CPT; (Cole et al., 2007; Smiley & Dweck, 1994; Ziegert et al., 2001) was administered by a trained experimenter alongside other measures of child behavior at age 5. The CPT consists of a series of possible and impossible puzzles, whereby reactions to a challenge (in this case, three impossible puzzles) are captured via an ecologically valid rating scale. Specifically, puzzles 1 and 5 were possible to solve and can be completed with the help of the research assistant as needed while puzzles 2 to 4 were impossible and had a time limit of 2-minutes. Images of the puzzle along with the rating scales can be found in a recent review published by our team (King et al., 2021).

To complement the internal (cognitive) processes related to completing the CPT, external processes (emotions and behaviors) were video-coded according to the DB-DOS. Given that the CPT does not necessarily elicit defiant behavior, the DB-DOS was adapted and the CPT were coded according to the following two domains: anger modulation (or irritability) and competence. Furthermore, the parent-context was left out given that the purpose of the CPT was to assess reactions to a challenging task. The possible puzzle trials are similar to the examiner-engaged

context because the research assistant is allowed to assist the child in completing the puzzles. For the impossible puzzle trials, the researcher is instructed to not assist the child and must limit their social engagement with the child, thus resembling the examiner-busy context. For anger modulation (or irritability), 6 different behaviors are noted: intensity of negative affect, predominance of negative affect, ease of negative affect, rapid escalation of negative affect, difficulty recovering and poor coping. For the competence scale, intensity of positive affect, predominance of positive affect, socially directed positive affect, social engagement and assertiveness were measured. These behaviors were noted across all 5 trials of the CPT. The scores were then totaled across all domains for each category to provide a global view of emotional regulation. In other words, two total scores were calculated: one corresponding to the 6 irritability items and a second one corresponding to the 5 competence items.

Analysis

Interrater Reliability: Because of the subjectivity in coding, three coders were assigned to code the puzzle videos according to the DB-DOS. Internal reliability was set at 80% with the second and third coders needing to demonstrate agreeableness with the primary coder on 4/5 behavior codes before going on to code independently. Additionally, 40% of the videos were double-coded and 25% triple-coded to establish interrater reliability. A total of 305 videos were coded. Of these, 75 (24.6%) were triple-coded, 121 (39.7%) were double-coded and the remaining (109 (35.7%)) were single- coded. For the 196 (64.3 %) videos which were either double- or triple-coded, we conducted intraclass correlation (ICC) statistics to determine the level of agreement between coders. Separate ICC statistics were derived for the irritability and competence scales. Before assigning final codes, all discrepancies in coding were discussed until consensus was achieved.

Overall Behavioral Patterns: Data-driven patterns reflecting total irritability and total competence scores across the CPT were fitted with *Extended Mixed Models Using Latent Classes and Latent Processes* (LCMM) (Proust-Lima C, 2020), a package available in R. Given that the 3-class and 4-class structures had very similar model fit statistics, we opted for the 3-class model due to power limitations. Logistic regression analyses were conducted to predict the probability of belonging to the resilient class.

G×E Analyses: Using alternating optimization (Jolicoeur-Martineau et al., 2018), LEGIT (Latent Environmental & Genetic InTeraction) constructs a generalized linear model based on G×E interactions, where G is a weighted sum of genetic variants and E is a weighted sum of the environment. For the current study, G consisted of all three polygenic scores (PGS), while E consisted of one or multiple measures of maternal depressive symptoms (MDS). Due to timing effects and their differential impact on the developing child, the separate and combined contributions of prenatal and postpartum depressive symptoms were assessed (e.g., prenatal depressive symptoms only, postnatal depressive symptoms only, and cumulative MDS (prenatal + postnatal depressive symptoms)). Because two comparisons were tested (class 1 vs. class 2 and class 3 vs. class 2), separate G×E analyses were conducted for each comparison. Overall, 3 separate models were tested (prenatal, postnatal and cumulative MDS) for each of the two comparisons. Consequently, we applied corrections for multiple testing to each set of analyses. Finally, where there were significant G×E interactions, post-hoc tests of environmental sensitivity were applied. These tests determined whether differential susceptibility, diathesis-stress, or vantage sensitivity applied to the interaction (Jolicoeur-Martineau et al., 2020).

Covariates: All models were adjusted for child sex, child age and maternal education (e.g., having a university education or higher) since these variables can influence child outcomes.

Prenatal and postnatal MDS were also controlled for in our postnatal and prenatal analyses respectively given that postnatal MDS could be influencing prenatal effects and vice versa. Lastly, genetic ancestry was accounted for by including the three principal components that were the most informative of population structure in this cohort (Silveira et al., 2017).

Imputation: The package Multivariate Imputation by Chained Equations available in R (van Buuren, 2021) was used to estimate missing values and generate 50 imputed datasets. Since it is not advised to impute genetic data, we limited the analyses to 260 as this was the total number of children for whom we had genetic data. Demographic data, puzzle scores, covariates as well as the predictor variables were all entered to inform the imputed values. The final imputed datasets consisted of estimated values corresponding to the outcome variable in question (e.g., responses on the CPT) as well as CESD scores (e.g., MDS) across the various time-points. These analyses were conducted in parallel to validate our findings and are featured in the Supplementary section of this paper.

