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Aggressive behaviour in children and adolescents with Conduct Disorder or Oppositional Defiant Disorder: neuropsychological characterization and drug treatments. Preliminary analysis of data from the European MATRICS project

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PhD Student: Carla Balia

Coordinator of the PhD Programme Prof. Paola Fadda

Supervisor Prof. Alessandro Zuddas

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1 INTRODUCTION

Aggression is an unlearned, rather than learned, behaviour (Blake & Grafman 2004), developed as part of our defence and protection (Vaeroy et al., 2019). Aggressive behaviour toward others can in fact be considered a normal dimension of the mammalian repertoire with adaptive advantages (Berkowitz, 1993) contributing to survival and adaptation. When aggression is excessive, out of context, or directed toward self, however, it is considered to be pathological. Growing older, most children learn to socialize and tend to inhibit or suppress these aggressive behaviours (Tremblay, 2010): accordingly, with healthy growth and development of the human brain, the ability to suppress aggressive behaviours increases while the impulsive aggressive tendencies diminish, and both evolve into the *age of reason* (Blake and Grafman, 2004). When children or adolescents fail to acquire effective self-regulation skills and age-appropriate abilities in expressing their needs and defending themselves, they often continue to manifest aggressive and rule braking behaviours. These individuals may fall within the category of Disruptive, Impulse—Control and Conduct Disorders (American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders Fifth Edition - DSM-5, 2013), the most severe of which is termed Conduct Disorder (CD).

Conduct disorders are characterised by repetitive and persistent patterns of antisocial, aggressive and/or defiant behaviour that amounts to significant and persistent global impairment.

Problems of aggression, oppositionality, and impulsivity, with or without attention deficit or hyperactivity, constitute the most prevalent psychopathology in children and adolescents. These disorders are among the most common and highly impairing mental and behavioural problems in children and young people are associated with a significant global burden (Erskine et al., 2014): they imply a significant impact on functioning and quality of life with strong long term negative effects on the individual and on families, and on society in general.

Aggressive behaviours of children and adolescents with CD or with Oppositive Provocative Disorder (ODD) are sometimes associated with callous-unemotional tracts (CU). In the last decade, many efforts have been made to obtain a better neuropsychological characterization of subtypes of CD and there has been a rapid progress in understanding the neurobiology of psychopathic traits, in particular of the CU component.

Understanding how aggressive CD/ODD subjects differ from control subjects with typical development in terms of neuropsychological functioning, as well as the correlations between aggressiveness, specific neuropsychological functions (attention, working memory, social cognition, capacity decision-making, understanding of emotions, motivation, etc.) and specific parameters of autonomic regulation (heart rate and skin conductance), would make it possible to obtain more precise information regarding the cognitive mechanisms underlying aggression and the biological mechanisms underlying the different types of aggressiveness.

Subjects with CD may exhibit different levels of deficits in both “cold” and “hot” executive functions and abnormal physiological parameters such as heart rate, electrodermal activity and cortisol levels. However, data on the prevalence of these characteristics are still conflicting and the proportion of the different types of deficits has not been completely clarified yet. Disruptive/conduct disorders are in fact heterogeneous disorders both for aetiology and for clinical expression, and their neurobiological bases have not been completely clarified.

Not all patients who receive a diagnosis of conduct disorder show similar pathophysiological mechanisms: it is likely that different mechanisms can lead to either a CD with psychopathic traits (CU traits) with a predominant instrumental aggression (low emotional reactivity, dysfunction in emotional/cognitive empathy, and deficit in decision making), or, on the contrary, to a CD with reactive aggression (impulsive aggression, exaggerated affective response, deficit in processing of social-affective stimuli and in cognitive control).

Some clinical evidence suggests the use of various drugs (psychostimulants, antipsychotics, mood stabilizers and other agents) to reduce CD problems, but

evidences are limited and also contradictory: no clear indications on the effectiveness of treatments depending on the type of aggression have yet been formulated.

With the aim of implementing the knowledge on aggression/antisocial behaviour and their treatment, the European Commission, through the FP7-HEALTH-2013-INNOVATION-1 program, funded the European MATRICS project (Multidisciplinary Approaches to Translational Research In Conduct Syndromes). Through a transactional approach, MATRICS includes studies finalized to identify neural, genetic and molecular factors involved in the pathogenesis of aggression/antisocial behaviour in preclinical (animal) models and clinical samples (stratified for the presence of callous unemotional traits), and proof-of-concept clinical studies in order to define the effects of medication on specific neuropsychological domains.

1.1 CONDUCT DISORDER

Conduct disorder (CD) is a severe disorder included in the diagnostic group of the Disruptive, Impulse—Control and Conduct Disorders described within the DSM 5 (APA, 2013). This diagnostic group includes other conditions involving anomalies in the self-control of emotions and behaviour, such as the Oppositional Defiant Disorder and the Intermittent Explosive Disorder. Many of the symptoms that define these disorders can occur to some degree in typically developing individuals. Thus, when determining if they are symptomatic of a disorder, as for the other psychiatric disorders, it is essential to consider frequency, persistence, pervasiveness across situations, and impairment associated to the problematic behaviours with respect to what is expected for age, gender and culture (APA, 2013).

1.1.1 Definition and diagnostic criteria

According to DSM-5 (APA 2013), Conduct disorder is defined as a repetitive and persistent pattern of behaviour, which violates the rights of others and major age-appropriate societal rules. The diagnosis of CD requires the presence of 3 of 15 criteria all of which should have been present in the last 12 months and one of which must have been present in the past 6 months. These 15 behavioural criteria are categorized into 4 dimensions:

- *Aggression to people and animals*: aggressive conducts that cause or threatens physical harm to other people or animals, such as bullying, threatening or intimidating behaviour, physical fights or forcing into sexual activity;
- *Destruction of property*: non aggressive conduct that causes property loss or damage, such as deliberate fire setting
- *Deceitfulness or theft*: such as breaking into someone else's property, frequently lying or breaking promises to obtain goods or favors or to avoid debts or obligations, or stealing;
- *Serious violation of rules* such as running away form home overnight.

In order to formulate the diagnosis of CD, behavioural symptoms must cause clinically significant impairment in social, academic or occupational functioning. The diagnosis should be made when symptoms are judged to be due to an “internal dysfunction” of the individual, rather than being a transient reaction to a negative environment (Wakefield et al., 2012).

Symptoms of the disorder vary with age, becoming more severe with modification in physical strength, cognitive abilities, and sexual maturity. DSM-5 defines three levels of severity (mild, moderate, severe) considering the number of conduct problems in excess of those required to make the diagnosis and/or the level harm to others caused by the conduct problems.

An additional specifier termed “*With limited prosocial emotions*” has been introduced to the CD definition in the DSM-5 to describe a subgroup of subjects with CD also showing Callous Unemotional (CU) traits. To qualify for this

specifier, a child must have displayed in multiple relationships and settings at least two out of the following four characteristics, for at least 12 months: *Lack of remorse or guilt*; *Callousness-lack of empathy*; *Unconcern about performance* (for example, at school); *Shallow or deficient affect* (a lack of or insincere expression of feelings to others). These characteristics must reflect the individual's typical (persistent) pattern of interpersonal and emotional functioning and not an occasional behaviour.

CU traits have been demonstrated positively correlated with measures of fearless or thrill-seeking behaviours and negatively correlated with measures of trait anxiety and with sensitivity to punishment cues (Frick & White, 2008; Pardini, 2003).

Subjects with limited prosocial emotions specifier tend to plan aggression for instrumental gain and are thought to be more likely to have childhood-onset type and to have a severity specifier rating of severe.

CU traits have been potentially identified and measured as early as 2 years of age (Waller et al., 2012). They can also be observed in individuals without CD who are affected by other disorders, such as Oppositional defiant disorder (ODD), Attention-deficit/hyperactivity disorder (ADHD) and, in adults, personality disorders (Herpers et al., 2012). A large multi-site cross-sectional design study found CU traits in 10–32% of those with CD and in 2–7% of non-CD participants in a community sample, and in 21–50% of those with CD and in 14–32% of non CD in a clinic-referred sample (Kahn et al., 2012).

DSM-5 also suggests to specify the subtype of CD based on the age of onset: *Childhood-onset type* (prior 10 years of age), *Adolescent-onset type* (after 10 years of age), or *Unspecified onset*. The childhood-onset subtype is thought to be associated with a more persistent and severe behavioural pattern. CD subtype will be extensively discussed in a later section.

1.1.2 Epidemiology

A meta-analysis of 41 studies conducted in 27 countries between 1985 and 2012, including 28 studies reporting data on CD in among children and adolescents, estimates a worldwide prevalence of conduct disorder of 2.1% (Polanczyk et al., 2015).

A previous meta-regression analysis including studies from 1987 to 2008 estimated a worldwide prevalence of CD of 3.2% (Canino et al., 2010)

More recent data from the 2016 National Survey of Children's Health (NSCH) indicate that in USA 7.4% of children aged 3-17 years (approximately 4.5 million) have a diagnosed behaviour/conduct problem (Ghandour et al., 2018).

CD prevalence rates increase from childhood to adolescence and are higher among males (Fairchild et al., 2019; NICE 2013; APA, 2013).

1.1.3 Aetiology

The aetiology of CD is complex and implies a combination of biological, genetic, environmental (and gene-environment interaction and correlation), psychological and social factors (Fairchild et al, 2019; APA, 2013) that may predispose, facilitate or aggravate the CD.

Salvatore and Dick (2018), defining CD as a moderately heritable psychiatric disorder, report that a number of suggestive genomic regions have been identified (indicating polygenic inheritance). They also show some evidence of a gene-environment interplay (meaning that CD genetic predispositions can contribute to selection into higher-risk environments) but concluding that more evidence are needed since mechanisms of risk from genes to CD are relatively unexplored.

In 2014 Frick et al. published a review on heritability of CU traits showing some evidence on genetically accounted variations of CU traits and on the genetically driven stability in CU traits during development (Frick et al., 2014a). More

recently it has been stated that heritability for CU traits is likely between 36-67% and that there is emerging evidence that the serotonin and oxytocin systems may play a role in CU traits but results need to be replicated (Moore et al., 2019).

Community/Family-level environmental factors as well as prenatal and perinatal risk factors may influence and modulate this disorder. Community-level risk factors include peer rejection, association with a delinquent peer group, neighbourhood exposure to violence. Family-level risk factors involve attachment disorganization (insecure attachment) resulting from maladaptive parenting (parenting styles characterized by educational inconsistency, harsh/ coercive discipline), parent-child conflicts, frequent changes of caregiver, trauma, abuse and deprivation (parental maltreatment). Also poverty, low socio-economic status and institutional living have been associated to CD. Among pre-natal factors the best documented are maternal smoking, alcohol or drug use and stress or anxiety during pregnancy, while perinatal factors include birth complications, parental psychopathology, malnutrition (Fairchild et al., 2019).

Many possible biological markers have been studied by many authors (including psychophysiological parameters, as well as structural anomalies and altered functioning in fronto-temporal-limbic circuits) but none of them can be yet considered a suitable marker to be used for diagnosing the disorder. In the last decade, numerous authors have found, in subjects with CD, deficits in verbal skills, both in “cold” and “hot” executive functions (for example, poor cognitive flexibility, impairment of decision-making, with anomalies in reward and punishment mechanisms) and in emotion processing (Johnson et al., 2015; Blair et al., 2014; Fairchild et al., 2009; Blair, 2013a, 2013b; Matthys et al., 2012) and alteration of autonomic parameters such as heart rate, skin conductance, and cortisol levels (Fairchild et al., 2019) which will be later discussed. All these functional deficits may be related to several underlying neurobiological abnormalities. Various brain structures and functions have been, in fact, implicated in aggressive and non-aggressive antisocial behaviour in human studies as well as in subject with low or high CU traits, with sometime heterogeneous and sometimes overlapping results.

Over the last decade many efforts has been made to achieve a better neuropsychological characterization of CD subtypes, leading to a better understanding of the neurobiology of psychopathic traits, particularly the callous–unemotional component (Marsh et al, 2008; Finger et al, 2008; Shirtcliff et al 2009; Jones et al 2009; Fairchild et al, 2009; Narhi et al, 2010; Finger et al, 2011; Blair, 2013a; White et al, 2013a; Lozier et al, 2014; Fairchild et al, 2014).

Preschool aggressive children with CD have been found showing impairments in inhibition, which are independent of any attention problems (Raaijmakers et al, 2008). Impaired executive functioning (i.e. planning ability and inhibitory control) have been linked specifically to reactive aggression (Ellis et al., 2009). However, selective attention and future orientation, two of the most important executive functions implicated in decision making, appear similarly impaired among antisocial youth irrespective of the presence of CU traits (Fanti et al., 2016; White et al., 2013b), suggesting that differences in reward and punishment mechanisms affect each CD subtype (Fairchild et al., 2009). Adolescents with CD often are found to have problems with verbal skills and executive function, including problems with selective attention, cognitive flexibility, concept formation and planning abilities (Lynam and Henry, 2000; Teichner and Golden, 2000; Johnson et al., 2015; Blair et al., 2014). Emotion processing can also be impaired in CD patients (Blair, 2013a, 2013b). Unfortunately the proportion of any one of these deficits is not clear as there are conflicting data across the various studies.

1.1.4 Neuroanatomy (structural *and* functional) and neuropsychological subtypes of CD

Different brain structures and functions are involved in antisocial behaviour in human studies (PFC, insula, amygdala, striatum). A recent meta-analysis showed a significant decrease in the volume of the right and left insula and left amygdala in youth with conduct problems including CD, ODD, antisocial behaviours and Disruptive Behaviour Disorders. Evidence for decreased volume in lateral and orbito-frontal prefontal cortex, medial prefontal cortex and cyngulate gyrus as well as in superior temporal and fusiform gyrus are, on the

other hand, less consistent across studies (Roger and DeBrito, 2016). A meta-analysis including 12 sMRI and 17 fMRI studies on individuals with ODD/CD (Noordermeer et al., 2016) shows evidence of smaller brain structures and lower brain activity in mainly hot executive functions-related areas: bilateral amygdala, bilateral insula, right striatum, left medial/superior frontal gyrus, and left precuneus; authors specify that this evidence is irrespective of the presence of ADHD comorbidity. Another meta-analysis (Alegria et al., 2016) of 24 fMRI studies found that the most consistent dysfunction in youths with disruptive behaviour disorders or conduct problems compared to controls is the underactivation in the rostral and dorsal anterior cingulate cortex and in the medial prefrontal cortex and ventral caudate that mediate reward-based decision making, which is typically impaired in CD.

It is unclear whether these findings generalize across the specific aggression phenotypes that characterize children and adolescents with CD/antisocial behaviour (e.g. childhood vs adolescent onset, presence or absence of CU traits, reactive vs instrumental aggression). No clear differences have been found in functional and structural brain imaging data between childhood onset and adolescent-onset aggression (Fairchild et al., 2011; Passamonti et al., 2010). Conversely, a more clear contrast between high and low CU traits was found in terms of activations of the amygdala: fMRI studies have shown that adolescents with CU traits, compared to adolescents without such traits, have a significantly reduced amygdala response to fearful faces expressions (Viding et al., 2012; Blair, 2013a; Finger et al., 2011; White et al., 2012). On the other hand, only few imaging studies have not yet analyzed the differential correlates of reactive (“impulsive”) versus instrumental (“predatory” or “covert”) aggression in CD.

Taken together, the data suggest that patients receiving a diagnosis of CD are heterogeneous and that their problems are underpinned by a range of different pathophysiological processes: It is likely, but not definitely shown, that different pathways can result a picture of CD with psychopathic traits with predominant instrumental aggression, or one of CD with reactive aggression.

A model explaining conduct disorder physiopathology has been proposed by Blair, defining the aetiological (genetic and environmental), neural, cognitive factors associated with the behavioural aspects of conduct disorder (Blair et al., 2013a; Figure 1). Blair describes the interplay of various aetiological factors and the resulting cognitive and behavioural phenotypes, and define two main phenotypes: "*CD with psychopathic traits*" (mainly associated with decreased amygdala striatal and vmPFC reactivity, and including CU traits, antisocial behaviour and instrumental behaviour, and frustration-based reactive aggression) and "*CD associated with anxiety and emotional lability*" (mainly associated with increased amygdala reactivity, and including threat-based reactive aggression and anxiety). Both forms are likely to show under-regulated responses to social provocation.

A different model of physiopathology try to explain the neurobiology of conduct disorders describing the altered functioning in three mental domains (Matthys et al., 2013):

1. Punishment processing: impaired learning to inhibit inappropriate behaviours based on aversive conditioning (making the association between inappropriate behaviour and punishment), seems to play a role in the onset of the ODD and CD from early infancy *affecting negatively on the development of empathy*. This impaired punishment processing appears associated with impaired fear conditioning and with deficits in emotion processing (especially fear and sadness) and amygdala hypofunction, which in turn relates with CU traits (Blair et al., 2016).

2. Reward processing: CD and ODD appear to be characterized by reward hyposensitivity which appears related to low basal heart rate (sympathetic nervous system hyporeactivity) (Beauchaine et al., 2008; Sijtsema et al., 2010; Lorber, 2004), and to decreased dopamine functioning (Matthys et al., 2013). In turn, these hyposensitivities can lead to *sensation or reward seeking behaviours*, which may themselves result in *antisocial behaviour (such as rule breaking)* or even *substance abuse*. Dysfunctions of the orbitofrontal circuits could explain *reactive aggressive behaviours* due to abnormalities in computations of expectation of reward (Blair, 2004; Rubia et al., 2009).

3. Cognitive control: impairments in executive functioning (Fairchild et al., 2009; Raaijmakers et al., 2008; Ellis et al., 2009) and structural deficits of the paralimbic system which include the orbitofrontal/ventromedial prefrontal cortex, superior temporal, cingulate cortices, and limbic brain regions (Rubia, 2011; Matthys et al., 2013), imply an impaired cognitive control over emotional behaviour, which may result in *reactive aggression* and *uncontrolled disruptive symptoms*. In particular, deficits in decision making are associated with the dysfunction of specific neurobiological substrates, mainly in terms of orbitofrontal cortex impaired functioning and reduced connectivity between the striatum and anterior insula (Séguin, 2009; Viding et al., 2012; White et al., 2013a; Finger et al., 2008; Blair, 2013a).

A more recent work (Blair et al. 2018) reviewed fMRI work on neuro-cognitive systems that are considered to be dysfunctional in subjects with conduct problems (i.e., CD, ODD or antisocial behaviour without formal clinical diagnosis), with the aim to highlight associations between dysfunctions in four neuro-cognitive systems (*empathy*, the *acute threat response*, the *reinforcement-based decision-making*, and *response inhibition*) and specific symptoms sets. Authors highlighted the high degree of overlap between the neural regions involved in the investigated functional processes (such as amygdala and the ventromedial PFC) and described consistent evidence for:

- *Empathy*: subjects with conduct problems show impairments in the *emotional Theory of Mind*, in the *response to the emotional expressions of others* and the *response to pain cues*, and level of dysfunction in this neuro-cognitive system (in particular decreased amygdala response) relates to level of CU traits.
- *Acute threat response*: subjects with conduct problems show reduced aversive conditioning and levels of amygdala response result positively associated with conduct problems, low CU traits and propensity for reactive aggression.
- *Response inhibition* and *Reinforcement-based decision-making* (involving reward sensitivity, processing of punishment and avoidance responses): impairments in these functions do not show clear relationship with level of CU traits, but are associated with increased levels of impulsive and

potentially antisocial behaviour, and with high comorbidity of CD/ODD with both ADHD and substance abuse (disorders which are typically associated with these dysfunctions).

1.1.4.1 Neurobiological substrates of CU traits

A particular set of neurodevelopmental impairments (decreased amygdala responsiveness to distress cues and decreased striatal and ventromedial prefrontal cortex, vmPFC, sensitivity to reinforcement signals that are critical for successful decision making) have been related by many authors with CD that is associated with psychopathic traits (Jones et al 2009, Marsh et al 2008, Marsh et al, 2011; Viding et al 2012; White et al, 2012; Marsh et al 2013; Carre et al 2013). A subgroup meta-analysis of fMRI studies within Alegria's work found that youths with disruptive behaviour disorder or conduct problems with psychopathic traits compared to controls showed reduced ventromedial prefrontal-hypothalamic-limbic activation, but also hyperfunctioning of rostral dorsolateral prefrontal cortex and right dorsal caudate, which may reflect poor affect reactivity and empathy in the presence of hyperactive cognitive executive control (Alegria et al., 2016).

Psychopathic traits have a core callous–unemotional component and a impulsive–antisocial component (Barry et al, 2000). Compared to youths with low psychopathic traits, youths with high CU traits showed significantly decreased associations between amygdala response and aggression (Harenski et al., 2014), less amygdala activation from negative stimuli (Frick and Viding, 2009), and when processing fearful and sad facial emotions and other non-verbal expressions (Marsh and Blair, 2008). The fact that they represent these stimuli less negatively make the individual with high CU more likely to engage in instrumental antisocial behaviours. The findings of low emotional reactivity with deficits in negative emotion processing, particularly in response to fear and distressing stimuli (Kimonis et al., 2008) and the low comorbidity with anxiety or mood disorder symptoms (less than is seen in youths with CD but no CU traits; Frick and White, 2008; Frick et al., 2014b) are in line with their being lower levels of amygdala responsiveness found in subpopulation of CD with high CU

(Blair, 2007; Marsh et al., 2008; Jones et al., 2009; Finger et al., 2011; Viding et al., 2012; White et al., 2012; Marsh et al., 2013; Lozier et al., 2014).

The specific cognitive impairments pattern related to psychopathic traits in terms of empathic dysfunction (cognitive empathy and emotional empathy) and decision making deficit, can be explained by its neurobiological substrates (Blair et al., 2013a).

Cognitive empathy, which involves the representation of the intentions and thoughts of other individuals (theory of mind), is usually not impaired in individuals with high CU traits as confirmed by the absence of abnormalities in areas responsible for this cognitive feature (Dolan et al., 2004; Sebastian et al., 2012). *Emotional empathy*, on the other hand, involves affective responses to emotional displays of other individuals (facial cues, body postures) and to verbal descriptions of the emotional states of other individuals. Individuals with Psychopathic traits usually show an emotional empathy deficit (in particular, responding to the fear, sadness, pain and happiness of others) (Blair et al,. 2001; Stevens et al., 2001; Dadds et al., 2006; Marsh & Blair, 2008; Woodworth & Waschbusch, 2008; Blair and Viding, 2008; Dawel et al., 2012) and are less concerned (relative to children with low CU traits) for victim's suffering. This functional impairment has been associated with the reduced amygdala and vmPFC responsiveness to distress cues (Blair, 2013a, 2013b). In other words, it is possible that, in these individuals, abnormalities in processing someone else emotions are limited to "*not feeling what others feel*" and do not extend to difficulties commonly seen in children with an impaired theory of mind, for example with autism spectrum disorders, who are "not knowing what others think". This pattern of difficulties and strengths may explain why children with high CU traits fail to develop "*affective empathy*" and are good at manipulating others to their own advantage, even if such behaviour will cause distress to somebody else (Viding et al, 2012). Data in this regard are not altogether consistent: in a broad research study of children with psychopathy traits Dadds et al. (2009) found that only male children, present a severe deficits in *affective empathy*, and that both males and females can present deficits also in *cognitive empathy*, at least until the pubertal years. On community sample of adolescents approximately 16-years old, Brouns found that in girls both affective and

cognitive empathy appears impaired, whereas in males CU traits involve affective more than cognitive empathy (Brouns et al., 2013).

In patients with CU traits abnormalities of fronto-temporal circuitry in terms of grey/white matter concentration have also been found in structural MRI studies (De Brito et al 2009; Huebner et al 2008) and can be linked to impairments in emotion processing, moral judgments and decision-making.

1.1.4.2 Neurobiological substrates of Reactive subtype of aggression

Another set of dysfunctions appears to be associated with a different conduct disorder presentation characterized by *reactive* and *unplanned* aggression (Coccaro et al, 2011). Usually individuals with this kind of aggression (that is with low CU traits) are more impulsive and show aggressive behaviours more situationally and unpredictably.

Three neural systems are thought to be critical for understanding this more reactive aggression and its neuropsychological features (Coccaro et al 2011):

I. *Neural systems* (including subcortical regions such as the hypothalamus, the brainstem and dorsal half of the periaqueductal grey [PAG] matter, and emotion-expression regions such as amygdala and insula) that support the experience of *aggressive impulses* and which appear to be regulated by the other two neural systems;
II. *Neural systems* (including rostral ACC, VMPFC, OMPFC, anterior insula) which underpin *decision-making circuits and social-emotional information processing* circuits that assess interpersonal cues and determine if behaviour is consistent with societal norms and values, giving the ability to evaluate the consequences of aggressing or not aggressing;
III. *Neural regions subserving emotion regulation*, which include dACC and fronto-parietal regions (DLPFC, DMPFC, VLPFC, OMPFC, VMPFC) that are involved in modifying or suppressing emotions and other impulsive motivational urges.

If the basic threat circuit (amygdala–hypothalamus–PAG) is overly responsive, either because of prior priming or inadequate regulation, the individual is more likely to form “hostile attribution biases” and to show an exaggerated affective response to perceived social threat, as evidenced by, for example, increased amygdala responses to fearful expressions, which is more likely to be found in youths with low CU traits and with reactive aggression (Blair, 2007; Frick and Viding 2009; Viding et al 2012; Blair 2013a; Choe et al., 2015). These individuals appear often hyper-vigilant to threat, are capable of showing empathy, and can appear emotionally over reactive (Frick and Viding, 2009; Jones et al., 2010); they also show more frequently mood or anxiety disorder symptoms (Lahey et al, 2002), which are commonly associated with increased amygdala responsiveness.

A recent study (Euler et al., 2014) found impaired cognitive control in reactive aggressive CD patients compared to healthy controls when distressing stimuli were presented, indicating a problematic interrelation of socio-affective processing and cognitive control.

Dysfunction within vmPFC and amygdala, together with deficit in striatum and anterior insula connections, are shown to be associated with deficits in decision making, specifically in reinforcement learning and the representation of reinforcement expectancies, which have been found to be abnormal in psychopathic youths (Seguin, 2009; Blair et al., 2013a). In particular, these young people show deficits in the capacity to link outcomes (rewards or punishments received after an action has been performed) with actions, partly because of deficit in prediction error signalling which is critical to spur reinforcement learning, and partly because of an abnormal representation of the expected value when considering whether to perform an action. This impairment, which, as said before, relates more to the impulsive–antisocial component of psychopathic traits, is also seen, at least partially, in patients with other externalizing disorders, such as attention-deficit hyperactivity disorder (ADHD), and in those at risk of developing drug addiction, alcohol abuse, and gambling (Blair 2013; Seguin 2009).

1.1.5 Autonomic nervous system (ANS) functioning in CD

Lower autonomic reactivity to stress has been reported by several authors (Fairchild et al., 2019). Multiple measures of the ANS suggest attenuated ANS functioning among children and adolescents with CD.

Children and adolescents with CD often exhibit attenuated resting heart rates (HR), skin conductance (SC), and electrodermal activity (EDA) when compared to age-matched controls, implicating a chronic ANS under-arousal which can lead to emotion dysregulation: a low autonomic reactivity can result in lower levels of anxiety and fear and ultimately lead to behavioural disinhibition (increased propensity for exhibiting risk-taking and antisocial behaviours and decreased propensity to avoid behaviours with negative consequences) as often shown in CD (Burke et al., 2002; Raine, 1993).

Reduced ANS functioning exhibited by individuals with CD. Lower ANS functioning results in less intense feelings of anxiety and fear, which in turn may reduce the need to exercise emotion regulation and (Burke et al., 2002).

A systematic review and meta-analysis of resting heart rate versus antisocial behaviour in children and adults confirmed previous evidence (Herpertz et al., 2007; Ortiz & Raine, 2004; Lorber, 2004; Raine and Jones, 1997; Raine et al., 1997; Rogeness et al., 1990; Raine et al., 1990) of association between low resting heart rate and higher levels of antisocial behaviour (including aggression and psychopathy), irrespective of sex and age (Portnoy, J. & Farrington, 2015). In contrast to these evidences, a more recent large European study found no differences in resting heart rate when comparing children and adolescents with CD with controls (Oldenhof et al, 2018). Also there is some evidence of associations between conduct problems and increased heart rate reactivity, as shown in a meta-analysis across 22 studies of children and adolescents (Lorber, 2004) which was not confirmed by other authors (Herpertz et al., 2007).

As for SC, Herpertz et al. (2007) found that child and adolescent males with CD displayed fewer resting SC fluctuations and fewer SC responses to emotional stimuli when compared to age-matched controls. Also, lower childhood resting SC levels have been found to predict antisocial behaviours during adolescence

on a longitudinal study by Van Bokhoven et al. (2005a). Evidence of low levels of SC and EDA (at baseline/after stimuli) in children and adolescents with CD/DBD are probably associated with CU traits and have also emerged from other studies (Herpertz et al., 2005; Lorber, 2004; Van Bokhoven et al., 2005a; Van Goozen et al., 2000).

1.1.6 Hypothalamic–pituitary–adrenal axis and CD

The hypothalamic–pituitary–adrenal (HPA) axis has often been implicated as one of the neurobiological bases of CD. Many studies have reported anomalies in cortisol levels in subject with CD, but, whilst evidence for basal and day cortisol profiles are heterogeneous, more consistent evidence are described for cortisol hyporeactivity to stress (Fairchild et al., 2019).

Fairchild et al. (2008) found significant difference between CD and controls on evening basal cortisol levels but not on morning basal cortisol levels; they also but found a significantly lower cortisol reactivity to stress in CD subjects.

Compared to controls, levels of cortisol are substantially reduced among adolescents with CD (Oosterlaan et al., 2005; Pajer et al, 2001; Shoal et al., 2003; van de Weil et al., 2004; Vanyukov et al., 1993). Pajer et al. (2001) studied plasma cortisol levels among adolescent girls aged 15–17 years: diminished morning cortisol levels were more strongly associated with antisocial girls, especially with those who did not have any other psychiatric disorders, compared to age-matched controls. Vanyukov et al. (1993) found a negative association between salivary cortisol levels and parent and self-reports of CD symptoms among pre-adolescent boys between 10 and 12 years of age. Oosterlaan et al. (2005) found a similar negative relationship between salivary cortisol levels and teacher-reported CD symptoms within a sample of children aged 6–12 years old. These researchers also found that low cortisol levels were more strongly related to aggressive CD symptoms, compared to non-aggressive CD symptoms. A longitudinal study on a community sample (Salis et al., 2016) found that concurrent HPA functioning is not significantly related to externalizing behaviour (assessed by using CBCL questionnaires) at ages 6 or 9; however,

more blunted cortisol rhythms at age 6 (less change across the day from morning to evening) predicted a greater increase in externalizing behaviour between age 6 and age 9 than did steeper cortisol rhythms: this association was driven by conduct problems and aggressive behaviour, rather than attention problems. Shoal et al. (2003) indexed resting salivary cortisol levels among pre-adolescent boys 10–12 years old, and subsequently compared the cortisol levels to personality and behavioural traits measured at 15–17 years of age. Atypically low levels of cortisol during pre-adolescence were associated with more aggression, less harm avoidance, and less self-control during mid adolescence. Based on these studies, many researchers believe that atypical cortisol levels represent one of the neurobiological bases for the extreme aggression that is often observed among children and adolescents with CD.

Some researchers have reported contradictory findings and substantial number of studies suggest a lack of relationship between CD and cortisol (Azar et al., 2004; Kruesi, et al., 1989; Scerbo & Kolko, 1994; van Goozen et al., 2000), with two studies reporting a positive association (McBurnett et al., 2005; Van Bokhoven, van Goozen et al., 2005b).

These conflicting findings may reflect the heterogeneity of CD severity and symptoms within study samples.

Van de Weil et al. (2004) found that cortisol levels were both relatively low and relatively high among children with disruptive behaviour disorders. The children who exhibited relatively low cortisol levels reported significantly more serious behaviour and conduct problems than children with relatively high cortisol levels. Within studies that did not separate children with CD into severity-based groups, the aggregation of cortisol levels across the sample may have hidden significant relationships. Differential findings regarding the relationship between cortisol levels and CD may also be due to different techniques used to measure cortical assays (e.g., salivary versus blood samples) and challenges in the timing of cortisol assays.

Lopez-Duran et al. (2009) analysed pre-stress and post-stress salivary cortisol levels in 7 years old children and found that an overactive HPA-axis response to stress was associated with reactive aggression, while not associated with

proactive aggression; subjects with proactive aggression showed a HPA-axis profile equivalent to that of non-aggressive children; also pre-stress cortisol levels were unrelated to both aggression subtypes.

Conflicting findings may also reflect comorbidity within the samples of individuals with CD. Potentially comorbid mental health disorders such as post-traumatic stress disorder (PTSD) and depression may be implicated (Kessler et al.,1995; Wolff & Ollendick, 2006).

As well as for autonomic parameters, the potential link between reduced cortisol levels and CD also supports an emotion dysregulation theory whereby reduced cortisol may reflect a lack of self-control, which results in more impulsiveness and carelessness (i.e., a lack of emotion regulation) and the aggressive behaviours associated with these traits (Shoal et al., 2003).

1.1.7 Comorbidity

Comorbidity is extremely common in children with CD. ADHD and ODD, which can represent previous conditions, are commonly diagnosed as comorbid conditions; other comorbid disorders are anxiety and depression, besides, in adolescence, substance use disorders (APA, 2013; Drabick et al., 2006; Levy et al., 2005).

Concurrent ADHD with or without other neurodevelopmental difficulties (such as reading and intellectual disabilities) is often present in childhood-onset subtype who also present earlier onset and more severe and persistent symptoms (Fairchild et al., 2019).

Anxiety or mood disorder symptoms are more frequent in individuals with CD with low CU traits (Frick and White, 2008; Frick et al., 2014b). Moreover, CD in childhood or adolescence could represent a risk for later depressive disorder in adulthood as showed by a prospective cohort study which reported that about 43% of adults with depression had a CD in childhood or adolescence, with no significant gender difference, but with an higher risk for subjects presenting early-onset persistent conduct problems (Stringaris et al. 2014).

Also, recently, a wide retrospective study found that CD represents a risk factor for psychosis (Rikinkumar et al., 2018).

1.1.8 Development, course and prognosis

The onset of CD may occur early, during preschool age, but diagnosis usually arrives later, by early/middle adolescence, when the first significant symptoms appear (or are more evident). Often a diagnosis of ODD precedes CD onset.

The course of CD is variable (APA, 2013): in most of subjects CD remits by adulthood. The childhood-onset type is the one which is thought to predicts a worse prognosis and an increased risk of criminal behaviour, persistent conduct disorder or antisocial personality disorder and substance-related disorders in adulthood. A diagnosis of CD is strongly related with poor educational performance (or occupational outcomes) and often leads to social isolation and increased contact with the criminal justice system in adolescence as well as in adulthood. Also, individuals with conduct disorder are at risk for later psychiatric disorders as adults.

