Published in final edited form as:
Eur Child Adolesc Psychiatry. 2015 February ; 24(2): 209–217. doi:10.1007/s00787-014-0567-2.

Differential Susceptibility to Maternal Expressed Emotion in Children with ADHD and their Siblings? Investigating Plasticity Genes, Prosocial and Antisocial Behaviour

Jennifer S. Richards[1,2], **Catharina A. Hartman**[3], **Barbara Franke**[4,5], **Pieter J. Hoekstra**[3], **Dirk J. Heslenfeld**[6], **Jaap Oosterlaan**[6], **Alejandro Arias Vásquez**[1,5], and **Jan K. Buitelaar**[1,2]

[1]Department of Cognitive Neuroscience, Donders Institute for Brain, Cognition and Behaviour, Radboud university medical center, Nijmegen, The Netherlands [2]Karakter Child and Adolescent Psychiatry University Center, Nijmegen, The Netherlands [3]University of Groningen, University Medical Center Groningen, Department of Psychiatry, The Netherlands [4]Department of Human Genetics, Donders Institute for Brain, Cognition and Behaviour, Radboud university medical center, Nijmegen, The Netherlands [5]Department of Psychiatry, Donders Institute for Brain, Cognition and Behaviour, Radboud university medical center, Nijmegen, The Netherlands [6]Department of Clinical Neuropsychology, VU University Amsterdam, The Netherlands

Abstract

Background—The differential susceptibility theory states that children differ in their susceptibility towards environmental experiences, partially due to plasticity genes. Individuals carrying specific variants in such genes will be more disadvantaged in negative but, conversely, more advantageous in positive environments. Understanding gene-environment interactions may help unravel the causal mechanisms involved in multifactorial psychiatric disorders such as Attention-Deficit/Hyperactivity Disorder (ADHD).

Methods—The differential susceptibility theory was examined by investigating the presence of interaction effects between maternal expressed emotion (EE; warmth and criticism) and the solitary and combined effects of plasticity genes (*DAT1, DRD4, 5-HTT*) on prosocial and antisocial behaviour (measured with parent- and self-reports) in children with ADHD and their siblings (*N*=366, *M*=17.11 years, 74.9 % male).

Corresponding author: Jennifer Richards, Radboud university medical center, Department of Cognitive Neuroscience / Karakter Child and Adolescent Psychiatry University Centre, Reinier Postlaan 12, 6525 GC Nijmegen, The Netherlands. Jennifer.Richards@radboudumc.nl.

Ethical Standard

Informed consent was signed by all participants (parents signed informed consent for participants under 12 years of age) and the study was approved by the ethics committee (Centrale Commissie Mensgebonden Onderzoek).

Declaration Of Interest

In the past 3 years, Dr. Buitelaar has been a consultant to / member of advisory board of / and/or speaker for Janssen Cilag BV, Eli Lilly, Bristol-Myer Squibb, Shering Plough, UCB, Shire, Novartis and Servier. He is not an employee of any of these companies, and not a stock shareholder of any of these companies. He has no other financial or material support, including expert testimony, patents, and royalties. In the past 3 years, Dr. Hoekstra has been a consultant to/member of advisory board of Shire. Dr. Oosterlaan has received an unrestricted investigator initiated research grant from Shire. Ms. Richards and Drs. Franke, Heslenfeld, Arias Vásquez and Hartman have no conflicts of interest do declare.

Results—Maternal warmth was positively associated with prosocial behaviour and negatively with antisocial behaviour, while maternal criticism was positively associated with antisocial behaviour and negatively with prosocial behaviour. No evidence of differential susceptibility was found.

Conclusions—The current study found no evidence for differential susceptibility based on the selected plasticity genes, in spite of strong EE-behaviour associations. It is likely that additional factors play a role in the complex relationship between genes, environment and behaviour.

Keywords

Maternal expressed emotion; antisocial behaviour; prosocial behaviour; GxE interaction

Introduction

Understanding the interaction between genes and environment may help unravel the causal mechanisms involved in multifactorial psychiatric disorders such as Attention-Deficit/ Hyperactivity Disorder (ADHD) [1]. A current perspective on Gene-Environment (GxE) interaction, the differential susceptibility theory, states that children differ in their susceptibility towards environmental experiences [2,3] and that this difference is (partially) explained by genes called “plasticity genes” [4]. Individuals carrying specific variants in such genes will be more susceptible to both negative and positive environments [4,5]. This view extends the more commonly applied diathesis-stress and dual-risk models, which focus only on the vulnerability to adverse effects of negative environments [6].

The dopamine receptor D4 (*DRD4*) and the serotonin transporter (*SLC6A4/5-HTT*) genes are the most studied candidate plasticity genes. The *DRD4* has a variant that differs in the number of a 48-base pair tandem repeat located in exon III of the gene. The repeat length ranges from 2 to 11. From these, the 7-repeat allele has been identified by numerous studies as a differential susceptibility variant [6,7], although there have also been null findings [8]. Children with the 7-repeat allele have been shown to be more susceptible to a range of parenting factors, like maternal sensitivity and positivity, when investigating children’s externalizing behaviour, physiological stress reactivity, sensation seeking, attachment, or social behaviour [9,6,10]. Specifically in the context of ADHD, which is the focus of the present study, it has been found that children with the 7-repeat allele were most likely to be diagnosed with ADHD when exposed to prenatal smoking, but also less likely when not exposed to prenatal smoking [11].

