The ACTION Newsletter

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

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In this issue

Antecedents of Aggression

Human aggression encompasses a wide range of behaviors and is related to many psychiatric disorders. Patients affected by bipolar disorder, psychosis, impulse control and personality disorders might present rates of aggression ranging from 26% to 84%. Aggression appears to have a specific longitudinal developmental trajectory starting from toddlerhood to adolescence. Environmental factors appear to modulate the liability to aggressive behavior determined by genetic factors. Indeed, the heritability of aggressive behaviors is substantial (28% to 40% depending on the symptomatology assessed). Consistently, having a mother with early onset antisocial behavior was a potent predictor of high levels of physical aggression in children assessed longitudinally from birth to 42 months of age. At the same time, the developmental trajectory to aggression appears to be modulated by environmental factors, such as low income, presence of mothers who smoked during pregnancy, mothers' coercive parenting behavior, and family dysfunction. Of note, specific epigenetic signatures of peripheral white blood cells seem to correlate with the manifestation of physical aggression during childhood. Taken together, these findings show that relevant antecedents for the manifestation of aggressive behavior later in life might exert an effect before birth, acting on and modulating the liability threshold determined genetically. This amount of evidence carries substantial clinical implications, as these environmental risk factors might be amenable to change, leading to effective preventive strategy and tailored treatment.

*Studies employing new opportunities in large scale genotyping, epigenetics and metabolomics technology will, in the future, help to explain heterogeneity and highlight pathways from molecule to phenotype. The **FP7-ACTION project** (Aggression in Children: Unravelling gene-environment interplay to inform Treatment and InterventiON strategies) aims to contribute to knowledge that will help children, their families, teachers and society at large. In particular, examples from autism and schizophrenia metabolomics research will provide new leads into biomarkers for psychiatric disorders. The identification at birth of pathways of metabolites involved with aggression will allow us to understand more on the genetics, intrauterine epigenetics and the perinatal programming of the brain. [*]*

*Within **ACTION**, twelve partners from the European Union, together with scientists from the USA and Australia, are collaborating to answer questions and respond to needs indicated by clinicians, social workers, parents and teachers of children with aggression problems.*

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[*] From: M. Manchia and V. Fanos, "Selected Abstracts of the 11th International Workshop on Neonatology. ABS 100, Brain mysteries from the womb to the adult: is aggression congenital?", Journal of Pediatric and Neonatal Individualized Medicine (JPNIM), vol. 4, no. 2, p. 231, 2015.

Comorbidity in young children

Childhood aggression is rarely an isolated problem. Children with aggression problems often also suffer from other emotional and behavioral problems. In psychiatry, such clustering of problems and disorders is referred to as 'comorbidity'. In the figure below, we show the extent to which aggression is associated with other problems. The information on children was provided by mothers of Dutch twins at the ages of 3 and 7 years. At age 3 ratings were given on the child's oppositional and overactive behavior (these are 'acting out' behaviors) and on withdrawn and anxious behaviors, as well as on sleep and somatic problems (for example, often stomach aches, headache or nausea). The figure presents correlations, for boys and girls separately, which can range between zero and one. Zero would mean that there is no association of aggression with other problems and one would mean that aggression always occurs together with other problems. The results are clear: at both ages aggression is correlated with all other symptom clusters. In 3-year olds aggression is particularly comorbid with oppositional and overactive problems, in children aged 7 and older there are especially strong correlations with rule breaking, attention and social problems, but also with anxious depression.

