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Parenting intervention effects on children's externalizing behavior: the moderating role of genotype and temperament

Geertjan Overbeek

Recent research suggests that children's heightened susceptibility to parenting may have a (poly)genetic basis, and may be grounded in children's temperament. However, much current evidence is of a preliminary—correlational—nature. Because in correlational designs alternative explanations for gene–environment ($G \times E$) or temperament–environment ($T \times E$) interactions cannot be discounted, it is pivotal to conduct experimental studies in which parenting is actively manipulated. Based on data from a recently conducted randomized trial ($n = 387$) of the Incredible Years parenting intervention, experimental evidence is provided for $G \times E$ and $T \times E$ interactions in an at-risk population of children aged 4–8 years. The discussion centers around the use of polygenic data and microtrial designs, and provides suggestions for how to integrate endophenotypes in tests of $G \times E$ and $T \times E$.

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Children's externalizing behavior is characterized by disobedience, defiance of authority, an angry or irritable mood state, and verbal or physical aggression toward others. A childhood-onset of externalizing behavior marks a heightened risk for a clinical diagnosis of externalizing disorders in young adulthood [1] and increases the likelihood of health problems, substance abuse, financial hardship and delinquency in adulthood [2]. Especially dysfunctional parenting and impaired family functioning have been identified as crucial factors in the development of children's externalizing behavior [3,4]. These findings imply that parenting interventions might yield significant reductions in children's externalizing behavior. Although meta-analyses indeed show that parenting interventions are effective [5] with sustained effects until months or

even several years later [6,7], these effects are generally of a limited size.

One possible explanation for the lower effect sizes for many parenting interventions is that children may differ in the extent to which they benefit from enriched parenting. Unfortunately, most intervention studies do not examine any differentiation in intervention response trajectories, and thus cannot speak to the issue of which children benefit most from improved, more positive parenting. Based on a differential susceptibility hypothesis, however, we would expect this. Specifically, the differential susceptibility hypothesis [8–11] implies that children most vulnerable to adverse parenting would also benefit most from positive parenting. Importantly, children's differential susceptibility may be grounded in children's genotype or temperament.

Indeed, different meta-analyses suggest that genetic polymorphisms related to the regulation of dopamine (*DAT1*, *DRD2*, *DRD4*) [12], serotonin (*5HTTLPR*) [13], and the degradation of specific enzymes (*MAOA*) [14], can modulate the effects of both adverse and enriched environments on children's pathological and prosocial development. There is also meta-analytical evidence that shows that children's susceptibility to parenting has a temperamental basis [15**]. Children with a difficult temperament, specifically, appear more vulnerable to negative parenting but also appear to profit more from positive parenting. The Slagt *et al.* [15**] meta-analysis showed that these inter-individual differences in susceptibility could be indexed across different outcome measures, such as children's externalizing and internalizing problems and children's levels of social and cognitive competence.

The meta-analyses reviewed above should be interpreted with caution, however, because they might to some extent be distorted by publication bias [16]. In addition, most studies meta-analyzed until now have relied on correlational research designs. Although such correlational studies provide much insight, they do come with several important limitations [see also 17*]. First, they are unable to rule out alternative explanations for gene or temperament-by-environment interactions ($G \times E$ and $T \times E$, respectively). More specifically, they do not control for confounding effects of the linkages between children's genotype or temperament and—in this case—the child's parenting context. For instance, children with a difficult temperament perhaps evoke more

controlling and harsh parenting, and this effect may confound any identified person–environment interaction in a correlational design. Second, most previous correlational studies on $G \times E$ or $T \times E$ have been underpowered because of limited variance in the pathological outcome and environmental risk measure and in the $G \times E$ or $T \times E$ interaction terms [see 18].

