



final meeting:

Childhood aggression and its comorbidities: dissemination meeting





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Key note 1: Lea Pulkkinen, Cascading effects of aggression in a longitudinal perspective Key note 2: Nick Martin, Pathways to the future of genetics discoveries in aggression.

Sessions

1. Heritability & Genes & Epigenetics. Chair Bartels

- 1. Hill Ip: Genome-Wide Meta-Analysis of Aggressive Behavior across Rater, Instrument and Age
- 2. Mandy Meijer: The interaction between genome and environment in aggressive behavior in a mixed population of health and disease
- 3. Veronika Odintsova: Genetics of Aggression Review// Systematic Review on GWAS findings on Aggression
- 4. Yayouk Willems: Environmental and Genetic contributions to low self-control
- 5. Lucia Colodro Conde: A twin study of oppositional defiant disorder behaviors using data from Australia and
 The Netherlands
- 6. Jenny van Dongen: Epigenome-wide association study meta-analysis of aggressive behavior
- Alex Neumann: Associations between DNA methylation and ADHD symptoms from birth to school age: A
 meta-analysis study from the PACE consortium
- 8. Rosa Mulder: Epigenomics of bullying: Changes in DNA methylation linked to peer victimization

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- 2. Sarah Medland: Does genetic risk of insomnia influence aggression?
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- 4. Margaritha Malanchini: Aggressive behavior in childhood and adolescence: the role of smoking during pregnancy, evidence from four twin cohorts in the EU-ACTION consortium
- Kaili Rimfield: School environment as related to developmental psychopathology (including aggression) in adolescence and early adulthood
- 6. Matteo Mauri: Sharing research: communication can help
- 7. Peter Roetman: Aggression in clinical practice
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- 1. Thomas Hankemeier or Amy Harms: Metabolomics in urine
- 2. René Pool: Heritabilities of normalized metabolic traits measured in urine
- 3. Fiona Hagenbeek: Urinary biomarkers and metabolites of childhood aggression
- 4. Roberta Pintus: Lipids and aggression: what is going on?
- 5. Pascal Aggensteiner: Amygdala activity in relation to Aggression-related traits
- 6. Dennis van't Ent: Examining genes-brain-behaviour relationships for aggression

4. Subtypes & Aggression. Chair prof. Jaakko Kaprio

- Andrea Allegrini: Examining genetic and environmental contributions to aggression subtypes in young adulthood
- Rosa Cheesman: Genetic analyses support a general dimension of psychopathology (including aggression) in childhood
- 3. Alyce Whipp: Teacher-rated aggression and co-occurring behaviors: a multi-site population-based investigation
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- 5. Antonio Noto: Tryptophan and Kynurenine metabolites may be related to aggressive behaviour in autism spectrum disorder





ABSTRACTS

Aggensteiner, Pascal: Amygdala activity in relation to Aggression-related traits

Background: Brain imaging studies have shown altered amygdala activity during emotion processing in children and adolescents with Oppositional Defiant Disorder (ODD) and Conduct Disorder (CD) compared to typically developing children (TD). Here we aimed to assess whether aggression-related traits (reactive and proactive aggression) and Callous-unemotional (CU) traits predicted variation in amygdala activity and skin conductance (SC) response during emotion processing. Methods: We included 208 participants (n=129 cases with ODD/CD and n= 79 TD), aged 8-18 years, across nine sites in Europe, as part of the EU Aggressotype and MATRICS projects. All participants performed an emotional face-matching fMRI task. Differences between cases and TD in affective processing, as well as specificity of activation patterns for aggression and CU traits were assessed. Simultaneous SC recordings were acquired in a subsample (n=64).

Results: Cases when compared to TD, showed higher amygdala activity in response to negative faces versus shapes. Aggression-related traits did not significantly influence amygdala activity; while stratification based on CU traits was more sensitive and revealed decreased amygdala activity in the high CU group. SC responses were significantly lower in cases and had a negative relationship with CU traits and aggression-related subtypes.

Conclusions: Amygdala activity and SC responses to emotional faces differ between cases with ODD/CD and TD, whilst CU traits moderate both central (amygdala) and peripheral (SC) responses. Our findings increase insights which could be used for personalized diagnostics and treatment.

Allegrini, Andrea: Multi-trait polygenic prediction of broad aggression in adolescence reveals cognitive, personality, psychiatric, and health-related correlates across four population cohorts

Similar to all behavioral traits, aggression is a complex heritable trait and shares at least in part its genetic background with several other complex traits. However, little is known about genomic contributions to the prediction of aggression, and its shared genetic roots with other complex traits in adolescence.

We constructed polygenic scores (PGS) for 250 cognitive, personality, psychiatric, and health-related traits and tested associations with broadly defined aggression (age 12 - 18) in four prospective twin cohorts – England, Netherlands, Finland and Sweden – for a total of 11,364 individuals of European ancestry.

Using a machine-learning (ML) framework, we tested joint prediction of the PGS, in the four independent cohorts by training and testing repeatedly in a leave-one-out fashion, in order to maximise genomic prediction of aggression, as well as exploring associations with other traits.

SNP heritability of aggression in the overall sample was 4%, defining the ceiling for polygenic risk prediction. Variance predicted in the four cohorts ranged between 0.6% and 1.7% (mean = 1.1.%). Top PGS for importance were consistent across training samples, with ADHD, BMI and smoking-related traits (e.g. maternal smoking around birth) associated with increased aggression; and health-related (e.g. Self-rated health) and cognitive relevant traits (e.g. EduYears) associated with decreased aggression. Our ML models did not highlight interaction patterns between PGS, but showed concordance in terms of feature importance, i.e. traits on which the model relies for prediction.

Intriguingly, these preliminary results point to a shared genetic architecture between broad aggression and several psychiatric and health-related traits. Furthermore, they are a first step towards a practical application of polygenic scores in the prediction of aggressive behaviors. These can be included in predictive models that integrate polygenic and environmental risk scores, increasing the predictive power of such models, especially once we break through the low SNP heritability ceiling.

