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Regular Article

Observer-rated environmental sensitivity and its characterization at behavioral, genetic, and physiological levels

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Abstract

This study investigated the psychometric properties of the Highly Sensitive Child-Rating System (HSC-RS), the existence of sensitivity groups, and the characterization of sensitivity at behavioral, genetic, and physiological levels in 541 preschoolers ($M(SD)_{age} = 3.56(0.27)$; 45%male; 87%Caucasian). Temperament, genetic, cortisol, and electroencephalography asymmetry data were collected in subsamples ($n = 94$-476). Results showed a reliable observational measure of sensitivity. Confirmatory factor and latent class analysis supported a one-factor solution and three sensitivity groups, that are a low (23.3%), medium (54.2%), and a high (22.5%) sensitivity group. Hierarchical regression analyses showed moderate associations between HSC-RS and observed temperament traits (i.e., behavioral level). In addition, a small negative association between HSC-RS and a genome-wide association study polygenic risk score (GWAS PGS) for Attention Deficit Hyperactivity Disorder was found. No relations with candidate genes, other GWAS PGS phenotypes, and physiological measures were found. Implications of our findings and possible explanations for a lack of these associations are discussed.

Keywords: cortisol; differential susceptibility; electroencephalography asymmetry; environmental sensitivity; observation measure; polygenic score; preschoolers; temperament

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Children differ in their environmental sensitivity (ES), defined as the degree to which they are affected by their experiences. Individual differences in ES have a neurobiological basis, are partially heritable (Assary et al., 2021, 2024), and can be observed in many species (Boyce & Ellis, 2005). Importantly, highly sensitive individuals are more responsive to both negative and positive exposures (Lionetti, Aron, et al., 2019; Slagt et al., 2018) in terms of both maladaptation and adaptation. This for-better and for-worse effect is captured by different theories including differential susceptibility (Belsky & Pluess, 2009), biological sensitivity to context (Boyce & Ellis 2005), and sensory processing sensitivity (Aron & Aron, 1997), recently integrated in the broader environmental sensitivity meta-framework (Pluess, 2015).

In the present study we will adopt an observational measure, the Highly Sensitive Child-Rating System (HSC-RS; Lionetti, Aron, et al., 2019), for the assessment and characterization of individual differences in sensitivity in young children. Specifically, we will first preliminarily test whether we can replicate the psychometric properties of the HSC-RS. Then, we will test whether we can distinguish different sensitivity groups in preschoolers aligning with previous empirical data on older samples showing that around 20 to 30% of the population is highly sensitive, around the same percentage is low sensitive, and the remaining has medium sensitivity levels (Lionetti et al., 2018; Pluess et al., 2018, 2020). Afterwards, in line with the main aim of this study, we will explore whether we can characterize observer-rated ES at multiple levels: behavioral (i.e., observed temperament traits other than ES), genetic (i.e. a candidate gene and GWAS based polygenic score), and physiological (i.e., cortisol and electroencephalography (EEG) asymmetry).

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Individual differences in environmental sensitivity

As reflected in the trait of Sensory Processing Sensitivity (SPS), individuals scoring high on ES process environmental information more deeply, pause and check before they act, are more aware of

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subtle information, are easily overstimulated, and emotionally and physiologically more reactive (Aron et al., 2012; Aron & Aron, 1997). ES has been conceptualized as a continuous and normally distributed trait (Pluess et al., 2018; Slagt et al., 2018; X. Zhang et al., 2023), but the investigation of sensitivity scores also showed that around 20 to 30% of individuals falls into a highly sensitive group (referred to as *orchids*), 40 to 50% into a medium sensitive group (referred to as *tulips*), and 20-30% into a low sensitive group (referred to as *dandelions*) that differ quantitatively from each other (Lionetti et al., 2018; Pluess et al., 2018, 2023). Individuals scoring in the high group are more influenced by the environment in a for-better and for-worse manner (Belsky et al., 2007), so that they benefit more from positive exposures (e.g., Slagt et al., 2018) as intervention programs (Nocentini et al., 2018; Pluess & Boniwell, 2015) and suffer more than others when exposed to negative environments (e.g., Slagt et al., 2018). Those scoring in the low group are more resilient, or less plastic and susceptible to environmental exposures, while the medium sensitive group show some sensitivity, though not so high as those scoring high on this trait.

Heightened ES likely originates from an increased neurobiological sensitivity, the heightened reactivity of specific neural systems (e.g., amygdala, prefrontal cortex) that are important for the perception and evaluation of environmental stimuli (Pluess, 2015). Evidence from neuroimaging studies showed higher activation and connectivity of brain areas related to depth of processing, physiological homeostasis, and self-regulation in sensitive individuals (Acevedo et al., 2014, 2017). Based on theoretical reasoning and current available empirical knowledge, neurobiological sensitivity has a genetic basis, is shaped by the environment, and is reflected in a heightened sensitivity at the physiological (i.e., heightened stress reactivity) and behavioral levels (i.e., sensory processing sensitivity (SPS); Aron et al., 2012; Greven et al., 2019; Pluess, 2015). In the last decade, several markers of heightened sensitivity at these multiple levels of analysis have been indeed proposed and identified (for a complete overview, see Belsky & Pluess, 2009, 2013). However, findings are not always consistent, as we will review below, and no study so far has investigated different markers of sensitivity within the same sample of individuals. Hence, it is largely unknown to which degree different etiologies of sensitivity overlap, such as whether sensitivity at an observational level would correspond to an increased sensitivity at a neurobiological level and vice-versa. Moreover, most studies on the genetic and physiological etiologies of ES were conducted in adults. Identifying these aspects in young children might be especially meaningful for understanding the early etiology of ES, as young children's sensitivities have been exposed to the environment for a shorter amount of time, developmentally speaking, compared to adults. Identifying its neurobiological and behavioral related correlates may deepen our understanding of both its developmental aspects and underlying mechanisms. The early developmental measure we have of sensitivity allows assessing the trait in children as young as three years old.

Applying a multilevel-analysis approach that consider genetic, behavioral, and physiological levels will allow us to examine whether previously studied markers of sensitivity are related to the same underlying construct of ES. Higher sensitivity at genetic, behavioral, and physiological levels might have an additive effect, potentially increasing the risk of developing psychological problems in more sensitive children (Cicchetti & Dawson, 2002), or enhancing their benefits from positive exposures. Identifying the objective markers of ES, might be crucial for developing targeted actions to support all children, depending on their levels of sensitivity. Moreover, examining the etiology underlying ES might enhance our understanding of how individual differences in ES are related to several mental health outcomes identified in previous studies. These outcomes include symptoms of psychopathology such as depressive symptoms and anxiety (Assary et al., 2024; Liss et al., 2005), sensory sensitivities in Autism Spectrum Disorder (ASD; Assary et al., 2024; Liss et al., 2008), Attention Deficit Hyperactivity Disorder (ADHD; Panagiotidi et al., 2020), and personality traits like neuroticism (Aron & Aron, 1997; Lionetti, Pastore, et al., 2019) and introversion (Aron & Aron, 1997). Additionally, ES is found to be related to school and work-related outcomes including cognitive performance (Bridges & Schendan, 2019), stress related symptoms, burnout in adults (Benham, 2006), and school burnout in adolescents (Weyn, Van Leeuwen, Pluess, Verschueren, et al., 2022).

The measurement of ES has been mostly restricted to self-report and parent-repot questionnaires (Aron & Aron, 1997; Boterberg & Warreyn, 2016; De Gucht et al., 2022; Pluess et al., 2020, 2023; Weyn et al., 2021) until more recently, when observational rating systems emerged for its assessment (Davies et al., 2021; Lionetti, Aron, et al., 2019). In the present study we used the HSC-RS, a measure designed to assess ES in 3-year-olds by operationalizing ES at the behavioral level, focusing on elevated sensory sensitivities and deeper processing of environmental information. The HSC-RS has been demonstrated to be a psychometrically robust tool with strong construct validity (Lionetti, Aron, et al., 2019). Observer-rated measures of ES are advancing the field with trained, independent observers rating the behavior of many children in the same standardized situations, which should facilitate a more objective identification of individual differences in ES. Moreover, the HSC-RS enables capturing different behaviors related to ES, such as pausing to check in new situations, taking time in decision-making, exploring new environments, and reactions to positive stimuli, in a controlled-way. These aspects of ES are less thoroughly captured in self- and parent report questionnaires measuring individual differences in ES (Greven et al., 2019).