As described above, individuals with CD with limited prosocial emotions, who are more likely to have childhood-onset type, tend to present a more severe disorder. CU traits seems to be relatively stable across childhood and adolescence (Frick and White 2008) with stability coefficients in the range of 0.5–0.7 among children followed over a period of 4–9 years (Frick et al., 2014a). They also often persist into adulthood (Lynam et al., 2007; Burke et al., 2007). CD with CU traits is thought to be associated with a poorer outcome than CD without (Frick and Dickens, 2006) especially when the problem behaviours start before the age of 10 years (Moffitt, 1993). They tend to be associated with more severe delinquency or aggression (Frick & Dickens, 2006) and stable pattern of antisocial behaviour (Herpers et al, 2012). A study exploring developmental trajectories of CU traits and conduct problems during childhood on a large sample from the Twins Early Development Study (N = 9578, aged 7–12), found that children with high or increasing levels of CU traits and concomitant high levels of conduct problems presented the most negative

outcomes at 12 years (including hyperactivity, peer problems, emotional problems), concluding that this population should be prioritized for targeted intervention (Fontaine et al., 2011).

Over the past few years, the limited prosocial emotions expressed by a significant percentage of adolescents with CD have been extensively investigated: the neurobiology of the CU traits and their interference with socialization and with the available therapeutic intervention has been established (Spain, 2004, Hawes et al, 2005, Waschbush et al., 2007; Blair 2013a) and thus indicate a form of CD that is more refractory to treatment and has a worse long-term prognosis (Frick and White, 2008; Scheepers et al., 2011; American Psychiatric Association, 2013). For this reason it is important to recognize and identify them as early in life as possible.

Over the last 20 to 30 years, specific pathways associated with the emergence and continuity of CD over time have been heavily investigated. A seminal article published by Moffit in 1993 proposed that two groups of patients can be differentiated by the courses, correlates and causes of their antisocial behaviour: (1) a life-course persistent (LCP) group with stable high levels of aggression and antisocial behaviour starting in childhood and continuing into adulthood, and (2) an adolescence-limited (AL) group of patients, whose antisocial behaviours are primarily non-aggressive, and who adopt pro-social roles and engage in more mature decision-making during the transition into adulthood. In Moffitt's taxonomy, early CD was related to neuropsychological deficits (i.e. deficit in inhibitory control, poor verbal abilities), leading to difficulties managing peer conflicts, regulating emotions and controlling impulses: no neuropsychological impairments were reported in the AL group. LCP was, therefore, considered the neuro-development disorder deriving from the interaction between individual vulnerability and environmental adversities, whereas the AL was considered to be more a social mimicry of deviant peers than a true neurobiological disorder.

in the last decades, many studies, by Moffitt's group and others, have challenged this two-category taxonomy: a childhood-limited trajectory has been characterized as a frequent form of disruptive behaviour (Odgers et al., 2007;

Odgers et al., 2008; Kretschemer et al., 2014) and an adolescent persistent pathway has been observed in girls (who rarely show a childhood-onset presentation) as well as in boys. Moreover, a significant impairment in neuropsychological functioning (i.e. facial emotion recognition measured by fMRI) was observed in adolescent patients with both childhood and adolescent onset (Passamonti et al., 2010; Fairchild et al., 2013).

Kretschemer et al. (2014), by analysing data from a longitudinal study, described four trajectories as low, childhood-limited (CL), adolescent-onset (AO) and early-onset persistent (EOP). Subjects with EOP conduct problems were at greater risk for almost all forms of later problems (including criminal involvement, substance use, risky sexual behaviour, gambling, anxiety, depression). Subjects with AO conduct problems consumed more tobacco and illegal drugs and engaged more often in risky sexual behaviour than individuals without childhood conduct problems.

A review by Fairchild et al. (2013) proposes that the differences between LCP and adolescent-onset forms of antisocial behaviour appear to be quantitative rather than qualitative and that adolescent-onset antisocial behaviour may also be a neurodevelopmental disorder, often leading to significant impairment in adult life. In other words, these two forms of antisocial behaviour differ in degree rather than in kind. Furthermore, structural and functional MRI studies suggest that the neural correlates of these two developmental subtypes of CD are more similar than they are different (Fairchild et al, 2011; Passamonti et al, 2010). Prospective longitudinal MRI studies that start in childhood age are required to more fully examine the neural correlates of these developmental subtypes of CD and improve our understanding of the validity of this distinction.

1.2 OPPOSITIONAL DEFIANT DISORDER

Oppositional Defiant Disorder (ODD) is another disorder often accompanied by aggressive behaviour, included in the diagnostic group of the Disruptive, Impulse—Control and Conduct Disorders described within the DSM 5. In ICD

10 it was classified as a subtype of Conduct Disorder, while in ICD 11 it is classified within the Disruptive behaviour or dissocial disorder (where Conduct Disorder is included as well).

Oppositional defiant disorder (ODD) is diagnosed if a child does not meet the criteria for CD, especially extreme physical aggression, but does exhibit a pattern of negative, hostile, and defiant behaviours for at least six months (Davison et al., 2005). Children diagnosed with ODD often lose their temper, argue with adults, refuse to comply with adult requests, and deliberately attempt to annoy others.

1.2.1 Definition and diagnostic criteria

According to DSM-5, ODD is defined as a frequent and persistent pattern of angry/irritable mood, argumentative/defiant behaviour, or vindictiveness lasting at least 6 months. The diagnosis of ODD requires the presence of at least 4 symptoms from any of the following categories; also, symptoms need to be exhibited during interaction with at least one individual who is not a sibling.

- *Angry/Irritable Mood*: often loses temper; is often touchy or easily annoyed; is often angry and resentful.
- *Argumentative/Defiant Behaviour*: often argues with authority figures or, for children and adolescents, with adults; often actively defies or refuses to comply with requests from authority figures or with rules; often deliberately annoys others; often blames others for his or her mistakes or misbehaviour.
- *Vindictiveness*: has been spiteful or vindictive at least twice within the past 6 months.

In order to formulate the diagnosis of ODD, frequency and intensity of the behaviours have to be outside a range that is normative for the individual's age, developmental level, gender, and culture. Also, behavioural symptoms must distress in the individual or others in the immediate context or impact negatively on social, educational, occupational, or other important areas of functioning.

DSM-5 defines three levels of severity (mild, moderate, severe) considering if symptoms are confined to one, two or more settings.

Subjects with ODD can present behavioural symptoms without mood symptoms. While in more severe cases the symptoms of the disorder are pervasive and affect multiple settings, mild ODD can be confined to one setting, which is most frequently the home.

1.2.2 Epidemiology

The rate of oppositional defiant disorder may vary depending on the age and gender of the child. The disorder appears to be slightly more prevalent in males than in females prior to adolescence (Loeber et al, 2000), but this male predominance is not consistently found in samples of adolescents or adults.

The meta-analysis published by Polanczyk et al. (2015) includes 28 studies reporting data on ODD and estimates a worldwide prevalence of ODD, 3.6% (Polanczyk et al., 2015). A previous systematic review found that the average prevalence estimate of ODD is around 3.3% across multiple cultures (Canino et al., 2010).

1.2.3 Aetiology

Aetiology of ODD can be derived by the combination of various factors (Burke et al., 2002): many of these are linked to CD aetiology too, suggesting that they can not be considered diagnostic or specific for ODD.

Among the biological and physiological, parents nicotine use (Tiesler and Heinrich, 2014) and pre-and perinatal complications (Speltz at al, 1998) are linked to ODD; abnormalities in the pre-frontal cortex and amygdala are also found (Matthys et al., 2013) and there is some evidence for genetic factors (Burke et al., 2002; Waldman et al., 2018; Mikolajewski et al., 2019). ODD is also correlated to environmental, such as insecure attachment, inconsistent or

neglectful educational practices, and social factors, such as peer rejection and community violence (Connor, 2002).

There is also some evidence (even if small than evidence for CD) of abnormalities in Autonomic Nervous System functioning and in Hypothalamic–Pituitary–Adrenal axis functioning. Van Goozen et al. (1998) investigated HR functioning at rest and during provocation among 8–11 year old boys diagnosed with ODD, and compared them to age-matched controls. HR was significantly lower at baseline and significantly higher during provocation and frustration conditions within the group of children with conduct problems. Authors also investigated cortisol levels among pre-adolescent boys between 8 and 11 years old, comparing boys with ODD and age-matched controls. The ODD group displayed a negative correlation between baseline cortisol levels and clinical measures of antisocial behaviour.

Deficit of “hot” and “cold” executive functions have been detected (Mikolajewski et al., 2019), such as deficits in inhibitory control (Lipszyc and Schachar, 2010), in working memory and deficits in emotion recognition (Rhodes et al., 2012; Matthys et al., 2012; Noordermeer et al., 2015).

1.2.4 Comorbidity

Comorbidity with ADHD o CD is common in children with ODD. CD can present as a comorbid condition or occur later as an evolution of the ODD itself to a more severe disorder. Some authors highlight that a comorbid ODD can be found in high percentages (up to 60 %) in ADHD (Connor and Doerfler, 2008). Other authors report that more than 60 % of ODD children do not present ADHD (Angold and Costello, 1996) and that only 10 % may develop a CD (Lavigne et al, 2001).

Anxiety, depressive disorders and substance use disorders can also present as comorbid disorders.

1.2.5 Development, course and prognosis

The onset of ODD usually occurs in children by late preschool or early elementary school (Canino et al., 2010).
Angry and irritable mood symptoms are linked to higher risk of comorbid anxiety or mood disorders, whereas behavioural symptoms predict higher risk of ADHD or conduct disorder (Waldman et al., 2018; Rowe et al, 2010; Stringaris et al., 2009). ODD often (but not always) precedes the development of CD, the childhood-onset type.

Comorbid ADHD or CD predict an higher risk of additional comorbid mood disorders and of substance use and abuse (Connor et al., 2010a), but is unclear if the association with higher rate of substance use disorders is mediated by the comorbidity with conduct disorder.

Also, children and adolescents with oppositional defiant disorder are at increased risk for a number of problems in adjustment as adults, including antisocial behaviour, impulse-control problems, substance abuse, anxiety, and depression.

1.3 TREATMENT FOR CONDUCT DISORDERS AND AGGRESSION

The best evidenced approaches to treatment are multimodal and encompass both pharmacological and psychosocial approaches, as well as acknowledging the role of caregivers, family, school, peers, and society at large (Pappadopulos et al., 2003; NCCMH, 2009).

Specific guidelines for the management of antisocial behaviour and conduct disorders in children and young people have been developed by the National Institute for Health and Care Excellence (NICE) in the UK (last update in 2017). Within these guidelines, recommendations include psychosocial interventions with pharmacological interventions.

1.3.1 Non pharmacological interventions

According to NICE guidelines, psychosocial interventions should be recommended for children and adolescent with a diagnosis of ODD or CD, or for children and adolescent in contact with the criminal justice system for antisocial behaviour. They should include Parent Training, Child Training, Foster carer training and child-focused social and cognitive problem-solving programmes.

Considering the heterogeneity of the risk factors and the variability of clinical phenotypes, some important information, such as social environment, family structure and settings in which the symptoms manifest themselves most severely, should be evaluated before staring therapeutic interventions.

In recent decades a series of psychosocial interventions (Lochman et al, 2011), including interventions on parents, such as the Positive Parenting Program (Graaf et al., 1998), and direct interventions on the child such as cognitive behavioural therapy (CBT), and interventions on parents, children (and, in some cases, on teachers) as the Coping Power Program (Lochman and Wells, 2002, 2004).

Most of these programs are aimed at preventing and treating behavioural problems, suggesting appropriate modalities of problem-solving, improving recognition of emotions and anger management, and favouring the acquisition of social skills and cognitive and emotional self-control.

1.3.2 Pharmacological interventions

Medication treatments are not usually considered as first line of treatments for CD or ODD. They are generally recommended to be reserved for those patients who do not respond to other interventions or who show increasing levels of aggressive and violent behaviours.

According to NICE guidelines, in fact, pharmacological interventions should not be offered for the routine management of behavioural problems. Treatment for

an ADHD comorbid condition should be considered (methylphenidate or atomoxetine); this could led to reduction in behavioural symptoms (De la Cruz et al, 2015; Dell'Agnello et al, 2009; Shih et al., 2018). Treatment with Risperidone, a D2 antagonist, should be considered for the short-term management of severely aggressive behaviour in young people with a conduct disorder who have problems with explosive anger and severe emotional dysregulation and who have not responded to psychosocial interventions. To date Risperidone has the indication only for short-term treatment of aggressive behaviour in patients older than 5 years old with conduct disorder and sub-average IQ.

Even though there are no medications currently licensed for the treatment of CD in normal IQ youth, medications are increasingly being used to treat CD and aggression and it has been commented on many times that the increase in use has outstripped the available evidence (Coghill and Smith, 2010). The choice of which medication to use is made mainly on the presence of comorbidity (which significantly complicates the clinical presentation and can make paediatric aggression within CD particularly difficult to manage), the presence of aggression and the adverse effect profile.

Despite the reality that use has out-paced the evidence, there is now a growing literature which suggests that there are indeed several medications that are at least somewhat effective in the treatment of aggression. The evidence to support these practices is still limited by inadequate measurement of aggression, small samples sizes and varying diagnoses. The effectiveness of medication treatments in real world clinical settings remains unclear and relatively unexplored (Schur et al., 2003).

The pharmacological options currently considered for the treatment of CD include off-label medications: psychostimulants (methylphenidate, dexamphetamine, lisdexamfetamine); antipsychotics (risperidone, aripiprazole, quetiapine, and haloperidol); mood stabilizers (lithium, divalproate/divalproex sodium, and carbamazepine) and other several agents including α2 receptor agonists and β-blockers (Pappadopulos et al., 2006; Barzman and Findling, 2008).

Of these, as will be discussed in the next review and meta-analysis chapter, Methylphenidate and Risperidone show the largest effects on aggression in randomized controlled trials; other antipsychotics showed clinical efficacy on CD but this evidence is mainly revealed by open label trials (Balia et al., 2018). There is some low quality evidence to support a small effect of mood stabilizers and other agents. Also, no sufficient data explore the relations between CU traits and medication effects. Evidence of efficacy of medication for the treatment of aggression in conduct disorders will be deeply discussed in the next chapter.

1.4 THE MATRICS PROJECT

Conduct Disorders are heterogeneous paediatric disorders characterized by severe aggression. Our understanding of the neurobiology to subtype aggression is limited.

With the aim of implementing the knowledge of behavioural, neurochemical, (epi)-genetic and neuroanatomical neuropsychological correlates of aggression in the CD and of identifying new targets for potential pharmacological therapies for the treatment of aggression, the European Commission, through the FP7 program -THEME HEALTH-2013-INNOVATION-1 [Paediatric conduct disorders characterised by aggressive traits and/or social impairment: from preclinical research to treatment], funded the European **MATRICS** project (**Multidisciplinary Approaches to Translational Research In Conduct Syndromes;** *http://matrics-project.eu*).

MATRICS is a multidisciplinary consortium (see Figure 2) of academic partners that focuses on the subtyping of aggression both within CD and the broader cross-disorder trait of aggression. MATRICS was designed with the purpose of testing the hypothesis that reactive and instrumental aggression result from aberrant autonomic reactivity coupled to the differential impairment of three basic neural functions: 1) regulation of control mechanisms of aggression, 2) emotional value rating of others, and 3) empathy and moral decision making.

Within MATRICS the same psychological tasks have been employed to assess these different domains both in animal aggression models and in human CD samples, concurrent with the assessment of neural, neurochemical, (epi)-genetic and autonomic nervous system markers. These data will be integrated with matching expression profiling from neurons derived from CD Induced pluripotent stem cells (IPSCs). MATRICS also examines how environmental risks, whether or not they interact with genetic factors, are translated in epigenetic and neural changes. MATRICS will data-mine (by using data from other European projects) existing large integrated imaging-genetics cohorts and prospective cohorts with follow-up into adulthood and the (epi)genetic profiling of an existing CD cohort, and collect a large new CD cohort and controls for collection of MRI, (epi)-genetic, biochemical and environmental measures. Through the use of machine learning tools multi-source and multi-level data will be integrated, to generate predictive algorithms of persistent aggression into adulthood. MATRICS includes also the development of novel animal models and neuro/biofeedback studies in high-risk and CD patients to add useful information to better understand the disorder.

The identification of new potentially ‘druggable’ targets and the conduction of pilot medication studies in CD patients also has been an important part of the project. This has been done after a deep data-mining of the evidence already published on effects of medication on aggression in CD, which led to identify drugs to be studied for their effects on neuropsychological and physiological features within proof-of-concept clinical studies. These tasks were the main tasks of Work Package 6 (WP6), the work package led by the University of Cagliari.

The next chapters illustrates (I) the review of evidence on efficacy of medication on aggression in CD and (II) the preliminary results from the clinical study on neuropsychological profiles and on the effects of single doses of four medications known to be effective in reducing aggression.

2 SYSTEMATIC REVIEW AND META-ANALYSIS ON PHARMACOLOGICAL INTERVENTIONS FOR CD

2.1 OBJECTIVES

The main objective of this work has been to systematically review and, where data are adequate, conduct meta-analyses on the efficacy of medication on aggression in children and adolescent with CD considering the impact of CU traits and possible different effects in the various subtypes of aggression.

2.2 METHODS

Studies were included if they met the criteria discussed in the following subsections.

2.2.1 Types of participants

Inclusion criteria: children (≥5 and <12 years), adolescents (≥12 and <18 years) both in-patients and out-patients who satisfied DSM criteria (American Psychiatric Association, 2013 or previous) or ICD criteria (WHO, 2007 or previous) for a primary or a secondary diagnosis of CD with no restriction on presence of comorbid disorders, gender, learning disability or socio-economic status of participants.

Exclusion criteria: studies including less than 50% of subjects with CD were not included in the *quantitative* analysis if data of CD sample were not extractable separately, but were included as appropriate for a *qualitative* analysis.

2.2.2 Types of interventions

Studies were included if they assessed any of the following drugs compared with placebo: methylphenidate, dexamphetamine, lisdexamfetamine, pemoline, atomoxetine, guanfacine, clonidine, risperidone, paliperidone, haloperidol, quetiapine, aripiprazole, olanzapine, lithium, divalproate/divalproex, carbamazepine, pindolol, propanolol.

Studies were included if they assessed efficacy of drugs both in the short term (outcomes up to 12 weeks) and in the medium term (up to 26 weeks). When available, studies assessing the efficacy of medication in the long term (≥1 year) were also considered.

Studies that allowed concomitant medication were included if the concomitant drug was given in a stable dose and for a specific comorbidity (e.g. methylphenidate as treatment for ADHD, divalproate for epilepsy, etc.).

Studies assessing one single dose of drug were excluded from the analysis but considered, when appropriate for the discussion.

2.2.3 Types of studies

As for the type of participants, for *quantitative* analysis only randomized double-blind placebo-controlled (RDBPC) trials were included. However, open-label prospective longitudinal studies, double blinded studies without a placebo arm and retrospective chart reviews were also collected for those medications for which double blind randomized trials were missing, in order to be discussed in the *qualitative* analysis.

2.2.4 Outcome measures

The primary outcome measure was the pre-post treatment change or means at end-point as assessed by ratings on the most frequently used scales, in order of

preference:

- specific scales/questionnaires for aggression: OAS (Overt Aggression Scale; Yudofsky et al., 1986), MOAS (Modified Overt Aggression Scale; Kay et al., 1988), CBCL (“aggressive behaviour” subscale; Achenbach, 1991), or other aggression scales, for example IOWA (Loney and Milich, 1982; Loney, 1987; Pelham et al., 1989a,b) and CAS (Halperin et al., 2002; Halperin et al., 2003);

- scales for conduct problems: Nisonger NCBRF (Aman et al., 1996, 2008), CBCL (“conduct problems” scale), Conners Rating Scale – CRS (Conners, 1989), Aberrant Behaviour Checklist irritability scale (ABC; Aman et al., 1985a,b), or other behaviour disorders scales;

- scales for CU traits: ICU (Inventory of Callous-Unemotional traits; Essau et al., 2006), or other CU scales.

Measures of global functioning, using ratings based on the following scales were also collected.

- C-GAS (Children’s Global Assessment Scale; Shaffer et al., 1983);

- CGI severity (Clinical Global Impressions; Guy, 1976);

- WHODAS (World Health Organization Disability Assessment Schedule; WHO, 2014).

2.2.5 Search strategy

A search for the most relevant published reviews and meta-analyses on the topic were performed (Connor et al., 2002; Pappadopulos et al., 2006; Barzman and Findling, 2008; Amaladoss et al., 2010; Huband et al., 2010; Loy et al., 2012; Pringsheim et al., 2015a,b). In a second search, individual trials published up to January 2016 and not included in the previous reviews, were considered by using the following research sources (PubMed, MEDLINE via Ovid SP, EMBASE via Ovid SP, PsycINFO via Ovid SP).

The search terms were: “CD”, “conduct disorder”, “aggression”, “bullying”, “violence”, “disruptive, impulse control, and conduct disorders”, “irritable mood”, “antisocial personality disorder”, “juvenile delinquency”, “C-U traits”, “ callous and unemotional”, “antipsychotics”, “dopamine antagonists”, “phenothiazines”, “butyrophenones”, “risperidone”, “Paliperidone Palmitate”, “Haloperidol”, “Quetiapine Fumarate”, “Aripiprazole”, “Olanzapine”, “stimulants”, “Amphetamines”, “Mph”, “Methylphenidate”, “Dextroamphetamine”, “Lisdexamfetamine Dimesylate”, “Pemoline”, Atomoxetine”, “Atomoxetine Hydrochloride”, “Guanfacine”, “Clonidine”, “anticonvulsants”, “mood stabilizer”, “Lithium”, “Lithium Carbonate”, “Valproic Acid”, “Divalproate”, “Divalproex”, “Carbamazepine”, “Pindolol”, “Propranolol”.

Search terms and syntax were adapted as required for each database.

2.2.6 Identification and selection of studies

Articles were screened by two of the authors on the basis of titles and abstracts and double coded. Assessment of articles for final inclusion was based on full text revision. Disagreements were adjudicated by a third author.

2.2.7 Data extraction

Sample information and outcome data of the included trials were entered into RevMan version 5.3 (http://ims.cochrane.org/revman). This provided a systematic record of study features.

Studies identified with electronic and manual searches have been listed with citation, titles and abstracts from all databases in Endnote. From each paper the following data have been extracted and inputted into an Excel file:

- Study citation, year of publication, setting, design, sample size, diagnostic criteria, inclusion and exclusion criteria;
- Characteristics of study participants including: mean and/or range of age,

presence and type of co-morbid mental health conditions, number randomised into each group;

- Characteristics of interventions including mean and maximum doses (when available) of the study drug, and presence of concomitant medications.

2.2.8 Data analysis

The pre-treatment – post-treatment within group design was used to analyse medication effects on measures of aggression. Individual effect sizes (ES), expressed in the mean difference (MD) or the standard mean difference (SMD), were calculated by using Rev Manager 5.3.

An ES of 0.2 represents a small effect, while an ES of 0.5 or 0.8 indicate respectively medium and large effects (Cohen, 1977).

Given the heterogeneity of sample characteristics and measures of outcome, a random effects model has been used, a priori. Heterogeneity has been assessed by using I^2 test.

A p-value of <0.05 was considered significant.

2.3 RESULTS

Tables 1–4 summarise the main information of the studies selected for inclusion through the systematic review. Considering the paucity of trials which include only CD subjects or a percentage of CD higher than 50% within the total sample, those with lower percentage of CD were considered too, but only for the purpose of a qualitative analysis. Percentage of CD subjects has been reported for each study, if this data was available.

Results are described according to the class of medication (antipsychotics, stimulants, mood stabilizers). Main outcome measures have been classified as

measures of aggression (such as MOAS/OAS, IOWA) and measures of conduct problems (such as Nisonger NCBRF, CRS).

For each class of medication some of the most important published reviews and meta-analyses based on RCT data have been summarized. The most relevant studies with other designs (i.e., open label trials, longitudinal studies, double blinded trials without a placebo arm and observational studies) have also been described briefly to allow for a wider discussion of the evidence.

Moreover, for studies including at least 50% of participants with a diagnosis of CD a meta-analysis were performed and the effect sizes for main outcome measures were calculated where the required data were available (Tables 5–8).

2.3.1 Stimulants

Stimulant medications are one of the most studied class of medication for aggression. Their efficacy has been extensively demonstrated in managing the core ADHD symptoms both in the short and the long term (Brown et al., 2005; Greenhill et al., 1999), as well as in ameliorating comorbid disruptive behaviour (Connor et al., 2002) including symptoms like aggression and irritability.

Previous systematic reviews and meta-analyses concluded that stimulants exert a medium to large effect on paediatric aggression in ADHD children in the context of a frequent comorbidity with ODD and/or CD (Connor et al., 2002; Pappadopulos et al., 2006; Pringsheim et al., 2015a).

Connor et al. (2002) examined the effect of stimulants on covert and overt aggression in a total of 683 children (mean age 9.7, range 7.7–14.4) with a diagnosis of ADHD and comorbid ODD/CD (75% of subjects) through meta-analysis including 28 RCT (21 on MPH, 5 on amphetamine “AMP” and 2 on pemoline “PEM”). The average dose of MPH was 22.18 mg/day, the average dose of AMP was 23.74, while in the two studies examining PEM the mean dosage was 145.15 mg/day. The mean duration of treatment was 13 days. Overt aggression and covert aggression were looked at separately wherever possible in the analysis. Overt aggression-related behaviours were defined as

“aggression resulting in a direct confrontation with the environment” (physical assault, verbal threats, oppositional and defiant behaviour, conduct problems, rage attacks, and irritability), whereas covert aggression-related behaviours were defined as “aggression that is furtive and hidden from the environment” (cheating, lying, stealing, and fire-setting). The overall weighted mean effect size was 0.84 for overt aggression and 0.69 for covert aggression in children with ADHD. Effect sizes based on overall ratings were comparable for studies of MPH (d = 0.80) and AMP (d = 0.83), and dose was not significantly associated with effect size. Stimulants resulted less effective for overt aggression in subjects with a comorbid diagnosis of CD.

The review of Pappadopulos et al. (2006) found that stimulants exert a medium to large effect on paediatric aggression with a mean effect size of 0.78. Data on the efficacy of stimulants for the reduction of impulsive aggression was mainly derived from clinical trials measuring aggression as a secondary outcome variable. This review included 18 RCTs of stimulants (16 on MPH, 1 combination of MPH and amphetamine mixed salts, and 1 combination of MPH, dextroamphetamine and pemoline) examining a total of 1057 subjects (average n = 55.6; 84.2% male; age = 9.1 years). Primary diagnoses included in the studies were ADHD (13), Autism (2), Mental Retardation (1), and Disruptive Behaviour Disorders (3), and all but 6 allowed for comorbid diagnoses of CD, ODD, or ADHD. The weighted average dose of MPH was about 0.93 mg/kg/day and there was evidence for higher methylphenidate doses to be linked to stronger effect sizes. The slightly lower effect size of 0.78 compared to the ES (0.84) found in the meta-analysis by Connor et al. (2002) on overt aggression (Connor et al., 2002), has been interpreted by Pappadopulos et al. (2006) to be due to the statistical influence of studies published after 2002. Pappadopulos meta-analysis, in fact, included the study of Aman et al. (2004) which had higher rates of discontinuation of treatment due to adverse effects that resulted in a modest overall effect size (0.52).

The systematic review and meta-analysis performed by Pringsheim et al. (2015a) is an update of the Connor et al. (2002) review. The authors included 12 papers published between 2002 and 2013 meeting the same inclusion criteria (i.e. placebo controlled randomized trials examining stimulant effects on

aggression related behaviours within the context of ADHD children and adolescents): of the identified studies 11 were on MPH both immediate release (IR) and long acting formulation, and 1 on lisdexamfetamine (LDX), including a total of 1681 participants. ODD or CD comorbidities were present in between 44% and 93% of subjects. As in Pappadopulos' review measures of conduct problems and aggression were included as secondary outcome in all studies and psychostimulants determined a significant benefit compared to placebo with an effect size of 0.84 (95% CI 0.59–1.10) on teachers' measures and 0.55 (95% CI 0.36–0.73) on parent-rated oppositional, behaviour, conduct problems, and aggression.

The characteristics of the most important trials included in the above mentioned reviews are summarized in Table 1.

Using an open label stimulant monotherapy optimization protocol Blader et al. (2010) concluded that among children whose aggressive behaviour develops in the context of ADHD and of ODD or CD, and who have had an incomplete response to stimulant treatment in routine clinical care, a systematic and well-monitored titration of stimulant monotherapy can result in clinically relevant reductions in the levels of aggression and avert the need for additional medications. Within the same protocol (Blader et al., 2013) the authors inferred that elevated baseline CU traits did not diminish the effectiveness of stimulant monotherapy in reducing aggressive behaviour, contrasting with previous findings of proactive aggression refractivity to treatment (Frick and White, 2008).

No high-quality studies investigating the efficacy of Dexamphetamine in aggressive children and adolescent with CD were identified.

One old study (Maletzky, 1974) examined the utility of Dexamphetamine in the treatment of delinquency in 28 adolescents. Dexamphetamine was effective when added to an ongoing psychotherapeutic regimen and its efficacy appeared to be correlated with a history or presence of hyperactive traits.

Pelham et al. investigated the efficacy of the long acting mixed amphetamine salts (Adderall, a racemic mixture of d-and l-amphetamine) compared to

methylphenidate, in a crossover placebo-controlled trial with seven treatment arms using different daily dosages (three MPH, three Adderall and one placebo) in 21 patients (aged 6–12 years) with a primary diagnosis of ADHD with or without ODD (N = 14) or CD (N = 5). No differences in aggression were reported between the two medications, but Adderall was more effective than methylphenidate on ADHD symptoms (Pelham et al., 1999).

Two studies investigated the effect of Pemoline on CD in adolescents (Riggs et al., 2004; Bostic et al., 2000). Despite being considered a stimulant, its effect appeared less strong than that observed for MPH (ES = 0.19). This may be explained by lower efficacy but may also have been affected by the choice of outcome measure (number of CD symptoms in the past thirty days and derived aggressive symptoms from parent's rating) and the age of the populations (subjects in the two PEM studies were older than subjects included in MPH studies).

2.3.2 Antipsychotics

Antipsychotics are increasingly used within clinical practice to manage aggression. Low doses of first generation antipsychotics (FGA) are effective for managing aggressive symptoms in children and adolescents (Campbell et al., 1984; Werry et al., 1976) however this comes at the cost of often worrisome side effects, and many argue that, whilst effective, as a class these drugs are unlikely to rep- resent optimal treatments for aggression. Atypical antipsychotics (second generation antipsychotics, SGA) have also been reported to be efficacious in the management of aggression (Schur et al., 2003; Pappadopulos et al., 2006; Loy et al., 2012; Pringsheim et al., 2015b). Literature highlights however that SGA are also often associated with significant advent events, especially weight gain, type II diabetes, and cardiac rhythm abnormalities (Schur et al., 2003), meaning that the safety profile of this class of drugs in this population still needs further investigation and certainly has to be taken into account when prescribing (Barzman and Findling, 2008; List and Barzman, 2011; Zuddas et al., 2011). However because of their safety profiles and lower rates for some serious adverse events (i.e. extrapyramidal symptoms)

compared to conventional antipsychotics (Connor et al., 2001; McConville and Sorter, 2004), SGA have largely replaced older antipsychotics in all patient groups, and clinicians tend to use them in preference to the typical antipsychotics, in those with CD and aggression (Campbell et al., 1997; Gillberg, 2000; Patel et al., 2002, 2005).

First-line SGAs include Risperidone, Olanzapine, Quetiapine, Aripiprazole.

Characteristics and main results of the most relevant trials on aggression are summarized in Table 2.

2.3.2.1 Risperidone

Risperidone is the most extensively studied antipsychotic for the treatment of aggression in children. Nonetheless, only one RCT investigating the efficacy of risperidone in a sample with >50% having a diagnosis of CD (Findling et al., 2000) was found. This study included 20 patients with aggressive CD (aged 6–14 years old, aver- age IQ). Patients with severe comorbid disorders were excluded; mean daily dose of risperidone was 0.028 mg/kg. Risperidone was superior to placebo on the Rating of Aggression Against People and/or Property Scale (RAAPP; Kemph et al., 1993), completed by the clinicians, while no significant difference was found using the parent rated CBCL-aggressive behaviour subscale.

Several risperidone trials have been conducted including mixed population with a Disruptive Behaviour Disorder (DBD, that is ADHD/ODD/CD/DBD not otherwise specified) or aggressive ADHD as a primary diagnosis with comorbidity including varying proportions of CD (less than 40% of the total sample), and several reviews and meta-analyses have investigated the efficacy of risperidone in these samples. The main characteristics of these studies are described in Table 2. Considering all the studies included in the published reviews that we have selected (Pappadopulos et al., 2006; Barzman and Findling, 2008; Zuddas et al., 2011; Loy et al., 2012; Table 2), sample sizes ranged from 13 to 335 (aged between 5 and 18 years). In four trials, the total number of participants was 25 or fewer (Findling et al., 2000; Buitelaar et al., 2001; Van Bellinghen and De Troch, 2001; Armenteros et al., 2007); three of

these were formally described as pilot studies (Findling et al., 2000; Van Bellinghen and De Troch, 2001; Armenteros et al., 2007). The other three trials had larger sample sizes, between 110 and 335 (Aman et al., 2002; Snyder et al., 2002; Reyes et al., 2006). All studies, except Armenteros', allowed the inclusion of participants with sub-average to borderline IQ (IQ 36–IQ 84). Mean dose of risperidone at endpoint ranged from 0.98 mg/day to 2.9 mg/day.

The first review to focus on the effects of risperidone on reducing aggression identified 9 RCTs that included a total of 875 subjects (average n = 97.2; 81.1% male; age = 9.2 years) with a range of primary diagnoses (CD, ODD, ADHD, DBD, Autism, PDD), reported a large overall effect size (weighted mean ES = 0.9; Pappadopulos et al., 2006).

Two more recently published reviews (Barzman and Findling, 2008; Zuddas et al., 2011) included only six randomized double blind studies of risperidone in child and adolescent samples (aged 5–17 years) with CD/DBDs and average IQ or sub average IQ (Findling et al., 2000; Buitelaar et al., 2001; Van Bellinghen and De Troch, 2001; Aman et al., 2002; Snyder et al., 2002; Reyes et al., 2006).

A Cochrane review on antipsychotics for disruptive behaviour disorders, published in 2012 (Loy et al., 2012), included one additional study (Armenteros et al., 2007), but excluded the Reyes study from the meta-analysis because they judged the design and objective of the trial to be markedly different from the other studies. In this review the authors calculated ES, for each study using aggression scale scores as the primary outcome measure, and performed two different meta-analyses on aggression. The first included three trials (combined n = 238): Aman et al., 2002 (moderate effect size of −0.61), Snyder et al., 2002 (large effect size of −0.72) and Van Bellinghen and De Troch, 2001 (large effect size of −1.26 but with large confidence intervals). Data from the ABC Irritability subscale reported a final mean difference score with risperidone treatment of 6.49 lower than that for placebo (95% CI [−8.79 to −4.19]). Authors state that the difference in scores of 6.49 points may be clinically significant, although this is borderline as other authors have considered a difference of at least 7 or 8 points in this scale as clinically significant (Owen et al., 2009; Hassiotis et al., 2009). The second meta-analysis was performed on data from two trials (n =

57), one with risperidone (Buitelaar et al., 2001: small effect size of −0.21 and a confidence interval overlap- ping the null value) and one with Quetiapine (Connor et al., 2008: small effect size of −0.13 and a confidence interval overlapping the null value); these studies used two different (but related) outcome measures for aggression (OAS-M and OAS, respectively). The effect estimate, obtained with the standardized mean difference, was non-significant (−0.18; 95% CI [−0.70 to 0.34]). In both these meta- analyses Armenteros' and Findling's studies were excluded because there were either no final or change scores on aggression presented (Armenteros'), or there were no outcome measure of aggression in common with the other studies (Findling's: ES calculated as a standardized mean difference with CBCL aggression subscale = −0.78). In summary, whilst the Cochrane review found limited evidence of efficacy for risperidone in reducing aggression and conduct problems in children and youths with DBD in the short term (four to 10 weeks) this was not overwhelming and was dependent on a small number of studies each of which had several important limitations.