Co-authors: Malanchini, M., Rimfeld, K., ACTION, Pingault, J.B., Plomin, R.

Allegrini, Andrea: Examining genetic and environmental contributions to aggression subtypes in young adulthood

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Research has demonstrated that the heritability of aggression is high, with longitudinal genetic correlations largely underlying stability in aggressive behaviour across development (Porsch et al. 2016). Previous research put forward suggestive evidence indicating partly distinct genetic contributions to subtypes of aggression in adolescence (Lightart, Bartels, Hoekstra, Hudziak, & Boomsma, 2005), and that genetic and environmental contributions to these subtypes differ between boys and girls.

Here, for the first time, we systematically investigate genetic and environmental architectures of aggression subtypes, physical and verbal, in males and females in early adulthood (age 21). Furthermore, building on results of an ongoing ACTION project, we explore the extent to which polygenic scores from adult psychiatric (e.g. ADHD) and cognitive related traits (e.g. educational attainment) differentially relate to verbal and physical aggression in males and females. This research will elucidate the extent to which a common genetic liability generalize between distinct forms of aggressive behaviour, or whether distinct genetic and environmental architectures define aggression subtypes and differ by sex. These findings will inform future investigations into aggressive behaviors and increase understanding of how psychiatric and cognitive related traits differentially relate to aggression subtypes in young adulthood.

Co-authors: Spargo, T. P., Pingault, J-B, Plomin, R.

Cheesman, Rosa: Genetic analyses support a general dimension of psychopathology (including aggression) in childhood

Introduction. Diverse behaviour problems in childhood correlate phenotypically, suggesting a general dimension of psychopathology that has been called the 'p' factor. The genetic architecture of childhood psychopathology also suggests a genetic p. This study systematically investigates the extent that phenotypic and genetic p mirror each other, measures how much genetic p predicts phenotypic p, and estimates how this common dimension manifests across time, raters, and measures. Methods. The sample included 7,026 twin pairs participating in the Twins Early Development Study (TEDS). For diverse measures of behaviour problems rated by children, parents and teachers at ages 7, 9, 12 and 16, (depressive symptoms, emotional problems, peer problems, autistic symptoms, hyperactivity, antisocial, conduct and psychopathy symptoms) we conducted principal component analyses to assess the variance explained by the first unrotated principal component, an index of p. We ran common pathway twin models using measures of psychopathology at each age for each rater to estimate genetic and environmental influences on p. A Cholesky decomposition of the first phenotypic principal component across four ages was used to assess the stability of p across time. We also used a polygenic p score derived from psychiatric disorders to predict phenotypic p for each rater at each age. Finally, to explore the polygenic structure, we used genomic structural equation modelling to analyse genome-wide genetic correlations between childhood psychopathology measures in TEDS. Results. Behaviour problems were consistently correlated phenotypically and genetically across ages and raters. Principal component analysis of measures of behavioural problems for each rater and age combination indicated a general phenotypic factor that was closely mirrored and predicted by a polygenic general psychopathology factor. P was substantially heritable, and manifests pervasively and consistently across diverse measures, across raters, and across time. Conclusions. We suggest that p is the highest level of a hierarchical genetic architecture of childhood psychopathology. The p factor has far-reaching implications for genomic research and, eventually, for diagnosis and treatment of behaviour problems. Next, we will include new data on direct and relational aggression at age 21 in order to assess how those traits play into p.

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Colodro Conde, Lucia: A twin study of oppositional defiant disorder behaviors using data from Australia and The Netherlands

Background. Oppositional defiant disorder (ODD) is primarily viewed as a younger-child, less severe version of conduct disorder and it emerges mostly before 5 years old, where symptoms of aggression and defiance are present. In the present study we examine the sources of variance of ODD related

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behaviours by using data from two non-clinical twin cohorts that are part of the ACTION Consortium: QIMR Berghofer Medical Research Institute or QIMRB (Australia), and the Netherlands Twin Register or NTR (The Netherlands).

Methods. QIMRB collected mother's report on ODD for 1,281 twins (51.6% females, mean age 14.3, SD = 3.7) using the SWAN questionnaire (Strengths and Weaknesses of Attention-Deficit/Hyperactivity Disorder Symptoms and Normal Behavior Scale; Swanson et al., 2001). Lifetime incidence of self-reported disruptive behaviour disorders for 6 months was collected using an ODD DSM-based screening question in 2,210 twins (61% females, mean age = 27, SD = 7.2). The NTR used the ASEBA Oppositional Defiant Problems scale to collect father's (N = 11,676) and mother's report (N = 16,584) and self-report (N = 4,841). The mean age of the children was 12.2 y.o. (SD = 0.4) for both parent's reports, and 16.9 y.o. (SD = 0.5) for self-report. The percentage of females was 50.6%, 50.9%, and 58.0% for mother's report, father's, and self-report, respectively. We tested structural equation models to estimate the proportion of variance due to genetic and environmental factors. Models were corrected for age and sex in all cases

Results. The best fitting model included additive genetic factors explaining 76% of the variance in ODD as measured by the SWAN and 59% of the disruptive behaviour report, with the rest of the variance explained by unique environmental factors and measurement error. Additive genetic factors explained 43%, 50.8%, and 37.4% of the variance in oppositional defiant problems reported by father, mother, and self-report, respectively. Common environment explained 41.4%, and 34% in father's and mother's report, but did not account for variation in self-report. The rest of the variance was due to unique environmental factors and measurement error. Genetic and environmental variance components of father's and mother's report could be equated to be same (p = .13). The phenotypic correlation between the father's and mother's report was 0.68 (of which 50% were explained by genetic factors, 32.6% by common environmental factors and the rest by unique environmental factors). The phenotypic correlation of each of those with self-report at a later age was 0.26 (with 67% and 80% of this correlation due to genetic factors for the father's and mother's report, respectively, and the rest due to unique environmental factors).