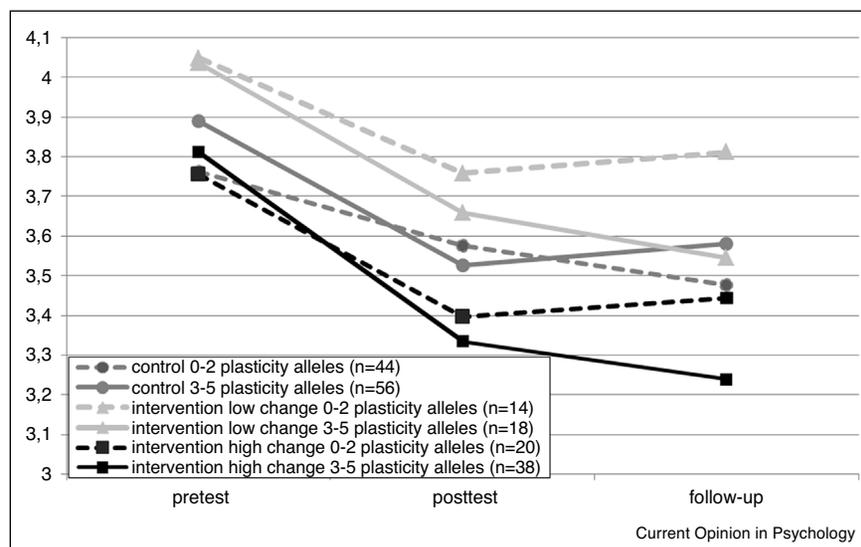
These issues of low statistical power and uncontrolled confounder mechanisms can be effectively resolved in experiments in which parenting is actively manipulated. This is increasingly recognized in the field, and lead us to develop project ORCHIDS [19]. Project ORCHIDS features a randomized controlled trial of the Incredible Years (IY) parenting intervention in an at-risk sample of 387 families of children 4–8 years, who were screened for elevated levels of disruptive behavior (*i.e.*, 75th percentile on the Eyberg Child Behavior Inventory). Eligible families were randomly allocated to a control group or to an intervention group that received 15 two-hour IY sessions. In these IY sessions, parents engaged in parent group discussions, did role-plays, and examined and discussed video-vignettes. The IY intervention is aimed at empowering parents and at guiding parents toward using more positive, reward-based parenting strategies (*e.g.*, child-led play and using praise and incentive schemes) and toward using sensitive, consequent disciplining practices (*e.g.*, limit setting, ignoring unwanted behavior) [20].

Our randomized trial of IY showed that it significantly increased parent-reported positive parenting and successfully reduced parent-reported negative parenting and

externalizing behavior in children [21]. Evidence for $G \times E$ emerged, showing that the IY intervention effects were much more pronounced in boys—not girls—with a high score on a dopamine-based polygenic index that comprised *DAT1*, *DRD2*, *DRD4*, *MAOA*, and *COMT* polymorphisms [22**]. The analyses also showed that, as expected, this effect was explained by improvements in positive parenting (Figure 1). Boys high on the polygenic plasticity index, and whose parents increased most in positive parenting, showed the greatest decline in parent-reported externalizing behavior from pretest to follow-up. Notably, the genetic moderation of the IY intervention effect was only present for parent-report data; when we analyzed observational data from parent–child interactions no significant $G \times E$ emerged. Perhaps this can be explained by the relatively limited variance in the observational measure of child externalizing behavior [21] in this study.

The ORCHIDS data also showed that the IY intervention effects were moderated by children’s temperament, with a significant $T \times E$ emerging for children’s effortful control—but not children’s negative reactivity. This interaction effect demonstrated that children higher on effortful control retained the beneficial behavior effect of IY at follow-up, whereas children low on effortful control bounced back to pre-intervention levels of disruptive behavior at follow-up (G Overbeek *et al.*, unpublished; Table 1). Although this appeared to support the notion of temperament-based differential susceptibility in children, our analyses also demonstrated that children’s temperament and externalizing behavior developed in

Figure 1



Incredible Years parenting intervention effects for boys (from: Chhangur *et al.* [22**]).

Note: ‘Low change’ and ‘high change’ categories refer to boys with, respectively, low or high levels of improvement in parent-reported positive parenting.

Table 1

Direct effects of Incredible Years and interaction effects with temperament

	B (S.E.)	β
Direct effects		
Incredible Years → externalizing $_{\Delta 12}$	-6.08 (1.59)**	-0.19
Incredible Years → externalizing $_{\Delta 23}$	3.87 (1.62)*	0.14
Negative affect → externalizing $_{\Delta 12}$	0.20 (1.39)	0.01
Negative affect → externalizing $_{\Delta 23}$	-0.22 (1.41)	-0.01
Effortful control → externalizing $_{\Delta 12}$	-1.03 (1.49)	-0.05
Effortful control → externalizing $_{\Delta 23}$	2.48 (1.51)	0.14
Interaction effects		
Negative affect × Incredible Years → externalizing $_{\Delta 12}$	-0.03 (1.63)	-0.00
Negative affect × Incredible Years → externalizing $_{\Delta 23}$	-0.94 (1.60)	-0.05
Effortful control × Incredible Years → externalizing $_{\Delta 12}$	1.68 (1.59)	0.07
Effortful control × Incredible Years → externalizing $_{\Delta 23}$	-3.22 (1.58)*	-0.16

Note: Model fit: $\chi^2(8) = 12.15, p = 0.145, CFI = 0.991, RMSEA = 0.037$. $\Delta 12$ denotes change from pretest to posttest (T_1 to T_2); $\Delta 23$ denotes change from posttest to follow up (T_2 to T_3).

