

The Genetics of Aggression: Where Are We Now?

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Aggression, an overt behaviour with the intention to inflict damage, is a physiological trait with important roles throughout evolution, both in defence and predation. However, when expressed in humans in the wrong context, aggression leads to social maladjustment and crime. This special issue is about the genetic and neurobiological basis for aggression. Most of the 12 works presented here have been prepared by members of five international consortia established under the auspice of the FP7 and H2020 programs of the European Union to investigate different aspects of aggression and related behavioural phenotypes, including delineation of subtypes, aetiological mechanisms, neurobiology, neuroimaging, biomarkers, animal models and development and assessment of new treatments. Research on human aggression has largely focused on the societal causes of violent behaviour with relatively little focus on the underlying neuroscientific basis. However, interesting findings are emerging which suggest that by identifying distinct pathways to aggression, better targeting of social, psychological and medical treatments, can lead to improved outcomes for individuals and society. This issue represents a state of the art review of current neurobiological understanding of human aggression and a starting point for concerted efforts to move the field towards the development of new strategies for prevention and treatment.

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This issue is about the genetic and neurobiological basis for aggression, an overt, usually harmful set of social behaviours with the intention to inflict damage. Aggression plays an important role in evolution, both in defence and predation and is part of the normal behavioural repertoire of most, if not all, species. However, when expressed in humans in the wrong context, aggression can lead to social maladjustment and crime. Clearly, aggression has a high cost to individuals and society, yet there remains considerable uncertainty about the best ways to manage aggressive behaviour. The role of aggression-related phenotypes within clinical psychiatry has been debated over the years with ambivalence displayed by mental health professionals towards behavioural problems such as conduct disorder and antisocial personality disorder [Kendell, 2002]. Whether human aggression should be viewed as criminal

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behaviour to be dealt with by the criminal justice system, a mental health problem to be managed by healthcare services, or a social problem to be managed by social support systems varies across time, local regions and different societal groups [Kendell, 2002]. Yet, such important considerations are based on a limited understanding of the neuroscientific basis for aggression and the potential for development of effective interventions.

The focus of this issue on aggression is timely in following on from a large investment by the European Union (EU) into research on the causes and treatment of aggression. Funded by the EUs FP7 or H2020 programs, five international consortia have been established to investigate different aspects of aggression and related behavioural phenotypes including delineation of subtypes, aetiological mechanisms, neurobiology, neuroimaging, biomarkers, the use of animal models, and development and assessment of new treatments. Nine out of 12 papers in this issue have been contributed by these collaborative projects which include: (i) AGGRESSOTYPE: Aggression subtyping for improved insight and treatment innovation in psychiatric disorders, www.aggresstotype.eu; (ii) ACTION: Aggression in Children, unraveling gene-environment interplay to inform Treatment and InterventiON strategies, www.action-euproject.eu; (iii) MATRICS: Multidisciplinary Approaches to Translational Research In Conduct Syndromes, matrics-project.eu;

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(iv) TACTICS: Translational Adolescent and Childhood Therapeutic Interventions in Compulsive Syndromes, www.tactics-project.eu; and (v) FemNAT-CD: Neurobiology and treatment of adolescent female conduct disorder: the central role of emotion processing, www.femnat-cd.eu).

Forensic research on human aggression has largely focused on the societal causes of violent behaviour with relatively little focus on the underlying neuroscientific basis. However, interesting findings are emerging which suggest that by identifying distinct pathways to aggression, better targeting of social, psychological and medical treatments, can lead to improved outcomes for individuals and society. An important direction has been the recognition that aggression does not reflect a single aspect of behaviour, but rather is underpinned by multiple different aetiological pathways, which are likely to need require different sets of interventions. One example has been the recognition that emotional dysregulation seen in some adults with attention deficit hyperactivity disorder (ADHD) is often responsive to stimulants [Posner et al., 2011], further evidenced by pharmaco-epidemiological studies that show 30–40% reductions in criminal convictions following treatment for ADHD [Lichtenstein and Larsson, 2013]. Other forms of aggression linked to callous and unemotional traits appear to have a particularly strong genetic basis, with particular patterns of neuro-cognitive vulnerabilities, requiring innovative new approaches to be considered [Viding and McCrory, 2012], such as biofeedback (see: www.aggressotype.eu). Among the EU funded consortia, several groups are searching for molecular and neurobiological targets for pharmacological development that, like the stimulants in ADHD, may provide greater control over self-regulation of aggressive behaviour. Other projects are focusing on the concept of compulsivity, reflecting repetitive and irresistible urges to behave in particular ways, overlapping with problems linked to aggression such as drug and alcohol use. The role of gender differences on aggressive behaviour is another focus for research, particular differences in emotional regulation and their expression as either the outward expression of violence towards others, or the inwards expression towards the self as in self-harming behaviour. One theme that holds all these projects together is the focus on providing a developmental account of aggression throughout the lifespan. It seems clear that in most cases aggression is linked to early developmental processes and it is these developmental pathways that need to be delineated to improve the targeting and development of effective interventions.