The *SLC6A4* gene, better known by its aliases, *5-HTT* and *SERT*, has a variable length (polymorphic) region with short (S) and long (L) repeat alleles in the promoter region, the *HTTLPR*. Research has revealed carriers of the short allele to be more susceptible to several family factors, (stressful) life events, and socioeconomic status [6,12–15], mostly in relation to depression and anxiety [6], but also in the context of positive outcomes such as social behaviour [12]. A study in individuals with ADHD reported that delinquents with at least one short allele were most likely to have persistent ADHD when they had experienced an adverse childhood environment, but least likely when the amount of adversity experienced was low [16].

A gene that has been investigated less often, but with equally interesting results in support of the differential susceptibility theory, is the dopamine transporter gene (solute carrier family 6 [neurotransmitter transporter], member 3 - *SLC6A3*, more commonly known as *DAT1*). Polymorphisms of the *DAT1* gene have been shown to contribute to children's susceptibility towards the environment in two studies investigating multiple plasticity genes. The first demonstrated that boys with a combined type ADHD diagnosis, carrying at least one 9-repeat of the variable number of tandem repeat (VNTR) polymorphism in the 3' untranslated region (UTR) of the *DAT1* gene, showed most conduct problems when exposed to high negative maternal expressed emotion (EE) and least conduct problems when exposed to low negative EE. The same result was found for carriers of at least one short allele of the *HTTLPR*, but not for carriers of the 7-repeat of the *DRD4* gene. The effect was strongest when boys carried susceptibility alleles of both *DAT1* and *5-HTT* genes [17; note that samples of the present study and this study overlap, but measures were on average 5.9 years apart]. The second, a community study, showed that individuals with the most plasticity alleles (from multiple genes including *DAT1, 5-HTT, DRD2* and *DRD4*) had the highest levels of later parental stress when they had experienced negative maternal parenting during adolescence, but the lowest levels when maternal parenting had been positive. In contrast to the former study, however, the *DAT1* 10-repeat of the 3'UTR VNTR instead of the 9-repeat was considered as the plasticity variant [18]. As both studies included heterozygous individuals with a combination of the 9- and 10-repeat allele in the more susceptible group, this could be the common factor explaining the seemingly opposing results. More research is needed to determine whether the 9- or 10-repeat drives the susceptibility.

The present study focused on differential susceptibility to parental EE in children with ADHD and their siblings. *DRD4*, 5-*HTT* and *DAT1* have been frequently linked to ADHD [19] and shown, as described above, to act as plasticity genes in children with ADHD. Furthermore, studies have shown that parents' negatively expressed emotions are associated with symptoms of ADHD, oppositional and conduct disorder in children with ADHD [e.g. 17,20–23]. We aimed to advance our insight into the differential susceptibility theory by investigating the possible presence of interactions between these plasticity genes and maternal EE on prosocial and antisocial behaviour in children with ADHD and their siblings. We hypothesized that children carrying the risk alleles of *DRD4*, *5-HTT* or *DAT1*, would be more susceptible to EE, and that this differential susceptibility effect would be the strongest in children carrying the highest number of plasticity alleles. That is, we expected carriers of the risk alleles to show the lowest prosocial and highest antisocial scores when faced with negative EE (i.e. low warmth and high criticism), but the highest prosocial and lowest antisocial scores when their mothers expressed positive EE (i.e. high warmth and low criticism).

Methods

Participants

Participants were selected from a follow-up (2009–2012) of the Dutch part of the International Multicenter ADHD Genetics (IMAGE) study, performed between 2003–2006 [see www.neuroimage.nl; 24]. At first enrolment, 365 families with at least one child with

combined type ADHD and at least one biological sibling (regardless of ADHD diagnosis) were recruited, in addition to 148 control families with at least one (unaffected) child and no formal or suspected ADHD diagnosis in first-degree family members. All families were invited for a follow-up measurement in Amsterdam or Nijmegen with a mean follow-up period of 5.9 years (*SD* =.74). Additional girls with ADHD (any type; N=37 families) and healthy control boys (N=34 families) were recruited to balance out the gender and age distributions between the ADHD and healthy control groups. A comprehensive assessment protocol was administered, encompassing behavioural questionnaires, a diagnostic interview and several neurocognitive measures from all family members, and an extensive magnetic resonance imaging (MRI) scanning protocol in participating children. Probands and their siblings were between 5–30 years, of European Caucasian descent, had an IQ ≥ 70 and no diagnosis of autism, epilepsy, general learning difficulties, brain disorders or known genetic disorders (such as Fragile X syndrome or Down syndrome). The complete cohort participating in the follow-up comprised of 323 ADHD families and 153 control families. From this total, 366 participants, from 242 families, had information on EE and genotype available and therefore met the inclusion criteria for analysis. Participant characteristics are shown in Table 1. Informed consent was signed by all participants (parents signed informed consent for participants under 12 years of age) and the study was approved by the ethics committee (Centrale Commissie Mensgebonden Onderzoek).

Diagnostics Assessment

To determine ADHD diagnoses at the follow-up measurement, a standardized algorithm was applied to a combination of questionnaires and a semi-structured diagnostic interview. An in-depth description is provided on www.neuroimage.nl.

