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### My dopamine has been busy: Research on gene by environment interactions in child externalizing behavior

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## CHAPTER 4

GENE BY ENVIRONMENT RESEARCH TO PREVENT  
EXTERNALIZING PROBLEM BEHAVIOR: ETHICAL  
QUESTIONS RAISED FROM A PUBLIC HEALTHCARE  
PERSPECTIVE

- KEYWORDS** – Gene by environment interactions  
Intervention  
Randomized-controlled-trial
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- ABSTRACT** – **The main public health advantages of examining gene by environment interactions (i.e., G × E) in externalizing behavior lie in the realm of personalized interventions. Nevertheless, the incorporation of genetic data in randomized controlled trials is fraught with difficulties and raises ethical questions. This paper has been written from the perspective of developmental psychologists who, as researchers, see themselves confronted with important and in part new kinds of ethical questions arising from G × E research in social sciences. The aim is to explicate and discuss ethical questions, based on the conviction that what is ethically salient in a research setting will also be relevant in that area of public healthcare incorporating research findings. The ethical questions discussed include: whether it is ethically responsible to withhold an effective treatment; to what extent genetic results should be disclosed; whether researchers should be allowed to collect genetic data of both child and parent; and what are costs and benefits of personalized interventions based on (genetic) screening. We made an attempt to address these questions, but it is up to researchers to determine whether the solutions are suitable for their G × E research in social sciences.**

A recent Dutch epidemiological study showed that 28.3 per cent of the general population develops one or more externalizing disorders during their lifetime (De Graaf, Ten Have, Van Gool, & Van Dorsselaer, 2012). These disorders take the form of either substance dependence or abuse, conduct disorder or attention deficit hyperactivity disorder. In particular, a childhood onset of externalizing problem behavior compromises individuals' healthy ageing over their life course, resulting in major repercussions for individuals and society at large. For example, externalizing problem behaviors are related to school dropout and unemployment, to increased risk of long-term disease and obesity, to higher likelihood of developing comorbid disorders such as depression or anxiety, and to higher risk of injury and mortality (Jokela, Ferrie, & Kivimäki, 2009; Von Stumm et al., 2011). This places an increased burden on mental healthcare, amounting to € 924 billion per year in the European Union (EU) alone (Gustavsson et al., 2011; Wittchen et al., 2011). We would like to argue that the key in reducing these problems lies in prevention. However, the effect sizes of preventive interventions that target externalizing problem behavior are modest at best (Dodge et al., 2015; Menting et al., 2013). Moreover, we realize that early screening and preventive measures in this regard have been associated with ethical concerns—discussed in this volume (cf. Munthe & Radovic, 2015) and beyond (e.g., Horstkötter, Berghmans, & De Wert, 2014; Horstkötter & De Wert, 2013; Singh & Rose, 2009). Nonetheless, in this paper we will focus on the question how to improve the effectiveness of preventive interventions, because effectivity is an important criterion for the justifiability of an interventional approach. Interventions targeting early externalizing behavior that are known to be ineffective or marginally effective are under all circumstances difficult to justify.

One way to improve effectiveness of intervention programs is to gain insight into individual differences in treatment responsivity. In accordance with a personalized medical perspective, this may help us to answer the question 'which intervention works best, for whom' (Belsky & Van IJzendoorn, 2015). In order to arrive at that answer, however, we may need to significantly improve our understanding of the interplay between individuals' genetic characteristics and crucial environmental factors (i.e., gene by environment interaction), such as parenting, that are targeted in many interventions for externalizing problem behavior. Extant research has identified specific allelic variations of genes (i.e. genetic polymorphisms) to function as 'risk alleles' under certain environmental adversity. This means that children carrying a specific polymorphism may be at increased risk for the development of externalizing problem behavior when exposed to maladaptive environments. The identification of children carrying such 'risk alleles' may enhance our capacity to identify those at greatest risk for the development of psychopathology at an early developmental stage (Kaufman & Perepletchikova, 2011). In addition, identifying children carrying genetic risk in the context of interventions might lead to superior knowledge about individual differences in treatment responsivity. Thus, one main public health advantage of research that further examines such gene by environment interactions (G × E) may be found in the realm of personalized interventions.

