Funded by the European Commission
Seventh Framework Programme
Grant agreement n° 602768

The ACTION Newsletter

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

N° 4, March 2018

In this issue

www.action-euproject.eu
info@action-euproject.eu

May 6-8, 2019

The final ACTION workshop
on all aspects of childhood aggression
will take place in the beautiful Sardinia, Italy

ACTION Newsletter 4. March 2018

*The ACTION project (**A**ggression in **C**hildren: Unraveling gene-environment interplay to inform **T**reatment and Interventi**ON** strategies), funded by the European commission (FP7/2007-2013), under grant agreement no 602768, brings together a team from academia and the industry. The main objective of ACTION is to improve the understanding of the causes of individual differences in aggression among children.*

Three of the projects described in this newsletter have come together, shared their data and conducted joint analyses to further the understanding of etiological mechanisms behind aggression and the consequences of aggression. What is rarely recognized in these joint efforts is the logistics behind them. In this editorial we will here list a few of the many impediments these endeavours may encounter. First, in collaborative projects the researcher in charge must be accustomed to the differences between the datasets and scales used, for instance "yes" might be denoted by "1" in a sample and by "2" in another. Second, data sharing inherently involves sending data to another place. For this to be done according to prevailing rules and regulations (which differ across countries) permission from ethical committees must be reviewed or sought. The actual sending of the data includes a two-part authentication as well as encrypted data, thus the researcher in charge needs to be familiar with these procedures. Finally, once the researcher has conducted the analyses and written them up, he/she needs to get approval from all co-authors. In some cases more than 50 people are involved. The researcher, thus, may need to bring together 50, sometimes contrasting, suggestions from a plethora of documents. Taken together, the studies by Vuoksimaa, Malanchini and Nivard discussed in this newsletter, are besides their scientific quality, remarkable achievements.

Two more studies (Cheng and Cederlöf) take advantage of the population based registries in Sweden. In the Scandinavian countries all citizens are assigned a personal identification number. This ID-number is then used in all contacts with all facets of the governing body. Thus it is possible to merge several registers (in these cases the prescribed drug register and the nation patient register) with the ID-number as a key in order to obtain data. This procedure is conducted by The National Board of Health and Welfare who also anonymizes the data.

Finally, the last part of this newsletter includes a joint effort by the University of Cagliari and the Vrije University of Amsterdam who have created an easy-to use interactive tool that depicts conditions and traits that co-occur with aggression. A great benefit of this tool is that it brings together all aggression data within the ACTION project and makes it accessible for everyone.

Paul Lichtenstein,
Professor in genetic epidemiology,
Karolinska Institutet

Sebastian Lundström,
Psychologist, PhD,
University of Gothenburg

Association between aggression and academic performance

Eero Vuoksimaa, University of Helsinki

Higher aggression often is associated with poorer academic performance, but the underpinnings of this association are not well understood. Levels of aggression differ across age and depend to some extent on the person who rates the behavior, so it is important to explore the effect of aggression on academic performance by looking at different ages and different raters, for example when studying children, their parents and teachers. Academic performance also can be measured either by teacher rated grade point average or by standardized test scores. In ACTION, we conducted a comprehensive analysis of the associations between aggression and academic performance in four twin cohorts covering childhood and adolescent aggression from 7 to 16 years. Academic performance measures were from 12 to 16 years. We measured aggression with three instruments: Child Behavior Checklist (in The Netherlands), Multidimensional Peer Nomination Inventory (in Finland) and the Strengths and Difficulties Questionnaire (in Sweden and in the UK).

We found a robust negative association between aggression and academic performance. Those with higher levels of aggression had poorer academic performance compared to those with lower levels of aggression. We found great congruence in the findings in the different countries (despite the different measurements, ages and raters). We also replicated these findings in within-family analyses. That is, are within twin pair differences in aggression are related to within twin pair differences in academic performance.

Greater childhood/adolescence aggression thus is associated with poorer school performance which in turn is related to poorer transition from school to work and also a risk factor for social exclusion. Early aggression prevention and intervention are not only important with regard to mental health and social life but may be beneficial also for achieving better school performance.