RESULTS

The ICC values (range: 0.712 to 0.778) demonstrate moderate to good interrater reliability (Koo & Li, 2016). As expected, there was a slightly lower ICC for those videos which were coded by 3 raters as opposed to 2 raters. Regardless of the number of raters, there was slightly more agreement among the codes corresponding to the competence scale (Table 1).

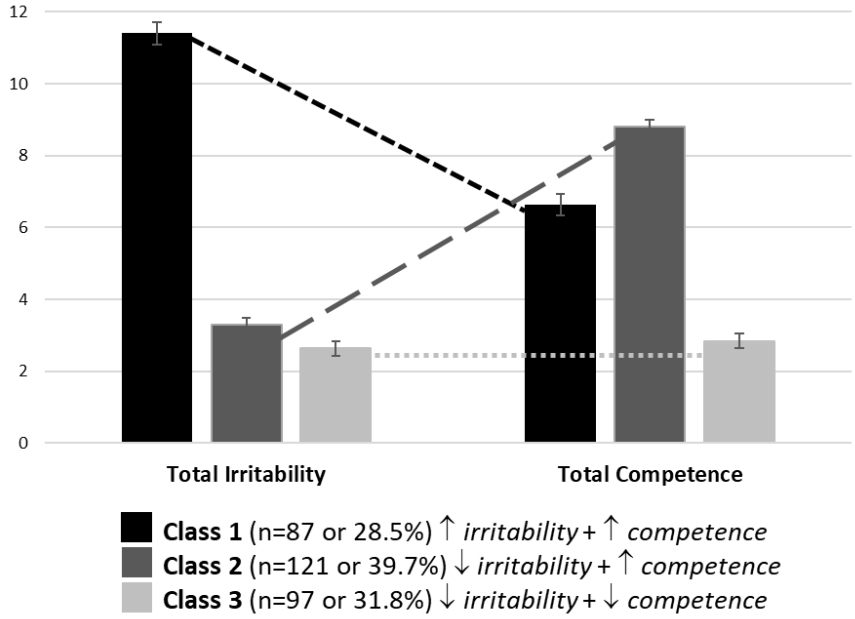
Table 1: Interrater Reliability

	2 Raters	3 Raters
Irritability	N = 726 (121 puzzles x 6 constructs)	N = 450 (75 puzzles x 6 constructs)
	ICC = **0.767** (95% CI: 0.735 < ICC < 0.795)	ICC = **0.712** (95% CI: 0.673 < ICC < 0.748)
	$F_{(725,715)} = 7.61$, $p = 3.62e\text{-}141$	$F_{(449,875)} = 8.49$, $p = 2.07e\text{-}157$
Competence	N = 600 (120 puzzles x 5 constructs)	N = 375 (75 puzzles x 5 constructs)
	ICC = **0.778** (95% CI: 0.743 < ICC < 0.808)	ICC = **0.742** (95% CI: 0.702 < ICC < 0.778)
	$F_{(599,536)} = 8.11$, $p = 2.85e\text{-}114$	$F_{(374,750)} = 9.61$, $p = 1.03e\text{-}148$

Identifying Behavioral Patterns on the CPT

There was a relatively equal distribution of children across the three classes. Given that we were predicting resilience, class 2 was the reference group and was compared against the other two classes. These children scored very low on the irritability scale, but high on competence (Figure 1), suggesting that they adapted more positively than negatively when faced with failure. Class 1 scored the highest on total irritability, but relatively high on the competence scale as well, indicating that these children displayed some signs of emotional dysregulation. The final group of children (class 3) maintained a very consistent neutral mood throughout the CPT and displayed neither negative nor positive emotions (flat effect). The mean total irritability score (regardless of class membership) was 5.4 (SD = 4.46; range = 0-18) while that for total competence was 6.28 (SD = 3.4; range = 0-14).

Figure 1: Behavioral Patterns on the Challenging Puzzles Task (CPT)

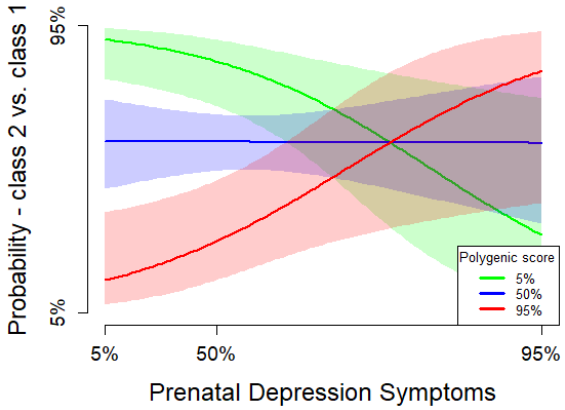


Comparison – Probability of Belonging to Class 2 (vs. Class 1): The model featuring exposure to prenatal MDS was the best fitting. There was a significant G×E interaction, with the GPC PGS driving the genetic effect along with the MDD PGS, albeit to a lesser extent. Compared to class 1 (emotionally dysregulated group), the profile of children who are most likely to belong to class 2 (the resilient group) have a combination of low genetic susceptibility and low exposure to MDS. The children who are least likely to belong to class 2 (the emotionally dysregulated group) were those who are genetically susceptible and who were exposed to low levels of prenatal MDS, regardless of their level of exposure to MDS. Children with moderate genetic susceptibility have a 50% probability of being in class 2. The plot also shows a slight trend of genetically susceptible children belonging to class 2 when exposure to prenatal MDS is high. However, the overlapping confidence interval bands when the environmental conditions are negative (high MDS), along with

tests of environmental sensitivity confirm that vantage sensitivity best represents the G×E interaction in this model (BIC = 212.42).