Age 3, mother report — BOYS MO / GIRLS MO
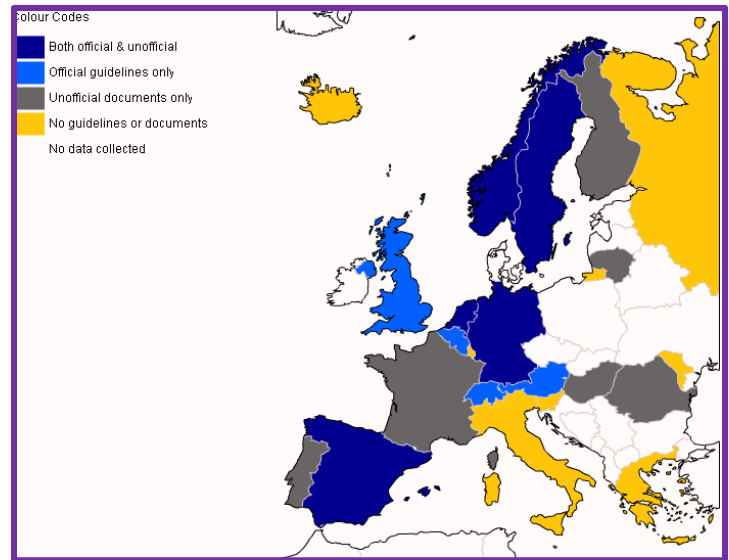
Age 7, mother report — BOYS MO / GIRLS MO
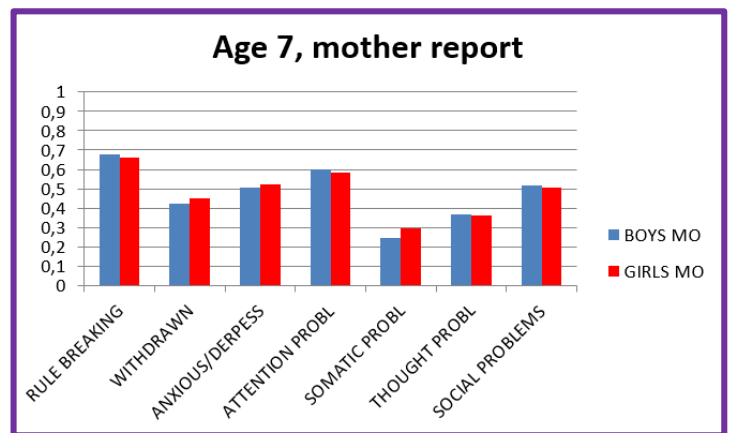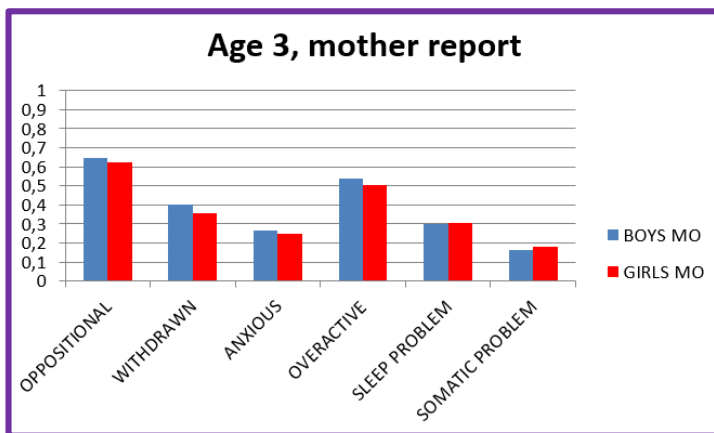
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European practices regarding children's aggression: an Inventory

Audri Lamers and Raluca Gatej, Curium-Lumc

Background. Severe Behavior Problems (SBP) are one of the most common reasons for clinical referrals in youth mental health and their management is extremely costly. In this regard, it is alarming that SBP in school-aged children is often too complex to be assigned an appropriate diagnosis, prevention program and/or effective treatment. Little is known about what clinical guidelines/documents are used for SBP in children across Europe. Similarly, an overview of the current clinical practices and critical needs amongst clinicians across Europe is missing. Therefore, an important **aim** of Work Package 2 is to make a European inventory across countries regarding:

Experts' opinions on:

1. the status and utility of and need for official clinical guidelines on SBP;
2. the status of and problems within current prevention and treatment programs for SBP.