Discussion. Using a variety of measures of ODD in different informants from two countries, we observed that ODD is moderately heritable. Common environmental effects were only observed in the parental reports from the NTR cohort. This might reflect genuine differences in the source of variation in ODD between these countries, or it might be a consequence of the difference measures employed. The equivalence in the decomposition of variance and correlations between father's and mother's report, implies a high degree of similarity in parental perception of ODD behaviours. Self-reported ODD behaviours 4 years later had a low correlation with the parental reports. The differences across age might reflect differential developmental trajectories, or they might reflect differences in the instruments.

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Hagenbeek, Fiona: Urinary biomarkers and metabolites of childhood aggression

Aggression is a heterogeneous phenotype, commonly defined as "hostile, injurious, or destructive behavior", and is highly prevalent in children with psychiatric disorders. To gain a better understanding of the etiology of childhood aggression, researchers and health professionals might benefit from efforts to identify potential predictive, or diagnostic, markers. A review of the biochemical biomarker literature indicated a possible role of inflammation markers, neurotransmitters, lipoproteins, and several classes of hormones in human aggressive behavior, but a shortcoming of much of the biomarker research in aggression has been the limited scope of biomarkers tested in any given study. To address this issue, a switch from single biomarker studies to metabolomics studies is warranted. Metabolomics aims to provide a holistic overview of the biochemical changes in disorders. Previously, a metabolomics study of aggression in adults reported that amino acid levels were associated to aggression in males with antisocial personality disorder.

The ACTION project has collected first-morning urine samples in 1360 twins from the Netherlands Twin Register (NTR), selected on the concordance of their mother-rated aggression status, and in 187 children referred to the Curium psychiatric children's hospital. All 1546 first-morning samples have been





analyzed by targeted-metabolomics platforms, designed to measure neurotransmitter pathways, and have been assessed for classic biomarkers, including Substance P and C-Peptide. Using mixed-model elastic net regression we aim to assess which biomarkers and metabolites best predict childhood aggression in the twin aggression data and then validate the results in the clinical cases as collected by Curium.

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Hendriks, Anne: A reaction to ACTION: What are the implications of five years of research on childhood aggression?

For the past five years, members from the ACTION (Aggression in Children: Unraveling gene-environment interplay to inform Treatment and interventION strategies) consortium conducted research to gain insights into the etiology of childhood aggression. These efforts yielded a large set of articles on a broad range of topics surrounding childhood aggression, including environmental predictors, diagnostics, genes, epigenetics, metabolomics, and much more. The aim of the present study is to summarize what this research has taught us about the prediction, diagnosis, and treatment of childhood aggression. To this end, we gathered all publications that acknowledged the ACTION consortium, which relate to prediction, diagnosis, and treatment of childhood aggression or other associated traits (e.g., attention-deficit/hyperactivity disorder). Included articles were either published or submitted. We systematically summarized the insights and findings of ACTION results. Next, we integrated the findings on the different topics surrounding childhood aggression to translate the implications of ACTION for future research and practice.

Ip, Hill: Genome-Wide Meta-Analysis of Aggressive Behavior across Rater, Instrument and Age

Aggressive behavior (AGG) in childhood and adolescence co-occurs with a wide range of externalizing and internalizing problems1. Individual differences in AGG can partially be explained by genetic differences between people2. Yet, attempts to link specific regions on the genome to AGG have thus far failed to return significant results3. Including repeated measures of AGG — whether that is by multiple raters, using various instruments, and/or over time — may be one approach to increase power for gene discovery and additionally provides insight into potentially specific molecular etiologies of AGG. Analyzing such data and interpreting the results from these analyses, however, require additional (statistical) considerations: combining repeated measures on the same subject might results in spurious associations as a result of correlated error, rather than a truly shared genetic signal across rater, instrument and age.

Here we perform a multivariate genome-wide association meta-analysis (GWAMA) on childhood AGG involving a large-scale international collaboration between 25 cohorts from Europe, USA, Australia and New-Zealand. When possible, cohorts were asked to stratify their sample by (1) who assessed the child, (2) which instrument was used to assess AGG and (3) the age of the child at assessment; and run a genome-wide association (GWA) analysis per stratum. The stratified analysis plan resulted in over 320,000 observations analyzed in 153 GWAs. To gain insight into potentially specific molecular etiologies, we meta-analyzed the GWAs (1) within rater, across age and instrument, (2) within rater-specific age-bins, across instrument, and (3) within instrument, across rater and age. Here, we focus on the interpretation of the data as provided by different raters.

Based on these analyses, genetic correlations between GWAMAs of maternal, paternal, teacher, and self-report of childhood AGG range between 0.39 and 0.78, and are largely in line with previous findings on rater-specific views based on twin studies4. The moderate to high genetic correlations between rater-specific GWAMAs indicate that raters largely assess the same latent genetic construct and that properly modelling the relation between raters will increase power to identify regions on the genome that are relevant for AGG. At the same time, the imperfect correlations show that exploring rater-specific views on AGG will provide a more complete overview of the genetic factors that underlie childhood AGG.

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Lagerberg, Tyra: Second-generation antipsychotics and risk of violent crime in adolescents and young adults

Objective: Prescriptions of second-generation antipsychotics (SGAs) in young people have increased markedly during the last two decades, with a large proportion prescribed to those who exhibit disruptive behaviors and aggression. This study aimed to investigate whether SGAs reduced the risk of violent crime in young people.

Methods: We followed a national cohort of individuals aged 15-24 years who have received at least one dispensed prescription of SGAs between 2006 and 2013 using data from Swedish national registers. Rates of violent reoffending during medicated periods were compared with rates during non-medicated periods using within-individual analyses.

Results: The cohort included 29,508 individuals (49.2% females) who received SGAs, and 6504 individuals who had been arrested for violent crimes during the follow-up. The within-individual analyses showed that SGAs were associated with a 16% lower rate of violent crime in young men (HR= 0.84; 95% CI, 0.78-0.91), while the association was not statistically significant in young women (HR=0.99; 95% CI: 0.86 to 1.15). When considering specific psychiatric diagnoses, SGAs were associated with the strongest reduction of violent crimes in young men diagnosed with schizophrenia spectrum disorders (HR= 0.74; 95% CI, 0.64-0.86).

