Journal of Psychiatric Research 70 (2015) 83–90

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/psychires

# Interacting effects of maternal responsiveness, infant regulatory problems and dopamine *D4* receptor gene in the development of dysregulation during childhood: A longitudinal analysis

Luise Poustka [a, h, *, 1], Katrin Zohsel [a, 1], Dorothea Blomeyer [a], Christine Jennen-Steinmetz [b], Brigitte Schmid [a], Patricia Trautmann-Villalba [a], Sarah Hohmann [a], Katja Becker [c], Günter Esser [d], Martin H. Schmidt [a], Daniel Brandeis [a, e, f, g], Tobias Banaschewski [a], Manfred Laucht [a, d]

[a] Department of Child and Adolescent Psychiatry and Psychotherapy, Central Institute of Mental Health, Medical Faculty Mannheim/Heidelberg University, Mannheim, Germany
[b] Department of Biostatistics, Central Institute of Mental Health, Medical Faculty Mannheim/Heidelberg University, Mannheim, Germany
[c] Department of Child and Adolescent Psychiatry, Medical Faculty, Philipps-University, Marburg, Germany
[d] Department of Psychology, University of Potsdam, Potsdam, Germany
[e] Department of Child and Adolescent Psychiatry, University of Zurich, Switzerland
[f] Zurich Center for Integrative Human Physiology, University of Zurich, Zurich, Switzerland
[g] Neuroscience Center Zurich, University and ETH, Zurich, Switzerland
[h] Department of Child and Adolescent Psychiatry, Medical University of Vienna, Austria

ARTICLE INFO

*Article history:*
Received 12 December 2014
Received in revised form
13 August 2015
Accepted 28 August 2015

*Keywords:*
Dysregulation
Childhood
Infant regulatory problems
Parenting quality
*DRD4*
Gene–environment interaction

ABSTRACT

Recent longitudinal studies have indicated that affective and behavioral dysregulation in childhood is associated with an increased risk for various negative outcomes in later life. However, few studies to date have examined early mechanisms preceding dysregulation during early childhood. Aim of this study was to elucidate early mechanisms relating to dysregulation in later life using data from an epidemiological cohort study on the long-term outcome of early risk factors from birth to adulthood. At age 3 months, mothers and infants were videotaped during a nursing and playing situation. Maternal responsiveness was evaluated by trained raters. Infant regulatory problems were assessed on the basis of a parent interview and direct observation by trained raters. At age 8 and 11 years, 290 children (139 males) were rated on the Child Behavior Checklist (CBCL). Additionally, participants were genotyped for the dopamine *D4* receptor (*DRD4*) exon 3 VNTR polymorphism. A significant three-way interaction between maternal responsiveness, *DRD4* genotype and infant regulatory problems was detected predicting the CBCL-dysregulation profile (CBCL-DP). Carriers of the *DRD4* 7r allele with regulatory problems at age 3 months showed significantly more behavior problems associated with the CBCL-DP during childhood when exposed to less maternal responsiveness. In contrast, no effect of maternal responsiveness was observed in *DRD4* 7r carriers without infant regulatory problems and in non-carriers of the *DRD4* 7r allele. This prospective longitudinal study extends earlier findings regarding the association of the CBCL-DP with early parenting and later psychopathology, introducing both *DRD4* genotype and infant regulatory problems as important moderators.



## 1. Introduction

Severe emotional and behavioral dysregulation in children and adolescents is a concept associated with both internalizing (anxious-depressed) and externalizing (disruptive) features. Dysregulation has recently been identified as a major risk for a variety

* Corresponding author. Department of Child and Adolescent Psychiatry and Psychotherapy, Central Institute of Mental Health, Medical Faculty Mannheim/Heidelberg University, PO Box 122120, D-68072, Mannheim, Germany.
*E-mail address:* luise.poustka@zi-mannheim.de (L. Poustka).
[1] Co-contributing first authors.

http://dx.doi.org/10.1016/j.jpsychires.2015.08.018
0022-3956/

of negative outcomes (Ayer et al., 2009; Biederman et al., 2009; Holtmann et al., 2011; Meyer et al., 2009). Problems with dysregulation are captured by a profile on the Child Behavior Checklist (Achenbach, 1991), the so called CBCL-dysregulation profile (CBCL-DP; Biederman et al., 2009; Holtmann et al., 2008) defined by peaks in the CBCL subdomains of attention, anxiety and aggressive behavior. This specific pattern of problems is suggested to be heritable (Hudziak et al., 2005) and quite stable throughout childhood (Althoff et al., 2006; Boomsma et al., 2006). Several studies have highlighted the significance of the CBCL-DP for psychopathology in demonstrating an increased risk for mood disorders, suicidality, substance abuse, personality disorders and disruptive behavior in affected children and adolescents (Ayer et al., 2009; Biederman et al., 2012; Holtmann et al., 2011; Meyer et al., 2009). In a cross-sectional study, Jucksch et al. (2011) found significant associations of the CBCL-DP with psychosocial adversities and impairment. Despite strong evidence for the prognostic and phenomenological value of the CBCL-DP, one major gap in current research is that there is hardly any information on early precursors or risk factors for the development of dysregulation. One of the few studies to date conducted in younger age groups (Kim et al., 2012) demonstrated that preschool children with the CBCL-DP displayed more negative temperament characteristics like high negativity and low effortful control and were exposed to more maladapted parenting compared to those without CBCL-DP. In a prospective, population-based study, Basten et al. (2013) found associations between dysregulation at age 5–7 years and higher levels of parental psychopathology and hostility at age 3 years, suggesting a strong role for parents' psychological problems and parenting style for the development of dysregulation in the offspring.