Clinicians' opinions on:

3. the diagnostic and treatment practices for SBP across the clinical European community;
4. the successful treatment elements and critical needs in clinical practices regarding SBP.

Status of official clinical guidelines and unofficial clinical documents for SBP in children

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Definition

Severe behavioural problems (SBP) in early childhood (6-12 years old) include persistent and frequent oppositional, aggressive and destructive behaviours (ie. severe disobedience or fighting) occurring in more than one life area, and interfering with functioning in the major life domains, such as home, school and peer relationships. From a categorical approach, SBP include Oppositional Defiant Disorder and Conduct Disorder (DSM-V, 2013). From a dimensional approach, SBP are placed at the severe end of a broader spectrum of behaviour problems among which aggression and externalizing problems figure prominently. This dimensional approach in conceptualising SBP is used in the present study.

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Two online semi-structured **interviews** were developed and implemented, one for academic experts with a nationally or internationally recognised authority in SBP and one for clinicians with a primary interest in SBP in school aged children. Data collection from academic experts has been completed and resulted in 29 completed interviews across 23 European countries. Regarding clinicians, at present, 47 interviews across 17 countries have been completed.

With regard to experts' **responses,**

(1) experts from 9 countries mentioned that they are aware of at least some official clinical guidelines for SBP in their countries. Additionally, experts from another 7 countries indicated the availability of unofficial documents for SBP management in their countries. According to experts' opinions, existing official guidelines are helpful for clinicians and further efforts should be directed towards implementing these guidelines in practice. With regard to unofficial clinical documents, experts' responses focused mainly on existing issues, highlighting to a much lesser extent their positive elements. Most experts prioritised the lack of specific recommendations and of official clinical guidelines for SBP as a critical issue. Insufficient or limited access to resources for assessment and treatment, inconsistency in the tools used and limited knowledge about existing recommendations amongst professionals were also perceived as important by experts in certain countries. Consensus emerged on experts' understanding of critical needs within the current guidelines and/or documents. A majority of experts was in favour of developing European clinical guidelines for SBP in children. Some highlighted the importance of implementing dissemination programs and randomised-controlled trials alongside guidelines to ensure their successful application in practice.

(2) Additionally, to our experts' knowledge, the availability of primary, secondary and tertiary prevention programs varies greatly across Europe. For instance, the experts from Switzerland, Norway and the Netherlands mentioned a range of preventions of all types available in their countries, usually consisting of school and parent evidence-based programs. In contrast, experts in countries such as Hungary, Greece and the Republic of Moldova pointed out that prevention programs are lacking, as far as they are aware. Similarly, the same diversity is noticeable regarding the availability of intervention/treatment programs across countries; consensus emerged on the critical needs with regard to interventions. Improving access to programs and educating staff in evidence-based modules was the most frequently called upon need. Demands for more evidence-based modules followed, whereas wider dissemination and better cooperation with mental health systems or special schools were also perceived as important.

With regard to **clinicians' responses** (data collection is still running),

(3) Family-based, behavioural and cognitive-behavioural treatment forms are preferred for treating SBP, although the treatment options are very diverse.

(4) Improving parent-child interactions, using parent and/or teacher interventions and a collaborative approach have been most frequently identified as successful treatment elements by clinicians across countries. With regard to clinicians' opinions on critical needs in practice, collaboration amongst institutions such as schools and legal systems on individual cases was by far the most frequently reported problem in their clinical practice. Additional concerns included a lack of technical and human resources and of (training in) evidence-based programs, poor parental engagement in treatment, stigma and long waiting times for referral to specialist services. Finally, clinicians who were not aware of any official clinical guidelines for SBP being available in their countries unanimously supported the idea of such guidelines being developed.

ACTION

Conclusions and future work.