Eero Vuoksimaa, PhD, is a senior researcher at the Institute for Molecular Medicine Finland, University of Helsinki.
Eero.vuoksimaa@helsinki.fi

Eero Vuoksimaa

Pharmacological treatment for aggression and violence: Evidence from national register-based studies

Zheng Chang, Karolinska Institutet, Stockholm

Since the marketing of second-generation antipsychotic (SGA) medications, these medications have been used increasingly to treat children, adolescents and young adults. Data from the US and several European countries consistently show a substantial increase in prescriptions of SGA among young people, with studies reporting a two to six-fold increase in prescriptions over the last decades. Youngsters with a variety of psychiatric conditions other than psychosis, most often were treated with SGA for disruptive disorders or aggression. However, we do not know to what extent SGA reduces violent crime; the most severe and costly form of aggression, in the population. To address this question, we undertook a national pharmaco-epidemiological study using data from population-based registers in Sweden. We explored the association between the use of SGA medication and violent crime in Swedish adolescents and young adults.

We identified 27,115 youngsters aged 15-24 years old in Sweden with at least one dispensed prescription of SGA from 2006 to 2013. With within-individual analyses we compared the rate of violent crime between treatment periods and non-treatment periods in the same individual. The first results indicate that treatment periods with SGA were associated with a moderate reduction in rate of violent crime (Hazard ratio = 0.90, 95% confidence interval 0.83-0.97). This association is weaker than what has previously been observed in adults receiving antipsychotics (Hazard ratio = 0.55, 95% confidence interval 0.47-0.64). As violence can be the outcome of multiple mental disorders, further analyses will explore the associations between SGA and violent crime in individuals with different diagnoses. Because of both short- and long-term potential side effects from SGA use, health care provides have to carefully weigh the risks and benefits when treating aggression and violence with SGA.

The next project

Many legal cases linking selective serotonin reuptake inhibitors (SSRIs) and violent behavior have been reported, but empirical research on the association is limited and inconclusive. A recent review showed that the risk of aggression was doubled in youths taking SSRIs, but there was no significant increase in adults. In contrast, ecological studies suggest an inverse association between rates of SSRI prescription and violent crimes. This project aims to investigate the whether SSRI use are associated with increase the risk of violent crime in Swedish adolescents and young adults. In addition, we will explore whether we can predict which groups are at high risk of violent crime after initiating SSRI treatment.

Zheng Chang, Ph.D., is assistant professor at the Department of Epidemiology and Biostatistics at the Karolinska Institute. His research focuses on understanding the risks and benefits of psychotropic medications (e.g., antidepressants, antipsychotics) using large-scale population data. For the ACTION Research Program, he is involved in studies on the treatment of aggression, under the supervision of Prof. Paul Lichtenstein.

zheng.chang@ki.se

Zheng Chang

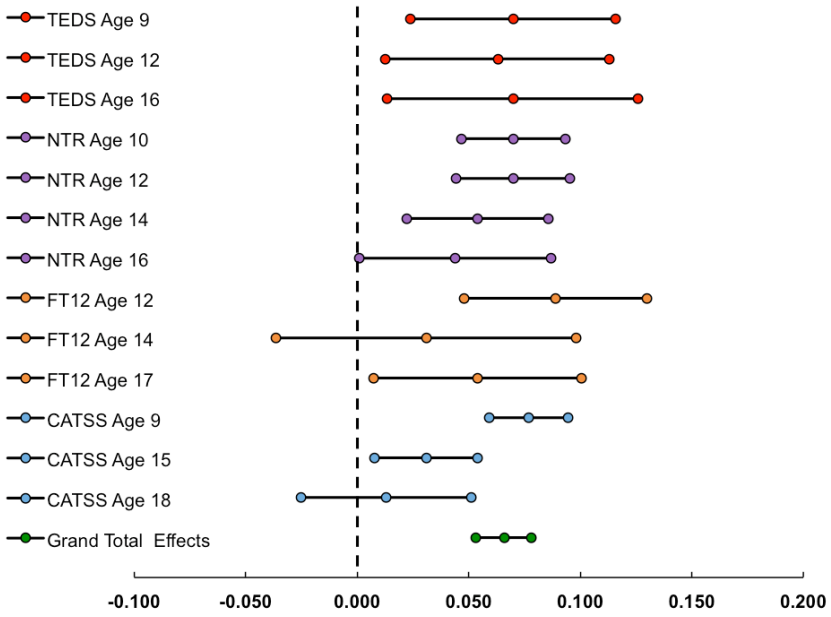
Aggressive behaviour in childhood and adolescence: a role for smoking during pregnancy