Table 2: Logistic Regression – Probability of Belonging to the Resilient Class (vs. Class 1)

Prenatal MDS (AIC: 180.74); *df* = 132	
Intercept	β = -3.15487, *p* = 0.77344
Genetic	β = -1.20462, *p* = 0.00292 **
Environment	β = 0.05554, *p* = 0.81614
Postnatal MDS	β = 0.00000, *p* = 0.99809
Sex_male	β = 0.00635, *p* = 0.98762
Maternal Education	β = -0.11179, *p* = 0.78610
Child Age	β = 0.71381, *p* = 0.74203
PC1	β = 0.56474, *p* = 0.89510
PC2	β = 3.67826, *p* = 0.53790
PC3	β = 12.40841, *p* = 0.03018 * **x**
G×E	β = 1.09494, *p* = 0.00288 **
GPC PGS	β = 0.4296, *p* = 0.00424 **
SUSC PGS	β = 0.2795, *p* = 0.02955 * **x**
MDD PGS	β = -0.2909, *p* = 0.02235 *



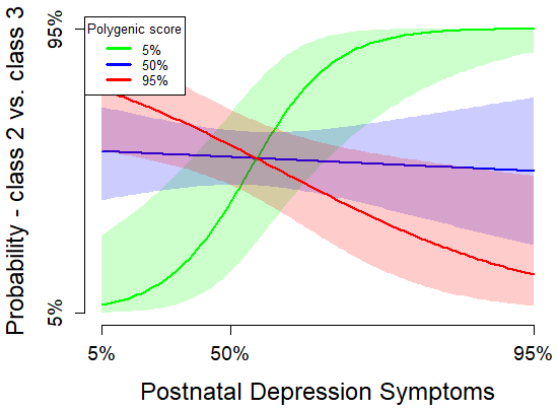
Notes: MDS = maternal depressive symptoms; PC = principal component; G×E = Gene-by-Environment interaction; GPC PGS = polygenic score corresponding to global psychopathology in children; SUSC PGS = polygenic score corresponding to susceptibility; MDD PGS = polygenic score corresponding to major depressive disorder; x = did not survive correction for multiple testing.

Comparison – Probability of Belonging to Class 2 (vs. Class 3): Model fit statistics indicated that the model featuring postnatal MDS was the best fitting. There was a significant G×E interaction with the GPC PGS driving the genetic effect. Compared to children in class 3 (flat affect), children were most likely to belong to class 2 if they had only one risk factor – either genetic susceptibility or exposure to high levels of postnatal MDS. Those who were most likely to belong to class 2 (the flat effect group) were children who had no risk factors (e.g., low genetic susceptibility and exposure to low levels of postnatal MDS) or those who had both risk factors (e.g., genetic susceptibility combined with exposure to high levels of postnatal MDS). The variation observed at both ends of MDS exposure (and in opposing directions) suggests that differential susceptibility could be explaining the G×E interaction. However, tests of

environmental sensitivity returned competing model fit statistics which is an indication that there was insufficient data to determine the type of interaction. Similar to the previous analyses, children with moderate genetic susceptibility do not show any specific tendency towards class membership and this is regardless of their level of exposure to postnatal MDS.

Table 3: Logistic Regression – Probability of Belonging to the Resilient Class (vs. Class 3)

Postnatal MDS (AIC: 193.32); *df* = 141	
Intercept	β = -0.72474, *p* = 0.93808
Genetic	β = 2.30783, *p* = 0.00180 **
Environment	β = 0.00040, *p* = 0.61706
Prenatal MDS	β = 0.25840, *p* = 0.28456
Sex_male	β = -0.58668, *p* = 0.12408
Maternal Education	β = -0.14817, *p* = 0.71314
Child Age	β = 0.21942, *p* = 0.90522
PC1	β = -7.07979, *p* = 0.06079 .
PC2	β = 10.37960, *p* = 0.04682 * **x**
PC3	β = -3.17225, *p* = 0.30126
G×E	β = -0.00506, *p* = 0.00096 ***
GPC PGS	β = 0.79247, *p* = 0.00109 **
SUSC PGS	β = -0.07991, *p* = 0.58880
MDD PGS	β = -0.12762, *p* = 0.41408



Notes: MDS = maternal depressive symptoms; PC = principal component; G×E = Gene-by-Environment interaction; GPC PGS = polygenic score corresponding to global psychopathology in children; SUSC PGS = polygenic score corresponding to susceptibility; MDD PGS = polygenic score corresponding to major depressive disorder; x = did not survive correction for multiple testing.

Model Validation & Test Correction

For the first comparison (class 1 vs. class 2), most of our findings survived correction with the exception of the SUSC PGS and the third principal component (PC3). The imputed data set validated a G×E interaction, with both the GPC and MDD PGSs driving the genetic effects. The imputations also revealed that PC3 was confounding the genetic effects, implying that population stratification may be biasing these findings. For the second comparison (class 3 vs. class 2), all of

our findings survived correction except for PC2. Similar to the first model, the imputed data set validated the G×E finding as well as the GPC PGS as the main driver of the genetic effects.