Markers of individual differences in environmental sensitivity at the behavioral level

At the behavioral level, established temperament traits have been found to indicate differential susceptibility to environmental influences. In infants and toddlers, negative emotionality and difficult temperament have been most often studied as sensitivity or plasticity factors (Belsky & Pluess, 2013; Belsky, 2005). Both traits are characterized by negative affectivity, influenced by environmental (e.g., parenting quality) and genetic factors, and found to predict several important developmental outcomes (Belsky & Pluess, 2013; Belsky, 2005). However, when it comes to older children, from around toddlerhood (from the age of 1 year old) and onwards, meta-analytical evidence suggests that negative affect and difficult temperament reflect risk rather than sensitivity to both negative and positive environmental influences (Slagt et al., 2018). It may be that highly sensitive children showing more difficult temperament and negative affect in the first months of life gradually learn to better regulate their emotional reactivity, thanks to their higher sensitivity to the environment, when experiencing positive and nurturing family contexts. In the present study we will examine how observed temperament traits, including sociability, dysphoria, fear/inhibition, exuberance, and constraint, validated in

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preschoolers and capturing broader aspects of temperament than only negative affect (Dyson et al., 2012), are associated with observer-rated sensitivity. In the model proposed by Dyson and colleagues (2012), sociability encompasses surgent interpersonal traits (e.g., initiative and dominance), dysphoria involves anger and sadness, fear/inhibition relates to negative emotions associated with feelings of punishment and potential loss, exuberance pertains reward-seeking behaviors, and constraint refers to impulse control. To characterize individual differences in ES at the behavioral level, we aim to examine the associations between these coded temperament traits and our observation measure of ES.

Markers of individual differences in environmental sensitivity at the genetic level

Aron and Aron (1997) hypothesized a genetic basis for SPS, for which evidence was found in a large twin study (Assary et al., 2021) reporting that 47% of the variance in ES was due to heritable factors and the other 53% to non-shared environmental influences, a result coherent with empirical findings accumulated across the last 20 years according to which some genetic variants have been associated with an increased sensitivity to the environment. For example, the short allele of the serotonin transporter gene (*5-HTTLPR*) seems to moderate environmental influences in a for-better-and-for-worse way (Belsky et al., 2009). Several studies showed that individuals carrying the short allele have more negative outcomes when they encounter multiple stressors, but in the absence of these stressors or in positive environments, they seem to function better than those carrying long alleles (for an overview, see van IJzendoorn et al., 2012). Similarly, the *DRD4* 7-repeat variant (e.g., Bakermans-Kranenburg & van Ijzendoorn, 2011), the *DRD2* A1 variant (e.g., Elovainio et al., 2007), the *DAT* 9-repeat variant (e.g., Lahey et al., 2011), the *COMT* val/val variant (e.g., Hygen et al., 2015) of dopamine related genes, and the Val66Met polymorphism of the brain-derived neurotrophic factor (*BDNF*) gene (Gunnar et al., 2012; Zhang et al., 2016) have been reported as markers of increased ES at the genetic level. However, candidate gene studies have been criticized because of small samples and often failing replication (Duncan & Keller, 2011). The use of cumulative candidate gene scores addresses some of these limitations (Belsky & Pluess, 2009; Keers & Pluess, 2017; Sonuga-Barke et al., 2009). A more recent approach is the use of Polygenic Scores (PGS) derived from large Genome-Wide Association Studies (GWAS). This approach considers thousands of gene variants across the whole genome by aggregating them into a single score for a specific phenotype (e.g., attention deficit disorder [ADHD]). In the present study, we will examine whether observer-rated ES is associated with a cumulative polygenic score consisting of previously identified genetic markers of sensitivity (Belsky & Pluess, 2009, 2013). To explore the genetic etiology of observer-rated ES more deeply, we will also employ a more robust, exploratory approach, by examining the associations between observer-rated ES and GWAS based PGSs underlying phenotypes (at the behavioral level; see above) that are often found to be positively and moderately associated with ES. Given that PGS can predict their phenotype, related phenotypes, intermediate traits, and environmental exposures (Pingault et al., 2022), examining the relationship between observer-rated ES and GWAS PGS can clarify how genetic factors contribute to behavioral ES (Bogdan et al., 2018). A recent genetic twin study found that the genetics underlying ES explained 2 to 12% of individual differences in anxiety, depressive symptoms, autistic symptoms, and subjective wellbeing, possibly driven by shared genetic and environmental influences (Assary et al., 2024). Yet these results were based on heritability and not on GWAS based data. Both a cumulative polygenic score and GWAS based PGS are included in the present study to examine markers of individual differences ES at the genetic level.

Markers of individual differences in environmental sensitivity at the physiological level

At the physiological level, the biological stress response system is considered a key candidate marker for individual differences in ES (Boyce & Ellis, 2005). Previous studies found that individuals who responded more strongly to a lab-induced stressor in terms of heightened cortisol response, showed lower rates of prosocial behavior, school engagement and academic competence when growing-up in the presence of adversity, as trauma, but also benefitted more showing better prosocial behaviors in the absence of adversity (Obradović et al., 2010). Most evidence for individual differences in ES as a function of physiological markers focused on cortisol reactivity (for an overview, see Belsky & Pluess, 2009; Greven et al., 2019). Some studies also found similar evidence for basal cortisol levels (e.g., Dougherty et al., 2011; Pascual-Sagastizabal et al., 2021). For example, Pascual-Sagastizabal et al. (2021), found that lower paternal authoritative parenting predicted boys' aggression only when boys had high basal cortisol levels. Yet these findings were not found for girls and in supportive parenting environments. A meta-analysis investigating sensitivity to treatment in anxiety patients found evidence for cortisol reactivity, but not basal cortisol, as a sensitivity marker (Fischer & Cleare, 2017). Thus, especially for basal cortisol, current research findings are inconsistent. In addition to theoretical suggestions (Boyce & Ellis, 2005), no empirical study examined the direct relation between ES at the phenotypic level and basal cortisol, and only one empirical study (Weyn, Van Leeuwen, Pluess, Goossens, et al., 2022) examined the relation with cortisol reactivity, but did not find any association. Therefore, more empirical studies examining the direct associations between the phenotypic manifestation of ES and basal cortisol and cortisol reactivity are needed.

Frontal EEG asymmetry (i.e., left frontal asymmetry [LFA]), or alpha activation in frontal regions, is another proposed marker of ES at the physiological level (Boyce, 2016) and has been associated with temperamental differences in terms of emotional experiences and motivational behavior. LFA has been associated with positive emotions and approach behavior, whereas right frontal asymmetry (RFA) has been associated with negative emotions, inhibition, and avoidance behavior (Boyce, 2016; Fox & Davidson, 1984; Gander & Buchheim, 2015). Previous studies indicate that individuals with LFA are more susceptible to the quality of the environment in a for-better (e.g., prosocial behaviors) and for-worse (e.g., impulsive behavior) manner, whereas RFA is mainly associated with a sensitivity to negative environments (e.g., withdrawal behavior) (Boyce, 2016; Fortier et al., 2014; Harmon-Jones et al., 2010; Mulligan et al., 2022; Peltola et al., 2014). In a meta-analysis, Peltola et al. (2014) concluded that frontal asymmetry is a moderator of the quality on the environment or child characteristics rather than directly associated with child outcomes. This has been confirmed by subsequent empirical studies (Fortier et al., 2014; Lopez-Duran et al., 2012; Mulligan et al., 2022). In addition to frontal asymmetry, parietal EEG asymmetry has been associated

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with temperamental differences in terms of emotional arousal (Heller et al., 1998) and the processing of emotional information (Heller, 1990; Shankman et al., 2011). Thus, both measures of EEG asymmetry have been examined as a moderator of associations between environmental factors and outcomes. However, no empirical studies investigated the relation between EEG asymmetry and other markers of ES.