Consensus on the need for official guidelines was reached by experts and clinicians alike. Such guidelines would support standardized clinical practices across Europe, building on the literature of aggression management in children. Future work will focus on involving more clinicians, with the aim of conducting a cross-country comparison on clinical practices and needs for SBP. Together with the other work packages, this study will contribute to the generation of a comprehensive model for the clinical management of childhood aggression and provides solid grounds for the creation of European clinical guidelines for this population.

Dr. Audri Lamers is Clinical Psychologist and Senior Researcher at Curium-LUMC, Centre for Child and Youth Psychiatry. For the ACTION research program she is responsible for the Inventory of European Practices, under the supervision of Professor Robert Vermeiren. Recently she successfully defended her PhD thesis on the parent-team therapeutic alliance in child psychiatry. Currently she continues combining clinical work and scientific research with a special interest in the application of scientific research results to improve the quality of clinical work.

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Raluca Gatej has been working as a student research intern at Curium-LUMC, Centre for Child and Youth Psychiatry since November 2015. She is currently enrolled in a MSc Child & Adolescent Psychology program, at Leiden University. Raluca assisted with the implementation, data collection and analysis, and scientific write-ups of the project, under the supervision of Dr. Audri Lamers.
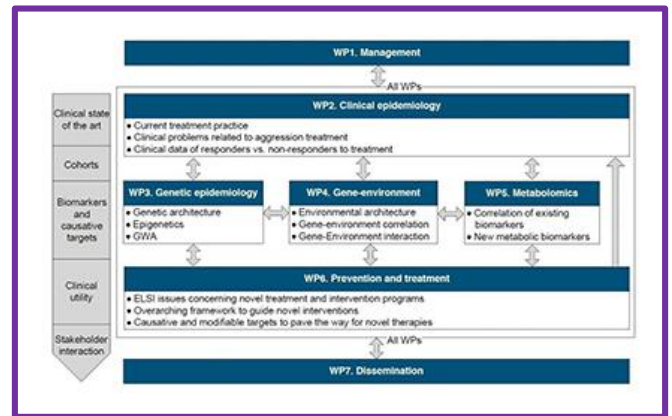
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Prevention and treatment: a systematic review of the literature

Anne Hendriks, Vrije Universiteit Amsterdam

We are currently conducting a systematic review of reviews and meta-analyses on the effectiveness of treatments for childhood aggression. There is a large range of treatments that includes universal prevention, selective prevention, indicated prevention, and intervention. Applying PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses ; see http://www.prisma-statement.org/), we conducted a systematic literature search, yielding 8279 results of which 211 appeared to be eligible and 64 met our inclusion criteria and were included in the review.

The role of WP6 within ACTION

The first part of the review will describe the effect sizes for the different types of treatment to provide an overview of effectiveness. The second part will examine the moderating effects found on treatment effectiveness. There is a wide variety of moderators of childhood aggressive behavior. We identified as important moderators child age, gender, pre-treatment levels of aggression, socioeconomic status, implementation characteristics, treatment characteristics, sessions, informants, and study quality. The third and final part of the review provides an overview of the communalities in research on the effectiveness of treatments for childhood aggression and the opportunities for future research by uncovering the less intensively studied topics in this area. With this review, WP6 aims to provide a comprehensive overview of the existing knowledge of the effectiveness of treatments for childhood aggression.

THE AUTHOR

Since August 2015, Anne has been working for ACTION as a PhD student at the Vrije Universiteit Amsterdam tutored by Prof. Catrin Finkenauer and Prof. Meike Bartels. Before this, she studied Child Development and Education at the University of Amsterdam.

Her main interests are child development and the implications of multiple informants.

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ACTION

Multidimensional Peer Nomination Inventory (MPNI): getting to know this Finnish-based emotional and behavioral problem scale

Alyce Whipp, University of Helsinki, Finland

There are many instruments for measuring emotional and behavioral problems in children and adolescents. In Finland, the FinnTwin12 researchers utilize an instrument designed by Finnish psychologist Dr Lea Pulkkinen called the Multidimensional Peer Nomination Inventory (MPNI). This instrument arose from work started in 1968 and evolved into the 37 item questionnaire that was used when twins were ages 12, 14, and 17 years (between 1994 and 2004).