Reliably identified and replicated  $G \times E$  can thus help boost effectiveness of current interventions aimed at reducing externalizing problem behavior. In the long run,  $G \times E$  research may even help to tailor such interventions to the needs of children and parents with specific constellations of genetic and family risk factors. Specifically, leading scholars suggested that in the long run, dependent on sufficiently replicable, generalizable, and explicable  $G \times E$  findings, it might become possible to target various genetic subgroups with interventions differing in intensity, duration, and even clinical focus (Rutter, 2012). In this light, findings from recent experimental studies that provided evidence for differential responsivity to interventions based on child genetic-makeups are highly intriguing (for meta-analysis see Van IJzendoorn & Bakermans-Kranenburg, 2015). Nevertheless,  $G \times E$  research—and the incorporation of genetic data in randomized controlled trials (RCTs) in particular—is fraught with difficulties and raises several serious ethical questions. This paper has been written from the perspective of developmental psychologists involved in conducting this kind of research and who, as researchers, see themselves confronted with important and in part new kinds of ethical questions arising from  $G \times E$  research in social sciences. The aim is to explicate and discuss these ethical aspects, based on the conviction that what is ethically salient in a research setting will also be relevant in the area of public healthcare that is supposed to incorporate such like findings. First, we will explain the central concepts that are currently used in  $G \times E$  research. Second, we will discuss ethical questions that researchers might encounter when conducting  $G \times E$  research in a randomized controlled trial, which we call from now on a ' $G \times E$  trial'. Partly, this will be based on our own experiences with conducting such a  $G \times E$  trial involving genetic susceptibility to parenting behavior and the provision of a modified environment, in our case a parent management training. The ethical questions we encountered refer to: (i) withholding effective intervention, (ii) disclosure of genotyping results, (iii) collecting genetic data of both child and parent, and (iv) implementing  $G \times E$  in clinical practice (see also Horstkötter et al., 2014; Horstkötter & De Wert, 2013; Munthe & Radovic, 2015 [this issue]; Singh & Rose, 2009).

### $G \times E$ interactions

The expression 'gene by environment interaction' ( $G \times E$ ) refers to the assumption that in order to understand human behavior neither genetic nor environmental factors should be evaluated in isolation, since most behavioral outcomes are the result of complex interactions between a certain genetic-makeups and specific environmental conditions. In social sciences,  $G$  is mostly operationalized in terms of one single genetic factor (candidate gene) that is related to an individual's sensitivity to a specific environmental ( $E$ ) condition. In the context of developmental psychology,  $G \times E$  means, for example, that the behavior of children carrying a specific allele of one defined gene, may be more negatively affected by adverse environmental conditions compared with other children who do not carry this specific allele, yet nonetheless suffer from the same conditions. More specifically, research found that children with the low-activity allele of the *MAOA* gene, a gene that is involved in the degradation of dopamine, more

often developed a conduct disorder when being maltreated, compared to maltreated children with the high-activity allele of this gene (for meta-analyse see Byrd & Manuck, 2014; Kim-Cohen et al., 2006). The low-activity allele of the *MAOA* gene can therefore be considered a 'risk allele', yet the risk will only become manifested when exposed to an environmental risk factor. Or in reasoning the other way around, some environmental risk factors have more impact in children carrying the low-activity allele than in children without such an allele.

