Emotional functioning in boys with ADHD: Identifying risk factors for comorbid Conduct Disorder

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Thesis summary

There is growing evidence that Attention Deficit Hyperactivity Disorder (ADHD) accompanied by Conduct Disorder (CD) is biologically as well as clinically distinctive. This subgroup shows greater symptom severity and poorer long-term prognosis than those with either CD or ADHD alone. The aim of the thesis is to build on existing neurobiological and emotional processing research and to identify mediators of risk for CD problems in ADHD, thereby highlighting targets for future intervention strategies.

This thesis involved in-depth experimental testing of emotion processing and physiological responding to emotion-provoking stimuli in a large clinical sample of boys with ADHD (N=204). About half of the sample met diagnostic criteria for a comorbid diagnosis of CD enabling us to compare emotional and physiological responding between these two groups (ADHD vs. ADHD+CD). This large sample also enabled us to analyse the contributing effects of callous and unemotional traits, oppositional defiant disorder symptoms and internalizing emotionality, as well as looking at the effects of symptom severity of CD and ADHD.

Each experimental chapter analysed responses to a different source of aversive cue. Pain sensitivity was assessed by looking at self-reported threshold and tolerance times and comparing these against increases in skin conductance level. Fear conditioning ability was analysed, looking at physiological responding to predict an aversive event. Stress reactivity was analysed by measuring emotional and cortisol responses to a psychosocial stressor and emotion regulation was assessed using an economic decision-making game.

The findings showed that boys with ADHD and comorbid CD differed significantly in their emotional and physiological responding to those with ADHD alone. The boys with CD had more problems in learning fear associations, a weaker cortisol stress response, and a higher pain threshold and longer tolerance time, reflecting lowered pain sensitivity. Boys with high levels of aggressive CD symptoms also showed emotion regulation difficulties causing increased irrational decision making. This highlights the importance of treating ADHD as a heterogeneous condition and of analysing the effects of comorbid disorders to help ensure that limited resources in the healthcare, social care and criminal justice systems are utilised more effectively and efficiently.

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Chapter 1: Introduction

Diagnoses and comorbidity

Attention-Deficit/Hyperactivity Disorder (ADHD; Diagnostic Statistical Manual 5th edition (DSM 5); American Psychiatric Association, 2013) is one of the most common developmental disorders in childhood, affecting approximately 3-5% of the population (Ford, Goodman, & Meltzer, 2003). ADHD is described as a persistent pattern of inattentive and/or hyperactive-impulsive behaviour that gets in the way of daily life and development. There are three presentations of ADHD: an inattentive presentation including symptoms such as difficulty concentrating, disorganization and being easily distracted, a hyperactive-impulsive presentation with symptoms such as excessive movement/noise and difficulty controlling impulses, and a combined presentation which includes symptoms of both (DSM 5, American Psychiatric Association, 2013). Symptoms typically present across multiple settings resulting in behavioural, academic and/or social impairments, putting children with ADHD at risk for a multitude of co-occurring mood, anxiety and disruptive behaviour problems across development. (DuPaul & Stoner, 2003; Reddy & DeThomas, 2006). Furthermore, approximately 60% of children with ADHD will continue to experience clinically significant symptoms into adulthood (Kessler et al., 2005).

ADHD has long been associated with a higher risk of antisocial behaviour in adulthood (Weiss & Hechtman, 1993). Follow-up studies of both community and clinical populations have found that ADHD is associated with delinquency and criminality, and studies of prison populations have found a high prevalence of childhood and/or adult ADHD amongst inmates (Curran & Fitzgerlad, 1999; Rosler et al., 2004). Although previous research has shown a clear association between ADHD and the development of

antisocial behaviour in adulthood, it is not yet clear whether this association reflects a true risk factor of ADHD or instead is moderated through an associated factor (Thapar, Langley, O'Donovan, & Owen, 2006), such as comorbid disruptive-behavioural disorders (DBDs; e.g. conduct disorder and oppositional defiant disorder) which are common in children and adolescents with ADHD.

Conduct disorder (CD) is the most common DSM diagnosis associated with delinquency, particularly with more serious and persistent delinquency (O'Shaughnessy, 1992). It is estimated to occur in 25% of children and up to 45% of adolescents with ADHD (National Research Centre on ADHD, 2004), and children are at 12 times increased risk of having ADHD or CD if they have the other disorder (Romano, Tremblay, Farhat, & Côté, 2005). CD is defined by a persistent pattern of behaviour in which the basic rights of others or societal norms are violated (DSM 5; American Psychiatric Association, 2013). Symptoms include fighting, bullying, stealing, vandalism and lying for personal gain, potentially causing physical or psychological harm to victims (Lahey & Waldman, 2012). These characteristic symptoms are associated with rising health and societal costs and have adverse consequences in adult life (Rutter, Giller, & Hagell, 1998). Loeber, Burke and Lahey (2002) indicated that 82-90% of adults with a diagnosis of Antisocial Personality Disorder (ASPD) met criteria for CD during adolescence, and of the individuals with Oppositional Defiant Disorder (ODD) who progressed to an ASPD diagnosis, nearly all showed intermediate CD.

Until recently ADHD was classified as a DBD alongside CD and ODD (DSM-IV-TR; American Psychiatric Association, 2000). The high rate of comorbidity between ADHD and ODD/CD had previously led many psychologists to question whether they were actually distinct syndromes or rather represented subtypes of the same disorder (Hinshaw, 1987). For example, many children with ADHD display defiant behaviour;

similarly, many children with ODD/CD show impulsive and hyperactive symptoms (Ghosh & Sinha, 2012). This old model of ADHD, however, has now been replaced with a new understanding of the disorder. ADHD is now considered a neurodevelopmental disorder alongside autistic spectrum disorders and dyspraxia (DSM-5; American Psychiatric Association, 2013). Neurodevelopmental disorders are considered to be the result of structural differences in the brain which are rooted in early developmental alterations and are associated with a spectrum of developmental setbacks or delays (Frick & Nigg, 2012; Van Herwegen, Riby, & Farren, 2015). CD on the other hand is classified as a behavioural disorder and thought to be determined by a number of potential causes, ranging from biological factors to environmental and social conditions **(**Murrihy, Kidman, & Ollendick, 2010**).**

CD typically has a later age of onset (Frick & Nigg, 2012; Loeber & Keenan, 1994) and although ADHD and CD may share certain temperamental features, this later onset suggests that correlates of ADHD may predispose children for developing CD (Steinberg & Drabick, 2015). There is evidence that those with ADHD accompanied by childhood-onset CD problems are clinically distinctive (Silberg, Moore & Rutter, 2014). This subgroup shows greater symptom severity than those with either CD or ADHD alone and has a considerably poorer long-term prognosis, with especially high rates of criminality and adult antisocial behaviour (Lynam, 1996). Furthermore, for the sub-group of children with ADHD who have CD problems, inherited factors appear to be especially important, more so than for CD or ADHD alone (Faraone, 2000; Thapar, Harrington, & McGuffin, 2001).

Unfortunately treatment is a challenge. Despite ADHD being the most common reason for Child Mental Health Service follow-up, currently used treatment strategies (medication and behavioural treatment) appear to have limited long-term effectiveness

on CD outcomes (Langley, et al., 2010; Molina, et al., 2009). There is thus a pressing need to identify appropriate targets for new types of psychological and pharmacological treatment.

Because comorbidity is common and often not controlled for, previous research findings of the risk factors and outcomes of ADHD and CD are likely to be blurred. More specific exploration of the similarities and differences between the two disorders is crucial if we are to advance the treatment of behavioural problems in young children and adolescents. To achieve this clinical groups are needed where comorbidities have been taken into account. Several theorists have suggested that characteristics of ADHD, such as impulsivity, are important components of an antisocial personality (Farrington, 1995; Gottfredson & Hirschi, 1990; Moffitt, 1993). However, ADHD may have been identified incorrectly as a precursor to CD due to its frequent comorbidity with ODD (Van Lier, van Der Ende, Koot, & Verhulst, 2007). Some research reviews suggest that boys with ADHD and ODD are no more likely to develop antisocial behaviour than boys with ODD alone (Lahey & Lober, 1997; Lilienfeld & Waldman, 1990). However, there is also evidence to suggest that ADHD is associated with an earlier onset of antisocial behaviour and some evidence to suggest antisocial youths with ADHD exhibit more extreme and persistent behaviour (Frick & Nigg, 2012; Loeber, Green, Keenan, & Lahey, 1995; Villodas, Pfiffner, & McBurnett, 2012). A sample of children with ADHD with and without comorbid CD needs to be investigated to gain a better understanding of their underlying similarities and/or differences in aetiology in order to be able to identify more specific intervention targets which are tailored to the needs of the different subgroups of such a heterogeneous condition.

Aetiology and overlap

ADHD and CD overlap behaviourally and clinically, with both disorders associated with extroverted, under-controlled behaviour (Rubia, 2011). There appear to be several predisposing factors that contribute to the development of CD and ADHD, some that they share and some that are unique to each disorder. Due to the high comorbidity between these disorders and research that has not always controlled for this, we lack a clear understanding of their distinct and/or varying cognitive and emotional problems, and their underlying neuropsychological and neurobiological characteristics. If we are able to untangle the causal risk factors for these disorders then we will be able to develop more specific and fitting interventions.

Causal factors for ADHD

Deficits in executive functioning are thought to be a hallmark of ADHD (Barkley, 1997). Executive functioning can be understood as an umbrella term that refers to the cognitive processes that allow for future, goal-oriented behaviour. It broadly includes a group of higher-order cognitive functions such as working memory, cognitive flexibility and inhibition (Miyake et al., 2000). Deficits in executive functioning can affect planning, mental flexibility, self-monitoring and social problem-solving skills (Hale et al 2009). ADHD is associated most consistently with deficits in tasks of sustained attention, timing functions and cognitive and motor response inhibition (Rubia, Smith, Taylor, & Brammer, 2007; Rubia, et al., 2001; Willcutt, Doyle, Nigg, Faraone, Pennington, 2005). The prefrontal cortex, caudate, and cerebellum are key areas showing deficits in ADHD (Arnsten & Pliszka, 2011). The network between these areas is affected by the neurotransmitters dopamine and norepinephrine and an appropriate

level and ratio of these neurotransmitters is required for optimal functioning of the PFC (Pliszka, 2005). It is thought that ADHD is caused by a disruption in this balance and medication which helps to alleviate ADHD symptoms works by helping restore this delicate balance (Sharma & Couture, 2014).

Causal factors for CD

Severe, persistent antisocial behaviour is thought to arise from the interaction of individual biological factors and adverse environmental conditions. Research suggests that children with CD have emotional problems and that these problems have a neurobiological basis (Van Goozen, Fairchild, Snoek, & Harold, 2007). Deficits in the function of the neurobiological systems that process stress and aversive cues from the environment seem particularly important. Children need to be sensitive to negative cues in order to inhibit negative behaviour and to learn to regulate their emotions and behaviour. The neurobiological system involved in punishment processing consists of the paralimbic system and amygdala, the autonomic nervous system (ANS), and the hypothalamus–pituitary–adrenal (HPA) axis (Matthys, Vanderschuren, & Schutter, 2013), and deficits in this system will lead to impaired socialization and a weakened moral conscience (e.g. less fear, guilt, and remorse in the anticipation of committing an antisocial act).

The amygdala and emotion processing

The amygdala is important for processing the value of stimuli, including the perception of threat signals in the environment (Adolphs, 2010; Amaral, 2003). Bilateral lesions to the amygdala abolish the response to fear-inducing stimuli, such as replica snakes in nonhuman primates (Prather et al., 2001), and neuropsychological studies of humans

with amygdala damage have shown impaired recognition of fear and anger (Adolphs, Tranel, Damasio & Damasio, 1994, 1995; Calder, 1996). The amygdala has a crucial role in several affective processes, such as emotional learning, mediating conditioned emotional responses, responding to various emotional stimuli (including facial expressions of emotions), and in social behaviour (Bechara, et al., 1995; Everitt, Cardinal, Parkinson, & Robbins, 2003; LaBar, LeDoux, Spencer, Phelps, 1995; Sengerie, Choci & Armony, 2008).

Impairments in emotional processing may arise therefore due to deficits in a neural system involving the amygdala, and a number of studies have provided indirect evidence for deficits in amygdala functioning in children with CD. For example, deficient amygdala activation has been reported during the viewing of affective pictures in clinical cases with CD (Sterzer, Stadler, Krebs, Kleinschmidt, & Poustka, 2005). Children with DBD have been shown to have a blunted response to auditory stimuli that typically elicit a startle reflex, similar to the response found in patients with amygdala damage (Angrilli et al., 1996; Van Goozen, Snoek, Matthys, Rossum, & Engeland, 2004). A negative correlation has also been shown between delinquency ratings and the magnitude of startle responses while viewing unpleasant pictures (Van Goozen, Snoek, Matthys, Rossum, & Engeland, 2004). Lastly, children with CD and/or psychopathic traits appear to have a problem with recognising facial expressions, in particular fear and sadness (Blair, Colledge, Murray, & Mitchell, 2001; Fairchild, Van Goozen, Calder, Stollery, & Goodyer, 2009; Woodworth, & Waschbusch, 2008). The sad and fearful expressions of others are hypothesised to cause an increase in physiological arousal and activate the brain stem threat response system, resulting in a withdrawal response and the inhibition of violence (The violence inhibition model; Blair, 1999).

Therefore deficits in processing these distress cues will disrupt this inhibition mechanism.

Physiological arousal

Measures of autonomic and central nervous system functioning, including skin conductance activity (Fowles, 1993; Raine, Venables & Williams 1990a), heart rate (Oritz & Raine, 2004; Patrick, 1994; Raine, 1993; Volavka, 1995), resting EEG (Raine, Venables, & Williams, 1990b), and HPA axis activity (McBurnett et al., 1991; Susman & Petersen, 1992; Van Goozen et al., 1998) have consistently been found to be associated with antisocial behaviour leading to the neurobiological theory that antisocial individuals are chronically underaroused (Raine, 1993, 1996; Van Goozen et al., 2007).

There are two main theoretical interpretations of reduced arousal in antisocial individuals. The sensation-seeking theory suggests that there is an optimal or normal state of arousal and being underaroused is an unpleasant physiological state (Zuckerman, 1979). Individuals with chronically low arousal levels seek out stimulation to raise their arousal levels and therefore antisocial behaviour should be seen as a form of sensation seeking, in that stealing a car or starting a fight might be stimulating and exciting for antisocial individuals. This was supported by El-Sheik, Ballard, and Cummings (1994), who found that preschool boys who chose to watch videotapes portraying intense anger had lower heart rates compared to individuals who chose to watch videotapes portraying mild anger. These boys also displayed higher levels of externalizing behaviour problems. Furthermore, resting heart rate at 3 years of age has been found to predict stimulation-seeking behaviour and aggressive behaviour at age 11 (Raine, Venables & Mednick, 1997).

A second theory of reduced arousal argues that an antisocial personality is indicative of low levels of fear (Raine, 2002). Antisocial and violent behaviour requires a degree of fearlessness to execute, for example, being unafraid of punishment by authority figures or physical injury. Fearless children are more likely to engage in antisocial behaviour to obtain social status and rewards because they are not concerned about the negative consequences of their antisocial actions. This lack of fear of socialising punishments in early childhood would further contribute to poor conscience development (Raine, 1993). The theory is supported by research findings showing that low autonomic nervous system (ANS) arousal also provides the underpinning for an uninhibited or fearless temperament in infancy and childhood (Baker, Shelton, Baibazarova, Hay, & Van Goozen, 2013; Kagan, 1997; Scarpa, Raine, Venables, & Mednick, 1997).

Reduced physiological arousal may also reflect a more general risk factor for antisocial behaviour because individuals with low arousal will have difficulty attending to and reacting to environmental cues that should help guide their behaviour and decision making.

The somatic marker hypothesis

The somatic marker hypothesis proposes that a defect in emotion and physiological arousal plays an important part in impaired decision making (Bechara & Damasio, 2005). Emotions are primarily expressed as changes in the representation of the bodily state (e.g. changes in heart rate, skin conductance). These changes in an individual's emotional state (somatic markers) become associated with factual aspects of a particular context which tells the individual whether, in simple terms, the context is good or bad. The theory suggests that when people are faced with a situation involving some factual aspects which have been previously categorised, the dispositional associations are

activated (Sobhani & Bechara, 2011). Therefore in a healthy person, who is faced with the option to commit an antisocial act, there will be activation of the association between knowledge of the antisocial act and punishment and the emotional aversion to punishment. The resulting aversive somatic marker should guide the person away from committing the antisocial act. However, if the somatic marker system functions less well or is impaired, there will be no somatic marker to guide this behaviour (Blair, 2001; Debowska, Boduszek, Hyland, & Goodson, 2014).

The main evidence supporting this hypothesis comes from research on gambling tasks, such as the Iowa Gambling Task (Bechara, Tranel, & Damasio, 2000). This game involves choosing between decks of cards which yield high immediate gain but larger future loss, i.e., disadvantageous decks, and decks which yield lower immediate gain but a smaller future loss, i.e., advantageous decks. Control participants avoid the disadvantageous decks and prefer the advantageous decks. However, patients with ventromedial and amygdala damage, areas known to be involved in emotion processing (Sobhani & Bechara, 2011), do not learn to avoid the disadvantageous decks, they prefer them. Research using a physiological measure (skin conductance response; SCR; Bechara, Tranel, Damasio, & Damasio, 1996) showed that control participants generated SCRs in response to wins and losses. Importantly, they also began to develop anticipatory SCRs when deciding which deck to choose, in particular before choosing the risky disadvantageous pack. However, although the ventromedial patients produced SCRs to wins and losses, albeit the responses were slightly lower, they displayed no SCR before picking a card. Furthermore, the amygdala patients completely failed to generate SCRs, even to wins and losses. This supports the hypothesis that decision making is guided by somatic or emotional markers (for a review see Bechara & Damasio, 2005).

Taken together these theories suggest that individuals who display severe antisocial behaviour show reduced physiological arousal and impaired processing of emotional stimuli. These deficits cause impaired decision making and individuals will have fewer restraints to regulate their emotions and behaviour. Research on whether these deficits are also found in ADHD is mixed. It is important to find out whether CD is only present with ADHD when emotional deficits are involved and whether emotional deficits play a role in ADHD alone. Importantly, this leads us to ask whether these emotion deficits could explain the comorbidity between ADHD and CD and therefore provide a clear route for intervention for this difficult group.

Can emotional deficits explain the risk for comorbid conduct disorder in ADHD?

Compared with executive functioning, relatively few studies have examined emotional functioning in ADHD. ADHD has been associated with increased emotional reactivity and with reduced emotion recognition, inhibition, and empathy (Cadesky Mota, & Schachar, 2000; Kats-Gold, Besser & Priel, 2007; Maedgen & Carlson, 2000; Sinzig, Morsch, & Lehmkuhl, 2008; Walcott & Landau, 2004); however, research has often failed to control for comorbid CD. Barkley (1997) argues that emotion dysregulation is a key component in the aetiology of ADHD because it is a secondary symptom of inhibitory control, meaning that the inability to inhibit responses also causes the difficulties with inhibiting emotional responses. However, other studies have found that inhibitory control and emotional processes are independent of each other (Blaskey, Harris, & Nigg, 2007) and instead it has been argued that children with ADHD only demonstrate emotional impairments in the presence of comorbid disorders, such as DBDs and internalizing mood disorders (Factor, Reyes, & Rosen, 2014).

The strongest evidence supporting this comes from studies comparing hot and cold executive functioning. There has been support to separate executive functioning into hot affective aspects and cold cognitive aspects, with hot executive functioning involving emotion regulation and motivation (Carlson, Zelazo & Faja, 2013; Schaefer et al., 2003). As previously mentioned, ADHD has consistently been associated with cold cognitive deficits, such as poor performance on tasks of sustained attention, timing functions and cognitive and motor response inhibition (Rubia et al., 2007; Rubia, et al., 2001; Willcutt et al., 2005). Children with CD alone have also been shown to have impairments on tasks of cognitive and motor inhibition (Herba, Tranah, Rubia & Yule, 2006). Furthermore, children with CD like those with ADHD have shown impaired sustained attention (Dougherty, Bjork, Marsh, & Moeller, 2000), and set-shifting (Lueger & Gill, 1990). However, these studies that claim to have shown experimentally that CD is associated with cold EF deficits failed to control for the effects of comorbid ADHD, and the evidence for a deficiency in individuals with CD without comorbid ADHD compared with typical control subjects is less consistent. In fact, several studies found no cognitive deficits (e.g., on set-shifting and inhibitory control tasks) in CD after controlling for ADHD (Avila, Cuenca, Felix, Parcet & Miranda, 2004; Klorman, et al., 1999; Scheres, Oosterlaan, Sergeant, 2001; Van Goozen et al., 2004).

However, on tasks involving hot executive functioning, children with CD, either alone or comorbid with ADHD, seem more impaired than children with ADHD alone (Rubia, 2011). Children with ODD or CD are consistently impaired on response perseveration tasks, in which they show a tendency to continue a response set for reward despite punishment (Matthys, Van Goozen, Snoek, & van Engeland, 2004) and delayed gratification tasks, in which they have to choose between a small immediate reward and a delayed larger one (Dolan & Lennox, 2013; Van Goozen et al., 2004). On gambling

tasks (like the IOWA gambling task), which measure reward-related long-term advantageous decision making versus impulsive short-term decisions, ADHD has been found to be associated with poor performance (Garon, Moore, & Waschbusch, 2006; Toplak, Jain, & Tannock, 2005), but these studies did not exclude comorbidity with CD. In fact, other studies indicate that pure ADHD groups do not differ from typical controls on decision-making tasks (e.g. Skogli, Egeland, Andersen, Hovik, & Øie, 2014) and one study, which used regression analyses to look at the effect of ADHD and CD symptoms, showed that CD was related to an impulsive, reward-related choice pattern (hot EF), whereas ADHD accounted for the deficits in tasks of motor inhibition and attention (cold EF; Hobson, Scott, & Rubia, 2011). These behavioural studies suggest that ADHD and CD have distinct EF deficits: ADHD appears to be associated with cognitive (cold) EF impairments, whereas CD is characterised by impairments in emotional (hot) EF. This may therefore explain why children with comorbid ADHD+CD have more problems and a worse prognosis than children with ADHD or CD only. Imaging studies can help clarify whether these behavioural findings reflect distinct underlying neurological impairments.

Rubia (2011) summarised the structural and functional brain imaging literature directly comparing children with ADHD and CD and concluded that there are disorder specific dysfunctions for each disorder. CD has consistently been associated with abnormalities of the hot paralimbic system, that mediate affect and motivation processes (encompassing the superior temporal lobes, lateral orbital and ventromedial prefrontal cortices, and underlying limbic structures, most prominently the amygdala), whereas ADHD is characterized predominantly by impairments in the cool-cognitive networks that mediate functions of inhibition and attention (including the striatal, parietotemporal, inferior frontal, and cerebellar regions). The emotional nature of the

hot executive functioning deficits now needs to be tested in more detail. Neurobiological methods can be used to directly measure physiological arousal and emotion functioning.