* $p < 0.05$.

** $p < 0.01$.

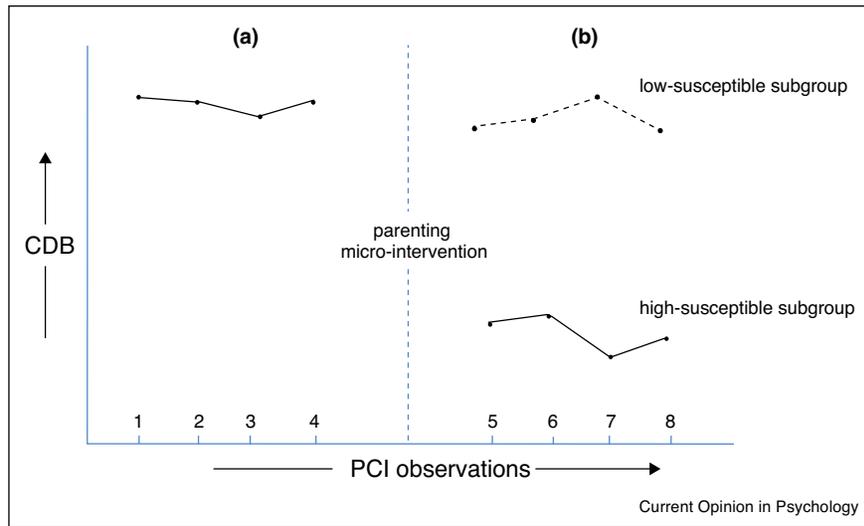
tandem. Specifically, children whose parents participated in the IY intervention simultaneously decreased in externalizing behavior and increased in effortful control (and decreased in negative reactivity). These findings are more in line with a *spectrum hypothesis*, which holds that difficult temperament may be a less intense, mild form of disruptive behavior. Maybe child 'temperament' in the form currently conceptualized and measured is not a separate entity that modulates the effects of parenting on child behavior, but rather maps onto a larger construct of externalizing behavior, with both temperament and externalizing behavior affected by parenting. Notably, our analysis of ORCHIDS data demonstrated that effortful control and negative reactivity were not related to children's score on a dopaminergic polygenic index.

In any case, our findings generally appear to be in line with evidence that emerged from other randomized controlled trials (RCTs) of parenting interventions. For example, one previous RCT that tested a video-feedback intervention to promote positive parenting and sensitive discipline (VIPP-SD), demonstrated that it was effective in reducing child disruptive behavior—but only for children who carried a *DRD4* 7-repeat allele [23]. Another RCT examined the effects of a behavioral parent training for parents of children with an ADHD diagnosis, and showed that children carrying one or no *DAT1* 10-repeat allele profited more strongly from intervention-induced changes in parenting compared to children with two *DAT1* 10-repeat alleles [24]. Finally, another RCT using the Incredible Years program showed that intervention outcomes may depend on the temperament profile of children. In this study, emotionally dysregulated children had a greater intervention-induced decrease in externalizing behavior compared to 'headstrong' children [25].

Although the outcomes of the intervention studies reviewed above may be debated on the extent to which they 'prove' the differential susceptibility hypothesis, they do suggest that gene-environment and temperament-environment interactions underlie the development of externalizing child behavior. In doing so, however, traditional RCTs provide omnibus tests of the effects of parenting interventions as a whole. It is crucial to note that such parenting interventions are like drug cocktails; they contain multiple, potentially efficacious ingredients (*i.e.*, discrete parenting behaviors taught) that are delivered together as one intervention package [26]. Little is known, however, about which changes in parenting behaviors drive the actual intervention effects [27,28]. Especially genetically and temperament-informed microtrials can solve this problem, by showing which specific changes in parenting behaviors lead to reductions in children's externalizing behavior, and for which subtypes of children the effects of these parenting changes come out strongest [29**]. Although some pioneering microtrials have recently been conducted [30,31*,32]—focusing on manipulations of parental self-efficacy and parents' sensitive play behaviors—these have not included gene or temperament measures to understand which children (or parents, for that matter) are most affected by the experimental manipulation.