Margherita Malanchini, King's College London & University of Texas at Austin

Maternal smoking during pregnancy (MSDP) is a major public health concern. Although the incidence of MSDP has generally been decreasing in the last two decades, in 2010 12.5% of Danish, 16.5% of Norwegian, 6.9% of Swedish and 15% of Finnish women still reported smoking while pregnant, with an even higher incidence of MSDP in younger mothers, mothers who were single, and mothers from low socio-economic backgrounds. As well as being associated with several adverse birth-related outcomes, including a heightened risk of low birth weight and pre-term delivery, MSDP has been associated with an increased risk of developmental disorders, psychiatric outcomes, and externalizing behavioural problems in offspring. It has been argued that socio-demographic factors, such as maternal age and education, or shared genetic and/or environmental effects, may account for the association between MSDP and children's behavioural outcomes. With this study we investigated whether MSDP predicted later aggressive behaviour in offspring, above and beyond several perinatal risk factors, across four large population-based European samples.

Participants were members of four prospective twin cohorts: Twins Early Development Study (TEDS), Netherlands Twin Register (NTR), Childhood and Adolescent Twin Study of Sweden (CATSS), and FinnTwin12 study (FT12); who collaborate in the EU-ACTION project. Data from more than 30,500 children and adolescents were analysed. All cohorts had collected data on MSDP and other perinatal variables, including parental education and occupation, parental age, birth weight, and maternal stress and drinking during pregnancy.

Data on aggressive behavior were available in all samples.



Forest plots showing the results of the meta-analyses exploring the effect size of the association between maternal smoking during pregnancy and offspring's aggression after accounting for the confounding effect of other perinatal measures. The central dot in every line indicates the mean estimate, while the two dots at the extremities of each line indicate the lower bound and upper bound 95% confidence intervals.

Funded by the European Commission under the Seventh Framework Programme

Because different measures had been adopted across samples and collection waves we created a harmonized measure of aggression, for four age categories: 9-10; 12; 14-15 and 16-18.

MSDP predicted aggression in childhood and adolescence. A meta-analysis across the four samples found MSDP to explain 0.4% of the variation. All perinatal factors combined, excluding MSDP, explained 1.2% of the variance in aggression across all ages and samples. The effects were consistent in males and females. In order to partly account for the potential confound of exposure to second-hand smoking during pregnancy and of a shared genetic predisposition for smoking and aggression, we tested whether paternal smoking and aggressive parenting strategies could account for the association between MSDP and offspring's aggression. We found that paternal smoking and aggressive parenting strategies did not account for the MSDP-aggression association, which is consistent with the hypothesis of a small causal link between MSDP and aggression.

Thus, we found that the link between MSDP and aggression in offspring was remarkably consistent across samples, though the effect size of the association was small. Similarly, a small effect was observed for the association between all other perinatal factors combined and aggressive behavior. This suggests that perinatal factors have a modest impact in shaping aggressive behavior later in development, and points to the importance of exploring the role of later experiences. This is part of ACTION's future research program.

Margherita Malanchini is a post-doctoral fellow at King's College London & University of Texas at Austin.
margherita.1.malanchini@kcl.ac.uk

Margherita Malanchini

Childhood aggression and adverse outcomes in emerging adulthood

Martin Cederlöf, Karolinska Institutet, Stockholm

Childhood aggression predicts several adverse outcomes later in life, particularly externalizing problems, but to some extent also internalizing problems. To date, most studies have been based on small number of children and it is unclear whether the associations between childhood aggression and subsequent internalizing problems remain after adjusting for externalizing problems. Therefore, we looked at information from the Child and Adolescent Twin Study in Sweden (CATSS), which is a longitudinal population-based twin study. We looked at whether there is an association and we examined the genetic and environmental contributions to the associations. In CATSS, we examined the association between childhood aggression (based on eight parent-reported items for 18,649 children) with adverse outcomes in emerging adulthood identified in Swedish national registers, including rates of clinically diagnosed mental disorders, prescription of anti-depressant/sedative medications, suicide attempts, alcohol/substance use disorders, criminal convictions, failure to reach eligibility for high school, and social welfare support.