These studies in executive functioning suggest that CD individuals have specific deficits in emotion and motivation that are not shared by those with ADHD alone (Arnsten & Rubia, 2012). It could be that executive functioning deficits associated with ADHD exacerbate the difficulties found in CD associated with antisocial behaviour but alone do not cause the risk. Specific deficits related to emotional processing and motivation, such as the processing of and physiological responding to punishment cues, may therefore hold the key to explaining why some individuals with ADHD develop antisocial behaviour and others do not and help explain the higher risk/greater severity found in those with ADHD+CD compared to those with ADHD alone. Therefore, research is needed to specifically test this hypothesis by testing whether deficits in emotion processing and motivation are associated with ADHD alone or only associated with comorbid CD.

The next section will outline the four paradigms which will be used to analyse the processing of aversive cues in boys with ADHD with and without CD. It is hypothesised that emotion processing deficits may explain the heterogeneity within ADHD and help explain the risk for antisocial behaviour. As discussed, diminished processing of punishment cues and low autonomic reactivity are key to theories of antisocial behaviour. Pain is arguably the most basic and fundamental punishment and therefore an ideal stimulus to measure this. A more complex aversive cue – a social competition stressor - will also be used to measure the activity of the HPA-axis. This is crucial to the body's fight or flight response and allows us to measure how individuals respond to stress. A deficit in the ability to form associations between a stimulus and

reinforcement, especially regarding punishment, is crucial in the development of antisocial behaviour. Fear conditioning ability will therefore be used to measure this type of associative learning. Lastly, it is hypothesised that the aforementioned may reflect an inability to generate visceral signals to guide behaviour and, in particular, to regulate emotions such as anger. Therefore, the ability to regulate emotions in response to unfair treatment will be tested.

The following sections will provide a basic introduction to these topics with a general discussion of how they relate to the development of antisocial behaviour. The introduction to each experimental chapter will then discuss in more detail the preceding research into ADHD and how this relates to the investigation of heterogeneity and the issue of comorbid CD.

Topics of interest

Pain perception

The main purpose of pain is to alert our attention to danger and to motivate us to avoid it. If an individual experiences pain as a result of a particular activity, he or she usually stops doing that activity, because pain has been identified as a warning sign that harm is occurring (Steeds, 2013). Pain is a subjective experience and describing it as such separates it from 'nociception'. Nociception is the encoding and processing of harmful stimuli in the nervous system (Loeser & Treede, 2008). Nociceptors are receptors in tissues which are activated specifically by painful stimuli. They respond to tissue damage caused by mechanical (e.g., pinching), intense chemical (e.g., chili powder in the eyes), or thermal (heat and cold) stimulation (Portenoy & Brennan, 1994). This

sensory information is transformed into an electrical signal by the receptors and transmitted from the periphery to the central nervous system (Steeds, 2013). Pain is the result of a complex interplay between the frequency of firing of the nociceptors, modulation from higher centres and the unique perception of the individual (Momin & McNaughton, 2009).

Pain is arguably the most basic and fundamental form of punishment or aversive cue. If a child has a reduced sensitivity to pain then he or she is less likely to refrain from engaging in activities that might result in injury, for example fighting. This is supported by research suggesting that a high pain tolerance is associated with behaving aggressively toward others (Niel, Hunnicutt-Ferguson, Reidy, Martinez, & Zeichner, 2007; Reidy, Dimmick, MacDonald, & Zeichner, 2009; Séguin, Pihl, Boulerice, Tremblay, & Harden, 1996), as well as with the ability to do harm to oneself (e.g., Franklin, Hessel, & Prinstein, 2011).

Fear conditioning

Emotion processing and learning play an important role in explanations of antisocial behaviour (Blair, Mitchell & Blair, 2005). Abnormal emotion processing has been observed in adolescents with DBD (Van Goozen et al., 2004) and psychopathic tendencies (Blair, Colledge, Murray, & Mitchell, 2001). Longitudinal research has consistently associated low fearful arousal with the development of severe antisocial behavior, particularly aggression (Loeber & Pardini, 2008). Furthermore, infants and children with a relatively fearless temperament display impairments in the development of empathy and guilt (Fowles & Kochanska, 2000). This is thought to be partly because they experience relatively little emotional arousal to cues of punishment for

misbehaviour and in response to distress cues in others (Frick & Viding, 2009). These research findings together propose that low temperamental fear may predispose the development of early conduct problems because it decreases the effectiveness of punishment-oriented socialisation techniques (Baker et al., 2013).

Fear conditioning is a basic form of learning in which fear is associated with a previously neutral stimulus. This is done experimentally by pairing a neutral stimulus with an aversive one, such as an unpleasant loud noise. Eventually the previously neutral stimulus alone will evoke a fear response that can be quantified with physiological measurements such as skin conductance responding (Sterzer, 2010). Research has consistently found that those who engage in antisocial behaviour show reduced skin conductance responses (SCR) to aversive stimuli or to stimuli that predict an imminent aversive stimulus, compared to those who do not engage in antisocial behaviour (Birbaumer, et al., 2005; Flor, Birbaumer, Hermann, Ziegler, & Patrick, 2002; Fairchild, Van Goozen, Stollery & Goodyer, 2008). Changes in skin conductance are a reliable measure of emotional arousal as they are strongly associated with sympathetic nervous system activity (Dawson, Schell, & Filion, 2007). Unusual patterns of skin conductance responding can therefore help to pinpoint impairments in emotion processing.

Stress

The hypothalamic-pituitary-adrenal (HPA) axis is thought to have an important role in explaining individual differences in antisocial behaviour because of its stress-regulating function (Van Goozen, Fairchild, & Harold, 2008). Physical and psychological stressors activate the HPA axis, which sets off the release of a series of hormones. The process

starts when the paraventricular nucleus of the hypothalamus produces and secretes the corticotropin-releasing hormone, which itself then triggers the anterior pituitary to release adrenocorticotropic hormone. The adrenocorticotropic hormone finally activates the adrenal glands, triggering them to secrete cortisol (Smith & Vale, 2006). Cortisol is the major stress hormone in humans and the end product of this activation. It affects several neurophysiological processes such as an increase in heart rate, the termination of digestive activity, and the utilisation of glucose as an energy source in a flight or fight type situation (De Kloet, 1991). These processes prepare the animal for action as a survival function.

Stress-regulating mechanisms are important factors contributing to individual differences in antisocial behaviour (Kerr, Pagani, Tremblay, & Vitaro, 1997; McBurnett, Lahey, Rathouz, & Loeber, 2000; Mezzacappa et al., 1997; Vanyukov et al., 1993). Research investigating antisocial adults has often analysed HPA axis activity and has found cortisol levels to be inversely related to the extent of behavioural deviance (King, Jones, Scheurer, Curtis, & Zarcone, 1990; Woodman, Hinton, & O'Neill, 1978; Virkkunen, 1985). Similar results have been found in children and adolescents with some studies measuring cortisol at basal level (e.g., Vanyukov et al., 1993; McBurnett et al., 2000; Pajer, Gardner, Rubin, Perel, & Neal, 2001), and others measuring cortisol levels under stress (e.g., Van Goozen et al., 1998; Van Goozen et al., 2000).

Stress hyporeactivity may reflect an incapability to produce internal signals to guide behaviour and, in particular, to regulate reactive aggression and anger (Van Goozen, Fairchild, Snoek, & Harold, 2007). Studies on nonhuman animals indicate that removing the hormonal response to stress may damage processing of social signals and lead to abnormal patterns of aggression (Haller, Halasz, Mikics, & Kruk, 2004). Additionally, these patterns of abnormal aggressive behaviour can be prevented by

imitating the hormonal response typically seen during aggressive encounters. In two studies of cortisol stress reactivity in antisocial children, those who did not show a cortisol response during stress, reported and showed stronger emotions (i.e., they reacted more aggressively towards their opponent), suggesting a mismatch between physiological and subjective arousal (Van Goozen et al., 2000; Snoek, Van Goozen, Matthys, Buitelaar, & Van Engeland, 2004). Furthermore, longitudinal studies have shown that low cortisol levels are predictive of aggressive behaviour 2-5 years later on (e.g. Shoal, Giancola, & Kirillova, 2003; McBurnett et al., 2000) and in one study this relationship appeared to be mediated by the effects of cortisol on a personality variable the authors labelled low self-control (Shoal et al., 2003).

Emotion regulation

Emotion regulation involves the process of influencing which emotions an individual has, when they have them, and how they experience and express them (Gross, 1998). It involves the manipulation of physiological and behavioural processes involved in emotional responding (Gross, 2013). Emotion dysregulation arises when an individual is unable to control the expression or experience of emotions efficiently. It is thought that this could impair functioning and initiate or maintain symptoms of psychopathology (Cole, Michel, & Teti, 1994).

It is hypothesised that the aggressive and antisocial behaviours displayed by individuals with CD reflect defects in the neurobiological circuits involved in both processing environmental cues that normally produce emotional restraint and voluntarily regulating negative emotions (Frick et al., 2003; Davidson, Putnam, & Larson, 2000). This circuit is likely to involve an inhibitory connection from regions of the prefrontal cortex, the

orbitofrontal cortex, and the amygdala. Too much or too little activation of the amygdala may give rise to either decreased sensitivity to social cues, that would usually regulate emotion, or to excessive negative affect (Davidson, Jackson, & Kalin, 2000). Normal individuals are able to regulate their negative emotions voluntarily and can also profit from restraint-producing cues in their environment, such as facial signs of fear or anger that also serve a regulatory role (Davidson, Putnam, & Larson, 2000). Research has shown that youths with externalizing problems such as DBD, when compared with age-matched peers or children with internalizing problems, tend to display lower levels of control and emotion regulation, as well as deficient emotion recognition when viewing facial expressions (Blair, Colledge, Murray, & Mitchell, 2001; Eisenberg et al., 2001). Furthermore, research suggests that individuals who lack emotion regulation abilities are more likely to exhibit impulsive, affective aggression (Card & Little, 2006; Frick et al., 2003; Rubin, Burgess, Dwyer, & Hastings, 2003). Rubin, Burgess, Dwyer and Hastings (2003) found that unregulated emotional and behavioural control observed during peer and mother–child interactions among toddlers at two years of age predicted externalizing problems at four years of age. This demonstrates that emotion dysregulation is predictive of childhood aggressive behaviours.

It is hypothesised that these difficulties with emotional processing result in deficiencies in feeling fear, guilt and empathy. These emotions would normally inhibit antisocial behaviour towards a victim and without them individuals with CD are less likely to avoid such behaviours (Davidson, Jackson, & Kalin, 2000; Frick et al., 2003). Additionally, children who experience high levels of harsh discipline are predisposed to difficulty in developing appropriate emotion regulation skills (Shields & Cicchetti, 1998), and to exhibiting an increased hypervigilance to cues of potential threat from others (Dodge, Bates, Pettit, & Valente, 1995; Pollak & Sinha, 2002).

There is clear theoretical reasoning to support why these deficits might predispose someone to antisocial behaviour and therefore might underlie why some individuals with ADHD develop comorbid CD. This range of negative events will enable the assessment of emotional processing and responding in an ADHD sample and enable us to investigate reasons for heterogeneity. There are other factors, however, that also need to be considered when assessing emotional functioning and risks for antisocial behaviour in ADHD.

Other points to consider

The majority of previous research has taken a categorical approach by comparing clinical groups and using clear cut-offs (e.g. Decety, Michalska, Akitsuki, & Lahey, 2009; Herpertz et al., 2008; Luman, Tripp, & Scheres, 2010). Although most research follows this framework of conceptualising psychopathology, there are problems associated with this category-based approach (Walton, Ormel, & Krueger, 2011). Sub-clinical symptoms, comorbidities and heterogeneity within disorders are common. It is therefore theoretically possible that two individuals with the same diagnosis may share no more than one common feature, but that two individuals with different diagnoses may share multiple traits. Consequently there has increasingly been a move towards more dimensional ways of studying psychopathology, for example by using correlational and regression analyses (e.g. Fairchild et al., 2009; Marsee, Silverthorn, & Frick, 2005; Passamonti et al., 2010). We therefore aim additionally to look at ADHD and CD symptoms continuously. We will also assess ODD symptoms, callous and unemotional traits and internalizing symptoms, which all have clinical and theoretical overlaps with ADHD and CD.

Oppositional defiant disorder

ODD is a condition in which a child displays an ongoing pattern of uncooperative, defiant, hostile, and annoying behaviour toward people in authority. The child's behaviour often disrupts his or her normal daily activities, including activities within the family and at school. For years ODD has commonly been viewed as being part of a CD diagnostic spectrum. It has been characterised as a less severe form of CD, which is often a developmental precursor to CD (WHO, 1992). This viewpoint was reflected in DSM-IV with an exclusion criterion for ODD if a CD diagnosis was present. However, although ODD frequently overlaps with CD and their symptoms are highly correlated (Angold, Costello, & Erkanli, 1999; Angold & Costello, 2009; Lahey et al., 2008), ODD and CD are comparatively distinct dimensions of psychopathology with some differing correlates and outcomes (Boden, Fergusson, & Horwood, 2010; Burke, Waldman, & Lahey, 2010). The exclusion criterion for CD has now been removed from the diagnosis of ODD in the DSM-5. CD, however, predicts adult antisocial outcomes more strongly than ODD (Biederman et al., 2008; Lahey, 2008) and ADHD with CD has been shown to be more severe in the domains of delinquency and overt aggression than ADHD with ODD (Connor & Doerfler, 2007). Therefore the main focus of this thesis was to look at the difference between participants with ADHD with and without CD. However, the effect of ODD symptom severity was also analysed.

Callous and unemotional traits

In the last decade a significant body of research has emerged refining how the key features associated with psychopathy may be expressed in children and adolescents (Frick, 2009; Salekin & Frick, 2005). There are clear reasons for studying psychopathy

in young people; it is hoped that the traits of psychopathy may provide one way to explain the heterogeneity associated with antisocial behaviour in young people and identify a more homogenous subgroup of youths who go on to become serious and persistent offenders in adulthood. Conceptualizations have focused largely on the presence of callous-unemotional (CU) traits. This trait describes an individual who displays limited empathy, shallow affect and general disregard for others (Frick & White, 2008). It corresponds closely to the affective dimension of psychopathy which is thought to be the core to the construct in adult samples (Hare & Neumann, 2008). Research suggests that this affective and interpersonal factor provides further prognostic value and unique information that is not contained in CD symptoms (Frick & Marsee, 2006). It also appears that antisocial behaviour with additional high CU traits is strongly heritable in children (Fontaine, Rijsdijk, McCrory, & Viding, 2010), whereas antisocial behaviour with low CU traits seems to be driven more by environmental factors (Viding, Jones, Frick, Moffitt, & Plomin, 2008). Furthermore, antisocial adolescents displaying additional CU traits exhibit a more chronic, severe, and aggressive pattern of conduct problems and delinquency with more police contact than those without CU traits (Frick, Stickle, Dandreaux, Farrell, & Kimonis, 2005; Scheepers, Buitelaar & Matthys, 2011). The importance of such traits has been acknowledged by including limited prosocial emotions as a specifier for CD in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2013; Frick, Ray, Thornton, & Kahn, 2014).

This research will therefore analyse the contributing effect of CU traits in order to determine whether they add additional predictability of emotional and physiological deficits above CD symptoms.

Internalizing symptoms

Although research has consistently shown strong associations between ADHD and externalizing disorders such as ODD and CD, internalizing disorders also commonly co-occur with ADHD (for a review, see Jarrett & Ollendick, 2008). ADHD is comorbid with externalizing disorders at a rate higher than anxiety disorders (Angold, Costello, & Erkanli, 1999; Biederman, Newcorn, & Sprich, 1991; Jensen, Martin, & Cantwell, 1997). However, the comorbidity of ADHD and anxiety is substantial with an average comorbidity rate of 25% found in clinical and epidemiological samples (Biederman et al., 1991; Jensen et al., 1997; Tannock, 2000).

The presence of externalizing symptoms does not mean the absence of internalizing symptoms. In fact anxiety disorders co-occur with conduct problems at higher than average rates in childhood, adolescence, and adulthood (Zoccolillo, 1992; Loeber & Keenan, 1994). However, research into this comorbidity has produced somewhat contradictory findings. For example, anxiety in childhood in the absence of early conduct problems is associated with a decreased risk of later antisocial behaviour (Graham & Rutter, 1973; Kohlberg, Ricks, & Snarey, 1984; Mitchell & Rosa, 1981; Sanson, Pedlow, Cann, Prior, & Oberklaid, 1996), but children with conduct problems who are socially withdrawn have been associated with more serious and persistent problems (Blumstein, Farrington, & Moitra, 1985; Kerr, Pagani, Tremblay, & Vitaro, 1997; Serbin, Moskowitz, Schwartzman, & Ledingham, 1991). Yet delinquents with higher levels of anxiety show lower rates of recidivism (Quay & Love, 1977).

Internalizing symptoms, however, are associated with hyperarousal levels, increased sensitivity to punishment cues and greater levels of fear (Grillon, 2002; Indovina, Robbins, Núñez-Elizalde, Dunn, & Bishop, 2011; Joiner, et al., 1999). This research

will therefore control for differences in internalizing emotionality to make sure they are not masking the effects of externalizing symptoms.

The current sample

The sample was recruited from an earlier genetic study of ADHD (Study of ADHD Genes and Environment – SAGE). SAGE participants were recruited from Child and Adolescent Mental Health Services in England and Wales. Children in the sample were of British Caucasian origin and met criteria for a lifetime diagnosis of DSM-III-R or DSM-IV ADHD, confirmed using the Child and Adolescent Psychiatric Assessment (CAPA, Angold et al., 1995), a semi-structured research diagnostic interview administered in SAGE. Cognitive ability was assessed using the Wechsler Intelligence Scale for Children IV (WISC-IV). Children with any known clinical or CAPA research diagnosis of Schizophrenia, bipolar disorder, Autistic Spectrum Disorder (ASD), Tourette's syndrome, or with an IQ<70, epilepsy, brain damage or any other neurological or genetic disorder were excluded from the study. Ethical approvals for SAGE and the follow-up studies described here were obtained from the Wales Multicentre Research Ethics Committee.

 Participants were eligible for inclusion in the present research if they were boys aged 10-17 years (N = 483). All had provided consent for re-contact regarding future research in SAGE. Three hundred families were traced (62.1%). Of these, 118 refused to take part (39.3% (24.4% of original 483)). An additional 8 participants were recruited through the National Centre for Mental Health (NCMH). A further 14 participants who had expressed an interest in participating in SAGE, but had not originally been seen,

were also included in the current study on the basis of a clinical diagnosis of ADHD. In total 204 adolescent males took part in the study.

Table 1 and Table 2 display demographic information collected during the SAGE study to give an idea of the characteristics of the ADHD and ADHD+CD groups. Although we do not have a full data set, this data provides us with an insight into the family types of the sample. The ADHD+CD group had a significantly lower gross annual family income and parents with fewer qualifications and occupations of lower social status. There was no significant difference between the family compositions of the groups but more than half of the sample came from one-parent families.

Table 1. *Demographic information for the clinical sample.*

	ADHD		ADHD+CD		
	Mean	SD	Mean	SD	p value
Approximate gross annual family income[1]	3.20	1.76	2.19	1.04	p<.001
Highest education of parent(s) completing questionnaire[2]	1.51	1.16	1.11	0.89	p<.05
Social status of family based on both parents' occupations[3]	5.30	3.28	6.86	3.14	p<.05

[1]1=up to £10,000, 2= £10,000-£20,000, 3= £20,000- £30,000, 4=£30-000- £40,000, 5= £40,000- £50,000, 6= £50,000- £60,000, 7= £60,000 +; ADHD: N=58, ADHD+CD: N=60.

[2]0=None, 2=GCSEs, 3=A-Levels, 3=University, 4=Postgraduate; ADHD: N=62, ADHD+CD: N=60.

[3]1= Managers and Senior Officials, 2=Professional Occupations, 3=Associate Professional and Technical Occupations, 4=Administrative and Secretarial Occupations, 5=Skilled Trades Occupations, 6=Personal Service Occupations, 7=Sales and Customer Service Occupations, 8=Process, Plant and Machine Operative Occupations, 9=Elementary Occupations, 10=Unemployed or Unclassified; ADHD: N=76, ADHD+CD: N=72.

Table 2. *Family composition of clinical sample*

	Living with one parent	Living with both parents	Living with carer	Total
ADHD	34	30	1	65
ADHD+CD	45	30	0	75

Note: A chi-squared test found no significant difference in family composition between the two clinical groups.

Participants were invited to Cardiff University with their parents/carers for a testing day which took about 4-5 hours. The day consisted of the four paradigms described in this thesis, a series of other computer tests and a set of questionnaires. Table 3 provides an outline of the testing day for the participants. Participants were paid £25 for taking part, lunch was provided and their travel was paid for.

Table 3. *Order of testing day for participants*

Order of testing day	Detail	Estimated duration	Variables used
Morning			
Consent forms	Written consent	5 minutes	
Questionnaires	Youth Psychopathic traits Inventory	10 minutes	All chapters
CANTAB	Computer tasks to measure cognitive functioning	15 minutes	
Fear conditioning	Computer based task and skin conductance recording	10 minutes	Chapter 3
WASI IQ test	2-subset test (matrix reasoning and vocabulary)	20 minutes	All chapters
Pain procedure	Heat induction and skin conductance recording	5 minutes	Chapter 2
DAWBA	Structured interview to assess child psychopathology	20 minutes	All chapters
Facial recognition task	Comuputer based task	10 minutes	
Lunch		30 minutes	
Afternoon			
Stress phase	Computer based competitive games	60 minutes	Chapter 4
Questionannires	Social Communication Questionnaire	10 minutes	
Ultimatum Game	Computer based task	10 minutes	Chapter 5
Cognitive tasks	Several cognitive computer games to assess reward processing	20 minutes	
Empathy task	Film clips and skin conductance recording.	20 minutes	

Goals and hypotheses of the thesis

In this chapter I have discussed what ADHD and CD are, how they overlap and why

this might be important. I have reviewed literature that suggests that negative emotion

processing is important in understanding individual differences in antisocial behaviour.

Furthermore, I have outlined the argument that physiological underactivity and low fear of punishment may predispose antisocial individuals to take risks or seek out stimulation and may help to explain poor socialisation and social conditioning. These in turn may lead to difficulties in emotion regulation and consequently the expression of anger and aggressive behaviour. In the following four experimental chapters I hope to further this research by analysing these potential deficits and risk factors for antisocial behaviour in a sample of boys with ADHD. It is important to find out whether such deficits are related to ADHD alone or are only linked through the association with comorbid CD. It is hoped that this will help uncover which individuals are most at risk, which types of interventions are likely to be most beneficial, and which individuals are most likely to benefit from intervention.

This will be done by analysing the following topics: 1) pain perception, 2) fear conditioning, 3) stress and 4) emotion regulation. Each experimental chapter will start with a discussion of the literature which has looked at these deficits in ADHD samples and highlight where research is limited and/or mixed and why further research is important. The chapters will then outline and present the findings of research which involved experimental testing of these deficits in a large clinical sample, analysing group differences between those with ADHD only to those with ADHD and comorbid CD. Each chapter will analyse additionally the effects of CD and ADHD symptom severity, CU traits, ODD symptoms and internalizing emotionality.