DISCUSSION

This study was the first of its kind to use a child-friendly stress paradigm (the CPT) to measure resilient outcomes. Not only was it possible to observe adaptations to stress in 5-year-old children, but we were also able to assess recovery from failure in the same task. Rich qualitative data which captured a range of emotions and behaviors elicited during the CPT was collected and a coding scheme based on a structured observational tool (the DB-DOS) was applied. We derived a 3-class structure from our data based on total scores across 2 domains: irritability and competence. Our findings indicated a relatively equal distribution of children across the three different classes: 1) high irritability + high competence; 2) low irritability + high competence; and 3) low irritability + low competence. Furthermore, we were able to replicate G×E interaction modeling from a previous study which examined the cognitive component of the CPT (King et al., 2022). For these models, our main predictors consisted of a combined genetic score of three PGSs as well as exposure to varying levels of MDS during critical periods of development. Two comparisons were conducted whereby membership to the resilient class (class 2) relative to the other classes (class 1: emotionally dysregulated; and class 3: flat affect) was the measured outcome.

The GPC PGS was the main driver of the genetic effects for both comparisons (although the MDS PGS had a very modest influence on the overall genetic effect in the first comparison). The fact that in our previous study, we found that the SUSC PGS was driving most of the genetic effects (King et al., 2022), suggests that there could be distinct genetic pathways that are

influencing each of our outcomes. For example, maybe there are specific variants within the SUSC PGS that play more of a role in cognition. Whereas the GPC PGS could be more implicated in behavioral and emotional regulation. The use of these GPCs in other studies could help elucidate this possibility.

Significant G×E interactions were detected for both comparisons. For the first comparison (class 1 vs. class 2), we found evidence of vantage sensitivity. Variation in class membership was most evident when the environment was favorable (when exposed to low levels of prenatal MDS). Under these conditions, the children lowest in genetic susceptibility were most likely to adapt positively (belong to class 2) in the face of a challenge (compared to emotionally dysregulated children). It is not counter-intuitive to expect that low risk (in this case, low genetic risk and low environmental risk) leads to positive outcomes since most research points to the strong relationship between ELA and the development of psychiatric disorders often in a dose-dependent manner, with more severe stressors leading to worse outcomes (Heim et al., 2008; Maglione et al., 2018).

For the second comparison (class 1 vs. class 3), there seems to be a trade-off whereby the presence of one risk factor (e.g., either genetic susceptibility or exposure to high levels of MDS) was associated with a higher probability of belonging to the resilient class. It is as though a little bit of risk can be beneficial, a concept supported by the stress inoculation theory (Crofton et al., 2015). Because when no risk factors were present, children were more likely to belong to the "flat affect" class. It was also equally probable to belong to the "flat affect" class when two risk factors were present (e.g., genetic susceptibility combined with exposure to high levels of MDS). Having a dampened stress response may not only be the result of effective emotional regulation skills and coping strategies, but it is also a common phenomenon among those who are exposed to chronic stress (Danese & McEwen, 2012; Voellmin et al., 2015). Prolonged activation of the stress system

may lead to allostatic load whereby the HPA axis becomes saturated and compensates by down-regulating the central negative feedback mechanism responsible for eliciting a stress response (Danese & McEwen, 2012). Therefore, exhibiting flat affect in the face of stress may be adaptive for those who present with no factors as well as for those who are particularly susceptible. Otherwise, our findings do not support the PPPP hypothesis. In the first comparison (class 2 vs. class 1), exposure to prenatal MDS did not result in increased sensitivity on the CPT among genetically susceptible children. In the second comparison, although genetically susceptible children appeared more sensitive to their environment, this was with regards to *postnatal* MDS exposure. However, since this comparison was underpowered, it is possible that certain effects were not detected.

In terms of future directions, the CPT holds promise for being a robust and comprehensive measure of resilience in children. We successfully applied DB-DOS coding to a range of positive and negative behaviors elicited by the CPT and this was evidenced by very acceptable interrater reliability. The fact that patterns of vantage sensitivity were detected suggests that the DB-DOS coding structure was generalizable enough to be able to capture individual variability in positive outcomes. Furthermore, we are the second study to include the competence scale of the DB-DOS, demonstrating that the DB-DOS can successfully apply to contexts outside the measurement of disruptive behavior.

Given that we used total scores across two domains: problems in anger modulation and competence, we neglected to take a more in-depth look at the individual coding categories within each of the domains. For example, we could glean additional insight about how children respond to a challenge using individual scores corresponding to: intensity and predominance of negative affect, ease of elicitation and rapid escalation of negative affect, difficulty recovering from failure,

coping with frustration poorly, intensity and predominance of positive affect, socially directed positive affect, social engagement and assertiveness. Information about some of these more specific external processes could then be incorporated into early interventions as a way to teach children emotional regulation strategies for managing stress.