Also important here are so-called 'gene  $\times$  gene  $\times$  environment interactions' ( $G \times G \times E$ ).  $G \times G \times E$  refers to two different processes. First, it refers to an effect of two or more genetic factors (i.e., at least two alleles) that are related to an individual's sensitivity to environmental conditions. The assumption is that children with two or more risk alleles may be more strongly affected by negative environmental conditions (i.e., polygenic effect) than children with none or only one of the risk alleles. For example, one study found that the more risk alleles children carried, the less self-regulation they manifested under unsupportive parenting conditions (Belsky & Beaver, 2011). Second,  $G \times G \times E$  have also been taken to refer to situations in which both parent and child carry a risk allele. This might affect both the parent and the child more strongly to negative environmental conditions, conferring a negative 'double whammy' effect of behavioral outcomes (Jaffee, Moffitt, Caspi, & Taylor, 2003). That is, parents with a risk allele may be more vulnerable to stress and thus show more maladaptive parenting when under stress themselves, and as a consequence their children who are also carrying a risk allele may in turn be more strongly affected by this maladaptive parenting.

### Gene-based differential susceptibility

There is increasing evidence that the genetic factors commonly identified as making children more vulnerable for environmental adversity, and hence constitute a risk for developing externalizing problem behaviors, may instead function as 'plasticity alleles'. That is the same children who are genetically most vulnerable when exposed to adverse environmental conditions may also be most positively affected by enriched environmental conditions as for example with warm, positive, and sensitive parenting. This idea is captured by the so-called 'differential susceptibility model' (Belsky et al., 2007; Belsky & Pluess, 2009, 2013; Boyce & Ellis, 2005). This model holds that some children are genetically more likely to be affected by parenting in a 'for better AND for worse' manner. Children will suffer severely if ignored or maltreated, but will flourish spectacularly when receiving adequate care. To put it in an widely used metaphor, it may be that we have overlooked that some children are like 'orchids'—they are susceptible children who are fragile and fickle but who are also capable of blooming spectacularly if given greenhouse care. Yet other children may be rather like 'dandelions': resilient children who are able to take root and survive almost anywhere and even find their way in adverse environments. In this context, the polymorphisms long regarded as risk alleles might therefore be better regarded as 'plasticity alleles'. A recent review (Belsky et al., 2009) and several single studies have suggested that

indeed specific polymorphisms located in various genes, for example *DRD2*, *DRD4*, *DAT1*, *MAOA*, *COMT* and *5-HTTLPR*, should be considered to function as susceptibility rather than vulnerability factors (Belsky & Pluess, 2009).

At the moment, the tenability of this genetic differential susceptibility model is still unclear. Importantly, many  $G \times E$  studies previously conducted did not meet all necessary preconditions for establishing differential susceptibility (Overbeek et al., 2012). One major issue is that they almost exclusively focused on dysfunction and environmental adversity. In doing so, however, these studies failed to address the question of whether susceptible children might also manifest more competence or happiness in response to environmental enrichment than their resilient peers.

### The ORCHIDS study

From an empirical perspective it is important to overcome this limitation of  $G \times E$  research. But also from a public health perspective it is particularly important to gain more knowledge on this issue, because several ethical concerns that take place when conducting  $G \times E$  research are also relevant for public healthcare that is supposed to incorporate such like findings. To test genetically based differential susceptibility, we conducted a genetically informed RCT: the ORCHIDS study (Observational Randomized Controlled Trial on Childhood Differential Susceptibility; see Chhangur, Weeland, Overbeek, Matthys, & Orobio de Castro, 2012). In this paper we will discuss questions on the basis of this study. Specifically, we tested whether a positive change in the parenting environment, based on the provision of the so-called 'Incredible Years' (IY) intervention, would be more effective in decreasing externalizing problem behavior in children with a plasticity allele than in children without such a plasticity allele. This study design would allow us to test the  $G \times E$  interaction, between a stimulating parenting environment and the specific genetic make-up of children such approached. Also, we aimed to test  $G \times G \times E$  within the child as well as between the child and parents. This was done to test whether children with two or more plasticity alleles would be more strongly affected by an induced positive environmental condition, compared with children with none or only one of the risk alleles.