Chapter 2 will assess the processing of and responding to a basic aversive cue. The study discussed will measure pain perception by testing self-reported pain threshold (the point at which a stimulus is perceived as painful) and pain tolerance (the point at which the pain becomes too much to withstand) during a heat induction procedure. Autonomic

physiological responding (skin conductance level) will also be measured and compared against the self-reported measures.

Chapter 3 will investigate associative learning with an aversive cue. The study discussed will assess emotional learning using a fear conditioning paradigm. Autonomic physiological responding (skin conductance level) will be again tested to see if individuals are able to learn to associate a neutral stimulus (a coloured slide) with a fearful one (a loud noise).

Chapter 4 will assess the processing of and responding to a more complex aversive stimuli. The study discussed will use a psychosocial stressor (social competition) to measure the HPA axis and its response to stress. Cortisol samples and mood ratings will be collected across the testing session so that a baseline and reactivity measure can be analysed.

Chapter 5 will investigate behavioural responding to a negative event. The study discussed will assess emotion regulation during a decision-making game with an opponent, in which the participants will be treated unfairly. Aggression in particular appears to be associated with a deficit in emotion regulation. Therefore aggressive symptoms in addition to CD severity will be assessed. In this chapter I was also fortunate to be able to include pre-collected data from a non-clinical control group in the analysis of the task.

The final chapter will summarise the findings from each of the experimental chapters, relating the findings back to emotional and neurobiological theories of antisocial behaviour. It will then discuss the limitations of the research and suggest where further research is required. Finally, potential implications of the research findings will be

outlined in terms of issues with heterogeneity and the current directions for the treatment of CD in ADHD.

Hypotheses

There were two main goals to the research. First, we aimed to assess whether boys with ADHD and comorbid CD have more emotion impairments than boys with ADHD only. We hypothesised that participants with ADHD and additional comorbid CD would show reduced pain sensitivity and physiological responding to a pain stimulus, deficient fear conditioning, a reduced stress response to an aversive psychosocial stressor, and increased emotion dysregulation.

Secondly, we aimed to assess dimensionally the role of ADHD and CD symptom severity. We hypothesised that CD symptom severity would significantly predict the severity of emotional deficits. We predicted that ADHD symptom severity would not be related to these outcomes. It was predicted that ODD symptoms would also be correlated with these deficits but not as strongly as CD symptoms. It would normally be expected that internalizing symptoms would be negatively associated with these deficits. However, we were unsure how this association would hold in the presence of co-occurring externalizing symptoms. Therefore we aimed to assess this association in an exploratory manner. It was hypothesised that CU traits would also be correlated with these emotional deficits; however, it was an exploratory aim to examine whether CU traits or CD severity would be the better predictor of emotion impairment.

All the experimental chapters have been published or are currently submitted as journal papers. They have therefore been presented in paper format. Due to this there is some overlap in the methods sections and introductory themes. However, the experimental

research paradigms and findings are unique to each chapter. The data collection of this

thesis was carried out by a small research team. The author collected the data from

roughly 40 of the participants. However, the data from the whole sample was included

in the analyses of the experimental tasks. The tasks were selected by the author in order

to answer her research question. All analyses were undertaken solely by the author of

this thesis, with advice provided by the supervisory team. All write-up was solely the

work of the author of this thesis, with the supervisory team (co-authors) providing

feedback and final approval of the submitted journal papers.

Chapter 2: Pain perception

Published paper

Introduction

Research findings highlight the importance of impaired affective response in children with Conduct Disorder (CD; Blair, Mitchell & Blair, 2005; Raine, 1997; Van Goozen, Fairchild, Snoek & Harold, 2008). Specifically, impaired fear conditioning (Fairchild, Stobbe, Van Goozen, Calder & Goodyer, 2010; Fairchild, Van Goozen, Strollery & Goodyer, 2008; Syngelaki, Fairchild, Moore, Savage & Van Goozen, 2013) attenuated startle and cortisol stress response when emotionally challenged (Fairchild et al., 2008; Van Goozen et al., 2007; Van Goozen, Snoek, Matthys, Van Rossum & Van Engeland, 2004), poor recognition of negative facial expressions (Fairchild, Van Goozen, Calder, Stollery & Goodyer, 2009; Marsh & Blair, 2008), and fearlessness and insensitivity to punishment (Blair, Harris 2007; Van Goozen et al., 2004) suggest reduced experience and processing of aversive emotional cues in those with CD. Physical pain is arguably the most basic and fundamental form of aversive cue, yet very little research has looked at pain sensitivity in children with CD or antisocial behaviour more generally.

Previous research has focused on the relation between pain sensitivity and aggression due to the argument that pain is a trigger to aggression because of its provocative nature (Berkowitz, 1993). However, acting aggressively towards others has been found to be associated with a high rather than a low pain threshold (Niel, Hunnicutt-Ferguson, Reidy, Martinez & Zeichner, 2007; Reidy, Dimmick, MacDonald & Zeichner, 2009; Séguin, Pihl, Boulerice, Tremblay & Harden, 1996), suggesting that pain sensitivity in some people is so low that it no longer acts as a motivational factor to regulate behaviour. Seguin et al. (1996) studied pain tolerance and aggression in adolescent boys with a history of aggressive behaviour. Pain tolerance was assessed via finger pressure

stimulation and aggressive behaviour was assessed over a 7-year period. The authors found that adolescents who showed persistent aggressive behaviour displayed the highest pain tolerance. However, pain sensitivity might also be associated with personality more generally; for example, reduced pain sensitivity has been found in extroverted and sensation-seeking individuals (Haier, Robinson, Braden & Williams, 1984) as well as incarcerated antisocial adults (Fedora & Reddon, 1993).

Children and adolescents with Attention-Deficit Hyperactivity Disorder (ADHD) are at high risk of displaying conduct problems. Approximately 30-50% of those with ADHD also meet criteria for a comorbid diagnosis of CD (Biederman, Newcorn & Sprich, 1991). Furthermore, when ADHD coexists with antisocial behaviour both problems are clinically more severe and persistent, and have a worse prognosis than when they occur alone (Thapar, Langley, O'Donovan & Owen, 2006). ADHD has been linked to abnormalities in somatosensory processing, which involves the processing of sensations from the body such as tactile and kinaesthetic information (Parush, Sohmer, Steinberg & Kaitz, 1997; Scherder, Rommelse, Bröring, Faraone & Sergeant, 2008). However, few studies have looked at pain perception. Studies in adult samples with ADHD have found higher levels of chronic (Kessler, Lane, Stang & Van Brunt, 2009) and widespread pain (Stray et al., 2013) compared to controls, but no difference in the report of past painful experiences (Scherder et al., 2008). Treister, Eisenberg, Demeter and Pud (2015) recently objectively measured pain sensitivity in adult participants with ADHD (n=30) and controls (n=30), and found that the ADHD group had a significantly lower pain threshold and tolerance time than the control group. Until now no study has examined pain sensitivity in children with ADHD or looked at the effect of comorbidity within ADHD. The present study examined pain perception in a large sample of

adolescent boys with ADHD, and examined the effect of severity of ADHD and CD symptoms on pain sensitivity.

Another variable closely related to conduct problems is psychopathic traits (Viding, Frick & Plomin, 2007). Psychopathic traits are related to a lack of empathy for others' pain (Caes et al., 2012; Decety, Chen, Harenski & Kiehl, 2013); one might therefore speculate that individuals, who are less responsive to self-experienced pain, might also have difficulty appreciating others' pain (Miller, Steven, Courtland, Maples & Amos, 2014). Research findings regarding self-experienced pain in psychopathy are mixed (Miller, Steven, Courtland, Maples & Amos, 2014). Previous research suggests that individuals high in psychopathic traits take longer to detect the presence of an electric shock, but do not differ in pain tolerance (Hare, 1968), although these individuals may tolerate higher levels of pain in response to incentives (Hare & Thorvaldson, 1970). Fedora and Reddon (1993) compared pain tolerance to electrical stimulation in prisoners high and low in psychopathic traits and found that both prisoner groups had a higher pain tolerance than a control group, but did not differ from one another. Cheng, Hung and Decety (2012) obtained the same results when comparing high and low callous and unemotional juvenile offenders. These personality traits, it is argued (Lahey & Waldman, 2012), identify those at greater risk for severe antisocial behaviour and reduced responsiveness to treatment (Hawes, Price, & Dadds, 2014). The importance of CU traits has been acknowledged by including limited prosocial emotions as a specifier for CD in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2013; Frick, Ray, Thornton & Kahn, 2014). We therefore aimed to explore the effect of CU traits in this sample.

Pain is an extremely difficult outcome to measure due to its subjective nature (Younger, McCue & Mackey, 2009). Previous research in antisocial groups has mainly used self-

report measures of pain sensitivity by either asking participants to report their threshold and/or tolerance points, or by taking self-report ratings of experienced pain (e.g. Séguin et al., 1996; Franklin, Hessel & Prinstein, 2011). These types of measurements, however, can be influenced by reporter biases, especially the motivation to impress the experimenter (Garofalo, Lawler, Robinson & Kenworthy-Heinge, 2006). Brown, Sheffield, Leary and Robinson (2003) showed that the mere presence of another person affected pain tolerance, and Reidy, Martinez and Zeichner (2009) found that pain tolerance was correlated with participants' conformity to gender roles. It would be interesting to measure physiological responses to pain to analyse the relationship between these and self-report measures. Autonomic nervous system responses are related to aversive stimuli and reduced in antisocial samples (Raine, 1996). Measurements of changes in skin conductance level have been used in pain research and found to correlate with self-reported ratings of pain (e.g. Treister, Kliger, Zuckerman, Aryeh & Eisenberg, 2012; Geuter, Gamer, Onat & Büchel, 2014). However, until now no study has examined the association between subjective and physiological responses to pain in high risk, clinically antisocial populations.

In this study we hypothesised that adolescents with ADHD and comorbid CD would have lower pain sensitivity (i.e., higher threshold and tolerance to pain) than those with ADHD alone, and that CD symptom severity and/or CU traits would inversely predict pain sensitivity.

Methods

Sample

Participants were recruited from Child and Adolescent Mental Health Services and Community Child Health Clinics in Wales. Children in the sample were of British Caucasian origin and met research criteria for a lifetime DSM-IV diagnosis of ADHD. Children with any known clinical or research diagnosis of schizophrenia, bipolar disorder, Autistic Spectrum Disorder (ASD), Tourette's syndrome, or with an IQ<70 (based on the administration of the Wechsler Intelligence Scale for Children, WISC; Wechsler, 1991), epilepsy, brain damage or any other neurological or genetic disorder were excluded from the study. In total 204 adolescent males with ADHD (mean age = 13.95 years, sd = 1.82; age range 10 – 17 years) took part. All participants came from community clinics and none were stimulant naive. Participants who continued to take ADHD medication (74.2%) were asked to come off medication at least 24 hours prior to testing.

Ethics Statement

Approval for this study was obtained from the South Wales Multicentre Research Ethics Committee. Informed written consent was obtained from parents of all participants and from adolescents aged over 16 years. For younger adolescents, written assent was obtained (in addition to the written consent from parents).

Clinical Measures

Child psychopathology was assessed using the Development and Well Being Assessment (DAWBA) structured interview using parents and children as informants (Goodman, Ford, Richards, Gatward & Meltzer, 2000). Parents completed the ADHD and CD/ODD sections and children the CD/ODD section. ADHD and CD diagnoses and symptom scores were generated from the DAWBA according to DSM-IV criteria (3+ symptoms; DSM-IV was still in use at the start of the study). CD symptoms were

counted as present when endorsed by either the parent or child. Based on this information participants were subdivided into two groups: ADHD only or ADHD with a research diagnosis of CD (ADHD+CD).

Callous-Unemotional traits were measured using the Youth Psychopathic traits Inventory (YPI; Andershed, Kerr, Stattin & Levander, 2002). The CU subscale has 15 items, and each item is answered on a 4-point Likert scale (score range 0 – 45). These 15 items were summed to achieve a CU trait score ('CU'). The reliability and validity of the YPI have been established (Andershed, Hodgins & Tengstrom, 2007).

Parent-rated emotional/anxiety symptoms were assessed using the Strengths and Difficulties Questionnaire (SDQ; Goodman & Goodman, 2009) completed as part of the DAWBA. The five emotional items were summed to obtain a total emotional symptom score ('SDQ emotion').

Cognitive ability was assessed using the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999) – 2-subset form (vocabulary and matrix reasoning) to create an Intelligence Quotient variable ('IQ').

Procedure

The pain induction procedure replicated the procedure described by Thompson, Keogh, French and Davis (2008). A Peltier-based thermode with a 5 cm by 5 cm aluminium contact pad was used for the thermal heat induction (www.psyal.co.uk). Participants were first asked to do a practice trial to familiarise themselves with the heat sensation and eliminate any substantial differences in baseline hand temperatures. The experimenter positioned the thenar eminence of the participant's non-dominant hand on the contact pad and participants were asked to hold it there for 30 seconds, with the temperature set at 40°C. For the experimental trial, the temperature of the pad was

increased to 48°C. Participants were asked to report when the heat sensation began to elicit pain ('threshold time') and when the pain became too much, at which moment they stopped the procedure by removing their hand from the thermode ('tolerance time'). These two self-reported times were recorded in seconds and participants were asked to stop after 90 seconds if they had not already done so. This limit was established as appropriate during pilot testing.

Skin Conductance Recording

Electrodermal activity was recorded using a skin conductance amplifier (PSYCHLAB Contact Precision Instruments, UK). Skin conductance paste (ABRALYT 2000, Chloride free abrasive electrolyte gel, supplied by Falk Minow Services DE-82211 Herrsching) was used to fill the 8 mm diameter silver/silver chloride electrodes, which were placed on the distal phalanges of the index and middle fingers of the dominant hand, using double-sided adhesive electrode collars.

SCL at reported threshold time ('SCL$_{threshold}$') and tolerance time ('SCL$_{tolerance}$') were recorded. In order to confirm that the SCL recording related to participants' perception of pain, the increase in SCL from the start of the procedure to the termination point was used to predict tolerance time. A larger increase in SCL was expected to predict a shorter tolerance time. The individual's increase in SCL was then divided by their tolerance time to create a pain ratio variable ('pain ratio'). Because participants would vary in how long their hands were on the pain stimulus it was important to take this into account when looking at their SCL during this time. A high pain ratio reflects a rapid SCL increase over a short tolerance time, signifying high sensitivity to pain, whereas a low pain ratio value reflects a slow SCL increase over a protracted tolerance time, reflecting low sensitivity to pain.

Data analysis

Two participants were excluded because of missing or incomplete DAWBA data, and eighteen participants had missing pain data, resulting in a sample of 183 participants. Over half (53.3%) of these met criteria for a comorbid diagnosis of CD. This is at the high end of estimated rates in ADHD (Biederman et al., 1991). Prevalence rates reported in the literature are usually based on younger age groups and our sample included adolescents (mean age = 13.97), with CD increasing with age. Reported and SCL threshold and tolerance variables were not normally distributed and therefore transformed using a log10 transformation. Transformation led to the SCL variables becoming normally distributed and the self-report variables becoming less skewed, but these were still not normal. However, comparison of parametric and non-parametric Mann-Whitney U test results led to the same findings. This outcome in combination with the large sample size gave us the confidence to use parametric tests; this also enabled us to carry out further analyses and look at the covariance effect of IQ. Between group differences were assessed using ANOVAs. Effect sizes are reported as eta squared (η^2_p; small$\geq$.01, medium$\geq$.06, large$\geq$.14; (Cohen, 1988)). Finally, Pearson correlations and multiple regressions examined the effect of clinical and demographic characteristics on pain variables and SCL. Analyses were carried out using SPSS 20.0 (SPSS Inc., Chicago, IL).

Results

Methodology check

The increase in SCL from baseline to pain tolerance point significantly (inversely) predicted pain tolerance time ($F[1, 183] = 34.1$, $p < .001$, $R = .40$, Beta = -.40)

suggesting that those with a slower SCL increase were able to keep their hand longer on the thermode. We then divided the SCL by tolerance time to create the pain ratio; this also significantly predicted tolerance time (F[1, 183] = 41.7, p <.001, R = .43 Beta = -.43). Because these two variables were highly correlated (r = .72), we subsequently only used the pain ratio in further analyses.

Clinical groups

The demographic data for the two subgroups and the results of the between-group analyses are presented in Table 1.

Table 1. Demographic and clinical characteristics of the ADHD and ADHD+CD subgroups

	ADHD (N=85)		ADHD+CD (N=98)		
	Mean	*SD*	*Mean*	*SD*	*p value*
Age	13.85	1.86	14.09	1.71	ns
IQ	90.26	9.86	84.76	9.33	*p* <.001
ADHD	11.67	4.86	13.17	4.27	*p* <.05
CD	1.00	0.80	5.77	2.42	*p* <.001
ODD	2.86	2.43	4.68	2.66	*p* <.001
CU	16.39	5.96	20.77	2.01	*p* <.001
SDQ emotion	4.73	2.75	4.98	2.66	ns

Note: All between group analyses were done using independent samples t tests; ADHD symptoms=ADHD symptom score; CD symptoms=CD symptom score; ODD=ODD symptom score; CU=callous/unemotional trait score; SDQ emotion=Strengths and Difficulties emotional symptom subscale score.

With respect to subjectively reported pain, the ADHD+CD group had a higher pain threshold time (M = 21.25, SE = 2.74) than the ADHD only group (M = 14.71, SE = 2.54; F[1, 181] = 5.19, p = .024, η^2_p = .03). The ADHD+CD group also had a higher tolerance time (ADHD+CD: M = 40.60, SE = 3.07; ADHD: M = 30.38, SE = 3.24;

$F[1,181] = 8.04$, $p = .005$, $\eta^2_p = .04$). When we controlled for the group differences in

IQ and ADHD symptom scores the difference in threshold time ($F[1, 172] = 5.96$, $p =$

.016) and tolerance time ($F[1, 172] = 9.85$, $p = .002$) remained significant.

There were no differences between the ADHD and ADHD+CD groups in $SCL_{threshold}$

($F[1, 181] = .78$, $p = .38$, $\eta^2_p = .004$), or $SCL_{tolerance}$ ($F[1,181] = 1.35$, $p = .25$, $\eta^2_p =$

.007), nor was there a difference in pain ratio (ADHD: M = .08, SD = . 13; ADHD+CD:

M = .07 =.18; $F[1,181]=.04$, $p=.84$)[1]. Fig. 1 illustrates that although the groups differed

in pain threshold and tolerance, there were no differences in the physiological response

at these points in time. This means that both groups had the same SCL when they

reached their threshold and tolerance points, but that the ADHD+CD group took

significantly longer to get there[2].

There was no difference between ADHD participants who did and did not take

medication on any of the pain variables (Threshold time: $p = .50$; Tolerance time; $p =$

.21; $SCL_{threshold}$: $p = .34$; $SCL_{tolerance}$: $p = .31$; $SCL_{increase}$: $p = .70$; Pain ratio: $p = .77$).
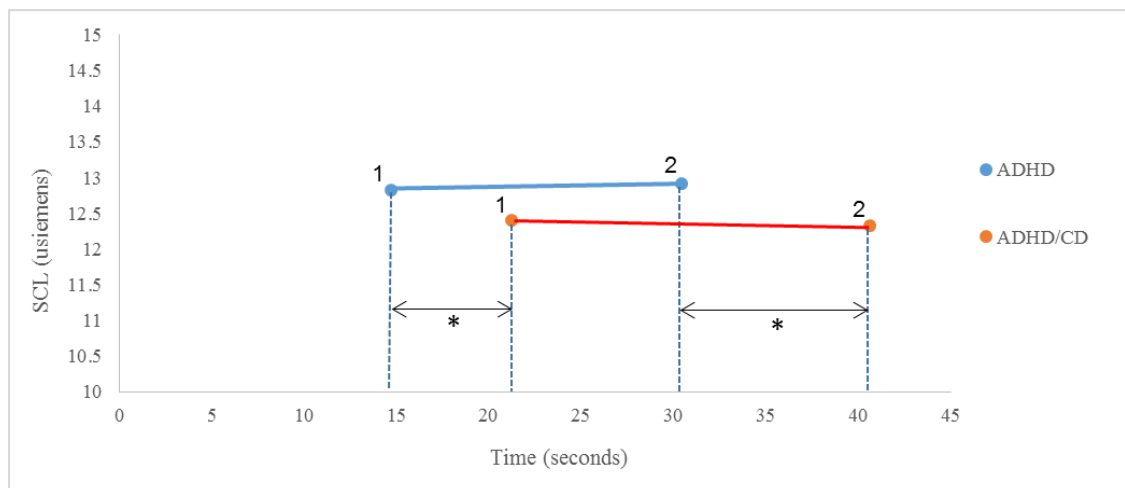
Figure 1. Mean skin conductance level at threshold and tolerance time for the ADHD and ADHD+CD groups. 1=threshold time; 2=tolerance time; *=p<.05.

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[1] Results of non-parametric Mann-Whitney U tests comparing ADHD and ADHD+CD groups revealed the same pattern of results: Threshold time: $U = 3328$, $p = .019$; Tolerance time: $U = 3216$, $p = .008$; $SCL_{threshold}$: $U = 3898.5$, $p = .456$; $SCL_{tolerance}$: $U = 3750.5$, $p = .246$.
[2] SCL baseline: ADHD only: M=5.77, SD=3.88; ADHD+CD: M=5.25, SD=2.08.

Clinical measures

Table 2 shows the pattern of correlations between the clinical variables and the pain measures.

Table 2. Correlations between clinical and pain sensitivity measures.

	ADHD	CD	ODD	CU	SDQ emotion	Threshold time	Tolerance time	SCLthreshold	SCLtolerance	Pain ratio
ADHD	-									
CD	.19**	-								
ODD	.59**	.41**								
CU	.11	.40**	.22**	-						
SDQ emotion	.28	.09	17*	-.02	-					
Threshold time	-.18*	.17*	-.06	.12	-.15	-				
Tolerance time	-.14	.19*	-.00	.21**	-.15	.68**	-			
SCLthreshold	.06	-.07	.02	-.04	.14	-.03	-.06	-		
SCLtolerance	.09	-.07	.02	-.05	.13	-.10	-.11	.98**	-	
Pain ratio	.17*	-.01	.13	-.17*	.09	-.31**	-.50**	.36**	.43**	-

*Note: * = p<.05, ** = p<.001. ADHD = ADHD symptom score; CD = CD symptom score; ODD= ODD symptom score; CU = callous/unemotional trait score; SDQ emotion= Strengths and Difficulties emotional symptom subscale score; Threshold time = time at which first experience of pain is reported; Tolerance time = length of time until procedure is terminate; $SCL_{threshold}$ = Skin conductance level at threshold time; $SCL_{tolerance}$ = Skin conductance level at tolerance time; Pain ratio = Skin Conductance increase divided by tolerance time.*

Table 2 shows that CD and ADHD symptom scores were each significantly correlated with pain threshold time. A multiple regression confirmed that both ADHD and CD symptom scores significantly predicted pain threshold time (F[2, 175] = 7.26, p<.001, R = 0.28); however, ADHD symptom scores inversely predicted pain threshold time (Beta = -0.23) and CD symptom scores positively predicted threshold time (Beta = 0.21).