Measures

Child social behaviour—Children's prosocial and antisocial behaviour were measured by means of the prosocial behaviour and conduct problems scales of the Dutch Strengths and Difficulties Questionnaire (SDQ), completed by parents and via self-report [25]. Both subscales consist of 5 items, each to be scored on a 3-point scale (0–2). After summing, scores on both scales could range from 0 to 10. The Dutch SDQ has demonstrated acceptable to good psychometric properties [25,26]. Moreover, the SDQ has shown substantial associations with independently diagnosed clinical disorders [27] and both parent- and self-report have been able to distinguish between disorders within a clinical sample [28]. In agreement, an internal consistency (self-/parent-report) of α=.63/.71 was revealed for prosocial behaviour and α= .57/.73 for conduct problems in the present study.

Parental expressed emotion—Parental expressed criticism and warmth were assessed during the semi-structured diagnostic interview, using codings originally derived from the Camberwell Family Interview [29]. Ratings were based on the overall impression of the interviewer, considering parent's expressed feelings only. Parents were unaware of the EE assessment during the interview. Only ratings of mothers were used in our study, as the data of fathers were far less complete.

Warmth was assessed by the tone of voice, spontaneity, sympathy, and/or empathy toward the child. *Little warmth (0)* was coded when there was only slight amount of understanding, sympathy, or concern or enthusiasm about or interest in the child or when parents did not display any of the qualities of warmth described below. *Moderate demonstration of warmth* (1) was coded when there was a detached and rather clinical approach, with little or no warmth of tone, but moderate understanding, sympathy, and concern. *Quite a lot of demonstration of warmth* (2) was coded when there was definite understanding, sympathy, and concern, but only limited warmth of tone. *A great deal of expressed warmth* (3) was coded when there was definite warmth, enthusiasm, interest in, and enjoyment of the child. Criticism was assessed by statements which criticized or found fault with the child based on tone of voice and critical phrases. *No expressed criticism* (0) or *little expressed criticism* (1) were coded when there was no or very little evidence during the interview that the parent disapproves or dislikes the child's behaviour. *Some criticism* (2) was coded when there were statements of dissatisfaction indicating that the parent was bothered, irritated or upset by the child's behaviour or characteristics. *Quite a lot of expressed criticism* (3) was coded when there were indications that the parent did not like or approve of the child's behaviour. *A lot of expressed criticism* (4) was coded when the parent mentioned critical comments indicating the respondent dislikes, resents, disapproves of, or is angered or annoyed by the child's behaviour or characteristics. High criticism was also based on harsh tone of voice, even if the statement did not meet the content criteria. For a statement to be considered critical, the inflection, pitch, and/or rate of speech had to be dramatically different from the baseline. The tone had to strongly indicate resentment and/or anger about the topic being discussed[17, 23]. The inter-rater reliability has been found to be adequate using similar codings for warmth and criticism (range .78–91 and .79–.86 respectively [30]. During the first measurement wave (the IMAGE study), an average agreement percentage of 96.6% (range 78.6–100) and a mean Kappa coefficient of .88 (range .71–1.00) were obtain across all sites for the total PACS-interview, including the EE ratings [31].

Genotyping—An extensive description of DNA extraction and genotyping in IMAGE is provided elsewhere [24]. Briefly, for the IMAGE sample (parents and children), DNA was extracted from blood samples or immortalized cell lines at Rutgers University Cell and DNA Repository, New Jersey, USA. Additional NeuroIMAGE samples were collected in the form of a saliva sample using Oragene kits (DNA-Genotek; see www.neuroimage.nl). The *DRD4*, *DAT1* and 5-*HTT* had been genotyped for previous studies by the IMAGE consortium [24,32]. No deviations from Hardy Weinberg equilibrium were found (*DRD4* p=.15, *DAT1* p=.78, 5-*HTT* p=.78). The *cumulative plasticity index* was created by scoring one point when either one or two copies of the plasticity alleles were present for a gene (i.e. the 7-repeat of the *DRD4* exon III VNTR, the 9-repeat of the *DAT1* 3'UTR VNTR, the short allele of the *HTTLPR*) and summing the points into a total score, range 0–3 [as in 18]. The genotype frequencies are shown in Online Resource 1, Table S1.

Socioeconomic status—Socioeconomic status (SES) was based on the last successfully completed education level [33] and calculated as the average total years of education of both parents (when information of both parents was available). Scores ranged from 6, for completion of primary school, to 17 years, when a university degree was obtained.

Missing Data

For prosocial and antisocial behaviour, 24.0% of the parent-reported and 28.1% of the self-rated data was missing. The missing data were replaced using multiple imputations (*m*=20 imputations). The following auxiliary variables were included in the imputation procedure: children's prosocial and antisocial behaviour from the first measurement wave (assessed with the Dutch SDQ parent version [25] in 2003–2006; the IMAGE study), and, as proxies for prosocial and antisocial behaviour, the Big-Five trait agreeableness (assessed with a Dutch adaptation [34] of the Big-Five questionnaire from Goldberg [35]) and oppositional problems (assessed with the Dutch version of the CPRS-R:L [36]) from the current sample.

Data Analyses

To assess the presence of gene-environment correlations, Pearson correlations were calculated between the plasticity genes of children and mothers, EE and child behaviour [6,37]. Linear mixed model analyses were used to investigate the fixed effects of EE, genotype and GxE interactions on prosocial and antisocial behaviour of children (parent- and self-report). In each model we estimated a random intercept to correct for familial dependency within the sample (for parent- and self-report the intraclass correlation was .22 and .17 for prosocial and .18 and .27 for antisocial behaviour, respectively). Age, gender, collection site and SES were included as covariates in all analyses. Maternal warmth and criticism were centred and analyzed separately. Separate models were run for each potential plasticity gene (i.e. *DAT1, DRD4, 5-HTT*) as well as for the cumulative plasticity index.