Conclusions: Among young men who received SGAs, rates of violent reoffending were lower during periods when individuals received SGAs compared with periods when they did not.

Co-authors: Chang, Z., Fazel, S., Månsson, C., Mataix-Cols, D., Lichtenstein, P., Hellner, C.

Lubke, Gitta: Predicting Childhood Aggression: Mining Large Datasets Followed by Confirmatory Modeling

Background: The aim was to predict childhood aggression, by analyzing data from two large European cohorts (N = 62,227), with a novel methodological approach.

Data: Participants came from the Child and Adolescent Twins Study in Sweden and the Netherlands Twin Register. The outcome measure was physical overt aggression as assessed around age 9,





psychometrically harmonized across multiple European cohorts. The large set of predictor variables consisted of demographics, prenatal characteristics, physical development, family environment, parenting, parental education level, life events, and behavioral symptoms.

Method: To avoid capitalization of chance, data were partitioned in four parts for different analysis steps. These included 1) exploratory data analysis and tuning meta-parameters for data mining, 2) fitting increasingly complex data mining models to assess which predictors had which types of effects, 3) assessment of model performance and importance of the predictor variables, and 4) fitting a confirmatory prediction model of aggression that integrated results of the data mining analyses.

Results: The prediction model confirmed linear main effects of predictor variables and included interactions of predictors with sex and cohort. Associations between the main predictors (non-physical aggression, ADHD, conduct disorder, maternal smoking during pregnancy, parenting style, and life events) and childhood aggression were in line with previous research, yet weaker, likely because we considered more predictors simultaneously.

Conclusion: Fitting all predictors simultaneously provided clear insight in the importance of predictors relative to each other. Externalizing, non-aggressive, behaviors had the strongest effects, and may act as salient targets for early detection and prevention of childhood aggression.

Co-authors: Hendriks, A., Luningham, J., Hong, M., Jacobucci, R.

Malanchini, Margaritha: Aggressive behavior in childhood and adolescence: the role of smoking during pregnancy, evidence from four twin cohorts in the EU-ACTION consortium

Background. Maternal smoking during pregnancy (MSDP) has been linked to offspring's externalizing problems. It has been argued that socio-demographic factors (e.g. maternal age and education), co-occurring environmental risk factors, or pleiotropic genetic effects may account for the association between MSDP and later outcomes. This study provides a comprehensive investigation of the association between MSDP and a single harmonized component of externalizing: aggressive behaviour, measured throughout childhood and adolescence.

Methods: Data came from four prospective twin cohorts - Twins Early Development Study, Netherlands Twin Register, Childhood and Adolescent Twin Study of Sweden, and FinnTwin12 study - who collaborate in the EU-ACTION consortium. Data from 30 708 unrelated individuals were analysed. Based on item level data, a harmonized measure of aggression was created at ages 9-10; 12; 14-15 and 16-18. Results. MSDP predicted aggression in childhood and adolescence. A meta-analysis across the four samples found the independent effect of MSDP to be 0.4% (r = 0.066), this remained consistent when analyses were performed separately by sex. All other perinatal factors combined explained 1.1% of the variance in aggression across all ages and samples (r = 0.112). Paternal smoking and aggressive parenting strategies did not account for the MSDP-aggression association, consistent with the hypothesis of a small direct link between MSDP and aggression.

Conclusions. Perinatal factors, including MSDP, account for a small portion of the variance in aggression in childhood and adolescence. Later experiences may play a greater role in shaping adolescents' aggressive behaviour.

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Martin, Nick: Pathways to the future of genetics discoveries in aggression

Behaviour genetics methods were first applied to aggressive behaviours in the 1960s. The study of individual differences on aggression was resumed in the 1980s, in the context of heated discussions on the role of genetics and socialization processes of human behaviour. Since then, twin studies and genome-wide association analyses have aimed to not only quantify the relative importance of genetics, environment, and their relationship, but to identify biomarkers of aggressive behaviours that can aid personalized interventions.

The ACTION consortium has used new approaches to create a large body of scientific evidence (including but not limited to over 90 published papers) on the aetiology, comorbidity, developmental courses, and

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correlates of aggression with a special focus on childhood. The gain in knowledge has provided information that needs to be integrated in the current understanding and interventions on aggression. The work over the last years has also opened more questions that can be answered with polygenic approaches. This talk will discuss the challenges and forthcoming opportunities for twin, GWAS, genetic risk prediction, and biomarker studies of aggression.

Mauri, Matteo: Sharing research: communication can help

Research and Computer Science (or Informatics) have a lot in common. It is quite clear that Informatics can grow only if supported by new technological research findings, and that Research can grow quickly if supported by customized tools that allow to simulate models, extract and process data. But these are just the most obvious things. When we say that Research and Informatics have a lot in common, we mean that they share also one of their main missions: the goal of sharing, in fact.

Research is not fruitful without the exchange of information through scientific works, workshops, conferences, international meetings among researchers, peer-reviewed processes, travels and other comparison opportunities.

Informatics would be just an algorithmic, enigmatic and self-referential game if stripped of its deeper goal: the capability of instantly breaking with new Information and new findings, making them available from the coldest part of the world to the warmest; Informatics is the reign of sharing. The word "Informatics" is inherently related to the term "information" and, consequently, "communication". As research can do, also communication can change everything in a second. Both can save millions of lives in a second: e.g. turning an epidemic into a controlled disease, in the first case; stopping a war, in the second case. What would happen if research and communication were misaligned? It is not a so rare situation. It happened in the past when the research mostly ignored, for more than 100 years, some intuitions to contain the puerperal fever, although those intuitions were in some cases also properly communicated [1][2]. It is happening today, when communication is not properly driving the science in the knowledge gap on vaccines [3]. Research and communication: both can save millions of lives in a second, we said before. Both can cause the contrary, especially if not aligned.