CD symptom scores and CU traits were highly correlated, and each correlated significantly with pain tolerance time. A stepwise regression revealed that only CU traits significantly predicted pain tolerance time (F[1, 181] =8.37, p=.002, R = 0.21, Beta = 0.21), with CD symptom score not adding to the model (p = 0.16).

ADHD symptom scores and CU traits both correlated significantly with the pain ratio reflecting physiological sensitivity to pain. A multiple regression showed that both ADHD symptom scores and CU traits significantly and independently predicted the pain ratio (F[2, 171] = 6.24, p=.002, R = 0.26), with ADHD positively (Beta = 0.20) and CU traits negatively predicting it (Beta = -0.20). Total CD scores did not predict the pain ratio.

Discussion

This was the first study to measure the effects of comorbid CD and CU traits on pain sensitivity in a large sample of adolescent boys with ADHD. Furthermore, no previous studies on pain in children with behavioural difficulties measured the physiological response to pain. SCL was measured during the procedure to investigate whether self-reported threshold and tolerance times were associated with participants' physiological responses to pain. We found that the increase in SCL from the start of the pain procedure to

participants' tolerance time significantly predicted tolerance time, suggesting a larger physiological response reflected a greater experience of pain. This provides support for using SCL as a measure of pain sensitivity alongside self-report and behavioural measures in these samples.

We found that males with ADHD and comorbid CD took longer to report initial pain and were able to endure it for longer, as reflected in their significantly higher pain threshold and pain tolerance times, than those with ADHD only. A relatively high pain threshold is thought to reflect a lower sensitivity to aversive stimulation, which has previously been found in adolescents with CD (e.g. Blair, 2007; Van Goozen et al., 2007). If negative stimuli are experienced as less aversive and consequently have less punishing effects, then it may be more difficult to socialize these individuals to behave in a prosocial manner (Lykken, 1995). However, although the groups differed in pain behaviour, there were no differences in the physiological response to pain at these points in time. This means that although both groups had the same SCL when they reached their threshold and tolerance points, the ADHD+CD group took significantly longer to get there (see Fig. 1). When examining relations with the clinical variables we found that CU traits predicted low physiological response to pain, whereas ADHD severity predicted higher physiological response. Specifically, more severe ADHD was associated with a more rapid SCL increase over a short tolerance time, whereas higher levels of CU traits were associated with a slower SCL increase over a protracted tolerance time.

Research shows that pain is perceived as less intense when individuals are distracted (Johnson, 2005). Spontaneous hypertensive rats (SHR; a widely used animal model of ADHD; Sagvolden, 2000) have been found to show reduced pain sensitivity, yet their pain

receptor neurons appear to be normal. In a study in which rats were first habituated to a hot plate the SHR rats no longer showed reduced pain sensitivity (Vendruscolo, Pamplona & Takahashi, 2004). This suggests that the pain insensitive phenotype of these SHR rats involves cognitive processes, for example, distraction. These findings suggest ADHD would be associated with a higher pain threshold. However, Treister at al. (2015) found that those with ADHD had a significantly lower pain threshold and tolerance time than controls and hypothesised that this was due to dopamine dysregulation. There is growing evidence that dopamine dysregulation plays a role in the neurobiology of ADHD (Tripp & Wickens, 2009) and in the processing of pain (Wood, 2008). Our results in an adolescent sample with ADHD support this as we found ADHD severity was associated with a greater sensitivity to pain.

A growing number of functional magnetic resonance imaging (fMRI) studies have shown remarkable similarities in the neural circuits involved in the processing of own and others pain (Botvinick et al., 2005; Jackson, Brunet, Meltzoff & Decety, 2006; Lamm, Batson & Decety, 2007; Moriguchi et al., 2007; Saarela et al., 2007). The results from the present study add to this debate: participants high in CU traits, who arguably lack empathy, showed an increased tolerance and slower physiological response towards their own pain, which might explain why they also have less empathy for others' distress.

The study had some limitations. First, we examined pain processing within a large sample of clinical cases with ADHD and there was no normal healthy control group for comparison. Only if a normal control group is included can we establish that ADHD is associated with higher or lower pain sensitivity. Second, future research could also include a sample of participants with CD without ADHD. If ADHD is associated with a lower and

CD with a higher pain threshold then individuals with CD without comorbid ADHD might have an even higher pain threshold than the participants in this study, and this would be an important observation. Third, we cannot be certain that the increase in SCL reflects the intensity of physical pain rather than other emotions (e.g. fear or excitement), since SCL changes are valence nonspecific. It is possible that the ADHD+CD group felt more ambivalent towards the pain stimulus or enjoyed it more and therefore had a greater pain tolerance. It may be beneficial in future research to measure other self-reported emotions. Furthermore, the accuracy of measuring the physiological response to pain could be improved by including other measures, for example, pupil dilation or heart rate (Treister et al., 2012; Geuter et al., 2014).

Lastly, we were unable to analyse in more detail the effect of medication on pain perception. Treister et al. (2015) found that the psychostimulant drug methylphenidate (Ritalin) increased pain threshold and tolerance in adults with ADHD. Although we asked our participants to come off medication 24 hours before testing, psychostimulant medication varies in how long it takes to leave the body. However, we found no differences on any of the pain variables between those with a prescription for medication and those without. Future research should, however, look into the different anti-nociceptive effects of different medications.

This study highlights the importance of considering comorbidity and heterogeneity of disorders when developing interventions. If reduced pain sensitivity reflects reduced reactivity to aversive cues more generally, including punishment, then punishment-based interventions for troublesome behaviour are less likely to be effective in treating certain types of CD, particularly those high in CU traits. Conversely, if ADHD without CD is

associated with an increased aversive cue sensitivity, interventions involving corrective feedback and learning from punishment are a treatment option for those with this behavioural profile.

There is very little research on the role of pain sensitivity in development more generally and psychopathology more specifically. We do not know, for example, whether pain sensitivity is a precursor of antisocial development. A young child with a high pain threshold might be less reserved about engaging in risky behaviour and less responsive to corrective feedback (Baker, Shelton, Baibazarova, Hay & Van Goozen, 2013). We also do not know much about the stability of, or individual differences in pain sensitivity. It is possible that pain thresholds change as a result of exposure to external events, for example in the case of a 'toughening up' as a result of childhood adversity, whilst being exposed to harsh parental discipline, childhood abuse or peer victimization. Longitudinal research is clearly needed to shed light on these important issues.

Chapter 3: Fear conditioning

Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD), a common childhood-onset disorder (Castellanos & Tannock, 2002), is a well-recognised risk for antisocial behaviour. Approximately 30-50% of children with ADHD develop conduct disorder (CD; Kutcher et al., 2004) and ADHD continues to be associated with elevated levels of antisocial behaviour in adulthood (Weiss & Hechtman, 1993, Klein et al, 2012). However, the processes that explain this link between ADHD and later antisocial behaviour remain poorly understood.

There are some key hypothesized risk pathways that require investigation (Van Goozen, Fairchild, Snoek, & Harold, 2007). Abnormal processing of emotionally aversive stimuli is one important risk process that is strongly associated with antisocial behaviour in the general population (Blair, Mitchell, & Blair, 2005; Raine, 1997; Van Goozen, Snoek, Matthys, Van Rossum, & Van Engeland, 2004, Van Goozen et al., 2007). Fear conditioning, as a measure of emotional learning, has been established as a correlate of anti-social behaviour in adults (Birbaumer et al., 2005; Flor, Birbaumer, Hermann, Ziegler, & Patrick, 2002; Raine, 1993). Fear conditioning is experimentally induced by pairing a previously neutral stimulus (conditioned stimulus; CS+) with an aversive one (unconditioned stimulus; US), for example, a loud noise. After repeated pairings of the CS+ and US, the initially neutral stimulus will elicit a response (conditioned response; CR), similar to that caused by the US. The reaction to this conditioned stimulus (CS+) is then compared to the reaction to a control stimulus, which has not been followed by the aversive stimulus (CS-). Skin conductance is a reliable measure of emotional arousal and often used as the UR in fear conditioning paradigms because unusual patterns of skin conductance

responding can help to pinpoint impairments in emotion processing (Dawson, Schell & Filion, 1990). It has been argued that impairment in this type of associative learning is a predisposing factor for antisocial behaviour, as individuals will not learn to associate particular situations, behaviours and contexts with punishment and this has important implications for interventions (Raine, 1993; Sterzer, 2010; Pine, 2010).

Impairments in emotion processing are thought to arise due to underlying deficits in the neural system involving the amygdala (Fairchild, Stobbe, Van Goozen, Calder, & Goodyer, 2009). Deficient amygdala activation has been reported during the viewing of affective pictures in clinical cases with early-onset CD (Sterzer, Stadler, Krebs, Kleinschmidt, & Poustka, 2005). The amygdala is also critically involved in emotional learning (Everitt, Cardinal, Parkinson, & Robbins, 2003). Lesion studies have shown that the amygdala is required for the acquisition of fear conditioned responses (Bechara, Tranel, Damasio, Adolphs, Rockland, & Damasio, 1995; LaBar, LeDoux, Spencer, & Phelps, 1995) and neuroimaging studies in humans have confirmed that the amygdala is activated during fear conditioning (Büchel, Morris, Dolan, & Friston, 1998). Consequently, conditioning ability has often been used as a peripheral measure of amygdala dysfunction (Fairchild, Van Goozen, Stollery, & Goodyer, 2008).

Although well replicated in adults, research examining fear conditioning and antisocial behaviour in young people is limited, with some noted exceptions; fear conditioning has been found to be impaired in adolescent males with CD (Fairchild et al., 2008) and adolescent females with CD (Fairchild, Stobbe, Van Goozen, Calder, & Goodyer, 2010). More recently, the severity of this emotional learning deficiency was found to be associated with the frequency of antisocial behaviour in a group of juvenile male offenders (Syngelaki,

Fairchild, Moore, Savage, & Van Goozen, 2012). Longitudinal studies have also found that reduced fear conditioning ability in 3-year-old children predicted aggressive behaviour at age 8 (Gao, Raine, Venables, Dawson, & Mednick, 2010a) and criminal behaviour at age 23 (Gao, Raine, Venables, Dawson, & Mednick, 2010b), suggesting that fear conditioning ability is an early marker of later behavioural problems.

A large proportion of studies into deficits in emotion functioning in CD children included participants with a comorbid diagnosis of ADHD, but only a few specifically analysed the contributing effects of ADHD. Herpertz et al. (2001, 2003) found that boys with comorbid ADHD+CD showed a reduction in autonomic responses and a more rapid habituation to orienting and aversive startling stimuli compared with age-matched children with ADHD alone, suggesting that this pattern of reduced ANS reactivity is found in children with CD, irrespective of comorbid ADHD. Gao, Raine, Venables, Dawson and Mednick (2010) found an association between fear conditioning response at age 3 and aggressive behaviour at age 8. Fear conditioned responses did not differ between high and low hyperactive-inattentive children. However, the criterion for this categorisation was based on teacher ratings and the internal reliability of the hyperactive-inattentive scale was relatively low (alpha =.50). Nevertheless, the findings are consistent with prior findings showing normal fear conditioning in children with a clinical ADHD diagnosis. Skin conductance and cardiac responses were measured, and ADHD children were found to be as equally responsive to signals related to punishment as controls (Pliska, Hatch, Borcherding, & Rogeness, 1993). Furthermore, deficient amygdala activation has been reported in clinical cases of comorbid CD and ADHD during the viewing of affective pictures, but when comparing pure ADHD children to healthy controls no abnormal functioning of the

amygdala or relevant prefrontal areas was found (Herpertz, et al., 2008). Until now, no study has looked at fear conditioning within an ADHD sample to directly assess the contributing effects of comorbid CD.

Individuals with CD in combination with Callous and Unemotional (CU) traits appear to have deficits in processing signs of fear and distress in others; they appear to be less sensitive to punishment, and show more thrill seeking or fearless behaviour (Scheepers, Buitelaar, & Matthys, 2011). It is unclear, however, whether these and other psychobiological characteristics found in youths with CD and CU traits are specifically associated with the CU traits or with the combination of CD and CU. For example, reduced SCL and HR in anticipation of, and in response to, an aversive stimulus has been found in adolescent boys with CU traits compared to controls (Fung, et al., 2005). However, in a subsequent analysis that looked at antisocial behaviour as a predictor of reduced responding, there was no difference between antisocial boys with high and low CU traits. In addition to this, various fMRI studies have found reduced amygdala reactivity in CD adolescents with CU traits in comparison to healthy controls, but in these studies comparisons were not made between CD individuals with and without CU traits (e.g. Jones et al., 2009). Fairchild's (2010) research on fear conditioning in females with CD did control for psychopathic traits and found that it was not a significant covariate and there was no difference in fear conditioning between those with CD who were high and low in psychopathic traits.

The aim of the present study was to test the hypothesis that in adolescent males with ADHD reduced skin conductance response to aversive stimuli during fear conditioning and impaired associative learning would distinguish those with and without significant

antisocial behaviour (ADHD only vs. ADHD+CD). We also aimed to assess the contributing effects of CD severity and CU traits on conditioning ability.

Methods

Sample

Participants were recruited from Child and Adolescent Mental Health Services and Community Child Health Clinics in Wales. Children in the sample were of British Caucasian origin and met research criteria for a lifetime diagnosis of ADHD. Children with any known clinical or research diagnosis of schizophrenia, bipolar disorder, Autistic Spectrum Disorder (ASD), Tourette's syndrome, or with an IQ<70 (based on the administration of the Wechsler Intelligence Scale for Children, WISC; Wechsler, 1991), epilepsy, brain damage or any other neurological or genetic disorder were excluded from the study. In total, 204 adolescent males with ADHD (mean age = 13.95 years, sd = 1.82; age range 10 – 17 years) took part in the present study. No participants were stimulant naïve but participants who were currently being prescribed stimulant medication were asked to come off their medication at least 24 hours prior to testing.

Ethical approval was obtained from the Wales Multicentre Research Ethics Committee. Informed written consent was obtained from all parents and adolescents aged over 16 years whereas written assent was obtained for adolescents below age 16.

Clinical measures

Child psychopathology was assessed using the Development and Well Being Assessment (DAWBA) structured interview using both parents and children as informants (Goodman et al., 2000). Parents completed the ADHD and ODD/CD sections and children the ODD/CD section of the DAWBA. Symptom scores and diagnoses were generated from the DAWBA according to DSM-IV criteria (the DSM-V had not been published at the start of the study) (APA, 2000). CD symptoms were considered present if endorsed by either the parent or child.

Internalizing symptoms, such as anxiety, are associated with increased sensitivity to punishment cues and greater levels of fear (Grillon, 2002; Indovina, Robbins, Núñez-Elizalde, Dunn, & Bishop, 2011; Joiner, et al., 1999). Furthermore, a meta-analysis of fear conditioning in 453 anxiety patients demonstrated modest increases in both acquisition of fear learning and conditioned responding during extinction (Lissek, et al., 2005). Therefore parent-rated emotional/anxiety symptoms were assessed using the Strengths and Difficulties Questionnaire (SDQ; Goodman et al., 2000). This was also completed as part of the DAWBA. The five emotional items (worries, unhappy, afraid, clingy, somatic) were scored on a 3-point Likert scale and summed to obtain a total internalizing emotional symptom score (score range 0-10).

Callous-Unemotional (CU) traits were measured using the Youth Psychopathic traits Inventory (YPI; Andershed, Kerr, Stattin, & Levander, 2002). The CU subscale of the YPI contains 15 items, and each item is answered on a 4-point Likert scale (score range 15 – 60). The reliability and convergent validity of the YPI with other measures of CU traits has been established (Andershed, Hodgins, & Tengstrom, 2007; Skeem and Cauffman, 2003).

Cognitive ability was assessed in all participants using the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999) – 2-subtest form (vocabulary and matrix reasoning).

Fear conditioning

The fear conditioning experiment replicated the procedure described by Bechara and Damasio (2002) and Fairchild et al., (2008). Participants viewed 48 coloured slides (red, blue, orange and green) presented on a computer screen. Ten of the 48 slides were paired with a loud (99 dB) aversive white noise lasting 1000msec, which was presented bi-aurally using headphones. The slides served as the visual conditioned stimuli (CS), the aversive loud noise was the unconditioned stimulus (US), and SCRs to the US and CS were measured as the dependent variables during conditioning. The coloured slides were presented for 3 seconds, with a 10 second inter-stimulus interval. White noise was paired with the conditioned stimulus positive (CS+) 2 seconds after slide onset.

The fear conditioning protocol was divided into three phases: a habituation phase (HAB), an acquisition phase (ACQ), and an extinction phase (EXT). The blue slides were reinforced with the US only during the acquisition phase. In the habituation phase 2 unreinforced blue slides (CS+) and 2 red slides (CS-) were mixed with other colours. The acquisition phase consisted of 8 unreinforced blue slides, 10 reinforced blue slides and 10 red slides. The extinction phase consisted of 6 unreinforced blue (CS+) and 3 red (CS-) slides. Each phase was scored by subtracting CS- from unreinforced CS+ to assess whether SCRs increased as a result of differential conditioning to the CS+.

Figure 1 portrays what we would expect in normal conditioning. Participants should respond similarly to the blue and red slides during the habituation phase. During the

acquisition phase, when the US is administered, participants should learn to fear the blue slides and learn to consider the red slides as 'safe' (Fairchild, et al., 2008). Participants' SCRs should return to normal levels during the extinction phase.
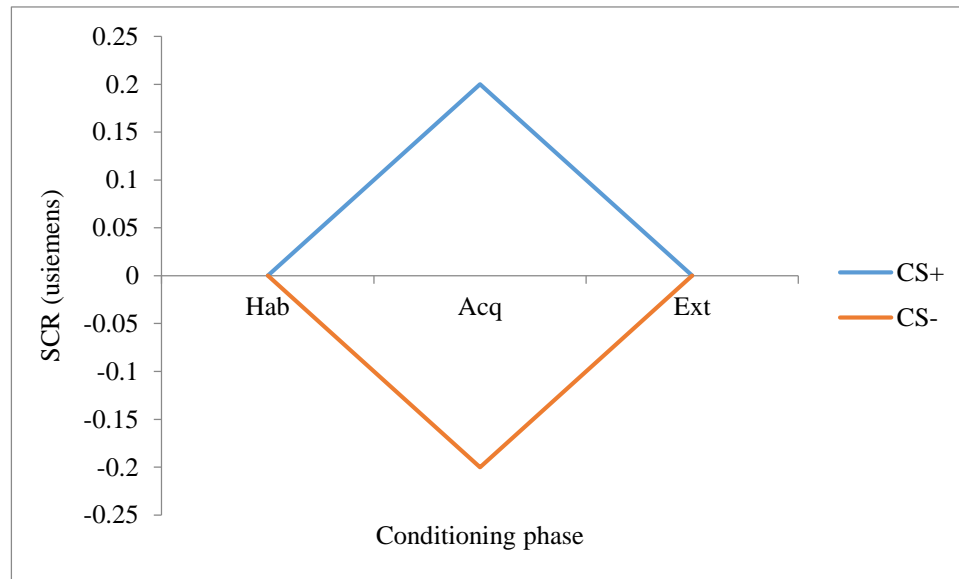
Figure 1. Illustrative diagram of normal conditioning. The blue line reflects 'fear' learning to the CS+ and the red line reflects 'safety' learning to the CS-.

After the experiment had finished, participants were asked to recall salient aspects of the task to ensure that they had been paying attention, i.e., how many and which colours they had seen, how many slides and which colour had been paired with the aversive sound. A recall score of 1.5 out of 5 was considered appropriate for inclusion (Bechara & Damasio, 2002; Fairchild et al., 2008).

Skin conductance recording

Electrodermal activity was recorded using a skin conductance amplifier (PSYLAB Contact Precision Instruments, UK). Skin conductance paste (ABRALYT 2000, Chloride free abrasive electrolyte gel, supplied by Falk Minow Services DE-82211 Herrsching) was used to fill the 8mm diameter silver/silver chloride electrodes, which were placed on the distal phalanges of the index and middle fingers of the non-dominant hand; electrodermal activity was sampled at 500 Hz. A SCR (skin conductance response) typically takes 4 or 5 seconds to complete and so SCRs were measured in the 6 second period following presentation of the CS. A valid SCR was considered to exceed an amplitude of .05 µSiemens (µs) (see Fairchild et al., 2008; Syngelaki et al., 2013). The internal consistencies (Cronbach's alphas) for the SCRs to the US and CS+ were 0.81 and 0.70 respectively.

Data analysis

Two participants had missing or incomplete DAWBA data and two participants had missing physiology data due to technical problems so they could not be included. Eighteen participants did not complete the fear conditioning task. These participants were generally of a younger age (mean: 12.1, only one participant was >13) and they usually asked to stop the task because they did not like the US (loud noise).

Nine participants had an estimated IQ <70 and so were not included. Three participants did not reach the >1.5 criteria and so were removed from the analysis but it was also noted that there were an extra 40 participants who did not answer correctly that blue was the colour that was paired with the US. This suggests that these participants were not concentrating on

which colour was presented with the noise thus potentially preventing the occurrence of conditioning. It could be argued that conditioning might still occur subconsciously, although this could not be ensured. It was therefore decided that only participants who knew that it was the blue slides that were paired with the US would be used and this left 130 participants for analysis. Importantly, as shown in Table 1, the omitted participants did not differ significantly in age, IQ, or ADHD/ CD symptom count.

Table 1. Descriptive characteristics of participants who correctly identified the blue slide and those who did not.

	Blue (N=130)		Not Blue (N=43)		
	Mean	*SD*	*Mean*	*SD*	*sig*
Age	14.13	1.73	13.74	1.99	$p = .22$
IQ	87.49	9.57	88.25	8.80	$p = .65$
ADHD	12.39	4.31	11.97	5.51	$p = .62$
CD	3.43	2.92	3.72	3.22	$p = .58$

Note: All between group analyses were done using independent samples t tests; ADHD =ADHD symptom score; CD =CD symptom score; IQ = Intelligence quotient

The fear conditioning variables were not normally distributed; however, transformations made the skew worse and therefore due to the large sample sizes it was felt that parametric tests were still suitable (Field, 2009). Mixed model ANOVAs were used to assess baseline SCR and US responding between groups. One–way ANOVAs were used to compare conditioning ability between groups by calculating a SCR difference score between CS

types for each of the conditioning phases. It was hypothesised that there would be no difference between groups in how participants would respond to the different CS types for the habituation and extinction phase. However, we predicted that there would be a significant difference between groups in how they responded to the CS types during the acquisition phase. Degrees of freedom were corrected using Greenhouse Geisser estimates of sphericity, where assumptions of sphericity were violated. Effect sizes were reported as partial eta squared (η_p^2; small $\geq .01$, medium $\geq .06$, large $\geq .14$; Cohen, 1988). Pearson's correlations and multiple regressions examined the effect of the clinical characteristics on conditioning ability. Analyses were carried out using SPSS 20.0 (SPSS Inc., Chicago,IL).

Results

The demographic data for the two subgroups and the results of between-group analyses are presented in Table 2.

Table 2. Means (with SDs) for the demographic and clinical characteristics of the ADHD and ADHD+CD subgroups.