Several studies suggest that risperidone may be helpful in augmenting the effects of psychostimulants in children with comorbid DBD and ADHD and sub-average IQ: efficacy for the risperidone remained significant regardless of combined use with the stimulants (Aman et al., 2002, 2004; Snyder et al., 2002). A modest effect of risperidone in combination with psychostimulants was also found in a small double-blind placebo-controlled study on treatment-resistant affective/impulsive aggression in children with a primary diagnosis of ADHD, comorbid DBD and average IQ (Armenteros et al., 2007). One recent additional study (the TOSCA study: Gadow et al., 2014; Aman et al., 2014; Farmer et al., 2015), a 6 week randomized trial, confirmed that the addition of Risperidone to stimulant treatment represented a good approach at reducing severity of parent-rated peer aggression ($p = 0.02$, Cohen's $d = 0.32$), improving social competencies and reducing impulsive aggression (ES = 0.29). This study will be better described in the paragraph at the end of the results section (CU modulation of medication efficacy on aggression).

Reyes et al. (2006) investigated the effect of long term risperidone maintenance in children and adolescents with CD (about 37% of the total sample), ODD or

DBD NOS (N=335; average or sub average IQ) in a placebo-controlled discontinuation study (six- week acute treatment open-label phase of risperidone, followed by six-week continuation treatment single-blind phase and then a six- months maintenance double-blind RCT). Authors concluded that patients who respond to initial treatment with risperidone would benefit from continuous treatment over the longer term. Effect size for the reduction of conduct problems was small, as calculated with NCBRF-CP using Hedges' g in Cochrane review for this study and (ES = −0.37), but no specific measure of aggression was reported.

2.3.2.2 Quetiapine

The only published randomized, double-blind, placebo- controlled study of Quetiapine, is a small 7-week study (N = 19; Quetiapine daily dose 200–600 mg; Connor et al., 2008). Although authors found that Quetiapine was effective in the treatment of adolescents with CD (with an ES = 2.3) as measured by significant change in the primary outcome measures (CGI-S and CGI-I), no differences were found on the parent-completed overt aggression scale (OAS), and the conduct problems subscale of the Conners' Parent Rating Scale (CPRS-CP). Specifically, the Cochrane review (Loy et al., 2012), reported small ES, calculated using Hedges' g: respectively −0.13 (OAS) and −0.14 (CPRS-CP), both with a confidence interval overlapping the null value.

Two open-label studies of Quetiapine in aggressive children, a very small 26-week open-label outpatient follow-up study (9 males, mean age 8.9 years; median Quetiapine dose at the end of the study: 150 mg/day, range 75–350) and a 8-week open-label outpatient trial (16 males, mean age 8.9 years; median Quetiapine dose at the end of the study: 150 mg/day, range 75–300) in aggressive children with CD suggested that Quetiapine might be a generally safe, well tolerated, and effective maintenance treatment for aggressive children with CD who initially respond to an acute therapeutic trial of quetiapine (Findling et al., 2006, 2007).

Another open-label study (Kronenberger et al., 2007) found that Quetiapine when added to methylphenidate was effective in reducing ADHD and

aggression in methylphenidate treatment-resistant adolescents with comorbid ADHD, CD/ODD, and aggression.

2.3.2.3 Aripiprazole

No randomized clinical trials of aripiprazole in CD children and adolescents have been identified. Several open label studies have reported a good tolerability and effectiveness for aripiprazole in children and adolescents with conduct disorder (Findling et al., 2009; Kuperman et al., 2011; Ercan et al., 2012). In particular, Aripiprazole was found to be well tolerated and effective in treating aggression in children and adolescents (N = 23; aged 6–17 years; daily dose: 1–15 mg adjusted for body weight) with conduct disorder in a small short 15-day open label study (Findling et al., 2009).

Kuperman et al. (2011) confirmed these data with a 6 weeks open label intent-to-treat design study, using a daily dose between 1 and 20 mg adjusted for body weight on an even smaller sample (N = 10), showing that Aripiprazole can reduce aggression categorized as physical aggression, verbal aggression, and aggression against objects and animals.

Ercan et al. (2012) investigated the efficacy of Aripiprazole in 20 patients (aged 6–16 years; mean daily dose: 8,55 mg; 2,5–10 mg/day) with ADHD and CD, concluding Aripiprazole can be well tolerated and effective in treating aggression in this clinical population.

2.3.2.4 Olanzapine

No randomized clinical trials were available for Olanzapine in CD population. Only one open-label study using Olanzapine in combination with Atomoxetine for the treatment of aggression was found. Holzer et al. (2013) conducted a 10 weeks trial to assess this combination to treat ADHD and comorbid disruptive behaviours. This poly-therapy was found to be effective in reducing ADHD symptoms and overt aggressive behaviour in a 10 week treatment period. Both medications were generally well tolerated, but the treatment was associated with significant weight gain. Within a retrospective study, exploring the efficacy and tolerability of olanzapine in 23 adolescents with severe CD who had not

satisfactorily responded to non-pharmacological intervention or mood stabilizers (lithium and/or valproate), olanzapine was associated with a significant improvement at the last available observation (6–12 month follow-up) in the MOAS; ($p < 0.001$) and the Children's Global Assessment Scale (CGAS; $P < 0.001$) scores; predictor of a better response was an impulsive-affective versus controlled-predatory type of aggression (Masi et al., 2006).

2.3.2.5 Paliperidone

No randomized controlled trials were identified for Paliperidone in CD population. Only one open-label trial investigated the efficacy of treatment with Paliperidone extended-release in children with behaviour disorders (Fernández-Mayoralas et al., 2012). This was a 16-week open-label study in 18 patients (mean age = 13.4 years; daily dose: 3 mg), previously unsuccessfully treated with risperidone, with severe and excessive irritability in the context of generalized developmental disorders or ADHD. Paliperidone was found to reduce severity of aggressive behaviour, as assessed by the Overt Aggression Scale, and showed to be safe and well tolerated.

2.3.2.6 Typical antipsychotics

Few studies have reported on the efficacy of typical antipsychotics in aggressive children with CD. Two randomized trials suggested that haloperidol (Campbell et al., 1984), molindone and thioridazine (Greenhill et al., 1985) can be effective in reducing aggression and CD symptoms in children between the ages of 5–12. Another study of children with ADHD or CD with sub-average IQs found thioridazine to be less effective than methylphenidate but better than placebo on teacher-rated measures of conduct problems and hyperactivity; similar results were not confirmed on parent-rated scales (Aman et al., 1991).

2.3.3 Mood stabilizers

Mood stabilizers have also been shown to reduce the aggression associated with CD. Those studied include Lithium, Divalproate/Divalproex sodium, and

Carbamazepine, all of which have multiple mechanisms of action. A review of six randomized controlled trials (RCTs) (5 lithium, 1 carbamazepine) reported a moderate average weighted effect size (0.4) in reducing aggressive symptoms (Pappadopulos et al., 2006).

Characteristics of the most important trials selected are summarized in Tables 3 and 4.

2.3.3.1 Lithium

Lithium is a mood stabilizer that has been shown to be efficacious in decreasing adolescent aggression in the context of ADHD (Pappadopulos et al., 2006; Connor et al., 2006; List and Barzman, 2011; Steiner et al., 2003a,b) and DBD (Amaladoss et al., 2010).

Several studies have shown that lithium treatment can decrease fighting, bullying, and temper outbursts in severely aggressive youth with CD, but contrasting results have also been reported (Rifkin et al., 1997; Campbell et al., 1984, 1995; Carlson et al., 1992; Malone et al., 2000). Rifkin et al. (1997) found no significant differences between lithium carbonate and placebo when examining the efficacy of lithium carbonate for the treatment of CD in 33 inpatients aged 12–17 years using a 2 weeks DBPLC trial. Campbell et al. (1984) conducted a 6-week DBPLC study of 61 hospitalized patients (aged 5.2–12.9), all diagnosed with CD, aggressive type. Patients were randomly assigned to lithium, haloperidol, or placebo for the following 4 weeks. Both haloperidol (optimal dosages ranged from 1.0 to 6.0mg/day) and lithium carbonate (optimal dosage: 500–2000 mg/day; mean serum level: 0.993mEq/L) were found to be significantly superior to placebo in decreasing aggressive and hostile behavioural symptoms as well as hyperactivity.

Campbell et al. (1995) confirmed similar results within a 6- week DBPLC study conducted in 50 children (mean age 9.4 years) with CD hospitalized for treatment-refractory severe aggressive- ness and explosiveness. After a 2-week placebo baseline period, children were randomly assigned to lithium or placebo treatment for 6 weeks. The mean optimal daily dose of lithium was 1248 mg (range 600–1800), and the mean serum level was 1.12 mEq/L.

Malone et al. in 2000 found that lithium was effective in short- term treatment for aggression in inpatients with CD hospitalized because of severe and chronic aggression. 40 patients (median age, 12.5 years) completed the treatment phase. Lithium (initial dose, 600 mg/d; final dose, 300–2100 mg/d) was statistically and clinically superior to placebo.

A meta-analysis conducted by Pringsheim et al. in 2015b, calculated the odd ratio of response or remission using data from three of the aforementioned studies (Campbell et al., 1995; Malone et al., 2000; Rifkin et al., 1997): the result was an odds ratio of 4.56 ($P < 0.001$), but authors highlighted the low quality of the studies.

A further study, with a smaller sample (N=11), showed that children treated for a minimum of 8 weeks with lithium carbonate improved in self-control, aggression and irritability. Part of the sample (N = 7) then entered in a double-blind placebo crossover design trial. Behavioural and cognitive improvements were maintained on placebo at the end of the trial (Carlson et al., 1992).

In 2009, Masi et al. published the results of their 6- to 12-month retrospective naturalistic study, based on clinical records of 60 consecutive patients diagnosed with CD (1/4 with ADHD) and treated with lithium. At the end of follow-up, 48.3% of the subjects were considered responders (10 receiving lithium monotherapy and 19 patients receiving lithium plus atypical antipsychotics). The results demonstrated the efficacy of lithium alone or in combination in reducing aggression.

2.3.3.2 Divalproate/Divalproex sodium

We found 2 randomized controlled trials, both suggesting that Divalproate is a potentially effective medication for aggressive children and adolescents; these trials were conducted on mixed populations including participants with CD.

In 2000, Donovan et al. published a 12-week 2-phase DBPLC crossover study 20 outpatients (10–18 years of age) with a diagnosis of CD or ODD (percentage of each was not clear; DSM-IV criteria) and explosive temper plus mood lability. Divalproex (DVPX) was titrated to achieve at week 2 blood level above 90 g/ml:

the final dose range was 750–1500 mg/d. Despite the heterogeneity of comorbid diagnoses (4 ADHD and 6 marijuana users), 85% completed at least 1 phase, and 75% completed both phases of the study. All 15 patients who began phase 2 completed it, and of these, 12 met criteria for improvement only during the medication phase, yielding a superior response to DVPX as compared with placebo (P = 0.003).

Blader et al. (2009) investigated the effect of divalproex in addition to open stimulant treatment (which had been started 5 weeks previously) in a 8 weeks RDBCT including children (aged 6–13 years) diagnosed with ADHD and DBD (ODD/CD) with stimulant- resistant chronic aggression. The percentage of children affected by CD was very low (11% of the total sample). They found that adding divalproex can result in increased rates of remission of aggression (odds ratio = 7.33, $p < 0.05$); adjusting for baseline aggression scale scores, the main effect of duration (weeks) was large ($p<0.001$). The treatment-by-week interaction was smaller ($p = 0.04$), indicating the steeper rate and magnitude of reductions in aggressive behaviour ratings associated with divalproex treatment. These results need to be discussed considering the concomitant treatment which might have influenced the outcomes.

Steiner et al. (2003a,b) conducted a 7-weeks comparative RCT of high versus low dose Divalproex sodium with no control group. Participants (71 hospitalized adolescent males aged 14–18 years with at least 1 crime conviction) were randomized into either high-dose (between 500 and 1500 mg/d or therapeutic plasma levels for seizure control between 50 and 120 g/ml) or low-dose (up to 250 mg/d) groups. The results concluded that self-reported weekly impulse control was significantly better in high-dose group ($P < 0.05$).

2.3.3.3 Carbamazepine

Only one DBPLC study evaluating the short-term efficacy and safety of carbamazepine in reduction of aggressiveness in CD (Cueva et al., 1996) was found. This was a 6-week trial, using a parallel design and including 22 children (aged 5.33–11.7 years) who received a diagnosis of CD with affective (impulsive) type of aggression and were hospitalized for treatment-resistant

aggressiveness and explosiveness. The optimal doses of Carbamazepine ranged from 400 to 800 mg (mean = 683 mg), at serum levels from 4.98 to 9.1 g/ml. Carbamazepine was not superior to placebo in reducing aggressive behaviour on any of the clinical outcome measures (including the OAS scale). The authors highlighted that during placebo baseline period a considerable number of children showed a reduction in aggression, maybe in response to hospitalization and structure alone.

A previous small open pilot study (Kafantaris et al., 1992) had shown effectiveness in hospitalized adolescents aged from 5.25 to 10.92 years (mean = 8.27) with aggressive behaviour and CD, producing clinically and statistically significant declines in aggressiveness and explosiveness. The small sample (N = 10) involvement of multiple raters and of various rating instruments made these data less reliable then a RCT.

2.3.4 Other agents

2.3.4.1 Selective norepinephrine reuptake inhibitors (SNRI): atomoxetine

Atomoxetine (ATX) has been approved as a treatment for ADHD. Its safety and efficacy for treating ADHD is well defined in the paediatric population and research has indicated that it may be linked to decreased emotional lability (Kaplan et al., 2004).

4 RCTs of ATX measured aggressive behaviour in a total of 857 subjects (average n = 214.3; 80.5% male; age = 10.5 years) with a primary diagnosis of ADHD and secondary diagnoses including ODD, depression, and generalized anxiety disorder (GAD). The mean dose of ATX was 1.3 mg/kg/day. Overall, ATX exerted a small average weighted ES (0.18) on paediatric aggression (Pappadopulos et al., 2006).

In a more recent 9-week, RDBPLC study in ADHD patients (6–17 years) with comorbid ODD or CD (Dittmann et al., 2011) atomoxetine was superior in reducing the symptoms of ADHD and CD, as measured by the SNAP-IV ADHD

score (effect size 0.72) and the ADDB-Inv disruptive behaviour score (effect size 0.61).

2.3.4.2 Alpha-2 agonists

Clonidine. The efficacy of the α-2 agonist clonidine was supported in a meta-analysis of 11 double-blind RCTs, published from 1980 to 1999, which showed that clonidine exerts a moderate effect on symptoms of ADHD and may help to ameliorate impulsive aggression (Connor et al., 1999).

1 RCT of clonidine examining 8 subjects with a primary diagnosis of autism and ADHD indicated its efficacy on aggression with an effect size of 1.10 (Jaselskis et al., 1992).

Clonidine was also shown to be effective in children with ADHD and comorbid aggressive ODD or CD by Connor et al. (2000), who conducted a pilot comparison of the tolerability and efficacy of MPH combined with clonidine, clonidine monotherapy or MPH monotherapy. This was a 3-month, randomised, double-blind, group comparison with eight subjects per group. All three treatments were found to be clinically effective by improving attention deficits, impulsivity, oppositional, and conduct symptoms. Authors concluded that clonidine, alone or in combination with MPH, is well tolerated and efficacious for the treatment of ADHD and aggressive ODD and CD. In another RCT of 67 children (6–14 years) with ADHD and comorbid ODD or CD, a combination of clonidine and stimulant treatment improved conduct problems over six weeks with a moderate effect size (weight-corrected Cohen's d of 0.60; Hazell and Stuart, 2003).

Guanfacine. Guanfacine is an α-adrenergic agonist similar to clonidine but with several potential advantages as it has a longer excretion half-life (Sorkin and Heel, 1986), and is less sedating and hypotensive than clonidine (Kugler et al., 1990). Like clonidine it is a licensed treatment for ADHD in children, reducing hyperactivity, increasing frustration tolerance, and decreasing irritability (Hunt et al., 1995). In an 8-week RCT of 34 children (mean age: 10.4) with ADHD and a tic disorder guanfacine produced a medium effect size (Scahill et al., 2001).

Guanfacine-extended release has also been found to be efficacious in reducing oppositional symptoms ($p < 0.001$) as well as ADHD symptoms in children (Connor et al., 2010b).

2.3.4.3 Beta-blockers

Buitelaar et al. (1996) examined the efficacy and side-effects of Pindolol, in children with (ADHD) within a prospective double blind placebo controlled comparison of pindolol and (MPH) lasting 4 weeks. Of the 52 ADHD children (7–13 years old) initially enrolled into the study only 32 completed the study because of side effects (Pindolol was associated with a higher incidence of paraesthesia and nightmares and hallucinations than MPH or placebo treatment). The outcome assessed by the Abbreviated Conners Rating Scales (ACRS) completed by parents, teachers, and by a psychologist during psychological testing revealed that Pindolol was just as effective as MPH in decreasing hyperactivity and conduct problems at home; however, had less therapeutic effects than MPH during psychological testing, and failed to reduce conduct problems in school.

2.4 META-ANALYSES OF STUDIES INCLUDING AT LEAST 50% OF SUBJECTS WITH DIAGNOSIS OF CD

2.4.1 Stimulants

According to inclusion criteria, 5 studies investigating the efficacy of methylphenidate on aggression in CD were identified and included to perform a meta-analysis (Table 5 and 6). Two of these were conducted in subjects with a primary diagnosis of CD (Kaplan et al., 1990 and Klein et al., 1997); the remaining three studies included a population of ADHD children and adolescent with comorbid CD in 55.5% (Pelham et al., 2005) and 68% (Taylor et al., 1987), and a comorbid condition of ODD/CD in the 64% of cases (Sinzig et al., 2007). In total, 242 subjects (aver- age n = 48.4; age = 10.66 years) were included.

The meta-analysis of these studies confirmed a significant effect of stimulant medication compared to placebo with an overall effect size of −2.62 (95%CI −4.67, −0.57; p = 0.01; I2 = 97%) using teachers' measures of conduct problems (Hedge's g) and an overall effect size of −2.43 (95%CI −5.39, 0.53; p = 0.11; I2 = 98%; Table 5) using parents' ratings of conduct problems. The analysis of measures of aggression (IOWA aggression) in two studies (Pelham et al., 2005 and Klein et al., 1997; Table 6) revealed a trend towards efficacy of methylphenidate using both parents' (SMD = −2.94; 95%CI −6.06, 0.18; p = 0.06; I2 = 97%) and teachers' ratings (SMD = −5.09; 95%CI −10.23, 0.05; p = 0.05; I2 = 98%).

2.4.2 Antipsychotics

According to inclusion criteria, only 2 studies were included in the meta-analysis (Findling et al., 2000 and Connor et al., 2008) investigating the efficacy of atypical antipsychotics (Risperidone and Quetiapine) on conduct problems and aggression in CD (Table 7). These studies were selected as they included only subjects with a primary diagnosis of CD, in total 39 subjects with a mean age of 11.65 years. The analysis of these studies, as already stated in Cochrane review (Loy et al., 2012), reveals a non-significant result when analysing the effect of antipsychotics medication (compared to placebo) by using measures of conduct problems (CPRS-CP) with an overall mean difference of −12.67 (95%CI −37.45, 12.11; p = 0.32; I2 = 90%). It was not possible to perform a meta-analysis on aggression measures used by these two studies: only mean change scores where available in Findling et al. (2000), so we were not able to use the SMD to pool the outcomes.

2.4.3 CU modulation of medication efficacy on aggression

Only two papers described the effects of CU traits on treatment response but reported not generalizable results.

The Treatment of Severe Childhood Aggression (TOSCA) study (Gadow et al., 2014; Aman et al., 2014; Farmer et al., 2015), aimed specifically to evaluate if child characteristics (including CU traits) could represent a predictor o moderator of treatment response. The TOSCA study included 168 children (aged 6–12 years, normal IQ) with severe physical aggression, ADHD, and co-occurring ODD/CD, who had already failed to respond optimally to a 3 weeks open trial of parent training and stimulant medication. Participants entered a 6 week randomized trial and were assigned to “basic therapy” (parent training plus stimulant plus placebo) or “augmented therapy” (parent training plus stimulant plus risperidone). Authors found that the “augmented” approach was superior to “basic therapy” at reducing severity of parent-rated peer aggression ($p = 0.02$, Cohen’s $d = 0.32$), with a major effect on physical aggression and on object aggression; no significant effect was found in teacher-rated peer aggression, although there was a significant effect for teacher-rated object aggression ($p = 0.03$; Cohen’s $d = 0.47$); no significant difference was found for CD symptoms severity (Gadow et al., 2014). Interestingly CGI scores were substantially improved for both “basic therapy” and “augmented therapy” groups at endpoint but did not discriminate between the two treatments, while parent rated social competency on the Positive-Social subscale of the NCBRF was significantly better for the “augmented” compared to the “basic” treatment, with and ES = 0.35 (ES = 0.46 from Week 3 to Week 9; Aman et al., 2014). Augmented therapy was also more efficacious in reducing reactive (impulsive) aggression (ES = 0.29), while effects on proactive aggression as measured by the Antisocial Behaviour Scale (Brown et al., 1996) were not significantly different (Aman et al., 2014) in line with prevailing thought in the field (Kempes et al., 2005) indicating that proactive aggression and conduct problems with CU traits may be more difficult to treat (Blair et al., 2014). In this work CU traits have been measured by a non validated CU score calculated as a composite of items from the Nisonger Child Behaviour Rating Form (NCBRF, cruelty or mean- ness to others; does not feel guilty), CASI-4R (physically cruel; does not care about causing pain/suffering; physically cruel to animals; emotionally cold; no interest in others’ feelings), and the Kiddie SADS-PL (physically cruel; cruel to animals; Kaufman et al., 1997). Surprisingly higher scores on callous/unemotional traits, as well as ADHD symptoms severity, predicted better

outcome on the NCBRF- Disruptive total, regardless of treatment assignment (Farmer et al., 2015).

Blader et al. (2013), in a open label stimulant optimization protocol conducted on 160 subjects, aged 6–13 year olds (mean age 9.31±2.02) with ADHD, ODD or CD, and significant aggressive behaviour, also examined the moderating effects of CU traits and proactive aggression on outcomes following optimized stimulant pharmacotherapy. In this case CU traits have been measured by the 6-item factor derived from the Antisocial Process Screening Device (APSD, Frick et al., 2014b) completed by parents. Neither CU traits nor proactive aggression at baseline diminished the effectiveness of stimulant monotherapy in reducing aggressive behaviour among children with ADHD. The hypothesis that CU traits could elevate the proactive aggression was not supported. Higher baseline ratings of proactive aggression and CU traits correlated with the severity of behavioural problems. However, children who experienced remission of overt aggressive behaviour also showed substantial reductions in post-treatment ratings of both CU traits and proactive aggression.

2.5 CLINICAL IMPLICATIONS

The paucity of reported evidences makes it impossible to clarify the real impact of CU traits on the effectiveness of drugs for aggression. In fact, possible effects of medication on specific subtypes of aggression and the specific role of CU traits in modulating medication efficacy have rarely been investigated. This may be due to the fact that, whilst the difference between “impulsive” aggression (“affective” or “overt”) and “predatory” aggression (“planned” or “covert”) has been extensively investigated over the last decade from a phenomenological perspective (Marsh et al., 2008; Finger et al., 2008; Shirtcliff et al., 2009; Jones et al., 2009; Fairchild et al., 2009; Närhi et al., 2010; Finger et al., 2011; Blair, 2013; White et al., 2013a,b; Lozier et al., 2014; Fairchild et al., 2014), the definition of the DSM-5 specifier “with limited prosocial emotions” is relatively recent.

The fact that very few studies in the present review included children and adolescents with a primary diagnosis of CD while the majority of them focused on ADHD and concomitant aggression and behaviour problems, and the fact that very few studies discriminate between types of aggression, makes it difficult to formulate recommendations for a tailored pharmacotherapy with regards the different forms of aggression in CD. Only one study specifically examined the effect of medication in a selected population of children and adolescents with a primary diagnosis of CD and impulsive aggression (Cueva et al., 1996). Another investigated impulsive aggression in a mixed sample (ADHD and CD/ODD; Armenteros et al., 2007), while the recent TOSCA study show some evidence on the impact of CU traits (Farmer et al., 2015) and on treatment response in different subtypes of aggression (Aman et al., 2014). None of the other studies examined aggression with this phenotypic specification.

More in general, this review partially supports the notion that pharmacotherapy may represent a potentially useful therapeutic approach to treat aggressive behaviour in children and adolescents with conduct disorder and that this may be helpful for those who have failed to respond to psycho-educational or psychological interventions. There are however still very few RDBT that have examined the efficacy of medication on aggression in children and adolescent with a primary diagnosis of CD. Only a few studies on aggression included more than 50% of subjects with CD within the total sample, making results of medication efficacy difficult to generalise to the broader CD population.

A wide range of pharmacological agents has been tried for the treatment of CD with the highest effect sizes being reported for stimulant medications and atypical antipsychotics.

Stimulant medications, the mainstay for the management of ADHD, are clearly an important potential therapeutic option for comorbid disruptive behavioural problems such aggression (Connor et al., 2002). However, an extensive examination of their impact on aggression in CD without ADHD has not yet been per- formed and the effect of stimulants on aggression are mainly derived as secondary outcome measure of efficacy form studies conducted in the ADHD population where Conduct Disorders is a comorbidity.

Previous reviews and meta-analyses reported good effect size for methylphenidate (mean around 0.7) with an even better efficacy for long acting formulations (Pappadopulos et al., 2006), in patients with ADHD and comorbid DBD. However severe aggression does not always respond to monotherapy with stimulant, especially in ADHD with comorbid CD (Connor et al., 2002). Therefore pharmacotherapy guidelines for ADHD with aggression propose beginning stimulant and behavioural treatments and adding antipsychotic medication only when aggression persists (Pliszka et al., 2006). Controlled evidence for the efficacy of risperidone addition to psychostimulants in children with comorbid DBD and ADHD is confirmed by some of the studies included here (Aman et al., 2002; Snyder et al., 2002; Aman et al., 2004; Armenteros et al., 2007). These data have been reinforced by the more recent TOSCA study, which unexpectedly reported higher scores on callous/unemotional traits as predicting better outcome on Nisonger Child Behaviour Rating Form Disruptive total, regard- less of treatment assignment (Farmer et al., 2015,). It should be noted that in this last study the authors created their own ad hoc callous/unemotional (C/U) composite variable using items from the NCBRF, the CASI-4R, and the Kiddie-SADS rather than a validated measures for CU traits. As a consequence it is difficult to interpret these findings or compare them to those from other studies. Another recent study examining the moderating effect of CU traits reported that pre-treatment CU traits and proactive aggression do not predict worse outcomes for aggressive ADHD children when receiving optimized stimulant pharmacotherapy (Blader et al., 2013).

Among the antipsychotics, Risperidone has the most evidence of efficacy, with effect sizes measured as SMD on ABC irritability subscale and CBCL aggression subscale ranging between 0.61 and 1.26 (Loy et al., 2012).

The sole Quetiapine study was a randomized double-blind clinical trial, revealing a positive effect on global primary outcome measures (CGI-S e CGI-I) but not in specific measures of aggression like OAS and CPRS (Connor et al., 2008). Other antipsychotics (Olanzapine, Aripiprazole) showed clinical efficacy on conduct disorder in open label trials, with no RCT data available yet.

In the real word clinical practice, atypical antipsychotics are currently largely used off label, with assumptions about long-term effectiveness (and safety) based only on these short-term (often open label) investigations and clinical experience. There is clearly a need for further more accurate investigations (Zuddas et al., 2011), however such trials are expensive and the incentives to industry to conduct them are low.

Psychostimulants should be considered as preferable to antipsychotics owing to fewer adverse effects and a better safety profile. Methylphenidate reduces aggression in youth with ADHD and there is a suggestion that it is also effective in conduct disorder without ADHD (Connor et al., 2002), therefore stimulants should be considered as the first option for treating aggression in CD with comorbid ADHD.

There is only very low quality evidence for the efficacy of mood stabilizers including Lithium and Divalproex. These data do however suggest a potential positive effect on remission of aggressive behaviour in CD for these medications. Whilst the RCTs of Divalproex were conducted on mixed sample, studies of lithium, included a mostly pure CD sample. But the lithium studies were conducted exclusively on hospitalized patients and may not be generalizable to community settings where it is much more difficult to get patients to comply with the demands of monitoring which requires regular blood tests.

The influence of IQ on treatment response to aggression in CD is difficult to fully evaluate, because many studies have chosen to include both patients with average IQ and sub-average IQ, and because authors tend to use different intelligence cut-offs to distinguish between patients with intellectual disability and patient with normal IQ.

The role of different informants on outcome measure should also be considered: results form methylphenidate studies, analysed in the present review, suggest teachers may be more sensitive to changes than parents (Klein et al., 1997; Sinzig et al., 2007). Higher teacher's sensitivity compared to parents, was also observed for the effect of psycho-educational intervention on conduct problems in ADHD children (Daley et al., 2014): teachers may be in a

more appropriate position to evaluate child behaviour in structured situations and relation with peers at a time of the day (morning, early afternoon) when psychostimulants could be more effective (peak plasma levels), compared to parents (early morning, late evenings). This should be considered in future studies.

In conclusion, it should be pointed out that, although several studies investigated the effects of medication on CD population, there is very little good-quality evidence to support the efficacy, effectiveness and safety of pharmacological treatments for aggression in CD.

To date, no drug has the approval for the treatment of CD in young patients, apart from short-term risperidone in children and adolescents with sub-average IQ. Clinical guidelines currently do not recommend pharmacological interventions for the disorder as a first-line intervention. We believe this to be correct due to the scarcity of the evidence.

2.6 LIMITATION

There are very clear and important limitations: most of the studies included in this review tend to be both low in quality and in power (small sample sizes, diverse measures of outcome, different designs and duration of trials, mixed samples). Particularly, most of the studies used different outcome measures depending on the selected population and generally according to comorbidities, thus evidencing different aspects of aggression and preventing an adequate comparison between them.

Other significant variables, such as the inclusion of concomitant psychosocial interventions or dosage of concomitant medication, are not well reported in many of the studies, further limiting the accuracy of the estimate of effect sizes and the validity of the meta-analysis.

Moreover, short term RCTs lasting only a few weeks do not allow firm conclusions about long-term efficacy, tolerability or safety. This is particularly

important as several potentially important adverse events are likely to become evident only after several months of treatment (Zuddas et al., 2011).

In addition, from a methodological perspective, it could be important that pharmacological interventions are tested in children and adolescents separately (Tcheremissine and Lieving, 2006). For example, lithium has been shown to be useful in children (Campbell et al., 1984) but not in adolescents (Rifkin et al., 1997). The rationale supporting these efforts is that the processes of maturation of the neural structures and neurotransmitter systems continue throughout childhood and adolescence, explaining different response in children and suggesting that future clinical trials should target separately the two groups of patients (Vitiello, 2001; Carrey, 2001; Wiznitzer and Findling, 2003).

Furthermore, an update of this research is strongly recommended to identify more recent evidence to broaden the knowledge on the effects of drugs in the treatment of different types of aggression.

2.7 FUTURE RESEARCH DIRECTIONS

What resulted clearly missing from the literature is a systematic comparison of the different medications in treating the different subtypes of aggressive behaviours in the context of CD, which can generate advice to assist in clinical decisions about who will respond best to which medication. Only one study explored the efficacy of stimulants in patients without ADHD as a primary diagnosis (Klein et al., 1997), trigging that the anti-aggressive effect of stimulants may be mediated by ADHD features. Specific studies in patients with ODD/CD without ADHD would be very useful, as well as longer-duration studies and placebo discontinuation studies, in order to evaluate both safety and efficacy of medication for disruptive and aggressive behaviour and to guide clinicians to the more effective choice considering the safety profile. Separate effects of medication according to gender may represent another important target for tailoring medication according to the need of patients to be explored in future studies.

As described in the introductory section, conduct disorder is significantly heterogeneous with regards neuropsychological functioning and neurobiological underpinning. In order to improve the currently poor outcome of the disorder (Zuddas, 2014), the relationships between the presence of CU traits and the different neuropsychological domains involved in the disorder and the effects of the medication on these specific neuropsychological domains should be much more extensively investigated.

3 MATRICS WP6-1 study: “The neuropsychological characterization of aggressive behaviour in children and adolescents with CD/ODD.”

The MATRICS_WP6-1 study received ethical approval from AIFA in July 2017 and from the Independent Ethics Committee of Cagliari in December 2017.

This study is a multicentre case-control study involving an ODD/CD cohort and a typical development (TD) controls cohort (subjects aged 10-17 years old), followed by a single-blind, placebo controlled, acute dose, cross-over, randomized medication challenge (involving the ODD/CD cohort only).

Due to late ethical approval achievement and to the actual difficulties in recruitment of the clinical sample (severe CD and aggressive subjects are commonly not compliant or motivated to participate in research studies and often urgently need a pharmacological treatment for managing acute episode of agitation), an extension of a six months period was required and obtained to broaden the number of samples and make evidence more solid.

3.1 RATIONALE

Children and adolescents with ODD or CD show a repetitive and persistent pattern of aggressive behaviour. ODD and CD have significant long-term implications for affected patients and their families and represent a significant public health problem. Whilst there is some evidence to support the use of various medications in reducing conduct problems, in the children and young people evidence is limited and requires further study. ODD and CD are causally heterogeneous and their neurobiological basis have not been completely clarified. Developing a better understanding of the neuropsychological characteristics underpinning these disorders and defining an autonomic and pharmacological acute response profile for pharmacological treatments known to be effective in reducing aggression will help in the identification of the potential mechanisms of action of these agents in order to facilitate the

development of novel pharmacological treatments specific for aggressive Conduct Disorder.

3.2 OBJECTIVES

3.2.1 Primary Objectives

The main goal was to first compare neuropsychological and autonomic functioning in children and adolescents with clinically relevant levels of aggression and diagnosis of ODD or CD to Typically Developing (TD) controls.

We primarily aimed to explore if conduct problems and aggression symptoms are related to specific neuropsychological (attention, working memory, decision making and risk taking, social cognition, delay aversion, emotional processing, motivation, cooperation, reward- punishment sensitivity), and autonomic (hearth rate, skin conductance, salivary cortisol) profiles, in order to differentiate subjects with aggression and CD/ODD from healthy controls. Moreover our aim was to examine if specific neuropsychological and autonomic profiles in patients with aggression symptoms permit to distinguish between reactive (“impulsive”, “affective” or “overt”) versus instrumental (“predatory”, “planned” or “covert”) aggression in order to better subtyping different aggressive behaviours.