Aggression can manifest in many forms. The MPNI gathers information on three major dimensions:

MPNI Questions

Direct Aggression:
1. Child may hurt others children when s/he is angry, e.g. by hitting, kicking, or throwing things at them
2. Child calls people names when they are angry with them
3. Child teases other children or attacks them for no reason at all?
4. Child bullies smaller and weaker children

Indirect Aggression:
1. Child spreads rumors about other people
2. Child excludes other children from the group

MPNI Questions (direct and indirect aggression)

1 Behavioral Problems (aggression [both direct and indirect], hyperactivity-impulsivity, and inattention),
2 Emotional Problems (depression, social anxiety, and victimization), and
3 Adjustment (constructiveness, compliance, helping behavior, and social activity).

For the FinnTwin12 study, the MPNI was collected on the twins via multiple informants including parents (age 12), teachers (age 12 and 14), the twins themselves (age 14 and 17) and the twins rated each other (age 14 and 17); additionally, at age 12, for a subsample of twins, classroom peers participated in a 'peer nomination' process utilizing this instrument. Classrooms participated together with a study representative administering the questions. Each student was asked to nominate up to 3 boys and 3 girls who best exemplified each question (e.g. 'Which of your classmates bully smaller and weaker kids?').

My initial project is to see how well these informants at different ages are able to predict antisocial personality disorder (ASPD) in young adulthood (age 22). ASPD was collected through a semi-structured interview which included DSM-IV-based criteria regarding ASPD; if a person met 3 or more of the ASPD criteria they were considered to have ASPD, this turns out to be the case for 4% of our twin population.

Results from looking at the parent and teacher (and sometimes peer) ratings show moderate correlations between the various informants, with twin and self-ratings being more highly correlated. While all informants appear to assess a twin's aggression in a way that predicts later ASPD, it seems that perhaps self-ratings (age 14 and 17) best predict later ASPD. The informants' assessments appear best able to predict certain criteria of the ASPD (namely, those criteria involving physical fights, breaking/entering, and property damage). Also of note, focusing specifically on direct or indirect aggression scales, informants' assessments for both aggression types appear to be able to predict an overall ASPD 'diagnosis' well (perhaps direct aggression better than indirect), though looking at the individual criteria items for ASPD, only direct aggression assessment appears to give consistent prediction.

ACTION

These results will help inform future FinnTwin12 analyses in ACTION, including my own future doctoral projects which will focus on substance abuse outcomes and their associations with adolescent aggression.

THE AUTHOR

Alyce Whipp received her MPH in Epidemiology with a concentration in Public Health Genetics in 2005 from the University of Michigan in the United States. She has recently been recruited to the Finnish Institute for Molecular Medicine (FIMM) to work on her doctorate degree at the University of Helsinki under the supervision of Drs Telle Korhonen and Eero Vuoksimaa in Dr Jaakko Kaprio's research group utilizing the FinnTwin12 dataset. Her current research focuses on general aggression measures in adolescence and associated behavioral problems (primarily substance (ab)use) in young adulthood.

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Statistical analysis strategies for metabolomics

Milena Lussu and Antonio Noto, University of Cagliari

The University of Cagliari, one of the 12 partners of ACTION, is involved in the project looking at biomarkers (metabolomics analysis) and also plays a leading role in dissemination. The research team, led by Professor Fanos, counts several international collaborations with particular focus in the field of paediatric diseases.

The team has been looking at metabolomics data from adult twins.

Metabolomics is the scientific study of chemical processes involving metabolites, which are increasingly seen as promising biomarkers for disease, including psychiatric disorders.