P-values are reported based on the pooled results of twenty imputations. A correction for multiple comparisons was employed based on the effective number of independent tests on each gene (M_{eff}) [38]. The M_{eff} was derived from the Eigenvalues of the correlation matrix between the four outcome measures (parent- and self-reports of prosocial and antisocial behaviour) adjusted for covariates (age, gender, collection site and SES). The M_{eff} was 3 and the adjusted *p*-value threshold $p=0.05/3=.017$. All analyses were performed with the Statistical Package for the Social Science, version 20.0.

Results

Testing for the presence of gene-environment correlations revealed no significant associations between maternal warmth and any of the children's plasticity genes (all *p*-values>.261, see Online resource 1, Table S2). However, maternal criticism was very weakly correlated with the *DAT1* ($r=.13$ $p<.05$) and the cumulative plasticity index ($r=-.14$ $p<.05$), though not with the *DRD4* or *5-HTT* plasticity indices. Considering the size of the correlations, there was no reason to believe that possible gene-environment interactions would solely reflect gene-environment correlations. Similarly, no significant associations were found between maternal genotype (*DAT1*, *DRD4* and *5-HTT*) and EE or child behaviour (all $p>.064$, see Online Resource 1, Table S2).

Prosocial behaviour

Both warmth and criticism were associated with prosocial behaviour when rated by parents ($B=.44$, $p<.01$; $B=-.53$, $p<.001$, respectively; see Online Resource 1, Table S3). This effect

was also found on self-reported prosocial behaviour for warmth (*B*=.35, *p*<.01), and marginally for criticism (*B*=−.21, *p*=.06). No significant main or GxE effects were found for *DAT1*, *DRD4* or *5-HTT* genotypes (all *p*-values>.161; see Online Resource 1, Table S3 and S4). Likewise, when the gene variants were combined to form the cumulative plasticity index, no main or GxE effects were revealed (all *p*-values>.513; see Online Resource 1, Table S3 and S4). Using the 10-repeat instead of the 9-repeat of the *DAT1* 3'UTR VNTR as the plasticity allele [as in 18] did not alter the results (all *p*-values>.224).

Antisocial behaviour

The analyses with child antisocial behaviour showed effects of both warmth and criticism on both parent-reports (*B*=−.49, *p*<.001; *B*=.78, *p*<.001, respectively) and self-reports (*B*=−.33, *p*<.01; *B*=.30, *p*<.01 respectively; see Online Resource 1, Table S3). No main or GxE effects were found for any of the plasticity genes (all *p*-values>.089; see Online Resource 1, Table S3 and S4). Similarly, no effects were found when the gene variants were combined to form the cumulative plasticity index (all *p*-values>.515; see Table S3 and S4). Again, using the 10-repeat instead of the 9-repeat of *DAT1* VNTR as the plasticity allele did not alter the results (all *p*-values>.172).

Supplementary analyses

Analyses performed on subsets of children, i.e. children with ADHD, only boys or only boys with ADHD, to investigate possible effects of ADHD or gender revealed similar results as described above. The same was true for analyses using an additive model instead of a dominant one for the cumulative plasticity index (thus with a range of 0–6 plasticity alleles). Additional analyses with common *DAT1* haplotypes (i.e. 10/6 and 9/6) having shown associations with ADHD previously [39,40] revealed no significant effects for either prosocial or antisocial behaviour (see Online Resource 1, supplementary material and Table S5). Finally, supplementary analyses were run with a binary variable comparing high versus low positive maternal EE in congruence with a previous study that reported GxE effects [PMEE; see supplementary material and Table S6; 17]. Similar to the main analyses, children in the low PMEE group had significantly lower scores on prosocial and higher scores on antisocial behaviour compared to children in the high PMEE group. For *DAT1* and *DRD4* genotype, no main or GxE effects were found. However, interaction effects were found for PMEE x *5-HTT*, and PMEE x Cumulative plasticity index, on parent-reported prosocial behaviour. These findings did not survive correction for multiple testing and were opposite to the direction previously reported in the literature.

Discussion

In this study we examined the differential susceptibility theory by investigating the presence of interactions between plasticity genes and maternal EE on prosocial and antisocial behaviour in children with ADHD and their siblings. We found that EE was associated with both prosocial and antisocial behaviour in the expected direction: when mothers expressed more warmth, children showed more prosocial and less antisocial behaviour, and conversely, when mothers expressed more criticism, children showed less prosocial behaviour and more antisocial behaviour. This is in agreement with previous literature [e.g.

17,20–22], although most studies focused only on antisocial behaviour. The current study, therefore, complements previous literature by showing not only the EE-antisocial, but the EE-prosocial association as well.

The results revealed no significant main effects of the ADHD candidate genes. Importantly, given the aim of the present paper, we found no GxE interactions on prosocial or antisocial behaviour. Only when including a categorical rather than a continuous measure of EE (high versus low PMEE) in supplementary analyses were two GxE interactions found; these, however, were opposite to the hypothesized direction and did not survive correction for multiple testing. Finally, analyses in subsamples (e.g. boys with ADHD), which had yielded meaningful GxE interactions in a previous study [17], did not change the results.