3.2.2 Secondary Objectives

3.2.2.1 Acute medication effects

As a secondary objective, we investigated the acute effects of medications, known to impact positively on aggression in the context of CD/ODD. In particular we aimed to identify the acute effect of medication on specific neuropsychological and physiological features possibly underlying different types of aggression (reactive/instrumental aggression). For this purpose, we specifically explored the responses to an acute medication challenge by the

administration of a single dose of a stimulant, a not stimulant SNRI and two antipsychotic medications (Methylphenidate, Atomoxetine, Risperidone, Aripiprazole) according to the previously mentioned evidences from literature (paragraph 7 of the introductive section). Exploring both the noradrenergic, serotoninergic, and dopaminergic systems will allow to identify the cognitive and physiological pathways underlying medication responses, in order to further improve knowledge on aggression.

3.2.2.2 Moderating/modulating factors

Another secondary objective was to evaluate the moderating or modulating role on the neuropsychological/autonomic response of the following variables: presence of CU traits, comorbidities, SES, age and gender, previous medication, source of information (patient, parents, teacher, clinician evaluation), family structure.

3.3 STUDY DESIGN

This is a multicentre, phase II, case-control design study followed by single blind, acute dose, cross-over, placebo controlled, randomized medication challenge trial, employing 3 phases: a screening and clinical assessment visit (*phase I*), a case control design (*phase II*), a subsequent randomised, single-blind, placebo controlled, single dose, cross-over, acute medication challenge (*phase III*).

(***Phase I***). All subjects (CD/ODD and TD controls) visited the Unit for a screening evaluation (Visit -1). During this visit, the study was explained to the patient and his or her parent or legal guardian, who then signed and dated the informed consent and assent documents. Patients underwent psychiatric screening assessments and all criteria for enrolment were verified.

(***Phase II***). CD/ODD children/adolescents and TD controls visited the Unit with their parent/guardian for two subsequent days (Visit 0a and 0b) and will underwent a baseline assessment (Table 9). During the testing days the

participants completed a neuropsychological testing battery. Testing were split up into 3 sessions. The first session included 5 tasks and lasts about sixty minutes; it will be administered during the first of the two days planned for baseline assessment. The second session, composed of 4 tasks and lasting about 50 minutes, was administered during the second of the two days planned for baseline assessment. The third session, composed of 4 tasks and lasting about 50 minutes, was again administered 45 minutes after the end of the second session, in order to allow for the participant to relax and to encourage them to focus on the tasks during the next session.

Furthermore, in order to minimize any impact of fatigue in a more general way across the study, the second and third sessions were administered in an alternating manner across the participants.

During baseline visits participants were also assessed on selected autonomic measures (heart rate, skin conductance, salivary cortisol) at rest and during the testing session.

(***Phase III***). CD/ODD children/adolescents were enrolled in one of the two randomised single-blind, placebo controlled, single dose, cross-over, acute challenge arms (Table 10). The control cohort did not take part to this phase. As illustrated in table 10, each subject was randomly exposed to a single dose of drug each week for three consecutive weeks according to the condition of their randomization group (A or B). Patients randomized to group A received a single dose of a stimulant, a single dose of antipsychotic medication and a single dose of placebo, each one in a different week (Visit 1, 2 and 3), according to the order of their allocation to group A1, A2 or A3. Following the same procedure, patients randomized to group B received a single dose of a not stimulant, a single dose of antipsychotic medication and a single dose of placebo, each one in a different week, according to their allocation to group B1, B2 or B3.

After the administration of a single dose of one of the four selected medication (Methylphenidate, Atomoxetine, Risperidone, Aripiprazole) or placebo patients underwent a subset of the tasks performed during the baseline assessment (only the second and the third session tasks, for a total task time of about one hour and forty minutes; Table 9).

During this phase participants were also reassessed on selected autonomic measures (heart rate, skin conductance, salivary cortisol) at rest and during the testing session as in the baseline assessment.

We controlled for practice effects by using parallel versions of tasks where available, and having a one-week medication free break between testing sessions.

3.4 STUDY POPULATION

3.4.1 Population

As per protocol, the target population was of 120 ODD/CD children (age 10 yrs – 17 yrs and 10 months at screening visit; e.g. 50% 10-14 and 50% 15-17) and 40 TD controls . The aim was to obtain a representative sample including both boys and girls, considering that CD occurs in approximately 2.5% of boys and 1.5% of girls (Rowe et al., 2010).

The TD group was matched to the ODD/CD group on the basis of age, gender and IQ.

3.4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must met all of the following criteria:

ODD/CD group:

- IQ ≥ 80 (Wechsler IQ scale, within the last two years before enrolment);
- Age between 10 years and 17 years and 10 month at the screening visit
- Diagnosis of ODD or CD, based on the DSM-5 including the semi-structured K-SADS-PL interview;

- Aggression in the clinical range, T ≥ 70 on the aggression or delinquency subscale of the Teacher Report Form (TRF), Youth Self Report (YSR), or Child Behaviour Checklist (CBCL); or score ≥ 27 on the Nisonger-CBRF D-Total (composite of Disruptive Behaviour Disorder subscales);

- The patient is eligible to be treated with a pharmacological therapy based on previous medical and instrumental cardiological assessments (personal and family cardiological history, ECG within the last six months; see 5.2.1.1) and based on previous blood chemistry (performed within the last six months), current physical and neurological examination;

- Patient is drug-naive for psychotropic medications or off any psychotropic medication (Psychostimulants, antipsychotics, SNRI, mood stabilizers or antidepressant) within the last six months.

- If the patient is a girl who is sexually active and of childbearing potential (WOCBP: Women of Childbearing Potential, defined as females aged ≥10 years old and younger girls who, at the discretion of the investigator, are deemed to be of reproductive potential), must have a negative urine pregnancy test at the Screening visit and at Baseline visit prior to randomization for phase III. The urine pregnancy test will be repeated, each week, during the randomised single-blind, placebo controlled, single dose, cross-over, acute challenge phase. The inclusion of WOCBP will required, throughout the study period, the use of condom and one of the following highly effective contraceptive measures:

  - Intrauterine devices

  - Hormonal contraceptives (oral, depot, patch, injectable, or vaginal ring).

  - Double barrier methods (e.g., condoms and diaphragms with spermicidal gel or foam).

- Subjects' parents/legal guardians must provide and sign informed consent documents; patients must provide informed consent, and sign consent or assent documents if capable and permitted according to the legal

requirements in the country;

- Patients meeting criteria for comorbid ADHD, Depression, Anxiety or PTSD (as to the clinical judgment of the investigator) will not be excluded from study participation.

TD group:

- IQ ≥ 80 (Wechsler IQ scale, within the last two years before enrolment);
- Age between 10 years and 17 years and 10 month at the screening visit;
- Aggression below the clinical range, T < 70 on the aggression or delinquency subscale of the Teacher Report Form (TRF), Youth Self Report (YSR), Child Behaviour Checklist (CBCL); and score < 27 on the Nisonger-CBRF D-Total (composite of Disruptive Behaviour Disorder subscales);
- Subjects have to be drug-naive for psychotropic medications;
- Subjects' parents/legal guardians must provide and sign informed consent documents; TD control must provide informed consent, and sign consent or assent documents if capable and permitted according to the legal requirements in each country;
- Subjects meeting criteria for any psychiatric condition will be excluded from study participation.
- If the patient is a girl who is sexually active and WOCBP, must have a negative urine pregnancy test at the Screening visit and at Baseline visit.

3.4.3 Exclusion criteria

A potential subject who met any of the following criteria was excluded from participation in this study:

ODD/CD group:

- IQ < 80 (Wechsler IQ scale, within the last two years before enrolment);
- The subject has a primary DSM-5 diagnosis of schizophrenia-related disorders, schizophrenia, bipolar disorder, Autistic Spectrum Disorder, depression or anxiety;
- The subject had any psychotropic medications (psychostimulants, antipsychotics, SNRI, antidepressant, mood stabilizers) within the last six months before screening visit;
- The subject is pregnant or nursing;
- The subject has a body weight < 30 Kg
- The subject has any acute or unstable medical condition that, in the opinion of the investigator, would compromise participation in the study. The patient will be excluded if presents with one or more of the following conditions: neurological disorder; seizure disorder on encephalopathy; other psychiatric disorder; cardiovascular disease; congestive heart failure; cardiac hypertrophy; arrhythmia; bradycardia (pulse<50bpm); respiratory disease; hepatic impairment or renal insufficiency; metabolic disorder; endocrinological disorder; gastrointestinal disorder; haematological disorder; infectious disorder; any clinically significant immunological condition; dermatological disorder; congenital or juvenile glaucoma or is at risk of acute narrow-angle glaucoma;
- The subject has a history of severe allergies to medications, in particular hypersensitivity to neuroleptics, or history of multiple adverse drug reactions, or the patient has any contraindications to the use of the study drugs as following:
    - Methylphenidate and Atomoxetine are contraindicated in patients known to be hypersensitive to these drugs or other components of the products; in patients with glaucoma; during treatment with monoamine oxidase inhibitors, and also within a minimum of 14 days following

discontinuation of a monoamine oxidase inhibition; in patients with severe hypertension, angina pectoris, cardiac arrhythmias, heart failure, recent myocardial infarction, hyperthyroidism or thyrotoxicosis;

- Risperidone is contraindicated in patients with a known hypersensitivity to either risperidone or paliperidone, or to any of the excipients in the formulation;

- Aripiprazole is contraindicated in patients with a history of a hypersensitivity reaction to aripiprazole;

- Moreover Aripiprazole and Risperidone must be used with caution in subjects with a history of seizures, hypertension, angina pectoris, cardiac arrhythmias, heart failure, recent myocardial infarction, cerebrovascular adverse event, dyslipidaemia and metabolic changes, a history of leukopenia, neutropenia, and agranulocytosis, or of hepatic impairment or renal insufficiency, neuroleptic malignant syndrome (NMS), diabetes, in patients with previous hyperprolactinemia, orthostatic hypotension suicidal thoughts and behaviours, alcohol abuse or dependence.

TD group:

- IQ < 80 (Wechsler IQ scale, within the last two years before enrolment);

- The subject has a primary DSM-5 diagnosis of ADHD, ODD, CD or any other psychiatric condition;

- The subject had any psychotropic medications (psychostimulants, antipsychotics, SNRI, antidepressant, mood stabilizers) within the last six months before screening visit.

- The subject is pregnant or nursing.

3.5 SAMPLE SIZE CALCULATION

Our approach to calculating sample size for this study is two-fold.

As per protocol, in order to analyse the case-control contrast on the dependent variables, setting alpha at .05 (two-tailed) we had calculated that a sample size of 120 ODD/CD cases and 40 TD has 80.5 % statistical power to detect a group difference with an effect size 0.30, allowing to include the covariates (gender, site, children vs. adolescents, IQ, comorbidity with ADHD). However, hypothesizing an effect size at 0.35 with a variance of 0.32, the 80.5 % statistical power to detect group differences with a sample size of 88 ODD/CD subjects and 40 TD would be preserved.

For the acute medication challenge phase of the study, setting alpha at 0.05 (two tailed) a sample size of 52 participants in each of the two studies has 80% power to detect a difference between the different conditions with an effect size of 0.4.

3.6 METHODS

3.6.1 Recruitment

CD/ODD group participants could be inpatient or outpatient or based on clinical referrals. TD controls were enrolled on a voluntary basis.

The planned number of participants was split between two Italian centres:

- Università degli Studi di Cagliari
- IRCCS Stella Maris, Calambrone, Pisa

3.6.2 Study procedures

3.6.2.1 The screening session assessment

The screening session (I) included the following psycodiagnostic evaluations:

- K-SADS-PL (Kaufman et al., 1997): a semi-structured diagnostic interview assessing psychopathology based on DSM-IV categories. Screening questions for the presence and severity of symptoms related to ADHD, ODD and CD or other psychiatric disorders. If a cut-off score is reached on the screening form, supplement questions are asked. Both the child/adolescent and parent/guardian will be interviewed.

- Wechsler Intelligence Scales: To get an estimate of IQ, WISC-IV (Wechsler Intelligence Scale for Children – Fourth Edition) or WAIS-IV (Wechsler Adult Intelligence Scale) will be administered, depending on age.

- **Questionnaires**:

  - *Child Behaviour Checklist* (CBCL), *Teacher Report Form* (TRF) e *Youth Self Report* (YSR) (Achenbach, 1991): questionnaires which provide a measure of general functioning as well as internalizing and externalizing problems and are part of the Achenbach System of Empirically Based Assessment (ASEBA) and are well validated, widely used and available in multiple languages.

  - *Conners' Parent Rating Scale-Revised Short Form* (CPRS-RS; Conners 1997, revised 2007): an abbreviated version of the factor-derived subscales that assess a cross-section of ADHD-related symptoms and problem behaviours. The parent or caregiver typically responds on the basis of the subject's behaviour over the past month.

  - *Behaviour Rating Inventory of Executive Function* (BRIEF; Gioia, Isquith, et al, 2000): a 86-item questionnaire fulfilled by parents about executive function behaviours at home and at school for children and adolescents ages 5–18.

- *Inventory of Callous Unemotional Traits* (ICU; Essau, et al., 2006): a 24-item questionnaire administered to parents designed to provide a comprehensive assessment of CU traits and including three subscales (Callousness, Uncaring, and Unemotional)**.**

- **Rating scales**:

  - *Modified Overt Aggression Scale* (MOAS; Kay, et al., 1988): a short, widely used rating instrument for assessment of verbal aggression, aggression against property, auto-aggression and physical aggression (Kay, Wolkenfeld, & Murrill, 1988). It needs to be administered by the clinician to the parent/caregiver

  - *The Nisonger Child Behaviour Rating Form* (NCBRF-TIQ) parent version: a 66-item measure used to assess child and adolescent behaviour in children with Disruptive Behaviour Disorder; it needs to be administered by the clinician to the parents/caregiver (Aman et al., 2008).

- **Other:**

  - *The Clinical Global Impressions-Severity* (CGI-S, Guy, 1976): a single-item rating of the clinician's assessment of the severity of symptoms in relation to the clinician's total experience (Guy, 1976; NIMH, 1985). Severity is rated on a 7-point scale (1 = normal, not at all ill; 7 = among the most extremely ill subjects).

  - *The Children's Global Assessment* (C-GAS, Shaffer et al., 1983): a global, one-dimensional clinician rating of social, family, academic and psychiatric functioning. Scores on the measure range from 1 (most impaired, persistent risk to hurt) to 100 (healthiest; no symptoms).

3.6.2.2 Risk assessment for pharmacological treatments (patients only)

The screening session (I) included the following evaluations to assess the risk of cardiological contraindications and the risk of experiencing cardiological adverse events:

- assessment of history of exercise syncope, undue breathlessness and other cardiovascular symptoms
- heart rate and blood pressure
- family history of cardiac disease and examination of the cardiovascular system
- an ECG, performed within the last six months
- a cardiological consultation if considered necessary by the investigator.

Also, a check of previous blood chemistry (within the last six months), an exhaustive medical history and a physical and neurological examination was performed in order to exclude any contraindication to the use of psychotropic medications.

3.6.2.3 The neuropsychological task battery

Some of the tasks used in this study, which mainly assess “cold” executive functions (set shifting ability, sustained attention and working memory) are from the neuropsychological battery, the Cambridge Neuropsychological Test Automated Battery (CANTAB; *https://www.cambridgecognition.com/cantab/*), a well known and validated cognitive software. CANTAB includes highly sensitive, precise and objective measures of cognitive function, correlated to neural network and is widely used in research field.

Most of the task used, the ones mainly assessing “hot” executive functions, are instead taken from EMOTICOM (Bland et al., 2016), an innovative and not yet commercialized neuropsychological battery, developed by the same research group which developed the CANTAB. This tasks assess 4 core domains of affective cognition (emotion processing, motivation, impulsiveness and social cognition).

All computerized tests were administered using a touchscreen tablet (10.1 inch screen). Apart from the first one (MOT), the other tasks were administered on a random sequence for each subject. During the Phase III each subject of the CD/ODD group have been then re-tested by using the same sequence he/her used during baseline assessment.

The baseline assessment (II) and the single-blind, placebo controlled, acute dose, cross-over randomised acute medication challenge for the ODD/CD population (III) will include the following neuropsychological tasks by the CANTAB and Emoticom batteries:

Baseline assessment (First session)

- ***Motor screening*** (MOT): a screening test from the CANTAB battery, the first one to be administered. It aims to familiarize the subject with the test material and to assess the presence of any limitations in the use of the device (vision problems, hearing problems, motors, etc.).

- ***Intra-Extra Dimensional Set Shift (IED)*** (Figure 3)

  IED (Cantab battery) is a test of rule acquisition and reversal. It features: visual discrimination and attentional set formation maintenance, shifting and flexibility of attention This test is primarily sensitive to changes to the fronto-striatal areas of the brain.

  This test is a computerised analogue of the Wisconsin Card Sorting test, and is sensitive to cognitive changes associated with schizophrenia, Parkinson's disease, and dopaminergic dependent processes.

  Administration time: 7 minutes.

  Task: Two artificial dimensions are used in the test (colour-filled shapes and white lines). Simple stimuli are made up of just one of these dimensions, whereas compound stimuli are made up of both, namely white lines overlying colour-filled shapes. The participant starts by seeing two simple colour-filled shapes, and must learn which one is correct by touching it. Feedback teaches the participant which stimulus is correct, and after six correct responses, the stimuli and/or rules are changed. These shifts are initially intra-dimensional (e.g. colour filled shapes remain the only relevant dimension), then later extra-dimensional (white lines become the only relevant dimension). Participants progress through the test by satisfying a set criterion of learning at each stage (six consecutive correct responses). If at any stage the participant fails to reach this criterion after 50 trials, the test terminates.

Outcome measures: This test has 18 outcome measures, assessing errors, and numbers of trials and stages completed.

- ***Face and Eyes Emotional Recognition Task (FEERT)*** (Figure 4)

The FEERT (EMOTICOM battery) measures the ability to identify emotions in facial/eyes expressions. Subjects choose between 4 basic emotions. Choice accuracy and latency are recorded.

Administration Time: Approx. 6 minutes each for face and eyes (12 minutes total).

Task: The participant is shown a series of faces which appear on the screen briefly and asked to identify the emotion (happiness, sadness, anger and fear). In the control condition, participants will be asked to identify the age of a face (older adult, middle aged, young adult and child). The stimuli are computer morphed images derived from the facial features of real individuals each showing a specific emotion, are displayed on the screen, one at a time, in six blocks of forty (emotion) and twenty (age). Each face is displayed for 250ms and followed by four buttons displayed on the screen, each describing an emotion. The participant must decide which is the appropriate emotion and touch the corresponding button. There are ten different images for each of the four emotions, each showing different levels of intensity.

Outcome Measures: The outcome measures for the Face and Eyes Recognition Task are accuracy across emotions and intensities, and overall response latencies.

- ***Delay Discounting (DD)***

DD (Emoticom battery) is a measure of inhibition/impulsivity and delay aversion that assesses the rate of discounting across delays and probabilities.

Administration Time: Up to 6 minutes

Task: There are ten conditions; five levels of delay (0 days, 30 days, 90 days, 180 days, 365 days) and five levels of probability (100%, 90%, 75%, 50%, 25%). Participants must decide whether they would prefer a standard amount (always £20) with an associated delay or probability compared to a random amount available now. The task calculates the indifference points of all ten

conditions before it terminates. The task will not end unless all indifference points have been found. The rate at discounting and steepness of the curve allows assessment of impulsivity and self-control.

Outcome Measures: Area under the curve (AUC) and k calculated from indifference points

- ***Moral Judgment (MJ)*** (Figure 5)

MJ (Emoticom battery) is a measure of moral judgment.

Administration Time: Approx. 20 minutes

Task: The moral judgement task uses cartoon figures to depict moral scenarios. The task assesses normative emotional reactions to being a victimiser or victim in a moral situation. Participants are asked to imagine how they would feel in the situation, depending on who they are asked to identify with.

Outcome Measures: The outcome measures of the task are ratings for the four emotions; guilt, shame, annoyance, and good/bad.

- ***Prisoner Dilemma (PD)***

PD (Emoticom battery) assesses cooperation.

Administration Time: Approx. 13 minutes

Task: Each trial participants must press the space bar as fast as they can in order to fill their jar with coins. The trial is manipulated so that either: the participant wins more coins, the opponent wins more coins or they both win equal amounts. The coins are combined and participants are asked to either split or steal the total sum of money. Participants are told that if they both choose to split, they get half the money each, and if they both steal, they get nothing. If they split and the opponent steals they get nothing and the opponent gets everything. Alternatively, if they steal and their opponent splits, they get everything and their opponent nothing. Participants are faced with three different opponents each with a different strategy: aggressive (tit for tat but starts with steal), tit for two tats (starts with split, then changes behaviour after the player stolen two times consecutively) and a cooperative player who always splits.

Outcome Measures: Split and steal behaviour across the three opponents and for each type of contribution (win, lose, draw). Response latency is also an outcome variable.

Baseline (second session) and each medication trial visit assessment

- ***Rapid Visual Information Processing (RVP)*** (Figure 6)

RVP (Cantab battery) is a sensitive measure of sustained attention.
Administration time: 10 minutes.
Task: A white box appears in the centre of the computer screen, inside which digits, from 2 to 9, appear in a pseudo-random order, at the rate of 100 digits per minute. Participants are requested to detect target sequences of digits (for example, 2-4-6, 3-5-7, 4-6-8) and to register responses using the press pad.
Outcome measures: The nine RVP outcome measures cover latency (reaction times), response accuracy, probabilities and target sensitivity.

- ***Delayed Matching to Sample (DMtS)*** (Figure 7)

DMtS (Cantab battery) assesses forced choice recognition memory for non-verbalisable patterns, testing both simultaneous matching and short term visual memory.
Administration time: 10 minutes.
Task: The participant is shown a complex visual pattern (the sample) and then, after a brief delay, four similar patterns. The participant must touch the pattern which exactly matches the sample.
Outcome measures: This test has 19 outcome measures, assessing latency (the participant's speed of response), the proportion of correct patterns selected, and probability of an error after a correct or incorrect response

- ***Progressive Ratio Task (PRT)***

PR Task (Emoticom battery) assesses participants' motivational 'breakpoint'.
Administration Time: Approx. 20 minutes
Task: Participants are presented with four red squares on the screen and are instructed to select the square that differs in size to the other three.

Participants are paid progressively less per trial as they continue with the task. They are also told that they can stop their participation in the task at any point, but that they still have to sit facing the screen for the remaining time (20 minutes minus the time they performed the task).

Outcome measures: are trials completed, post reinforcement pause (PRP) and running rate (RR).

- ***Face Affective Go/NoGo Task (FAGNG)*** (Figure 8)

FAGNG (Emoticom battery) assesses information processing biases for positive and negative facial expressions

Administration Time: Approx. 5 minutes

Task: Participants are given a target emotion (happy, sad, neutral), and asked to press a button only when the target emotion is present. The test consists of several blocks, each of which presents a series of faces from three different affective categories: Positive (Happy faces), Negative (Sad faces), and Neutral (emotionless faces).

Outcome Measures: The Face Affective Go No-Go records proportions of Hits, Misses, Correct Rejections (CR) and False Alarms (FA). This is used to calculate sensitivity and bias across six conditions.

- ***New Cambridge Gambling Task (New CGT)*** (Figure 9)

NCGT (Emoticom battery) assesses decision-making and risk-taking behaviour outside a learning context.

Administration Time: Approx. 8 minutes

Task: On each trial, the participant is presented with a pie chart some of which is red and some of which is blue. At the left of the screen are chips worth 5p, 10p and 20p and participants must select two chips to place each time they bet on the pie chart. This is followed by a spinning pointer, which lands on either of the colours and thus provides feedback for the participant. There are two types of conditions; a no loss condition and a no win condition which allows the separation of reward and punishment. In one condition, participants will either double or keep the money they bet. In the other condition, participants will either keep or lose the money they bet. There are 15 trials in each condition.

Outcome Measures: The six CGT outcome measures cover risk taking, quality of decision-making, deliberation time, and overall proportion bet.

- ***Reinforcement Learning Task (RLT)***

RLT Task (Emoticom battery) assesses reward and punishment sensitivity.
Administration Time: Approx. 11 minutes
Task: Participants are shown coloured circles, and asked to make a choice between the two. Participants receive feedback and are continually updated on their scores. There are two conditions; one condition is a no lose condition whereby participants either win (50p) or don't win (0p). The second condition is a no win in condition whereby they lose (50p) or don't lose (0p). Participants must learn from sampling the circles, which of the two is the better option. Probabilities are set to 70/30. In the transfer phase, the circles are mixed into all possible pairs and participants must make a decision about which circle is most likely to win money and least likely to lose money (no feedback given). This transfer phase shows sensitivity to wins and losses.
Outcome Measures: Outcome measures include learning rate, response times, accuracy and choices in the transfer.

- ***Theory of Mind (TOM)*** (Figure 10)

TOM (Emoticom battery) assesses information sampling in socially ambiguous situations.
Administration Time: Approx. 15 minutes
Task: Participants are shown a scene, with three faces (feelings), three thoughts and three facts about the scene hidden from view. Participants are allowed to select any four pieces of information to be revealed. Once participants have selected four pieces of information, they can choose from three possible outcomes of the situation (negative, positive or neutral). Participants are asked to indicate how confident they are about their choice. All outcomes are equally plausible and there is no correct answer.
Outcome Measures: Information sampling, preference for feelings, thoughts and facts, outcome choice and outcome choice confidence.

- ***Ultimatum Game*** (UG)

  UG (Emoticom battery) assesses fairness sensitivity and punishment tendency.

  Administration Time: Approx. 18 minutes

  Task: Participants complete a task in which they can win money. This money is then combined with their opponent's winnings. Next, participants are informed whether they get to decide how the money is split or if the opponent decides. If the opponent decides, the participant gets the choice to either accept or reject their offer. These offers have seven divisions where the opponent gets 90%, 80%, 75%, 70%, 65%, 60% or 50%. If the participant accepts, they each get the allotted amount, and if they reject, they both get nothing. When the participant decides, they can choose from four divisions *(80/20, 70/30, 60/40, 50/50).*

  Outcome Measures: The outcome measure is "accept" percentage for each level of opponent offers (90%, 80%, 75%, 70%, 65%, 60% or 50%). This can also be broken down by contribution (win, lose or draw). Response latency is also an outcome measure.

3.6.2.4 Physiological measures

- *Saliva cortisol samples collection*: Participants were asked to collect saliva using a "passive drool" method in order to measure salivary cortisol. One baseline and one stress samples were collected before and after the testing session; for example, if the testing session was supposed to start at 9:30 a.m., samples were collected at the following time points: 1) at 9:15 a.m. before the first session; 2) at the end of the third session at 12:00 p.m. If the participant experienced difficulty spitting, sugar- and flavour-free chewing gum were provided to assist salivation. They were asked to rinse their mouths with water and then waited approximately 1 min. before producing each sample. All samples were centrifuged after collection and then frozen and stored at -20°C until assay.

  Cortisol levels were assessed by an external lab (Ospedale San Raffaele, Milano).

- *Autonomic measure by using Empatica E4*: During the performance of the all above-mentioned tasks, subjects will undergo to an autonomic profile measurement by a wristband able to record Heart Rate (HR) and Heart Rate Variability by a Photoplethysmography technique. HR will be recorded for five minutes while the participant will be at rest to yield baseline and continuously during the performance of the whole neuropsychological battery. The same wristband will allow to record the electro-dermal activity in terms of Skin conductance (referred to as Galvanic Skin Response) Arousal and Excitement.

3.6.2.5 Vital Signs, Body Temperature, Height and Weight

Before and after 15 minutes by the end of the neuropsychological testing sessions, vital signs (blood pressure, heart rate) were recorded. Body temperature, height and weight were recorded and physical examinations was also performed.

3.6.2.6 Single acute medication administration

Within the single-blind, randomised, placebo controlled, single dose, cross-over, medication challenge, the ODD/CD subjects were randomly assigned to have a single dose of placebo or two of the following medications once a week for three consecutive weeks: Methylphenidate, Atomoxetine, Risperidone, Aripiprazole.

The investigator or his/her designee was responsible for explaining the characteristics of the investigational agent(s) and possible adverse effects to the patients and his/her parents/legal guardian, maintaining accurate records of study drug dispensing at each visit.

Patients received a single dose of medication, at the investigator study site, one hour and a half before the beginning of the first testing session (e.g. 8.00 a.m. if the testing session is supposed to start at 9:30 a.m.). The time of administration had been estimated as the best time in order to evaluate the change of the performance on the various tasks during the pharmacodynamics window for these medications.

Dosages of each medication had been chosen according to the available literature considering the safety and tolerability of each drug on a single administration. Single doses were assigned to the participants according to their weight range.

Weight (kg)	***MPH (Medikinet)***	***ATX (Strattera)***	***RISPERIDONE (Risperdal)***	***ARIPIPRAZOLE (Abilify)***
≥50	***20 mg***	***40 mg***	***1 mg***	***5 mg***
≥35–<50	***15 mg***	***25 mg***	***0.5 mg***	***2.5 mg***

3.6.2.7 Method of Assignment to Treatment

At baseline visit CD/ODD patients were randomly assigned to Group A or Group B: each subject was given a precise sequence of drug administration within group (e.g. A1/A2/A3) as shown in Table 10.

Assignment to medication groups was determined by a computerized randomization list generator, set by the pharmacist from the Department of the University of Cagliari, not directly involved into patient screening and assessment.

To ensure groups were balanced among sites, the randomization had been stratified by age and gender.

3.6.2.8 Blinding

The acute dose challenge study was one single-blind phase (Study Period III).

Patients were aware about the medication or dose that they have been assigned or whether they are taking active drug or placebo at each testing session.

Investigators were unblinded to the patient's treatment.

The single blind design and the unblinding of the investigator will not affect the outcome of the study as the task administration is automated with set scripts and outcome measures are objectively determined by the computer.

3.6.2.9 Concomitant therapy

Concomitant medications with primarily central nervous system activity were not permitted during this study (Psychostimulants, Antipsychotics, SNRI, Mood Stabilizers and Antidepressant medication are not allowed within the last six months).

No concomitant psychotropic medication was allowed during baseline visit or study period III. If the patient was on any other medication for any chronic condition, the investigator, according to his clinical judgment and upon consent by the patient and patient's parent, could allow the co-administration of the two drugs or suggest to taper off, stop or completely wash out the concomitant medication before baseline visit.

3.6.3 Withdrawal of individual subjects

Subjects could leave the study at any time for any reason if they wished to do so without any consequences. The investigator could decide to withdraw a subject from the study for urgent medical or psychiatric reasons. A patient had to be withdrawn from the study, where required according to the Summary Of Product Characteristics (SmPC) recommendation, and in the following cases:

- in case of occurrence of suicidal behaviour
- if a patient develops signs and symptoms indicative of Neuroleptic Malignant Syndrome (NMS), or presents with unexplained high fever without additional clinical manifestations of NMS.
- In case of signs and symptoms of tardive dyskinesia appear or other extrapyramidal symptoms
- exacerbation of pre-existing psychotic or manic symptoms
- emergence of new psychotic or manic symptoms

- aggressive or hostile behaviour
- epilepsy (if seizure frequency increases or new-onset seizures occurs)
- in case of severe neutropenia (absolute neutrophil count <1x109/L)
- if the patient becomes pregnant
- if the patient and his or her parent(s)/legal representative (s) fails to comply with study procedures

If a subject withdrew from the study, data collected up until that point were used but no further data will be added.

3.6.4 Outcome measures: Study parameters/endpoints

3.6.4.1 Main outcome measures

Main outcome measures include the following:

- Quantitative and qualitative measures from the neuropsychological tasks: reaction times (response latency), accuracy (number/percentage of errors), test completion, learning rate, motivation, cooperation, reward-punishment sensitivity on the neuropsychological tasks from CANTAB and EMOTICOM batteries;

- Physiological measures: heart rate, skin conductance and salivary cortisol levels at rest and during test performance.

3.6.4.2 Secondary study parameters/endpoints

Secondary endpoints include measures to investigate the association between severity, type of aggression and performance on the neuropsychological tasks:

- Screening questionnaires: TRF, YSR, CBCL, CPRS, BRIEF, ICU

- Screening rating scales: MOAS and Nisonger interview

- CGI-S, C-GAS

3.6.5 Safety reporting

Selected medication doses are clinically relevant according to clinical practice, SCP and previous clinical studies in children and adolescents, but nonetheless not so large as to risk significant levels of peripheral side effects.

However, the investigators were trained to check for skin rash, chest pain, palpitation, stomach ache or cramps, tics, extrapyramidal symptoms and any adverse event, defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the medication and reported spontaneously by the subject or observed by the investigator. Any adverse event was recorded in the Case Report Form.

All AEs were followed until they have abated, or until a stable situation has been reached, and, depending on the event, follow up, additional tests or medical procedures as indicated, were discussed and set if needed. No need for referral to the general physician or a medical specialist occurred.

The University of Cagliari and the IRCSS Stella Maris comply with national guidelines for procedures in the case of adverse events; no serious adverse event occurred.

3.7 STATISTICAL ANALYSIS

3.7.1 Primary study parameter(s)

3.7.1.1 Cognitive-behavioural measures

For each task, mean reaction time, accuracy rate and other quantitative parameters will be calculated for every participant have been calculated.

Chi-square or one-way analysis of variance (ANOVA) tests have been used to assess group differences in case of data meeting assumptions of normality and homogeneity of variance, while covariates will be firstly explored by using

analysis of covariance (ANCOVA) and, thereafter, by determination of simple effects or interactions. All other data have been compared using appropriate non-parametric tests (e.g. Mann–Whitney U test) or by using a bootstrap-based non-parametric ANOVA. Simple and multiple regression models have been applied on the whole sample and on CD/ODD group with the descriptive measures of CU traits and aggression as dependent variables, and all outcome measures as the main predictors. Covariates included are age, gender, IQ.
To explore the potential effects of medication, data from the medication acute challenge have been entered into a bootstrap repeated-measures ANOVA for analysis.

Neuropsychopharmacological response to medication is defined as score change on the primary measures from each task. As each of the neuropsychological tasks is designed to measure a different aspect of functioning, and therefore can be seen as representing a separate experiment, a level will be not adjusted for the main comparative analyses.

Correlations, simple and multiple regressions, and ANCOVAs are used to preliminary investigate demographic, clinical, neuropsychological and neuro-psychopharmacological predictors of clinical response, to establish their role as moderating or modulating variables, and to define the correlation between severity, CT traits and neuropsychological/autonomic profiles.

Physiological data processing is still ongoing: these data (cortisol levels, autonomic parameters) will be included in next step analysis.

3.8 PRELIMINARY RESULTS

In total, 68 aggressive subjects with CD/ODD and 40 TD controls have been enrolled in the study. For this preliminary analysis data from a partial sample of the CD/ODD group (n=63) and from the complete sample of TD controls has been included. Of the neuropsychological measures, only data from the following tasks were included (Table 11): IED (Intra-Extra Dimensional Set Shift), DMS (Delayed Matching to Sample) and RVP (Rapid Visual Information

Processing) from the CANTB battery, FEERT (Face and Eyes Emotional Recognition Task), FAGNG (Face Affective Go/NoGo Task), MJ (Moral Judgment), TOM (Theory of Mind) and NCGT (New Cambridge Gambling Task) from the EMOTICOM battery.