In our study, we invoked the IY intervention as a positive environmental stimulus that is able to realize the enriching environment that susceptible children respond to particularly well. IY aims to improve parenting skills in order to reduce children's externalizing problem behavior, and enhance children's prosocial and competent behavior (Webster-Stratton & Hammond, 1997; Webster-Stratton, 1994). Previous RCTs have provided evidence that the program is effective in ameliorating parental behavior and via this route, is able to reduce externalizing problem behavior in children (for meta-analysis see Menting et al., 2013).

We considered the main advantage of using an RCT design to increase statistical power and thereby to indeed identify potential  $G \times E$ . This superior power is based

on the active manipulation of an environmental factor of interest, which in our case, was dichotomized (i.e., intervention with and without plasticity alleles vs. control group with and without plasticity alleles). However, the envisioned incorporation of genetic data in this RCT raised several ethical questions directly linked to the domain of public healthcare. In the second part of this paper, we would now like to present and discuss these questions, because we think the ethical questions of  $G \times E$  research regarding externalizing behavior have been given insufficient attention so far, while much emphasis is being put on potential clinical applications (Bakermans-Kranenburg & Van IJzendoorn, 2015; Van IJzendoorn & Bakermans-Kranenburg, 2015).

### Ethical questions raised in $G \times E$ research

#### Withholding effective interventions

Like most healthcare RCTs involving human participants,  $G \times E$  trials raise the question whether it is justifiable to withhold interventions from participants in order to accomplish scientific objectives. The debate contributes to the overall view that, although researchers usually do not have professional obligations to provide medical care to participants, they have ethical obligations to avoid exploiting them (Resnik, 2008). In order to justify withholding (effective) treatment to the control group, researchers should clearly state the scientific objectives and clinical as well as potential social or public health gain of the study (Miller & Brody, 2002). In (bio)medical sciences, placebo-controlled RCTs are widely used as a first step of bringing new drugs into the market and justification of withholding treatment through scientific objectives seems to be very well accepted (Kolko, Bukstein, & Barron, 1999; Punja, Zorzela, Hartling, Urichuk, & Vohra, 2013; Wolraich et al., 2001). By contrast, the incorporation of biological or genetic data, and the use of control groups, currently seems to be less accepted in social sciences. Research in this area most often solely uses psychological measurement data rather than participants' genetic data and uses waiting list conditions rather than control conditions. However,  $G \times E$  trials incorporate both by including psychological measurements and genetic data to gain knowledge in both psychological as well as in biological processes. Thus, a traditional division between biological and social behavioral disciplines seems no longer justifiable:  $G \times E$  research transgresses previous boundaries and contains a biological and a psychological compound that are closely related to individual outcomes. Initially this has been met with reluctance in the social sciences to accept  $G \times E$  trials in which control groups are withheld; certain interventions may well be reconsidered. We argue that withholding an effective intervention to control groups in a  $G \times E$  trial setting in social sciences can be justified, on the ground that it is an empirical necessity and provided that these individuals are permitted to receive care as usual and are therefore not withheld of (mental) healthcare, as was the case in the ORCHIDS study.

The scientific objective of the ORCHIDS study was to test the differential susceptibility

hypothesis. More specifically, we wanted to examine whether children with (more) plasticity alleles—who have been previously shown to do worse under negative parenting conditions—will indeed do better under positive parenting conditions compared to their resilient peers without those plasticity alleles. By testing whether these genetically based susceptible children showed most improvement after their parents received the IY intervention, we tested the ‘for better’ part of the differential susceptibility equation. In doing so, we hoped to gain insight into the malleability of these susceptible children who, for a long time, had been thought to be not susceptible, but vulnerable and fragile. But to get to know whether any behavioral change in these children’s behavior is due to an enriching environment (instead of for example children simply aging), we needed to be able to compare children who received intervention to a control group.