The present study

The main objective of the present study was to characterize behaviorally assessed ES at behavioral, physiological, and genetic levels in a large sample of three-year-old children and to understand its underlying etiology. The first aim was to test the psychometric properties of the recently developed behavioral rating system of ES in children (HSC-RS; Lionetti, Aron, et al., 2019). In a previous study (Lionetti, Aron, et al., 2019), initial evidence was found for a psychometrically reliable and valid measure of ES in a subsample of the current study ($n = 292$). Therefore, in the current study we expected to replicate the factor structure, distribution, and reliability in the total sample ($n = 541$). Secondly, we investigated whether we could identify different sensitivity groups. Based on previous studies in primary school children (10 years onwards), adolescents (Pluess et al., 2018, 2023), and adults (Lionetti et al., 2018), we expected to find evidence for a normally distributed trait with individuals falling into three sensitivity groups with around 30% of individuals falling into a high sensitivity group, 40% into a medium sensitivity group, and 30% falling into a low sensitivity group. Third, in line with the main aim of the current study, we aimed to characterize observed sensitivity in young children in terms of proposed markers of ES at multiple levels of analysis: behavioral, physiological, and genetic. No study thus far investigated these different levels within the same sample. Therefore, it is not clear to what extent higher sensitivity at the phenotypic level corresponds to an increased sensitivity at the genetic and physiological levels. At the behavioral level, we examined whether there is potential overlap between observer-rated sensitivity and the examined temperament traits and to what extent observer-rated sensitivity captures unique behaviors characteristic of ES, such as depth of information processing, awareness of subtleties, and sensory sensitivities, that are not accounted for by the examined temperament traits, thereby establishing its discriminant validity. Specifically, we anticipated a positive and moderate association between observer-rated ES and the temperament traits fear/inhibition, dysphoria, and constraint. Conversely, we expected a negative association between observer-rated sensitivity and the traits of sociability and exuberance. These anticipations were based on the ES framework, which suggests that more sensitive children show pause and check behaviors, process information more deeply, are more aware of subtle information, have low sensory thresholds, and display a heightened emotional and physiological reactivity (Aron et al., 2012; Aron & Aron, 1997; Pluess et al., 2018). At the genetic level, we expected a positive association with a cumulative polygene score of candidate genes previously associated with sensitivity (see Table 1; Belsky & Pluess, 2009, 2013). To explore the genetic etiology of observer-rated ES more deeply, we also examined associations between observer-rated ES and several GWAS-derived PGSs of phenotypes (at the behavioral level) previously found to be positively and moderately associated with ES, such as neuroticism, anxiety, ASD, ADHD, depression, educational attainment, cognitive performance, intelligence, and negatively with the PGS for extraversion, and disinhibition. Based on these associations, we expected that ES and these phenotypes might share the same genetic etiology. Regarding cortisol, we anticipated a positive association between the HSC-RS and cortisol reactivity during stressful laboratory situations (Boyce & Ellis, 2005). For basal cortisol and EEG asymmetry, we did not have specific hypotheses because findings in literature regarding these markers as a moderator between environmental factors and outcomes are inconsistent and no empirical studies so far have directly examined the relation between ES at the phenotypical level and these sensitivity markers at the physiological level. To summarize, regarding the psychometric properties, sensitivity groups, associations with temperament, the candidate gene polygenic score, and cortisol reactivity we had specific hypotheses. However, analyses regarding associations with GWAS based PGS, basal cortisol, and EEG asymmetry were explorative.

Materials and methods

Participants and procedure

In total, 559 3-year-old ($M_{age} = 3.56$ years, $SD_{age} = 0.25$ month, 45.5% = female) children from Long Island, NY, participated in the Stony Brook Temperament Study (Klein & Finsaas, 2017). Families with a child between 3 and 4 years of age were recruited from a suburban community sample by commercial mailing lists and afterwards screened by phone. Exclusion criteria were not having at least one English speaking parent and having significant medical conditions or developmental disabilities. Most participants were Caucasian (87.1%), lived with both parents (94.2%), 55% of the mothers and 47% of the fathers had a college degree or higher. Participating families provided informed consent and were paid for participation. For 541 children data on observer-rated ES and temperament were available ($M\ (SD)_{age} = 3.56\ (0.27)$ years, 45.8% = female; $M\ (SD)_{HSC\text{-}RS} = 4.04\ (0.93)$). For 334 of the observed children EEG data were available ($M\ (SD)_{age} = 3.58\ (0.26)$ years, 52.6% = female; $M\ (SD)_{HSC\text{-}RS} = 4.12\ (0.88)$) (others did not give their consent or were excluded due to artifacts in the data). Regarding cortisol, reactivity data were available for 147 of the observed children ($M\ (SD)_{age} = 3.63\ (0.24)$ years, 51.3% = female; $M\ (SD)_{HSC\text{-}RS} = 3.95,\ 0.96$), and basal cortisol ($M\ (SD)_{age} = 3.62\ (0.21)$ years, 43.6% = female; $M\ (SD)_{HSC\text{-}RS} = 3.97\ (0.97)$) for 90 of the observed children. Cortisol data were only collected in a subset of the children for the aims of another project (Dougherty et al., 2009, 2011). Candidate genetic data were available for 458 of the observed children ($M\ (SD)_{age} = 3.56\ (0.26)$ years, 46.9% = female; $M\ (SD)_{HSC\text{-}RS} = 4.08\ (0.94)$ and GWAS data for 418 of the observed children ($M\ (SD)_{age} = 3.55\ (0.26)$ years, 47.1% = female; $M\ (SD)_{HSC\text{-}RS} = 4.04\ (0.92)$).

The lab visit for the 3 years old children took approximately two hours. Children participated in 12 episodes (i.e., Risk room, Tower of patience, Arc of toys, Stranger, Car go, Transparent box, Exploring new objects, Pop-up snakes, Impossibly perfect green circles, Popping bubbles, Snack delay, and Box empty) of the Laboratory Temperament Assessment Battery (Lab-TAB; Goldsmith et al., 1999) and one newly developed episode (i.e., Exploring new objects). The episodes were designed to elicit different emotional and behavioral reactions. All episodes lasted between 3-5 minutes, were videotaped through a one-way mirror, and coded by trained researchers. The temperament and ES behaviors were independently coded by different trained researchers at different times (i.e., temperament was coded many years before the coding for ES). Before and during the lab visit,

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Table 1. Descriptive statistics of included genetic variants for the candidate gene polygenic sensitivity score

Gene	Variant	Original study	Coding	*N*	MAF	HWE	Genotypes *n* cases
SLC6A4	VNTR (5-HTTLPR)	(Hayden, Olino, et al., 2013)	SS/S/L = 1 (/LL = 0)	476	0.14	$\chi2 = 0.28$, $p = .87$	S/S: 92; S/L: 241; L/L: 143
DRD4	VNTR (11p15.5)	(Smith et al., 2012)	At least 1 7R allele or longer = 1 (no 7R allele or longer = 0)	475	0.27	$\chi2 = 0.09$, $p = .96$	At least 1 7R or longer allele: 174 /; no 7R or longer allele: 302
DRD2	rs1800497	(Hayden et al., 2010)	At least 1 A1 allele = 1 (no A1 allele = 0)	476	0.25	$\chi2 = 2.41$, $p = .30$	At least 1 A1 alle: 164; no A1 allele: 312
DAT1	VNTR (5p15.3)	(Hayden, Hanna, et al., 2013)	At least 1 9R allele = 1 (no 9R allele = 0)	476	0.37	$\chi2 = 0.16$, $p = .92$	At least 1 9R allele: 238; no 9R allele: 232
BDNF	rs6265	(Hayden, Olino, et al., 2013)	At least 1 Met (A) allele = 1 (Val/Val = 0)	476	0.37	$\chi2 = 5.95$, $p = .05$	At least 1 met-allele: 244; no met-allele: 232
COMT	rs4680	(Sheikh et al., 2013)	Val/Val = 1 (Met/Val & Met/Met = 0)	476	0.14	$\chi2$ (1) = 0.16, $p = 92$	At least 1 val-allele: 319, no val-allele:157

Note. SLC6A4 = Serotonin Transporter gene polymorphism (5-HTTLPR); DRD4 = Dopamine Receptor D4; DRD2 = Dopamine Receptor D2; DAT1 = Dopamine Transporter gene (SLC6A3); BDNF = Brain-Derived Neurotrophic Factor; COMT = Catechol-O-Methyltransferase; VNTR = Variable Number Tandem Repeat; N = Number of participants with genotype data after quality control; MAF = Minor Allele Frequency; HWE P = Hardy-Weinberg Equilibrium.

cortisol and genetic data were collected. During a subsequent lab visit (within 2 weeks), the basal EEG measures were taken. Ethical approval for the present study was obtained from the institutional review board of Stony Brook University (study name: Observations of Active and Inactive Children, protocol number: 88,933–35).

