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EDITORIAL

Focused issue on conduct disorder and aggressive behaviour

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Conduct disorder (CD) and aggressive behaviour in children and adolescents show an increasing prevalence in Western societies [4, 8]. Children and adolescents dropping out of school or living in youth welfare institutions show a particularly high rate of CD, oppositional and aggressive behaviour [3]. CD and aggressive behaviour show phenotypic overlap, but are also distinct entities. Aggressive behaviour is a symptom of many psychiatric disorders, and also is an adaptive human behaviour related to the chance to survive. CD is a defined psychiatric disorder which comprises symptoms additional to aggression including rule breaking and dissocial behaviour, and can only be diagnosed if the related behaviour causes impairment for the individual and/or his/her family. CD poses a strong risk for detrimental adult outcomes, affecting individuals, their families, and society as a whole. Longitudinal studies following CD youth into early adulthood have found increased rates of failure to complete high school, high rates of early pregnancy, substance abuse, criminality, and health-related problems [5, 7]. In females with CD, additionally, high rates of early pregnancy have been described [9]. While evidence-based international clinical guidelines, which summarize the current state of the art regarding diagnosis and intervention of CD, such as NICE [10], emphasize a strong evidence for interventions in childhood; research on effective treatments of CD and aggressive behaviour in adolescence, and on preventive measures for detrimental adult outcomes is still in its infancy. Our understanding of the underlying neurobiology of CD remains rudimentary, and predictors of longitudinal outcomes associated with CD and aggression have rarely been studied despite their clinical and societal impact [6].

In 2013, within the 7th Framework for Research (FP7), the European Commission called for applications for "Paediatric conduct disorders characterized by aggressive traits and/or social impairment: from preclinical research to treatment". Four large research and innovation projects were funded with a total of over 20 million Euro: ACTION (coordinator Dorret Boomsma), AGGRESSOTYPE (coordinator Barbara Franke), FemNAT-CD (coordinator Christine M. Freitag), and MATRICS (coordinator Jeffrey Glennon).

The *ACTION* consortium (Aggression in Children: Unravelling gene–environment interplay to inform Treatment and InterventiON strategies) includes genome-wide association meta-analysis (GWAMA) of longitudinal aggression and attention problems in twin and population cohorts; and epigenetic genome-wide association (EWAS) meta-analysis of aggression in children and adults, and related genotype–environment studies. A "biomarker in urine" project looks both at classical biomarkers for aggression and at biomarkers from multiple metabolomics platforms. Metabolites from a range of chemical classes and biochemical pathways were tested for stability within an individual and suitability for predicting aggression. ACTION includes large-scale epidemiological and outcome studies making use of existing childhood data in twins, birth cohorts and clinical samples, and the population data from Sweden (homepage: www.action-euproject.eu).

Aggressotype (aggression subtyping for improved insight and treatment innovation in paediatric psychiatric disorders) uses subtyping of aggression into impulsive and instrumental to guide its approaches. Through coordinated analyses in

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humans and different (human-induced pluripotent stem cell derived, zebrafish, and mouse) models, aggression aetiology as it applies to ADHD and paediatric conduct disorder was studied. Different levels from molecule to system were investigated: DNA (genetics, epigenetics), RNA (gene expression), neural circuits (neuroimaging), cognition (neuropsychology), behaviour, and diagnosis. A second layer of work is dedicated to predicting, preventing, and treating aggression. Here, interdisciplinary data integration is used to design predictive algorithms and identify biomarkers. Non-pharmacological biofeedback in aggressive children is explored as early intervention, and methylphenidate is tested for its application in the psychiatric care of criminal offenders (homepage: www.aggressotype.eu).

The *FemNAT-CD* consortium (Neurobiology and Treatment of Adolescent Female Conduct Disorder: The Central Role of Emotion Processing) focusses on female adolescent CD and the role of emotion processing in CD. A large ($N > 1800$) case–control sample was collected within the study, with multi-level genetic, epigenetic, endocrinological, neurophysiological, neurocognitive, and brain imaging data available. The broad phenotypic assessment, including all comorbid psychiatric disorders, as well as data on environmental risk factors will allow delineating CD aetiologies and subtypes. In addition, a randomized controlled intervention study on a program based on dialectic behavioural and trauma-sensitive methods for females with CD/ODD living in youth welfare institutions (START Now) has been currently finalized. Targeted pharmaco-challenge and animal studies focus on oxytocin challenge and serotonergic compounds to study their role in emotion processing (homepage: www.femnat-cd.eu).

MATRICS (Multidisciplinary Approaches to Translational Research In Conduct Syndromes) examines the interplay between arousal dysregulation and failure of top-down control processes over emotional and cognitive processing resulting in aggression and rule-breaking behaviour. This is studied in human-induced pluripotent stem cell-derived neurons, patients with oppositional-defiant disorder (ODD) or CD, and animal models with altered stress reactivity resulting in epigenetic and transcriptomic regulators (DNA methylation, microRNA) as key molecular underpinnings in both animal and human data sets. Using Bayesian machine learning approaches, the dependencies between different cognitive domains and gene–environment interactions are investigated, while bio-/neuro-feedback approaches are utilized to train juveniles with CD on how to cope with their reactivity to triggers. MATRICS also examines the cognitive underpinnings of a range of pharmacological interventions (methylphenidate, dexamphetamine, atomoxetine, risperidone, aripiprazole, and oxytocin) to alter cognitive and emotional reactivity in rodents and those with ODD/CD (homepage: www.matrics-project.eu).