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Supplementary Table 1:

Logistic Regression Analyses – Probability of Belonging to Class 2 (vs. Class 1)

		Non-Imputed	Imputed
Emotional Regulation Prenatal MDS (AIC: 180.74)	**Intercept**	β = -3.15487, *p* = 0.77344	β = 2.24241, *p* = 0.74372
	Genetic	β = -1.20462, *p* = 0.00292 **	β = -0.82620, *p* = 0.00208 **
	Environment	β = 0.05554, *p* = 0.81614	β = -0.09248, *p* = 0.56638
	Postnatal MDS	β = 0.00000, *p* = 0.99809	β = -0.00052, *p* = 0.31951
	Sex_male	β = 0.00635, *p* = 0.98762	β = -0.09243, *p* = 0.73580
	Maternal Education	β = -0.11179, *p* = 0.78610	β = -0.31448, *p* = 0.27492
	Child Age	β = 0.71381, *p* = 0.74203	β = -0.27455, *p* = 0.83943
	PC1	β = 0.56474, *p* = 0.89510	β = -1.45579, *p* = 0.55521
	PC2	β = 3.67826, *p* = 0.53790	β = 2.03244, *p* = 0.38071
	PC3	β = 12.40841, *p* = 0.03018 * **x**	β = 8.25651, *p* = 0.00310 **
	G×E	β = 1.09494, *p* = 0.00288 **	β = 0.58884, *p* = 0.01440 *
	GPC PGS	β = 0.4296, *p* = 0.00424 **	β = 0.43664, *p* = 0.00437 **
	SUSC PGS	β = 0.2795, *p* = 0.02955 * **x**	β = 0.22698, *p* = 0.08986 .
	MDD PGS	β = -0.2909, *p* = 0.02235 *	β = -0.33638, *p* = 0.00969 **
Emotional Regulation Postnatal MDS (AIC: 185.93)	**Intercept**	β = -3.00766, *p* = 0.7815	β = 2.28036, *p* = 0.73979
	Genetic	β = -1.26359, *p* = 0.1104	β = -1.28647, *p* = 0.01043 *
	Environment	β = 0.00022, *p* = 0.7765	β = -0.00051, *p* = 0.32784
	Prenatal MDS	β = -0.10964, *p* = 0.6177	β = -0.08780, *p* = 0.58286
	Sex_male	β = 0.06040, *p* = 0.8782	β = -0.08984, *p* = 0.74139
	Maternal Education	β = 0.03208, *p* = 0.9370	β = -0.26382, *p* = 0.35449
	Child Age	β = 0.63767, *p* = 0.7666	β = -0.28729, *p* = 0.83227
	PC1	β = 2.45831, *p* = 0.6214	β = -0.90475, *p* = 0.71652
	PC2	β = 4.50494, *p* = 0.4136	β = 0.72564, *p* = 0.75779
	PC3	β = 11.64528, *p* = 0.0396 * **x**	β = 7.82709, *p* = 0.00490 **
	G×E	β = -0.00029, *p* = 0.8449	β = 0.00075, *p* = 0.36573
Emotional Regulation Cumulative MDS (AIC: 184.15)	**Intercept**	β = -2.10423, *p* = 0.8443	β = 2.43789, *p* = 0.72191
	Genetic	β = -1.35249, *p* = 0.0904 .	β = -1.30128, *p* = 0.00915 **
	Environment	β = 0.00002, *p* = 0.9778	β = -0.00061, *p* = 0.14453
	Sex_male	β = 0.07296, *p* = 0.8529	β = -0.09748, *p* = 0.72014
	Maternal Education	β = 0.01441, *p* = 0.9715	β = -0.27199, *p* = 0.33960
	Child Age	β = 0.47872, *p* = 0.8218	β = -0.30232, *p* = 0.82328
	PC1	β = 2.47931, *p* = 0.6159	β = -0.97374, *p* = 0.69635
	PC2	β = 3.97722, *p* = 0.4696	β = 0.81406, *p* = 0.72753
	PC3	β = 11.64617, *p* = 0.0381 * **x**	β = 7.88685, *p* = 0.00452 **
	G×E	β = -0.00011, *p* = 0.9369	β = 0.00074, *p* = 0.34046

Notes: MDS = maternal depressive symptoms; PC = principal component; G×E = Gene-by-Environment interaction; GPC PGS = polygenic score corresponding to global psychopathology in children; SUSC PGS = polygenic score corresponding to environmental sensitivity; MDD PGS = polygenic score corresponding to major depressive disorder; **x** = did not survive correction for multiple testing.

Supplementary Table 2:

Logistic Regression Analyses – Probability of Belonging to Class 2 (vs. Class 3)