Measures

Environmental sensitivity

ES was measured using an observer rating system (HSC-RS; Lionetti, Aron, et al., 2019). The HSC-RS system consists of 10 rating scales coded for behaviors that are deemed to reflect ES: (a) Pause to check before exploring a new environment, (b) Cautious and collaborative attitude towards the experimenter, (c) Attending to experimenter's directions, (d) Compliance with the experimenter's request, (e) Fearfulness in response to the stranger's entrance, (f) Hesitancy paired with curiosity, (g) Positive response/overexcitement, (h) Attention to toy's detailed features (e.g., toys with different textures, making sounds, lights, are moving), (i) Careful perseverance when trying to open the box, and (j) Preference for complying with drawing beautiful circles. The development and validation of the scales are explained in a previous paper (Lionetti, Aron, et al., 2019), but will be summarized here. As a first step, a prototypical behavioral profile was created based on theoretical and empirical studies on ES (Aron & Aron, 1997; Pluess et al., 2018). These behaviors include pause and check behaviors, depth of information processing, attention to details, sensory sensitivities, and emotional reactivity to positive and negative environments. As a second step, based on the prototypical profile, observable markers of sensitivity were identified using the Laboratory Temperament Assessment Battery (Lab-TAB; Goldsmith et al., 1999) episodes (see further; Dyson et al., 2012; Olino et al., 2010). Based on a stratified random procedure and exploratory statistical analyses, 10 scales out of seven Lab-TAB episodes (i.e., Risk room, Tower of Patience, Stranger Approach, Exploring new objects, Pop-up snakes, Transparent box, and Impossibly perfect children) were retained (see Table A1 for an overview of the episodes and the ES scales). The 10 sensitivity scales were rated on a 7-point Likert scale with higher scores reflecting higher sensitivity. All episodes were coded by three trained researchers and a good inter-rater agreement for the overall mean score was obtained based on 37% of the sample (ICC = .91, 95% CI[.85-.94].

Temperament

Established temperament traits (i.e., Sociability, Dysphoria, Fear/Inhibition, Exuberance/Interest, and Constraint versus Impulsivity) were measured with an adapted version (Olino et al., 2010) of the original Lab-TAB procedure (Goldsmith et al., 1999). The Lab-TAB provides standardized episodes that are designed to elicit a variety of behaviors and emotions that were rated based on facial, bodily and vocal manifestations of relevant behaviors in the specific episodes (Dyson et al., 2012; Olino et al., 2010). The Lab-TAB episodes were scored independently (and many years earlier) from the observer-rated ES scores and by different trained researchers. More information on the laboratory coding procedure of the temperament traits can be found in previously published papers of Dyson et al. (2012) and Olino et al. (2010). Through 12 episodes (see above at procedure), five established dimensions of temperament were identified using exploratory (in half of the sample) and confirmatory factor (in the other half of the sample) procedures which are explained in detail in Dyson et al. (2012). Sociability includes the variables sociability, initiative, and dominance; Dysphoria includes anger and sadness; Exuberance includes positive affect, anticipatory positive affect, and interest; Fear/Inhibition includes fear, behavioral inhibition, and clingy; and Constraint versus Impulsivity includes impulsivity (reversed scored), compliance, and inhibitory control. In the present study, we used the identified five higher-order factors, instead of the separate variables.

Candidate genes

DNA was obtained from buccal cells (i.e., by rubbing the inside of the cheek with two swabs), using the Qiagen DNA Micro Kit (Qiagen, Valencia, California, USA). Extracts were stored at 4°C during analyzing the data and at -80°C for long-term storage. For the polymerase chain reaction (PCR), the Applied Biosystems thermal cycler Gene Amp 9700 (Applied Biosystems, Foster City, California, USA) was used. PCR results were separated on polyacrylamide gels, stained with ethidium bromide, and visualized

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and documented via an UV imaging system (BioRad Labs, Mississauga, Ontario, Canada). Information on the genetic analyses (i.e., primers, PCR amplification, PCR products) can be found in the original papers: *5-HTTLPR* and *BDNF* (Hayden, Olino, et al., 2013), *DRD2* (Hayden et al., 2010), *DRD4* (Smith et al., 2012), *DAT1* (Hayden, Hanna, et al., 2013), and *COMT* (Sheikh et al., 2013).

A candidate cumulative polygenic sensitivity score, that is, a composite score based on multiple susceptibility alleles that were found in previous studies to moderate effects of both negative and positive environmental influences (Belsky & Pluess, 2009), was created. The cumulative polygenic score (ranging from 0 to 6; with higher scores indicating higher sensitivity) was computed with a score of 1 for each of the following (or 0 in the absence of these): a) at least one short allele of *5-HTTLPR* (e.g., Belsky & Pluess, 2009; Caspi et al., 2010), b) at least one 7R or longer allele of *DRD4* (e.g., Bakermans-Kranenburg & van Ijzendoorn, 2011), c) at least one A1 allele of *DRD2* (e.g., Brody et al., 2013), d) at least one 9R allele of *DAT1* (e.g., Lahey et al., 2011), e) Val/Val alleles of *COMT* (e.g., Hygen et al., 2015), and f) the Val/Met or Met/Met alleles of *BDNF* (e.g., Gunnar et al., 2012). These recoded genotypes were then summed and averaged to form a candidate polygenic sensitivity score as an index of genetic sensitivity. As follow-up, analyses were also run separately with the individual candidate genes. Descriptive information of the included genetic variants can be found in Table 1. All genetic data were analyzed by researchers who were blind for the purpose of the study.

GWAS based polygenic scores (PGS)

DNA for GWAS was obtained using standard DNA saliva-based collection kits, Genotek's Oragene kit. Genotyping of saliva samples was performed in a single batch at the Genomics Shared Resource at Roswell Park Cancer Institute, using the Infinium Global Screening Array (Illumina, San Diego, CA, USA), according to protocols of the manufacturer.

Data were imputed on the Michigan Imputation Server pipeline v1.2.4, using the Haplotype Reference Consortium reference panel (McCarthy et al., 2016). Before imputation, genotypes were filtered for ambiguous strand orientation, missingness rate >5% (by marker exclusion, then by individual), Hardy-Weinberg equilibrium violation ($p < 10\text{-}6$), sex mismatch ("sex check" function for X chromosome homozygosity estimate), and non-European ancestry (assessed via self-report) principal component analysis against the reference panel from the 1000 Genomes data). After imputation, the SNPs were excluded for imputation $R2 < 0.5$, average call rate below 90% and minor allele frequency below 0.1%. PLINK was used to handle genetic data and perform quality control (Purcell et al., 2007). Samples of less than 80% genetic European ancestry were excluded.

Polygenic Scores (PGS) were created using summary statistics from previously published GWAS discovery samples from European ancestry: ADHD (Demontis et al., 2019), ASD (Grove et al., 2019), cognitive performance (Lee et al., 2018), depression (Levey et al., 2021), disinhibition (Karlsson Linnér et al., 2019), educational attainment (Lee et al., 2018) (van den Berg et al., 2016), anxiety (GAD) (GAD; Levey et al., 2020), intelligence (Savage et al., 2018) and neuroticism (Werme et al., 2021). PGSs were computed using the PRSice 2.0 software (Euesden et al., 2015), with $r2 = .1$ threshold of clumping, by aggregating genetic variants up to varying thresholds of significance, weighted by the associations in the GWAS sample. The first 10 genetic ancestry principal components (PCs) were obtained as measures of population stratification and controlled for in all analyses.

