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AN ITALIAN PILOT STUDY ON EPIGENETIC FACTORS IN EARLY CHILDREN'S EATING DISORDERS

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Abstract

Infants' feeding disorders represent a crucial health problem for physical and psychological wellbeing during childhood. The international literature on this issue has recently focused on possible genetic and epigenetic variables that could be associated with various clinical manifestations of feeding disorders (Avoidant-Restrictive Feeding Disorder ARFID) among infants, such as children's dopamine transporter (DAT1) genotype and methylation, children's emotional functioning and maternal psychopathological risk. On the basis of the bio-psycho-social model, this pilot study aims to empirically investigate the relationship between children's DAT1 methylation, children's emotional-behavioural profiles and maternal psychopathologic risk, in families with preschool-age children with three different ARFID subtype (i.e., irritable/impulsive (I/I), sensory food aversions (SFA), and post-traumatic feeding disorders subtypes (PTFD)). Participants were 69 children and their mothers who were assigned to three different groups according to the clinical ARFID subtypes. Mothers' psychopathological symptoms and offspring's emotional–behavioral functioning were assessed through several questionnaires. Children's DNA was collected using buccal swabs. The findings show that children's genotype is associated with different feeding disorders subtypes and significant differences between the study groups with reference to children's DAT1 total methylation, children's emotional-behavioural problems, and maternal psychopathological risk. A relationship between maternal psychopathological risk, children's genotype and children's emotional-behavioural functioning was established in this study. This complex gene-environment interplay indicates a crucial implication in shaping children's psychopathological problems and diseases such as ARFID. This study provides information on the issue of infants' feeding disorders that may be useful in implementing early assessment and treatment programmes.

Keywords: Feeding disorders, gene-environment interaction

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1. Introduction

Feeding disorders in early childhood are indicated nowadays as a severe problem that can impair infants' and young children's psychological and social functioning (APA, 2013). The prevalence of feeding disorders among infants and children is increasing globally, showing data of approximately 25% of children with typical development and 80% of children affected by developmental disorders (Bryant-Waugh, 2013; Robson et al., 2019). These diseases can be characterized by difficulties in intaking nourishment despite food availability, such as in the case of Avoidant-Restrictive Feeding Disorder (ARFID), the new diagnostic category of Feeding and Eating Disorders added in the last edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (APA, 2013).

With regard to this type of problem, the international scientific literature is increasingly focusing on both relational and environmental correlates, such as maternal psychopathology maladaptive and aspects of the parent-child relationship (Ammaniti et al., 2010; Tarbell & Allaire, 2002) and individual factors, such as genetic configurations of offspring (Cimino et al., 2019).

2. Problem Statement

Today, empirical evidence and theoretical models underline the complexity of the developmental trajectories of children's psychopathological problems, in which it is possible to track down various aspects, such as early family maladaptive relationships, parental psychopathological traits and specific genetic predispositions of the children (Cimino et al., 2018; Golds et al., 2020; Pennell et al., 2016). Thus, as suggested by the new research lines of developmental psychopathology framework (Cicchetti, 2013; Davies & Cicchetti, 2004), since children's physical and emotional well-being develop over time and through early relational experience, behavioral and psychological problems in early childhood can be the outcome of a chain of interconnected factors that deserve to be assessed, individually and in their interaction (Tronick & Hunter, 2016).Consistently, the scientific literature examines different aspects of the topic in question, focusing in particular on psychological, biological and social variables in ARFID, also with reference to the different diagnostic subcategories (Lucarelli et al., 2018).