Without doubts, dissemination and communication of scientific results are now acknowledged as crucial parts of the research process [4]. The European Union (EU), through Research & Innovation Framework Programmes, has a clear position about that: the dissemination of scientific research projects is in fact nowadays mandatory, and governed by contracts between the European Union and the recipients of funding. In addition, EU recommends a diversified science divulgation, that stimulates creativeness and requires a digital presence [5]. That's why we started this article comparing Research and Computer Science.

In this context, the University of Cagliari, Department of Surgical Science, has a significant role; it is in fact currently leading, in collaboration with VU University Amsterdam, the dissemination of an important EU funded project, trying to share the research findings in an innovative and easy-readable way, hoping to give a consistent contribution in the understanding of the causes and comorbidities of some important childhood mental health problems.

The ACTION project (Aggression in Children: unravelling gene-environment interplay to inform Treatment and InterventiON strategies, FP7/2007-2013, grant agreement no. 602768), works to improve the understanding of the causes of individual differences in aggression among children in order to better inform the development of prevention and treatment strategies. One of the most relevant activities done within this project, exploiting at best the possibilities of Informatics, is the release of an interactive tool (picture 1) that shows the comorbidities of child aggression with other 22 childhood psychopathologies [6][7]. Recently the ACTION consortium has also released a video in computer graphics in order to reach a broad audience of researchers and stakeholders, using at the same time an easy, and iconic, language [8]. Finally, during the last month of activities the consortium will release another interactive tool, focused on the aggression in children starting by teacher ratings.

Co-authors: Paire, B., Fanos, V.

with aggressive behaviours.





Insomnia is linked to emotional and behavioural difficulties particularly in young people. Insufficient sleep, overtiredness and insomnia have been found to predict externalising behaviours including aggression. Whilst associations between sleep quality and emotional and behavioural difficulties have been found in young people, the extent to which genetic liability for insomnia can predict aggression is unknown.

This is a collaborative project involving ~14,000 participants across 5 cohorts from the ACTION Consortium. Using data collected from QIMR participants we assessed insomnia and aggression from the Buss-Perry Aggression Scale, we replicated our findings with data from four additional cohorts from Finland, The Netherlands, and the UK. We used polygenic risk scores from the Jansen et al. (2018) GWAS of insomnia to test whether genetic risk for insomnia predicted aggression or any of its components. Data were analysed using linear mixed models including the effects of age, sex, their interaction, genetic principal components, and a genetic relationship matrix to account for relatedness. Insomnia polygenic risk scores predicted aggression traits in the QIMR sample (total aggression score, physical aggression, anger, hostility; but not verbal aggression). The results were replicated at a nominal level in the cohorts from Finland and the UK but did not in the Dutch sample. These results suggest that genetic vulnerability to insomnia may be a useful predictor of aggression. Prevention and early treatment interventions remain important to treat the behavioural manifestations

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arising from insomnia, such as emotion dysregulation and distress intolerance, which are associated

Meijer, Mandy: The interaction between genome and environment in aggressive behavior in a mixed population of health and disease

Aggressive behavior is often observed in neurodevelopmental disorders, such as attentiondeficit/hyperactivity disorder (ADHD). However, aggression is thought to be present as a continuous trait in the general population, with the extreme end of the spectrum marked as pathological. Besides genetics, environmental adversity might play an important role in the expression of aggressive behavior. One way to study the interaction between genetics and the environment is by examining DNA methylation profiles. We hypothesize that DNA methylation profiles correlated with aggressive behavior might explain part of the environmental effects. Therefore, 72 individuals (persistent ADHD n = 35, remittent ADHD n = 18, healthy controls n = 19) were selected from the NeuroIMAGE study, a Dutch longitudinal cohort consisting of adolescents and young adults. Whole blood was drawn, DNA was isolated, and an epigenome-wide association study (EWAS) was performed with the Infinium® MethylationEPIC BeadChip (Illumina). After quality control, methylation levels were correlated with aggressive behavior measured as a score of callous traits obtained from the inventory of Callous-Unemotional Traits. Age, gender, and smoking scores were used as covariates. Ten extra covariates obtained from a surrogate variable analysis were used to take blood cell type composition and genetic background into account. No genome-wide significant CpG sites were associated with aggression measured as callousness. However, six sites reached the suggestive significance threshold (p-value < 5*10-5). The most significant site negatively correlated with callousness was located in the 3'UTR of SEC14L1 (p-value = 2.17*10-6), suggesting overexpression of the gene. SEC14L1 is thought to inhibit acetylcholine release, whereas the stimulation of acetylcholine receptors attenuates aggressive behavior in both mice and humans. Moreover, a CpG site just upstream of the transcription start site of CSNK1E was positively correlated with callousness (p-value = 2.35*10-6). CSNK1E is one of the central clock genes, regulating the biological clock. Accumulating evidence suggests that aggressive behavior has a highly circadian (throughout the day) and infradian (throughout the year) rhythm. Moreover, this gene has been linked to psychiatric disorders with a high co-morbidity of aggression before. All suggestive significant CpG sites were not known to be mQTLs during adolescence and therefore might reflect the interaction of the environment on the genome rather than the effect of genomic context. All in all, although replication will be essential, these methylation sites are of interest to further study the mechanisms of aggressive behavior often observed in neurodevelopmental disorders.





Co-authors: Klein, M., Hannon, E., Mill, J., Franke, B.

Mulder, Rosa: Epigenomics of bullying: Changes in DNA methylation linked to peer victimization

Peer victimization amongst children is ubiquitous and associated with pervasive mental health problems as well as suicide risk. However, very little is known about the biological pathways that change after exposure to peer victimization. In the current study, we aimed to identify changes in DNA methylation associated with exposure to peer victimization in two population-based cohorts, Generation R Study and ALSPAC.

Epigenome wide DNA methylation profiles were generated with the Infinium HumanMethylation450K BeadChip array from peripheral blood drawn at 6 and 10 years of age in Generation R and at 7 and 17 years of age in ALSPAC, for a total of 1352 children. Peer victimization was measured at 8 years in Generation R and at 9 years in ALSPAC.