Cortisol

Basal cortisol was measured at home in the morning (i.e., 30 minutes after wakening) and in the evening (i.e., 30 minutes before bedtime, at 8.16 am and 8.15 pm on average). A cortisol collection kit (i.e., with a cotton dental roll dipped into 0.025g of cherry Kool-Aid® mix) was given to the parents to collect the cortisol at home. Parents were instructed that children should avoid any food or drink intake before sampling. Collected samples were sent back to the lab by post where it was stored at -20°C. For a more detailed procedure, see Dougherty et al. (2009). Cortisol reactivity was measured during the lab visit of the Lab-TAB procedure. Children came to the lab at 10 am or 2 pm and were asked to not eat or drink one hour, two hours for caffeinated products, before the lab visit. Children participated in all 12 episodes of the Lab-TAB procedure. Cortisol reactivity in children was measured during the Stranger Approach, Transparent box, and Box Empty episodes. Four cortisol saliva samples were collected at (a) baseline (i.e., 20 minutes after getting used to the lab), (b) 30 minutes after the Stranger Approach episode (60 minutes after baseline), (c) 60 minutes after the Transparent box episode (90 minutes after baseline), and (d) 20 minutes after the Box Empty episode (130 minutes after baseline). The index that is used for cortisol reactivity is Area Under the Curve during stress exposure. For a detailed overview of the measurement of cortisol reactivity, see Dougherty et al. (2011). All four variables (basal cortisol am, basal cortisol pm, AUCg, and AUCi) were investigated.

EEG asymmetry

Resting EEG was recorded for 6 minutes in a noise canceling room while the child was asked to sit. The child was asked to alternate between eyes open and closed every minute. EEG was recorded using a 32-electrode channel Lycra following the 10/20 labeling system according to the guidelines of the American Electroencephalographic Society (1994). A reference electrode was placed on the nose and above and under the left eye, on the left side of the left eye, and one electrode on the right side of the right eye to capture blinks. Data were collected at a sampling rate of 512 Hz using the Active Two system (Biosemi, Amsterdam, The Netherlands) and a 0.16-40.00 Hz bandpass filter was used to all channels. Afterwards, data were converted to Neuroscan 4.1 (Charlotte, NC) using PolyRex (Kayser, 2003). Data were split into 1.024 epochs. To maximize data retention, each epoch overlapped by 50%. By visually inspecting the data, artifacts, such as eye blinks, were removed. To compute power spectra, a Fourier transformation was applied. As recommended for young children, the alpha band ranged from 6-10 Hz. For more information, see Goldstein et al. (2019).

EEG asymmetry was computed by taking the difference between the frontal (F4-F3 and F8-P7) and parietal electrode pairs (P4-3 and P8-P7) after taking the natural logarithm: Ln(right) -Ln(left). Positive scores indicate greater left-sided asymmetry, and negative scores indicate greater right-sided asymmetry. Scores close to zero indicate symmetry between left and right activity.

Data analysis

Psychometric properties of the highly sensitive child-rating system

Given that an Exploratory Factor Analysis (EFA) and a Confirmatory Factor Analysis (CFA) were already performed in a subsample of the total sample ($n = 292$; 54% male; $M_{age} = 3.7$;

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$SD_{age} = 0.26$), we ran a CFA in order to test whether we can replicate the one-factor solution that was previously found in (Lionetti, Aron, et al., 2019). CFA was run in R (package Lavaan) with Full Information Maximum Likelihood estimation to deal with missing data and using robust maximum likelihood estimation to control for non-normality. An acceptable fit is obtained when the Comparative Fit Index (CFI) is .90 or above, the Root Mean Square Error of Approximation (RMSEA) is .06 or below, and Standardized Root Mean Squared Residual (SRMR) is .08 or below (Kline, 2005). More recently RMSEA and SRMR values higher than 1 are seen as a poor fit (Hopwood & Donnellan, 2010; Kline, 2016). Because CFA was already performed on a subsample of the data (Lionetti, Aron, et al., 2019), we added a sensitivity analysis in which we reran the CFA on the newly added data only. Based on the results of the CFA (both in the total sample and in the newly added data only, see further), we also included a sensitivity analysis without item 7. Next, internal consistency of the items (with Cronbach's alpha (α) > .70 indicating adequate reliability), descriptive statistics (means, standard deviations, and skewness of the data), were examined as well as associations with age, and gender differences.

Identification of different sensitivity groups

The existence of sensitivity groups was examined using Latent Profile Analysis (LPA) in Mplus (Version 8.2). The indicators of the LPA were the 10 item scores of the HSC-RS. The fit of models with one to six classes were compared, individuals were assigned to the profile for which they had the highest posterior probability, and Full Information Maximum Likelihood was used as estimator. The best fitting solution was identified based on the Akaike's Information Criteria (AIC), Bayesian Information Criteria (BIC), Lo-Mendell-Rubin adjusted likelihood test (LMR-A) and Entropy (Nylund et al., 2007). AIC and BIC are comparative fit indices and the model with the lowest fit indices shows a better fit than a model with higher AIC and BIC values. Entropy provides an indication of how clearly individuals can be categorized into the different groups, with values from 0.80 indicating good fit and higher values approaching 1 indicating a higher confidence in class categorization. A significant LMR-A indicates that the specified model fits the data better than the more parsimonious model with one class fewer. Results will also be inspected visually.

Characterisation of highly sensitive children at multiple levels of analysis

As a next step we aimed to characterize sensitive individuals, as measured with the HSC-RS (based on the continuous measure as well as on the group solution) in terms of temperament (i.e., observer-rated temperament dimensions), genetics (i.e., candidate gene and genome-wide polygenic scores), cortisol (i.e., basal cortisol and cortisol reactivity in reaction to stress), and frontal and parietal EEG asymmetry.

First, Pearson bivariate and partial (for the GWAS data; controlling for the first 10 PCs) correlations between the HSC-RS score and the variables of interest were calculated. Second, stepwise regression analyses were run with HSC-RS as outcome variable, gender as control variable (Step 1), and the variables of interest (i.e., temperament, candidate gene polygenic score, cortisol, EEG asymmetry) as Step 2 predictors. Because observer-rated ES was calculated based on overlapping episodes as observer-rated temperament, we also checked for collinearity using the Variance Inflation Factor (VIF). Regarding the GWAS-based PGS; gender (Step 1) and the first 10 gene-wide principal components (i.e., PC1-PC10; Step 2; to adjust for population stratification) were included as covariates. The ten PGS were included as predictors at Step 3. Based on these results, we also ran a more parsimonious model including only the GWAS based PGS of ADHD as this PGS was the only significant one with the highest effect size. This analysis was data-driven and therefore exploratory. For each regression model, we provide R^2, Cohen's f^2 and Cohen's d to indicate the effect size of the entire model and the separate predictors. For R^2, values indicate: very weak variance (<0.02), weak variance (0.02-0.13), moderate variance (0.13-0.26), and substantial variance (>0.26). For Cohen's d, values indicate: very small effect (<0.20), small effect (0.20-0.50), medium effect (0.50-0.80), and large effect (≥0.80). For f^2, values indicate: very small effect (<0.02), small effect (0.02-0.15), medium effect (0.15-0.35), and large effect (>0.35) (Cohen, 1988). Regarding cortisol reactivity, an interaction with the time of visit (morning or afternoon) was included to control for circadian patterns of cortisol. HSC-RS was included as a continuous score in all regression analyses. As an additional and exploratory analysis, using (M)ANOVAs, we examined whether the three sensitive groups differ also qualitatively from each other across the different levels of analyses. These results will only be reported in Appendices (Figure A3 and Figure A4). We corrected for multiple testing to avoid false positive findings by using False Discovery Rate (Benjamini & Hochberg, 1995).

Transparency and openness

Throughout this manuscript, we reported transparently on our sample, data in- and exclusions, all manipulations, all measures in the study, and how the data were analyzed. The present study (theoretical background, hypotheses, and data analysis plan) was preregistered in Open Science Framework: (https://osf.io/q3e9s/?view_only=afad2edaa09e40e0a9d2b08316e27e2c). The data and materials are not publicly available due to ethical reasons, but a pseudonymized version can be obtained from the first author.