3.8.1 Sample characteristics

For the preliminary analysis a partial sample of 63 CD/ODD (52 males, 11 females) and 40 TD (38 males, 2 females) was included (Tab. 12). Mean age is 13.29 years (±1.94 SD) for CD/ODD, 12.85 years (±1.65 DS) for TDC. The two groups are homogeneous for age and gender but differ significantly for total IQ (98.93 for CD/ODD, 116.85 for TDC; p<.001) and other Indices as measured by Wechsler scales (Tab. 13).

Within the clinic sample, 53 subjects have a primary diagnosis of ODD, 10 have a primary diagnosis of CD. 58 (92.1%) have a comorbid ADHD, 22 have a Trauma- and Stressor-Related Disorder, 14 an Anxiety Disorder, 6 a Depressive Disorder, and 3 have a Tic Disorder; also, 29 of them have a Learning Disorder.

3.8.2 Case-control study

3.8.2.1 Comparison between groups: assessment interviews and questionnaires

Also scores from all the Nisonger Child Behaviour Rating Form (NCBR) - Typical IQ version subscales significantly differ between groups (p <0.001) (Table 14), with higher scores for CD/ODD group (indicating behavioural problems) except on the Positive Social Scale, where lower scores indicate lower social competence.

All scores from the MOAS scale are also significantly higher for the CD/ODD group (p <0.001), thus confirming greater aggressiveness in this group,

including any type of aggression: verbal, physical, against property and self-directed (Table 15).

Groups significantly differ in all ICU and CPRS-SF subscale ($p < 0.001$) with higher scores for the CD/ODD group, indicating in this group a greater presence of CU traits, oppositional behaviour, inattention and hyperactivity (Table 16 and 17).

The Syndrome Scales Scores from the ASEBA questionnaires (CBCL, YSR and TRF) also revealed statistically significant differences between groups (mainly $p < 0.001$), with higher scores in the clinical group in almost all examined areas, except for "Anxious/Depressed" subscale of the YSR questionnaire and "Somatic complaints" subscale of the TRF questionnaire (Table 18, 19, 20).

CD/ODD group shows significantly higher scores in all subscales and composite scales of BRIEF questionnaire, except for "Shift" and "Organization of materials" subscales, indicating greater impairment in executive functions for the clinical group (Table 21).

3.8.2.2 Comparison between groups: tasks from the CANTAB battery

Performance on IED (Intra-Extra Dimensional Set Shift) task does not show any significant difference between groups (Table 22).

On DMS (Delayed Matching to Sample) task CD/ODD subjects show significantly lower percentage of correct answers, both to simultaneous stimuli ($p<0.01$) and to delayed stimuli ($p<0.001$), significantly lower (Table 23).

On RVP (Rapid Visual Information Processing) task significantly lower scores were found for CD/ODD group on "Sensitivity to the target" ($p<0.001$), while higher scores for the same group were found on "Total false alarm" ($p<0.001$), "Mean latency" and "Median Latency" (both $p<0.01$, $p<0.01$). Groups did not significantly differ with regard to accuracy (“Probability to hit”) on this task (Table 24).

3.8.2.3 Comparison between groups: tasks from the EMOTICOM battery

Face and Eyes Emotional Recognition Task (FEERT)

From the FEERT, parameters of accuracy (percentage of correct responses) and speed (reaction times, RT) were analyzed. Both parameters were analyzed for total stimuli (all emotions) and for each of the four basic emotions (happiness, sadness, anger, fear).

On the Face Emotional Recognition Task (FEERT-FACES), CD/ODD subjects were significantly less accurate producing less "total correct" responses ($p<0.05$), with significantly less correct responses for "sadness" ($p<0.05$) and "fear" ($p<0.05$). The clinical group was also significantly faster (lower RT) in providing "total correct" responses ($p<0.05$), specifically in recognizing "anger" and "fear" ($p<0.05$). Both CD/ODD and TDC subjects showed positive Affective Bias, with no difference between groups (Table 25). For technical reasons data from this task was collected only for part of the samples (46 patients and 24 controls): consequently, measures from FEERT-Faces have not been included in regression models nor in analysis performed on CD/ODD subgroups derived from stratification per CU traits.

On Eyes Emotional Recognition Task (FEERT-EYES), patients were less accurate in recognizing the total stimuli ($p<0.001$), producing less "total correct" responses each of the four basic emotions: “happy” ($p<0.01$), “sad” ($p<0.01$), “anger” ($p<0.05$) and “fear” ($p<0.05$) and significantly faster (lower RT) in recognizing “sadness” ($p<0.05$) (Table 26).

Face Affective Go/NoGo (FAGNG)

On FAGNG the CD/ODD subjects produced less correct responses (CR = correctly not given, HIT = correctly given and CR+HIT: $p<0.001$) and higher incorrect responses (FA (false alarm) = incorrectly given; MISS = incorrectly not given false alarm: $p<0.01$; FA+MISS $p<0.001$) showing worse accuracy. No significant difference in reaction times (RT) was found between groups. Both CD/ODD and TDC subjects showed negative Affective Bias, with no difference between groups (Table 27).

Moral Judgment (MJ)

On MJ task, when comparing the intensity of emotional assessments of moral situations, statistically significant differences were found on (Table 28):

- feeling guilty in the role of an agent, in both intentional and accidental harm (GUILT agent intentional/unintentional condition; $p<0.001$), with lower scores in CD/ODD group;
- feeling ashamed in the role of an agent, in both intentional and accidental harm (SHAME agent intentional/unintentional condition; $p<0.001$), with lower scores in CD/ODD group;
- feeling good in the role of an agent ($p<0.01$), in both intentional and accidental harm (BAD/GOOD agent intentional/unintentional condition; $p<0.01$ and $p<0.05$ respectively), with higher scores in CD/ODD group;
- feeling annoyed in the role of a victim, in both intentional and accidental harm (ANNOYED victim intentional/unintentional condition), with lower scores in CD/ODD group ($p<0.01$).

Theory Of Mind (TOM)

On TOM task, CD/ODD subjects chose a significantly higher percentage of "faces" compared to TDC ($p<0.05$) (Table 29).

New Cambridge Gambling Task (NCGT)

On NCGT, mean bet was significantly higher in both loss ($p<0.05$) and in the win ($p<0.01$) conditions for the clinical group indicating more risky behaviours. CD/ODD subjects showed significantly lower risk adjustment score both in the loss ($p<0.05$) and in the win ($p<0.001$) condition (Table 30).

3.8.2.4 Correlations between ICU scores and measures from CANTAB and EMOTICOM tasks

Pearson's correlation coefficient (r) and Spearman's correlation (r_s) have been calculated to analyse correlation between variables, respectively when they had a normal or not normal distribution.

A positive correlation has been found between Callousness and total ICU score and IED Total errors (inverse measure of accuracy in visual discrimination and of attentional skills) respectively: r_s=.335, p=.012; r_s=.265, p=.048, while a negative correlation has been found between Callousness and total ICU score and the number of stages completed on the same task (measure of maintenance, shifting and flexibility of attention), respectively: r_s=-.377, p=.004; r_s=-.289, p=.031.

Callousness subscale also positively correlates with DMS percentage of correct simultaneous responses (r = .318; p = .018).

Total ICU score negatively correlates with FEERT EYES percentage of correct responses for "anger" (r=-.260, p=.043; Figure 11), while Callousness and Total ICU score negatively correlates with percentage of correct responses for "sadness" (respectively r_s= -.302 p = .018; r_s = -.306 p = .017; Figure 12).

On MORAL JUDGMENT positive correlations were found between Total ICU score and ”feeling good” in the role of agent (total: r = .296, p= .021, intentional harm: r = .274, p= .033), between Callousness and feeling “guilty” in the role of a victim of an intentional and accidental harm (respectively r_s=.312, p=.014 and r_s=.275, p=.032; total r_s=.319, p=.012), and between Callousness and feeling “ashamed” as a victim (total: r_s=.253, p=.049; intentional harm: r_s=.299, p=.019); negative correlations were found between ICU Uncaring and feeling “annoyed” as a victim (total: r_s=-.356, p=.005; intentional harm: r_s= -.337, p= .008, accidental harm (r_s = -.307, p= 016) and feeling “ashamed” as an agent (total: r_s=-305, p=.017; intentional harm: r_s=-.327, p=.010; accidental harm: r_s=-.262, p=.04).

ON FAGNG task a positive correlation (r_s=-271, p=.038) between Unemotional ICU score and latency of incorrect responses (mean false alarm RT).

No correlation has been found between ICU scores and measures from RVP, New Cambridge Gambling Task and Theory of Mind task.

3.8.2.5 Regressions: predictors for ICU scores

Within the whole sample (CD/ODD + TDC) the more consistent model predicting ICU traits was a model including as predictors FAGNG %CR+HIT, feeling shame as an agent and IQ (respectively B=-.205, beta=-.189, p<.05, B=-2.575, beta=-.257, p<.01, B=-.372, beta=-378, p<.000): the model explains the 36.6% of the variance of ICU total scores (F= 17.10, p <,001). Risk adjustment in win condition (but not in loss condition) revealed a significant (but weak) predictor of ICU traits using the linear simple regression, but when added to the previous model its contribute was not significant.

Preliminary regression analysis performed to explore possible predictors of CU traits and aggression in CD/ODD subjects revealed that:

- By performing simple regressions RVP "probability of hit" (a measure of accuracy) negatively predicts ICU total score (F= 4.31, p <,05; R^2=.08; B=-12.6, beta=-.28);
- ICU total score are also negatively predicted by accuracy in recognition of sad [Eyes ERT] (F= 7.78, p <,01; R^2=.12; B=-.175, beta=-.341) and by risk adjustment in win conditions (F= 6.96, p <,05; R^2=.12; B=-2.54, beta=-.353);
- No significant predictive model has been found by combining more variables (CANTAB/Emoticom measures, age at onset/diagnosis, IQ, or CV) into a hierarchical regression.

3.8.2.6 Comparison between CD/ODD subgroups by levels of CU traits

CD/ODD group has been split based on total ICU score into a "low CU traits" group (ICU tot ≤32, N=21) and a "high CU traits" group (ICU tot >32, N=40). The two groups significantly differ for all partial scores from the ICU (p=.000), but did not show significant differences in age at screening, age at time of diagnosis and age at time of symptoms onset, sex, IQ, disease severity and level of overall functional impairment.

No significant difference was found comparing the two groups on MOAS and NISONGER scales and on the CPRS questionnaire.

On the other hand, CD/ODD with high CU traits revealed significantly higher scores on the Aseba questionnaires on "Withdrawn-depressed", "Attention problems" and "Rule breaking behaviour" subscale of CBCL ($p<.05$) and on "Withdrawn-depressed" ($p<.05$), "Social problems" ($p<.01$), "Thought problems" ($p<.01$), "Aggressive behaviour" ($p<.05$), "Externalizing problems" ($p<.05$) and "Total problems" ($p<.05$) subscale of YSR (Table 31 and 32).

On the BRIEF questionnaire only the "Behaviour regulation index" score was significantly higher in the group with high CU traits ($p <0.01$) (Table 33).

The two groups did not significantly differ in any of the CANTAB battery analyzed tasks (IED, DMS and RVP).

As for the EMOTICOM tasks, significant differences were only detected in the FEERT EYES task. In particular, subjects with high CU traits showed significantly lower percentage of total correct responses ($p <0.05$; in particular correct responses in the recognition of "sadness" and "anger", and significantly lower total reaction times ($p <0.05$; in particular reaction times for "sadness" and "fear"), indicating in this group less accuracy and higher speed of execution (Table 34).

3.8.3 Single-blind, placebo controlled, acute dose, cross-over, randomized medication trial

56 of the 63 subjects from the CD/ODD group agreed to continue the trial entering the phase III after randomization to the two treatment arms: 29 subjects (Group A) were randomly administered single dose of placebo, Methylphenidate and Aripiprazole, 27 subjects (Group B) were randomly administered single dose of placebo, Atomoxetine and Risperidone.

Repeated measures were performed for both randomization groups, reordering the data considering the drugs administered visit by visit.

The neuropsychological tasks, which were repeated after single doses of drugs (visit V1 to V3) after being assessed at baseline (visit V0b), include: DMS

(Delayed Matching to Sample) and RVP (Rapid Visual Information Processing) from the CANTB battery, FAGNG (Face Affective Go/NoGo Task), TOM (Theory of Mind) and NCGT (New Cambridge Gambling Task) from the EMOTICOM battery.

3.8.3.1 Repeated measures for single doses of drugs in Group A

No significant differences in any measure from CANTAB task were found after administration of single doses of drugs (Table 35 and 36).

On the other hand, the analyses of the EMOTICOM tasks revealed significant differences for the following tasks:

- FAGNG: HIT and MISS percentages are respectively higher and lower after single dose of Methylphenidate compared to Aripiprazole. CR + HIT and FA + MISS percentages are respectively higher and lower after single dose of Methylphenidate compared to baseline ($p<.05$; Table 37; Figure 13); no significant differences in mean RT (Figure 14) or in Affective Bias;
- NCGT: Win risk adjustment is significantly higher after single dose of Aripiprazole compared to baseline ($p<.05$; Table 38; Figure 15).

No significant differences were found in Theory Of Mind (Tab. 39).

ICU total score, added as a covariate, does not significantly predict a dependent variable change.

3.8.3.2 Repeated measures for single doses of drugs in Group B

No significant differences were found in any task (Table 40, 41, 42, and 43), except for the FAGNG (Table 44) on the following measures:

- mean RT HIT: reaction times for correct responses were significantly longer after single doses of placebo and Risperidone compared to baseline (respectively $p<.05$ and $p=.000$; Figure 16);
- mean RT FA: reaction times for incorrect responses were significantly longer after single doses of placebo and Risperidone compared to baseline

(respectively p<.05 and p<.01), and shorter after single doses of Atomoxetine compared to placebo (p<.05; Figure 16);
- higher % of CR and CR + HIT responses and lower % of FA and FA + MISS after single doses of Atomoxetine compared to baseline (p<.05; Figure 17).

ICU total score, added as a covariate, does not significantly predict a dependent variable change.

3.9 DISCUSSION

The preliminary results of the present study show that, compared to TDC, aggressive subjects with CD/ODD with normal IQ show:

- deficit in sustained attention, matching and short-term memory skills;
- difficulty in recognizing emotions;
- deficit in affective attentional control, with an altered voluntary control over reactivity to external emotional stimuli;
- anomalies in emotions reactions and moral judgment of the situation: they feel lower intensity of emotions as guilt and shame and feel greater well-being when they do wrong (acting as a victimizer); they experience less sense of annoyance when they suffer (being a victim);
- more risky behaviours with anomalies in decision-making and risk assessment, showing a reduced response to rewards and punishments.

Also, considering aggressive CD/ODD patients only, preliminary results show that:

- patients with higher CU traits have more difficulties in emotion recognition (particularly negative ones);
- no significant difference were observed between high and low CU CD/ODD when assessing “cold” executive functions.

Finally, the administration of a single dose of medications showed that:

- methylphenidate and atomoxetine improve accuracy in measures of affective

attentional control (on FAGNG task);

- there is limited evidence of effects of aripiprazole and of risperidone (D-2 modulating medications), respectively on risk assessment (significantly improved on NCGT) and on affective attentional control (significantly increased latency on FAGNG, combining with a slight - even though not significant - increased accuracy), both these effects possibly related to reduction of impulsivity;
- at this very early stage of the analysis ICU total scores do not seem to predict a different response to medications;
- no drug administered led to a significant deterioration in cognitive and affective performance compared to baseline and placebo.

3.9.1 Neuropsychological features of CD (case-control study)

The main objective of the case-control design study is to compare the neuropsychological functioning in children and adolescents with clinically relevant levels of aggression and diagnosis of ODD or CD to Typically Developing (TD) controls.

High ADHD comorbidity (92%) and higher prevalence of males (82,5%) in our samples is in line with epidemiological data reported in the literature (APA, 2013; Nock MK et al, 2007; Rowe R. et al, 2010).

The CD/ODD subjects scored higher in the questionnaires filled out by parents and teacher in the areas related to behavioural difficulties (e.g. “opposition”, “aggression”), as well as for other dimensions. Self-report questionnaire revealed poor insight abilities: patients mean T score were in the “sub-clinical” range, indicating insufficient abilities in recognizing and express their emotion and behaviours.

Compared to controls, subjects with CD/ODD showed significant difficulties in all the investigated cognitive domains (memory, language, attention and visual-spatial skills), and in the executive functions, especially inhibition, planning, problem solving and behavioural control, in line with previous studies (Johnson

et al., 2015; Blair et al.,2014; Blair, 2013a; Matthys et al, 2012; Hobson et al., 2011; Fairchild et al, 2009). Interestingly no difference has been found in attentional flexibility and shifting, confirming previous evidence from Hobson et al. (2011), who investigate executive functions in ODD/CD with or without ADHD.

Results of the FEERT task show that the CD/ODD group is impaired in recognizing all main emotions, in particular negative ones (sadness and fear) if we consider both eyes and facial. In these patients incorrect labelling could contribute to inappropriate response activated by emotional signals incorrectly coded: for example, a negative facial emotion (e.g. sadness) can be exchanged for another one (e.g. anger) affecting the ability to understand the subtleties of others' perspectives which is a key component of empathy (Dawel et al., 2012) and generating disproportionate defence reactions (hostile attributional biases and intention-cue detection deficits as predictive for reactive aggression; Dodge and Cole., 1987).

Results for response latency in emotional stimuli recognition need further analysis to allow discriminating between reaction times for correct and for incorrect response. It should also be highlighted that in our study the FEERT task resulted to be very difficult even for healthy controls, in particular the EYES version (average of the correct answers is between 55 and 65% in the eyes and face versions respectively). This could have led to frustration effects (surely more difficult to manage and control for CD/ODD subjects) and consequently disengagement in the task, leading to a possible deterioration in the performance of the subjects compared to their real abilities.

Moreover, CD/ODD subjects present impairment in emotion regulation, as resulted by the FAGNG, a task assessing attentive affective control skills (biased emotional attention), confirming previous evidence (Kohls et al., 2020; Euler et al., 2014).

As for moral judgment, CD/ODD group present a deficit in this area with poor empathy, as revealed by less intense feeling of guilt and shame when acting as a victimiser. These subjects, on the other hand, feel less annoyed when they play the role of a victim, both in conditions of intentional and accidental harm.

These data are in agreement with previous reports (see Frick PJ et al, 2014b; Stuewig J. et al, 2010; Muris et al, 2015, where lack of guilt and shame are mainly associated to externalizing problems).

On Theory of Mind task, which investigates Cognitive Empathy, measures of information sampling in socially ambiguous situations were collected.: CD/ODDs tend to select a greater number of faces, compared to thoughts and facts, to help resolve ambiguity and interpret the proposed cartoon. This could be explained by the weak verbal skills of these subjects, a deficit widely described by several authors (Fairchild et al, 2009; Lynam & Henry, 2000; Teichner & Golden, 2000; Johnson et al., 2015; Blair et al., 2014).

Regarding decision-making ability, data from the New Cambridge Gambling Task Measure allowed to assess risk-taking behaviour and to investigate reward seeking and punishment avoidance separately, revealing that CD/ODD tend to bet larger amounts of money (risky decision) irrespectively of the probability to win or to lose, thus indicating poor decision making abilities with poor strategies of risk assessment adjustment. This result is in line accordingly to previous evidence (Fairchild et al., 2019; Byrd et al., 2018; Blair et al, 2018; Sonuga-Barke et al., 2016; Hobson et al., 2011).

3.9.1.1 The role CU traits in CD

Within the studied sample, CU traits, (evaluated by the parent-rated ICU questionnaire), resulted significantly prevalent in aggressive CD/ODD subjects compared to TDCs, even when considering one dimension at a time (“Callousness”, “Unemotional” and “Uncaring”), thus confirming that CU traits are associated with patterns of aggressive behaviour and conduct problems (Enebrink et al, 2005; Frick & Dickens, 2006; Frick & White, 2008; Kruh et al., 2005).

By exploring neuropsychological outcomes, higher CU traits are associated with lower emotion recognition ability, confirming evidence from other authors (recently, Kohls et al., 2020).

We also found a significant (even if small) correlation between ICU total score (and sub-scales scores) and several measures from the task assessing emotional reactions to being a victimiser (agent) or a victim in a moral situation (Moral Judgment) showing anomalies that can be linked to a deficient emotional theory of mind (Blair et al., 2018). In our sample, higher CU traits (measured as ICU total score) positively correlate with feeling good in the role of a person doing an intentional wrong. Greater “Callousness” is associated with higher guilt and shame when in the role of a victim. Higher “Uncaring” component negatively correlate with feeling shame when doing wrong, and with feeling annoyance in the role of a victim. These anomalies help subjects with High CU traits in manipulating others for their own benefit, disregarding the distress caused to them (Viding et al, 2012) and, as widely described in literature (Blair, 2013a), are probably the expression of a deficit in emotional empathy, which implies a deficit in representation of the emotional state of the others and in responding to emotional displays and to verbal descriptions of the emotional states of the others (feeling the emotions of the other people), rather then a deficit in representation of the intention and beliefs of the others (which is related to cognitive empathy which is more likely affected in subjects Autism).

As for cold executive functions, the only significant (negative) correlations were found between CU traits (and in particular Callousness) and measures of accuracy in visual discrimination and shifting/flexibility of attention.

In order to better understand the neuropsychological and neurobiological characteristics of these subjects, the CD/ODD sample has been stratified based on the severity of CU traits.

Contrary to what is reported in the literature Dandreaux & Frick, 2009; Silverthorn, et al., 2001; Frick and White, 2008; Frick et al., 2014b), in our sample, when compared to low CU subjects, high CU subjects do not present an earlier onset of the disorder neither a lower prevalence of anxiety symptoms. They also do present more depressive symptoms, self-reported social problems and aggressive behaviours, and parent-rated attentions problems and rule breaking behaviours, but, contrary to what expected, they do not present a

more severe disease, nor a lower global functioning then low CU subjects. No significant difference was found in parent ratings of executive function.

Patients with high ICU traits show more difficulties in recognizing negative emotions, in particular “sadness” and “anger”. Also they were significantly faster in reaction times, especially in identifying “sadness” and “fear”. These results confirm the anomalies in recognizing sadness and fear described by may authors as associated to a less amygdala activation during the processing of facial emotions (Dawel et al., 2012; Marsh & Blair, 2008).

On the contrary, no significant differences were observed between high and low CU CD/ODD when assessing the explored "cold" executive functions (flexibility, short term visual memory and sustained attention).

Even when exploring possible predictors for CU traits in the whole sample (including patients and controls), no cold executive functions seem to significantly contribute to explain the variance of CU): within our preliminary analysis the predictive variables that have proved to be most important as predictive of CU traits are accuracy in task assessing biased emotional attention (FAGNG), ability in feeling shame when acting as a victimizer (MJ) and total IQ. Further analysis is needed including socio-demographic variables and physiological parameters to better clarify association with IQ (which is complex with contrasting evidence in literature), and to better explain variance of CU. No consistent predictive models have been found to predict CU traits in CD/ODD population.

Taken together, these date indicate that emotional empathy but not “cold” cognitive domains may associate with CU, as confirmed by many authors (Rizeq et al., 2020; Blair et al., 2006; Hiatt et al., 2004; Schiffer et al., 2014).

3.9.2 Responses to an acute medication challenge by the administration of a single dose

Although some clinical evidence suggests the use of various drugs to reduce CD problems, in the developmental age such evidences are limited and also

contradictory (Schur et al., 2003), and clear indications on the effectiveness of treatments depending on the type of aggression have not yet been formulated, with several clinicians prescribing these drugs off-label. Recent literature suggests the effectiveness of some medications in the treatment of aggression, in particular psychostimulants, D-2 modulators and mood stabilizers, but further studies are needed (Balia et al., 2018).

Within the present work we investigated the acute effects of a single dose of medication on specific neuropsychological variables. Analyses have been performed according to the randomization group (group A = placebo, methylphenidate and aripiprazole; group B = placebo, atomoxetine and risperidone).

In patients randomized to **group A**, the single dose of **Methylphenidate** resulted in a significant improvement of affective attentional control (accuracy) at the FAGNG task (higher percentage of correct answers and less errors) both compared to baseline evaluation and to assessment after a single dose of aripiprazole.

In the same task, a trend of increase of mean reaction times due to both methylphenidate and aripiprazole has been detected; even if this change was not statistically significant it could indicate an effect of advantageously reduced impulsivity at least for MPH, which, as highlighted above, is responsible of improvement in accuracy in this task. Thus, Methylphenidate, by improving attentional abilities and reducing impulsivity, may improve the ability to discriminate the affective stimuli.

Aripiprazole resulted effective in improving the risk assessment of win, in the New Cambridge Gambling Task; the underlying mechanism is possibly related to the reduction of impulsive behaviours induced by this medication.

In the sample of patients randomized to **group B**, the only significant effect of the administration of a single dose of drug was evidenced by the FAGNG task: while assessing attentive affective control, the administration of **Risperidone** resulted, compared to baseline assessment, in an increase of mean reaction times both for correct and incorrect responses. However, the same effect was

also found when patients were on placebo (compared to baseline): further analysis are ongoing to interpret this result correctly. The increasing of reaction time associated with Risperidone was however also associated to a slight improvement of accuracy (although not significant) both compared to baseline and placebo assessments, evidencing a possible positive effect of this drug in helping to manage impulsivity rather than an adverse event causing a slowdown as for mild sedation.

Within the same FAGNG task, **Atomoxetine** significantly improved accuracy compared to baseline, meaning that ATX appear to improve affective attentional control. Contrary to what reported by other studies evidencing that single doses of ATX could improve reaction times compared to placebo and other medications (Chamberlain et al., 2006, 2009, Bari et al., 2011), in the present sample we found a slight increase of reaction times, which could be related to a reduction of impulsivity.

No significant worsening of performance was found in group A neither B, showing that none of the selected medication can determine, by a single administration, any worsening of cognitive function.

The results of the present work confirm support the evidence of efficacy of stimulants (Methylphenidate) and non-stimulants (Atomoxetine) for CD/ODD in comorbidity with ADHD (Connor et al, 2002; Lettinga et al, 2011; Pappadopulos et al, 2006). Methylphenidate is one of the most used medication for the treatment of aggression and behavioural problems in the context of a comorbid condition of CD/ODD and ADHD, but data on efficacy are mainly derived by studies assessing aggression as a secondary outcome (Balia et al., 2018). in ADHD subjects Methylphenidate has been proved to be more effective, than ATX, in improving reaction time and reducing omission errors but, although both drugs led to an improvement in symptoms, their effects on the cognitive measure was not statistically associated to changes in symptoms (Bédard et al., 2015). Also there is some evidence of effects of both drugs on frontal-striatal-thalamus-parietal circuits in patients with ADHD, but with an associated effect of efficacy on sustained attention after MPH which is not found after ATX (Kowalczyk et al., 2019). This is in line with previous studies evidencing an

improvement of sustained attention after several weeks on treatment with atomoxetine, rather than after a single dose administration (Shang & Gau, 2012).

The results of the present study show that a single dose of risperidone or aripiprazole did not significantly improved working memory, discrimination abilities or accuracy compared to placebo, as confirmed by the work of Chung et al. (2012). This is in contrast with the recent work by Murphy et al., (2016), where single doses of aripiprazole determined an increased activation of the dorso-lateral-prefrontal cortex and improved accuracy in discrimination skills compared to placebo.

All these data, suggest that the administration of single doses of medication can have immediate effects on neurobiological correlates, although clinical and neuropsychological effects may not necessarily coincide.

Although many youths with CD and CU traits seem to respond to treatment, most studies have found that CU traits predict relatively poor treatment outcomes, independent of conduct problem severity before treatment (Frick et al. 2014a, Hawes et al., 2014). In our study, at this early stage of the analysis, CU traits do not appear to modulate the effects of medications, contrarily to an expected association with a poorer response for patients with high CU traits (Frick et al. 2014a). Further analyses including the whole sample are needed to confirm this result.

3.10 CLINICAL IMPLICATIONS

The results of the present study confirm a significant impairment of aggressive children and adolescents with CD/ODD in executive functions (sustained attention, working memory, inhibition), difficulties in recognition of emotions (especially sadness) and emotionally salient stimuli with an additional impairment in moral judgment assessment. These deficits can explain difficulties in controlling behavioural responses to external stimuli and can be

considered at the basis of aggressive behaviours and social difficulties often observed in this particular population.

The high comorbidity with ADHD confirms the impact of inattention and impulsiveness on the global impairment of these subjects possibly worsening the severity of the disease and predisposing to the persistence of antisocial behaviours (Noordermeer et al., 2016; Dolan & Lennox, 2013). The frequent ADHD comorbidity in samples included in research studies makes it difficult to trace different phenotypes for ADHD and for Conduct Disorders, if different phenotypes actually exist considering the frequent overlap between the two disorders in clinical population.

Data on the effects of drugs support the efficacy of methylphenidate and atomoxetine on the modulation of attentional skills and inhibition, the improvement in the accuracy of performance and in the ability to discriminate affective stimuli also in CD/ODD patients and not only in ADHD. Further analyses will better clarify the effects of D-2 modulators.

Considering that none of the selected drugs led to a significant deterioration in performance compared to baseline and placebo, these data will contribute to the development of specific guidelines for selecting appropriate medication according to patients aggressive characteristics.

3.11 LIMITS OF THE STUDY AND FUTURE PROSPECTS

This work has some limitations to be considered.

- First of all, these results are derived from partial analysis on a partial sample with limited sample size, lower than initially assumed. This was mainly due to the complexity of managing this type of patients (e.g. poor compliance, high commitment required of the patients with repeat of testing sessions once a week for a period of at least 5 weeks). Also, many pre-screened patients were not eventually enrolled into the study because of their clinical severity that often required an immediate treatment. Moreover,

some patients were delayed from data analysis due to their unreliable performance (sometimes patients did not follow the rules during task administration, sometimes dropped the session or did not present at one or more study visit).

- High rate of comorbid ADHD do not allow the study of a sample with a pure diagnosis of behavioural disorder, making it more difficult to recognize boundaries between ADHD and CD/ODD profiles.
- The Emoticom tasks are not standardized in a paediatric population and the version of the tests administered in this study is an "experimental" version: this has implied that some data has been lost or has not been processed;
- Some of the Emoticom tasks include word stimuli (especially Theory of Mind and Moral Judgment), thus requiring a good reading level that may not be suitable for use in all young subjects and may require additional effort;
- Unbalanced gender distribution made not possible to evaluate gender differences;
- The study protocol was designed with the aim to differentiate high CU versus low CU subjects, without including specific measures for impulsive vs proactive aggression: their inclusion would have clarified the association between subtypes of aggression and CU traits and would have added useful information on drug effects.

Further analyses of the neuropsychological measures (including assessment of learning component) as well as additional analyses of drug effects are needed to confirm and clarify the results of the present work. For example, analysis of the socio-demographic factors and other clinical variables (such as family history of psychiatric disorders or previous treatments) are ongoing to explore their effects on predictive model for CU traits or conduct problems and for drug effects as well. Logistic regressions and structural equation modelling (SEM, a multivariate statistical analysis technique) will be performed to better characterize clinical phenotypes with the neuropsychological and autonomic measure.

Analysis of autonomic measures (heart rate variability and EDA) and cortisol levels (at rest and after stress) is in progress to reveal specific characteristics

that differentiate CD/ODD subjects from healthy subjects and high CU from low CU subjects, possibly exploring the moderating/modulating role of these measures on drug response.

Finally, prevalence of side effects and possibly their impact on drug response effects will be explored to add information on treatment for aggression useful in real clinical practice.

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5 Tables

Table 1. Characteristics of the studies showing **effects of Stimulants on aggression in CD**

Author	Type of study	Primary diagnosis	Comorbid diagnosis	N	CD %	Age, M [range] (years)	IQ (mean)	Drug	mean Dose at endpoint mg/d [range] (mg/kg/d)	Duration of treatment (weeks)	Outcome measures of aggression or conduct problems	Main Results
Klein, 1997	DBPLCRT	CD	ADHD	83	100	10.4 [6-15]	≥ 70	MPH-IR	(1.87)	5	IOWA-A CTRS QBCL	MPH > PL on aggression and conduct problems ($p < 0.001$)
Kaplan, 1990	DBPLCRT†	ADHD	CD	6	100	14.4	n.a	MPH-IR	30.55	6	ABC CTRS	MPH > PL on aggression measured by ABC ($p<0.05$)
Taylor, 1987	DBPLCRT†	ADHD	CD	38	68	8.5	n.a.	MPH-IR	(0.74)	3	-	MPH > PL on Conduct Behaviours
Sinzig, 2007	DBPLCRT	ADHD	ODD/CD	85	64 ODD/CD	9.8	n.a	MPH-MR	[20-60]	5	ODD/CD symptom checklist (P/T)	MPH > PL on aggression measures ($p<0.001$)
Pelham, 2005	DBPLCRT	ADHD	ODD, CD	27	55.5	9.76	(112.38)	MTS	12.5-37.5 cm^2	6	IOWA O/D	MPH > PL on conduct measures ($p<0.05$)
Buitelaar, 1996	DBPLCRT	ADHD	CD	32	62.5	9.15	n.a.	MPH-IR Pindolol	20	4	ACRS	MPH = pindolol > PL on conduct problems at home Pindolol < MPH on conduct problems at school
Gadow, 1990	DBPLCRT	ADHD	CD/ODD	10	45.5	8.9 [5.9- 11.9]	> 75	MPH-IR	(0.3-0.6)	2	ATRS IOWA-A PCS	MPH > PL on non-physical ($p = 0.06$), physical ($p<0.01$) and verbal aggression ($p = 0.07$)
Pelham, 1989a	DBPLCRT	ADHD	CD, ODD, LD	24	25	9.08 [5.8- 11.3]	(102,4)	MPH-IR	(0.3)	1	IOWA-A	MPH > PL on Conduct problems ($p<0.10$)
Hinshaw, 1992	DBPLCRT††	ADHD	CD, ODD	44	18	9.5 [6-12]	(106.3)	MPH-IR	(0.30-0.38)	5	CBCL	MPH > PL on stealing and property destruction ($p<0.01$)

Author	Type of study	Primary diagnosis	Comorbid diagnosis	N	CD %	Age, M [range] (years)	IQ (mean)	Drug	mean Dose at endpoint mg/d [range] (mg/kg/d)	Duration of treatment (weeks)	Outcome measures of aggression or conduct problems	Main Results
Smith, 1998	DBPLCRT†	ADHD	CD/ODD	46	15	13.8 [12-17]	(101)	MPH-IR	[0,18-0,36-0,54]	5	IOWA CRS	MPH > PL on conduct and defiant behaviours (p=0.05)
Kolko, 1999	DBPLCRT	ADHD	CD/ODD	16	44	9.6	n.a.	MPH-IR	(1,35)	6	IOWA OAS MB-PC	MPH > PL on I/O (p<0.001), OAS (p<0.045) and Mood/beh (p<0.03)
Wolraich, 2001	DBPLCRT	ADHD	ODD, CD, Tic, Anxiety, Depression	282	11	9.0	n.a	MPH-IR MPH-OROS	10-60 18-54	4	IOWA O/D	MPH > PL on conduct problems (p<0.001)
Pelham, 1999	DBPLCRT†	ADHD	ODD, CD	25	32	9.6	average	MPH AMP	10-17.5 7.5-12.5	6	IOWA O/D	AMP and high MPH > PL on conduct measures (p<0.001)
Pelham, 1990	DBPLCRT†	ADHD	ODD, CD	22	18	10.39	(105.68)	MPH IR/ER AMP Pemoline	20 10 56.25	6.5	Abbreviated CRS	Drugs > PL on conduct measures
Palumbo, 2008	DBPLCRT	ADHD	CD	122	3-16	9.4	n.a	MPH -IR Clonidine	60 max 0.6 max	16	IOWA O/D Abbreviated CRS, CGAS	MPH> PL on CGAS (p=0.002)
Gorman, 2006	DBPLCRT	ADHD	ODD/CD	22 ADHD-C 19 ADHD-I	44	8.74 9.47	106.41 109.1	MPH	(0.96) 25-50	6	IOWA A/O parent and teacher	MPH> PL on aggression in ADHD-C
Evans, 2001	DBPLCRT†	ADHD	ODD, CD	45	15	13.8	101	MPH	[0,18-0,36-0,54]	8	IOWA O/D	MPH> PL on conduct measures (p<0.0001)

n.a.: not available
MPH: methylphenidate; **IR**: immediate release; SR: Sustained-release; **MR**: Modified release; **MTS**: Methylphenidate Transdermal Delivery System; **PL**: placebo.
CD: Conduct Disorder; **ODD**: Oppositional Defiant Disorder; **ADHD**: Attention Deficit/Hyperactivity Disorder; **DBD**: Disruptive Behaviour Disorder; **DBD nos**: Disruptive Behaviour Disorder not otherwise specified.
IOWA CRS: Inattention/Overactivity With Aggression Conners Rating Scale; **IOWA-A**: IOWA Aggression; **IOWA O/D**: IOWA Oppositional/Defiant; **CTRS**: Conners Teacher Rating Scale; **QBCL**: Quay Revised Beahviour Checklist; **ABC**: Aberrant Behaviour Checklist; **ACRS**: abbreviated Conner Rating Scale; **ATRS**: Abbreviated Teacher Rating Scale; **PCS**: Peer Conflict Scale; **CBCL**: Child Behaviour Checklist; **OAS**: Overt Aggression Scale; **MB-PC**: Mood/behaviour-Peer Conflict; **CRS** : Conners Rating Scale;.
† cross over design.
†† cross over laboratory study.