Within this scenario, this special issue contains 12 works that cover different aspects in the study of aggression-related phenotypes. Three of them focus on the identification of common risk variants through genome wide association studies (GWAS) and meta-analytical approaches, three other works test gene-by-environment interactions, one paper deals with the longitudinal heritability of aggression, and the last one addresses the discovery of biochemical markers related to aggressive behavior. Finally, we also include four scholarly reviews.

Although different studies of antisocial and severe aggression have been performed in adults, showing a substantial underlying biology, little is known in children. This issue includes the largest study so far that explores children's aggressive behavior, using GWAS data from 19,000 subjects, which identifies suggestive

associations with common variants in a region on chromosome 2p12 and in the *AVPR1A* gene, encoding the arginine vasopressin receptor 1A [Pappa et al., 2016]. A second study investigates the role of common variation in the susceptibility to oppositional defiant disorder (ODD), an antecedent of aggressive behavior, in a sample of 750 children with attention-deficit/hyperactivity disorder (ADHD) from the International Multicentre ADHD Genetics (IMAGE) study, focusing on several candidate genes but also performing gene-set and multivariate GWAS analyses [Aebi et al., 2016]. Finally, an exploratory GWAS analysis of aggressiveness measures in 1,060 adult ADHD subjects identifies nominal findings that are enriched in a follow-up sample of childhood ADHD of the IMAGE consortium with oppositionality data available [Brevik et al., 2016].

A second group of three papers focuses on gene-environment interactions. LoParo et al. [2016] present the results of a lab study of 235 Finnish young men in whom the effects of common genetic variation at the oxytocin receptor gene (*OXTR*) on aggression levels are tested, and its interaction with alcohol exposure investigated. In a second study, the catechol-o-methyltransferase gene (*COMT*), a risk factor for several psychiatric conditions, is studied in a Swedish population-based cohort of around 1,800 adult individuals to explore the susceptibility to physical and verbal aggressive behavior in the context of adverse and favorable environments [Tuvblad et al., 2016]. A third work performs a meta-analysis of the well-known *5-HTTLPR* polymorphic region, a repeat in the promoter region of the serotonin transporter gene, across eight studies including around 7,000 subjects [Tielbeek et al., 2016]. As many previous studies have shown controversial results, the authors' aim is to test the robustness of the potential effect on antisocial behavior of the interaction between this genetic variation and environmental adversity.

During the last 25 years many studies have identified biochemical compounds that are potentially involved in aggression and its subtypes. Several reviews have gathered some of these works to extract conclusions, but in general they have focused on certain classes of metabolites. In this issue, the paper by Hagenbeek et al. [2016] performs a meta-analysis of all statistically significant associations of aggression with metabolites irrespective of biochemical class, and discuss on the possible application of metabolomics in aggression research.

The last original research paper of this issue addresses the problem of aggression heritability [Porsch et al., 2016]. As both low and high levels of aggression can be detrimental to survival and reproduction, it has been postulated that aggression is under stabilizing selection, which implies that variation in aggression will show significant heritability. In this work, the authors assess the longitudinal heritability of childhood aggressive behavior in two large twin cohorts from the Netherlands and the UK, including 17,000 children assessed at age 7 years and followed up until 11–12 years. The results show that genetic correlations are the main reason for stability of aggressive behavior.

This special issue also includes four review papers that provide a very comprehensive update in aggression genetics. Freudenberg et al. [2016] review the genetic mechanisms and molecular pathways that underlie aggression in non-human vertebrates, by comparing previous research performed in zebrafish and mouse.

Zhang-James and Faraone [2016] present a review based on the hypothesis that rare genetic variations identified in Mendelian disorders with documented aggressive symptoms can point at genes involved in the complex multifactorial forms of aggression. To do that, they run pathway and connectivity analyses with 86 genes selected from the Online Mendelian Inheritance in Man (OMIM) catalog. Another review by Fernández-Castillo and Cormand [2016] focuses on the candidate genes for aggression produced by previous reports of candidate-gene association studies (CGAS) and genome-wide association studies (GWAS). CGAS have studied mainly dopaminergic, serotonergic, and hormone candidates, whereas top findings in the GWA studies point at estrogen receptor signaling, neurodevelopmental processes, synaptic plasticity, and axon guidance. Finally, our last review summarizes the current knowledge of the genetics of human aggression based on twin studies, genetic association studies, animal models, and epigenetic analyses with the aim to differentiate between mechanisms involved in reactive (impulsive) or proactive (instrumental) aggression [Waltes et al., 2016].

To conclude, this issue represents a state of the art review of current neuroscientific understanding of human aggression and a starting point for the current concerted efforts to move the field towards new insights that will impact on the way we develop strategies for prevention and treatment. We hope you will enjoy reading it!

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