The four consortia are committed to collaborate wherever possible, and the present focused issue in *European Child + Adolescent Psychiatry* (ECAP) is one example of such collaboration. Since the projects are running between 2013 and 2019, work in progress is reported in this issue. In December 2017, the EC invited the four consortia to a policy workshop in Brussels organized by the EC's health research directorate, namely Andreas Holtel and colleagues. The consortia presented research outputs that 'call for translation' in terms of guideline development regarding treatment recommendations, and uptake by public health, policy makers, and/or by industry for the development of new products or product development tools. A wealth of emerging findings showed good potential for societal and/or industrial impact. The EC summarized that "EU-funded conduct disorder and aggression research is a convincing showcase for what can be achieved, if complementary research efforts are bundled under a common concept and strategies tailored to the respective research area". Key to justifying EU research support is—apart from the European Research Association building objective—the impact this research generates for patients, European societies including European industries. Thus, many FP7 and H2020 calls explicitly require translational efforts and/or industry involvement. In addition to gauging the potential, the workshop in Brussels aimed at learning which obstacles to successful translation are being encountered and to discuss which possible remedies and support measures could be envisaged. The following aspects were presented and discussed at the workshop:

1. Preclinical animal models for aggression research (studied by AGGRESSOTYPE, FemNAT-CD, and MATRICS).
2. New biomarker options based on distinct biological aetiologies: genetic and epigenetic developmental trajectories (studied by ACTION, Aggressotype, and FemNAT-CD); biological biomarker discovery in urine (studied by ACTION).
3. New intervention options: randomized controlled phase-III trial on methylphenidate in adult prisoners (studied by AGGRESSOTYPE), randomized controlled multicentre phase-IIa trial on the START Now-intervention in female adolescents (studied by FemNAT-CD); pilot phase-IIa studies with methylphenidate, atomoxetine, risperidone, and aripiprazole (studied by MATRICS) and oxytocin (studied by FemNAT-CD).
4. The role of psychiatric comorbidity in subtyping CD with and without callous unemotional traits (studied by FemNAT-CD, and MATRICS).
5. Improvement of evidence-based clinical guidelines and translating these into practice (studied by ACTION, AGGRESSOTYPE, FemNAT-CD, and MATRICS).

Taken together, the workshop showed that the cluster of CD/aggression research consortia has indeed developed into a highly interactive research community that presents traits of good cluster corporate identity, across confines of individual projects. The EC concluded that EU-funded research on conduct disorders and aggression is yielding a plethora of research findings that are of high translational value and hence apt to generate impact on citizens and patients as well as on public health systems and the commercial biomedical sector. Results from the presented CD/aggression research projects call for EU-wide dissemination of results and their uptake by public health systems.

It was also recognized that CD research proves to be a particularly challenging target area for clinical research, as important determinants in the socioeconomic context (family situations and/or educational systems) require interdisciplinary research. The pathway from clinical research findings to treatment recommendations and guidelines is not sufficiently clear to all actors involved, e.g. with respect to valid methodology and requirements of clinical studies. The functioning of the public health sector and the importance of health economics are not sufficiently accounted for, as evidenced, e.g. by the design of studies testing costly interventions that will not be taken up in a real-life public health context.

Research on CD and aggression can be considered as a particularly challenging field as:

- CD and aggressive behaviour overlap, but they are not synonymous. The nosology of CD and different forms of antisocial and aggressive behaviour are not unambiguous; comorbidity is the rule, hence requiring precise evidence-based subtyping—a prime area for personalized medicine aiming to profile individuals with multidimensional disorders.
- The time span of disorder development is crucial, throughout childhood into adolescence and early adulthood, and hence longitudinal as well as age-specific studies are needed.
- Recognition of heterogeneity in the mechanisms leading to CD and aggression is needed; many risk factors are still unknown. Those that have been identified often have low specificity, and we know little about their interplay at different levels; in addition, environmental risk factors are measured very differently across studies, complicating comparisons.
- Clear gender-specific manifestations of a range of CD/aggressive behaviours are found, suggesting the need of gender-specific treatment guidelines.
- High-risk target groups present with most severe symptoms, hence those with the greatest need of prevention and treatment, are the ones most difficult to reach for research as well as for interventions.
- Approaches to CD and aggressive maladaptation in public health systems are very diverse in different EU countries, with guidelines, even where available, often not being implemented.
- Industry interest in developing new drugs for CD/aggression is low, partly due to previous failures with drug trials. Enabling framework conditions and support from public side are needed to substitute for, or trigger, more industry interest.
- The identification of new aetiological models, providing an entrance to drug and biomarker development, is essential.

Given the progress achieved by the four consortia, presented in this focused issue as well as at the EC workshop, researchers, clinicians, as well as stakeholders emphasized the need to further support CD and aggression research at the EU level.

In this focused issue of ECAP, we present selected works from the consortia showing how we deal with some of the challenges listed above. We present a review on females with CD [[6] (FemNAT-CD)] and several original articles on diagnostic, measurement, and treatment aspects of the target phenotype [[1] (ACTION); [11] (AGGRESSOTYPE)], longitudinal genetic and environmental influences on CD and aggressive behaviour [[13] (ACTION)], and on cognitive aspects of CD [[2] (MATRICS); [12] (FemNAT-CD)]. The coordinators of the consortia, which are the guest editors of this focused issue, hope you will enjoy this selection.

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