We found that methylation levels of cg17312179, located in the 5' untranslated region of RAB14 decreased for victims whereas they increased for non-victims (b=-2.67e-03, SE=4.97e-04, p=7.17e-08). Enriched Gene Ontology pathways for the differentially methylated sites (P<0.001, n=644 CpGs) included for cardiac functioning and neurodevelopmental processes. The top 1000 CpG sites tended to have low levels of methylation and decreasing levels of DNA methylation in victims, with increasing levels in non-victims. This is the first study that reveals changes in methylation associated with peer victimization at the epigenome-wide significance level. Results from our epigenome-wide association study suggest that exposure to peer victimization might be associated with changes in Golgi apparatus functioning.

Neumann, Alex: Associations between DNA methylation and ADHD symptoms from birth to school age: A meta-analysis study from the PACE consortium

Attention-deficit and hyperactivity disorder (ADHD) is a common childhood disorder with a substantial genetic component. However, to what extent epigenetic mechanisms play a role in the etiology of the disorder is much less well-known. Previous studies have identified several DNA methylation sites associated with ADHD. Yet, large epigenome-wide analyses (EWAS) featuring multiple independent cohorts are lacking. We performed an EWAS within the Pregnancy And Childhood Epigenetics (PACE) Consortium to identify DNA methylation sites associated with ADHD symptoms, the first prospective meta-analytic EWAS in child psychiatry. As DNA methylation changes over time, we performed two EWAS at two methylation assessment periods: birth and school-age. We examined associations of DNA methylation in cord blood with repeatedly assessed ADHD symptoms (age range 4-15 years) in 2477 children from five cohorts and DNA methylation at school-age (age 7-9 years) with concurrent ADHD symptoms (age 7-11 years) in 2374 children from ten cohorts. The regression estimates correlated with 0.30 between both time points, after exclusion of dependent samples, suggesting that the association between DNA methylation and ADHD is to some extent age independent. At birth, we identified 9 probes that were associated with later ADHD symptoms. Peripheral DNA methylation in only one of these probes correlated consistently with brain methylation. This probe (cg01271805) lies in the promotor region of ERC2, which regulates neurotransmitter release. Another genome-wide significant probe (cg25520701) lies within the gene CREB5, which is associated with neurite outgrowth and its genetic variants were previously related to ADHD. In contrast, no probes reached genome-wide significance when ADHD was associated with school-age DNA methylation, indicating that the methylation profiles of ADHD have higher explanatory power at birth. In conclusion, the results suggest that DNA methylation at birth may hold promise as a prognostic indicator for ADHD risk, but future studies are needed to confirm the utility as biomarker and presence of causal pathways.

Noto, Antonio: Tryptophan and Kynurenine metabolites may be related to aggressive behaviour in autism spectrum disorder

New insights suggest that aggressive behaviour of autistic patients might be related to the presence of certain bacteria or microbial imbalance, the so called dysbiosis. The presence of this latter can be identified by means of metabolomics. Metabolomics allows the identification of the whole sets of circulating small molecules produced by eukaryotic and prokaryotic cells (1). Metabolites can play a

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causative role in psychiatric disorders by passing into the brain through the blood-brain barrier causing either a modulation of behaviour and peripheral inflammation (2). In particular, the presence of tryptophan and its by product kynurenine have potent neuropsychiatric effects (3). The purpose of our study is to investigate the presence of these two metabolites in a cohort of autistic patients which are eventually compared to healthy controls' subjects. Materials and Methods: 99 subjects (57 toddlers and 42 adolescents) were enrolled in the study: 52 autistic spectrum disorder (ASD) patients, and 47 healthy controls. Parents of both ASD children and healthy controls gave written informed consent before the inclusion in the study. ASD patients were recruited at the Children Psychiatry Unit of the University Hospital of Rome Tor Vergata (Italy) and the Pediatric Division of University of Bari (Italy). Exclusion criteria for ASD included genetic syndromes, neurological disorders, ongoing acute diseases and known inborn errors of metabolism. Results: Urine samples collected from both ASD and healthy controls cohorts were analysed and compared through GC-MS and multivariate statistical analysis. 99 samples (31 ASD cases and 26 controls and 21 ASD cases and 21 controls) underwent OPLS-DA analysis. Among the detected metabolites belonging to ASD patients, tryptophan, and kynurenine were identified. Conclusion: Recent advances highlight the potential mechanisms, involving bacterially-derived metabolites through which brain behaviour and immunoregulation are influenced.

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Odintsova, Veronika: Genetics of Aggression Review// Systematic Review on GWAS findings on Aggression

Aggressive behavior is a heritable trait with evolutionary origins. Aggressive behavior can be maladaptive, and cause harm, but may also be adaptive to for survival and fitness. Epidemiological and molecular genetic studies seek to advance an understanding of the genetic architecture of aggression. At this moment, human genome-wide association studies (GWAS) have not yet achieved genome-wide significant results, but several projects are ongoing. To generate a comprehensive view of the complex genetics of human aggression, we undertook a systematic literature search with use of a new software tool based on machine learning. Family, twin, GWAS and candidate genes studies with large samples were included in analysis. The selected studies were analysed for approach to aggression measurement, psychiatric comorbidity, genotyping methods and genes effect. Further studies should improve the association search by using a systematic approach and standardized measurements to identify genes that underlie aggressive behavior.

Co-authors: Pool, R., Roetman, R.J., Van Dongen, J., Vermeiren, R., Boomsma, D.I.

Pintus, Roberta: Lipids and aggression: what is going on?

Aggression and violent behavior are a major global health problem according to WHO [1]. They can affect people of every age and every social class and violence can be exerted towards one' self or others. Today, despite all the efforts of scientific community, the ethiology of aggression is still unclear but several neurobiological hypotheses are being made in order to unravel the mystery. In particular, there is a growing interest on neuronal networking and synapsis function and the biological factors that influence the proper functioning of the brain.

One of them are lipids and cholesterol. The latest is present in the brain and it represents up to the 25% of total presence in the whole body. It is directly involved in synaptic function, because it is a component of the so-called lipid rafts, together with sfingomyelins and gangliosides. If these components are missing there would be no formation of lipid raft and thus a delay or an improper function of the circuit involved in behavior in humans.