Table 2. Characteristics of the studies showing effects of Antipsychotics on aggression in CD

Author	Type of study	Primary diagnosis	Comorbid diagnosis	N	CD %	Age, M [range] (years)	IQ	Drug	mean Dose at endpoint mg/d [range] (mg/kg/d)	Permitted concomitant medication	Duration of treatment (weeks)	Outcome measures of aggression or conduct problems	Main Results
Findling, 2000	DBPLC RCT	Aggressive CD	*	20	100	9.2 [6-14]	Average IQ	**RISP**	[0.75–1.5] (0.028)	-	10	RAAPP	RISP > PL (p<.01)
												CBCL	RISP = PL on AB RISP > PL (p<.05) on DB
												CPRS	RISP > PL (p<.001) on CP
Buitelaar, 2001	DBPLC RCT	CD/ODD/ADHD with overt aggression	ADHD	38	n.a.	13.9 [12-18]	60-90	**RISP**	2.9 [1.5-4] (0.04)	-	6	ABC	RISP > PL (p<.05)
												OAS-M	*sign. worsening on OAS-M and ABC after wash-out*
Van Bellinghen, 2001	DBPLC RCT	Persistent behavioural disturbance**	n.a.	13	n.a.	10.8 [6-14]	66-85	**RISP**	1.2 (0.05)	Mph (N=1, discontinued during trial), Valproate (N=1)	4	ABC-I	RISP > PL (p<.05)
Aman, 2002	DBPLC RCT	CD/ODD/DBD nos	ADHD	118	39.83	8.4 [5-12]	36-84	**RISP**	1.16 (0.04)	Stimulant permitted (stable dose for at least 30 days before starting)	6	ABC-I	RISP > PL
												BPI-AB	RISP > PL
Snyder, 2002	DBPLC RCT	CD/ODD/DBD nos	ADHD	110	37,27	[5-12]	36-84	**RISP**	0.98 [0.4-3.8] (0.033)	Stimulant permitted (stable dose for at least 30 days before starting)	6	ABC-I	RISP > PL (p<.001)
												BPI-AB	RISP > PL (p<.01)
												NCBRF	RISP > PL (p<.001) on CP
Armenteros, 2007	DBPLC RCT	ADHD + aggression (impulsive type)	ODD, CD	25	24	[7-12]	≥ 75	**RISP**	1.08	All patients on Stimulant (stable dose for at least 3 weeks before starting)	4	CAS-P, CAS-T	RISP > PL on CAS-P (p<.05)
TOSCA Study, (Gadow, 2014; Aman, 2014; Farmer, 2015)	†	Aggressive ADHD + OOD/ODD&CD	-	168	26,19	8.9 [6-12]	97.1±14.1	**RISP**	1.7	All patients on MPH	6	ADHD-SC4	BT + RISP > BT + PL in PCS (p<.05)
												NCBRF TIQ	BT + RISP > BT + PL in D-t (p=.01)
												ABS	BT + RISP > BT + PL in RB (p=.01)
												CU composite	Predictor of better outcome on NCBRF D-t
Connor, 2008	DBPLC RCT	CD	***	19	100	14.1 [12-17]	Average IQ	**QUET**	294 [200-600]	-	7	OAS, CPRS CP	QUET = PL
												CGI-S, CGI-I	QUET > PL (p<.01)

DBPLC RCT: double-blind placebo-controlled randomized clinical trial. Mph: Methylphenidate; RISP: Risperidone; PL: Placebo; QUET: Quetiapine; DBD: Disruptive Behaviour Disorder; DBD nos: Disruptive Behaviour Disorder not otherwise specified.
RAAPP: Rating of Aggression Against People and/or Property Scale; CBCL (AB and DB): Child Behaviour Checklist (Aggressive Behaviour and Delinquent Behaviour subscale); CPRS (CP): Conners Parent Rating Scale (conduct problem subscale); OAS-M: Overt Aggression Scale – Modified; ABC: Aberrant Behaviour Checklist; ABC-I: Aberrant Behaviour Checklist-Irritability scale; BPI-AB: Behaviour Problem Inventory- Aggressive Behaviour subscale; NCBRF CP/D-t (TIQ): Nisonger Child Behaviour Rating Scale conduct problem subscale/Disruptive behaviour scores (typical IQ version); CAS-P: Children's Aggression Scale-Parent; CAS-T: Children's Aggression Scale-Teacher; ADHD-SC4 (PCS): ADHD Symptom Checklist-4 (Peer Conflict Scale); ABS(PB/RB): Antisocial Behaviour Scale (Proactive Behaviour subscale + Reactive Behaviour subscale).
† [3 weeks open trial of parent training and stimulant medication (Basic therapy, BT) +] 6 weeks RCT (Basic therapy + Placebo vs Basic therapy + Risperidone); * Moderate to severe ADHD, significant psychiatric disorders excluded; ** "Persistent behavioural disturbance" = e.g., hostility, aggressiveness, irritability, agitation, hyperactivity (Van Bellinghen & De Troch, 2001); * psychotic disorders and mood disorders, alcohol/substance abuse/dependence, and sub-average IQ excluded**

Table 3. Characteristics of the studies showing effects of Lithium on aggression in CD

Author	Type of study	Primary diagnosis	Comorbid diagnosis	N*	CD %	Age, M [range] (years)	IQ	mean Dose at endpoint mg/d [range] (mg/kg/d)	Permitted concomitant medication (mg/d)	Duration of treatment (weeks)	Outcome measures of aggression or conduct problems	Main Results
Campbell, 1984	DBPLC RCT (LI/HAL)	Aggressive CD	-	61	100	9 [5.2 to 12.9]	n.a.	LI: [500-2000] HAL: [1-6]	-	4	CPRS, CTQ, CPTQ	On CPRS: LI > PL (p<.001) HAL > PL (p<.001) LI=HAL
Carlson, 1992	†	Explosive-aggressive/ ODD/CD	ADHD, Bipolar Dis.	11 7 analysed	n.a.	8.5 [5,11-12,20]	81-129	[600-1500] (28)	Mph	> 8	IGRS	LI > PL : clinical but not statistical improvement in aggression
Campbell, 1995	DBPLC RCT	CD with severe aggressiveness and explosiveness	n.a.	50	100	9.4 [5-12]	n.a.	1248 (41.6)	.	6	CPRS, CPTQ	LI > PL significant decrease in aggression factor (CPRS)
Malone, 2000	DBPLC RCT	aggressive CD	-	40	100	12.5 [10-17]	PL: 81.4 (9.7) LI: 87.9 (12.2)	[900-2100]	-	4	OAS	LI > PL (p<.05)
Rifkin, 1997	DBPLC RCT	CD	**	33	100	15.15 [12-17]	>70	-	-	2	OAS, BRS, CTRS	LI = PL

† 8 weeks crossover open treatment with LI (N=11) + DBPLC RTC (N=7)
*** All these four studies were conducted on hospitalized patients**
**** psychosis or mood disorders and pervasive developmental disorder excluded**
DBPC RCT: double-blind placebo-controlled randomized clinical trial. n.a.: not specified;
LI: Lithium; HAL: Haloperidol; PL: Placebo; Mph: Methylphenidate.
CD: Conduct Disorder; ODD: Oppositional Defiant Disorder; ADHD: Attention Deficit/Hyperactivity Disorder; DBD: Disruptive Behaviour Disorder; DBD nos: Disruptive Behaviour Disorder not otherwise specified.
CPRS: Children's Psychiatric Rating Scale; CTQ: Conners Teacher Questionnaire, CPTQ: Conners Parents-Teacher Questionnaire; IGRS: Inpatient Global Rating Scale; OAS: Overt Aggression Scale; BRS: Behaviour Rating Scale; CTRS: Conners Teacher Rating Scale.

Table 4. Characteristics of the studies showing effects of Divalproate on aggression in CD

Author	Type of study	Primary diagnosis	Comorbid diagnosis	N	CD %	Age, M [range] (years)	IQ	mean Dose at endpoint mg/d [range] (mg/kg/d)	Permitted concomitant medication	Duration of treatment (weeks)	Outcome measures of aggression or conduct problems	Main Results
Donovan, 2000	DBPLC crossover RCT	CD/ODD and explosive temper + mood lability	ADHD (n=4) marijuana use (n=6)	20 (15 completed)	n.a.	13.8 (10-18)	>70	[750 - 1500]	Marijuana, Prescribed stimulant	12	MOAS + SCL90 anger-hostility scale	DVPX > PL (p<.001)
Blader, 2009	†	ADHD + CD/ODD with stimulant-resistant chronic aggression	Mood dis. (n=2) Anxiety dis. (n=2)	30 randomized, 27 analysed	11,11	(6-13)	n.s.	571	All patients on MPH-ER	8	Retrospective M-OAS CBCL Tscore externalizing	DVPX + MPH-ER > PL + MPH-ER in inducing remission of aggression (odds ratio=7.33, p<.05; CI=1.16–46.23)

† [5 weeks open stimulant treatment phase +] 8 weeks randomized double blind (divalproex + stimulant vs placebo + stimulant)
DBPC RTC: double-blind placebo-controlled randomized clinical trial.
DVPX: Divalproate; PL: Placebo; MPH-ER: Methylphenidate-Extended Release.
CD: Conduct Disorder; ODD: Oppositional Defiant Disorder; ADHD: Attention Deficit/Hyperactivity Disorder.
MOAS: Overt Aggression Scale – Modified; SCL90: Symptom Checklist (90 items); CBCL: Child Behaviour Checklist.

Table 5. Main outcome measures of conduct problems (studies on Stimulants)

Study	Measure	Medication			Placebo			Effect Size (Std. Mean Difference)	95% CI
		mean	SD	total	mean	SD	total		
Taylor, 1987	CTRS (teacher rated)	0.83	1.4	38	1.4	1.61	38	-0.37	[-0.83, 0.08]
Kaplan, 1990	CTRS (teacher rated)	0.5	0.7	6	1.1	0.6	6	-0.85	[-2.05, 0.36]
Klein, 1997	CTRS (teacher rated)	1	0.1	36	1.9	0.1	35	-8.90	[-10.48, -7.33]
Sinzig, 2007	ODD/CD checklist (teacher rated)	0.31	0.41	43	0.82	0.58	42	-1.01	[-1.46, -0.56]
								-2.62	*-4.67, -0.57*
Klein, 1997	CPRS (parent rated)	1	0.1	37	1.4	0.1	37	-3.96	[-4.76, -3.16]
Sinzig, 2007	ODD/CD checklist (parent rated)	0.8	0.63	43	1.4	0.64	42	-0.94	[-1.39, -0.49]
								-2.43	*-5.39, 0.53*

CTRS: Conners Teacher Rating Scale; CPRS: Conners Parent Rating Scale; ODD/CD checklist: ODD/CD-Symptom-Checklist (FBB- SSV: Fremdbeurteilungsbogen für Störungen des Sozialverhaltens)

Table 6. Main outcome measures of aggression (studies on Stimulants)

Study	Measure	Medication			Placebo			Effect Size (Std. Mean Difference)	95% CI
		mean	SD	total	mean	SD	total		
Klein, 1997	IOWA -A (teacher rated)	5.2	0.6	36	9.9	0.6	35	-7.75	[-9.14, -6.36]
Pelham, 2005	IOWA O/D (teacher rated)	1.2	1.5	27	8.7	3.9	27	-2.50	[-3.23, -1.78]
								-5.09	*-10.23, 0.05*
Klein, 1997	IOWA -A (parent rated)	6.0	0.5	37	8.3	0.5	35	-4.55	[-5.44, -3.66]
Pelham, 2005	IOWA O/D (parent rated)	3.2	2.7	27	8.1	4.2	27	-1.37	[-1.96, -0.77]
								-2.94	*-6.06, 0.18*

IOWA-A: IOWA Aggression; IOWA O/D: IOWA Oppositional/Defiant

Table 7. Main outcome measures of conduct problems and of aggression (studies on Antipsychotics)

Study	Drug	Measure	Medication			Placebo			Effect Size (Mean Difference)	95% CI
			mean	SD	total	mean	SD	total		
Findling, 2000	RISP	CPRS-CP (parent rated)	-28.0	13.86	8	-1.75	16.5	9	-26.25	[-40.69, -11.81]
Connor, 2008	QUET	CPRS-CP (parent rated)	11.3	7.7	9	12.2	4.4	10	-0.90	[-6.62, 4.82]
									-12.67	*-37.45, 12.11*
Findling, 2000	RISP	CBCL aggressive behaviour (parent rated)	-24.2	17.1	9	-11.5	14.23	10	-12.70	[-26.93, 1.53]
Connor, 2008	QUET	OAS (parent rated)	43.3	55.6	9	49.4	27.8	10	-6.10	[-46.30, 34.10]

CPRS: Conners Parent Rating Scale – conduct problem; CBCL Child Behaviour Check-list; OAS: Overt Aggression Scale.

Table 8. Main outcome measures of aggression (studies on Mood Stabilizers)

Study	Drug	Measure	Medication			Placebo			Effect Size (Mean Difference)	95% CI
			mean	SD	total	mean	SD	total		
Malone, 2000	LITHIUM	OAS	-2.4	2.44	20	-1-17	4.15	20	-1.23	[-3.34, 0.88]

OAS: Overt Aggression Scale.

Table 9: Neuropsychological Assessment

Task	Battery
First Day (Visit 0a): Testing Session (aprx 60 min)	
Intra-Extra Dimensional Set Shift (IED)	CANTAB
Face and Eyes Emotional Recognition Task (FEERT)	EMOTICOM
Delay Discounting (DD)	EMOTICOM
Moral judgment (MJ)	EMOTICOM
Prisoners Dilemma (PD)	EMOTICOM
Second Day (Visit 0b,1,2,3): First Session (aprx. 50 min.)	
Rapid Visual Information Processing (RVP)	CANTAB
Delayed Matching to Sample (DMS)	CANTAB
Progressive Ratio Task (PRT)	EMOTICOM
New Cambridge Gambling Task (NCGT)	EMOTICOM
Second Day (Visit 0b,1,2,3): Second Session (aprx. 50 min.)	
Face Affective Go/NoGo (FAGNG)	EMOTICOM
Reinforcement Learning Task (RLT)	EMOTICOM
Theory of Mind (ToM)	EMOTICOM
Ultimatum Game (UG)	EMOTICOM

Table 10: Single-blind, placebo controlled, acute dose, cross-over, randomized medication challenge

Screening	**Baseline Assessment**	***Acute Challenge***		
Visit -1 Week -4/-1	Visit 0a & 0b Week 0	Visit 1 Week 2 (acute)	Visit 2 Week 3 (acute)	Visit 3 Week 4 (acute)
Group A Aggressive ODD/CD (N = 60)	Group A1	Placebo	Drug A	Drug B
	Group A2	Drug B	Placebo	Drug A
	Group A3	Drug A	Drug B	Placebo
Group B Aggressive ODD/CD (N = 60)	Group B1	Placebo	Drug C	Drug D
	Group B2	Drug D	Placebo	Drug C
	Group B3	Drug C	Drug D	Placebo
Controls (N = 40)		*No further follow up*		

*(ODD/CD patients and TD controls)

**(only ODD/CD patients)

Drug A = MPH; Drug B = Aripiprazole; Drug C = ATX; Drug D = Risperidone.

Group A: will receive a single dose of a stimulant (Drug A), a single dose of antipsychotic (Drug B) and placebo, each one in a different week, according to their allocation to group A1, A2 or A3.

Group B: will receive a single dose of not stimulant (Drug C), a single dose of antipsychotic (Drug D) and placebo, each one in a different week, according to their allocation to group B1, B2 or B3.

Table 11 List of neuropsychological outcome measures included in the preliminary analysis

CANTAB	
INTRA-EXTRA DIMENSIONAL SET SHIFT (IED) *Measure of visual discrimination and attentional set formation; maintenance, shifting and flexibility of attention*	
Total errors (adjusted)	A measure of accuracy: lower scores indicate better performance.
Stages completed	Indicate the number of stages completd (a total of 9). Higher scores indicate better performance ability of shift.
DELAYED MATCHING TO SAMPLE (DMS) *Measure of matching and short term visual memory*	
% correct simultaneous	Percentage of correct simultaneous responses: accuracy in recognizing the correct image in when the target is present.
% correct all delays	Percentage of correct responses selceted when the target stimulus and the distractors after the stimulus had been hidden with delays of 0 ms, 4000 ms, 12000 ms.
% correct	Percentage of total correct responses.
RAPID VISUAL INFORMATION PROCESSING (RVP) *Measure of visual sustained attention*	
Total false alarm	Number of timest he subject responds outiside the response window of a target sequence
Probability to hit	Measure of accuracy: hits/(hits+misses)
RVP A'	Signal detection measure of Sensitivity to the target, regardless of response tendency (measure of how good ist he subject in detecting target sequences using probability of hit and probability of FA
Mean Latency	Reaction time to stimuli (ms)

EMOTICOM	
FACE AND EYES EMOTIONAL RECOGNITION TASK (FEERT) Measure of the ability to identify emotions in facial/eyes expressions	
% correct Happy % correct Sad % correct Angry % correct Fear % correct tot	accuracy across all four emotions and for each emotion (happiness, sadness, anger or fear): correct responses
Affective Bias	Affective bias scores were calculated by subtracting accuracy for sad faces from accuracy for happy faces (% Happy correct-% Sad correct). Higher values indicate a difficulty in recognizing sadness
Mean Tot RT - Mean Happy RT - Mean Sad RT - Mean Anger RT - Mean Fear RT	overall response latencies: mean reaction times are calculated for total stimuli and for each of the four emotions. higher scores indicate longer time in providing a correct answer.
MORAL JUDGMENT (MJ) Assesses normative emotional reactions to being a victimiser (agent) or a victim in a moral situation	
GUILT agent - GUILT agent intentional - GUILT agent unintentional - GUILT victim - GUILT victim intentional - GUILT victim unintentional BAD/GOOD agent - BAD/GOOD intentional - BAD/GOOD unintentional - BAD/GOOD victim - BAD/GOOD victim intentional - BAD/GOOD victim unintentional ANNOYED agent - ANNOYED agent intentional - ANNOYED agent unintentional - ANNOYED victim - ANNOYED victim intentional - ANNOYED victim unintentional SHAME agent -SHAME agent intentional - SHAME agent unintentional condition - SHAME victim - SHAME victim intentional - SHAME victim unintentional	ratings (0 to 7) for the emotions: guilt, bad/good, shame and annoyance. results can be looked at across all condition: agent/victim condition (situations in which the subject is asked to identify himself with the victim or with the victimizer) combined with intentional/unintentional condition (situations in which an intentional or accidental harm is acted) in order to explore the effect of intention upon moral emotions in moral scenarios. higher scores indicate greater intensity oft he emotion: greater guilt, greater wellbeing, annoyance, shame

FACE AFFECTIVE GO/NOGO (FAGNG) Assessment of information processing biases for positive and negative facial expressions (biased emotional attention)	
% HIT *% CR* *% HIT+CR*	Measures of accuracy in recognition of a target facial emotion (happiness, sadness, neutral), sad o neutral): HIT= correct responses CR = correct rejections (correctly not given responses) Higher values indicate greater accuracy
% FA *% MISS* *% FA+MISS*	Measures of accuracy in recognition of a target facial emotion (happiness, sadness, neutral), sad o neutral): FA = incorrect responses MISS = incorrectly not given responses. Higher values indicate less accuracy
mean RT HIT	Mean reaction times (RT) for hit responses. (HIT=correct answers). Higher values indicate greater latency.
mean RT FA	Mean reaction times (RT) for false alarm (FA=incorrect responses). Higher values indicate greater latency
Affective Bias	Affective bias scores are calculated by subtracting the sad target/happy distract condition RT from the happy target/sad distractor condition RT (mean HIT happy/sad RT – mean HIT sad / happy RT). Higher values indicate greater difficulty in recognizing sadness
THEORY OF MIND (TOM) Measures of information sampling in socially ambiguous situations	
% faces % thoughts % facts	Measure of the proportion of faces (feelings)/ thoughts/facts that are selected by the subjects to help resolve ambiguity

NEW CAMBRIDGE GAMBLING TASK (NCGT) Measure to assess decision-making and risk-taking behavior and to investigate reward seeking and punishment avoidance separately.	
Win Risk adjustments Loss Risk adjustments	risk-taking behavior assessment in win and in loss condition risk adjustment (RA) score using the formula: Risk adjustment = (2*bet at 90%) + (1*bet at 80%) + (0*bet at 70%) - (1*bet at 60%) - (2*bet at 50%)/Average bet. RA was calculated for win and loss conditions separately.
Win Mean Bet Loss Mean Bet	average value of chips placed on each level of probability was calculated separately for the win and loss conditions

Tab. 12 Samples characteristics

	CD/ODD (n=63)	TDC (n=40)	p
	mean (SD)	*mean (SD)*	
Age at streening	13.29 (±1.94)	12.85 (±1.65)	n.s.
Age at onset	8.59 (±3.25)	-	
Age at diagnosis	11.23 (±2.9)	-	
	n (%)	*n (%)*	
Male	52 (82.5%)	38 (95%)	n.s.
Female	11 (17.5%)	2 (5%)	
ODD	53 (84.1%)	-	
CD	2 (3.2%)	-	
ODD + CD	8 (12.7%)	-	

Tab. 13 Comparison between CD/ODD and TDC: IQ

	CD/ODD	TDC	p
	mean	*mean*	
VCI	104.09	115.95	**<.001**
PRI	104.33	118.45	**<.001**
WMI	89.50	105.03	**<.001**
PSI	91.90	106.85	**<.001**
IQ	98.93	116.85	**<.001**

IQ: Intelligence Quotient; Verbal: VCI: Verbal Comprehension Index; PRI: Perceptual Reasoning Index; WMI: Working Memory Index; PSI: Processing Speed Index.

Tab. 14 Comparison between CD/ODD and TDC: NISONGER CBRF Typ. IQ version scale

	CD/ODD (n=63)	TDC (n=40)	p
	mean (SD)	**mean (SD)**	
Positive social	11.34 (± 4.28)	25.28 (± 3.30)	**<.001**
Overly sensitive	6.80 (± 3.06)	2.53 (± 2.07)	**<.001**
Oppositional	21.95 (± 3.20)	3.68 (± 3.10)	**<.001**
Conduct Problem	14.52 (± 5.95)	1.13 (± 1.24)	**<.001**
Hyperactive	7.05 (± 2.99)	1.02 (± 1.49)	**<.001**
Inattentive	14.72 (± 3.76)	2.50 (± 3.18)	**<.001**
Withdrawn/dysphoric	15.77 (± 9.55)	4.20 (± 3.34)	**<.001**
Social competence	*11.34 (± 4.28)*	*25.28 (± 3.30)*	***<.001***
D-Total [cut off =27]	*36.64 (± 7.43)*	*4.85 (± 3.79)*	***<.001***
ADHD Total	*21.70 (± 5.98)*	*3.53 (± 4.43)*	***<.001***

Tab. 15 Comparison between CD/ODD and TDC: MOAS scale

	CD/ODD (n=63)	TDC (n=40)	p
	mean (SD)	**mean (SD)**	
verbal aggression	2.44 (± 0.65)	0.08 (± 0.27)	**<.001**
aggression against property	3.80 (± 1.92)	0.05 (± 0.32)	**<.001**
auto-aggression	2.11 (± 2.81)	0 (± 0)	**<.001**
physical aggression	6.30 (± 3.61)	0.1 (± 0.63)	**<.001**
Total	14.54 (± 5.56)	0.23 (± 0.86)	**<.001**

Tab. 16 Comparison between CD/ODD and TDC: ICU questionnaire

	CD/ODD (n=63)	TDC (n=40)	p
	mean (SD)	mean (SD)	
Callousness	14.59 (± 5.75)	3.95 (± 2.14)	**<.001**
Unemotional	7.31 (± 3.22)	3.82 (± 2.12)	**<.001**
Uncaring	15.48 (± 5.47)	7.11 (± 3.2)	**<.001**
TOT [cut off =30]	37.89 (± 10.28)	14.87 (± 5.23)	**<.001**

Tab. 17 Comparison between CD/ODD and TDC: CPRS-SF questionnaire

	CD/ODD (n=63)	TDC (n=40)	p
	mean (SD)	mean (SD)	
Oppositional	70.88 (± 15.33)	42.58 (± 7.81)	**<.001**
Cognitive problems/Inattention	70.18 (± 15.41)	43.71 (± 4.63)	**<.001**
Hyperactivity	68.77 (± 17.71)	43.16 (± 5.52)	**<.001**
ADHD Index	73.51 (± 14.34)	43.39 (± 4.94)	**<.001**

Tab. 18 Comparison between CD/ODD and TDC: CBCL questionnaire

	CD/ODD (n=63)	TDC (n=40)	p
	mean (SD)	mean (SD)	
Anxious-Depressed	64.60 (± 9.88)	52.97 (± 5.06)	**<.001**
Withdrawn-Depressed	64.25 (± 9.83)	53.71 (± 5.19)	**<.001**
Somatic Complaints	59.23 (± 7.74)	53.68 (± 4.29)	**<.001**
Social Problems	64.80 (± 8.83)	52.05 (± 3.41)	**<.001**
Thought Problems	62.72 (± 8.64)	51.63 (± 3.31)	**<.001**
Attention Problems	69.25 (± 8.89)	51.84 (± 3.49)	**<.001**
Rule Breaking Behavior	67.58 (± 6.44)	51.21 (± 2.94)	**<.001**
Aggressive Behavior	74.75 (± 9.07)	51.03 (± 1.78)	**<.001**
Internalizing Problems	64.62 (± 8.69)	48.05 (± 9.62)	**<.001**
Externalizing Problems	71.40 (± 6.3)	43.53 (± 7.27)	**<.001**
Total Problems	69.77 (± 6.58)	42.63 (± 10.41)	**<.001**

Tab. 19 Comparison between CD/ODD and TDC: YSR questionnaire

	CD/ODD (n=63)	TDC (n=40)	p
	mean (SD)	mean (SD)	
Anxious-Depressed	57.85 (± 7.91)	55.03 (± 6.13)	.082
Withdrawn-Depressed	56.20 (± 6.09)	53.00 (± 0.94)	**.017**
Somatic Complaints	57.07 (± 6.07)	53.89 (± 5.68)	**.047**
Social Problems	56.39 (± 7.19)	53.06 (± 5.45)	**.023**
Thought Problems	59.04 (± 8.85)	51.64 (± 3.81)	**<.001**
Attention Problems	65.15 (± 10.95)	52.53 (± 4.29)	**<.001**
Rule Breaking Behavior	61.57 (± 8.59)	51.53 (± 3.71)	**<.001**
Aggressive Behavior	69.17 (± 9.58)	52.92 (± 4.84)	**<.001**
Internalizing Problems	56.26 (± 9.71)	49.47 (± 9.77)	**.002**
Externalizing Problems	66.09 (± 8.26)	46.11 (± 8.74)	**<.001**
Total Problems	62.57 (± 8.52)	45.94 **(±** 10.03**)**	**<.001**

Tab. 20 Comparison between CD/ODD and TDC: TRF questionnaire

	CD/ODD (n=63)	TDC (n=40)	p
	mean (SD)	mean (SD)	
Anxious-Depressed	60.05 (± 5.73)	56.37 (± 7.01)	**.012**
Withdrawn-Depressed	59.92 (± 9.95)	52.80 (± 3.71)	**<.001**
Somatic Complaints	55.26 (± 6.27)	53.03 (± 3.71)	.082
Social Problems	64.38 (± 6.05)	52.33 (± 5.01)	**<.001**
Thought Problems	58.36 (± 8.76)	51.70 (± 2.81)	**<.001**
Attention Problems	69.02 (± 9.60)	51.07 (± 2.80)	**<.001**
Rule Breaking Behavior	68.76 (± 7.22)	51.43 (± 3.47)	**<.001**
Aggressive Behavior	74.84 (± 10.18)	51.33 (± 2.93)	**<.001**
Internalizing Problems	60.04 (± 6.69)	52.00 (± 8.95)	**<.001**
Externalizing Problems	72.56 (± 7.18)	44.67 (± 7.01)	**<.001**
Total Problems	69.36 (± 6.69)	45.33 (± 8.60)	**<.001**

Tab. 21 Comparison between CD/ODD and TDC: BRIEF questionnaire

	CD/ODD (n=63)	TDC (n=40)	p
	mean (SD)	mean (SD)	
Inhibit	42.79 (± 29.39)	27.84 (± 18.78)	**.007**
Shift	33.21 (± 24.66)	24.58 (± 16.4)	.061
Emotional Control	40.35 (± 25.33)	29.32 (± 19.69)	**.026**
Initiate	35.79 (± 24.88)	25.71 (± 17.96)	**.034**
Working memory	39.75 (± 24.61)	25.37 (± 16.05)	**.002**
Plan/organize	43.12 (± 20.83)	28.13 (± 16.07)	**<.001**
Organization of materials	32.46 (± 23.97)	25.84 (± 20.12)	.164
Monitor	37.89 (± 24.98)	27.26 (± 19.15)	**.029**
Behaviour Regulation Index	64.11 (± 14.4)	38.42 (± 9.09)	**<.001**
Metacognition Index (MI)	82.47 (± 26.12)	52.50 (± 12.72)	**<.001**
Global Executive Composite	121.19 (± 45.78)	65.29 (± 25.41)	**<.001**

Tab. 22 Case control study: comparison on IED (a task from CANTAB battery)

	CD/ODD (n=58)	TDC (n=39)	p
	mean (SD)	mean (SD)	
Total errors (adjusted)	39.12 (±25,36)	27.10 (± 34.611)	.051
Stages completed	8.19 (± 1.115)	8.54 (± 1.536)	.198

Tab. 23 Case control study: comparison on DMS (a task from CANTAB battery)

	CD/ODD (n=56)	TDC (n=40)	p
	mean (SD)	mean (SD)	
% total correct	77.009 (± 13.28)	87.188(± 9.938)	**.000**
% correct (simultaneous)	92.50 (± 12.098)	98.50 (± 6.6216)	**.005**
% correct (all delay)	71.845 (± 15.73)	83.416 (± 12.15)	**.000**

Tab. 24 Case control study: comparison on RVP (a task from CANTAB battery)

	CD/ODD (n=53)	TDC (n=40)	p
	mean (SD)	mean (SD)	
RVP A' (sensitivity to the target)	0.81 (± 0.07)	0.86 (± 0.05)	**.000**
Probability of hit (Accuracy)	0.44 (± 0.22)	0.48 (± 0.18)	.399
Total false allarm (incorrect/missed)	20.49 (± 25.82)	3.75 (± 7.69)	**.000**
Mean latency (RT)	588.04 (± 189.55)	483.08 (± 104.1)	**.002**
Meann latency	517.92 (± 203.25)	416.36 (± 84.10)	**.004**

Tab. 25 Case control study: comparison on FEERT - FACES (a task from EMOTICOM battery)

	CD/ODD (n=46)	TDC (n=24)	p
	mean (SD)	mean (SD)	
%Tot correct	55.81 (± 12.81)	65.88 (± 11.93)	**.002**
% Happy correct	69.67 (± 18.39)	77.92 (± 13.26)	.056
% Sad correct	48.59 (± 17.53)	62.08 (± 18.05)	**.003**
% Anger correct	41.09 (± 18.31)	46.88 (± 15.38)	.190
% Fear correct	63.91 (± 17.31)	76.67 (± 15.85)	**.004**
Affective bias ***(% Happy correct - % Sad Correct)***	21.09 (± 16.79)	15.83 (± 18.74	.237
Mean Tot RT	1.65 (± 0.42)	1.90 (± 0.44)	**.023**
Mean Happy RT	1.49 (± 0.53)	1.68 (± 0.65)	.213
Mean Sad RT	1.76 (± 0.53)	2.01 (± 0.51)	.074
Mean Anger RT	1.78 (± 0.59)	2.13 (± 0.77)	**.037**
Mean Fear RT	1.55 (± 0.46)	1.78 (± 0.38)	**.046**

Tab. 26 Case control study: comparison on FEERT - EYES (a task from EMOTICOM battery)

	CD/ODD (n=62)	TDC (n=37)	p
	mean (SD)	mean (SD)	
Tot correct %	43.08 (± 15.23)	55.709 (± 16.21)	**.000**
Happy correct %	44.68 (± 22.28)	58.11 (± 21.86)	**.004**
Sad correct %	36.61 (± 20.15)	50.41 (± 22.74)	**.002**
Anger correct %	45.97 (± 17.89)	54.59 (± 17.21)	**.021**
Fear correct %	45.08 (± 20.21)	59.73 (± 20.47)	**.001**
Affective bias ***(%Happy correct-%Sad Correct)***	8.06 (± 22.45)	7.70 (± 25.48)	.941
Mean Tot RT	1.67 (± 0.55)	1.79 (± 0.46)	.253
Mean Happy RT	1.70 (± 0.63)	1.73 (± 0.49)	.814
Mean Sad RT	1.68 (± 0.63)	1.97 (± 0.49)	**.023**
Mean Anger RT	1.62 (± 0.55)	1.70 (± 0.44)	.476
Mean Fear RT	1.67 (± 0.63)	1.78 (± 0.68)	.407

Tab. 27 Case control study: comparison on FAGNG (a task from EMOTICOM battery)

	CD/ODD (n=57)	TDC (n=40)	p
	mean (SD)	**mean (SD)**	
Mean RT HIT	.46 (.10)	.47 (.06)	**.430**
Mean RT FA	.42 (.10)	.39 (.06)	**.159**
AFFECTIVE BIAS ***(happy target/sad distractor RT – sad target/happy distractor RT)***	-.011 (.12)	-.005 (.09)	**.778**
% CR	29.89 (9.44)	37.22 (6.19)	**.000**
% FA	20.10 (9.44)	12.77 (6.19)	**.000**
% HIT	37.45 (7.97)	41.29 (5.30)	**.009**
% MISS	12.54 (7.97)	8.70 (5.30)	**.009**
% CR+HIT	67.35 (13.14)	78.52 (9.43)	**.000**
% FA+MISS	32.64 (13.14)	21.47 (9.43)	**.000**

Tab. 28 Case control study: comparison on MJ (a task from EMOTICOM battery)

	CD/ODD (n=63)	TDC (n=39)	p
	mean (SD)	mean (SD)	
GUILT agent	4.90 (1.47)	6.13 (.66)	**.000**
GUILT agent (intentional condition)	4.61 (1.66)	6.07 (.74)	**.000**
GUILT agent (unintentional condition)	5.19 (1.44)	6.19 (.78)	**.000**
GUILT victim	2.12 (.87)	1.83 (.83)	**.103**
GUILT victim (intentional condition)	2.18 (0.933)	1.93 (.84)	**.173**
GUILT victim (unintentional condition)	2.06 (.941)	1.73 (.95)	**.096**
SHAME agent	4.24 (1.59)	5.56 (.80)	**.000**
SHAME agent (intentional condition)	3.92 (1.71)	5.36 (.99)	**.000**
SHAME agent (unintentional condition)	4.55 (1.61)	5.77 (.83)	**.000**
SHAME victim	2.52 (1.04)	2.66 (1.10)	**.511**
SHAME victim (intentional condition)	2.88 (1.19)	3.31 (1.17)	**.074**
SHAME victim (unintentional condition)	2.16 (1.08)	2.01 (1.19)	**.516**
BAD/GOOD agent	2.98 (1.26)	2.32 (.80)	**.005**
BAD/GOOD agent (intentional condition)	3.11 (1.39)	2.36 (.85)	**.003**
BAD/GOOD agent (unintentional condition)	2.85 (1.28)	2.28 (.88)	**.018**
BAD/GOOD victim	2.74 (1.17)	2.45 (.88)	**.181**
BAD/GOOD victim (intentional condition)	2.71 (1.21)	2.36 (1.18)	**.166**
BAD/GOOD victim (unintentional condition)	2.78 (1.23)	2.53 (.70)	**.256**
ANNOYED agent	3.64 (1.40)	3.21 (1.54)	**.149**
ANNOYED agent (intentional condition)	3.52 (1.46)	3.26 (1.45)	**.380**
ANNOYED agent (unintentional condition)	3.76 (1.54)	3.16 (1.68)	**.068**
ANNOYED victim	5.37 (1.13)	6.09 (.75)	**.001**
ANNOYED victim (intentional condition)	5.43 (1.22)	6.02 (.79)	**.001**
ANNOYED victim (unintentional condition)	5.31 (1.20)	5.98 (.81)	**.003**

Tab. 29 Case control study: comparison on TOM (a task from EMOTICOM battery)

	CD/ODD (n=58)	TDC (n=40)	p
	mean (SD)	mean (SD)	
% faces/72	23.01 (± 17.69)	13.61 (± 17.43)	**.011**
% thoughts/72	45.83 (± 21.78)	50.69 (± 17.01)	.240
% facts/72	31.05 (± 11.96)	35.69 (± 12.48)	.067

Tab. 30 Case control study: comparison on NCGT (a task from EMOTICOM battery)

	CD/ODD (n=59)	TDC (n=40)	p
	mean (SD)	mean (SD)	
Mean Bet (win condition)	.24 (± 0.01)	.23 (± 0.01)	**.009**
WIN Risk adjustment	.25 (± 1.29)	1.25 (± 1.33)	**.000**
Mean Bet (loss condition)	.28 (± 0.01)	.23 (± 0.01)	**.036**
LOSS Risk adjustment	.51 (± 1.31)	1.15 (± 1.43)	**.023**

Tab. 31 Comparison between CD/ODD subgroups by ICU Total score: CBCL questionnaire

	ICU ≤ 32 (n=21)	ICU > 32 (n=39)	p
CBCL	**Mean (SD)**	**Mean (SD)**	
Anxious-Depressed	63.86 (± 8.4)	65 (± 10.7)	n.s.
Withdrawn-Depressed	60.5 (± 8.8)	66.3 (± 9.8)	**0.028**
Somatic Complaints	59.19 (± 7.8)	59.26 (± 7.8)	n.s.
Social Problems	62.43 (± 5.6)	66.08 (± 10)	n.s.
Thought Problems	62.48 (± 7.7)	62.85 (± 9.2)	n.s.
Attention Problems	66 (± 5.6)	71 (± 9.9)	**0.040**
Rule Breaking Behavior	65.3 (± 6.3)	68.8 (± 6.3)	**0.046**
Aggressive Behavior	73.71 (± 9)	75.3 (± 9.2)	n.s.
Internalizing Problems	62.86 (± 7.7)	65.6 (± 9.3)	n.s.
Externalizing Problems	70.5 (± 5.4)	71.9 (± 6.7)	n.s.
Total Problems	69.19 (± 5.8)	70.08 (± 7)	n.s.