We extracted a childhood aggression factor used as the exposure. As outcomes we defined a general factor as well as two factors reflecting internalizing and externalizing problems, We then examined if childhood aggression predicted internalizing problems after taking the overlap with externalizing problems into account. Finally, we examined the genetic and environmental contributions to these associations using twin modeling.

Childhood aggression predicted all outcomes in emerging adulthood. Furthermore, the childhood aggression factor was positively associated not only with the general factor and the independent externalizing factor, but also the independent internalizing factor. That is, the association between the childhood aggression factor and the internalizing factor remained after adjusting for its overlap with the externalizing factor.

The twin analyses showed that genetics contributed to the association between childhood aggression and all three outcome factors, whereas the shared environment seemed to be more important for the association between childhood aggression and the externalizing problems. The non-shared environment contributed significantly but marginally to all associations.

Childhood aggression is an important indicator of a host of adversities in emerging adulthood. Prevention and intervention of aggression at an early age may pay large dividends above and beyond aggressive behavior as it may also reduce anxiety, depression and several functional outcomes. Also, the twin analyses suggested that different outcomes might require different treatments.

Martin Cederlöf is a Ph.D and a project coordinator at Karolinska Institutet.
martin.cederlof@ki.se

Martin Cederlöf

Identifying genetic variants related to childhood and adolescent aggression and symptoms of ADHD

Michel Nivard, Vrije Universiteit, Amsterdam

Within the ACTION consortium several cohorts have followed children throughout their development, starting at very early ages (e.g. 1.5 to 3 years). Regularly parents, teachers or children are invited to fill in questionnaires which reflect upon the child's behavior. Among these are questionnaires developed to measure aggression and aggressive behavior and questionnaires designed to measure symptoms of ADHD. Previous work in the ACTON consortium, has shown both aggression and symptoms of ADHD to be heritable, which means that individual differences in aggression are partly attributable to genetic differences between children. What has as of yet eluded scientist is which genes contribute to aggression.

The ACTION cohorts have over the years genotyped a subset of the children in their studies, measuring stretches of DNA in the human genome that differ between people. Using the aggression data and the genotype data each cohort will associate genetic variants with aggressive behavior, the results are uploaded to a central server and then meta-analyzed across the cohorts. This means that we test whether the association between a genetic variant and aggression is present in all or most of the cohorts before we decide the finding is robust and can be used to better understand the causes of aggression.

Our first findings suggest that aggression in childhood genetically correlates to psychopathology and adverse economic outcomes in adulthood. Aggression as rated by mothers correlates moderately to self-ratings and teacher-ratings of aggression. We aim to follow up any findings with biological annotation of genes identified and to study the evolutionary origins of aggression by taking our genetic findings and data obtained from ancient genomes obtained from mummies or other old human remains. The data we generate will enable a perspective on aggression and its comorbidities and evolutionary effects on childhood aggression.

Michel Nivard is a post-doctoral fellow at the VU Amsterdam, specialized in statistical genetics and in genetics of psychopathology and health.
m.g.nivard@vu.nl

Michel Nivard

An interactive tool shows comorbidities of child aggression with other childhood psychopathologies

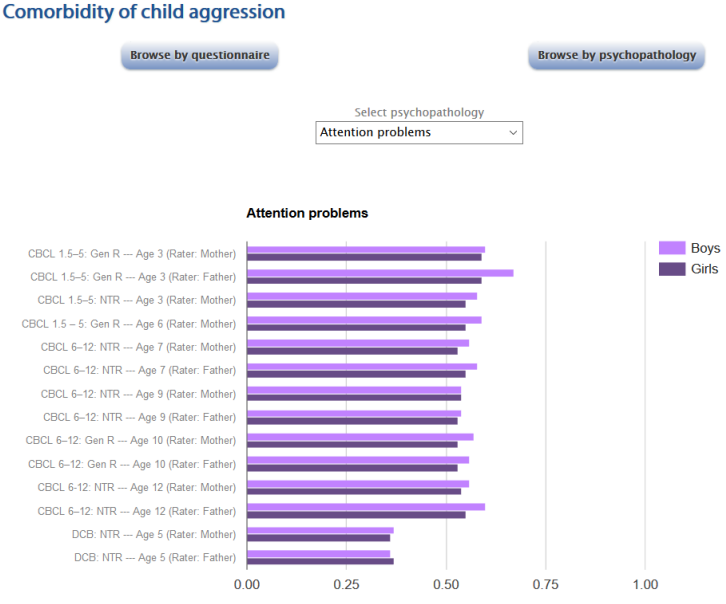
Matteo Mauri, University of Cagliari and Anne Hendriks, Vrije Universiteit Amsterdam