		Non-Imputed	Imputed
Emotional Regulation Prenatal MDS (AIC: 203.27)	**Intercept**	β = -2.33452, *p* = 0.8336	β = -1.52861, *p* = 0.81322
	Genetic	β = -0.36901, *p* = 0.3678	β = -0.68688, *p* = 0.00677 **
	Environment	β = -0.27394, *p* = 0.3178	β = 0.15962, *p* = 0.31113
	Postnatal MDS	β = 0.00055, *p* = 0.4773	β = 0.00013, *p* = 0.80189
	Sex_male	β = 0.64887, *p* = 0.1305	β = -0.02021, *p* = 0.93798
	Maternal Education	β = -0.27447, *p* = 0.5380	β = -0.12630, *p* = 0.64021
	Child Age	β = 0.42694, *p* = 0.8460	β = 0.30351, *p* = 0.81231
	PC1	β = 2.28023, *p* = 0.5243	β = -1.19438, *p* = 0.62892
	PC2	β = -2.63126, *p* = 0.3659	β = 0.05265, *p* = 0.98129
	PC3	β = 10.31303, *p* = 0.0245 *	β = 1.06651, *p* = 0.61664
	G×E	β = 0.98249, *p* = 0.0185 *	β = 0.12231, *p* = 0.61473
	GPC PGS	β = 0.4059, *p* = 0.0628 .	β = 0.44923, *p* = 0.02078 *
	SUSC PGS	β = 0.2555, *p* = 0.1317	β = 0.32464, *p* = 0.08296 .
	MDD PGS	β = -0.3386, *p* = 0.1019	β = -0.22613, *p* = 0.21955
Emotional Regulation Postnatal MDS (AIC: 193.32)	**Intercept**	β = -0.72474, *p* = 0.93808	β = -3.13296, *p* = 0.63434
	Genetic	β = 2.30783, *p* = 0.00180 **	β = 1.13625, *p* = 0.00611 **
	Environment	β = 0.00040, *p* = 0.61706	β = 0.00035, *p* = 0.51289
	Prenatal MDS	β = 0.25840, *p* = 0.28456	β = -0.14958, *p* = 0.34858
	Sex_male	β = -0.58668, *p* = 0.12408	β = -0.05157, *p* = 0.84303
	Maternal Education	β = -0.14817, *p* = 0.71314	β = 0.02488, *p* = 0.92703
	Child Age	β = 0.21942, *p* = 0.90522	β = 0.58715, *p* = 0.65175
	PC1	β = -7.07979, *p* = 0.06079 .	β = -3.89657, *p* = 0.08052 .
	PC2	β = 10.37960, *p* = 0.04682 * **x**	β = 1.04735, *p* = 0.62415
	PC3	β = -3.17225, *p* = 0.30126	β = 0.10595, *p* = 0.96028
	G×E	β = -0.00506, *p* = 0.00096 ***	β = -0.00231, *p* = 0.00775 **
	GPC PGS	β = 0.79247, *p* = 0.00109 **	β = 0.50053, *p* = 0.02233 *
	SUSC PGS	β = -0.07991, *p* = 0.58880	β = -0.23930, *p* = 0.22882
	MDD PGS	β = -0.12762, *p* = 0.41408	β = 0.26017, *p* = 0.18988
Emotional Regulation Cumulative MDS (AIC: 194.85)	**Intercept**	β = -2.06621, *p* = 0.82285	β = -3.58486, *p* = 0.58428
	Genetic	β = 2.08179, *p* = 0.00259 **	β = 1.11235, *p* = 0.00646 **
	Environment	β = 0.00065, *p* = 0.30577	β = 0.00055, *p* = 0.19218
	Sex_male	β = -0.57545, *p* = 0.12782	β = -0.04037, *p* = 0.87628
	Maternal Education	β = -0.12766, *p* = 0.74889	β = 0.02550, *p* = 0.92506
	Child Age	β = 0.45077, *p* = 0.80505	β = 0.65134, *p* = 0.61483
	PC1	β = -6.75327, *p* = 0.07671 .	β = -3.77728, *p* = 0.08889
	PC2	β = 8.83943, *p* = 0.07007 .	β = 0.92938, *p* = 0.66317
	PC3	β = -2.78047, *p* = 0.35727	β = 0.11259, *p* = 0.95773
	G×E	β = -0.00420, *p* = 0.00117 **	β = -0.00200, *p* = 0.01028 *
	GPC PGS	β = 0.77126, *p* = 0.0019 **	β = 0.45680, *p* = 0.04182 * **x**
	SUSC PGS	β = -0.09346, *p* = 0.5638	β = -0.26042, *p* = 0.20605
	MDD PGS	β = -0.13528, *p* = 0.4069	β = 0.28278, *p* = 0.17029

Notes: MDS = maternal depressive symptoms; PC = principal component; G×E = Gene-by-Environment interaction; GPC PGS = polygenic score corresponding to global psychopathology in children; SUSC PGS = polygenic score corresponding to environmental sensitivity; MDD PGS = polygenic score corresponding to major depressive disorder; **x** = did not survive correction for multiple testing.

Table 3: Characteristics of the Sample

Demographic Variable	**N (%)**
Partnered (married/common-law)	544 (94.4)
Gender of child (male)	338 (54.2)
Ethnicity (White/European)	192 (83.5)
Site (Montreal)	433 (59.2)
Maternal education (university or higher)	293 (48.9)

GENERAL DISCUSSION

The work presented in this dissertation represents a significant contribution to the field of resiliency research as well as contemporary models of environmental sensitivity with our findings lending support to the differential susceptibility, vantage sensitivity and in some cases, the PPPP hypotheses. Patterns of environmental sensitivity cannot be detected if one is only focused on measuring negative factors. These studies explore the developmental factors that shape how one responds to stress. Many developmental theories suggest that stress exposure tends to have more of a negative impact on individuals who are genetically susceptible, with psychopathology resulting from stress activating biological risk (Daskalakis et al., 2013; McEwen, 1998). Therefore, an individual's history of adversity should be interpreted in the context of their genetic predisposition. It is further recommended to combine measures of genetic susceptibility with other measures of risk to improve the accuracy of risk assessments because PGSs still only explain a modest amount of variance with respect to various psychiatric disorders (e.g., 2% to 11%) (Murray et al., 2021).