Table 32. Comparison between CD/ODD subgroups by ICU Total score: YSR questionnaire

	ICU ≤ 32 (n=15)	ICU > 32 (n=30)	p
	Mean (SD)	**Mean (SD)**	
Anxious-Depressed	57.93 (± 6.8)	57.4 (± 8.3)	n.s.
Withdrawn-Depressed	52.5 (± 4)	58 (± 6.3)	**0.015**
Somatic Complaints	56.4 (± 8.2)	56.9 (± 7.6)	n.s.
Social Problems	53.3 (± 4.6)	57.4 (± 7.4)	**0.009**
Thought Problems	56.5 (± 6.4)	59.5 (± 8.8)	**0.007**
Attention Problems	62.8 (± 9.8)	65.9 (± 11.4)	n.s.
Rule Breaking Behavior	59.07 (± 7.8)	62.23 (± 8.4)	n.s.
Aggressive Behavior	66.9 (± 9.1)	69.6 (± 9)	**0.045**
Internalizing Problems	54.2 (± 7.9)	56.8 (± 10.3)	n.s.
Externalizing Problems	63.8 (± 7.7)	66.6 (± 7.9)	**0.035**
Total Problems	59.3 (± 7.2)	63.5 (± 8.1)	**0.013**

Table 33. Comparison between CD/ODD subgroups by ICU Total score: BRIEF questionnaire

	ICU ≤ 32 (n=21)	ICU >32 (n=36)	p
	Mean (SD)	**Mean (SD)**	
Inhibit	34.7 (± 25.6)	47.5 (± 30.7)	n.s.
Shift	26.3 (± 22.8)	37.2 (± 25.1)	n.s.
Emotional Control	33.6 (± 23.8)	44.3 (± 25.7)	n.s.
Initiate	28.9 (± 21.8)	39.8 (± 26)	n.s.
Working memory	33.6 (± 23.8)	43.3 (± 24.7)	n.s.
Plan/organize	36.2 (± 17.2)	47.2 (± 21.9)	n.s.
Organization of materials	25.1 (± 19.5)	36.8 (± 25.5)	n.s.
Monitor	31 (± 21.9)	41.9 (± 26)	n.s.
Behaviour Regulation Index	57.7 (± 13.6)	67.8 (± 13.7)	**0.009**
Metacognition Index (MI)	80.4 (± 23.5)	83.7 (± 27.8)	n.s.
Global Executive Composite	123.6 (± 39.8)	119.8 (± 49.4)	n.s.

Table 34. Comparison between CD/ODD subgroups by ICU Total score: FEERT Eyes (EMOTICOM)

	ICU ≤ 32 (n=20)	ICU > 32 (n=40)	p
	Mean (SD)	**Mean (SD)**	
Tot correct %	49 (± 14.9)	41.3 (± 14.4)	**0.016**
Happy correct %	49 (± 24.7)	43.1 (± 21.2)	n.s.
Sad correct %	46 (± 20.1)	33 (± 18.9)	**0.017**
Anger correct %	53.5 (± 13.9)	43.5 (± 18.2)	**0.012**
Fear correct %	47.5 (± 23.4)	45.4 (± 17.7)	n.s.
Affective bias	3 (± 26.7)	10.1 (± 20.3)	n.s.
Mean Tot RT	1.9 (± 0.7)	1.6 (± 0.4)	**0.032**
Mean Happy RT	1.9 (± 0.8)	1.6 (± 0.5)	n.s.
Mean Sad RT	1.9 (± 0.7)	1.6 (± 0.5)	**0.042**
Mean Anger RT	1.8 (± 0.6)	1.6 (± 0.5)	n.s.
Mean Fear RT	1.9 (± 0.9)	1.6 (± 0.4)	**0.015**

Table 35. Repeated Measures (GROUP A): DMS (CANTAB)

GROUP A (n= 21)	V 0b	V Placebo	V MPH	V ARI	p
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
% correct	75.1 (± 14.3)	73.9 (± 13.8)	73.6 (± 17.4)	73.2 (± 13.3)	n.s.
% correct (simultaneous)	90.95 (± 12.6)	91.4 (± 11.1)	92.9 (± 9.6)	92.92 (± 10.4)	n.s.
% correct (all delay)	69.8 (± 16.3)	68.1 (± 16.7)	67.1 (± 21.01)	66.6 (± 15.2)	n.s.

Table 36. Repeated Measures (GROUP A): RVP (CANTAB)

GROUP A (n= 21)	V 0b	V Placebo	V MPH	V ARI	p
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
RVP A'	0.81 (± 0.06)	0.83 (± 0.07)	0.82 (± 0.09)	0.83 (± 0.08)	n.s.
Probability of hit	0.49 (± 0.22)	0.49 (± 0.21)	0.52 (± 0.20)	0.53 (± 0.19)	n.s.
Total false allarm	27.4 (± 29.3)	16 (± 23)	20.4 (± 21.8)	19.6 (± 21.9)	n.s.
Mean latency (RT)	604.4 (± 170.2)	585.3 (± 186)	517 (± 195.8)	555 (± 142.6)	n.s.

Table 37. Repeated Measures (GROUP A): FAGNG (EMOTICOM)

GROUP A (n= 23)	V 0b	V Placebo	V MPH	V ARI	p
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Mean RT HIT	0.43 (± 0.1)	0.45 (± 0.1)	0.46 (± 0.07)	0.47 (± 0.1)	n.s.
Mean RT FA	0.42 (± 0.1)	0.43 (± 0.1)	0.39 (± 0.08)	0.44 (± 0.1)	n.s.
AFFECTIVE BIAS	-0.13 (± 0.1)	-0.05 (± 0.2)	-0.09 (± 0.1)	-0.03 (± 0.1)	n.s.
% CR	29.8 (± 10.2)	31.8 (± 12.2)	33 (± 10)	30.7 (± 9.4)	n.s.
%FA	20.2 (± 10.2)	18.2 (± 12.2)	17.02 (± 9.9)	19.3 (± 9.4)	n.s.
%HIT	36.27 (± 9)	37.28 (± 10.4)	40.7 (± 7.5)	36.3 (± 9.2)	**0.028 (MPH > ARI)**
% MISS	13.73 (± 9)	12.71 (± 10.4)	9.3 (± 7.5)	13.7 (± 9.2)	**0.028 (MPH < ARI)**
% CR+HIT	66.05 (± 14.7)	69.05 (± 17.2)	73.7 (± 13.5)	67.02 (±14.3)	**0.020 (MPH > V0b)**
% FA+MISS	33.95 (± 14.7)	30.94 (± 17.2)	26.3 (± 13.5)	33 (± 14.3)	**0.020 (MPH < V0b)**

Table 38. Repeated Measures (GROUP A): NCGT (EMOTICOM)

GROUP A (n=25)	V 0b	V Placebo	V MPH	V ARI	p
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
WIN Risk adjustment	0.075 (± 1.6)	1 (± 1.4)	0.91 (± 1.5)	1.1 (± 1.2)	**0.025** (ARI > V0b)
LOSS Risk adjustment	0.65 (± 1.3)	0.85 (± 1.6)	0.47 (± 1.6)	0.72 (± 1.8)	n.s.

Table 39. Repeated Measures (GROUP A): TOM (EMOTICOM)

GROUP A (n=22)	V 0b	V Placebo	V MPH	V ARI	p
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
% faces/72	23.2 (± 19.6)	21.9 (± 18.4)	19.1 (± 17)	25 (± 15.6)	n.s.
% thoughts/72	44.9 (± 22.5)	42.4 (± 20.5)	46.2 (± 23.1)	41.9 (± 15.9)	n.s.
% facts/72	31.9 (± 10.4)	35.7 (± 10.3)	34.7 (± 13.9)	33.1 (± 11.4)	n.s.

Table 40. Repeated Measures (GROUP B): DMS (CANTAB)

GROUP B (n= 19)	V 0b	V Placebo	V ATX	V RIS	p
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
% correct	76.6 (± 14.5)	70.8 (± 16.6)	72.5 (± 11.4)	72.6 (± 12.5)	n.s.
% correct (simultaneous)	92.1 (± 12.7)	86.3 (± 18.6)	91.1 (± 12.4)	93.7 (± 10.1)	n.s.
% correct (all delay)	71.4 (± 17.3)	65.6 (± 17)	66.3 (± 14.3)	65.6 (± 15.8)	n.s.

Table 41. Repeated Measures (GROUP B): RVP (CANTAB)

GROUP B (n= 20)	V 0b	V Placebo	V ATX	V RIS	p
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
RVP A'	0.8 (± 0.08)	0.8 (± 0.07)	0.8 (± 0.06)	0.8 (± 0.07)	n.s.
Probability of hit	0.41 (± 0.3)	0.42 (± 0.2)	0.41 (± 0.2)	0.39 (± 0.2)	n.s.
Total false allarm	18 (± 25.6)	17.4 (± 34.5)	17.2 (± 30.9)	16.9 (± 38.2)	n.s.
Mean latency (RT)	554.5 (± 225.9)	564 (± 218.6)	568.1 (± 205.6)	526.6(± 171.8)	n.s.

Table 42. Repeated Measures (GROUP B): TOM (EMOTICOM)

GROUP B (n =18)	V 0b	V Placebo	V ATX	V RIS	p
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
% faces/72	15.1 (± 12)	16.8 (± 16.9)	17.8 (± 17.3)	18.1 (± 14.9)	n.s.
% thoughts/72	52.4 (± 20.3)	53.1 (± 19)	54.1 (± 20.1)	50.3 (± 19)	n.s.
% facts/72	32.2 (± 14)	30.1 (± 10.5)	28.1 (± 8.1)	31.6 (± 10.9)	n.s.

Table 43. Repeated Measures (GROUP B): NCGT (EMOTICOM)

GROUP B (n=22)	V 0b	V Placebo	V ATX	V RIS	p
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
WIN Risk adjustment	0.41 (± 1.1)	0.52 (± 1.2)	0.39 (± 1)	0.49 (± 1.1)	n.s.
LOSS Risk adjustment	0.39 (± 1.5)	0.86 (± 1.5)	0.8 (± 1.3)	0.3 (± 1.2)	n.s.

Table 44. Repeated Measures (GROUP B): FAGNG (EMOTICOM)

GROUP B (n= 20)	V 0b	V Placebo	V ATX	V RIS	p
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Mean RT HIT	0.47 (± 0.09)	0.5 (± 0.1)	0.49 (± 0.09)	0.55 (± 0.08)	**0.018** (PI > V0b) **0.000** (RIS > V0b)
Mean RT FA	0.41 (± 0.09)	0.48 (± 0.11)	0.43 (± 0.08)	0.50 (± 0.11)	**0.01** (PI > V0b) **0.000** (RIS > V0b) **0.028** (ATX < PL)
AFFECTIVE BIAS	-0.04 (± 0.1)	-0.06 (± 0.1)	-0.04 (± 0.1)	-0.03 (± 0.2)	n.s.
% CR	30.96 (± 8.4)	33.5 (± 8.4)	35.5 (± 8.1)	35.2 (± 10.4)	**0.023** (ATX > V0b)
%FA	19.04 (± 8.4)	16.5 (± 8.4)	14.5 (± 8.1)	14.8 (± 10.4)	**0.023** (ATX < V0b)
% CR+HIT	68.4 (± 12.8)	71.9 (± 12)	76.1 (± 12.1)	72.7 (± 14.3)	**0.01** (ATX > V0b)
% FA+MISS	31.6 (± 12.8)	28.1 (± 12)	23.9 (± 12.1)	27.3 (± 14.3)	**0.01** (ATX < V0b)

6 Figures

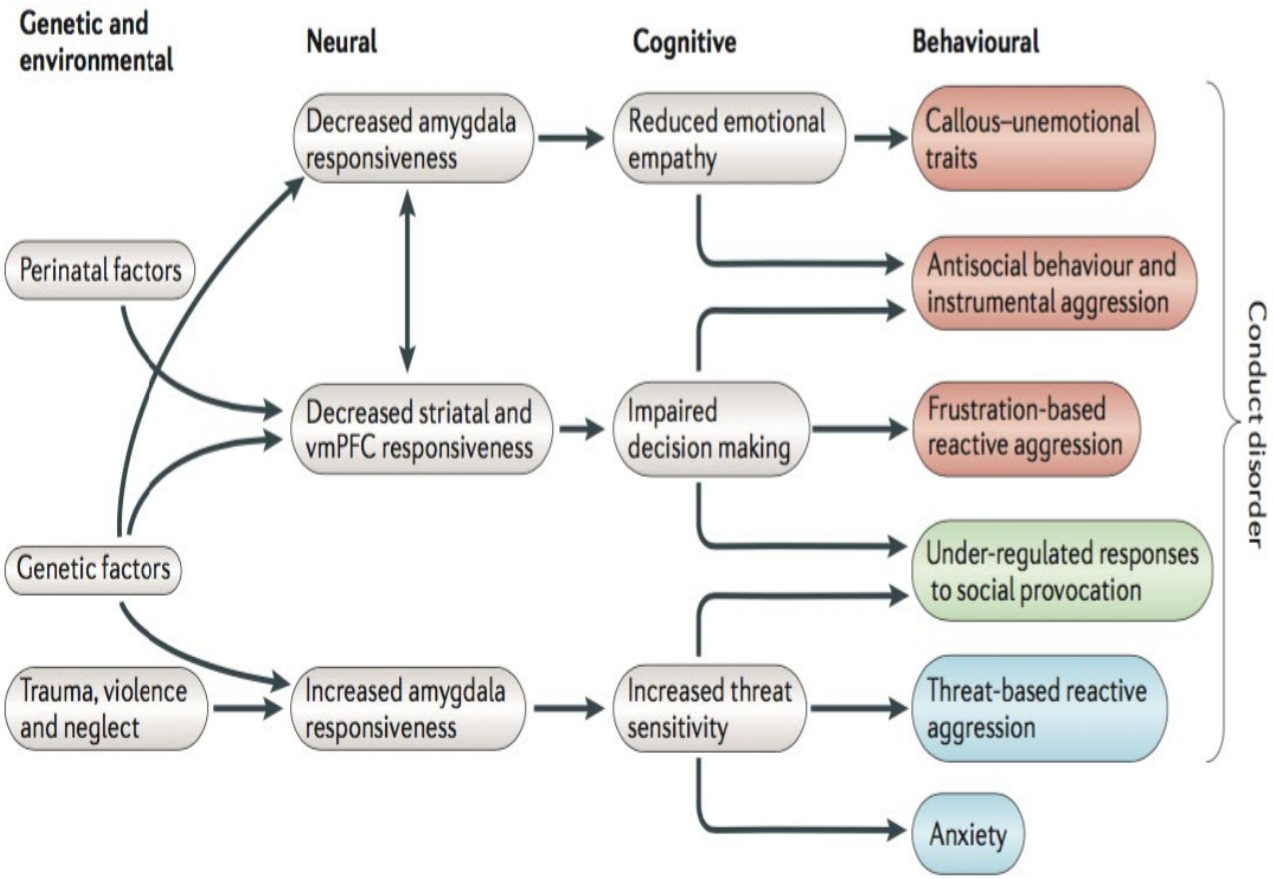

Figure 1: A framework for understanding conduct disorder

Picture from *Blair R.J,R (2013a). The neurobiology of psychopathic traits in youths. Nature Review Neuroscience 14(11):786-99*. In red the phenotype named by authors as “CD with psychopathic traits” (mainly associated with decreased amygdala striatal and vmPFC reactivity, and including CU traits, antisocial behaviour and instrumental behaviour, and frustration-based reactive aggression); in blue the phenotype named as “CD associated with anxiety and emotional lability”.

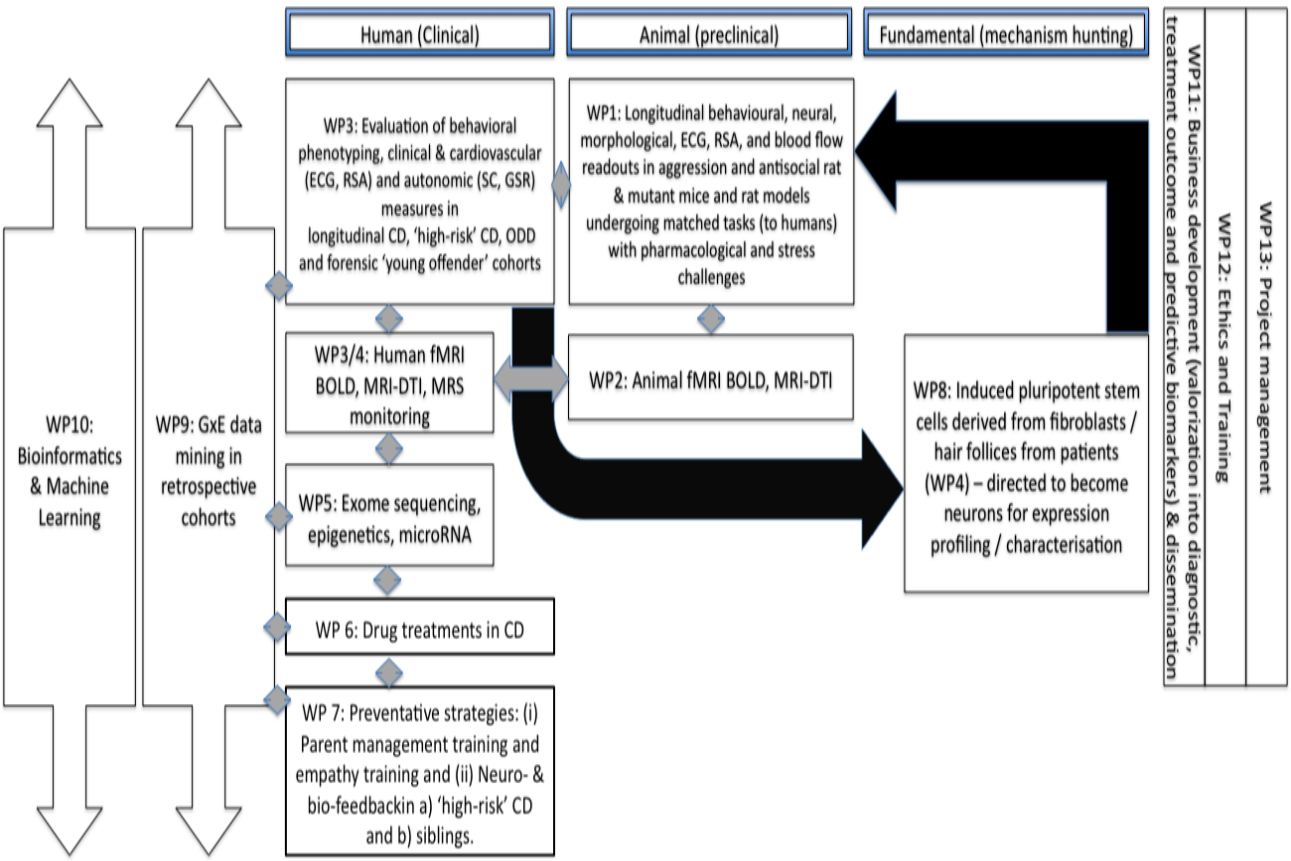

Figure 2. The European MATRICS project: the work packages.

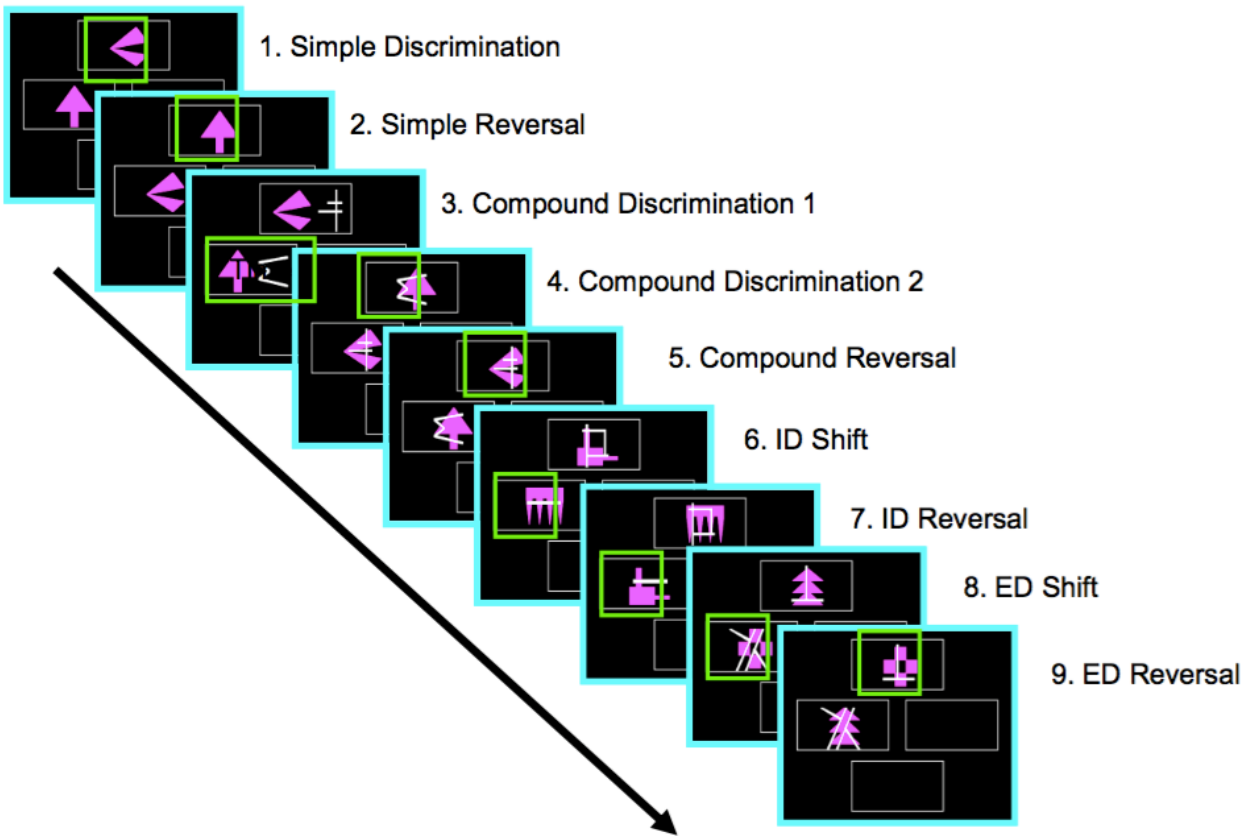

Fig. 3. Intra-Extra Dimensional Set Shift (IED): the stages in the IED test

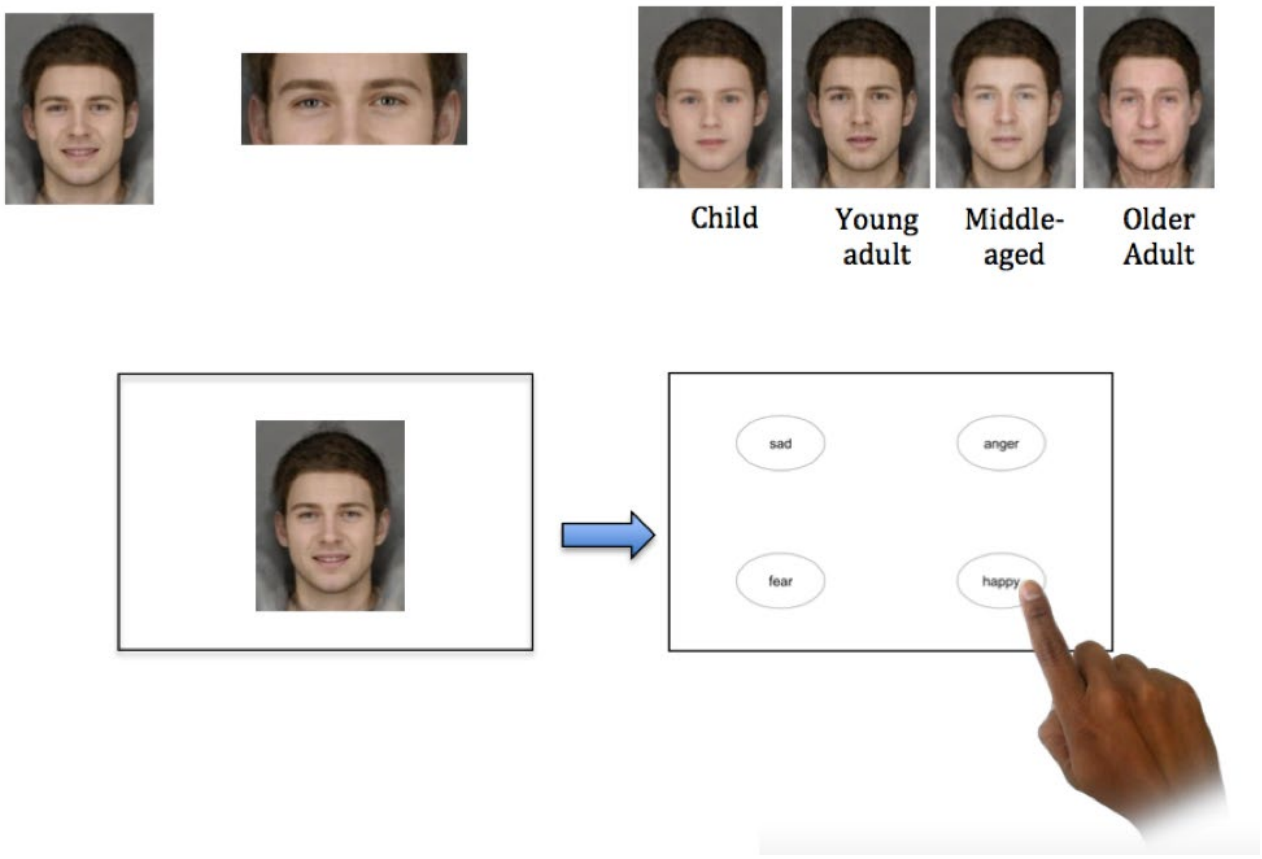

Fig. 4. Face And Eyes Emotional Recognition Task (Feert)

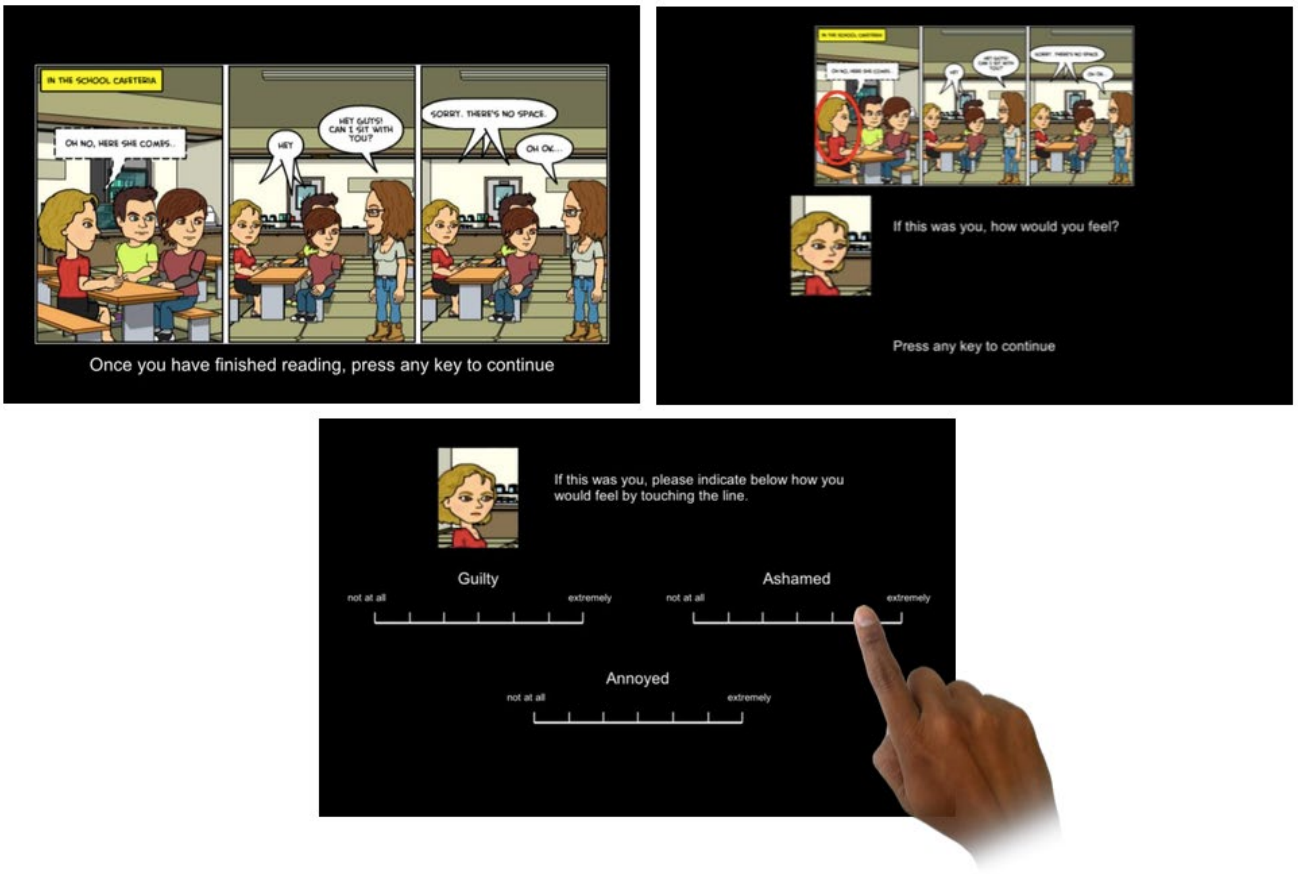

Fig. 5. Moral Judgment (MJ)

Fig. 6. Rapid Visual Information Processing (RVP): the RVP test screen in the training stage.