Metabolomics data typically consist of 100s of data points and in a typical metabolomics analysis, standardised procedures and appropriate statistical approaches are required to maximise the information extraction. Classification models are often used to compare two or more conditions (e.g. controls vs aggressive

Multivariate statistical analysis

persons) in order to investigate the potential differences in the metabolic profiles. The aim of our study project is to identify specific metabolites as biomarkers for aggression. To this purpose, aggression information is used to define persons into either aggressive classes, characterised by subjects with high scores on a standardised questionnaire, or a control class, persons having the lowest values for aggression scores.

In metabolomics there are two kinds of analyses that can be performed: univariate and multivariate analysis. Univariate methods analyse metabolomic features independently. They are common statistical analysis approaches and, therefore, their main advantage is their ease of use and interpretation. However, their main disadvantage is that they do not take into account the presence of interactions between the different metabolic features. Several univariate analysis methods are available for metabolomics data analysis. The selection of the method will depend on the statistical properties of the feature's distribution.

In contrast to univariate, multivariate analysis methods take into account all the metabolomics features simultaneously and, consequently, they can identify relationship patterns between them. These pattern-recognition methods can be classified into two groups: supervised and unsupervised methods. In unsupervised analysis methods, as principal component analysis (PCA), the similarity patterns within the data are identified without taking into account the class membership. In supervised methods, as partial

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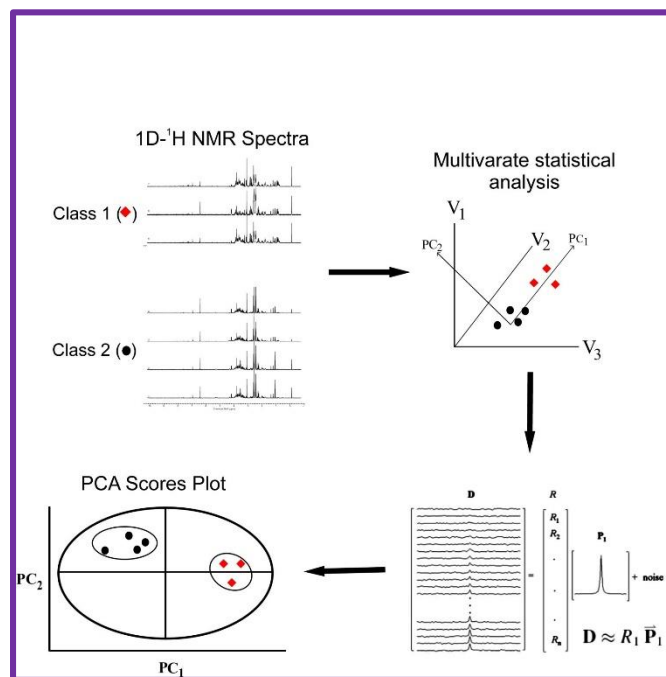
least square-discriminant analysis (PLS-DA), the class labels are used in order to identify single features or feature combinations that are more associated with a phenotype of interest. Supervised methods are also the basis for building prediction models.

Milena joined the University of Cagliari's Metabolomics Group in October 2006, to start the thesis project "Metabolomic analysis in newborns with intrauterine growth retardation". She holds a Master Degree in Pharmaceutical Chemistry and Technology and now she is attending the Postgraduate School in Clinic Pathology at the University of Sassari (Italy). Her scientific activities include the use of Nuclear Magnetic Resonance Spectroscopy, the application of statistical multivariate data analysis to the resulting spectra and pathways analysis.

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Antonio joined the University of Cagliari's Metabolomics Group in January 2011 as a research fellow. He holds a master's degree in biotechnology and molecular medicine and a Ph.D with a focus on asthma genetics. His scientific activities include the use of Gas Chromatography/ Mass spectrometry, the application of univariate and multivariate statistical analysis.

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Sum scores in twin growth curve models: Practicality vs. bias

Justin M. Luningham, University of Notre Dame, US

Longitudinal studies of childhood aggression in twins and relatives allow researchers to 1) to investigate how aggression develops as children get older, and 2) to disentangle the genetic and environmental contributions to aggression. The first step of these studies is to collect repeated measurements of childhood aggression across a span of development. Analysis of these repeated measurements provides the average degree of stability and change in aggression, as well as the amount of variability in these developmental pathways.