Nowadays, it has been widely found that offspring's emotional-behavioural problems are related to parental psychopathology (Middeldorp et al., 2016; van der Pol et al., 2016), just as maladaptive parent-child relationship and maternal psychiatric problems (depression, eating disorders) can be related to specific eating difficulties in early childhood (Cerniglia et al., 2017; Murray et al., 2016). Moreover, the influence of parental psychopathological profiles on children's problems has also recently been examined in relation to the genetic vulnerability (Goodman & Gotlib, 1999). In this regard, research demonstrated the importance of genetic characteristic and epigenetic aspects in the onset of childhood eating disorders, including ARFID (Lampard et al., 2014). In fact, different studies have indicated that the influence of environmental variables (such as the supportive or maladaptive relationship between parents and children) on offspring's psychological wellbeing seem to be related to underpinning mechanism of polymorphism and DNA methylation (Champagne & Curley, 2009; Duman & Canli, 2015; Hübel et al., 2019). More in particular, investigation have also identified genetic pattern linked with eating disorders and eating problematic conducts, demonstrating the relevant role played by a gene that encodes dopamine transporter

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protein, that is DAT1 (Blum et al., 2013) also in various psychopathological problems (Leventakou et al., 2016; Pinsonneault et al., 2011). In addition, significant associations between maternal psychopathologic profiles and children's DAT1 methylation have been reported (Weaver et al., 2004).

3. Research Questions

From what has been related so far, the relationship between environmental factors, such as maternal psychopathology or parent-child quality relationships, and children's emotional and behavioral problems has been well documented in the theoretical and empirical literature. Besides, other characteristics that seem to increase the chance of developing feeding disorder and other problems in early childhood, such as genetic risk factors, are less well understood. To our knowledge, many studies on genetic and epigenetic elements focused primarily on adolescents and adult population, while little attention has been given to samples of early children (Cimino et al., 2019; Golds et al., 2020). Moreover, to our knowledge, no study was yet conducted on DAT1 polymorphism and methylation in children with avoidant/restrictive food intake disorder (ARFID). This lack of data on this topic may contribute to delay in understanding the complex interplay between psychological, genetic and epigenetic factors in early feeding disorders.

4. Purpose of the Study

In an effort to more clearly understand the various mechanisms that may be involved in the relationships between parental psychopathological aspects and child developmental problems, the current study aims to explore genotype-environmental interaction (GxE), considering the possible mediating role played by dopamine transporter (DAT1) gene. In the study, the *Developmental Psychopathology* theoretical framework that highlights the dynamic interplay between genetic and environmental risk factors in shaping children development was adopted. More specifically, this was a pilot cross-sectional study conducted to examine the relationship between children's DAT1 methylation, children's emotional-behavioural profiles and maternal psychopathologic risk, in families with preschool-age children with three different ARFID subtype (i.e., irritable/impulsive (I/I), sensory food aversions (SFA), post-traumatic feeding disorders subtypes (PTFD)).

5. Research Method

5.1. Sample and procedures

Thanks to the collaboration with public and private mental health clinics and pediatric hospitals in central Italy we recruited N= 69dyads of children (50% males and 50% females, from 24 to 36 months; average age= 29 months; SD = 3.14). Mother-children dyads were 96% Caucasian and 88% of the mothers belong to families with an average socioeconomic status (Bornstein & Bradley, 2014). According to the clinical ARFID subtypes children and their mothers are assigned to three subgroups:

Group 1, comprised children with ARFID I/I subtype diagnosis, and their mothers (N = 23); Group 2, comprised children with ARFID SFA subtype diagnosis, and their mothers (N = 23); Group 3, comprised children with ARFID PTFD subtype diagnosis, and their mothers (N = 23).

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Mothers were contacted by trained psychologists who explained in details the scope of the study and its aim. Researchers in person have administered the self-report questionnaires (described below). Mothers' psychopathological symptoms and offspring's emotional–behavioral functioning was assessed through several questionnaires. Children's DNA (polymorphism and methylation status of DAT1) was collected through buccal swabs (Isohelix Swab Pack).

All the mothers have filled the questionnaires out independently and in accordance with the Helsinki Declaration they signed an informant consent form. The study was approved by the Ethical Committee of the Psychology Faculty at the Sapienza University of Rome.

5.2. Measures

The *Child Behavior Checklist* (CBCL1 ½-5 Achenbach 2000; Italian version by Frigerio et al., 2004) is a report form questionnaire that assesses children's emotional and behavioral functioning through 99 items and through which the parent is asked to answer.