	ADHD (N=62)		ADHD+CD (N=68)		
	Mean	*SD*	*Mean*	*SD*	*p value*
Age	13.97	1.72	14.28	1.74	ns
IQ	89.96	10.02	85.24	8.61	p < .05
Memory	4.06	0.65	3.84	0.73	ns
ADHD	12.15	4.44	12.61	4.21	ns
CD	1.02	0.76	5.63	2.37	p < .001
ODD	2.91	2.47	4.48	2.63	p < .05
CU	17	5.74	19.76	6.84	p < .05
SDQ Emotion	4.53	2.85	5.4	2.7	ns

Note: ADHD symptoms=ADHD symptom score; CD symptoms=CD symptom score; ODD=ODD symptom score;
CU=callous/unemotional trait score; SDQ emotion=Strengths and Difficulties emotional symptom subscale score.

As expected, the ADHD+CD group had significantly more CD and ODD symptoms, and CU traits than the ADHD only group. Importantly, there was no difference in ADHD symptoms or internalizing emotional scores. There was a significant difference in IQ and therefore any significant between-group difference was followed up using IQ as a covariate.

Probes

A mixed model ANOVA was conducted on the skin conductance responses to the red and blue slides during the habituation phase. This was to make sure there was no difference in baseline SCR between groups before the US (loud noise) had been administered. There was no main effect of CS type [$F(1, 128)=.00$, $p=.99$, $\eta_p^2=.00$] meaning that there was no difference in SCRs to the different colours during baseline. There was also no main effect of group [$F(1, 128)=.735$, $p=.393$, $\eta_p^2=.005$] indicating that the groups had similar SCR levels at baseline, and no CS type x group interaction [$F(1, 128)=.15$, $p=.70$, $\eta_p^2=.001$].

A mixed model ANOVA was then used to look at whether there were any differences in SCRs to the 10 probes (US; aversive loud bursts of noise) across the groups (see Figure 1). A main effect of time was found [$F(2.57, 328,33)=58.19$, $p<.001$, $\eta_p^2=.31$] reflecting a significant habituation effect occurring across the 10 US presentations. No main effect of group was found ($F(1, 128)=1.03$, $p=.31$, $\eta_p^2=.01$], indicating that both groups found the US equally aversive and no significant time x group interaction was found ($F(2.57, 328.33)=1.45$, $p=.23$, $\eta_p^2=.01$].
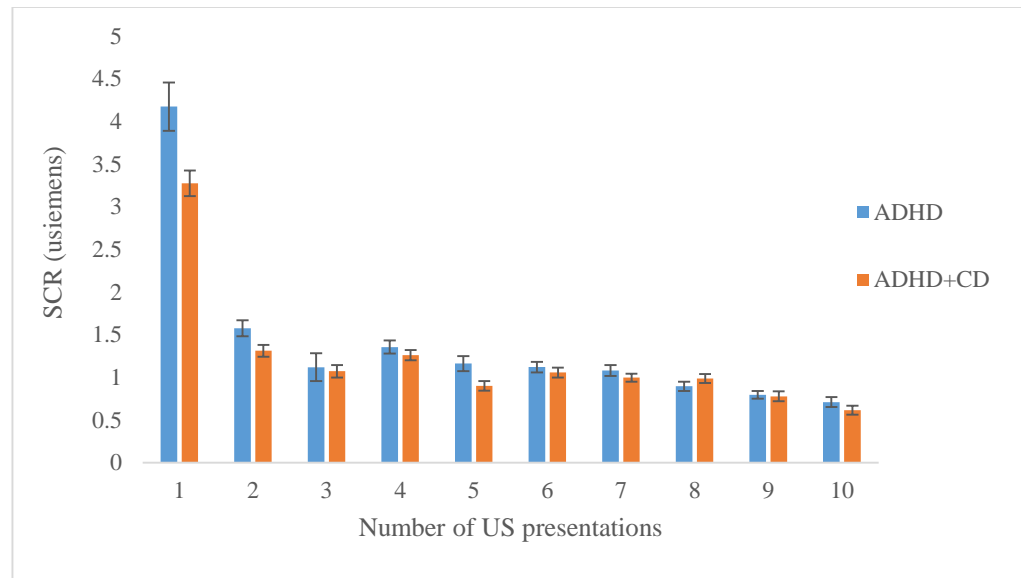
Figure 2. Skin conductance responses (SCRs) to the 10 presentations of the aversive unconditioned stimulus (US) of adolescent boys with ADHD only and ADHD + CD. Error bars are ± 1 SE.

Conditioning

Difference scores between the CS+ and CS- were calculated to compare conditioning ability between groups. There was no significant effect of group in the habituation [$F(1, 128)=.15$, $p=.70$, $\eta_p^2=.001$] or extinction phase [$F(1, 128)=.02$, $p=.90$, $\eta_p^2=.00$]; there was however a significant group effect in the acquisition phase [$F(1, 128)=8.45$, $p<.05$, $\eta_p^2=.06$], with the ADHD+CD showing a significantly smaller difference in SCR between the two CS types during this conditioning phase (see Figure 3 and 4). This difference remained significant after controlling for IQ (p=.008). Results of non-parametric Mann-Whitney U tests comparing ADHD and ADHD+CD groups revealed the same pattern of

results: Habituation: $U=1,148$, $p=.08$; Acquistion: $U=993$, $p=.007$; Extinction: $U=1,1351$,

$p=.64$[2].
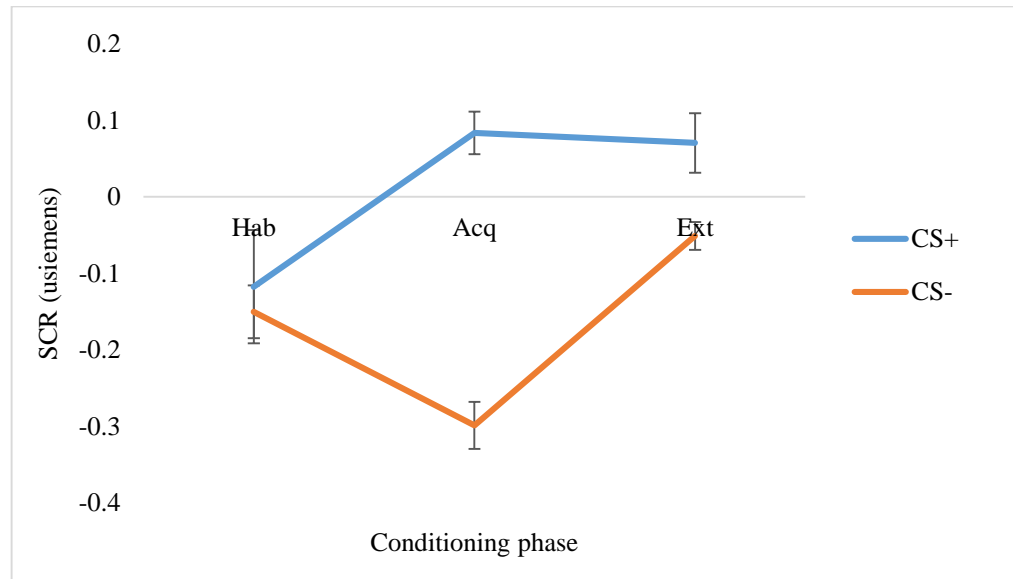
Figure 3. Mean skin conductance response (SCR) to the blue slides (CS+) and the red slides (CS-) in adolescent boys with ADHD only. Hab= habituation phase; Acq= acquisition phase; Ext= extinction phase. Error bars are ± standard error.

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[2] Means and standard deviations of SCR to the CS+ and CS- for the subgroup of 40 participants who did not answer correctly that blue was the colour paired with US: Hab CS+: Mean = -.05, SD = .38; Acq CS+: Mean = .04, SD = .42; Ext CS+: Mean = .15, SD = .46; Hab CS-: Mean = -.02, SD = .46; Acq CS- = .11, SD = .41; Ext CS-: Mean = .10, SD = .23. This data indicates that these participants did not distinguish the CS+ from the CS-.
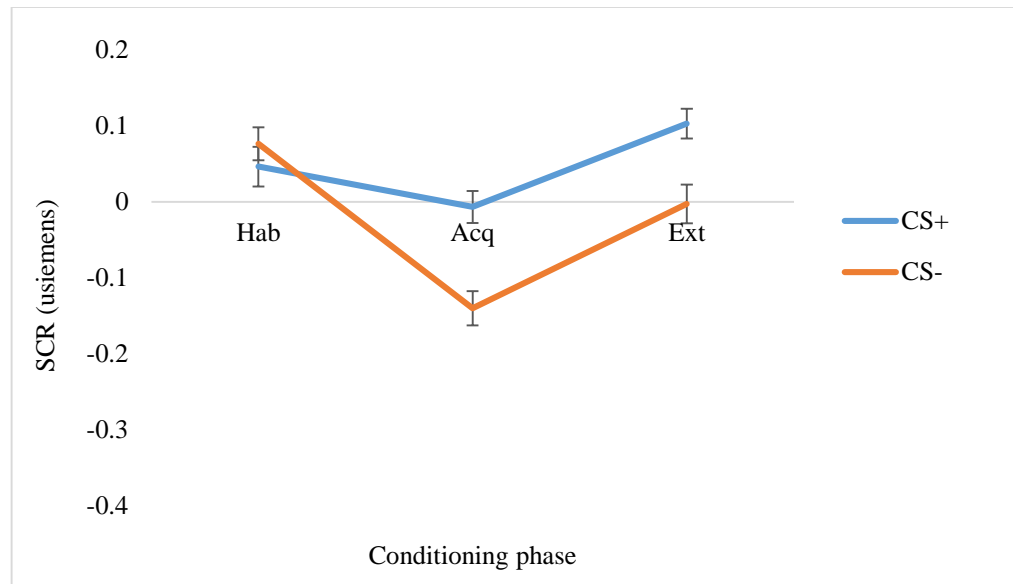
Figure 4. Mean skin conductance response (SCR) to the blue slides (CS+) and the red slides (CS-) of adolescent boys with ADHD and CD. Hab= habituation phase; Acq= acquisition phase; Acq2= acquisition 2; Ext= extinction. Error bars are ± standard error.

Table 3 shows that only CD symptom severity was significantly correlated with differential conditioning during the aquisition phase, with ADHD symptoms and CU traits being unrelated. A regression showed that CD severity significantly (inversely) predicted differential conditioning during the Acquisition phase [$F(1, 128) =6.26$, $p<.05$, $R =.22$, Beta =-.22].

Table 3. Correlations between clinical characteristics and conditioning ability

	ADHD	CD	ODD	CU traits	SDQ	Acq
ADHD	-					
CD	.11	-				
ODD	.53**	.38**	-			
CU traits	.20*	.30**	.25**	-		
SDQ	.30**	.14	.24**	-.01	-	
Acq	.03	-.22*	.10	-.05	.06	-

*Note: ADHD=number of ADHD symptoms; CD=number of CD symptoms; ODD=number of ODD symptoms; CU traits= callous-unemotional traits subscale score; SDQ =Strengths and Difficulties emotional symptom subscale score; Acq = Differential conditioning between the CS types during the Acquisition phase. * = p<.05, ** = p<.001.*

Discussion

The present study aimed to assess fear conditioning in adolescent boys with ADHD, using an established fear conditioning paradigm and physiological methods. It is the first study of fear conditioning in an ADHD sample that controlled for the presence of comorbid CD. Consistent with predictions, male adolescents with ADHD and CD showed reduced autonomic responsiveness in the conditioning experiment compared with those who only had ADHD and no CD. The ADHD+CD group showed significantly reduced differential SCR responding to the CS types compared to the ADHD only group and this was significantly predicted by CD severity and unrelated to ADHD symptoms; these differential patterns were observed despite both groups showing significant SCR habituation to the US. These findings are consistent with previous data from male adolescents with CD (Fairchild et al., 2008) and antisocial behaviour in adulthood (Birbaumer et al., 2005; Flor, et al., 2002; Raine, 1993) and suggest that fear conditioning is a neurobiologically defined measure of functioning that increases risk of antisocial behaviour across age groups and across diagnostic groups.

Our results, suggesting that deficits in emotional learning are specifically associated in ADHD children with CD, may help to explain why this subgroup of ADHD children develops antisocial behaviour and has clinically more severe and persistent problems and a worse prognosis (Thapar, Langley & O'Donovan, 2006). They also support the idea that ADHD alone is not a sufficient risk factor for the development of antisocial behaviour and that deficits in learning from punishment are important; ADHD children without CD showed increased SCRs to the CS+ (which predicted the US) relative to the CS− (which did not predict the US). These findings suggest that the risk pathways to antisocial behaviour in children with ADHD are underpinned by altered physiological processes in response to emotional learning.

This is the first fear conditioning study which used the criteria that participants must be able to correctly identify which colour slide was paired with the noise. Previous studies (e.g. Fairchild, et. al., 2010; Syngelaki, 2012) also used Bechara and Damasios' (2002) protocol of asking memory questions after the procedure with a <1.5 cut off for exclusion. However, this can easily be achieved without paying too much attention by simply listing three colours. If participants do not pay attention and therefore do not know that blue was paired with the noise, this might be the reason for the low SCR rather than evidence of a deficit in conditioning. Our study enabled us to rule this possibility out. The current findings can also shed some light on the specifics of the conditioning deficit; whilst the ADHD+CD group did learn to associate the US (loud noise) with the CS (blue noise), they failed to produce the UR (increased SCR) in response to the CS. For the CD group, being presented with a stimulus that they knew might be followed with an unpleasant loud noise did not increase their SCR and therefore we can infer that their physiological response

system did not prepare them for an aversive event. This suggests that although they learnt that blue was associated with an unpleasant stimulus, they did not learn to fear the blue slides.

This study supports the theory that inadequate fear conditioning predisposes the individual to the development of antisocial behaviour. A lack of fear means that situations that are normally linked to punishment are less likely to be avoided (Raine, 1996). It is thought that 'normal' individuals learn to avoid committing antisocial acts by associating stimuli connected with antisocial and criminal behaviour to societal punishments (Blair, 2007; Raine, 1996). This produces an increase in anxiety whenever the individual considers committing an antisocial act, which then motivates the individual to avoid such stimuli and prevents them from carrying out antisocial behaviour. These results have implications for arousal-based theories of CD behaviour (Raine, 2002). The absence of lower baseline SCR levels in CD, and equal responding to the US is incompatible with the hypothesis that CD children are driven to their behavior by stimulation-seeking motives (Zuckerman, 1994); instead, deficient conditioning findings are more supportive of fearlessness accounts (Raine, 2002; Van Goozen et al., 2007).

We found that CD severity was the only predictor of conditioning ability. CU traits were not related, supporting previous research in adolescent girls with CD (Fairchild et al., 2010). Our study suggests that CD symptom severity is more important in explaining differences in emotion learning than variation in CU traits. Few studies have looked at clinical measures continuously and some inconsistent findings could therefore have been caused by varying sample sizes.

Longitudinal studies have shown that impaired fear conditioning in early childhood may predict involvement in antisocial behaviour (Gao, et al., 2010) whereas enhanced conditioning may act as a protective factor (Raine, 1996). Although we found that this affective deficit was associated with antisocial behaviour it is not known whether this - or similar deficits - preceded the occurrence of CD problems (and might be causal) or if it represents a consequence of it. Future prospective studies in younger groups of high-risk children with ADHD need to establish whether the observed emotional deficits precede the onset of conduct problems and worsening of symptoms.

Although ADHD symptoms were not significantly associated with conditioning ability, future research should endeavour to include a non-clinical control group and a CD only group. There is growing evidence to suggest that when ADHD coexists with CD both problems are clinically more severe and persistent, and have a worse prognosis than when they occur alone (Thapar, Langley, & O'Donovan, 2006). It would be interesting, therefore, to see whether conditioning ability in participants with CD+ADHD differs from those with CD only.

The fact that ADHD was not associated with conditioning ability supports previous research which found no difference in fear conditioning in children with ADHD compared to controls (Pliska, Hatch, Borcherding, & Rogeness, 1993). A recent study by Maier et al. (2014) also found normal physiological responding during the fear conditioning in adults with ADHD compared to controls. However, during a modified version of the conditioning paradigm, in which the CS and UCS were only linked verbally (i.e. subjects are told that CS and UCS will occur together) rather than by being paired together, differences in neural responding were found. These results suggest that individuals with ADHD show a deficit in

processing verbally transmitted aversive information, which is central for conveying fear information in social contexts. The authors failed, however, to control for comorbid antisocial personality disorder and more research is therefore needed.

There was a relatively large number of participants who did not correctly identify blue as the CS. Previous research has not identified how many participants did not answer this question correctly and therefore it is not known whether this was a large amount and whether this was due to poor concentration within an ADHD sample. However, the participants who failed to do this did not significantly differ in ADHD symptom severity, and so it would appear that there is not a direct relationship with severity of ADHD. Future studies could increase inclusion rates by telling participants beforehand that they will be given memory questions after the task to assess concentration levels.

The findings from the present study have potentially important clinical implications. Currently approved treatments of ADHD include medication and behavioural interventions that are based on social learning theory (NICE guidelines; Kendall, Taylor, Perez, & Taylor, 2008). Thus far long term benefits of such treatments in terms of antisocial outcomes in children with ADHD have not been demonstrated (Langley et al., 2010). If impaired emotional learning is a critical risk process then existing behavioural and psychosocial interventions might have to be enhanced for some individuals to address these deficits.

In conclusion this study of adolescent boys with ADHD found a significant difference in fear conditioning ability between those with and those without comorbid conduct disorder. Conditioning ability was significantly predicted by CD symptoms and unrelated to ADHD symptom severity. Further research is needed to better understand how these emotional

learning processes relate to behaviour using a longitudinal design in order to gain an insight into longer term outcomes. Furthermore, a better understanding of the subgroups within ADHD and CD would be helpful in ensuring that limited resources in the healthcare, social care and criminal justice systems are utilised more effectively and efficiently.

Chapter 4: Cortisol

Paper under review

Introduction

The Hypothalamic-Pituitary-Adrenal (HPA) axis plays a critical role in mediating physiological responses to stress, enabling organisms to adapt to environmental changes (Marquez, Nadal, & Armario, 2006). The regulation of the HPA axis, with cortisol as its end product, appears to be dysfunctional in several psychiatric disorders (Tsigos & Chrousos, 2002). Research interest in HPA axis activity in Attention-Deficit/Hyperactivity Disorder (ADHD) has focused on the theoretical notion of underarousal and the putative need in those with ADHD to increase their levels of arousal to avoid boredom (Stadler et al., 2011; Zuckerman, 1994). Reduced baseline cortisol levels or a blunted cortisol response to psychological stress have been found in children with ADHD compared with healthy controls (Blomqvist et al., 2007; Isaksson, Nilsson, Nyberg, Hogmark, & Lindblad, 2012; Ma, Chen, Chen, Liu, & Wang, 2011). However, other studies found positive associations between ADHD symptoms and cortisol in population-based samples (e.g., Palma, Fernandes, Muszkat, & Calil, 2012) or comparable cortisol levels in children with and without ADHD (e.g., Cakaloz, Akay, & Bober, 2005; Freitag et al., 2009; Palma et al., 2012; Snoek, Van Goozen, Matthys, Buitelaar, & Van Engeland, 2004). These mixed results could be due to variations within ADHD samples, especially in relation to comorbid disorders, sample size and hormone measurement techniques (see Fairchild, 2012, for a review).

Adolescents with ADHD are a heterogeneous population, with 30-50% of children with ADHD in clinical settings also meeting criteria for Conduct Disorder (CD; Biederman, Newcorn, & Sprich, 1991). There is clear and much more consistent evidence that HPA axis activity is altered in those with CD and Oppositional Defiant Disorder (ODD; Fairchild

et al., 2008; Kariyawasam, Zaw, & Handley, 2002; Oosterlaan, Geurts, Knol, & Sergeant 2005; Van Goozen, Matthys, Cohen-Kettenis, Buitelaar, & Van Engeland, 2000). It has been hypothesised that blunted cortisol reactivity reflects fearlessness and is associated with deficient emotion regulation and inhibition of antisocial behaviour (Van Goozen, Fairchild, Snoek, & Harold, 2007). However, previous studies on cortisol secretion in children with ADHD have not always controlled for comorbid disruptive behaviour disorders (DBDs) such as CD or ODD (e.g., Blomqvist et al., 2007). Consequently, the first aim of this study was to investigate adolescent boys with ADHD and compare those with or without a comorbid diagnosis of CD in terms of baseline cortisol and cortisol stress reactivity.

Studies that did assess and control for comorbid DBDs have still obtained mixed results. This may be due to differences between studies in cortisol measurement techniques or saliva collection protocols. Some studies found lower baseline cortisol levels in children with ADHD and comorbid ODD/CD, but not in children with non-comorbid ADHD (Cakaloz et al., 2005; Freitag et al., 2009), whereas others found reduced baseline cortisol levels in non-comorbid ADHD (Ma et al., 2011; Van West, Claes, & Deboutte, 2009) and one study found no effect of DBD comorbidity within an ADHD sample (Isaksson et al., 2012).

The HPA axis is a dynamic system that not only responds to psychological and physical stress, but also exhibits a marked diurnal rhythm (Kirschbaum & Hellhammer, 1989). Therefore studies that have only assessed cortisol at one (e.g., Ma et al., 2011) or two (Cakaloz et al., 2005) time points may be difficult to interpret, especially if they have not controlled for time of awakening or time of sample collection. Furthermore, some research

has relied on participants collecting cortisol samples themselves (e.g., Freitag et al., 2009; Isaksson et al., 2012), which requires participants keeping to a strict timescale and carefully following collection protocols. Problems with adherence to a saliva collection protocol might be particularly pronounced in young people with ADHD who have difficulties with concentration, organisation and being forgetful; this could lead to both false positive and false negative findings (Kudielka, Schommer, Hellhammer, & Kirschbaum, 2004).

Even when cortisol reactivity to a stressor has been investigated, there are inconsistent findings. Reduced cortisol reactivity to stress has been found in children with ADHD and comorbid DBD compared to children with ADHD alone (Hastings, Fortier, Utendale, Simard, & Robaey, 2009; Snoek et al., 2004). Other studies found associations between ADHD symptoms and reduced cortisol stress reactivity after controlling for comorbid DBD (Pesonen et al., 2011; Van West et al., 2009). However, the choice of stressor is important. For example, some previous studies have used inadequate or relatively weak stressors, such as cognitive tests (e.g., Yang, Shin, Noh, & Stein, 2007). The present study used an established psychosocial stress induction protocol that elicited feelings of anger, failure and negative social evaluation (e.g., Fairchild et al., 2008; Snoek et al., 2004; Van Goozen et al., 2000), and involved collecting eight cortisol samples under strict experimental conditions.

When analysing the effects of CD, it is also important to assess the effects of anxiety/depression symptoms as it is increasingly recognised that comorbidity between externalizing and internalizing problems is common (Lahey & Waldman, 2012). Anxiety or depressive symptoms are frequently reported to be associated with *increased* cortisol activity or reactivity (Knight, Avery, Janssen, & Powell, 2010). Thus patterns of cortisol

reactivity in ADHD can be further complicated by patterns of comorbid emotional symptoms as well as conduct disorder (e.g., Hastings et al., 2009).