Thus far, as described above, a number of studies have investigated the interaction effects between parenting and genes, specifically on child (anti-)social behaviour. Most have focused on antisocial behaviour and the *DRD4*, and, to a lesser extent, the *5-HTT* and *DAT1* genes. For *DRD4* the results are the most consistent, with carriers of the exon III VNTR's 7-repeat allele showing the most or least antisocial behaviour when faced with negative or positive parenting, respectively [41,42]. However, two other studies were unable to support these findings [17,43]. In addition, one study showed children to be differentially susceptible to parenting on prosocial behaviour [10]. Likewise, carriers of the *HTTLPR* short allele have been found to display a pattern of differential susceptibility towards parenting on social [12] and antisocial behaviour [17]. However, for *DAT1* the results are less clear. Only one study, so far, has reported on the interplay with parenting on antisocial behaviour [17]. Moreover, no previous studies have reported on *DAT1* or *DAT1* x Environment effects on prosocial behaviour. In all, previous findings are heterogeneous, with most obvious potential explanations being the relatively small sample sizes employed hitherto (N<169; except for [17]) and the use of diverse measures of parenting. This seems to indicate that there is not yet sufficient evidence for a robust and general GxE effect of parenting and *DRD4*, *DAT1* and *HTTLPR* on children's social behaviour.

Besides sample size and inconsistency of environmental exposure, there are a number of factors that are likely to play a role in the genetically based susceptibility to the environment and therefore explain the heterogeneity across findings. For example, there could be alleles involved from other genes which could interact with the genes under study and the environment in numerous ways [7]. Moreover, besides genetic susceptibility, studies have shown child temperament and physiological reactivity to influence children's susceptibility to environmental experiences [see for a recent review 7]. Another factor that could play a role is age. Whereas the present study included participants with a mean age 17 years, most previous studies investigated younger children, with only one study including children above eight years old [17]. It is currently unknown if differential susceptibility to the environment decreases with age. In all, heterogeneity among findings may be caused by the complexity inherent to development; arguably, one genetic risk variant combined with the variance of one environmental factor is unlikely to demonstrate fully consistent effects across samples.

An alternative explanation for not finding GxE effects and the contradictory findings in the literature is that the causal pathway modelled in most GxE studies is only partly valid. We can think of at least three complicating influences that would perturb hypothesized GxE effects. First, parenting or EE could be related to parental genotype. Since parental and child genotype are linked, this could explain any interactions found between parenting, child genotype and child behaviour [37]. We checked for any parental gene-environment correlations, but as reported, none were found. Nonetheless, parental gene-environment correlations may very well play a role in findings of other studies, as these correlations are seldom reported. Second, rather than parental EE eliciting child behaviour (i.e. parent effect model), it could also be that the causation is reversed, that is, child behaviour elicits parental EE (i.e. a child effect model). In this case the null findings would be expected. However, since evidence has been found for both parent effect [44,45] and child effect models [46,21], it is more likely that both causation models are valid and complementary in capturing the underlying mechanisms. Third, if reverse causation plays a role, the model could become even more complicated if we take into account that mothers could be differentially susceptible to environmental experiences, in this case their children's behaviour. Again, although complicated, these causal pathways are, in our view, not farfetched in terms of actual developmental processes, and may therefore explain heterogeneity in findings.

Our study should be viewed in the context of some strengths and limitations. Strengths of this study were the theory-driven approach, use of multiple informants and inclusion of positive as well as negative measurements of both environment and behaviour. Though it would have been even better to obtain positive and negative measures on one continuous scale, many GxE studies have failed to include the positive side of behavioural outcome at all [6]. Limitations were the missing values for child behaviour and the sample size. Power calculations performed with Quanto 1.2.4 [47] revealed we had adequate power to detect GxE effects with an explained variance (R^2) of 3–5% or higher (see supplementary material and Table S7 for details). This means we had adequate power to detect the larger but not smaller effects. Previous literature has suggested effect sizes of GxE interactions are substantially smaller than initially thought, with an explained variance of 10% considered very large, 1% large and even .01% moderate [48]. This also raises questions about the sample sizes and findings of the studies discussed above. Moreover, methodological issues, such as selected inheritance mode and allele frequency have an impact on the power [48]. Thus replication studies are needed with sufficient power to detect even the smallest of effects.

Overall, we can conclude that the current study found no evidence for differential susceptibility, based on our selection of plasticity genes. Previously reported associations between maternal EE and prosocial and antisocial behaviour were confirmed in our data. As clearly pointed out by the proponents of the differential susceptibility theory themselves, there are several factors that potentially play a role in the contribution to environmental susceptibility [e.g. age, prenatal environment, temperament, physiological stress reaction; 49,7]. This, together with the heterogeneous findings in the literature, indicates more research is needed before firm conclusions can be drawn. Preferably this would be with large samples in order to detect small differential susceptibility effects, if present.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

This work was supported by NIH Grant R01MH62873 (to Dr. Faraone, Department of Psychiatry and of Neuroscience and Physiology, SUNY Upstate Medical University, New York, USA), NWO Large Investment Grant 1750102007010 (to Dr. Buitelaar) and grants from Radboud university medical center, University Medical Center Groningen and Accare, and VU University Amsterdam.