In general, parenting quality constitutes an important source of influence on behavioral outcome in their children. In particular, negative parenting including low responsiveness has been implicated in the later development of both externalizing and internalizing disorders (Campbell, 2002; Campbell et al., 2000; Laucht et al., 2001; Schmid et al., 2011). Maternal responsiveness, defined as the consistent and adequate response to infant's signals, is considered as a key parenting dimension that can serve as a powerful protective factor (Pasalich et al., 2011; Shaw et al., 2003). Moreover, evidence from recent research suggests that the association between rearing experiences and behavioral problems may be particularly pronounced in those children with adverse temperament characteristics. When exposed to negative, unresponsive or harsh parenting, so called “difficult” children were reported to be at risk for a broad range of behavior problems including disturbed self-regulation, conduct disorder, and aggressive behavior (Bates et al., 1998; Gilliom and Shaw, 2004; Kim and Kochanska, 2012; Lahey et al., 2008). Unresponsive parenting was shown to increase the risk for behavioral problems in temperamentally difficult children, while the risk was buffered in those children exposed to more responsive parenting (Kochanska and Kim, 2013). In this line, Keenan et al. (1998) suggested negative temperament traits to be the earliest measurable problem behavior in infants, with a high continuity to internalizing disorders in later life. The clinical classification system for infants (Zero to Three, DC 0–3R) subsumes these early observable, adverse temperament traits under the concept of regulatory problems (RP, Zero to Zero to Three, 2005). Infants with RP have difficulties with self-regulation and exhibit fussiness, irritability, poor self-calming or under-reactivity to stimuli as well as feeding and sleeping difficulties. In a recent meta-analysis, Hemmi et al. (2011) reported a strong association of RP in infancy with later externalizing and internalizing problems and ADHD, particularly in families with a high range of multiple risk factors. Schmid and Wolke (2014) suggested a cascade model in which early RP represent the starting point of a trajectory of dysregulation through time, with persistent RP indicating a “general dysregulation syndrome”.

Another powerful factor rendering children more or less vulnerable to their environment seems to be their genetic makeup (e.g., Caspi et al., 2002). Genetic variation in dopaminergic neurotransmission has been suggested to act as a susceptibility factor for behavior problems (Bakermans-Kranenburg and van Ijzendoorn, 2006, 2007), implying a moderating effect of gene polymorphisms on the associations between rearing environments and developmental outcome. The *DRD4* gene has been investigated specifically with regard to a wide range of issues associated with regulation problems, like ADHD and impulsivity (Congdon et al., 2008; Faraone et al., 2005; Swanson et al., 2000), infant temperament (De Luca et al., 2001), aggression (Benjamin et al., 2002; Schmidt et al., 2002) and self-regulation (Berry et al., 2014).

Located on chromosome 11p14, the *DRD4* gene contains a variable number of tandem repeats (VNTR) polymorphism in exon 3. One allelic variant of this polymorphism, the exon 3 7-repeat (7r) allele, has been associated with lower dopamine reception efficiency and, in this line, with decreased attention and reward sensitivity (Robbins and Everitt, 1999), resulting in higher rates of mainly externalizing psychopathology during childhood. Investigating the joint contribution of *DRD4* and environmental influences in the development of childhood behavioral problems, Bakermans-Kranenburg and van Ijzendoorn (2006) found carriers of the *DRD4* 7r allele to display greater levels of externalizing behaviors in preschool years when exposed to insensitive parenting compared to non-carriers (Bakermans-Kranenburg and van Ijzendoorn, 2006). In our own sample, results by Becker et al. (2010) demonstrated that variation in the *DRD4* gene moderated the association of RP in infancy with later ADHD symptoms. According to these results, RP in infancy represented a risk factor for the development of ADHD later in life, but only if the genetic risk variant of *DRD4* 7r was present.

The majority of gene x environment (GxE) studies on children's genotypes and maternal responsiveness has been investigated using two-way interactions (see Kochanska et al., 2011). By contrast, studies involving two-way interactions which vary across levels of a third variable, like interactions between genotype, parental care and other factors with a proposed role in the development of later psychopathology are still rare in GxE research. However, recent studies suggest such complex patterns of interaction. For example, Cleveland et al. (2015) showed that a prevention program for alcohol use in adolescents reduced drinking risk, but only in *DRD4* 7r carriers with high levels of maternal involvement. Cicchetti et al. (2014) found that genetic variants associated with greater risk for borderline symptomatology after maltreatment experience were additionally moderated by gender, thus providing important implications for understanding variability in early predictors of psychopathology.

Following up our own findings on a cohort of children at risk (Becker et al., 2010, 2007; Holtmann et al., 2011; Laucht et al., 2001), we aimed to examine the complex interplay of maternal responsiveness, *DRD4* gene and infant RP relating to later dysregulation in a prospective study since birth. We focused on maternal responsiveness, as this constitutes one of the most important factors in early self-regulation, with low responsiveness being associated with poor behavioral control in infancy (Cerezo et al., 2008). Based on the literature reviewed above, we hypothesized the presence of a three–way interaction, such that carriers of the *DRD4* 7r allele would show higher scores on the CBCL-DP during childhood, when exposed to low maternal responsiveness and that this effect would be more pronounced in children with RP than in those without.