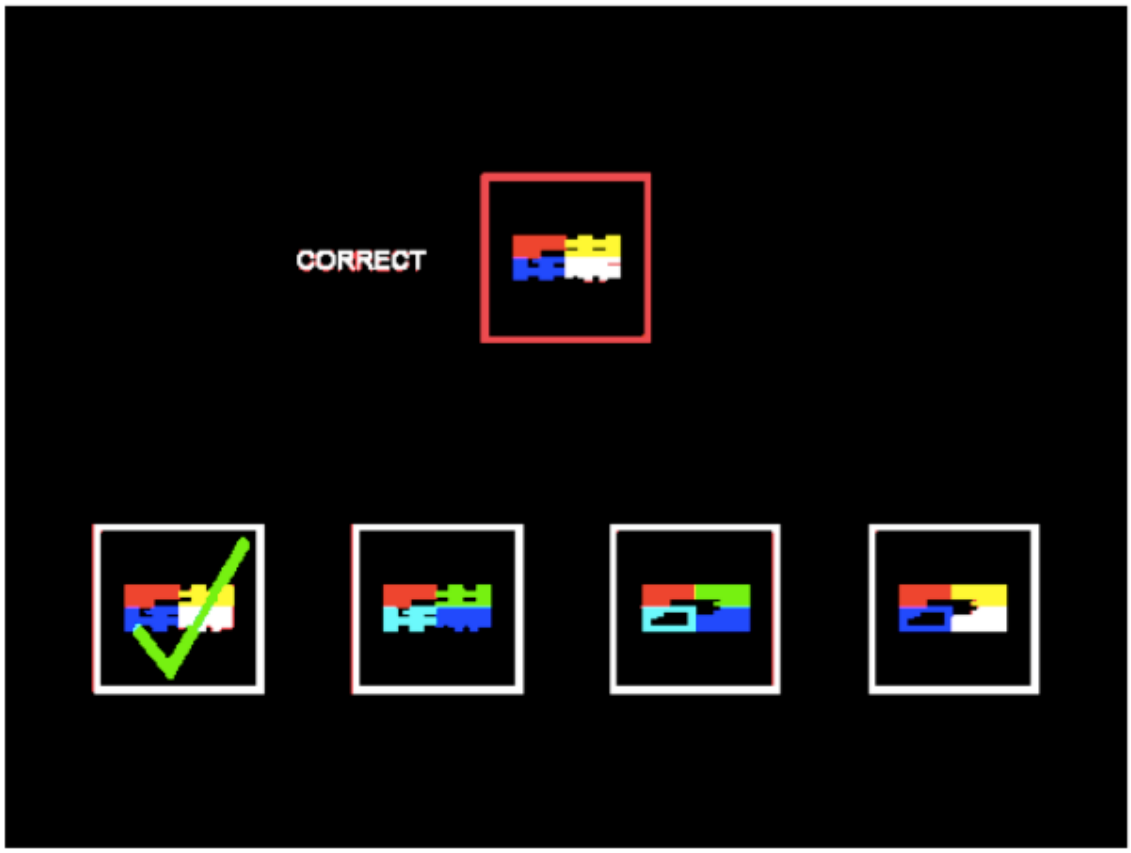

Fig. 7 Delayed Matching To Sample (DMS): the DMS test screen

Fig. 8. Face Affective Go/Nogo (FAGNG)

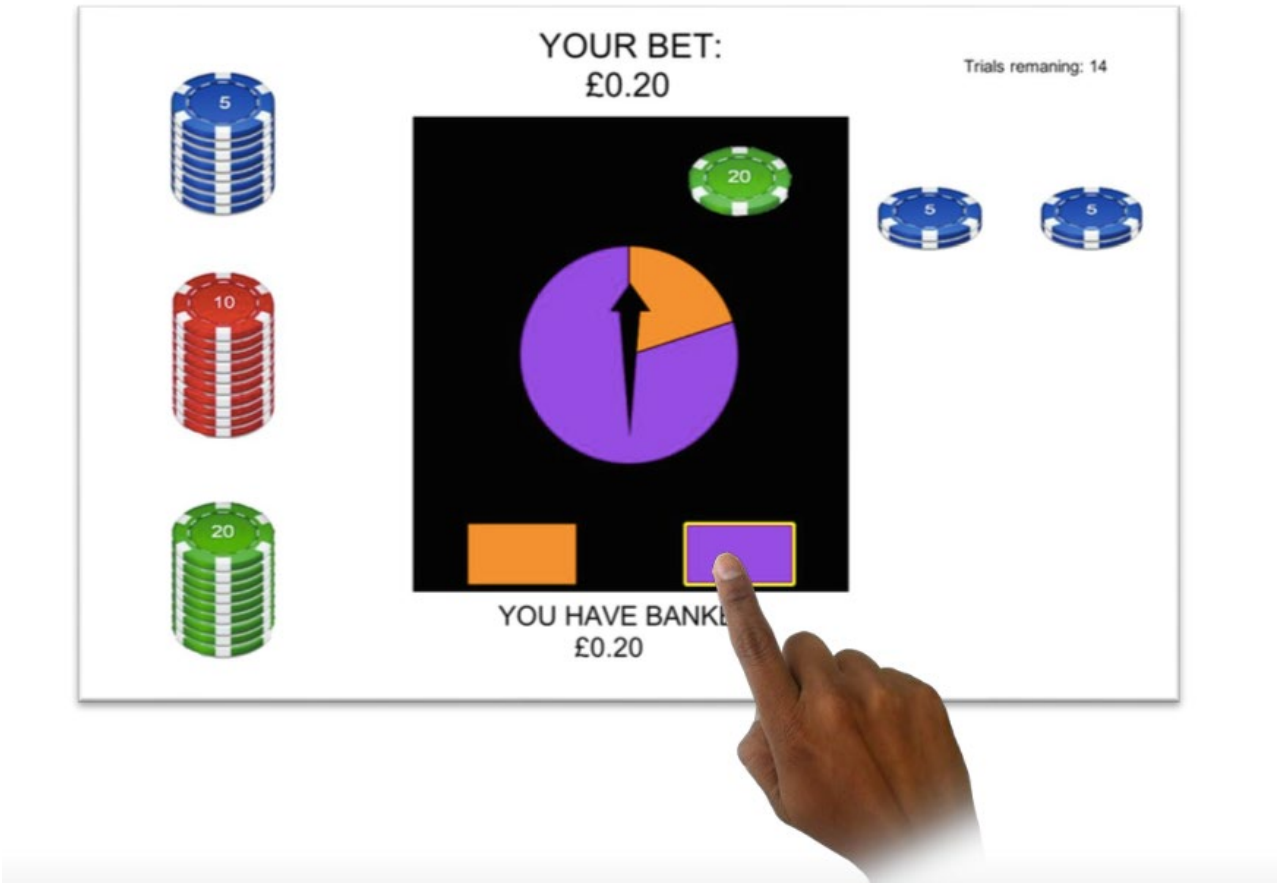

Fig. 9. New Cambridge Gambling Task (NCGT)

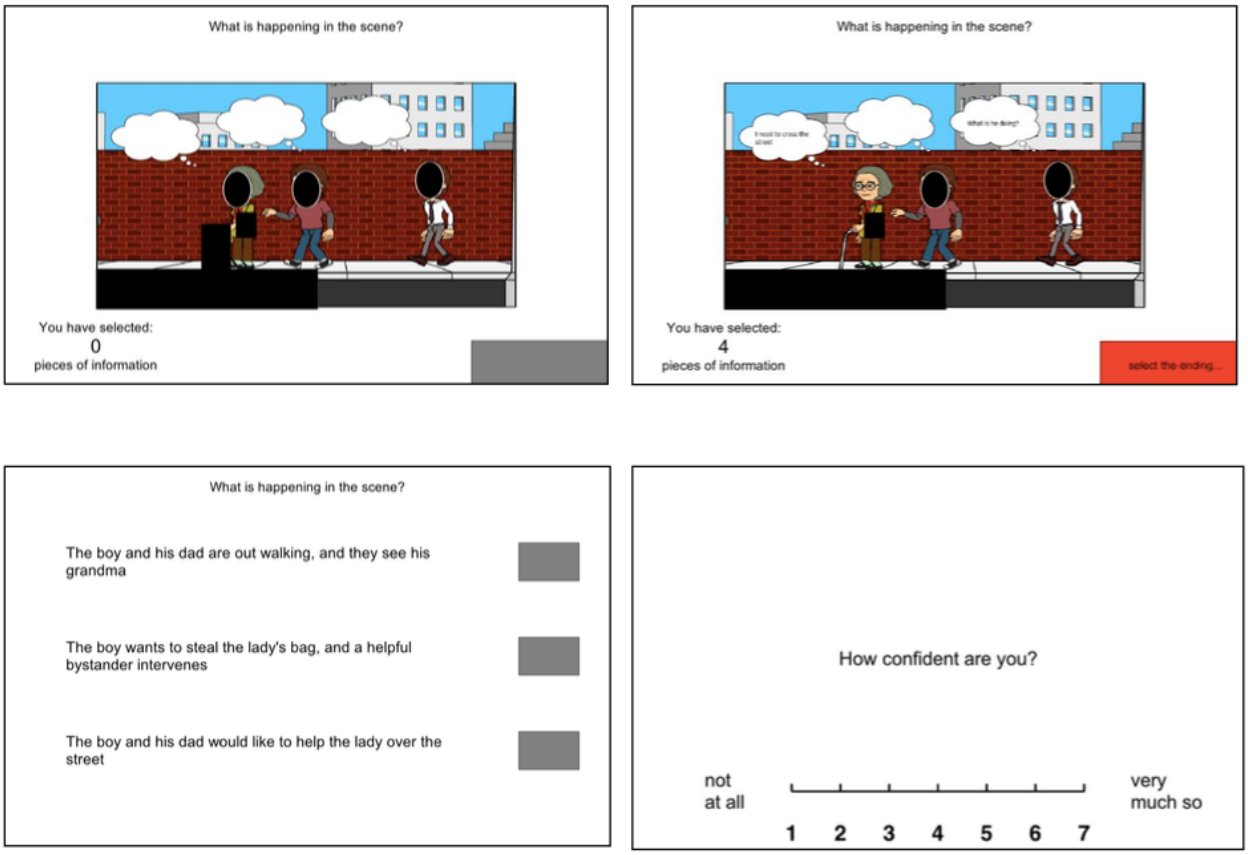

Fig. 10. Theory of Mind (TOM)

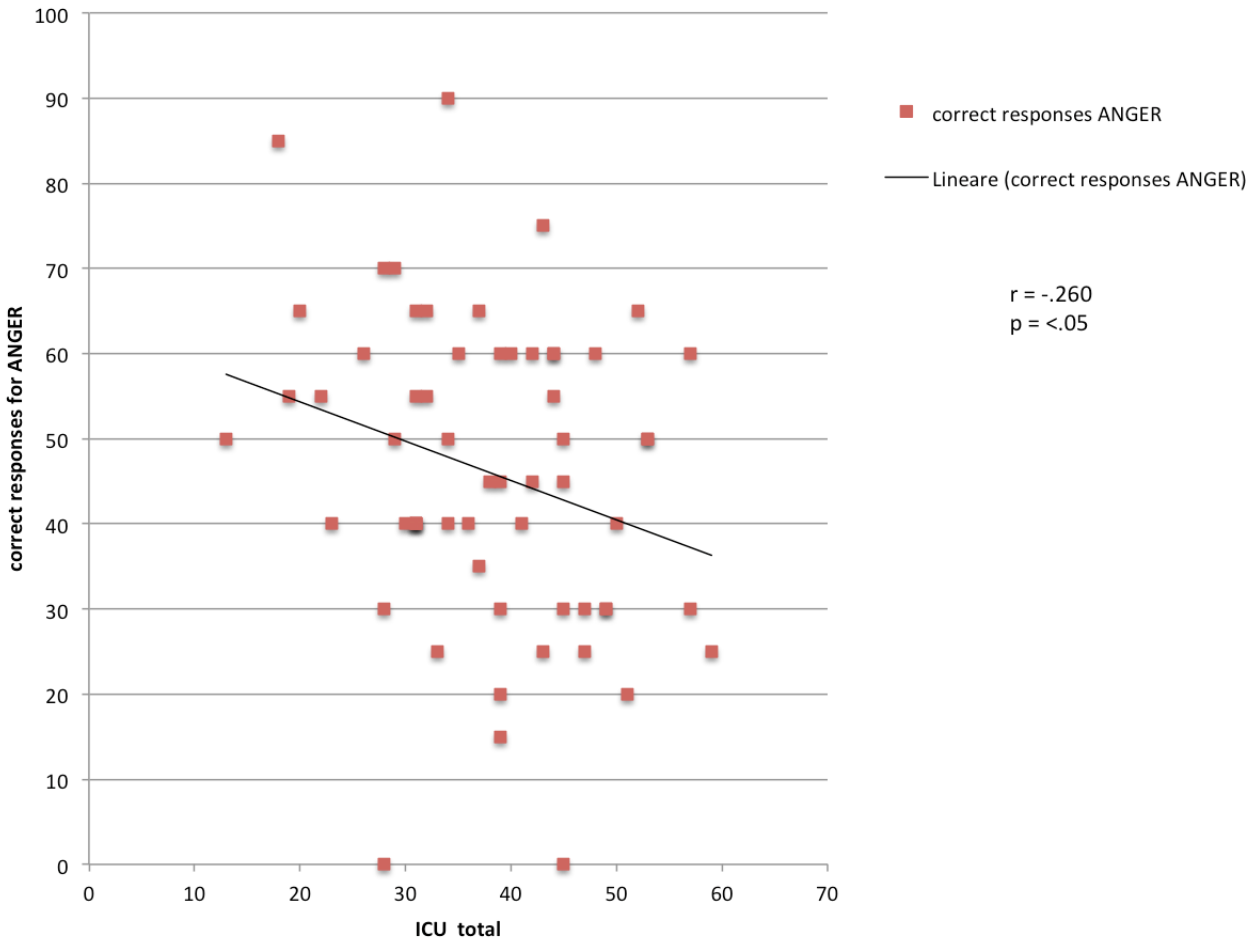

Fig. 11. Correlation between ICU tot score and accuracy in recognition of anger on FEERT eyes.

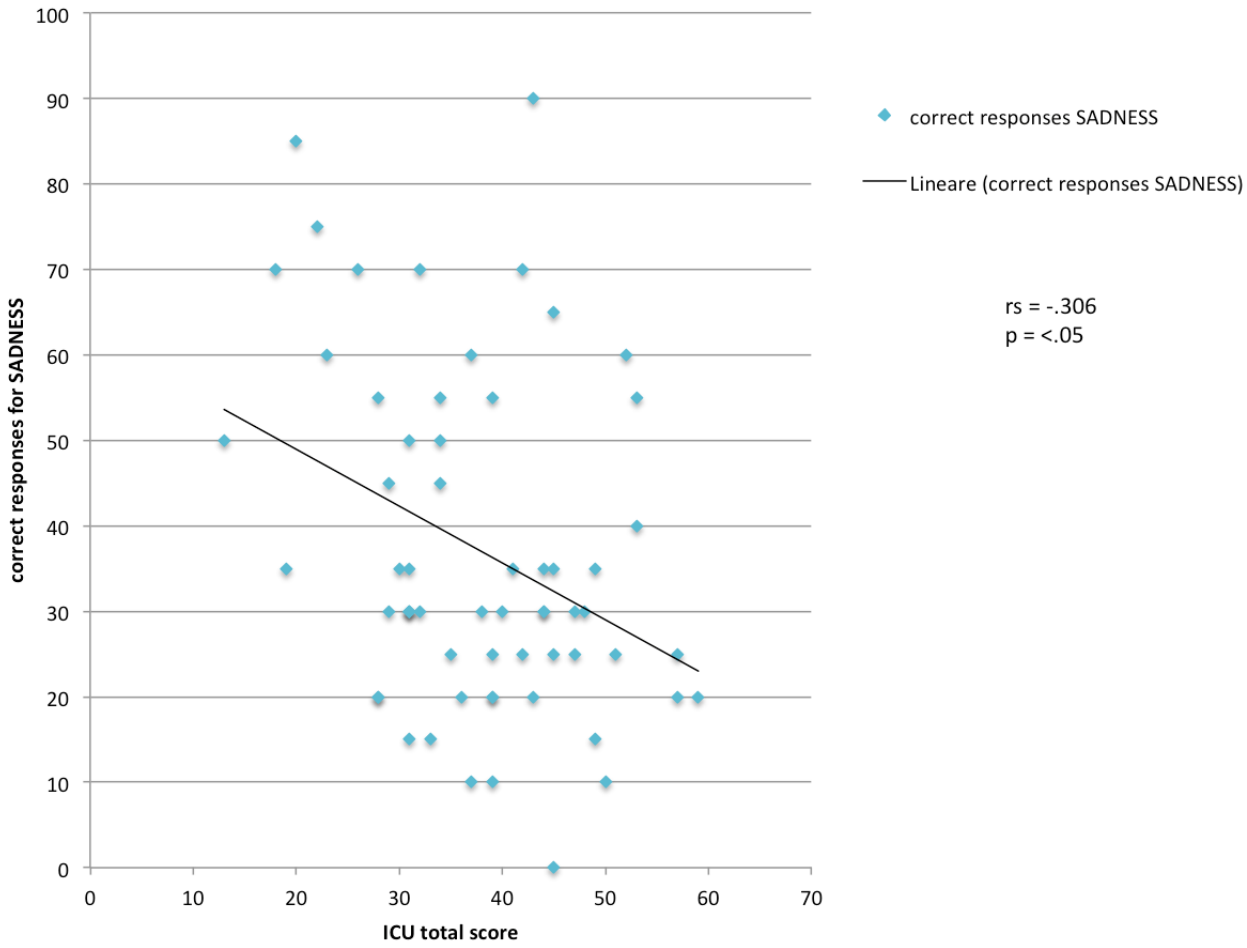

Fig. 12 Correlation between ICU tot score and accuracy in recognition of sadness on FEERT eyes.

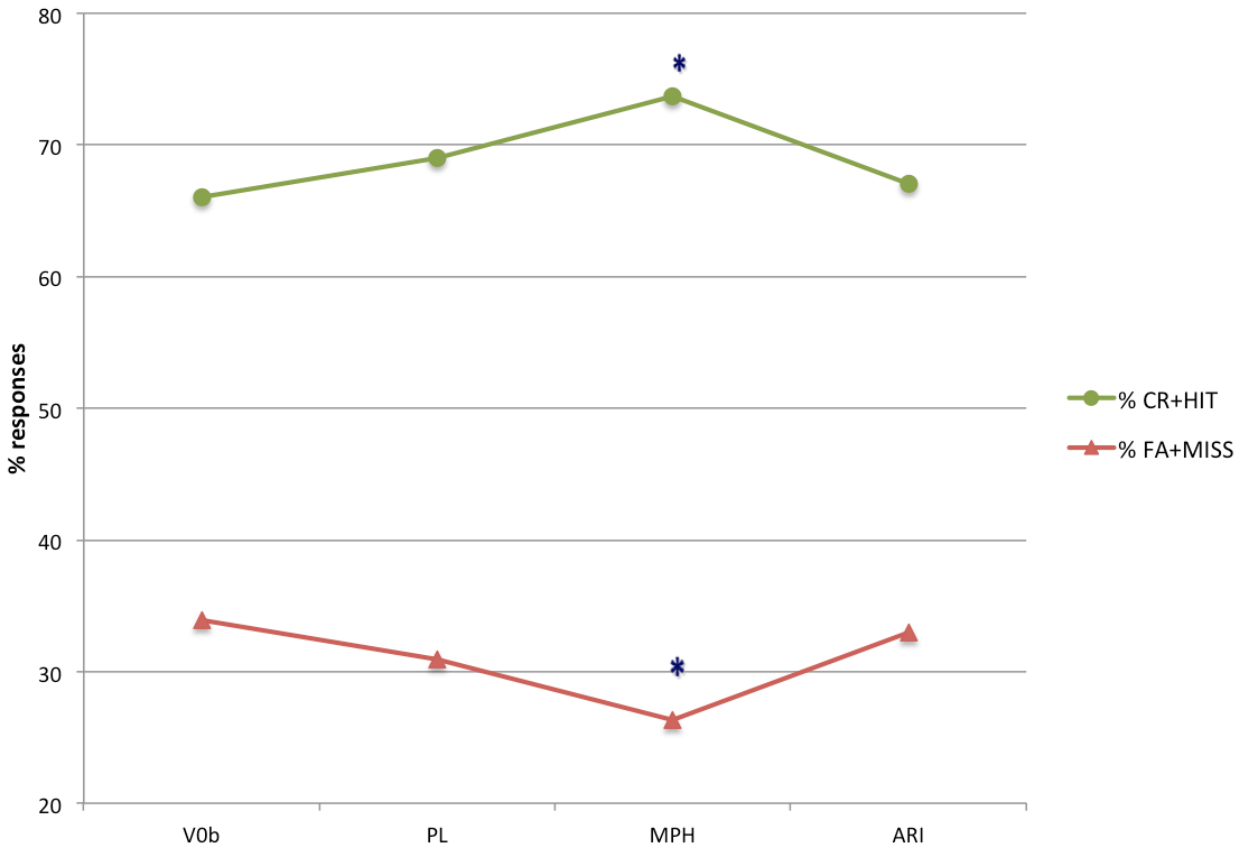

Fig. 13. Repeated measures Group A: effects of drugs on percentage of correct and incorrect responses on FAGNG task. Compared to baseline, Methylphenidate significantly improved accuracy by increasing the percentage of correct responses and reducing the percentage of errors (p = 0.020)

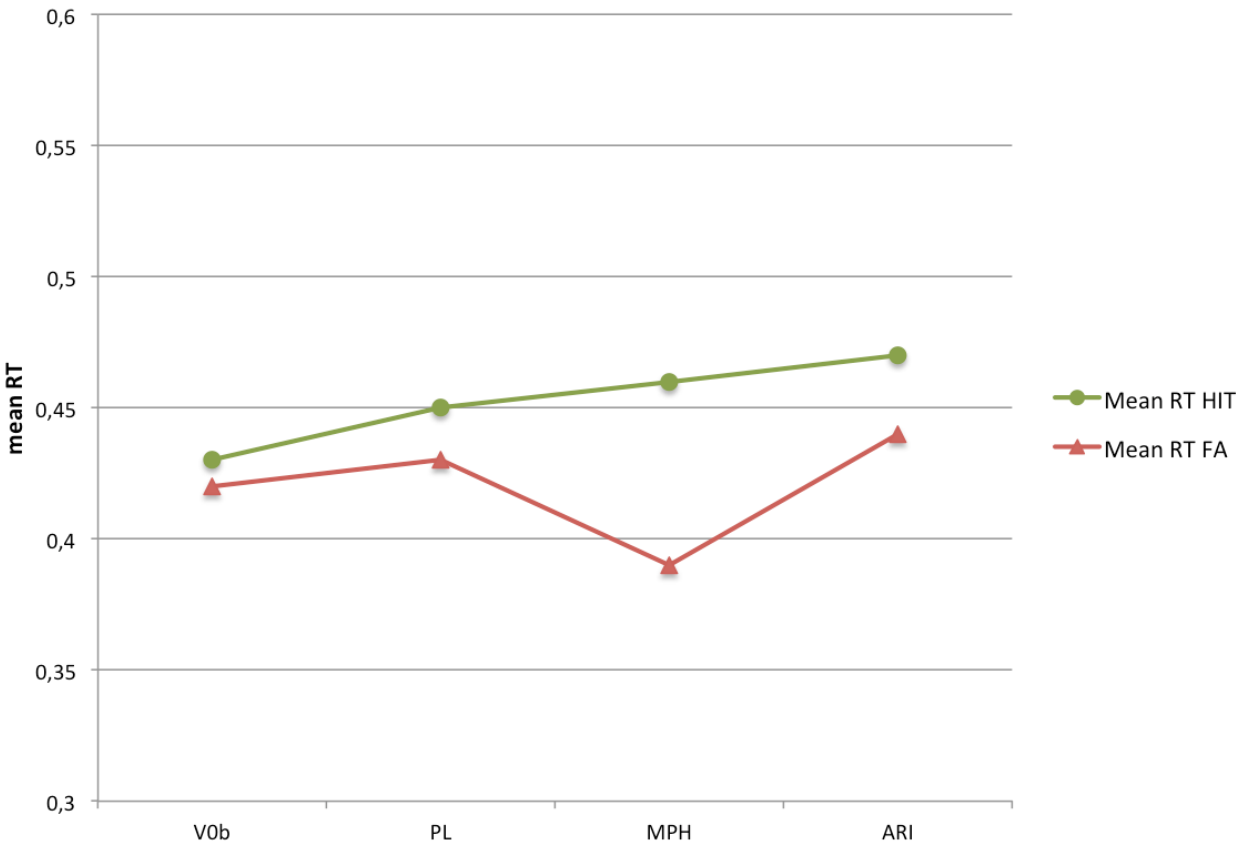

Fig. 14. Repeated measures Group A: effects of drugs on reaction times (RT) on FAGNG task. No drug administered significantly changed responses latency.

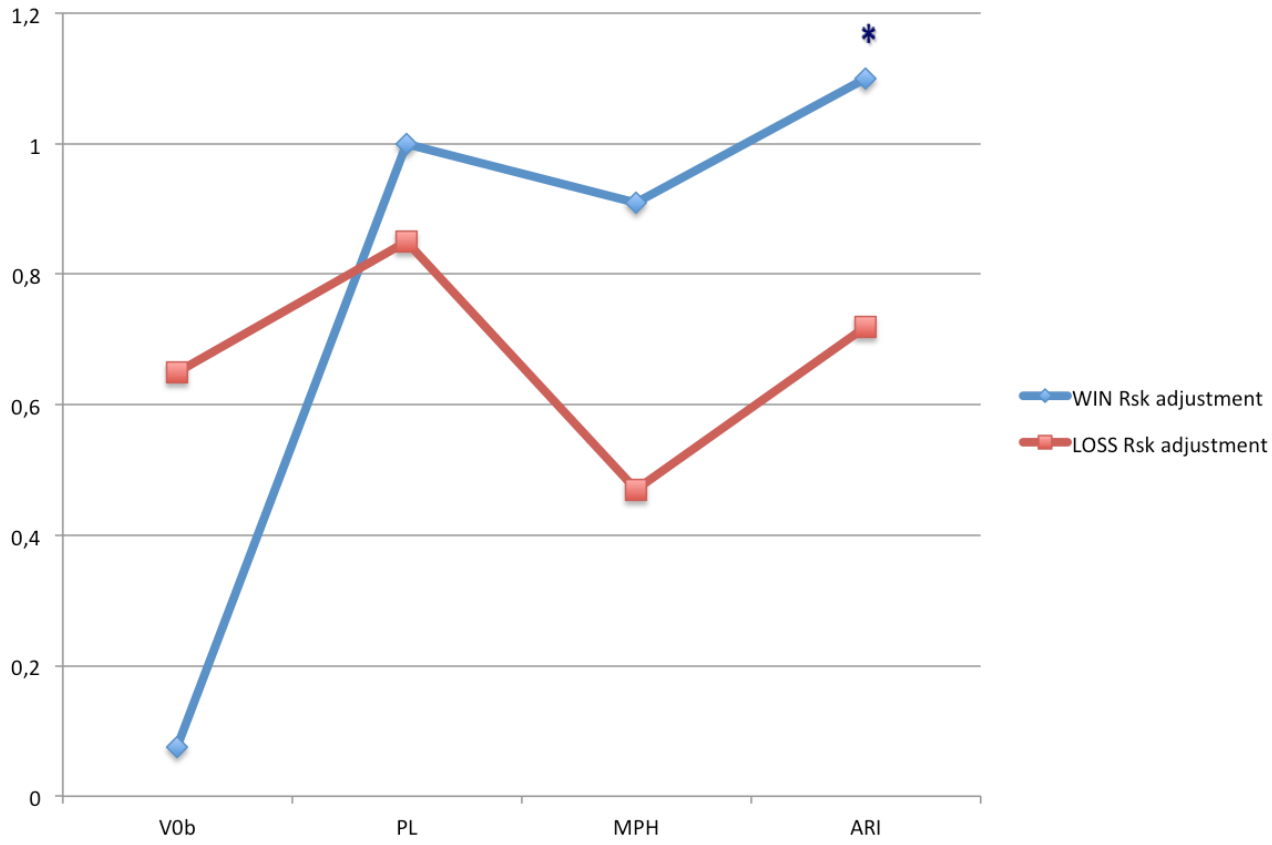

Fig. 15. Repeated measures Group A: effects of drugs on risk adjustment on NCGT. Compared to baseline Risk adjustment in win condition is significantly higher after single dose of Aripiprazole ($p<.05$).

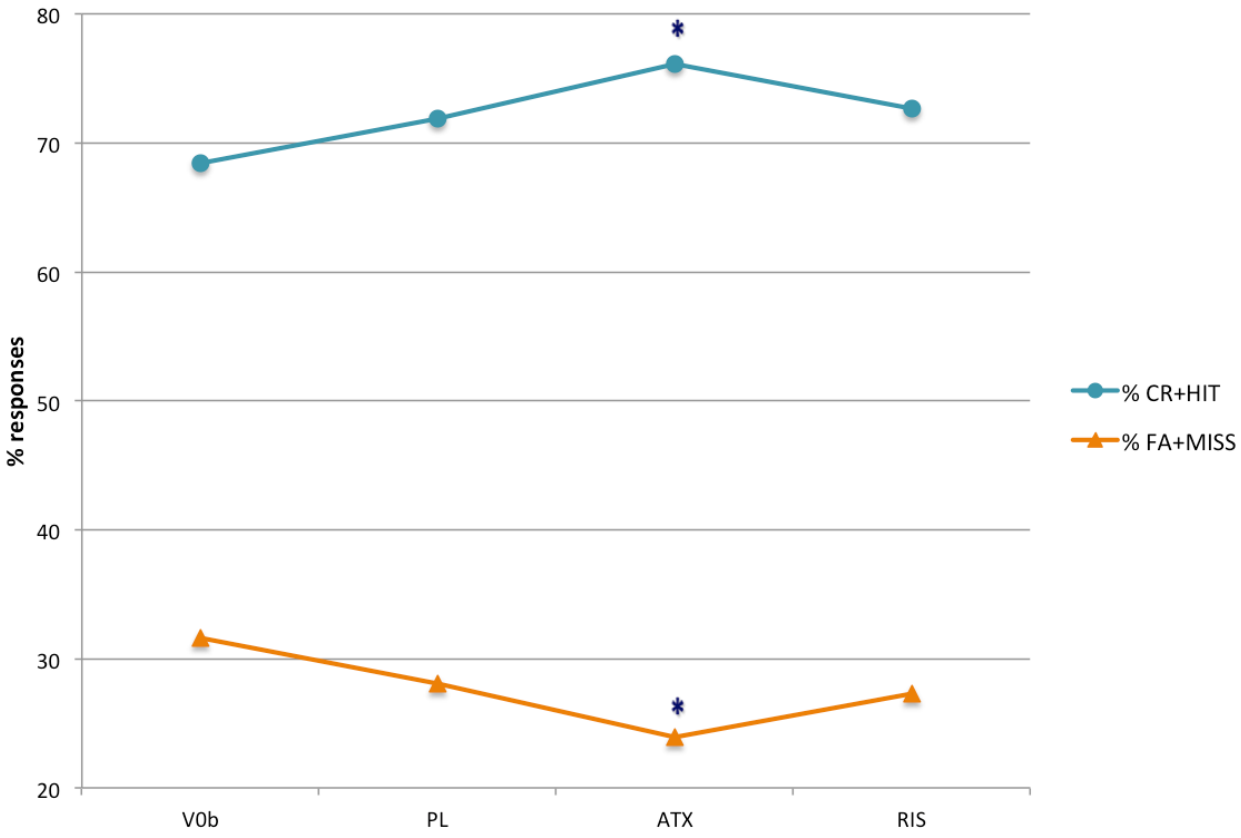

Fig. 16. Repeated measures Group B: effects of drugs on percentage of correct and incorrect responses on FAGNG task. Compared to baseline, Atomoxetine significantly improved accuracy by increasing the percentage of correct responses and reducing the percentage of errors (p = 0.01)

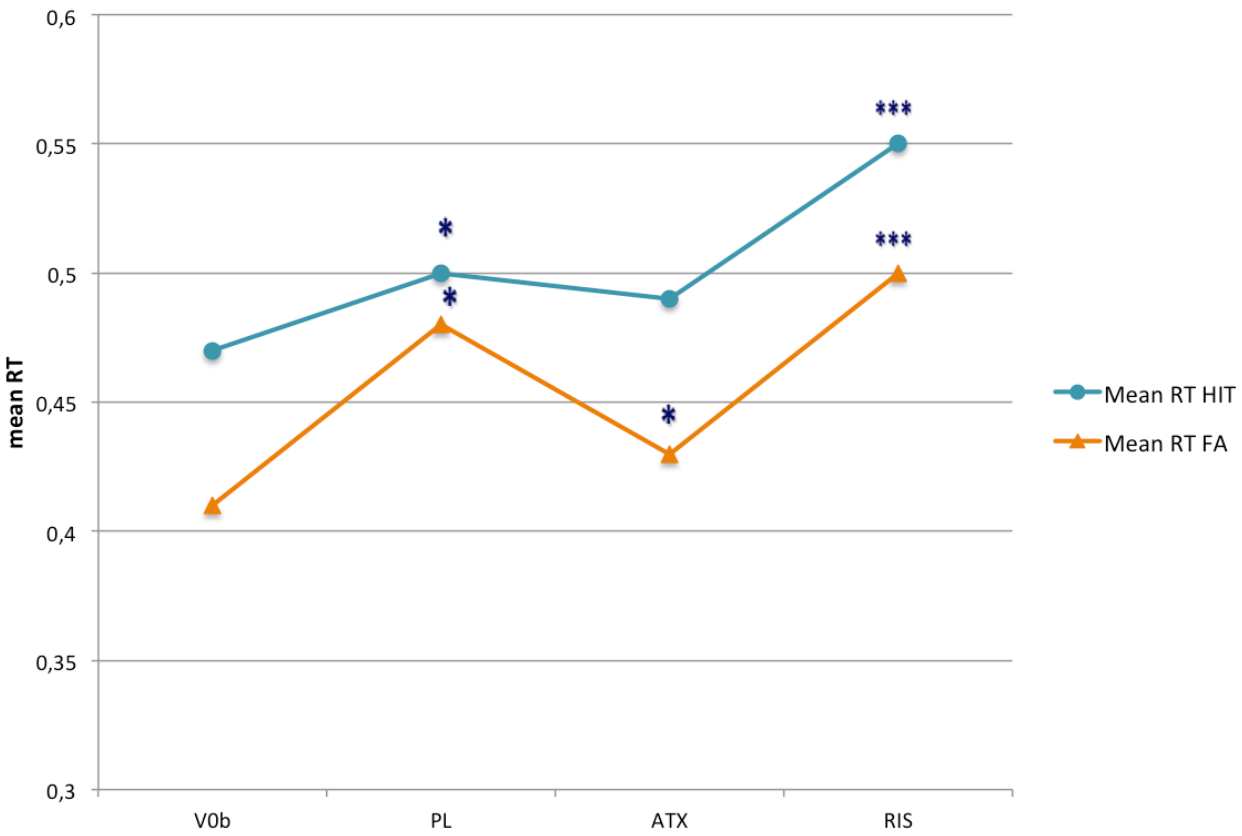

Fig. 17. Repeated measures Group B: effects of drugs on reaction times (RT) on FAGNG task. Compared to baseline, risperidone and placebo significantly changed reaction times recorded for correct and incorrect responses ($p=0.000$ and $p < 0.05$ respctively), while atomoxetine significantly reduced reaction times recorded for incorrect responses compared to placebo but not to baseline.