References

1. Wermter A-K, Laucht M, Schimmelmann BG, Banaschweski T, Sonuga-Barke EJS, Rietschel M, Becker K. From nature versus nurture, via nature and nurture, to gene x environment interaction in mental disorders. Eur Child Adolesc Psychiatry. 2010; 19:199–210. [PubMed: 20024596]
2. Belsky J. Variation in susceptibility to environmental influence: An evolutionary argument. Psychol Inq. 1997; 8(3):182–186.
3. Belsky, J. Differential susceptibility to rearing influences: An evolutionary hypothesis and some evidence. In: Ellis, BJ.; Bjorklund, DF., editors. Origins of the social mind: Evolutionary psychology and child development. New York: Guilford Press; 2005. p. 139-163.
4. Belsky J, Jonassaint C, Pluess M, Stanton M, Brummett B, Williams R. Vulnerability genes or plasticity genes? Mol Psychiatry. 2009; 14(8):746–754. [PubMed: 19455150]
5. Ellis BJ, Boyce WT. Differential susceptibility to the environment: toward an understanding of sensitivity to developmental experiences and context. Dev Psychopathol. 2011; 23(1):1–5. [PubMed: 21262035]
6. Belsky J, Pluess M. Beyond diathesis stress: differential susceptibility to environmental influences. Psychol Bull. 2009; 135(6):885–908. [PubMed: 19883141]
7. Belsky J, Pluess M. Beyond risk, resilience, and dysregulation: Phenotypic plasticity and human development. Dev Psychopathol. 2013; 25:1243–1261. [PubMed: 24342838]
8. Bakermans-Kranenburg MJ, van Ijzendoorn MH. Differential susceptibility to rearing environment depending on dopamine-related genes: new evidence and a meta-analysis. Dev Psychopathol. 2011; 23(1):39–52. [PubMed: 21262038]
9. Belsky J, Pluess M. Genetic moderation of early child-care effects on social functioning across childhood: a developmental analysis. Child Dev. 2013; 84(4):1209–1225. [PubMed: 23432522]
10. Knafo A, Israel S, Ebstein RP. Heritability of children's prosocial behavior and differential susceptibility to parenting by variation in the dopamine receptor D4 gene. Dev Psychopathol. 2011; 23(1):53–67. [PubMed: 21262039]
11. Pluess M, Belsky J, Neuman RJ. Prenatal smoking and attention-deficit/hyperactivity disorder: DRD4-7R as a plasticity gene. Biol Psychiatry. 2009; 66:e5–e6. [PubMed: 19500778]
12. Drury SS, Gleason MM, Theall KP, Smyke AT, Nelson CA, Fox NA, Zeanah CH. Genetic sensitivity to the caregiving context: the influence of 5httlpr and BDNF val66met on indiscriminate social behavior. Physiol Behav. 2012; 106(5):728–735. [PubMed: 22133521]
13. Hankin BL, Nederhof E, Oppenheimer CW, Jenness J, Young JF, Abela JR, Smolen A, Ormel J, Oldehinkel AJ. Differential susceptibility in youth: evidence that 5-HTTLPR x positive parenting is associated with positive affect 'for better and worse'. Transl Psychiatry. 2011; 1:e44. [PubMed: 22833190]
14. Kochanska G, Kim S, Barry RA, Philibert RA. Children's genotypes interact with maternal responsive care in predicting children's competence: diathesis-stress or differential susceptibility? Dev Psychopathol. 2011; 23(2):605–616. [PubMed: 23786699]
15. Pluess M, Belsky J, Way BM, Taylor SE. 5-HTTLPR moderates effects of current life events on neuroticism: differential susceptibility to environmental influences. Prog Neuropsychopharmacol Biol Psychiatry. 2010; 34(6):1070–1074. [PubMed: 20573579]