In the ORCHIDS study we used the evidence-based IY intervention, which was only offered to parents in the experimental group. The effectiveness of the training has been shown multiple times (for meta-analysis see Menting et al., 2013). This might lead to the thought that a control group in a RCT is apparently withheld from an effective intervention. However, a control group in this case is an empirical necessity to generate evidence that participants are indeed being differentially susceptible to preventive interventions. Such evidence might create more realistic expectations of intervention efficacy. Weak intervention effects might lead to a dead end, not only in  $G \times E$  research but also in terms of policymaking in public healthcare. Policymakers might, in turn, be concerned about limited interventional impacts and cost-effectiveness and thus they might be less inclined to support interventions or to roll out evidence-based interventions on a larger scale when its effectiveness is modest. This way the intervention effect might in fact be underestimated for a specific group: the susceptible children with a plasticity allele (and possibly overestimated for children without such a plasticity allele).  $G \times E$  trials, with a control group, can generate a basis of proof for this relatively new idea (Bakermans-Kranenburg & Van IJzendoorn, 2015).

One might also argue that if we take the assumption of differential susceptibility seriously, we should take into account the possibility that an intervention may be offered to (sub)groups of families—that is the resilient ones—for whom this intervention might not be that effective. At the same time this means that the control group, who do not receive intervention, will contain similar families who anyhow would not have profited very much from the intervention and for whom it might make little sense to argue that they are withheld from an effective intervention. However, it does not follow that those who prove relatively resilient (i.e., less susceptible) do not benefit at all from any interventions. Notably, it just might be that the less susceptible children need an expanded duration, range, or intensity to reach the same effect as the more susceptible ones. Thus, withholding an effective intervention would do harm to these families (Belsky & Van IJzendoorn, 2015). More research is needed to test whether this is truly the case, but until then, families with

children carrying none or fewer plasticity alleles should not be excluded from any intervention solely based on their genetic-makeup.

Taken together, in a  $G \times E$  design it is unclear what should count as withholding of treatment. But as soon as the possibility of plasticity alleles is taken into account and we want to gain more knowledge on differential susceptibility to intervention, a situation of equipoise might come into existence. This might justify the set-up of  $G \times E$  trials that makes use of a control group in order to investigate—again—an intervention that otherwise had been recognized as a small to moderate effective program. Only this design allows us to gain insight into potential differences in susceptibility, to improve our ability to determine what works for whom, and to avoid old-fashioned ‘one size fits all’ approaches in the future (Belsky & Van IJzendoorn, 2015).

## Disclosure of results

The rapid expansion of knowledge on human molecular genetics has led to an extensive debate about whether genetic data should be disclosed to participants (Jarvik et al., 2014; Quaid, Jessup, & Meslin, 2004; Savulescu & Skene, 2012). Main arguments for full disclosure whatsoever are that participants expect an element of reciprocity when participating in research (Hoeyer, 2010), that disclosure may be the main motivation to participate (e.g., Sutrop & Simm, 2004), and that participants should be informed about any results that may be valuable to their (psychological) well-being (Knoppers, Joly, Simard, & Durocher, 2006). Main arguments for not disclosing results are that participants are not capable of adequately interpreting genetic information, leading to unclear or false conclusions (Klitzman, 2006) and that social scientists do not have the appropriate expertise to communicate results on genetics at a clinical level (Clayton & Ross, 2006). Although no consensus on this issue has yet been reached, the extreme positions of either full disclosure or no disclosure whatsoever have seldom been defended. On a middle ground, therefore, scholars stated that further discussion should no longer address whether (genetic) data should be disclosed, but instead should address how best to make an appropriate selection of results to be disclosed (see Bredenoord, Kroes, Cuppen, Parker, & Van Delden, 2011; Bredenoord, Onland-Moret, & Van Delden, 2011).