Furthermore lipids are involved in the formation of synaptic vesicles, myelin and they are neurotransmitter as well. Thus, if the amount of lipids available in the brain is not enough, the signaling among neurons may be altered.

Authors reviewed the recent literature concerning the role of lipids in aggressive behavior in humans and the results pointed out that low lipid levels in the blood are present in people with aggressive





behavior. Furthermore, in adults, there are increasing evidences that cholesterol-lowering drugs, such as statins may lead to aggressive behavior.

Moreover there are studies that state that the administration of omega 3 and fish oil in children may improve their level of aggression.

Nevertheless further studies are needed to confirm these hypotheses. Maybe the answer to aggressive behavior in humans may be given by the new "omics" technologies such as metabolomics that would help to understand the mistery of aggression, given the fact that it could detect all the metabolites present in biological tissues and fluids. In the future, maybe it would be possible to have biomarkers of aggression and treat these people in a personalized way, improving their quality of life and that of their families.

Co-authors: Dessì, A., Mecarini, F., Bardanzellu, F., Fanos, V.

Pool, René: Heritabilities of normalized metabolic traits measured in urine

In the context of the ACTION project, metabolic traits and more classical biomarkers have been measured in urine samples of 1360 young twins (average age 9 years) participating in the Netherlands Twin Register (NTR) and 186 children recruited via childhood psychiatric clinics (Curium). The metabolic traits have been measured by the Leiden Academic Centre for Drug Research (LACDR) on two metabolomics platforms, one reporting on 66 amine levels and one reporting on 22 organic acid levels. Metabolic profiles can be viewed as readouts of the health state of individuals as metabolites directly participate in biological (or pathological) pathways. Hence, these profiles could provide clues for biomarkers for psychiatric disorders such as aggression. Standardized phenotyping was performed in the NTR and the Curium groups.

Molecular concentrations in urine are highly dependent on hydration level and can differ for numerous reasons between children. Therefore, before utilizing metabolic profiles in (statistical) analyses, such profiles need to be normalized on a sample (individual) level. We will discuss normalization strategies that can be applied on the metabolomics data based on these data themselves or by using information on the classical biomarkers that were assessed by Leiden Good Biomarkers Sciences (GBS). We will explore and provide a strategy that fits our needs best. After QC and normalization we estimate twin correlations and heritability of the normalized metabolic traits, based on genetic structural equation modeling. Where possible, these values will be compared to corresponding heritability estimates we determined in blood samples of adults.

Co-authors: Hagenbeek, F.A., Hankemeier, T., Kluft, C., Fanos, V., Harms, A.C., Roetman, P.J., Vermeiren, R.R.J.M., Boomsma, D.I., Bartels, M.

Pulkkinen, Lea: Cascading effects of aggression in a longitudinal perspective

Aggression is aroused by situational factors in interaction with biological dispositions. Vulnerability to aggression may cause a cascading effect that refers to the situation where problems or changes in one domain may bring about problems or changes in other related domains, in the other words, where difficulties are spreading. Cascading effects have been studied in the Jyväskylä Longitudinal Study of Personality and Social Development (JYLS) in which the development of a random sample of children (N = 369, 53 % males) has been followed from age 8 to age 50 (through ages 14, 20, 27, 36, and 42). The participation rate at each follow-up was around 85%. At the beginning, the focus of the study was on children's aggressive and nonaggressive coping with social problems. Peer nomination and teacher rating were used at ages 8 and 14. At later ages, personal interviews and several international inventories have been used for data collection. For the study of the continuity of coping styles and cascading effects, the follow-up studies have covered many spheres of life including personality, education and work, family, health and health behavior, and criminality. The results did not show continuity of childhood aggression into adulthood except in cases where aggression was intensive and consistent through adolescence. A cascading effect can be found in a process where aggression destroys peer and teacher relations and results in a pattern of school maladjustment which, in turn, is associated with long-term unemployment in adulthood both directly or indirectly, either via problem drinking or via low education and lack of occupational alternatives. High aggression (above 75th percentile) often occurs together with other conduct problems, and later with criminal offending. The





study also reveals environmental factors such as low child-centeredness of parents that increase individuals' vulnerability to aggression.

Rimfield, Kaili: School environment as related to developmental psychopathology (including aggression) in adolescence and early adulthood

The statistics of mental health problems in the UK portrays a dark picture: 1 in 10 children have diagnosable mental health disorders - approximately three children in every classroom. Childline, a free counselling service for children in the UK, reported that children's top concern is stress and anxiety related to school work and exam performance. These mental health problems may have a long shadow later in life for children. They also affect children's families and society as a whole, with the cost of mental health problems in the UK being estimated at £100 billion per year (see https://www.england.nhs.uk/wp-content/uploads/2016/02/Mental-Health-Taskforce-FYFV-final.pdf). In addition, anxiety and stress during childhood are associated with self-harm and suicide. However, links between school experiences and mental health problems remains a grossly under-investigated research

In this project, I will use both twin/family and DNA methods to examine the aetiology and causal directions of the associations between educational experiences and developmental psychopathology, including aggression.

Objective 1: Clarify the phenotypic associations between educational experiences and developmental psychopathology across adolescence and emerging adulthood

Objective 2: Use statistical genetic techniques to investigate the genetic aetiology and causal directions of the associations between educational experiences and developmental psychopathology across adolescence and emerging adulthood.

These results will have far-reaching implications for clinicians and educationalists, including an impetus to develop intervention programs that increase educational achievement while reducing mental health problems.

Co-author: Plomin, R.

Roetman, Peter: Aggression in clinical practice

Vast amounts of scientific evidence as well as clinical insights emphasise the heterogeneous nature of aggression, which can be subdivided into many different subtypes (e.g., proactive vs. reactive aggression, covert vs. overt). Furthermore, aggression co-occurs with a multitude of other conditions (e.g., psychopathic personality traits, internalizing problems), while environmental factors influence its expression and variability (e.g., parental history of mental disorder, low socio-economic status). Ultimately, functioning and longitudinal outcomes are related to this vast variety. To advice clinical practice, it is crucial to consider the actual purpose of the predictions (e.g., prevention) and the 'profile' of individual youths. The presentation will discuss findings from ACTION-initiated research, including research that has focussed on aggressive behaviour subtypes and its associated risk factors in both community and clinical settings. We will discuss to what extent constructs, like proactive and reactive aggression, psychiatric comorbidity, psychopathic traits, and history of parental mental disorders, are relevant for advancing clinical practice.