The research questions regarding the psychometric properties (Aim 1), identification of different sensitivity groups (Aim 2), characterization of observer-rated sensitivity at the behavioral (i.e., temperament), genetic (i.e., cumulative polygenic candidate genes score and the GWAS based PGS) and physiological level (i.e., basal cortisol, cortisol reactivity, frontal and partial EEG asymmetry; Aim 3) were preregistered. However, given that the genetic data was not available yet when preregistering this study, we did not include the MAOA candidate gene and the GWAS based PGS for openness (not available in the data). On the other hand, because additional GWAS based PGS were available in the data, we included GWAS based PGSs for cognitive performance, educational attainment, intelligence, ADHD, and disinhibition in addition to the preregistered GWAS based PGSs for extraversion, depressive symptoms, neuroticism, autism, and anxiety. In addition, we conducted a posthoc exploratory analyses that was not preregistered. Based on the results of the GWAS based PGS, we reran the hierarchical regression analyses with only the ADHD GWAS based PGS. Furthermore, we added additional sensitivity analyses. First, we reran the CFA without Item 7 and on the newly added dated only in addition to the planned CFA on the full sample. Second, we reran the same regression analysis for temperament, but with separate dimensions of dysphoria (sadness and anger).

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Results

Psychometric properties of the highly sensitive child-rating system

CFA on the full sample indicated an acceptable fit for the one-factor solution (CFI = .91; RMSEA = .097; SRMR = .051). The RMSEA value was higher than acceptable, and the remaining indices indicated an acceptable model fit. Results are in line with the fit and model that was found in Lionetti, Aron, et al. (2019) based on both EFA and CFA. In the present study, all items had a factor loading > .50 on the HSC factor, except item 7 (λ = .36). Regarding the CFA on the newly added data only, model fit indices (CFI = .90; RMSEA = .095; SRMR = .055) and factor loadings (all λ> .60, except for item 7 (λ = .35)) were similar. Because the factor loading of Item 7 was lower than the other factor loadings, we reran the CFA excluding item 7 (Positive response/overexcitement) as a sensitivity analysis. Results did not indicate an improved model fit for the one-factor solution without item 7 (CFI = .91; RMSEA = .099; SRMR = .0552). Based on the model fit indices and on theoretical reasons (as we believe that positive emotional reactivity in response to a positive experience is an important feature of ES) we decided to retain Item 7. The scale showed good internal consistency (Chronbach's α = 0.84) of the total scale and normally distributed scores on the items (Table A2). Finally, a significant difference for gender ($p = .004$) was found, with girls (M (SD) = 4.23 (.94)) scoring higher on the HSC-RS than boys (M (SD) = 88 (.08)). No significant correlation with age was found, however the age range in the present study was very limited.

Identification of different sensitivity groups

LPA indicated strongest support for a three-group solution (highest entropy and significant LMR-A) (Table 2). About 23.3% ($n = 123$) of the children were identified as low sensitive, 54.2% ($n = 300$) as medium sensitive, and 22.5% ($n = 118$) as being highly sensitive. We also examined and plotted the four-group solution (Figure A1) in which the highly sensitive group was further divided into a very small very highly sensitive group (7.4%) and a somewhat lower but still highly sensitive group (30.1%). However, based on the LPA, previous findings and parsimony reasons, the three-group solution was retained. Children in the highly sensitive group scored higher on all sensitivity items (measured across the different environmental situations) than children in the medium sensitive group who scored higher on all items than children in the low sensitive group. Only on Item 4 (Compliance with the experimenter's request) the medium sensitive group scored high (but not as high as the high sensitive group) and on Item 7 (Positive response/overexcitement) the low sensitive group seem to score average, but still lower than the medium sensitive group (Figure A1 and Table A3).

Characterisation of highly sensitive children at multiple levels of analysis

The descriptive statistics of all variables and bivariate correlations with HSC-RS can be found in Table 3. Results showed significant HSC-RS associations with temperament ranging from low ($r = -.13$) to relatively high ($r = .54$). Moreover, a small but significant negative association with the GWAS PGS for ADHD was found. No significant associations were found between HSC-RS, candidate genes, cortisol and EEG asymmetry. The descriptive statistics of the different variables, separately for the low, medium, and high sensitive groups, are presented in Table A4. Pearson correlations between the different variables are presented in Table A5. Results showed that within the different levels of analyses, significant small to large associations were found between the temperament measures, between the GWAS based PGS, between cortisol reactivity, and EEG asymmetry measures. Across different levels of analysis, significant associations were found between temperament traits and GWAS based PGS phenotypes of ADHD and extraversion and parietal EEG asymmetry. Significant small associations between the GWAS based PGS phenotypes of disinhibition, educational attainment, anxiety and intelligence and cortisol measures were found, and between the GWAS based PGS phenotypes of ADHD, ASD, cognitive performance, educational attainment, intelligence and neuroticism, and EEG asymmetry. For the cumulative polygenic score, only a significant association with frontal EEG asymmetry was found. Detailed information on the direction and the strength of the associations can be found in Table A5.

Table 2. Latent profile analyses on the items of the Highly Sensitive Child-Rating System

	AIC	BIC	Entropy	LMR-A
1 class	18,408.884	18,494.752		
2 classes	17,208.075	17,341.171	0.824	1205.397***
3 classes	**16,800.775**	**16,981.099**	**0.840**	**423.187***
4 classes	16,657.245	16,884.796	0.827	163.173**
5 classes	16,581.855	16,856.634	0.810	96.003
6 classes	16,512.190	16,834.196	0.819	90.360

Note. *$p < .05$; **$p < .01$; ***$p < .001$.

Characterisation based on behavioral markers of sensitivity

The results of the hierarchical regression analyses indicated that the model with gender and all five temperament traits ($F(5,509) = 85.77$, $p < .001$, $f^2 = .92$, $d = 1.92$) explained 47.5% of the variance in observer-rated sensitivity. Specifically, a significant association with all temperamental traits, except exuberance (β = .02, $p = .472$), was found. Higher scores on observer-rated sensitivity were associated with lower sociability/assertiveness (β = −.41, $p < .001$, $d = -0.47$), lower dysphoria (β = −.11, $p = .003$, $d = -0.13$), higher fear/inhibition (β = .11, $p = .002$, $d = 0.13$) and more constraint (β = .42, $p < .001$, $d = 0.50$) (Table A6). VIF scores were all lower than 1.33, which indicates no evidence for problems with collinearity. As a sensitivity analysis, we reran the model with the separate dimensions of dysphoria, namely sadness and anger. Results (Table A7) showed that observer-rated ES was associated with less sadness (β = −.09, $p = .02$, $d = -0.11$) and that there was no association with anger (β = −0.01, $p = .870$).

Characterisation based on genetic markers of sensitivity

Regarding the candidate genes, results (Table A8) indicated that the model with gender and the polygenic sensitivity score ($F(1, 452) = 3.27$, $p = .071$, $f^2 = 0.05$, $d = 0.42$) explained 5% of the variance in observer-rated sensitivity but did not reach the .05 significance level. When examining coefficients, we observed a statistically significant effect of gender (β = .21, $p < .001$, $d = 0.21$) and a non-significant effect of the candidate gene polygenic score (β = .08, $p = .071$, $d = 0.08$). Regarding the follow-up analysis, with

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Table 3. The descriptive statistics, bivariate and partial pearson correlations with Highly Sensitive Child-Rating System

Variable	*N*	*M* (*SD*)	Range	*r*HSC-RS	*p*
Observer-rated sensitivity	541	4.04 (0.92)	1.60–6.90	/	
Temperament					
Sociability/assertiveness	516	0.00 (1.00)	−4.07–2.41	−.47***	< .001
Dysphoria	516	0.00 (1.00)	−1.69–6.68	−.29***	< .001
Fear/inhibition	516	0.00 (1.00)	−2.34–3.91	.16***	< .001
Exuberance	516	0.00 (1.00)	−3.63–2.81	−.13**	.002
Constraint	516	0.00 (1.00)	−4.32–1.84	.54***	< .001
Cumulative candidate genetic score	458	0.52 (0.20)	0.00–1.00	.07°	.083
GWAS polygenic score phenotypes					
GWAS ADHD	399			−.12*	.022
GWAS ASD	399			.01	.788
GWAS cognitive performance	399			.03	.625
GWAS depression	399			−.06	.387
GWAS disinhibition	399			.02	.625
GWAS educational attainment	399			−.02	.774
GWAS Extraversion	399			−.07	.215
GWAS anxiety (GAD)	399			.03	.626
GWAS intelligence	399			.06°	.260
GWAS of neuroticism	399			.04	.495
Cortisol					
Basal morning cortisol	94	0.55 (0.19)	0.10–1.18	.10	.592
Basal evening cortisol	92	−1.53 (0.40)	−2.24 - -0.44	−.01	.851
Cortisol reactivity increase (AUCi)	156	5.00 (0.85)	1.54 – 7.81	.00	.180
Cortisol reactivity to ground (AUCg)	131	6.24 (0.44)	5.38–8.08	.08	.499
EEG asymmetry					
Frontal asymmetry (F4-F3)	352	−.01 (0.14)	−0.39–145	.01	.845
Frontal asymmetry (F8-F7)	352	−0.05 (0.24)	−0.89–1.46	−.04	.371
Parietal asymmetry (P4-P3)	352	.05 (0.24)	0.89–1.46	.05	.503
Parietal asymmetry (P8-P7)	352	0.13 (0.28)	−1.63–1.25	.00	.965

Note. Cortisol variables were log-transformed (ln(X + 100)). The temperament variables were standardized with $M = 0$, $SD = 1$. For the GWAS data partial correlations, controlling for the first 10 PC, were run. Regarding the other variables, bivariate correlations were run. °$p < .10$; *$p < .05$; **$p < .01$; ***$p < .001$.

the individual candidate genetic variants as separate predictors (Table A9), no significant associations were found.