Another potentially important source of heterogeneity that is closely related to conduct disorder, is variation in callous-unemotional (CU) traits. These traits identify those at greater risk for severe antisocial behaviour (Lahey & Waldman, 2012) and reduced responsiveness to treatment (Hawes, Price, & Dadds, 2014). The importance of such traits has been acknowledged by including limited prosocial emotions as a specifier for CD in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2013). CU traits have been linked to lower baseline cortisol levels and a blunted cortisol response to stress (O'Leary, Loney, & Eckel, 2007). However, the impact of CU traits on cortisol activity has been predominantly investigated in non-clinical samples free of psychiatric disorders (Loney, Butler, Lima, Counts, & Eckel, 2006). An exception to this was a study that reported reduced cortisol responses to stress in participants with ADHD and high levels of CU traits – with over half of the participants having a comorbid DBD diagnosis - compared to those with ADHD with low levels of CU traits (Stadler et al., 2011). This finding now needs to be replicated in a larger clinical sample of adolescents with ADHD (the sample size in the latter study was N=36).

The present study aimed to assess cortisol levels at baseline (pre-stress samples taken under experimental conditions) and in response to stress (area under curve with respect to increase; Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003) in a sample of adolescent males with ADHD, and to explore the contributions of CD diagnosis, ADHD severity, CD symptom severity, CU traits and internalizing symptoms. To our knowledge

this is the largest study of experimentally-induced stress reactivity in an ADHD or CD sample.

Methods

Sample

Participants were recruited from Child and Adolescent Mental Health Services and Community Child Health Clinics in Wales. Children in the sample were of British Caucasian origin and met research criteria for a lifetime diagnosis of ADHD. Those with any known clinical or research diagnosis of schizophrenia, bipolar disorder, Autistic Spectrum Disorder (ASD), Tourette's syndrome, or with an IQ<70 (based on the administration of the Wechsler Intelligence Scale for Children, WISC; Wechsler, 1991), epilepsy, brain damage or any other neurological or genetic disorder were excluded from the study. In total, 202 adolescent males with ADHD (mean age = 13.95 years, sd = 1.82; age range 10 – 17 years) took part in the present study. No participants were stimulant naïve but participants who were currently being prescribed stimulant medication were asked to come off their medication at least 24 hours prior to testing.

Ethical approval was obtained from the Wales Multicentre Research Ethics Committee. Informed written consent was obtained from all parents and adolescents aged over 16 years whereas written assent was obtained for adolescents below age 16 years.

Clinical measures

Child psychopathology was assessed using the Development and Well Being Assessment (DAWBA) structured interview using both parents and children as informants (Goodman,

Ford, Richards, Gatward, & Meltzer, 2000). Parents completed the ADHD and ODD/CD sections and children the ODD/CD section of the DAWBA. Symptom scores and diagnoses were generated from the DAWBA according to DSM-IV criteria (the DSM-5 had not been published at the start of the study) (APA, 2000). CD symptoms were considered present if endorsed by either the parent or child. Parent-rated emotional/anxiety symptoms were assessed using the Strengths and Difficulties Questionnaire (SDQ; Goodman et al., 2000). This was also completed as part of the DAWBA. The five emotional items (worries, unhappy, afraid, clingy, somatic) were scored on a 3-point Likert scale and summed to obtain a total emotional symptom score (score range 0-10).

Based on information from the DAWBA, participants were allocated to two groups: ADHD and ADHD with comorbid CD.

Callous-Unemotional (CU) traits were measured using the Youth Psychopathic traits Inventory (YPI; Andershed, Kerr, Stattin, & Levander, 2002). The CU subscale of the YPI contains 15 items, and each item is answered on a 4-point Likert scale (score range 15 – 60). The reliability and convergent validity of the YPI with other measures of CU traits has been established (Andershed, Hodgins, & Tengstrom, 2007).

Cognitive ability was assessed in all participants using the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) – 2-subtest form (vocabulary and matrix reasoning).

Psychosocial stress induction procedure

Participants arrived at our laboratory in the morning and completed a battery of questionnaires and neuropsychological tests including the WASI before lunch. During this time they were asked to provide three baseline cortisol samples approximately 40 minutes

apart from each other. After lunch they were informed that they would be taking part in a competition with an opponent of a similar age with a cash prize for the winner. This procedure is described in detail elsewhere (Van Goozen et al., 2000; Fairchild et al., 2008); briefly, it involves inducing provocation and frustration between the participant and a pre-recorded video opponent who are both competing for a cash prize. The competition begins with a frustration-inducing game in which the participant performs a difficult, computer-based manual precision task under time pressure while believing they are being watched by the video opponent and experimenter. By design, all participants fail to achieve their target score and receive negative evaluations of their performance from the opponent. This feedback is standardised by using a video recording of the competitor, who criticises the participant's performance in a competitive and derogatory way. Following this task, participants complete three further challenging tasks aimed at increasing performance uncertainty and sense of failure. Three stress cortisol samples were taken during the competition, approximately 20 minutes apart from one another. Finally, mood was restored by the participant watching their opponent perform poorly, resulting in the participant winning the competition (and the cash prize). Two post-stress recovery samples were collected 20 minutes apart while participants completed some final non-challenging tasks and questionnaires. Please see Figure 1 for a schematic representation of the stress-induction procedure.
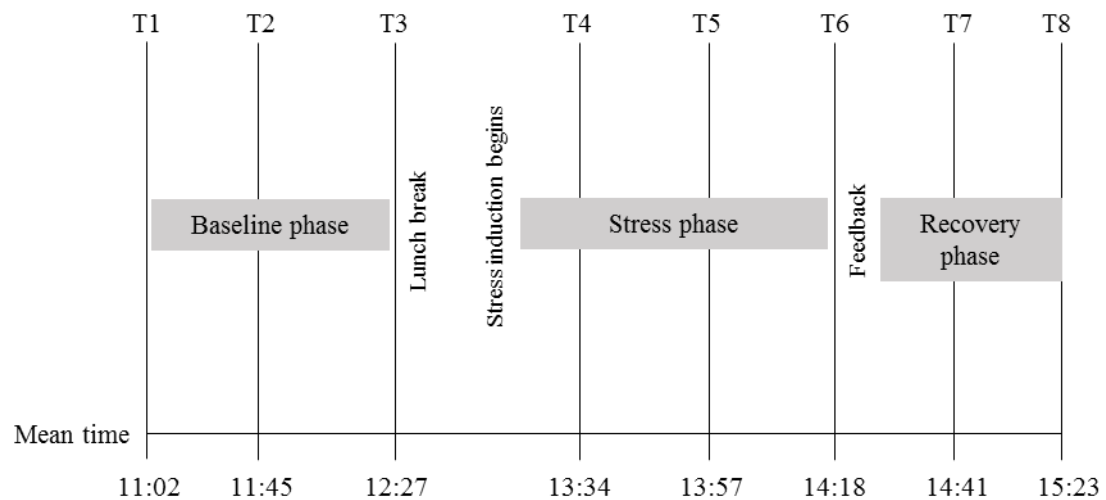
Figure 1. Schematic representation of the test procedure and mean cortisol and mood rating sampling times.

Procedure for saliva collection and analysis

A synthetic swab (polyethylene) was placed into the mouth and chewed/sucked on for 60 seconds, after which it was placed into a plastic sample tube (Salivettes) and stored at -20°C. Cortisol levels were determined employing a competitive solid phase time-resolved fluorescence immunoassay with fluorometric end point detection. The intra-assay coefficient of variation was between 4.0% and 6.7%, and the corresponding inter assay coefficients of variation were between 7.1% -9.0% (Dressendörfer, Kirschbaum, Rohde, Stahl, & Strasburger, 1992). Results are reported in nmol/L.

Self-rated emotions

Participants rated their emotional responses eight times using an adaptation of a clinical self-rating scale (Von Zerssen, 1986). The scale contained 11 items (happy/gloomy, well/sick, cheerful/not cheerful, good/bad, liked/not liked, satisfied/not satisfied, worried/not worried, embarrassed/not embarrassed, ashamed/not ashamed, afraid/not afraid, and angry/not angry), which participants rated using 9-point ordinal scales. Subjective ratings occurred at the same times as saliva collection.

Data analyses

Two participants were excluded because of missing or incomplete DAWBA data. A cortisol baseline measure was calculated from the average of the three cortisol samples taken before the stress phase of the testing day began. The area under the curve with respect to increase (AUCi) was used to quantify cortisol reactivity, making use of the repeated measurements and emphasizing the change over time rather than the starting level (Pruessner et al., 2003). A negative mood score was calculated for each of the cortisol sampling times which was the sum of the 11 emotion ratings and the scores for positive emotions were reversed during scoring. The cortisol and mood variables were not normally distributed; however, due to the large sample sizes, and the fact that non-parametric tests showed the same pattern of results, it was felt that parametric tests were still suitable (Field, 2009).

Between group differences were assessed using ANOVAs, with Greenhouse-Geisser correction applied where assumptions of sphericity were violated. Effect sizes are reported as eta squared (η^2; small≥.01, medium≥.06, large≥.14; Cohen, 1988). Pearson's correlations

and multiple regressions examined the effect of the clinical characteristics on baseline

cortisol and cortisol stress reactivity. Analyses were carried out using SPSS 20.0 (SPSS

Inc., Chicago, IL).

Results

The demographic data for the two subgroups, and the results of between-group analyses are

presented in Table 1.

Table 1. Means (with SDs) for the demographic and clinical characteristics of the ADHD

and ADHD+CD subgroups.

	ADHD (n=95)		ADHD+CD (n=107)		
	Mean	*SD*	*Mean*	*SD*	*p value*
Age	13.74	1.87	14.1	1.76	ns
IQ	90.23	10.24	84.31	9.35	p<.001
ADHD	11.74	4.91	13.15	4.17	p<.05
CD	0.96	0.78	5.69	2.41	p<.001
ODD	2.84	2.46	4.73	2.65	p<.001
CU traits	31.38	6.01	35.64	6.99	p<.001
SDQ Emotional	4.78	2.75	5.07	2.71	ns

Note: All between group analyses were done using independent samples t tests; ADHD=number of ADHD symptoms; CD=number of CD

symptoms; ODD=number of ODD symptoms; CU traits=callous-unemotional traits subscale score; SDQ Emotional=Strengths and

Difficulties emotional symptom subscale score.

The ADHD only and ADHD+CD groups differed significantly in terms of ADHD, ODD

and CD symptom severity, as well as CU traits, but there was no difference in emotional

symptoms as measured by the SDQ. Although there was a significant group difference in IQ, IQ was not significantly associated with cortisol (r baseline cortisol = -.11, p>.05; r AUCi = .14, p>.05). IQ was therefore not included as a covariate in subsequent between-group analyses.

Self-reported emotions

There was a main effect of time, $F(3.59, 689.04) = 49.88$, p<.001, η^2=.21, but no effect of group [$F(1, 192) = .05$, p=.82, η^2 =.00] and no significant group x time interaction [$F(3.59, 689.04) =1.71$, p=.15, η^2=.01], indicating that the stress paradigm induced negative emotions in both groups to an equal extent (see Fig. 1.). Non-parametric Mann-Whitney U tests also found no significant effect of group on these 8 mood samples (p<.05).

Cortisol

The ADHD and ADHD+CD groups did not differ in baseline cortisol $F(1, 201) = 2.24$, p= .14, η^2 = .01). However, analysis of the AUCi values for the cortisol response showed a significant group difference, $F(1, 201) = 6.33$, $p = .01$, $\eta^2 = .04$), reflecting more pronounced cortisol stress reactivity in the ADHD than the ADHD+CD group. Results of non-parametric Mann-Whitney U tests comparing ADHD and ADHD+CD groups revealed the same pattern of results: Baseline cortisol: $U = 5,560.50$, $p = .25$; AUCi: $U = 4,104.00$, $p = .018$.

Figure 1 presents schematically the cortisol and negative mood profiles of ADHD and ADHD+CD groups, illustrating that the groups had similar self-reported mood profiles, but

different cortisol profiles with the ADHD+CD group showing an attenuated cortisol response to stress.
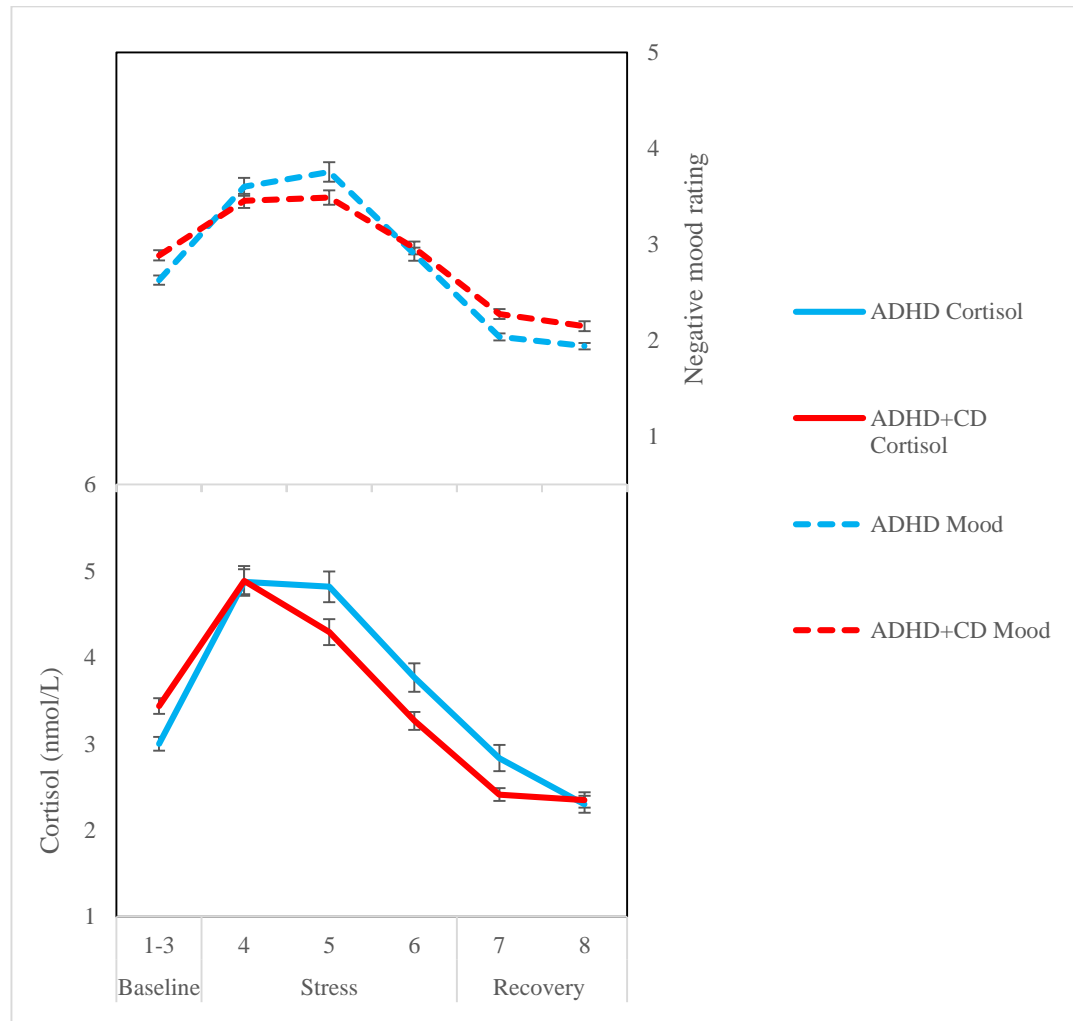
Figure 2. Mean cortisol levels and negative mood scores during baseline, stress and recovery phases for the ADHD and ADHD+CD groups. Error bars show +/- 1 standard error.

Table 2 shows that ADHD, ODD and CD symptoms were all significantly correlated with baseline cortisol. However, only ADHD and CD symptom severity significantly predicted variance in baseline cortisol in a regression analysis ($F = 6.88$, $p= .001$, $R = .26$). ADHD symptoms were inversely related to baseline cortisol, whereas CD symptoms were positively related to baseline cortisol (see Table 3). Anxiety scores and CU traits did not correlate with cortisol levels.

Table 2. Pearson's correlations of clinical characteristics and different measures of cortisol secretion

	ADHD	CD	ODD	CU traits	SDQ Emotion	Baseline cortisol	AUCi cortisol
ADHD	-						
CD	.19**	-					
ODD	.57**	.42**	-				
CU traits	.11	.40**	.18*	-			
SDQ Emotion	.28**	.10	.22**	-.05	-		
Baseline cortisol	-.20**	.14*	-.14*	-.05	.01	-	
AUCi cortisol	-.05	-.17*	.06	-.11	.04	-.36**	-

Note:. ADHD=number of ADHD symptoms; CD=number of CD symptoms; ODD=number of ODD symptoms; CU traits=callous-unemotional traits subscale score; SDQ Emotion=Strengths and Difficulties emotional symptom subscale score; Baseline cortisol=average of three baseline cortisol samples; AUCi cortisol=area under the curve with respect to increase. * = p<.05, ** = p<.001

Table 3. Regressions of clinical predictors on baseline cortisol

Step		b	$SE\ b$	β
1	(Constant)	4.04	.34	
	ADHD symptoms	-.07	.03	-.21**
2	(Constant)	3.87	.34	
	ADHD symptoms	-.09	.03	-.24**
	CD symptoms	.09	.04	.16*

Note: R^2 for step 1=.04; $\triangle R^2$ for step 2 =.03; *=p<.05, **=p<.001.

Only CD symptoms showed a significant inverse correlation with cortisol reactivity
(AUCi); a regression showed that CD severity significantly predicted cortisol reactivity
($F = 6.19$, $p = .01$, $R = .17$; see Table 4).

Table 4. Regression of CD symptoms on cortisol stress reactivity

Step		b	$SE\ b$	β
1	(Constant)	16.68	49.54	
	CD symptoms	-26.94	10.82	-.17*

Note: R^2 for step 1=.03; *=p<.05

Discussion

The first aim of this study was to investigate, in a sample of those with ADHD, whether a pattern of reduced HPA activity was specific to those with ADHD and comorbid CD relative to those with ADHD alone by investigating both cortisol baseline and stress reactivity levels. The second aim was to analyse dimensionally the effect of ADHD and CD symptom severity, CU traits and emotional symptoms on cortisol baseline levels and stress reactivity. To this end we studied cortisol levels in 202 male adolescents with ADHD, of whom 107 also met criteria for a diagnosis of CD, under baseline conditions and during a psychosocial stressor that involved frustration and competition. No differences were found between the two groups (ADHD vs. ADHD+CD) in baseline cortisol levels. These results are in contrast with some studies reporting lower baseline cortisol levels in children with ADHD and comorbid DBD compared to children with ADHD only (Cakaloz et al., 2005), but are in line with other findings (Snoek et al., 2004).

When looking at the variables continuously, however, both ADHD and CD symptom levels predicted baseline cortisol. CD symptoms related positively to baseline cortisol levels, whereas ADHD symptom severity inversely predicted baseline cortisol. Imeraj et al. (2012) found a flatter cortisol slope in their ADHD only group, which was explained by morning hypo-arousal and evening hyper-arousal, whereas the ADHD+ODD group showed a steeper cortisol slope with morning hyper-arousal and evening hypo-arousal. We have previously found a trend towards higher baseline cortisol levels when measuring cortisol during the day in CD adolescents (Fairchild et al., 2008), which is in agreement with the positive correlation found for CD symptoms.

In terms of cortisol stress reactivity, the findings are consistent with previous results

showing reduced cortisol stress responses in adolescent males with comorbid ADHD and ODD when compared to those with ADHD alone (Snoek et al., 2004). The current findings showed significantly reduced reactivity - as measured by the area under the curve with respect to increase (AUCi) - in those with ADHD+CD compared to those with ADHD only. Interestingly, the two diagnostic groups did not differ in self-reported negative emotions, with both groups reporting an increase in negative moods during stress exposure. Thus we observed in the ADHD+CD group a greater discrepancy between the intensity of self-reported negative moods and cortisol reactivity, whereas the non-comorbid ADHD group showed parallel increases in negative moods and cortisol.

We found that CD severity was the only predictor of our cortisol reactivity measure (AUCi); CU traits did not predict cortisol levels at baseline or stress reactivity. ODD symptoms were inversely correlated with baseline cortisol, but they did not enter the model with ADHD and CD symptoms when using a stepwise regression. The lack of an association between cortisol and CU traits contradicts previous research that found reduced cortisol stress reactivity in ADHD participants with high CU traits (Stadler et al., 2011), but a possible explanation for this discrepancy is that the ADHD and high CU traits group were also higher in conduct problems than the low CU traits group. Our study suggests that CD symptom severity is more important in explaining differences in cortisol reactivity than variation in CU traits. Few studies have looked at clinical measures continuously and some inconsistent findings could therefore have been caused by varying methods for eliciting a cortisol response.

It is important to note that CD was not associated with hypo-activity of the HPA axis at baseline, but rather a specific *hypo-reactivity* during stress. This has implications for

arousal-based theories of CD behavior (Van Goozen et al., 2007). The absence of lower baseline cortisol levels in CD is incompatible with the hypothesis that CD children are driven to their behavior by stimulation-seeking motives (Zuckerman, 1994); instead, reduced reactivity findings are more supportive of fearlessness accounts (Van Goozen et al., 2007). A possible explanation is that more frequent exposure to stress may result in adrenocortical habituation among CD children to some types of stress, leading to reduced stress reactivity. However, the apparently diminished reactivity of the HPA axis in CD children was not related to their perception and interpretation of the stressor; the ADHD and ADHD+CD groups perceived the stressor as equally threatening and frustrating. It is possible that HPA axis reactivity and subjective arousal are less well coordinated in children with CD, perhaps due to the effects of stressful events in early life that could partly be evoked by ADHD behaviours (Harold et al., 2013). Early life stress could lead to alterations in developing neurobiological systems including the HPA axis (Lupien et al., 2009) as could genetic factors (Bartels, Van den Berg, Sluyter, Boomsma, & De Geus, 2003).

The results of this study indicate that amongst adolescent boys with ADHD, a pattern of reduced HPA reactivity during stress is observed in those with comorbid CD. The better prognosis of ADHD relative to ADHD+CD could reflect the results of intact responsivity to social conditioning due to an increased reactivity of the HPA axis or due to greater exposure to stressors leading to both increased aggression and HPA axis dysfunction in the comorbid group. It is also relevant from a clinical point of view that we found that the pattern of low HPA axis activity under stress was more apparent in those with more severe conduct problems. If HPA axis dysfunction is a key risk mechanism mediating the

developmental pathway from ADHD to CD, modulating this system may be helpful in the treatment of children with ADHD - either through psychosocial and/or pharmacological interventions. A better understanding of the mechanisms involved in the development, persistence and prognosis of disruptive behavior disorders should ultimately result in more effective interventions.

This was the largest study to date to investigate stress reactivity in adolescents with a clinical diagnosis of ADHD. The participants were well-characterized from a psychiatric perspective with information collected from multiple informants. We collected multiple saliva samples under highly controlled experimental conditions, and used an effective psychosocial stressor to induce cortisol reactivity, as well as measuring subjective responses to the stressor. However, the present study was also subject to a number of limitations. Firstly, we did not include a healthy control group or a 'pure' CD group for comparison with the ADHD or ADHD+CD groups. However, previous studies using the same paradigm have assessed the former groups and were able to show that healthy controls show increased cortisol responses to stress, whereas this reaction is blunted in adolescents with CD or ODD (Fairchild et al., 2008; Snoek et al., 2004; Van Goozen et al., 2000).