In line with Bredenoord, Onland-Moret, and colleagues (2011), we believe that the ethical question that should be addressed is: Under which circumstances should results be disclosed to participants? However, there are a few things we need to take into account before discussing this further. First of all, research on  $G \times E$  interactions is still in its infancy and findings need replication and extension before we can know their full implications (e.g., Duncan & Keller, 2011; Rutter, 2012). Second, to date  $G \times E$  results are only applicable at a group level. Most processes in developmental psychology are non-ergodic, meaning that results at the group level do not automatically hold true for each individual within that group (Molenaar, 2008). Third, there is a problem with explaining genetic results to children. Research in  $G \times E$  in social

science, and particular in developmental psychology, often includes under-aged children. In accordance, parents need to give their informed consent for the use of their children's genetic data. Full disclosure would mean that parents are responsible for explaining such information—on whether their child has certain specific alleles or not, and what this means precisely—to their child, because the results are primarily disclosed to the parents (Hamilton, Bowers, & Williams, 2005). This may lead to an ineffective or incorrect communication of the results to children, which would be of little use. Another problem is that this information has no individual clinical value. Moreover, even if it would have individual clinical value, children may not want to know this information—and in this procedure it would be hard for researchers, who are responsible for an adequate and ethically sound dissemination of their research findings, to monitor this process (Tarini, Tercyak, & Wilfond, 2011).

In the ORCHIDS study we decided that informing parents about their individual child's genetic information would offer no immediate personal benefit but instead might give families an unnecessary 'overload' of information that is difficult to interpret. Also, such information may give rise to false genetic determinism in parents and may create adverse developmental effects in families. For example, based on information about their child's genotype, parents might believe their child is at increased risk for adversity and pathological development, and because of this may treat their child differently (e.g., increasing their strict behavioral control or even administering harsh discipline). Nevertheless, we hypothesized that disclosure on a group level would do no harm. In accordance, we decided to give parents the results of the study on  $G \times E$  for the total sample, to which they belonged. Thus, as parents may expect an element of reciprocity and may be more motivated to participate when outcomes are communicated, we decided to do so in an accessible and nuanced way without providing them information about the genetic-make up of their individual child (e.g., popular scientific article and newsletters, see Knoppers et al., 2006). We realize that disclosure of genetic data might be questioned not only in a research setting, but particularly also in a related—future—clinical setting. Critical scholars, for example, uttered the concern that resilient children might be increasingly ignored or left help-less (Wasserman, 2004). We will revert to this point in due course.

### Collecting genetic data from children and parents

The next step for  $G \times E$  trials might be to investigate the genetic effect of multiple plasticity alleles in combination with an environmental condition (i.e.,  $G \times G \times E$ ) rather than with one plasticity allele (i.e.,  $G \times E$ ). The possession of a plasticity allele in parent and child might confer a 'double whammy' effect (Jaffee et al., 2003): extra heightened susceptibility, due to possessing more than one plasticity allele. In the ORCHIDS study we wanted to investigate this effect. To that end we hypothesized that parents with a plasticity allele would benefit the most from the IY intervention and that, in turn, their significant change in positive parenting behavior would be cumulatively beneficial if their child also carried this plasticity allele. To date, however,

such  $G \times G \times E$  effects have gone almost entirely untested in genetically informed research designs. One reason for this seems to be that  $G \times G \times E$  research generates or is faced with new research-related ethical dilemmas.

A further ethical question might consist in the additional burden of parents when their genetic sample is collected. One might argue that this burden, even though very small (i.e., one saliva swab), is unnecessary since the scientific yield may be minimal. In this case, scientific yield may be minimal because the strong genetic association between parent and child (i.e., heritability) might lead to an underpowered test of effect (i.e., there are only a few families in which children and their parents are not genetically alike). Indeed there is a great overlap of about 50 per cent between parents' DNA and that of their offspring. In our view, however, this line of reasoning does not withstand close scrutiny. Given that every gene has two alleles, from which the child inherits one of the mother and one of the father, the actual genetic overlap between a given parent and offspring can be much smaller than 50 per cent. That, however, might require the separate collection of parental genetic data; or at least it would require an explicit discussion of how much, or how little, overlap is needed to consider the separate collection of parental DNA either justified or not. This discussion, which could be considered a discussion on the specific risks and benefits of an innovative research approach, will have to take place with local IRBs in charge of approving such projects. Likewise, however, we would like to argue it should take place in the bioethical discourse that from a theoretical point of view will have to settle the ethical boundaries of research beyond former disciplinary boundaries.