16. Retz W, Freitag CM, Retz-Junginger P, Wenzler D, Schneider M, Kissling C, Thome J, Rosler M. A functional serotonin transporter promoter gene polymorphism increases ADHD symptoms in delinquents: interaction with adverse childhood environment. Psychiatry Res. 2008; 158(2):123–131. [PubMed: 18155777]
17. Sonuga-Barke EJ, Oades RD, Psychogiou L, Chen W, Franke B, Buitelaar J, Banaschewski T, Ebstein RP, Gil M, Anney R, Miranda A, Roeyers H, Rothenberger A, Sergeant J, Steinhausen HC, Thompson M, Asherson P, Faraone SV. Dopamine and serotonin transporter genotypes moderate sensitivity to maternal expressed emotion: the case of conduct and emotional problems in attention deficit/hyperactivity disorder. J Child Psychol Psychiatry. 2009; 50(9):1052–1063. [PubMed: 19490304]
18. Beaver KM, Belsky J. Gene-environment interaction and the intergenerational transmission of parenting: testing the differential-susceptibility hypothesis. Psychiatr Q. 2012; 83(1):29–40. [PubMed: 21553075]
19. Caylak E. Biochemical and genetic analyses of childhood attention deficit/hyperactivity disorder. Am J Hum Genet Part B: Neuropsychiatr Genet. 2012; 159B(6):613–627.
20. Psychogiou L, Daley DM, Thompson MJ, Sonuga-Barke EJS. Mothers' expressed emotion toward their school-aged sons. Associations with child and maternal symptoms of psychopathology. Eur Child Adolesc Psychiatry. 2007; 16:458–464. [PubMed: 17876512]
21. Cartwright KL, Bitsakou P, Daley D, Gramzow RH, Psychogiou L, Simonoff E, Thompson MJ, Sonuga-Barke EJS. Disentangling child and family influences on maternal expressed emotion toward children with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2011; 50:1042–1053. [PubMed: 21961778]
22. Pfiffner LJ, McBurnett K, Rathouz PJ, Judice S. Family correlates of oppositional and conduct disorders in children with attention deficit/hyperactivity disorder. J Abnorm Child Psychol. 2005; 33(5):551–563. [PubMed: 16195950]
23. Richards JS, Arias Vásquez A, Rommelse NNJ, Oosterlaan J, Hoekstra PJ, Franke B, Hartman CA, Buitelaar JK. A Follow-Up Study of Maternal Expressed Emotion Toward Children With Attention-Deficit/Hyperactivity Disorder: Relation with Severity and Persistence of ADHD and Comorbidity. J Am Acad Child Adolesc Psychiatry. 2014; 53(3):311–319. [PubMed: 24565358]
24. Brookes K, Xu X, Chen W, Zhou K, Neale B, Lowe N, Anney R, Franke B, Gill M, Ebstein R, Buitelaar J, Sham P, Campbell D, Knight J, Andreou P, Altink M, Arnold R, Boer F, Buschgens C, Butler L, Christiansen H, Feldman L, Fleischman K, Fliers E, Howe-Forbes R, Goldfarb A, Heise A, Gabriels I, Korn-Lubetzki I, Johansson L, Marco R, Medad S, Minderaa R, Mulas F, Muller U, Mulligan A, Rabin K, Rommelse N, Sethna V, Sorohan J, Uebel H, Psychogiou L, Weeks A, Barrett R, Craig I, Banaschewski T, Sonuga-Barke E, Eisenberg J, Kuntsi J, Manor I, McGuffin P, Miranda A, Oades RD, Plomin R, Roeyers H, Rothenberger A, Sergeant J, Steinhausen HC, Taylor E, Thompson M, Faraone SV, Asherson P. The analysis of 51 genes in DSM-IV combined type attention deficit hyperactivity disorder: association signals in DRD4, DAT1 and 16 other genes. Mol Psychiatry. 2006; 11(10):934–953. [PubMed: 16894395]
25. van Widenfelt BM, Goedhart AW, Treffers PD, Goodman R. Dutch version of the Strengths and Difficulties Questionnaire (SDQ). Eur Child Adolesc Psychiatry. 2003; 12(6):281–289. [PubMed: 14689260]
26. Muris P, Meesters C, van den Berg F. The Strengths and Difficulties Questionnaire (SDQ)--further evidence for its reliability and validity in a community sample of Dutch children and adolescents. Eur Child Adolesc Psychiatry. 2003; 12(1):1–8. [PubMed: 12601558]
27. Goodman R, Renfrew D, Mullick M. Predicting type of psychiatric disorder from Strengths and Difficulties Questionnaire (SDQ) scores in child mental health clinics in London and Dhaka. Eur Child Adolesc Psychiatry. 2000; 9(2):129–134. [PubMed: 10926063]
28. Klasen H, Woerner W, Rothenberger A, Goodman R. [German version of the Strength and Difficulties Questionnaire (SDQ-German)--overview and evaluation of initial validation and normative results]. Prax Kinderpsychol Kinderpsychiatr. 2003; 52(7):491–502. [PubMed: 14526759]
29. Brown GW. The Measurement of Family Activities and Relationships: A Methodological Study. Human Relations. 1966; 19:241–263.