We did not systematically collect information on exposure to significant early life events and can therefore only speculate about the possible mechanisms underlying our findings. Children with CD have been exposed to significantly greater environmental adversity than children with ADHD alone (Schachar & Tannock, 1995), and the reduced HPA axis reactivity that we found in the ADHD+CD group could therefore have been caused by differences in the early lives of the children we studied (Isaksson, Nilsson, & Lindblad,

2013). Longitudinal prospective studies from an early age onwards are needed in order to investigate the effect of adverse early life events on HPA axis (re)activity in a more detailed way. Genetic factors are also known to contribute strongly to the presence of conduct problems in ADHD (Thapar, Langley, Owen, & O'Donovan, 2007) as well as stress responsiveness (Wüst, Federenko, Hellhammer, & Kirschbaum, 2000). Thus the contribution of genetic risk factors will also need to be examined in future investigations.

We found no effect of anxiety and depressive symptoms on cortisol baseline or reactivity, in contrast to other studies (e.g., Pruessner et al., 2003). Although we used a widely used questionnaire (the SDQ) to measure internalizing symptoms, the internalizing subscale contains just five items and there may not have been sufficient variability within the sample to detect significant relationships.

This study was not designed to take into account the effects of diurnal variation in cortisol secretion. We collected eight samples spread over an experimental testing day (approximately five hours) and the stress phase always occurred in the afternoon, which is the part of the day that is least affected by varying circadian rhythms (Maheu, Collicutt, Kornik, Moszkowski, & Lupien, 2005).

Finally, although the present study shows that males with ADHD and CD show a weaker neuroendocrine response to challenges that involve frustration and provocation than those with ADHD alone, it is not clear to what extent these findings would generalize to other types of stress (although see Popma et al., 2006). Future research should examine reactivity to fear-inducing challenges.

In summary, this study of adolescent boys with ADHD found a significant difference in cortisol reactivity to a psychosocial stressor between participants with ADHD alone and those with ADHD and comorbid CD. Blunted cortisol reactivity is hypothesised to reflect fearlessness and is associated with deficient emotion regulation and inhibition of antisocial behaviour. This may, therefore, partly explain the severity of behaviour problems seen in individuals with comorbid ADHD and CD. Future research should use longitudinal methods to analyse the developmental pathway between childhood adversity, ADHD symptoms and HPA axis development, in order to identify the best strategy for intervention.

Chapter 5: Emotion regulation

Introduction

It has long been recognized that children with Attention Deficit Hyperactivity Disorder (ADHD) have difficulty regulating their emotions. In particular, research has shown that children with this disorder exhibit greater emotional reactivity (Jensen & Rosen, 2004), higher levels of negative affect (Braaten & Rosen, 2000), and lower levels of emotional awareness (Factor, Rosen & Reyes, 2013). Emotion regulation is defined as an individual's ability to modify an emotional state so as to promote adaptive, goal-oriented behaviours (Thompson, 1994). Emotion dysregulation arises when these adaptive processes are impaired, leading to behaviour that defeats the individual's interests (Shaw, Stringaris, Nigg & Leibenluft, 2014). Although prevalence rates of emotion dysregulation in ADHD are high (Stringaris & Goodman, 2009) the clinical significance of these findings and how specific they are to ADHD, remain unclear. It has not yet been established, for example, whether deficits in emotion regulation are evident in all children with ADHD or perhaps only in a subgroup of children with this disorder.

In the early conceptualisation of ADHD, emotion dysregulation was considered a cardinal symptom (Clements, 1996). It was only with the introduction of the DSM-III (American Psychiatric Association, 1980) that emotion regulation became an associated feature rather than a diagnostic criterion. The current conceptualization of ADHD is made up of two age-inappropriate behavioural dimensions, these being inattention and hyperactivity–impulsivity (ADHD; DSM 5; American Psychiatric Association, 2013). However, many argue that emotion dysregulation should be more of a consideration in the assessment of ADHD due to its impact on psychological, physical and social outcomes (Abelson, Liberzon, Young & Khan, 2005; Gross, 2002). Conceptual theories of emotion regulation

and ADHD can now generally be characterised by three separate models; emotion dysregulation as a core feature of ADHD, emotion dysregulation as a distinct but correlated dimension to ADHD, or the addition of emotion dysregulation and ADHD as a distinct entity (Shaw et al., 2014).

Barkley (2010) argues that emotion dysregulation is a core feature of ADHD and stems from executive functioning difficulties at the neurological level. Specifically, the inability to inhibit responses causes the difficulties with selective attention, hyperactivity, and impulsivity inherent in ADHD, as well as an impaired ability to inhibit strong emotional responses. However, emotion dysregulation is a dimensional trait that undercuts the traditional divide between internalizing and externalizing diagnoses, and it is not unique to ADHD (Achenbach & Rescorla, 2001). Regulation of emotions is compromised in children with Disruptive Behavioural Disorders (DBDs), like Conduct Disorder (CD) and Oppositional Defiant Disorder (ODD), as well as mood disorders. A recent study by Factor, Reyes and Rosen (2014) suggests that ADHD alone is not sufficient for children to display significantly impaired emotional regulation, but it is only in the presence of a comorbid disorder that this pattern of deficiency begins to emerge.

Between 30% and 50% of children with ADHD meet criteria for Conduct Disorder (Biederman, Newcorn & Sprich, 1991) and this subgroup shows greater ADHD symptom severity than those with ADHD alone and worse outcomes (Thapar, Langley, Owen & O'Donovan, 2007). This group also appears to have higher familial and genetic loading for ADHD (Faraone, Biederman & Monuteaux, 2000) especially those with aggressive CD symptoms (Hamshere et al., 2013). However, previous research on emotion regulation in children with ADHD has not always considered the effects of comorbid CD (Norvilitis,

Casey, Brooklier & Bonello, 2000; Scime & Norvilitis, 2006; Singh et al., 1998). It is difficult therefore to know whether it is the core features of ADHD that are linked to emotion dysregulation or whether the relationship is explained by associated CD.

Studies on emotion regulation have primarily used retrospective, self-report questionnaires. Experimental studies (e.g. Melnick & Hinshaw, 2000; Walcott & Landau, 2004) have often used frustration-eliciting tasks to assess emotion regulation; for example, by asking participants to hide their emotions from a confederate competitor. In this type of paradigm, however, the participants have no real motive to regulate their emotion apart from complying with the experimenter's demands. Economic decision-making games, such as the Ultimatum Game (UG), provide another way of measuring emotion regulation by assessing effects on decision making (Crockett, Clark & Tabibnia, 2008; Lieberman Guth, Schmittenberger & Schwarze, 1982; Koenigs & Tranel, 2007; Koenigs, Kruepke & Newman, 2010). These paradigms involve two players interacting to decide how to divide a sum of money. One player (the proposer) offers a portion of the money to the second player (the responder). The responder can either accept the offer (in which case both players split the money as proposed) or reject the offer (in which case both players get nothing). Traditional economic theories, which view decision making as a rational, cognitive process (e.g. Fishburn, 1970) state that all offers, regardless of their fairness, should be accepted. Previous studies, however, have found that offers made to the responder which are comparatively small - and therefore deemed as unfair (20% of the total) - have a 50% chance of being rejected by most individuals (Guth, 1982; Bolton & Zwick, 1995).

Most individuals experience a negative emotional response and increased arousal when receiving unfair offers (van't Wout, Kahn, Sanfey & Aleman, 2006) and a number of

studies provide evidence that emotion regulation processes are a critical component in the UG. Negative emotions such as anger and frustration provoke participants to penalise their opponent rather than to make a utilitarian decision (Fehr & Gachter, 2002; Pillutla & Murnighan), and the rejection of unfair offers increases when feelings of sadness are induced (Harle & Sanfey, 2007). The percentage of accepted unfair offers is influenced by the use of specific emotion regulation strategies such as reappraisal (Grecucci, Giorgetta, van't Wout, Bonini & Sanfey, 2013; van't Wout, Chang & Sanfey, 2010) and when participants are asked to 'stay calm' they accept more unfair offers (Kirk, Gollwitzer & Carnevale, 2011) suggesting that the ability to regulate negative emotions is necessary for the (rational) acceptance of unfair offers.

The rejection of unfair offers has been found to be associated with activity in neural substrates involved in negative emotions, such as the amygdala (Gospic et al., 2011) and anterior insula (Sanfey, Rilling, Aronson, Nystrom & Cohen, 2008). Ventromedial prefrontal cortex (VMPC) damage is reliably associated with poorly controlled emotional responses. In response to relatively minor provocation or frustration, patients with such damage are often irritable, angry, argumentative, and even abusive (Anderson, Barrash, Bechara & Tranel, 2006; Berlin, Rolls & Kischka, 2004), yet generally show shallow affect. Similarities have been observed between patients with VMPC damage and patients with psychopathy (Damasio, Tranel & Damasio, 1990; Eslinger & Damasio, 1985; Koenigs & Tranel, 2007) and Koenigs et al. (2010) found similarly high rejection rates to the UG in VMPC damage patients and prisoners with low-anxiety psychopathy. In a community sample, Viera et al. (2014) showed that the rejection rate of unfair offers was associated with VMPC activity in those with high psychopathy scores compared to those

with low psychopathy scores; they interpreted this as reflecting an angry reaction to the frustration of not obtaining the desired outcome.

The results of studies in children and adults assessing emotion regulation suggest that age is an important factor. It is consistently found that adolescents reject more unfair offers than younger children and adults (Murnighan & Saxon, 1998; Harbaugh, Krause & Liday, 2003; Hoffman & tee, 2006), suggesting that there is a U-shaped developmental trajectory. This is consistent with the conceptualization of a peak in emotional reactivity during adolescence (Brenhouse & Anderson, 2011). However, until now no studies have examined emotion regulation using the UG in a clinical sample of adolescents with ADHD.

When assessing the contributory effects of comorbid externalizing disorders it is important to consider the clinical and aetiological heterogeneity of disorders such as CD and Oppositional Defiant Disorder (ODD; Stringaris & Goodman, 2009); not all children who engage in antisocial behaviour will display emotion regulation problems. Frick and Morris (2004) argue deficits in emotion regulation are likely to underlie conduct problems that involve the angry and overt confrontation of others (e.g. fighting and assault), but are less likely to be associated with conduct problems that are not associated with confrontation or negative affect (e.g. stealing, vandalism). Burt and Donnellan (2008) also argue that there are unique personality correlates of different forms of antisocial behavior. They found that aggression was uniquely predicted by high stress reaction (e.g., easily upset, has unaccountable mood changes), but this was not related to non-aggressive rule breaking behavior. This suggests that adolescents who display high aggressive CD symptoms might have more difficulty regulating their negative emotions during the UG and reject more unfair offers.

Callous-Unemotional traits (CU) are another potentially important source of heterogeneity when looking at externalizing disorders. Such personality traits identify those at greater risk for severe antisocial behaviour (Lahey & Waldman, 2012) and reduced responsiveness to treatment (Hawes, Price & Dadds, 2014). The importance of such traits has been acknowledged by including limited prosocial emotions as a specifier for CD in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2013; Frick, Ray, Thornton & Kahn, 2014). CU traits are characterised by low prosocial emotions and behaviours, including shallow or blunted affect, lack of guilt or remorse, physiological underarousal, and low empathy. Individuals who lack empathy and are not concerned about the emotions of others may be less likely to be driven by anger and the motivation to punish the proposer. This was supported in a non-clinical sample, which found that students scoring high on psychopathic traits rejected fewer unfair offers, interpreted as favouring self-interest (Osumi & Ohira, 2010). However, this contradicts Koenigs et al.'s (2010) study of psychopathic inmates, and also contrasts with results of more recent studies, which found no differences in rejection rates between high and low psychopathy scorers in community adults (Viera et al. (2014) and adolescents (White, Brislin, Meffert, Sinclair & Blair, 2013) or between healthy and high psychopathy scoring incarcerated individuals (Radke, Brazil, Scheper, Bulten & De Bruijn, 2013).

Only a few studies have examined emotion regulation using the UG in adolescents (Harbuagh et al., 2003; Hoffman & Tee, 2006; Murnighan & Saxon, 1998; White et al., 2013), and we are not aware of any study that has done so in a clinical sample of adolescents with ADHD. This study compared the decision making of those with ADHD against those with ADHD and CD; with respect to the latter group we distinguished

between those with low aggressive CD symptoms and high aggressive CD symptoms. Within these groups we also looked at the effect of additional CU traits. We included a sample of typically developing adolescent males for comparison.

Method

Sample

Participants were recruited from Child and Adolescent Mental Health Services and Community Child Health Clinics in Wales. Children in the sample were of British Caucasian origin and met research criteria for a lifetime diagnosis of ADHD. Children with any known clinical or research diagnosis of schizophrenia, bipolar disorder, Autistic Spectrum Disorder (ASD), Tourette's syndrome, or with an IQ<70 (based on the administration of the Wechsler Intelligence Scale for Children, WISC; Wechsler, 1991), epilepsy, brain damage or any other neurological or genetic disorder were excluded from the study. In total, 204 adolescent males with ADHD (mean age = 13.95 years, sd = 1.82; age range 10 – 17 years) took part in the present study. No participants were stimulant naïve but participants who were currently being prescribed stimulant medication were asked to come off their medication at least 24 hours prior to testing.

Male control participants (NCs), aged 13-18 (mean age= 15.14 years; N=47) were recruited from local comprehensive schools and youth centres in relatively deprived areas in Cardiff. This group had been matched based on age, gender, IQ and socioecemonic status to an ASB sample from a previous research project (Bowen, Morgan, Moore & Van Goozen,

2014). The Youth Self Report (YSR; Achenbach, 1991) was used to screen for ADHD and CD. All NCs completed the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) and the UG. Nobody had estimated IQ scores of < 70.

Ethical approval was obtained from the Wales Multicentre Research Ethics Committee. Informed written consent was obtained from all accompanying parents and adolescents aged over 16 years. Written assent was obtained for younger adolescents.

Clinical measures

Child psychopathology was assessed using the Development and Well Being Assessment (DAWBA) structured interview using both parents and children as informants (Goodman et al., 2000). Parents completed the ADHD and ODD/CD sections and children the ODD/CD section of the DAWBA. Symptom scores and diagnoses were generated from the DAWBA according to DSM-IV criteria (the DSM-V had not been published at the start of the study; American Psychiatric Association, 2000). CD symptoms were considered present if endorsed by either the parent or child. Given previous findings suggesting that DSM-IV defined aggressive CD items index CD heterogeneity (Hampshere et al., 2013; Lahey & Waldman, 2012), those with CD were further examined according to whether or not they had a high (>3) number of aggressive symptoms (as defined by DSM).

Oppositional defiant disorder (ODD) has previously been viewed as being part of a CD diagnostic spectrum. It is characterised as a less severe form of CD, which is often a developmental precursor to CD (WHO, 1992). However, ODD has since been shown to have some important diagnostic utility; in particular, the ability to predict risk for later emotional disorders after controlling for CD (Loeber, Burke & Pardini, 2009). In the DSM-

5, the exclusion criterion for CD has now been removed from the diagnostic criteria for ODD. ODD was therefore also assessed using the DAWBA to control for differences between groups.

Callous-Unemotional (CU) traits were measured using the Youth Psychopathic traits Inventory (YPI; Andershed, Kerr, Stattin, & Levander, 2002). The CU subscale of the YPI contains 15 items, and each item is answered on a 4-point Likert scale (score range 15 – 60). The reliability and convergent validity of the YPI with other measures of CU traits has been established (Andershed, Hodgins, & Tengstrom, 2007; Skeem & Cauffman, 2003].

Parent-rated emotional symptoms were assessed using the Strengths and Difficulties Questionnaire (SDQ; Goodman & Goodman, 2009). This was also completed as part of the DAWBA. The five emotional items (worries, unhappy, afraid, clingy, somatic) were scored on a 3-point Likert scale and summed to obtain a total emotional symptom score (score range 0-10).

Cognitive ability was re-assessed on all current participants using the Wechsler Abbreviated Scale of Intelligence (Welscher, 1997) – 2-subset form (vocabulary and matrix reasoning). All the participants came from community clinics and none were stimulant naive. Participants who continued to take stimulant medication were asked to come off medication 24 hours prior to testing.

The Ultimatum Game

In the Ultimatum Game (Koenigs & Tranel, 2007) two players are given the opportunity to split a sum of money. One player (the proposer) proposes a way to split an amount of money with another player (the responder). These offers vary in fairness and the participant

must simply accept or reject the offers made to them. If the responder accepts the offer, both players are paid accordingly. If the offer is rejected, neither player is paid. The participants were instructed that the offers were real, and had been made by previous participants to the same study. This was made more believable by asking participants to propose their offer (out of the options below) and after they had done so, their offer was stored to the database for use in future research (Koenigs et al., 2010). In fact, the experimenter predetermined the offers, and photographs of the opponents/responders were taken from the Amsterdam Dynamic Facial Expression Set (Van der Schalk, Hawk, Fischer & Doosje, 2011).

Offers made were either 5/5 (keep 5, give 5 points), 6/4 (keep 6, give 4 points), 7/3 (keep 7, give 3 points), 8/2 (keep 8, give 2 points), or 9/1 (keep 9, give 1). Participants were the responders in a series of 22 trials, in which they saw a photograph of a different person during each trial who made them an offer. In accordance with Koenigs and Tranel's (2007) paper, offers were generated in the following frequencies: two offers of 5/5 distribution, two offers of 6/4, six offers of 7/3, six offers of 8/2 distribution, and six offers of 9/1 distribution. Sanfey et al. (2003) asked participants to rate what offers they considered to be fair, irrespective of whether they decided to reject or accept an offer. Of their participants, 58% considered any offer less than 5/5 as unfair, with the remaining 42% deeming anything less than 7/3 to be unfair. Therefore, although 100% of the participants deemed the offers of 8/2 and 9/1 unfair, participants were divided with respect to the fairness of the 6/4 and 7/3 offers. For these reasons, the offers were grouped into three groups: truly fair (5/5), very unfair (8/2 and 9/1) and moderately unfair (7/3 and 6/4).

Data Analyses

Two ADHD participants had incomplete DAWBA data so they could not be included. Eight ADHD participants did not complete the UG due to noncompliance; these participants had significantly more aggressive CD symptoms (p<.05). Ten participants had an estimated IQ < 70 and were excluded. Therefore, 184 ADHD participants were included in the analysis as well as 47 control participants referred to as normal controls (NC). The ADHD group consisted of those with ADHD only (ADHD; n=90). Those with additional CD (ADHD+CD; n=94) were split into those with low aggressive CD symptoms (ADHD+CD/LA; n=64), and high aggressive CD symptoms (ADHD+CD/HA n=30) based on whether they were below or above the mean (mean =3.33 symptoms). Between subject ANOVAs were used to test differences in offers and acceptance rates between groups. Offers were grouped into three offer types; completely fair (5/5) moderately fair (6/4 and 7/3) and highly unfair (8/2 and 9/1). Because the UG variables were not normally distributed, follow up Bonferroni pairwise comparisons were bootstrapped and reported with 95% confidence intervals. Non-parametric Kruskal-Wallis tests were also conducted and found the same results (test values given in footnote[2]). Effect sizes are reported as partial eta squared (η^2_p; small≥.01, medium≥.06, large≥.14; Cohen, 1988). Anomalies (+/- 3 standard deviations away from the mean for each group) were removed and replaced with the mean of that variable. There were 7 data points that were mean-corrected which were all due to a high rejection of the 5/5 offer and, therefore, it was thought that these may have been done by mistake. One way ANOVAs were used to compare demographic and clinical variables between groups. Spearman's correlations examined the effect of these clinical

variables on the UG outcome variables. Analyses were carried out using SPSS 20.0 (SPSS Inc., Chicago, IL).

Results

The demographic data for the two subgroups, and the results of between-group analyses are presented in Table 1.

Table 1. Demographic and clinical characteristics of groups.

	NC (N=47)		ADHD (N=90)		ADHD+LA/CD (N=64)		ADHD+HA/CD (N=30)		sig	post hoc
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
Age	15.19	1.33	13.70	1.89	14.28	1.80	13.47	1.55	p<.001	NC > ADHD & ADHD+LA/CD & ADHD+HA/CD
IQ	88.00	9.46	93.41	10.33	88.92	9.18	86.57	8.70	p<.05	ADHD > ADHD+LA/CD & ADHD+HA/CD
ADHD	N/A	N/A	11.78	4.95	13.03	4.29	13.50	4.02	ns	
CD	N/A	N/A	.98	.14	4.45	.16	8.00	.24	p<.001	ADHD < ADHD+LA/CD < ADHD+HA/CD
Aggressive CD	N/A	N/A	.20	.43	1.19	.79	3.50	.63	p<.001	ADHD < ADHD+LA/CD < ADHD+HA/CD
Non Aggressive CD	N/A	N/A	.78	.73	3.27	1.36	4.50	1.93	p<.001	ADHD < ADHD+LA/CD < ADHD+HA/CD
CU traits	N/A	N/A	16.56	6.15	19.28	7.19	22.28	5.32	p<.001	ADHD < ADHD+LA/CD & ADHD+HA/CD
ODD	N/A	N/A	2.91	2.46	4.41	2.72	5.37	2.53	p<.001	ADHD < ADHD+LA/CD & ADHD+HA/CD
SDQ Emotion	N/A	N/A	4.75	2.80	4.90	2.43	5.33	3.08	ns	

Note: all between group analyses were done using one-way ANOVAs; ADHD=number of ADHD symptoms; CD = total number of CD symptoms; Aggressive CD =number of aggressive CD symptoms; Non-aggressive CD=number of non-aggressive CD symptoms; CU traits= callous-unemotional traits subscale score; ODD=number of ODD symptoms; SDQ Emotion=Strengths and Difficulties emotional symptom subscale score.

Table 1 shows that there was a significant difference in age due to the control group being older than the three clinical groups. There was also a significant difference in estimated IQ with the ADHD group having a higher IQ score than the two CD groups. Therefore, when significant results were found, follow up ANCOVA tests were performed in order to analyse the effect with age and IQ as covariates.

There was no difference between the three clinical groups in ADHD severity or the emotion subscale of the SDQ. There was also no significant difference between the CD groups for CU traits and ODD symptoms but these groups were significantly higher than the ADHD only group.

The Ultimatum Game

First, the original proposed offers were compared. A between subjects ANOVA found no significant difference between groups, F (3, 227) =1.48, p=.22, η_p^2 =.02.

