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Facts of aggression

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CHAPTER 1

GENERAL INTRODUCTION

Aggression in its different manifestations comprises an integral part of history and everyday life; ranging from cataclysmic armed conflicts to acts as mundane as an employer giving its employee "the silent treatment". The famous 18th century philosopher Jean-Jacques Rousseau proposed that this has not always been the case, painting an image of a prehistoric world populated by peaceful hunter-gatherers where aggression and violence were almost non-existent (Rousseau, 1754). He proclaimed that modern civilization, primarily through private ownership, caused man to stray from their natural disposition of peacefulness, luring it into a deviant, unnatural, and aggressive state. Logically, when the modern 18th century man was allowed to approximate its original natural state, serious conflict would be a thing of the past. Especially children were considered a prime target for his endeavor, because they would not have been exposed to the degenerative influences of modern society.

Although Rousseau's point of view appeals to many, archaeological findings suggest his vision of aggression and antisocial behavior to be more nuanced. Very clear indications of inter-group violence have been found in Kenya dating back to 10.000 BCE (Lahr et al., 2016). At the edge of a lagoon, at least 10 hunter-gatherers met their violent ends, showing signs of lethal sharp-force (probably by arrows) and blunt-force trauma. Even so, less conclusive evidence of human aggression dates back 24.000 years ago (Trinkaus & Buzhilova, 2012). Descending even further into the abyss of time, the 780.000-year-old remains of Homo Antecessor, which is considered a common ancestor of Homo Sapiens, showed signs of non-ritual cannibalism (Fernández-Jalvo, Díez, Bermúdez de Castro, Carbonell, & Arsuaga, 1996).

Of course, these indications that aggression has been around for the entirety of mankind's existence and their common ancestors' does not automatically render it a good thing or negates the evil and suffering which some aggressive acts entail. This is also a reason why Rousseau's ideas resonate with a lot of people; it provides a feeling that man, especially children, is essentially good and that its surroundings predispose it to aggressive and antisocial acts. Importantly, these archeological findings do indicate that an inclination to resort to aggression under certain circumstances is a very integral part of the human condition. In this thesis I aim to gain a deeper understanding of childhood aggression and its consequences.

Human aggression consists of a very diverse set of behaviors, ranging from explicitly overt expressions, like physical aggression and name calling, to covert

expressions like gossiping, and social exclusion (Vitaro, Brendgen, & Barker, 2006). Because of this heterogeneity a wide variety of aggressive typologies have been proposed, for example: based on the intentions of the perpetrator (Raine et al., 2006), its visibility to bystanders (Crick, Casas, & Mosher, 1997), whether the aggressive act is direct or indirect (Card, Stucky, Sawalani, & Little, 2008), and more. Each of these subtypes try to answer different questions that arise when studying aggression and antisocial behavior, think of sex differences (i.e., direct or indirect aggression) or relating aggression to biology (i.e., reactive or proactive). Although these different definitions answer different questions with varying success, they do emphasize that aggression is a very multifaceted and complex construct to study.

Beside this heterogeneity, it is also crucial to realize that the occurrence of these different types of aggression fluctuate drastically depending on developmental stage (Vitaro et al., 2006). For example, physical aggression has its onset 12 months after birth and peaks at ages 2-4 years after which it decreases substantially (Tremblay, 2014). This desistance from physical aggression can reflect either improved inhibition of aggressive tendencies or the ability to engage in types of aggression which require more cognitively demanding strategies like manipulation or deception. Therefore, more "refined" types of aggression arise later in childhood and adolescence, while other less sophisticated types typically subside. Because children also differ greatly in their environments, experiences, and propensities, there is large individual variety to what extent and in which forms aggressive behaviors are expressed.

Interestingly, it seems beneficial to be aggressive from time to time; with aggression being correlated to positive outcomes, like the assertion of social dominance or social desirability (Little, Rodkin, & Hawley, 2007). This would also explain why human aggression has been around for a long time; under certain circumstances it pays to be aggressive, therefore ensuring its continuity as a prevalent human behaviour. However, despite of this, aggression often seems to come at a considerable cost: an overwhelming majority of the literature indicates that aggression is associated with lower functioning. A wide variety of problems are related to aggression, proximal child characteristics like ADHD symptoms, internalizing problems, (Bartels, Hendriks, Mauri, Krapohl, Whipp, Bolhuis, Conde, Luningham, Fung Ip, et al., 2018), accident proneness (King & Parker, 2008), lower cognitive abilities (Barker et al., 2007), and poor school performance (Vuoksimaa et al., 2020), as well as distal child characteristics, like

low socioeconomic status, exposure to harsh and insensitive parenting (Campbell, Spieker, Vandergrift, Belsky, & Burchinal, 2010; Wakschlag & Keenan, 2001), peer victimization (Barker et al., 2008), exposure to violence, and substance abuse (Ondersma, Delaney-Black, Covington, Nordstrom, & Sokol, 2006). In sum, although aggression is associated with some positive characteristics it seems to be predominantly a risk indicator for various problems.

In addition to the strong relationship between aggression and concurrent worse functioning, there is a general consensus that especially childhood-onset aggression is associated with a considerable risk of future adverse outcomes spanning into adulthood (Fergusson, John Horwood, & Ridder, 2005; Rivenbark et al., 2018). The seminal work of Moffit (1993) first described that childhood-onset antisocial behavior, which includes aggression, confers an important risk marker for life-course-persistent antisocial behavior as compared to adolescent-onset antisocial behavior. Children on this life-course-persistent path are very likely to belong to a tiny fraction of the population which commits a vast majority of crimes, for example, 1% of Sweden's population is responsible for 63% of all violent crime convictions (Falk et al., 2014). Besides severe antisociality, the life-course-persistent antisocial lifestyle is associated with all sorts of other negative long-term outcomes, like physical health problems (e.g., chronic bronchitis, decreased oral health), homelessness, unemployment, having no qualifications, and overall financial problems (Odgers et al., 2008). Notably, twenty-five to sixty percent of adults with a psychiatric disorder had a disruptive behavior disorder in childhood (Kim-Cohen et al., 2003). This clearly shows that childhood aggression can be considered a public health threat and a prominent marker for future problems, warranting considerable efforts in terms of prevention and treatment.

Despite all of this, there is also room for optimism. Fortunately, two thirds of aggressive children appear to grow out of their problems and achieve relatively good outcomes, while the other third follows the life-course persistent antisocial lifestyle with its associated low functioning (Odgers et al., 2008; Wertz, 2019). Although this is a positive message, it also complicates matters: which children with aggression will grow up to flourish and which will flounder? The presence of childhood aggression as a risk indicator should be expanded by additional characteristics that enables us to differentiate between those children that have bad prognoses and those that achieve relatively good functioning later on.

The ACTION (Aggression in Children: unraveling gene-environment interplay to inform Treatment and InterventiON strategies; http://www.action-

euproject.eu/) consortium was founded in 2014 to answer several aspects of this question. ACTION aims to study childhood aggression, focussing on a) clinical epidemiology and current classification and treatment problems; b) genetic epidemiology, including genome-wide association studies and epigenetics; c) gene-environment correlation and interaction; d) biomarkers and metabolomics. This thesis was written within the framework of the ACTION, and shared its aim to gain insight in the etiology, predictors, and outcomes of aggression and antisocial behavior. The first part of this thesis will focus on more conventional prediction of outcomes and continuation of aggression and antisocial behavior on the basis of the following constructs: parental psychopathology (**Chapter 2**), anxiety and depression (**Chapter 3**), and Oppositional Defiant Disorder symptoms (**Chapter 4**). The second part of this thesis focusses on novel biological markers of aggression and consists of a review on the genetics of aggression (**Chapter 5**), and a study on the metabolomics of aggression (**Chapter 6**).

THIS THESIS

Settings

The chapters in this thesis were based on multiple community and clinic-referred samples. In the **second and third chapters**, twins from the Child and Adolescent Twin Study in Sweden (CATSS) were used. The CATSS is a nationwide longitudinal study that targets all twins born in Sweden since July 1992 (Anckarsäter et al., 2011). Parents of twins were contacted by telephone in connection with the twins' ninth birthday (twins born from July 1, 1992 to June 30, 1995 were included at age 12 years). The families were contacted again in connection with the twins' 15th birthday and again at age 18. The follow-up at 15 years includes twins born in 1994 and onward, whereas the follow-up at 18 years includes twins born in 1992 and onward. At both follow-up assessments, at least one parent and both twins were invited to participate.

In the **fourth chapter** on Oppositional Defiant Disorder subtypes, clinic-referred 6- to 18-year-olds from Curium-LUMC, a center for child and adolescent psychiatry in the Netherlands, were studied. The data were collected as an integral part of a clinical protocol between October 2008 and October 2017. The sample consisted of children and adolescents between 5 and 18 years old who were consecutively referred for a diverse range of psychiatric problems. Parent, teachers, youths, and clinicians provided information.

The **fifth chapter** consists of a literature review. Specifically a review of reviews on aggression and a review of genome-wide association studies of aggression and antisocial behavior.

In the **sixth chapter**, again a clinic-referred sample from Curium-LUMC was studied. In contrast with the fourth chapter, these children were enrolled in the Biobank of Curium-LUMC and were aged 6- to 13-years. Children were included between February 2016 and January 2018. This Biobank targets 6- to 12-year-olds and collects, amongst others, morning urine and phenotypical data from the parents and teachers. In the same chapter Dutch twins of the same age from the longitudinal Netherlands Twin Register (NTR) were included (Boomsma et al., 2006; Ligthart et al., 2019).

Outline of the studies described

The second chapter focusses on the association between parental mental disorders and childhood disruptive behavior (DB), which includes aggression, and how both relate to adolescent outcomes. Although longitudinal outcomes of parental psychopathology and child DB have been extensively studied, up until now no study has focused on the combination of both constructs in a longitudinal setting spanning from childhood to adolescence. This chapter aims to investigate whether children with DB and parents with a mental disorder have worse outcomes in adolescence than children with DB and parents without a mental disorder.

The third chapter investigates the co-occurrence between DB, depression, and anxiety in childhood and adolescence. Symptoms of anxiety and depression are often seen in children with DB. However, it is not yet clear whether these associations are related to increased DB in adolescence. Furthermore, it is not clear whether cross-sectional and longitudinal associations are likely to be causal. To investigate whether causal relationships are likely, a discordant co-twin design is used to stringently control for genetic and environmental confounding.

The fourth chapter focusses on Oppositional Defiant Disorder (ODD) symptoms in a clinic-referred setting. ODD symptoms can be divided in irritable and oppositional symptoms and are correlated to different types of problems. Latent Class Analysis is used to investigate whether children and youths can be classified into separate classes on the basis of their parent- and teacher-reported ODD symptoms at referral. The clinical utility of the resulting classes is studied

by comparing these on clinically relevant outcomes at the end of referral, like psychiatric classifications, treatment outcome, and other psychological problems.

The fifth chapter gives a review of the molecular genetic research on aggressive and antisocial behavior, including genetic linkage, candidate gene, and genome-wide association studies. The behavior genetics literature is also covered, as well as the definition and measurement of aggression. This review furthermore includes the first application of a machine-learning-assisted literature search.

The sixth chapter covers the first metabolomics study targeting childhood aggression including both 6- to 12-year-old clinic-referred children and community-residing twins. Two platforms are used one targeting amines and a second targeting organic acids, as well as other biomarkers of larger molecular weight.

The seventh and final chapter will summarize and discuss the results of chapters two to six, provide key conclusions, clinical implications, and suggestions for future research.