Regarding the results of the GWAS based PGS, results (Table A10) indicated that the model with gender, the first 10 principal components, and the 10 GWAS PGS ($F(10, 374) = .1.24$, $p = .261$, $f^2 = 0.6$, $d = 0.50$) explained 3% of the variance in observer-rated sensitivity and was not significant. Only for the GWAS PGS for ADHD, a significant negative association with observed sensitivity was found (β = -0.13, $p = 0.017$, $d = -0.12$). Results of hierarchical regression analyses (Table A11) with the first 10 principal components (PCs) and only the GWAS PGS of ADHD (β = −0.12, $p = 0.02$, $d = -0.11$) explained 9% of the variance in observer-rated sensitivity and was significant ($F(1, 383) = 5.46$, $p = .02$, $f^2 = 0.10$, $d = 0.63$). The additional variance that was explained by adding the ADHD PGS to the first 10 PCs was 1.3%. After correcting for multiple testing, the PGS for ADHD remained significant.

Characterisation based on physiological markers of sensitivity

Results regarding the cortisol measures indicated that the model with gender and time of the visit, basal cortisol, cortisol reactivity, and interactions between cortisol reactivity and time of the visit ($F(6, 71) = .58$, $p = .1.06$, $f^2 = 0.11$, $d = 0.66$) explained 10% of the variance in observer-rated sensitivity but was not significant, although results indicated small to medium effect sizes. Results regarding EEG asymmetry, indicated that the model with gender and frontal and parietal asymmetry ($F(4, 328) = 0.56$, $p = .692$, $f^2 = 0.03$, $d = 0.36$) explained 3% of the variance in observer-rated sensitivity and was not significant.

Discussion

The present study had three main aims. The first was to test the psychometric properties of a recently developed observation-

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rating scale that measures ES, the Highly Sensitive Child-Rating System (HSC-RS; Lionetti, Aron, et al., 2019) in a large sample of preschoolers. The second aim was to examine whether we could identify different sensitivity groups within this sample. The third aim was to characterize ES in terms of temperament, genes (i.e., polygenic scores based on candidate genes and GWAS for several phenotypes that have been found to be related to ES), cortisol (i.e., basal cortisol and cortisol reactivity), and EEG asymmetry (i.e., frontal and parietal). The present study is the first to investigate all these different characteristics of ES across multiple levels of analysis in the same sample of individuals, using more objective measures of ES than relying on self- and parent reported questionnaire data.

Regarding the first aim, evidence was found for a one-factor solution, which is in line with the results found in a subset of the sample (Lionetti, Aron, et al., 2019). In addition, the HSC-RS showed good internal consistency and normally distributed item scores suggesting that the measure was able to capture enough variability in the sample considered. We found a significant difference in gender, with girls scoring slightly higher than boys on observer-rated ES. This trend (i.e., slightly higher scores for girls) is comparable to that previously reported in observational and self-report studies (Lionetti, Aron, et al., 2019; Pluess et al., 2018). No association with age was found, however, the age range was very small.

Regarding the second aim, evidence was found for three quantitatively distinct sensitivity groups: a low sensitive group (23%), a medium sensitive group (54%), and a high sensitive group (23%). These groups are referred to as dandelions, tulips and orchids, respectively, in previous studies (Lionetti et al., 2018; Pluess et al., 2018). The highly sensitive group scored higher on all items across the different episodes/environments that elicit different kinds of behavior than the medium sensitive group, who in turn scored higher on all items than the low sensitive group. These results are in line with the three class solution that was found using self-report questionnaires in older children (10 years onward) (Pluess et al., 2018) and adults (Lionetti et al., 2018). By applying a categorical approach in addition to a continuous approach we were able to test whether we could replicate the same three-group structure that was found in other age groups in the current sample of preschoolers. Most research, including the present study, focused mainly on the high sensitive group, however, very little is known about the low sensitive group and how being low on sensitivity is associated with psychopathology and transdiagnostic mechanisms, such as, callous unemotional traits. Importantly, for the main analyses in the manuscript we applied a continuous score of ES given the risk of loss of variability in the data and classification errors with categorical approaches. The latter we tried to keep at a minimum by checking the classification quality (e.g., posterior probabilities, entropy), plotting the results visually, and comparing the results with theory and findings from previous studies in independent samples.

As a third aim, we examined whether we could characterize ES in terms of temperament, genetic variables, cortisol, and EEG asymmetry. We found evidence for established temperament factors as significant, but non-overlapping, correlates of observer-rated ES. More sensitive children showed higher fear/inhibition, more constraint, less sociability/assertiveness, and less dysphoria than less sensitive children. These results are in line with theory given that traits such as fear, shyness, and behavioral inhibition are understood to reflect aspects of environmental sensitivity (Aron et al., 2012). For dysphoria, findings might be less straight-forward as both this trait and ES are assumed to be associated with fear and anxiety (Liss et al., 2005). However, in the present study dysphoria was measured as a combination of anger and sadness (Dyson et al., 2012). Therefore, we ran a sensitivity analysis with the separate dimensions of sadness and anger (instead of the combined factor dysphoria). Results showed that observer-rated ES was negatively associated with sadness and there was no association with anger. These results are in line with the meta-analysis and study of Slagt et al., (2016, 2018) that found that negative affect (which encompasses sadness and anger among other negative emotions) does not enhance a for-better and for-worse sensitivity as ES does. Possibly, ES is only associated with sadness or other negative outcomes when more sensitive children are exposed to negative environments, such as conflicts at home, but not when they are exposed to positive environments, such as parental support. Moreover, we found a positive association between ES and constraint and a negative association between constraint and dysphoria, which might also explain the observed negative association between dysphoria and ES. Based on our results we can conclude that observer-rated ES was strongly associated with other markers of sensitivity at the behavioral level, especially with higher scores on fear/inhibition and constraint. However, given the ES and temperament were both based on the same Lab-TAB episodes of the same sample, we cannot rule out that at least a part of the variation is explained by shared method variance. The observation that 47.5% of the variance in observer-rated ES was explained by observed temperament traits (i.e., sociability, dysphoria, fear/inhibition, exuberance, and constraint), suggests that ES partially overlaps with the established temperament factors, but also reflects other aspects of sensitivity at the behavior level. These can include depth of information processing and sensory sensitivity, not captured by the observed temperament traits and the Lab-TAB coding we adopted. Future research should investigate the relationships between sensitivity and the various temperament dimensions in more depth. For example, temperament traits such as orienting sensitivity might be more related to depth of information processing in observer-rated ES.

Pertaining to the investigation of associations between observer-rated ES and genetic factors, we did not find a significant association with the cumulative polygenic score. Future studies should consider exploring genetic correlates of ES in bigger samples. Regarding the GWAS PGS, results indicated no evidence for an association between observer-rated sensitivity and the GWAS PGSs for personality, psychopathology, and cognitive performance. However, a small and significant negative association with the GWAS PGS for ADHD was found, with more sensitive children scoring significantly lower on the PGS than less sensitive children. The negative association between the GWAS PGS for ADHD and ES could be related to inhibition and impulsivity problems, observed in ADHD and ES in opposite directions. ADHD is associated with low levels of inhibition and high levels of impulsivity (American Psychiatric Association, 2013), whereas ES is associated with high inhibition and low impulsivity (Greven et al., 2019; Lionetti, Aron, et al., 2019). Yet, a previous study (Panagiotidi et al., 2020) found support for a positive association between ADHD and ES, which could be driven by the sensory sensitivities, ease of excitation and emotional reactivity that is found in both phenotypes. Future studies should further examine the associations between ES and ADHD more deeply and across multiple levels of analysis (e.g., also looking at the neural correlates).