### Implementation of knowledge on $G \times E$ in clinical practice

The aim of  $G \times E$  research in public healthcare is to gain knowledge on what works for whom, in order to tailor interventions in duration, intensity and clinical focus. Even though public healthcare might benefit from such kind of research in the long run, its application might also raise several ethical questions. Specifically, it raises the question of how to implement the knowledge that some children, the resilient ones, are less or non-responsive to interventions in an ethically justifiable way. The danger lurks that these children will not be prioritized to receive the intervention although they need help as much or possibly even more than others. These children, however, may well benefit from interventions that are tailored to their specific neurobiological characteristics (Matthys et al., 2012). Thus, especially for these potentially less susceptible children it seems important to develop a rich array of care and assistance and thus this group should never be neglected socially because of their genetically predisposed resilience (Ellis, Boyce, Belsky, Bakermans-Kranenburg, & Van IJzendoorn, 2011).

Another ethical question that comes up is: How valid the implications of  $G \times E$  trials then really are for public healthcare? And even if we get to the point of reliable implications—how are we going to identify the more plastic families that are supposed to be most (or even exclusively) susceptible for an intervention? Are we going to apply

genetic testing? Some scholars predict that genetic testing will become increasingly important as a guide to prevention, drug treatment, and clinical management (Burke et al., 2002; Van Goozen & Fairchild, 2008). But as Munthe and Radovic (2015) [this issue] argued, even if we could locate an inherent plasticity characteristic through genetic screening, no evidence could be found that such a trait would manifest itself as a plasticity factor; this is because it is the interaction with the environmental condition itself that reveals such a factor. Therefore, we also need knowledge on 'why' these children are more susceptible. Specifically, we need to know which neurobiological endophenotypes underlie such an interaction between G and E. In addition, genetic screening could present collective risks to an identifiable subgroup (Sharp & Foster, 2000). For example, a genetic screening that associates a plasticity allele with a genetic disposition for externalizing behavior problems could lead to group stigmatizing and discrimination (Rodriguez, 2012; Viding, Larsson, & Jones, 2008). Thus, we are still far from a point where researchers can claim that we should give an intervention to some children and not to others due to their genetic make-up. With the current state of knowledge, genetic screening for differential susceptibility would lead to too many false decisions (Belsky & Van IJzendoorn, 2015). However, it might very well be that in the future we come to a point where we gain knowledge into neurobiological endophenotypes associated with genetic plasticity, which makes (genetic) screening in the context of preventive intervention more appropriate.

## Conclusion

Similar to what is currently happening in modern (bio)medicine, it is important to gain insight into individual differences in 'treatment responsivity' to behavioral interventions. Several candidate genes have been proposed as markers for such differences in responsivity. Increasing our knowledge on G × E may help to tailor personalized interventions, and in turn boost the currently small to modest effectiveness of interventions aimed at reducing children's externalizing problem behavior (Bakermans-Kranenburg & Van IJzendoorn, 2015; Van IJzendoorn & Bakermans-Kranenburg, 2015). However, there are several ethical questions involved in conducting G × E trials to shape such intervention strategies. We made an attempt to address some of these questions that social scientists in this field often encounter when designing a study. We have offered a description of ethical considerations in the ORCHIDS study and the chosen solution. It is up to researchers to determine whether these solutions might be suitable for their G × E trials. However, even if researchers are able to effectively resolve these questions, they should not neglect additional concerns about implementing G × E results in public healthcare and should prepare for ethically sound future practices. How this can be realized, however, needs further debate.

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