In this article we shortly describe a joint consortium's project developed under the coordination of prof. Bartels, Boomsma and Fanos.

The ACTION consortium maintains an active website, available at http://www.action-euproject.eu.

At this website, the consortium has an interactive tool where it is possible to graphically and numerically find out how child aggression coexist with other childhood psychopathologies: the tool is available at http://www.action-euproject.eu/ComorbidityChildAggression.

The results summarized in the tool are based on comorbidity analyses carried out in the ACTION consortium and will be published in the Journal of European Child and Adolescent Psychiatry (ECAP). The interactive tool can be browsed by questionnaires (i.e., A-TAC, CBCL, DCB, SDQ, MPNI) or by psychopathology (e.g., ADHD, Autism, ODD, OCD, Attention problems, Anxiety, Depression, Emotional reactivity, Sleep problems, Social problems, Rule breaking, Thought problems).



A screenshot of the "Comorbodity of child aggression" tool

This interactive tool renders it possible to view descriptive statistics in a graphically appealing fashion suitable for the scientific as well as the non-scientific community.

Since its kick-off in 2014, the ACTION project's results and outcomes are displayed to a broad public of researchers and parents on its official website. In addition, the website offers news on events, publications and presentations that stems from the ACTION consortium and is continuously updated.

Even before publication of the paper, the comorbidity tool was already visited more than 1500 times.

Matteo Mauri is a web manager in love with science. Copywriter and graphic designer, he is a research collaborator at the University of Cagliari. Since 2012 he is involved in the scientific dissemination of several European R&D projects in the areas of computer security, biometrics, video surveillance, machine learning, neonatology, pediatric disorders, childhood and adolescence psychopathology.

matteo.mauri@diee.unica.it

Matteo Mauri

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.

a.m.hendriks@vu.nl

Anne Hendriks

ACTION Publications of the year 2017

Join our publications on
http://www.action-euproject.eu/biblio

- K. (Koen) Bolhuis, Lubke, G., van der Ende, J., Bartels, M., van Beijsterveldt, T., Lichtenstein, P., Larsson, H., Jaddoe, V., Kushner, S. A. (Steven A., Verhulst, F., Boomsma, D. I., and Tiemeier, H., **"Disentangling Heterogeneity of Childhood Disruptive Behavior Problems Into Dimensions and Subgroups"**, *American Academy of Child and Adolescent Psychiatry. Journal*, vol. 56, pp. 678–686, 2017.
  DOI, Google Scholar, BibTex

- G. J. Lewis, Asbury, K., and Plomin, R., **"Externalizing problems in childhood and adolescence predict subsequent educational achievement but for different genetic and environmental reasons"**, *Journal of Child Psychology and Psychiatry*, vol. 58, pp. 292–304, 2017.
  DOI, Google Scholar, BibTex

- D. Zabaneh, Krapohl, E., Simpson, M. A., Miller, M. B., Iacono, W. G., McGue, M., Putallaz, M., Lubinski, D., Plomin, R., and Breen, G., **"Fine mapping genetic associations between the HLA region and extremely high intelligence"**, *Scientific Reports*, vol. 7, p. 41182, 2017.
  Google Scholar, BibTex

- L. W. Wesseldijk, Bartels, M., Vink, J. M., van Beijsterveldt, C. E. M., Ligthart, L., Boomsma, D. I., and Middeldorp, C. M., **"Genetic and environmental influences on conduct and antisocial personality problems in childhood, adolescence, and adulthood"**, *European Child {&} Adolescent Psychiatry*, 2017.
  DOI, Google Scholar, BibTex