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Regarding the characterization of observer-rated sensitivity at the physiological level, we found no evidence for significant associations with basal cortisol, cortisol reactivity, or frontal or parietal EEG asymmetry. For cortisol and EEG asymmetry, findings in literature about the identification of these measures as markers of sensitivity are inconsistent. Another recent study found no relevant associations between self-reported ES and the physiological activation of the stress system (Weyn, Van Leeuwen, Pluess, Goossens, et al., 2022). It could be that being more sensitive at the behavioral level does not directly translate in being more sensitive at the physiological level. A possible explanation (Pluess, 2015) might be that whether heightened sensitivity manifests itself in heightened cortisol levels and EEG asymmetry depends on the quality of the early (e.g., harsh parenting, conflicts in the home environment) or concurrent environment, an idea in line with the biological sensitivity to context theory (Boyce & Ellis, 2005) and the adaptive calibration model (Del Giudice et al., 2011). According to this view, we might expect that sensitive children will have moderate basal cortisol levels and heightened cortisol reactivity when they experience supportive environments, high basal cortisol levels and reactivity when they experience stressful environments, and low basal cortisol levels and reactivity when they experience extremely dangerous situations. The same could be the case for EEG asymmetry at rest, with more sensitive children showing higher LFA (e.g., associated with approaching behaviors; Boyce, 2016) when experiencing positive environments and higher RFA (e.g., associated with inhibition behaviors; Boyce, 2016) when experiencing negative environments, as evidenced in previous empirical studies and review papers (Gander & Buchheim, 2015). For parietal asymmetry, it might be that more sensitive children show only higher right parietal activity (e.g., associated with less positive affectivity and more negative affectivity; Shankman et al., 2011) when experiencing negative environments, but not when experiencing positive environments. However, these hypotheses remain to be tested. Although individual differences in ES are already observed in very young children (Kim & Kochanska, 2012; Lionetti, Aron, et al., 2019; Slagt et al., 2018), it might be that the manifestation of ES at physiological level might get more pronounced later in life due to interactions with consecutive negative or positive environments. Given that our sample was very young and these patterns manifest in interaction with environmental quality, these associations should also be investigated in older children and adolescents while taking different kinds of environments (e.g., home, school and social environments) into account.

Strengths, limitations, and further research

An important strength of the present study is that we were able to examine individual differences in objectively assessed ES and its characterization at multiple levels of analyses (i.e., behavioral, genetic, and physiological level) in a relatively large sample of preschoolers using a recently developed and reliable observational method. We examined ES, temperament, candidate gene polygenic score, individual candidate genes, GWAS based PGS for ten different phenotypes, basal cortisol, cortisol reactivity, and frontal and parietal EEG asymmetry. To our knowledge, this was the first study that investigated all these different variables at different levels of analyses within the same sample, exploring to what extent levels of ES, coded at an observational level, overlapped with other behavioral, genetic, and physiological sensitivity markers. Moreover, most studies on ES at the behavioral level used self- or parent report measures, whereas in the present study we used a validated observational measure (HSC-RS). Using an observational measure is a strength (e.g., Majdandžić & Van Den Boom, 2007) as the data is based on trained observers' judgements that might be less socially biased than self- or parent reports. As trained observers score the behaviors of many children to the same standardized episodes that elicit specific, also low frequent behaviors, observers were able to objectively identify individual differences in ES. Moreover, with the HSC-RS measure, we were able to capture behaviors related to depth-of-processing (a core element related to ES; Aron & Aron, 1997) such as pause and check behaviors, taking time in decision-making, exploring new environments, and reactions to positive stimuli, that are currently not captured by self- or parent report questionnaires (Greven et al., 2019). To generalize our findings and to make them more ecologically valid, a next step will be to develop and validate an observation method for ES that can be used in different settings, such as the home environment, the class environment, or in a therapeutic session. An important limitation of the current study is that observer-rated temperament and ES were measured using the same episodes, although by independent coders and using a different validated coding system. Results indicated that despite this overlap in measurements and potential shared method bias, temperament explained 47.5% of the variance in observer-rated ES. Further studies should examine the associations between temperament and observer-rated ES using different observational techniques. Another limitation is the unequal sample size for some of the analyses, with lower sample sizes for the physiological data than for the genetic and temperament data. Follow-up analyses showed that the different subsamples differed not only in their sample sizes but also slightly in their mean scores and variations on ES (Figure A2). Third, genetic and physiological variables have small effects and therefore require large sample sizes. Consequently, our analyses were likely underpowered for the physiological and genetic analyses, should be considered as exploratory, and need to be replicated in further research. Moreover, relations of the behavioral level with the physiological and genetic levels are small and difficult to detect (Evans et al., 2013; Peng et al., 2021). This is in line with our results showing only a few small associations between the measured constructs across different levels of analysis. A possible explanation could be that some markers reflect more state sensitivity (i.e., momentary and fluctuating levels of sensitivity; e.g., cortisol reactivity), whereas other markers reflect more trait sensitivity (i.e., a general and stable tendency of sensitivity; e.g., observer-rated sensitivity, genes, and temperament traits). Future studies should further disentangle trait versus state sensitivity, explore relationships across different levels in bigger samples, and should develop a design that is specifically designed to measure individual differences in ES, starting from the theory of ES, such as sensitivity towards both positive and negative stimulations (Aron & Aron, 1997; Greven et al., 2019; Pluess, 2015), that is not limited to the Lab-TAB episodes (Dyson et al., 2012; Olino et al., 2010). Future research should also consider including measures of the early childhood environment and neural analyses to better understand the underlying mechanisms of ES and its connection to conditions like ADHD. Fourth, our sample consisted mainly of Caucasian

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children and observers. In terms of generalizability of the results, it is important to validate the HSC-RS also in non-Western children with non-Western observers as there could be a cultural bias. Therefore, in the present study the HSC-RS is only validated for Western cultures.

Implications

We believe that observer-rated sensitivity is a promising tool as an objective measure of sensitivity in preschoolers, including the assessment of depth of processing. However, we are more cautious about assessing individual differences in sensitivity across multiple levels, given that there was no evidence that sensitivity at the behavioral level was associated with physiological markers. This may explain a more complex relationship which is dependent on other factors, such as early parenting experiences or environmental stressors. Regarding genes, we recommend the use of polygenic scores, but they need to be improved further by developing polygenic scores specifically for the ES phenotype and tested in larger samples. The observation that the different markers at different levels are not strongly associated in the present study, as well as in a previous study on ES in adolescents (Weyn, Van Leeuwen, Pluess, Goossens, et al., 2022), suggests that the behavioral markers of sensitivity should currently be prioritized for measuring individual differences in ES. Based on the results of the behavioral markers, we found that highly sensitive children might benefit from calm and independent environments, whereas low sensitive children might benefit more from social and exuberant activities. Aligning the school and home environment to the preschoolers' needs based on their sensitivity levels might be associated with better learning outcomes and an increased wellbeing of the preschoolers.

Conclusion

The aim of the present study was to examine the psychometric properties of a recently developed observational measure of sensitivity in preschoolers, to explore the existence of different sensitivity groups, and to examine individual differences in environmental sensitivity at phenotypical, genetic, and physiological levels of analysis in the same sample. Results showed evidence for (a) a reliable observational measure of sensitivity, (b) the existence of three sensitivity groups, that are, a low, medium, and high sensitivity group, (c) moderate, associations with common temperament traits, and (d) a small negative association with the GWAS PGS for ADHD. No associations were found with the candidate sensitivity genes and other PGSs. Regarding cortisol and EEG asymmetry, no significant associations were found. A possible explanation is that the quality of consecutive experienced environments may shape associations with physiological markers. Further research should investigate how the environmental and genetic factors interact in the development of sensitivity at the behavioral and physiological levels.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0954579424001883.

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Competing interests. All authors declare that there are no conflicts of interest.

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