In delineating an ecologically valid microtrial of children's susceptibility to parenting—looking at real-time parent-child interactions—a fruitful approach might be to rely on examinations of interrupted time series (ITS). An ITS experiment [33] can help to estimate a developmental trajectory across repeated measurements of children's externalizing behavior, which is at one point interrupted by a micro-level parenting intervention (see Figure 2).

Figure 2



Hypothesized outcome of interrupted time series.

Note: CDB = child disruptive behavior; PCI observations = parent-child interaction observations; numbers denote interaction episodes.

One advantage of an ITS approach is the significantly increased statistical power, because of the multiple measurements at the pre- and post-intervention stage. Another advantage is that the ITS approach, compared to pre-post RCTs, allows for a more refined test of competing hypotheses about potentially non-linear intervention effects. Thus, because an ITS approach allows for the analysis of multiple complex change processes, it may prove invaluable for studying gene or temperament-based differential susceptibility to parenting in children. It will be crucial, however, to perform such ITS studies in at-risk families, characterized by dysfunctional parenting practices or aversive parent-child interactions. Only in such samples will a pre-intervention episode truly constitute a 'for worse', negative parenting condition. Also, because micro-interventions are not expected to bring about large effects on distal outcomes [26], it will be essential to examine the parenting and child behavior outcomes in ecologically valid, observed parent-child interactions directly following a manipulation of the parenting context [see 31*].

In our ORCHIDS study [21] we followed up on recent calls from geneticists to move away from overly simplistic, single candidate gene analyses. However, our—and others'—use of cumulative polygenetic indices [34] is still relatively limited, as it relies on using only a handful of markers, or relies on breaking down the overall polygenetic index into separate categories of more versus less susceptible subgroups. Such an approach may neither resolve the problem of low statistical power, nor does it fully exploit all genetic information available. In addition, simply summing different genetic markers may be a poor conceptual reflection of the more complex interrelations

among them [35]. Specifically, it does not seem likely that every genetic marker has a similar impact (as is implicitly assumed in a cumulative approach). Rather, one genetic marker may be dominant, or the co-existence of specific markers may lead to synergistic, rather than additive, effects. In future research, polygenetic indices ideally contain variants that are part of a genetic pathway with a known neurobiological function. Ideally, also, such genetic variants have established links to an outcome of interest, through GWAS [11,36].

Do the findings from ORCHIDS and related RCTs on $G \times E$ and $T \times E$ have any real-life implications or benefits for clinical practice? We think they do, but in the longer run and when several prerequisites are met. Specifically, if experimental research (*i.e.*, RCTs, micro-trials, and ITS experiments) yield $G \times E$ effects with sufficiently large effect sizes that are replicated across studies and that generalize to real-world clinical settings, clinicians and child practitioners may benefit greatly. These benefits primarily relate to increased cost-effectiveness and precision of clinical practice [37]. If parents and children benefit more from parenting interventions that are designed to meet their specific needs, based on their genetic or temperamental susceptibility, it becomes possible to target subgroups with interventions differing in intensity, duration, and even clinical focus. In addition, genetically or temperamentally informed micro-trials can be used to examine etiological processes underlying children's externalizing behavior. This provides crucial input for improving the specificity of parenting interventions, identifying the child and parent characteristics and family dynamics that need to be targeted for optimal result [38].

The last point may be especially relevant, given that currently the developmental processes through which $G \times E$ and $T \times E$ affect children's externalizing behavior are unclear [39**]. A crucial question remains: how does children's (poly)genetic susceptibility work? The answer to this question may be found in the examination of endophenotypes, or bio-behavioral traits. These endophenotypes may determine how children react to parental behaviors and emotions in the socialization process [37,40]. Indeed, it has been demonstrated that individuals' reactivity to environmental stimuli can be gauged on different levels: neurobiological, psychophysiological, and behavioral. For example, patterns of activity in brain areas [41,42], hostile reactivity in aversive family interactions [43], facial muscle tension, and respiratory sinus arrhythmia [44,45] may all be likely 'candidate endophenotypes' to include in our examinations of gene-by-parenting and temperament-by-parenting interactions in explaining variance in child externalizing behavior.

Conflict of interest statement

The author reports no conflicts of interest.

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