To our knowledge, this is the fourth study to use the susceptibility PGS (Assary et al., 2021; Davidson et al., 2021; Pluess et al., 2022) initially developed by Keers and colleagues (Keers et al., 2016). Variants associated with environmental sensitivity were used to construct this PGS whereby environmental sensitivity was based on within-pair variability in emotional problems among > 1000 monozygotic twins. The original study found that although environmentally sensitive children were more likely to develop emotional problems in the context of negative parenting, they also benefitted more from treatment (Keers et al., 2016). This represents the first study to find evidence for the differential susceptibility hypothesis using a genome-wide approach.

Given that our best models and most significant findings corresponded to the analyses featuring prenatal MDS as the predictor, we believe that there is something about the prenatal period that is driving our effects. In fact, our findings in Study 2 appear to be consistent with PPPP, a theory based on the premise that prior risk (in this case, exposure to prenatal MDS) renders the fetus particularly sensitive to its postnatal environment (Hartman & Belsky, 2018a). From an evolutionary point of view and given that the environment is unpredictable, natural selection should favor offspring that varies in their susceptibility (Belsky & Pluess, 2009). Evidence of PPPP is likely masked by the focus on the negative impacts of prenatal stress on child outcomes. Otherwise, there are two considerations to keep in mind when interpreting the effects of prenatal MDS in our sample: 1) MDS were highest prenatally, a finding that is consistent with other longitudinal studies (Choi et al., 2022; Fredriksen et al., 2016; Verreault et al., 2014). The fact that MDS were higher during pregnancy could explain why prenatal MDS were exerting a stronger effect on outcomes; 2) prenatal MDS were based on raw scores while postnatal and cumulative MDS were based on AUC estimates. This difference in measurement could have introduced some variability in our findings.

General Limitations

There are some important limitations to consider, with a small sample size being the most obvious. Although we imputed some missing data, it is likely that with a larger sample size, our findings could be interpreted with more certainty, particularly in relation to tests of environmental sensitivity (with modest sample sizes, the accuracy of these tests are lower). Secondly, although our findings support the differential susceptibility and vantage sensitivity hypotheses, these findings are not based on a valid positive environmental measure, but rather the absence of MDS. We have been critical of the same approach applied to resiliency research, whereby a lack of

psychopathology has been systematically evaluated in place of actual resilience measures. However, in both cases, defaulting to the absence of symptoms reflects the fact that there is a lack of available maternal wellness and positive outcome measures. This is likely because the field has focused almost exclusively on adverse environments and negative outcomes. Some considerations for measuring nurturing and supportive environments include: maternal warmth and responsiveness, positive parenting and protective caregiving, as well as access to supportive resources (Boyce et al., 2021; Ungar, 2011).

Another general limitation is that our analyses featured variable PGS thresholds which may lead to inconsistent results. Before proceeding with our main analyses, model fit statistics were conducted to guide PGS threshold selection (Neumann, 2022). However, because research in the field of polygenic scores is still relatively young, it is likely that more robust methods of PGS threshold selection will emerge in the near future. On a similar note, PGSs do not capture rare SNPs, copy number variants or SNPs located in non-coding regions even though there is evidence suggesting that such variants can carry some regulatory functions (Chen & Tian, 2016; Mistry et al., 2018; Niitsu et al., 2019). Finally, even though the CPT is a dynamic, non-static measure, it is still a brief, lab-based measure that does not fully capture all aspects of resilience and it is very context-specific. On the other hand, outcomes are often selected for their generalizability, but are too ambiguous to apply across contexts or cultures. Despite the fact that the CPT taps into a very specific type of stress, its ecological validity makes it a reliable task that can signal to caregivers when an intervention may be required. Some children will generalize their failure to future tasks (Smiley et al., 2010); therefore, it can be crucial to correct negative self-perceptions and attribution styles when children are struggling with failure.

Given that the focus of the current research was measuring G×E interactions in the prediction of resilience, the use of a PGS that matched the phenotype in question would have been ideal. However, the two polygenic resilience scores known to date are based on genetic variation associated with resistance to disease, namely schizophrenia and Parkinson's (Hess et al., 2021; Liu et al., 2022). Again, the measured phenotype is not resilience, but rather the absence of disease symptoms. Therefore, the challenge of relying on proxy genetic measures of resilience remains. Of the available psychiatric PGSs out there, the SUSC PRS (Keers et al., 2016) remains the most applicable when it comes to understanding the genetic etiology underlying resilience and differential susceptibility. It is recommended that this PGS be applied to different populations and using a larger sample size to validate it as an acceptable genetic measure of environmental sensitivity.

Implications & Future Directions

In terms of providing a cohesive and ecologically valid framework for studying resilient functioning, it would be worthwhile to explore how cognitive appraisals could be combined with the behaviors and emotions elicited by the CPT. Some questions to consider are: what is the likelihood that an emotionally dysregulated child (class 1) will report hopefulness or motivation in the face of a challenge? Are children who demonstrate overall resilience (as measured by endorsing positive self-appraisal, hopefulness, and motivation) more likely to exhibit positive behaviors (be in class 2) as well? Is social engagement associated with a more positive outlook when faced with a challenge or do positive affirmations predict a higher likelihood of overcoming failure? Are certain coping strategies more effective than others? To examine whether there is overlap between class membership on the cognitive appraisal component of the CPT and class membership on the observational/behavioral component of the CPT, odds ratios can be conducted

to determine the probability of overlap from one class to the other. Otherwise, we can consider creating a latent factor of resilience which would combine various cognitive, behavioral and affective elements of resilience. The latent factor could even include individual puzzle scores as well as scores corresponding to the 6 irritability items and the 5 competence items. When taken together, the CPT has the capacity to tap into specific features of resilience, such as having an adaptive stress response, rapid stress recovery, high coping self-efficacy, strong cognitive reappraisal, emotional regulation and self-confidence (Southwick & Charney, 2012). Therefore, the resulting factor could be a very comprehensive measure of resilience that could potentially be used in other populations.