30. Schachar R, Taylor E, Wieselberg M, Thorley G, Rutter M. Changes in family function and relationships in children who respond to methylphenidate. J Am Acad Child Adolesc Psychiatry. 1987; 26:728–732. [PubMed: 3667503]
31. Chen, W.; Taylor, E. PACS interview and genetic research in ADHD. In: Oades, R., editor. Attention-Deficit/Hyperactivity Disorder HKS: Current ideas and ways forward. 1 edn. New York: Nova Science Publishers Inc; 2006. p. 3-20.
32. Xu X, Duman EA, Anney R, Brookes K, Franke B, Zhou K, Buschgens C, Chen W, Christiansen H, Eisenberg J, Gabriels I, Manor I, Marco R, Muller UC, Mulligan A, Rommelse N, Thompson M, Uebel H, Banaschewski T, Buitelaar J, Ebstein R, Gill M, Miranda A, Mulas F, Oades RD, Roeyers H, Rothenberger A, Sergeant J, Sonuga-Barke E, Steinhausen HC, Taylor E, Faraone SV, Asherson P. No association between two polymorphisms of the serotonin transporter gene and combined type attention deficit hyperactivity disorder. Am J Hum Genet Part B: Neuropsychiatr Genet. 2008; 147B(7):1306–1309.
33. Buis, ML. Ph.D. thesis, Faculty of Social Sciences. VU-University Amsterdam., Amsterdam; 2010. Inequality of educational outcome and inequality of educational opportunity in the Netherlands during the 20th century.
34. Gerris, JRM.; Houtmans, MJM.; Kwaaitaal-Roosen, EMG.; Schipper, JC.; Vermulst, AA.; Janssens, JMAM. Parents, adolescents, and young adults in Dutch families: A longitudinal study. Nijmegen, the Netherlands: University of Nijmegen, Institute of Family Studies; 1998.
35. Goldberg LR. The development of markers for the Big-Five factor structure. Psychological Assessment. 1992; 4:26–42.
36. Conners CK, Sitarenios G, Parker JD, Epstein JN. The revised Conners' Parent Rating Scale (CPRS-R): factor structure, reliability, and criterion validity. J Abnorm Child Psychol. 1998; 26:257–268. [PubMed: 9700518]
37. Knafo A, Jaffee SR. Gene-environment correlation in developmental psychopathology. Dev Psychopathol. 2013; 25(1):1–6. [PubMed: 23398748]
38. Li J, Ji L. Adjusting multiple testing in multilocus analyses using the eigenvalues of a correlation matrix. Heredity (Edinb). 2005; 95(3):221–227. [PubMed: 16077740]
39. Asherson P, Brookes K, Franke B, Chen W, Gill M, Ebstein RP, Buitelaar J, Banaschewski T, Sonuga-Barke E, Eisenberg J, Manor I, Miranda A, Oades RD, Roeyers H, Rothenberger A, Sergeant J, Steinhausen HC, Faraone SV. Confirmation that a specific haplotype of the dopamine transporter gene is associated with combined-type ADHD. Am J Psychiatry. 2007; 164(4):674–677. [PubMed: 17403983]
40. Franke B, Vasquez AA, Johansson S, Hoogman M, Romanos J, Boreatti-Hummer A, Heine M, Jacob CP, Lesch KP, Casas M, Ribases M, Bosch R, Sanchez-Mora C, Gomez-Barros N, Fernandez-Castillo N, Bayes M, Halmoy A, Halleland H, Landaas ET, Fasmer OB, Knappskog PM, Heister AJ, Kiemeney LA, Kooij JJ, Boonstra AM, Kan CC, Asherson P, Faraone SV, Buitelaar JK, Haavik J, Cormand B, Ramos-Quiroga JA, Reif A. Multicenter analysis of the SLC6A3/DAT1 VNTR haplotype in persistent ADHD suggests differential involvement of the gene in childhood and persistent ADHD. Neuropsychopharmacol. 2010; 35(3):656–664.
41. Bakermans-Kranenburg MJ, van Ijzendoorn MH. Gene-environment interaction of the dopamine D4 receptor (DRD4) and observed maternal insensitivity predicting externalizing behavior in preschoolers. Dev Psychobiol. 2006; 48(5):406–409. [PubMed: 16770765]
42. Bakermans-Kranenburg MJ, Van IMH, Pijlman FT, Mesman J, Juffer F. Experimental evidence for differential susceptibility: dopamine D4 receptor polymorphism (DRD4 VNTR) moderates intervention effects on toddlers' externalizing behavior in a randomized controlled trial. Dev Psychol. 2008; 44(1):293–300. [PubMed: 18194028]
43. Propper C, Willoughby M, Halpern CT, Carbone MA, Cox M. Parenting quality, DRD4, and the prediction of externalizing and internalizing behaviors in early childhood. Dev Psychobiol. 2007; 49(6):619–632. [PubMed: 17680609]
44. Hirshfeld DR, Biederman J, Brody L, Faraone SV, Rosenbaum JF. Associations between expressed emotion and child behavioral inhibition and psychopathology: a pilot study. J Am Acad Child Adolesc Psychiatry. 1997; 36:205–213. [PubMed: 9031573]
45. Asarnow JR, Tompson M, Hamilton EB, Goldstein MJ, Guthrie D. Family-expressed emotion, childhood-onset depression, and childhood-onset schizophrenia spectrum disorders: is expressed

emotion a nonspecific correlate of child psychopathology or a specific risk factor for depression? J Abnorm Child Psychol. 1994; 22(2):129–146. [PubMed: 8064026]

46. Hale WW 3rd, Keijsers L, Klimstra TA, Raaijmakers QA, Hawk S, Branje SJ, Frijns T, Wijsbroek SA, van Lier P, Meeus WH. How does longitudinally measured maternal expressed emotion affect internalizing and externalizing symptoms of adolescents from the general community? J Child Psychol Psychiatry. 2011; 52(11):1174–1183. [PubMed: 21401595]
47. Gauderman, WJ.; Morrison, JM. QUANTO 1.1: A computer program for power and sample size calculations for genetic-epidemiology studies. 2006. http://hydra.usc.edu/gxe
48. Duncan LE, Keller MC. A critical review of the first 10 years of candidate gene-by-environment interaction research in psychiatry. Am J Psychiatry. 2011; 168(10):1041–1049. [PubMed: 21890791]
49. Pluess M, Belsky J. Prenatal programming of postnatal plasticity? Dev Psychopathol. 2011; 23(1): 29–38. [PubMed: 21262037]

Table 1

Participant characteristics

	N	M	SE	Range
Maternal warmth	366	1.55	.04	0–3
Maternal criticism	366	1.70	.05	0–4
Prosocial behaviour *parent-report*	366	7.33	.12	1–10
Prosocial behaviour *self-report*	366	7.75	.11	2–10
Conduct behaviour *parent-report*	366	2.70	.12	0–10
Conduct behaviour *self-report*	366	2.45	.11	0–10
SES	366	11.33	.12	5–17
Age	366	17.11	.16	7.8–28.2
Gender				
Male	274	74.9%		
Female	92	25.1%		
ADHD diagnosis				
Combined subtype	128	35.0%		
Inattentive subtype	133	36.3%		
Hyperactive-impulsive subtype	23	6.3%		