As children age, however, certain questionnaire items used to assess aggression can change in meaning or relevance. For example, a common item measuring aggression asks if a child "threatens others." An aggressive 3-year-old

Second-order Latent Growth Model

may not manifest his or her aggression by threatening simply because they have not developed the social understanding or verbal capacity to issue the threat; the same child at age 12 might exhibit a similar level of aggression, but may increasingly use threats to display aggressive behaviors. This is a case where changes in the *measurement instrument itself* may lead to an incorrect interpretation of development – an up-tick in aggression scores, due to more endorsement of the threatening item, has to do with changes in the meaning of the item rather than increased aggression.

We investigated the consequences of this issue specifically for aggressive behaviors. When behavioral problems are measured, multiple items are required to capture a range of related actions and attitudes. Scores on the items are often combined into a sum score, which has an intuitive meaning and allows for straightforward comparisons across ages. However, sum scores force all items to have the same weight, and therefore the same meaning across ages, ignoring the problem described above. What are the implications of this issue for modeling developmental trajectories and analyzing the longitudinal genetic and environmental influences?

Our study revealed exactly how changes in the measurement instrument, rather than changes in the inherent aggression of children, could lead to incorrect interpretations of typical developmental trajectories when a sum score of the items is used at each age. We quantified the degree of misinterpretation due to measurement changes that are ignored by the sum score such that researchers can contextualize the results of their studies. We also showed that the genetic and environmental components of these trajectories are accurate even when changes in measurement muddy the accuracy of the trajectories themselves.
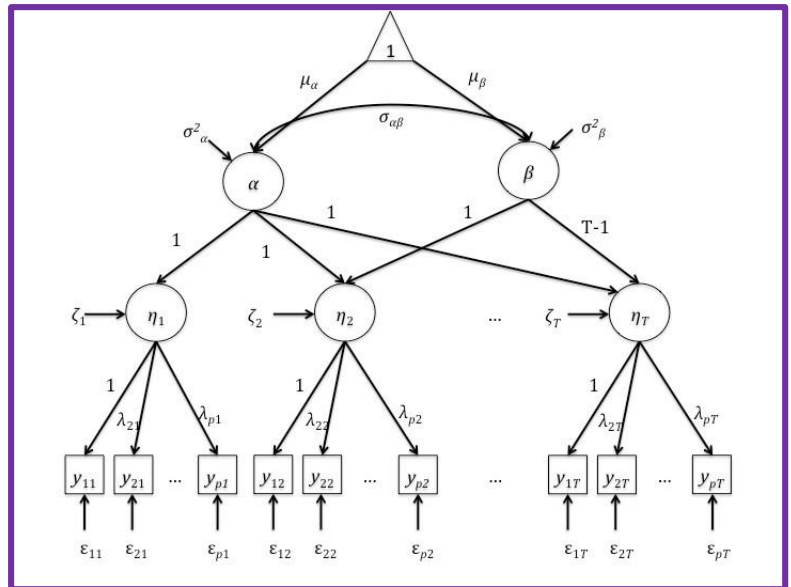
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This study provides important insight into the use of sum scores in longitudinal genetic analyses in ACTION, and the pattern of findings can be extended to measurement differences across groups (i.e., partner cohorts).

THE AUTHOR

Justin is a PhD student in Quantitative Psychology at the University of Notre Dame in the United States. In 2014, Justin joined the Genetics and Statistical Learning Lab under the supervision of Prof. Gitta Lubke. His research interests include psychological measurement, mega-analysis, and longitudinal modeling of complex phenotypes.

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ACTION Publications

The ACTION Project is proud to present its second series of publications, written between December 2015 and July 2016.

View the full list of our publications at
http://www.action-euproject.eu/biblio

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