This research highlights that when studying only one end of the spectrum, a whole range of contexts, behaviors and outcomes are overlooked and the potential is lost for discovering new avenues of treatment and intervention. For example, the information gained from studying adaptive behaviors could provide insight into the various mechanisms and protective factors involved in the regulation of stress which in turn, could guide therapeutic approaches for young children. From a neurobiological point of view, the neural mechanisms involved in emotional regulation are strengthened during critical periods of development, and these periods will ultimately shape how a child responds to stress (Boyce et al., 2021). Therefore, early interventions could potentially prevent mental health issues from worsening while bringing one's strengths to the surface.

To promote adaptive functioning in the face of stress, it would be worthwhile to teach children how to sit with discomfort and how to turn failures into opportunities, rather than pushing obstacles and negative feelings away. This idea is consistent with the stress inoculation theory which refers to the process of developing resistance to future stressful events by being exposed to

mildly stressful experiences early in life (Agnafors et al., 2016; Crofton et al., 2015; Cui et al., 2020; Daskalakis et al., 2013; Elmore et al., 2020). The concept underlying these theories are related to how vaccines work in that exposure to a low and non-harmful dose of a virus can protect one from future disease due to developed immunity (Lewitus & Schwartz, 2009; Rutter, 2006). It is important to note that inoculation stress is not solely based on being exposed to stress early in life, but rather having learned coping strategies as well as positive and adaptive responses to mild stressors. In a context of increased helicopter or bulldozer parenting where parents tend to overprotect their children by removing obstacles from their life and rescuing them from challenges, the child is deprived of the opportunity to learn how to manage their emotions in response to difficult circumstances (Sharman, 2014). As a result, these children become more vulnerable to mental health problems in adulthood as they have not learned how to cope with stress and may be more developmentally delayed when regulating their emotions (Schwartz, 2018; Vigdal & Brønnick, 2022). In recent years, colleges and universities have seen an unprecedented surge in visits to campus counseling centers as more and more students are struggling with mental health issues. Facing real life for the first time (according to campus counsellors), many students lack the ability to emotionally regulate themselves and often go into crisis-mode when they encounter their first significant disappointment or failure (Estroff Marano, 2015). Add the fact that children of today are growing up alongside the internet, it has become habitual to use social media outlets as a way to distract oneself and escape or avoid dealing with negative emotions (Brailovskaia & Margraf, 2020; Lin et al., 2017). However, in order to build resilience, it is necessary that children experience small adversities and minor challenges in a gradual way (King et al., 2020).

Regardless of the type of parenting a child is subjected to, it is necessary that all children develop emotional regulation and coping skills early on so that they are prepared to face the

challenges that life will throw at them. Whether these skills are taught at home, at school, in the streets or within a therapeutic setting, there are clear long-term benefits that can apply across contexts. Incorporating versions of the CPT or other challenging games can be a way to introduce stress in a controlled manner, while allowing the caregiver to support the child in managing their emotions. If applicable, it can even be useful to coach children on how to shift their thinking around how they perceive stress, something that has already proven possible and effective in modifying one's stress response (Crum et al., 2013). At the end of the day, it is our adaptive stress responses which have enabled all living organisms to survive; without it, we would not be able to meet the unpredictable demands that life throws our way.

General Conclusion & Summary

The findings from this dissertation hold promise for an ecologically-valid measure of resilience in young children that can be used in various settings. Detecting resilient outcomes in the context of genetic susceptibility and exposure to varying levels of MDS provides a better understanding of the developmental origins of resilience. More specifically, our findings lend support to contemporary models of environmental sensitivity, namely differential susceptibility, vantage sensitivity and in some cases, the PPPP theory. Building on this evidence, we can work towards an approach that views certain individuals as more sensitive, rather than defaulting to a pathological lens. From there, we can imagine treatment models that cultivate enriching environments and that recruit supportive resources, particularly in the context of risk. Alongside this approach, it could be useful to teach adaptive strategies that promote flexibility, because recovery is an important feature of the resilient process. It implies not only a capacity to withstand challenging circumstances, but also an ability to adapt and potentially grow from the experience (Masten, 2007). In terms of addressing the "*nature*" side of things, the science may not be advanced enough to introduce standardized genetic testing, but if we had to identify genetically susceptible individuals, the SUSC PGS is proving to be a promising candidate. We are the fourth study to use this PGS to date and the results have been consistent thus far (Assary et al., 2021; Davidson et al., 2021; Keers et al., 2016; Pluess et al., 2022).

In summary, it is my hope that this research will contribute to a body of evidence that will convince policy makers to recognize the importance of investing in accessible, sustainable, and supportive resources throughout the community, education, healthcare and public sectors. By supporting families and nurturing supportive environments in contexts where risk factors are more

prevalent, we will not only build resilient families, but we will build resilient communities and ultimately, a more resilient society.

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