It is composed of three different symptomatic scales, Internalizing, Externalizing, and Neither Internalizing, Nor Externalizing, structured as a three-point Likert scale (from 0 = "not true" to 2 = "very true or often true"). The principal syndrome scales are: Emotionally Reactive, Anxious/Depressed, Somatic Complaints, Withdrawn, Attention Problems, Aggressive Behavior, and Sleep Problems. The tool has a good internal consistency (Cronbach's αvalue of 0.79).

The *Symptom Checklist-90-Items-Revised* (SCL-90-R; Derogatis, 1994) is a 90-item self-report tool aimed at evaluating psychological symptoms and psychological distress in adults or adolescents. It is composed of nine different dimensions (somatization, obsessive-compulsivity, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism) and a Global Severity Index (GSI). Items are measured on a Likert scale ranging from 0 (not at all) to 4 (extremely). Prunas et al. (2012) developed the Italian validated version of SCL-90-R, showing that the instrument have good internal coherence (α coefficient=0.70–0.96).

5.3. Data analysis

A hierarchical regression analyses were performed to verify whether children's DAT1 genotype moderate the relationship between parental psychopathological risk and offspring psychological functioning. Moreover, a Pearson correlation analyses were carried out to explore possible correlations between offspring's genotype and parents' psychopathological risk.

Moderation analyses were carried out through the Process macro for SPSS (Hayes, 2017). All data were performed with IBM SPSS software version 25.0 (IBM, Chicago, IL, USA).

Children's Dopamine Transporter methylation status, emotional-behavioral functioning, and maternal psychopathological profiles.

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6. Findings

A series of univariate analysis of variance (ANOVA) were carried out to explore children's DAT1 methylation, children's emotional-behavioral profiles and maternal psychopathological risk in the three groups, considering the group (I/I, SFA, PTFD, NC) as independent variables.

With regard to children's genotype profiles, results show significant differences between the study groups with reference to children's DAT1 total methylation, children's emotional-behavioural problems and maternal psychopathological risk ($p < 0.0001$).

In particular, results indicated that children of the Group 1(I/I diagnosis) had higher levels of DAT1 methylation than all other groups ($p < 0.0001$), while children with an SFA diagnosis (Group 2) showed higher levels of DAT1 methylation than children with PTFD diagnosis ($p < 0.0001$).

With regard to children's emotional and behavioral functioning children of Group 1 (with I/I diagnosis) and children of Group 3 (with a PTFD diagnosis) showed higher levels of psychopathological problems compared to children of the SFA group ($p < 0.0001$).

As regards maternal psychopathological risk, mothers of Group 1(children with I/I diagnosis) reported higher scores than mothers of Groups 2 and 3 ($p < 0.0001$).

Finally, as regard the dynamic interplay between the environmental and individual variables, results show a significant association between maternal psychopathological risk and children' DAT1 methylation, and a moderated association with children's DAT1 genotype. In addition, a significant association between maternal psychopathological risk, children's DAT1 9/x genotype and children's emotional-behavioral problems was found.

7. Conclusions

Overall, this preliminary study suggests the relevant relationship between maternal psychopathological risk, children's genotype and children's emotional-behavioural functioning. This complex gene-environment interplay seems to have a crucial implication in shaping children's psychopathological problems and diseases such as ARFID. In particular, a crucial role in individual genetic risk might be played by the 9/x genotype, that influences the effects of methylation on children's problems.

Furthermore, the study highlighted the complex interaction between children's DAT1 genotype and environmental factors, such as mothers' psychopathology. Thus, this pilot study highlights the presence of complex patterns of psychological, genetic and epigenetic variable that need further and more in-depth analysis.

This study has some limitations. First, parents' and children's variables were assessed using only self-report instruments. In addition, parental psychopathological risk was assessed without taking into account paternal risk profile and its possible influence on offspring's psychological functioning. Moreover, causes of the genotype-environment interactions are still unclear and need to be investigated further with a larger sample than the one used in the current study.

Despite these limitations this study provided information about infants' feeding disorders issue that may also be useful to implement early assessment and treatment programmes. For these reasons, investigating the mutual influences between children's and their parents' variables should continue to

provide even more knowledge about the individual adaptive functioning and well-being in developmental age.

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