- S. Selzam, Dale, P. S., Wagner, R. K., DeFries, J. C., Cederlöf, M., O'Reilly, P. F., Krapohl, E., and Plomin, R., **"Genome-Wide Polygenic Scores Predict Reading Performance Throughout the School Years"**, *Scientific Studies of Reading*, vol. 21, no. 4, pp. 334 - 349, 2017.
  Google Scholar, BibTex

- O. Fedko, Wesseldijk, L. W., Nivard, M. G., Hottenga, J. - J., van Beijsterveldt, C. E. M., Middeldorp, C. M., Bartels, M., and Boomsma, D. I., **"Heritability of Behavioral Problems in 7-Year Olds Based on Shared and Unique Aspects of Parental Views"**, *Behavior Genetics*, vol. 47, pp. 152–163, 2017.
  DOI, Google Scholar, BibTex

- Z. Ayorech, von Stumm, S., Haworth, C. M. A., Davis, O. S. P., and Plomin, R., **"Personalized Media: A Genetically Informative Investigation of Individual Differences in Online Media Use"**, *PLOS ONE*, vol. 12, pp. 1-10, 2017.
  DOI, Google Scholar, BibTex

- S. Selzam, Krapohl, E., von Stumm, S., O'Reilly, P. F., Rimfeld, K., Kovas, Y., Dale, P. S., Lee, J. J., and Plomin, R., **"Predicting educational achievement from DNA"**, *Mol Psychiatry*, vol. 22, no. 2, pp. 267 - 272, 2017.
  Google Scholar, BibTex

- M. Mauri, Hendriks, A., Fanos, V., Boomsma, D. I., and Bartels, M., **"Selected Abstracts of the 13th International Workshop on Neonatology. ABS 72, An interactive tool shows comorbidities of child aggression with other childhood psychopathologies. Utilities and statistics of the website www.action-euproject.eu"**, *Journal of Pediatric and Neonatal Individualized Medicine (JPNIM)*, vol. 6, no. 2, 2017.
  DOI, Google Scholar, BibTex

- R. Pintus, Dessì, A., Noto, A., and Fanos, V., **"Selected Lectures of the 13th International Workshop on Neonatology. LECT 71, Aggressiveness from fetus to adult: the twins case"**, *Journal of Pediatric and Neonatal Individualized Medicine (JPNIM)*, vol. 6, no. 2, pp. 97-98, 2017.
  DOI, Google Scholar, BibTex

- M. Manchia and Fanos, V., **"Selected Lectures of the 13th International Workshop on Neonatology. LECT 70, Integrating microbiomics and metabolomics data in behavioral complex traits: a role in aggression?"**, *Journal of Pediatric and Neonatal Individualized Medicine (JPNIM)*, vol. 6, no. 2, p. 96, 2017.
  DOI, Google Scholar, BibTex

- F. A. Hagenbeek, van Dongen, J., Kluft, C., and Ligthart, L., **"Selected Lectures of the 13th International Workshop on Neonatology. LECT 39, Self-reported aggressive behavior in humans and biomarkers: a focus on lipids and methylation"**, *Journal of Pediatric and Neonatal Individualized Medicine (JPNIM)*, vol. 6, no. 2, pp. 52-55, 2017.
  DOI, Google Scholar, BibTex

- J. M. Luningham, McArtor, D. B., Bartels, M., Boomsma, D. I., and Lubke, G., **"Sum Scores in Twin Growth Curve Models: Practicality Versus Bias"**, *Behavior Genetics*, vol. 47, pp. 516–536, 2017.
  PubMed, DOI, Google Scholar, BibTex

- M. Manchia and Fanos, V., **"Targeting aggression in severe mental illness: the predictive role of genetic, epigenetic, and metabolomic markers"**, *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, vol. 77, pp. 32–41, 2017.
  PubMed, DOI, Google Scholar, BibTex

- E. Smith-Woolley, Rimfeld, K., and Plomin, R., **"Weak associations between pubertal development and psychiatric and behavioral problems"**, *Translational Psychiatry*, vol. 7, no. 4, p. e1098 -, 2017.
  Google Scholar, BibTex

Contributors