Table 2. Offers proposed

	NC (N=47)		ADHD (N=90)		ADHD+CD/LA (N=64)		ADHD+CD/HA (N=30)	
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*
Proposed Offer	1.77	1.13	1.97	1.41	2.30	1.63	2.34	1.78

Note: offers were scored accordingly; 5/5 = 1, 6/4 = 2, 7/3 = 3, 8/2=4, 9/1 = 5

We then compared the acceptance rates for the different offer types between the groups. Between group ANOVAs showed that the groups did not differ in acceptance rates for the fair offers [F(3, 227) =.53, p=.66, η_p^2 =.01] or highly unfair offers [F(3, 227)=2.36, p=.07, η_p^2 =.03]. However, the groups did differ significantly in acceptance rates for the moderately unfair offers [F(3, 227) =3.07, p=.03, η_p^2 =.04] and this remained significant

after controlling for age and IQ (p=.03) [3]. Follow up bootstrapped pairwise comparisons showed that this effect was driven by the ADHD+CD/HA group rejecting significantly more offers than the other three groups (Control group: p =.007, 95% CIs = -.32, -.06; ADHD only: p =.034, 95% CIs = -.26, -.01; ADHD+CD/LA: p=.005, 95% CIs= -.34, -.06).
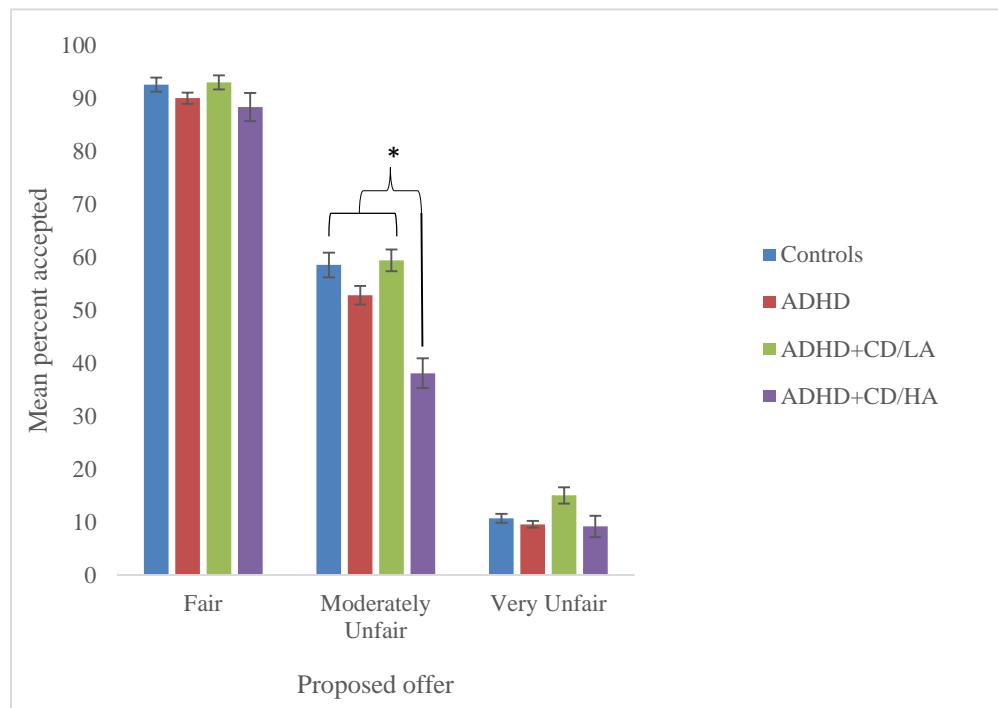
Figure 1. Percentage of Ultimatum Game offers accepted by adolescent males; normal controls, ADHD only, ADHD+CD/LA, and ADHD+CD/HA. Error bars show +/-1 SE. *=p<.05.

Due to the difference found between the two CD groups we wanted to explore the variation in symptoms between them. As shown in Table 1 the high aggressive group also reported more non-aggressive symptoms. It was therefore important to find out

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[3] Result of nonparametric Kruskal –Wallis tests: Proposed offer: χ^2= 2.16, p = .54; fair offers: χ^2= .59, p = .90; moderately unfair offers: χ^2=9.39, p=.03; highly unfair offers χ^2=2.43, p=.49.

whether it was aggressive symptoms in particular, or CD severity in general that predicted performance on the UG. Table 2 shows that both total CD

score and aggressive CD score were significantly correlated with the acceptance rate of moderately unfair offers, but aggressive CD symptoms were more

strongly correlated. None of the other demographic characteristics, including CU traits, were correlated.

Table 3. Correlations between the demographic characteristics and the acceptance rate of moderately unfair offers of the adolescents with ADHD and comorbid CD

	Age	IQ	ADHD	CD	Aggressive CD	CU traits	ODD	SDQ Emotion	Mod unfair
Age	-	-	-	-	-	-	-	-	-
IQ	.02	-	-	-	-	-	-	-	-
ADHD	-.21*	.24*	-	-	-	-	-	-	-
CD	-.14	-.08	.18	-	-	-	-	-	-
Aggressive CD	-.32**	-.17	.10	.66**	-	-	-	-	-
CU traits	-.02	-.05	.12	.21*	.16	-	-	-	-
ODD	-.09	.05	.45**	.27*	.33**	.15	-	-	-
SDQ Emotion	-.17*	.06	.22**	.07	.06	-.07	.18*	-	-
Mod unfair	.19	-.05	-.18	-.21*	-.25*	-.11	-.06	-.04	-

Note: ADHD =number of ADHD symptoms; CD = total number of CD symptoms; Aggressive CD =number of aggressive CD symptoms; ODD =number of ODD symptoms; CU traits= callous-unemotional traits subscale score; SDQ

Emotion =Strengths and Difficulties emotional symptom subscale score; Mod unfair=acceptance rate of moderately unfair offers. p<.05=, p<.001=*

Discussion

This study sought to examine whether ADHD adolescents in general have a problem with emotion regulation, or whether this is a specific problem in those with CD especially those with predominantly aggressive symptoms. No study until now has examined economic decision making using the UG in a clinical sample of youths with ADHD, with or without CD. This study supports previous work (Factor et al., 2014) suggesting that children with ADHD show significantly higher levels of emotional dysregulation than control children only in the presence of a comorbid disorder.

Unsurprisingly, the vast majority of the adolescents accepted the fair offers and rejected the unfair offers. Generally our adolescent male groups accepted fewer unfair offers than those reported for adults (Koenigs & Tranel, 2007; Sanfey et al., 2008). This supports the suggestion of a peak in emotional reactivity during adolescence (Brenhouse & Anderson, 2011). There were no differences between the four adolescent groups' acceptance rates for fair (5/5) and seriously unfair offers (9/1 and 8/2); however, a significant group effect was found for the moderately unfair offers (6/4 and 7/3), suggesting that problems in emotion regulation become more apparent under ambiguous conditions.

Follow-up tests showed that the ADHD with aggressive CD group rejected significantly more moderately unfair offers than any other group. Previous studies claim that the rejection of unfair offers is due to anger and a desire to punish the opponent, and the responder's ability to regulate anger and frustration therefore plays a critical role in task performance (Pillutla & Murnighan, 1996). All three clinical groups reported the same amount of internalising emotionality in the SDQ. However, when faced with being treated unfairly, group differences in the ability to regulate externalising emotions

became clear. Our results suggest that emotion regulation difficulties are not found in adolescents with ADHD alone, but rather only in those who have additional aggressive behaviour. This reflects their clinical presentation: being unable to control their aggressive behaviour (Frick & Morris, 2004).

The results suggest that ADHD alone is not associated with emotion dysregulation during the UG compared to normal adolescents supporting the view that emotion dysregulation is not a core feature of ADHD. The fact that the biggest difference between groups was between the two CD groups highlights the importance of treating CD as a heterogeneous disorder. The results showed that aggressive symptoms correlated with performance on the UG better than overall CD severity, supporting the idea that aggressive antisocial behaviour has a different aetiology than non-aggressive behaviour (Lahey & Waldman, 2012; Hamshere et al., 2013).

In the present study participants were told that the aim of the game was to gain as many points as possible. Apart from this, there was no other incentive for them to win. The use of real reward incentives might, therefore, have a large impact on the rate of offers accepted. Further research is needed to help determine this in order to facilitate the development of more specific interventions for CD. For example, intervention programmes may be more beneficial by focusing on emotion regulation management in individuals with aggressive CD, whilst working with incentive-based goals in individuals with low-aggressive CD.

Unlike aggression, CU traits did not influence the acceptance of offers, supporting some previous studies, which found no significant difference between individuals scoring high or low in psychopathy (Radke et al., 2013; Viera et al., 2014; White et al., 2013), but not others (Osumi & Ohira, 2010; Koenigs et al., 2010). Previous studies have

found that aggressive behaviour is positively correlated with negative emotionality and dysfunction (Burt & Donnellan, 2008) whereas CU traits are negatively correlated with these same traits (Frick, 2012). In a modified version of the UG Radke et al. (2013) found that offenders high in psychopathy, like controls, took the context of the offer into consideration (i.e., whether the proposer had a fair or unfair alternative offer to choose from), whereas offenders low in psychopathy did not, suggesting stronger impairments in social decision-making. However, even if similar behavior patterns are shown in high and low psychopathy scorers, these might represent different motivations as suggested by recent imaging studies (Viera et al., 2014; White et al., 2013), and this now needs to be tested further in clinical samples. Koenigs et al. (2010) observed poorer regulation during the UG in low-anxious psychopathic offenders in comparison with high-anxious psychopathic and non-psychopathic offenders. However, due to the small sample sizes (n=6) and lack of a non-ASB control sample, further research is needed. Our groups did not differ significantly in internalising emotionality (measured by the SDQ) and it may be the case that the low anxiety component of psychopathy drives regulation problems. Further research is needed using a clinical sample of children with disruptive behaviour problems and improvements could be made by using a combination of parent, teacher and behavioural observation to assess CU traits, as suggested by the new CU specifier for the CD diagnosis in the DSM-5.

An issue that needs further exploration is the assumption that the acceptance of unfair offers is the rational decision. From an economic perspective, the rejection of offers is irrational because it results in a personal loss. However, from a social perspective, rejection of unfair offers can be seen as a rational, altruistic action to preserve social norms. Rather than maximizing self-interest, the participant chooses to punish the socially inappropriate action from the proposer for the good of the general population

(Fehr & Fischbacher, 2003; Knoch, Pascual-Leone, Meyer, Treyer & Fehr, 2006). This would explain why similar rejection rates are found in a modified version of the UG in which the participants play on behalf of a third party, compared to one played by themselves (Civai, Corradi-Dell'Acqua, Gamer & Rumiati, 2010). We would argue that it is unlikely that boys high in aggressive CD symptoms rejected offers for the 'good of the general population' and this is supported by a recent imaging study, which found differences in response to the UG between severely antisocial adolescents and controls (van den Bos et al., 2014). That study found decreased right inferior frontal gyrus (rIFG) activity in antisocial youngsters during the UG and no correlation between rIFG activity and behavioural responses, as was found in the controls. These results complement previous studies that suggest that juvenile antisocial behaviour is associated with difficulties in engaging the regulatory processes associated with the frontal cortex (Sterzer & Stadler, 2009; Fairchild et al., 2009), in particular the rIFG, which is associated with response inhibition (Aron, Behrens, Smith, Frank & Poldrack, 2007; Hampshire, Chamberlain, Monti, Duncan & Owen, 2010). This supports the notion that the rejection of unfair offers in antisocial populations is due to deficient self-regulatory processes. Further research should now investigate more thoroughly participants' reasoning behind the rejection of offers in order to support this.

Another limitation of the study is that during the UG task no direct measure of participants' emotional responses, such as psychophysiological recordings or subjective ratings, were obtained. Because we did not measure participants' emotional response to offers, we do not know how much participants needed to self-regulate. One would assume that the more intense the shift in emotion, the more regulatory resources would be needed in order to modify that emotion. It is difficult, however, to determine from this study whether the boys with aggressive CD had deficient regulatory resources or

experienced a more intense emotional reaction. Previous findings of reduced psychophysiological responding to aversive stimuli in the sample group would suggest the former (Van Goozen, Fairchild, Snoek & Harold, 2007; Fairchild, Van Goozen, Stollery & Goodyer, 2008). Future research including such additional measures should help untangle the various potential factors affecting performance on the UG. The simplicity of the paradigm is also well suited for testing this sample using brain imaging techniques.

Emotion dysregulation is a dimensional trait that is not unique to ADHD. It is important to uncover to what extent individuals with ADHD and comorbid CD develop emotion regulation deficits for reasons which are different from those with CD alone by testing psychopathology in non-ADHD samples. Longitudinal studies are needed in order to define how the developmental trajectories interact with one another; to see, for example, whether emotion regulation difficulties bridge the development of aggressive behaviour in children and adolescents with ADHD or whether factors underlying both ADHD and comorbid aggressive CD (i.e. temperamental or biological factors) lead children to demonstrate impairing levels of emotional dysregulation. Furthermore, existing treatments need to be modified to address the role of emotional regulation in children with ADHD. They should incorporate cognitive-behavioural techniques to teach emotion recognition and physiological relaxation exercises for negative emotions (Kovacs et al., 2006; Suveg, Kendall, Comer & Robin, 2006) and encourage problem-solving techniques to help children adjust and self-regulate when their expectations are not met (Kazdin, Siegel & Bass, 1992).

In conclusion, this study of adolescent boys with ADHD and controls found a significant difference in the acceptance rate of ambiguously unfair offers of boys with ADHD and highly aggressive CD. The results suggest that it is the subgroup of boys

with both ADHD and predominantly aggressive CD that has difficulty with emotion regulation, which causes them to make more 'irrational' decisions. Importantly, boys with ADHD alone did not differ from controls in performance on the decision-making task. Further research is needed to better understand how emotion regulation influences decision-making and antisocial behaviour in the short and longer term amongst adolescents, including those with psychiatric disorder.

Chapter 6: General discussion

The main aim of this thesis was to improve our understanding of the heterogeneity found in ADHD and the risk for antisocial behaviour. More specifically, the thesis investigated emotional processing, emotional learning and emotion regulation, using physiological and experimental measures. Deficits in responding to aversive cues, conditioning ability to a punishment, reactivity to stress, and regulating emotions have commonly been associated with severe antisocial behaviour, and are key to most theories of the development of conduct disorder. Deficits in emotional functioning have also been found in ADHD samples, however studies have not always controlled for comorbid CD. It is not clear whether ADHD alone, or only the presence of comorbid CD, is associated with these deficits and a risk for antisocial behaviour in adulthood.

The thesis consisted of 4 empirical chapters, investigating a clinical sample of 204 adolescent boys with ADHD, roughly half of whom also met diagnostic criteria for comorbid CD. It was hypothesised that problems in these emotional systems would be increased in those with comorbid CD compared to those with ADHD alone, thus explaining the risk for antisocial behaviour in this clinical group. This chapter describes and discusses the main findings of this research, outlines its strengths and limitations, and puts forward suggestions for future research.

Overview

Pain Perception

Diminished processing and experience of aversive emotional cues is a common component of theories on the development and persistence of antisocial behaviour. Chapter 2 described the first study (to our knowledge) to measure the effects of comorbid CD and CU traits on pain sensitivity in an ADHD sample. We found that the boys with comorbid CD took longer to report initial pain and were able to endure it for longer, as reflected in their significantly higher pain threshold and pain tolerance times, than those with ADHD only. However, although the groups differed in pain behaviour, there were no differences in the physiological response to pain at these points in time. This means that although both groups had the same SCL when they reached their threshold and tolerance points, the ADHD+CD group took significantly longer to get there. When examining relations with the clinical variables we found that CU traits predicted low physiological response to pain, whereas ADHD severity predicted higher physiological response. Specifically, more severe ADHD was associated with a more rapid SCL increase over a short tolerance time, whereas higher levels of CU traits were associated with a slower SCL increase over a protracted tolerance time.

A relatively high pain threshold is thought to reflect a lower sensitivity to aversive stimulation, which has previously been found in adolescents with CD (e.g. Blair, 2010; Van Goozen, Fairchild, Snoek, & Harold, 2007). If negative stimuli are experienced as less aversive and consequently have less punishing effects, then it may be more difficult to socialise these individuals to behave in a prosocial manner (Lykken, 1995). ADHD symptom severity predicted a higher physiological response to pain which suggests that without comorbid CD this sample is not at risk for such socialising difficulties.

As well as potentially causing difficulties with socialising, reduced sensitivity to pain in oneself may reduce the ability to empathise with pain in someone else. Poor recognition of negative facial emotional expressions and a lack of empathy appear to be important for the development of antisocial behaviour (Fairchild et al., 2009; Marsh & Blair, 2008). Being less responsive to pain experienced by self and others may then make it easier for an individual to engage in antisocial behaviour, especially aggressive or violent behaviour. A growing number of functional magnetic resonance imaging (fMRI) studies support this idea. Remarkable similarities have been found in the neural circuits involved in the processing of both the first-hand experience of pain and the experience of viewing other individuals in pain (Jackson, Brunet, Meltzoff, & Decety, 2006). These studies have reliably shown that observing pain in others stimulates activation of the same neural circuit involved in the processing of the motivational and affective dimension of pain in oneself (Botvinick et al., 2005; Lamm, Batson & Decety, 2007; Moriguchi et al., 2007; Saarela et al., 2007). The results from this study support this idea; participants high on CU traits, who may also lack empathy, showed an increased physiological tolerance towards their own pain.

There is also research to suggest that physical pain shares many of the same neural and psychological mechanisms as the pain of social exclusion. Multiple researchers have proposed that as animals evolved to become more social, the same physiological systems used to monitor physical events were also used for social events (Panksepp, 1988; Eisenberger & Lieberman, 2005; MacDonald, Kingsbury, & Shaw, 2005; MacDonald & Leary, 2005). In other words, the social pain system "piggybacked" onto the pre-existing physical pain system. Both physical pain and social pain are thought to operate via periaqueductal grey brain structures, the anterior cingulate cortex, and the

opioid and oxytocin neuroendocrine systems (Rossi, Pasternak, & Bodnar, 1993; MacDonald & Leary, 2005).

One implication of this is that the factors that have an effect on one type of painful reaction should also have an effect on the other type. A stimulus that causes physical pain should be accompanied by an emotionally painful reaction, while emotionally numbing experiences should co-occur with physical numbness (DeWall & Baumeister, 2006). Social exclusion and rejection have been shown to often cause individuals to act in a detached, emotionally numb manner (Twenge, Catanese & Baumeister, 2002; Zadro, Williams, & Richardson, 2004). This shutdown of the emotion system might be adaptive in terms of instantly reducing a person's suffering, in the same way that physical injuries often generate an analgesia that saves an individual from feeling acute, ongoing pain for the duration of the injury (Twenge, Catanese & Baumeister, 2003). Interestingly, nonhuman animal studies have shown that isolation from conspecifics and separation from caregivers results in decreased sensitivity to physical pain (for a review see MacDonald & Leary, 2005). Furthermore, if people respond to social exclusion by becoming physically numb to pain, which in turn leads to emotional numbness, this emotional numbness would then affect how they respond to various other emotional events. Indeed, in a series of experimental studies, DeWall and Baumeister (2006) found that excluded people became less sensitive to physical pain, and also more emotionally insensitive to others; participants empathised less with another's physical and emotional pain. This in turn could lead to less sociable behaviour and thus increase the risk of social rejection further.

Research thus far has focused on the immediate effects of mild social exclusion. It would be interesting to measure the effects of chronic social exclusion or the effects of an acute childhood incident. Children with ADHD are at increased risk of peer rejection

due to their impulsivity and often immature nature (Bagwell, Molina, Pelham, & Hoza, 2001) and this could therefore be a possible pathway to pain numbing and insensitive CD type symptoms.

Fear conditioning

Learning to form associations between stimuli and punishments is thought to be key to socialization. Chapter 3 aimed to assess fear conditioning, using an established fear-conditioning paradigm and physiological methods. It is the first study of fear conditioning in an ADHD sample that controlled for the presence of comorbid CD. Consistent with predictions, boys with comorbid CD showed reduced autonomic responsiveness in the conditioning experiment compared with those who only had ADHD and no CD. The ADHD+CD group showed significantly reduced differential SCR responding to the CS types compared to the ADHD only group and this was significantly predicted by CD severity and unrelated to ADHD symptoms. These findings are consistent with previous data from male adolescents with CD (Fairchild et al., 2008) and antisocial behaviour in adulthood (Birbaumer et al., 2005; Flor, et al., 2002; Raine, 1993) and suggest that deficits in learning from punishment increases risk of antisocial behaviour across age groups and across diagnostic groups. These findings also suggest that the risk pathways to antisocial behaviour in children with ADHD are underpinned by altered physiological processes in response to emotional learning.

Longitudinal research is scarce, however findings from a few studies suggest that deficient conditioning ability precedes the onset or predicts the persistence of antisocial behaviour. Poor fear conditioning in typically developing 3-year-olds has been associated with later aggression and criminal behaviour (Gao, Raine, Venables, Dawson, & Mednick, 2010), and Baker, Shelton, Baibazarova, Hay and Van Goozen

(2013) showed that 1 year old infants with lower physiological arousal were more verbally and physically aggressive at age 3. If reduced biological activity is associated with fearlessness, deficient emotion regulation and aggressive behaviour in young children, this may provide an objective physiological predictor of later severe antisocial behaviour and enable the identification of children who may be at risk long before problematic behaviour is displayed (Van Goozen, 2015).

Stress

Variations in how individuals respond to stress play a role in temperamental differences, with low activity associated with a more fearless and aggressive temperament (Van Goozen, 2015). Chapter 3 aimed to investigate whether in a sample of those with ADHD, a pattern of reduced HPA activity was specific to those with ADHD and comorbid CD relative to those with ADHD alone by investigating both cortisol baseline and stress reactivity levels. The results showed no significant difference between groups in baseline cortisol but a decreased reactivity to a psychosocial stressor in the ADHD+CD group compared to the ADHD only group. This suggests that the better prognosis of ADHD relative to ADHD+CD could reflect the results of intact responsivity to social conditioning due to an increased reactivity of the HPA axis or a greater exposure to stressors leading to both increased aggression and HPA axis dysfunction in the comorbid group.

The cause of an underactive HPA axis is still unknown. It is thought, however, that it may be the outcome of variances in genetic make-up (Wüst, Federenko, Hellhammer, & Kirschbaum, 2000), early alterations in brain development following pre- or postnatal acute stressful events (Glover, O'Connor, & O'Donnell, 2010; Lupien, McEwen, Gunnar, & Heim, 2009; Van Goozen, Matthys, Cohen-Kettenis, Buitelaar, & Van

Engeland, 2000), or persistently higher levels of stress over a longer period of time due to adverse rearing environments (Isaksson, Nilsson, & Lindblad, 2013; Rutter & Silberg, 2002). These may all lead to alterations in the set point of the HPA axis (Liu et al., 1997).

Indeed, children with CD have been exposed to significantly greater environmental adversity than children with ADHD alone **(**Deault, 2010; Hurtig et al, 2007; Schachar & Tannock, 1995**).** Studies of nonhuman animals have shown that early life stressors can have long-term effects on the functioning of the HPA axis, which persist into adulthood (Gunnar & Fisher, 2006). For example, Liu et al. (1997) found that varying the amount of licking and grooming behaviour in rat mothers affected their newborn offspring's capability to handle stress when adult. Furthermore, they found that newborns who had received a normal amount of grooming behaviour from their mothers had a higher number of stress-hormone receptors in the hippocampus than rats that had received less grooming behaviour. This suggests that maternal behaviour can have a direct and lasting effect on the development of the stress systems of offspring. The replication of this type of research in humans is obviously difficult; however, evidence from a few studies on institutionalized children and mothers with prenatal anxiety suggests similar processes are involved (Gunnar, Morison, Chisolm, & Schuder, 2001; