ACTION

ACTION: Aggression in Children: Unraveling gene-environment interplay to inform Treatment and InterventiON strategies

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D 3.7 Report on the longitudinal genetic architecture for aggression throughout childhood into adulthood and insights in underlying causes of comorbidity with other behavioral and emotional problems

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D3.7
Report on the longitudinal genetic architecture for aggression throughout childhood into adulthood and insights in underlying causes of comorbidity with other behavioral and emotional problems

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Summary: This document describes the deliverable 3.7. We conducted two projects to gain insight in the stability of aggression and its genetic architecture. In the first project we analyzed all longitudinal aggression data of the Young-Netherlands Twin Register. In the second project we combined two large datasets of the Netherlands and the United Kingdom.

Keywords: Aggression, stability, childhood, longitudinal

A. Project I: Stability of Aggression

MAIN FINDINGS:

1. A decline in AGG is observed across age in the maternal and self-ratings. This decline is much less pronounced in teacher ratings.
2. At younger ages boys score significantly higher on aggression than girls. Throughout development, this difference decreases and then shifts to significant higher scores for females in young adulthood.
3. Longitudinal correlations are high between ages 3 and 12 (between .40 and .72) for the maternal ratings by the CBCL. Teacher rating stability is also high (between .45 and .54), as are correlations between ages 14 and 22 (between .30 and .61) for the ratings by the self-report YSR and the ASR.

CLINICAL SIGNIFICANCE:

The results of our analyses have extremely important clinical implications. To our knowledge the present study is the first to examine the longitudinal stability of aggressive behavior across childhood and adulthood. Importantly, the results of the present study demonstrate that aggression, regardless of the informant, is a highly stable trait across development. This is particularly important to clinicians because our data indicate that individuals who are rated as highly aggressive in childhood are likely to remain highly aggressive in adulthood.

High scores on aggressive behavior on the Child Behavior Checklist have consistently been shown to be predictive of oppositional defiant disorder, conduct disorder, antisocial behavior and substance use disorders. The last of these two disorders directly account for a significant degree of human suffering and health care costs and are extremely difficult to treat in adulthood. Given the substantial morbidity and mortality, the difficultly in treating these conditions in adulthood, combined with our findings that high scores in childhood predict high scores in adulthood, it seems clear that clinicians and scientists become even more vigilant about screening for and developing new intervention and prevention programs aimed at reducing aggression in childhood.

From our data, taking a 'boys will be boys' approach and waiting for childhood for aggression to resolve on its own is a bad bet. Just how to 'treat' childhood aggression remains an elusive target. However, medication interventions have been largely ineffective at treating core aggressive behaviors. Given the myriad of environmental (particularly family, socioeconomic, abuse, neglect, and lack of parent training) and genetic factors that influence the etiology of aggressive behavior, we suggest it is time to take a full court press on the identification and treatment of childhood aggression. Such approaches could and should include screening all children, early in life, for

aggressive behavior in the same way children are currently screened for autistic traits. Following a similar model, children with high scores on aggression, and who are thus at high risk for aggressive adult behavioral outcomes, should benefit from an expanding set of new treatment approaches. In the same way that Applied Behavioral Analyses (ABA) is offered to children with Autism Spectrum Disorders, new family-based behavioral therapies should be tested in children and families with aggressive behavior problems. These programs should include health promotion, illness prevention and family based intervention approaches (Hudziak and Ivanova, 2016) in order to do all that we can diminish the negative consequences and sequellae of clinically significant aggressive behavior in childhood. Keeping in mind that we have almost no effective treatment for these same traits in adulthood, it seems obvious and propitious that new treatment approaches must be developed during childhood, when neuroplasticity and the possibility of changing brain-behavior outcomes is the greatest. In the same way modern medicine reacted to the importance of intervening on another stable child behavioral trait (autism spectrum illness) results of the present project suggest that aggression is a similarly stable trait, and investing in early interventions may help to substantially offset the costs of aggressive behavior to individuals, families, healthcare systems, and society

DETAILED DESCRIPTION OF THE STUDY

Introduction

Early-onset and clinically significant aggressive behavior is associated with substantial costs for individuals, families, health care systems, and societies (Raaijmakers et al., 2011). A portion of these costs can be explained by criminal activity with research suggesting that peer-reports of aggression in childhood and adolescence significantly and positively predict official records of offending in adulthood (Dubow et al., 2014). However, such costs are also due to increased utilization of health, social, and educational services (Lavigne et al. 1998; Leventhal et al. 2000). Despite the human and economic costs associated with clinical levels of human aggression, aggression's role in maintaining dominance is well documented in many fields including biology, ethology, and anthropology. Such work implies that a moderate level of sub-clinical aggression may be a positive and adaptive trait resulting in both greater accesses to resources and enhanced reproductive success (Hawley, 2015).

Work by Verhulst and van der Ende (1995) shows that across 2-, 4-, 6-, and 8-year intervals the correlations for aggressive behavior in males are .65, .60, .52, and .48, respectively. These significant rates of stability across childhood are also reflected in females with Hofstra et al. (2000), reporting stability correlations over a 14 year period to be .53 for females and .33 for males in a cross-lagged longitudinal design. Genetic studies suggest that between 51%-72% of the variance in aggression during childhood is accounted for by genetics (Hudziak, 2003; van Beijsterveldt et al., 2003).

To date, most studies of aggression have focused on aggressive behavior in childhood or adulthood. To our knowledge no studies have examined the stability of aggressive behavior across both childhood and adulthood. Using a sample of 22,043 individuals between the ages of 3-22, the present study sought to investigate the phenotypic stability of aggressive behavior across age, gender, and informant. Using the Achenbach System of Empirical Based Assessment (ASEBA), aggression was assessed with the age-appropriate surveys such that maternal were being collected at ages 3, 7, 10, and 12, and with self-reports were collected at ages 14, 16, 18, 20, and 22. These data were combined with teacher ratings at ages 7, 10, and 12. We compared results for the official Aggressive Behavior syndrome scales of the ASEBA taxonomy with a 14-items sum score based on items that are identical at all age groups, and are part of the aggressive behavior syndrome scale at some, but not all ages. It was hypothesized that in both males and females, aggressive behavior would evidence a high degree of longitudinal stability.

Methods

Subjects

The present project, reports on the stability of aggressive behavior based on maternal ratings of twin pairs at ages 3, 7, 9/10, and 12 years, self-report at ages 14, 16, 18, 20 and 22 years, and teacher ratings at ages 7, 9/10, and 12 years. The data used in the present study were collected in a twin-family sample and therefore are not independent. As a result, we randomly selected one individual per family to be included in these analyses.

The total sample size consists of 22,043 randomly selected unrelated individuals (51.3% females) with at least one measurement of aggression between age 3 and 22. Of these individuals, 174 individuals participated at 8 time point, while 35.3% of the sample participated at only one time point.

Aggression measurement

Aggressive behavior was assessed by the age-appropriate surveys of the Achenbach System of Empirical based Assessment (ASEBA). The ASEBA surveys are screening tools for behavioral and emotional problems from early childhood to late adulthood. In the current study we analyzed maternal ratings on the Child Behavior Checklist (CBCL) 1½-5 and 6-18 for ages 3, 7, 10, and 12. At ages 14, 16, and 18 we analyzed the Youth Self Report (YSR), and the Adult Self Report (ASR) was used at ages 18, 20 and 22. At ages 7, 9/10 and 12, aggressive behavior was also assessed with the ASEBA Teacher Report Form (TRF). Parents, participants, and teachers were asked to fill out the items (i.e., roughly 120 items per survey) on a 3-point scale based on the occurrence of the behavior during the preceding 6 months. The scale ranges from 0 to 2 (0: if the problem item was not true; 1: if

the items was somewhat or sometimes true; 2: if the items was very true or often true). To ascertain the level of aggressive behavior of each participant we applied two scoring methods to the ASEBA surveys:

1. AGG-ASEBA: Aggressive behavior was scored based on the summation of items according to the ASEBA profiles. The number of items and the content of the items are age-specific. Supplementary table 1 provides an overview of the age-appropriate items shown in italics. As can be seen in table 2, the number of items varies per ASEBA instrument, with 19 AGG items for the CBCL 1½-5; 18 items for the CBCL 6-18; 17 items for the YSR; 15 items for the ASR; and 20 items for the TRF.

2. AGG-14items: Aggressive behavior was also scored based on 14 items that were assessed at all ages and were part of the ASEBA survey, but not necessarily of the AGG syndrome scale at all ages. These continuously assessed items are bold-faced in table 2. A drawback of this approach is that at age 3 only 7 of the 14 items are present. Consequently, analyses using the AGG-14items rely on data from age 7 onwards. Additionally, some of the 14 items belong to the AGG syndrome scale on the CBCL and YSR but not on the ASR. For example, item 19 (i.e. *demands attention*) is part of AGG syndrome scale at younger ages, but belongs to the Intrusive syndrome scale on the ASR.

Analyses

To compare the two approaches of AGG assessment (i.e. AGG-ASEBA and AGG-14items), the means and variance of the sum scores were first estimated in whole group of children and next for males and females separately. All analyses were performed in SPSS version 22 for Mac. Within age sex-differences in means and variances were tested with ANOVA's and independent sample T-tests respectively. Paired sample t-tests were used to test for longitudinal change in means and variances both for the whole group as well as for males and females separately. To gain insight into the within-person stability of aggressive behavior from early childhood to young adulthood we estimated longitudinal correlation coefficients. Using both methods of AGG assessment, we calculated the longitudinal correlation structure for the whole group for both AGG sum scores (AGG-ASEBA versus AGG-14items) and next for males and females separately. All data were included such that subjects were not required to have data at all ages.

Results

Irrespective of the change in number of items across age, a significant decline ($p \leq .01$) in AGG-ASEBA was observed. Both for AGG-ASEBA-and AGG-14item, at younger ages boys scored signficantly higher on aggression than girls. However, over the course of development, this difference decreased and reversed such that girls had significantly higher aggression scores than boys

in young adulthood. However, teacher ratings documented that in both males and females, a significant increase in aggressive behavior between ages 7 and 10, and a significant decline after age 10.

Using both the AGG-ASEBA and AGG-14items, variance decreased with age and was significantly different for boys and girls at all ages (except age 18). At younger ages there was a large sex-difference in variance whereas the variance was comparable at older ages. Indeed, using the AGG-14items, variance did not differ between males and females at older ages. Variance is lower than for maternal ratings at the same ages, but similar sex-differences with significant higher variances in boys than in girls is observed.

The phenotypic correlation pattern shows the expected decrease by increasing time-interval. Strikingly 1695 randomly selected independent individuals had an AGG score at age 3 and at age 22, resulting in a significant correlation of .18. The AGG-ASEBA correlations were strongest when the same ASEBA instrument and the same informant were used. For example, longitudinal correlations are high (ranging between .40 and .72) between the maternal ratings with the CBCL, and within the ratings with the YSR (ranging between .56 and .61) and the ASR (.53). A drop in stability was observed on the transition of maternal report to self-report with the YSR and from the YSR to ASR. The stability in AGG based on 14 overlapping items (AGG-14items; below the diagonal in table 3a-c) throughout development is strikingly similar to the AGG- ASEBA syndrome scale. The stability in teacher ratings were comparable to maternal ratings. Correlations between ages 7 and 10 were .54 and .55 for the ASEBA and 14 item scale respectively. Correlations were highly significant between age 7 and 12 (.45 AGG-ASEBA and .44 AGG-14 items), but also between age 10 and 12 (.53 AGG-ASEBA and .52 AGG-14items). Using either the AGG-ASEBA or AGG-14 items the stability of aggressive behavior was similar for boys and girls.

STATUS: The results of this project will be submitted summer 2016 in the position paper of ACTION in the special issue of European Child and Adolescent Psychiatry.

B. Project II: The longitudinal genetic architecture of aggresion in NL and UK

MAIN FINDINGS:

1. For both the CBCL as well as the SDQ reliability, stability and heritability of aggressive behavioral problems is high.
2. The heritability of aggression at ages 7, 9/10 and 12 year ranges between 42% and 78%.
3. In boys shared environment explained around 20% of the variation in aggression across all ages while in girls its influence was absent around age 7 and only came into play at later ages.
4. Longitudinal genetic correlations were the main reason for stability of aggressive behavior.
5. Individual differences in CBCL-Aggressive Behavior and SDQ-Conduct disorder throughout childhood are driven by a comparable but significantly different genetic architecture.

CLINICAL SIGNIFICANCE:

From a clinical point of view the stability of aggression and the stable influences of genetic factors from young age onwards indicates that a wait and see policy might not be the best approach to help children and their families who suffer from aggressive problems. Detection and identification of aggressive problems at young age might help to prevent further suffering. Common environmental influences shared by children from the same family are significant in boys for in the NTR and TEDS, but solely for females in TEDS. This is an interesting finding which may point to cultural differences between the Netherlands and the UK, but may also result from the different instruments used in the two studies. We need to investigate whether some instruments may be more sensitive to detecting influences of the shared family environment than others and also whether the same instrument behaves differently across cultures. Further for both NTR and TEDS non-shared environmental influences are stable and age specific. While this can be partly explained by measurement errors an alternative explanation is that the effect of environmental events on aggressive behavior is temporary and decays over time. Suggesting constant but heterogeneous environmental effects. Taken together, these results, in combination with the relative high heritability estimates, plea for studies into gene-environment interplay to inform the development of new treatment strategies

DETAILED DESCRIPTION OF THE STUDY

Introduction

As has been shown in Project I (see above) the stability of aggressive behavior in children is generally high. A number of behavior genetic studies have investigated the etiology of the stability in aggressive behavior. Van Beijsterveldt et al. (2003) observed in a longitudinal Dutch sample of 3- to 12-year olds that stability across age intervals ranged from 0.41 to 0.77 and genetic factors accounted for most of this stability. A genetic longitudinal model suggested a dynamic developmental process consisting of transmission of existing genetic effects interacting with new genetic influences.

In this project we make use of the continued longitudinal data collections in TEDS (Twins Early Development Study; Haworth et al., 2012) and NTR (Netherlands Twin Register; van Beijsterveldt et al. 2013) to analyze the longitudinal data on aggressive behavior in children aged 7 – 12 years. The two cohorts assessed parental longitudinal ratings on aggression conduct problems in very large sample sizes, which enable investigation of differences between sexes on the age-sepecific effects of genetic and environmental factors and estimation of longitudinal genetic and environmental correlations. Importantly, sample sizes are sufficiently large to assess effects of common environment, shared by children growing up in the same family/household (Martin, Eaves, Kearsey & Davies, 1978; Posthuma & Boomsma, 2000).

Methods

Subjects

In this study longitidinal data of the Netherlands Twin Register (NTR) en the Twin Early Development Study (TEDS) are combined and compared.

For the NTR data of maternal rating at ages 7, 10, and 12 were analyzed for twin born between 1986 and 2005. To assess aggressive behavior the Child Behavior Checklist versions 4-18 and 6-18 was used (Achenbach, 1991; Achenbach and Rescorla, 2003). Maternal ratings on AGG were available for 10,765 twin pairs at age 7, 8,557 twin pairs at age 10, and 7,176 twins pairs at age 12.

For TEDS data of parental (maternal or paternal ratings) at ages 7, 9, and 12 were analyzed for twins born between 1994 and 1996. The conduct problem scale with five separate items was used to measure aggression within TEDS. Parental ratings were available for 6,897 twin pairs at age 7, 3,028 twin pairs at age 9 and 5,716 twin pairs at age 12. Reduced sample size at age 9 can be explained by a shift in contacting scheme from phone to in-person interviews.

Analyses

To gain a first impression of stability and heritability of aggression across age, longitudinal within person, twin correlations and cross-twin-cross-age correlations were estimated for each cohort as a function of zygosity. Next, we applied longitudinal analyses to investigate to what extent preexisting and new genetic and environmental factors influence the dynamic development of aggression

Results

Boys scored higher than girls, but for both scales, the sex differences attenuated with age. Variance is larger for boys than girls for both cohorts at all ages. Variances in MZ and DZ twins are very similar, ruling out important contributions of sibling interaction or rater contrast effects (Eaves, Last, Young, Martin, 1978; Boomsma, 2014). The longitudinal phenotypic correlations in boys and in girls are high and reflect strong stability of aggressive behavior between ages 7 and 12. The twin correlations show a consistent higher correlation within MZ than DZ pairs suggesting additive genetic influences on aggression regardless of assessment instrument. Correlations between same-sex and opposite-sex DZ twin pairs are similar, indicating no qualitative sex-differences. In addition, twin correlations seem similar across different age groups indicating comparable genetic influences throughout development. Genetic influences on the covariance of aggression between ages is also to be expected given the higher MZ than DZ cross-twin-cross-age correlations.

The heritability of aggression at ages 7, 9/10 and 12 year ranges between 42% and 78%. The lowest estimate (42%) is observed for females at age 10 in the TEDS sample, while the highest estimates are observed for females at age 7 (78%) and age 10 (76%) in the NTR sample. A number of differences could be observed between NTR and TEDS. Heritability is somewhat lower in TEDS than NTR across sexes and differences between boy and girl estimates are slightly larger in NTR. Nevertheless, overall both studies are rather similar with respect to the influence of genetic and environmental components on aggressive behavior, despite the differences in assessment instruments. Partitioning of genetic effects into influences from prior ages demonstrated that the latent genetic factor in T1 is a major contributor to the genetic variance at T2 and T3, indicating that preexisting genetic factors play an increasingly important role in explaining variation in aggressive behavior (see table VI). The influence of T1 on subsequent ages is stronger in NTR than TEDS, which is also reflected by the relatively larger longitudinal correlation in NTR. This stability in underlying genetic effects is also reflected in the high genetic correlations. Genetic correlations are in the ranges of .76-.85 for NTR and .64 and .77 for TEDS. These high genetic correlation in combination with the significant genetic influences on the stability of aggressive behavior indicates that genes are the major driving force of the persistence of aggressive behavior throughout childhood regardless of the assessment instrument.

STATUS: This project and its results have been published as

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