Co-authors: Nooteboom, L., Finkenauer, C., Siebelink, B., Lundström, S., Andershed, H., Lopez-Romero, L., Lichtenstein, P., Colins, O., Vermeiren, R., Boomsma, D.I.

Van Dongen, Jenny: Epigenome-wide association study meta-analysis of aggressive behavior

Epigenetic mechanisms, such as DNA methylation, regulate gene expression and mediate genetic and environmental influences on complex traits. Previous studies have reported emerging evidence for associations between aggressive behavior and DNA methylation levels at various loci in peripheral tissues (such as blood and saliva). As part of ACTION, two epigenetic projects have been performed: 1) an EWAS meta-analysis (EWAMA) of aggressive behavior and genome-wide DNA methylation in blood assessed with the Illumina 450k or EPIC array and 2) collection of novel genome-wide DNA methylation





data in buccal swabs from aggression-concordant and aggression-discordant monozygotic twins and clinical cases with the Illumina EPIC array.

The EWAMA includes 20 cohorts with data for 14438 peripheral blood samples (mean age at blood sampling ranging from 4 to 70) and 2195 cord blood samples. The mean age at phenotypic assessment ranges from 6 to 72 and multiple instruments were used to assess aggressive behavior or conduct problems, such as the Child Behavior Check List (CBCL), Strength and Difficulty Questionnaire (SDQ), Multidimensional Peer Nomination Inventory (MNPI), ASEBA adult self-report (ASR), DSM Conduct Disorder Symptom Scale, Multidimensional Personality Questionnaire (MPQ), Temperament and Character Inventory (TCI), and the NEO personality questionnaire.

Illumina EPIC array methylation data have been generated for 1608 individuals, including 1419 monozygotic twins and 189 children referred to the Curium psychiatric children's hospital. These data will be analysed to identify DNA methylation marks in buccal swabs that are associated with aggressive behavior.

Co-authors: Hagenbeek, F., Roetman, P., Vermeiren, R., Kluft, K., BIOS consortium, ACTION consortium collaborators, Bartels, M., Boomsma, D.I.

Van't Ent, Dennis: Examining genes-brain-behaviour relationships for aggression

Behavior genetic studies clearly demonstrated that aggression and the stability of aggressive behavior over time are controlled by genetic factors (e.g., van Beijsterveldt et al 2003). Combined with evidence for brain changes associated with aggression and related traits (Blair 2016, Blair et al 2018) and a strong influence of genetic architecture on the brain (Hibar et al 2015), it is likely that the influence of genetic variation on aggressive behaviour is, partly, mediated by the brain. Unfortunately, at present, we still know little about the interplay between genes, the brain and aggressive behavior and very few neuroimaging genetic studies have been performed with a specific focus on aggression. In this study we present the first attempt to explore how genetic variation couples to individual differences in the brain and aggressive behavior by utilizing information on the expression of genes throughout the brain which has become available over the last years (Hawrylycz et al 2012, Wang et al 2018). Specifically, to identify brain regions that are enriched with regard to the genetic architecture of aggressive behaviour, we used this prior information to identify sets of most strongly expressed genes per brain region. In a second step, we then tested the resulting gene sets for enrichment with respect to the genetic background of aggression as indicated by genome-wide association (GWAS) statistics (Pappa et al 2016). This method was recently succesfully used by our group to examine the neurobiology of well-being (Baselmans et al 2019). The brain regions indicated by our expression informed approach will be compared with the aggression related brain changes as indicated by previous neurobiological studies.

Co-authors: Noordijk, S., Baselmans, B.M.L., De Geus, E.J.C., Boomsma, D.I.

Whypp, Alice: Teacher-rated aggression and co-occurring behaviors: a multi-site population-based investigation

Abstract: Teachers represent an important resource in ascertaining the breadth and depth of a child's behavioral and emotional problems. A child's aggression or possible associated co-occurring behaviors (e.g., attention problems, anxiety) may be differentially expressed in different settings. The interplay between these factors in the school setting is not well characterized. Here, we used teacher ratings from four population-based cohorts (NTR, GEN-R, TEDS, FT12) of ACTION to investigate associations between aggression and co-occurring behaviors. Teacher-rated data from children at ages 7, 9, 10, 12, 14 (n=18,367, 49.4% boys; n=2300, 45.9% boys; n=8592, 49.9% boys; n=12,656, 48.9% boys; n=1441, 48.4% boys, respectively) were available based on the following instruments: Teacher Report Form (NTR, GEN-R), Strengths and Difficulties Questionnaire (TEDS), Multidimensional Peer Nomination Inventory (FT12). Associations were examined between aggression and other externalizing problems (anxiety, depression) and prosocial behavior. As expected, correlations of aggression with other externalizing behaviors were moderate to high (0.46–0.79). Correlations of aggression with depressive/withdrawn symptoms were low (0.13–0.29), while aggression—anxiety correlations had the broadest range ((-0.10)–0.38). Prosocial

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behavior was negatively correlated with aggression ((-0.33)–(-0.54)). Although the mean levels of aggression differ substantially by sex, the correlations of aggression and other co-occurring behaviors are notably more similar between the sexes. These population-based multi-country associations help to clarify the complexity of the problems surrounding aggressive children at school, and can assist in creating and providing the appropriate resources and interventions in schools to address these complexities.

Co-authors: Vuoksimaa, E., Korhonen, T., Rose, R.J., Pulkkinen, L., van Beijsterveldt, C.E.M., Bolhuis, K., Tiemeier, H., Plomin, R., Kaprio, J., Bartels, M., Boomsma, D.I.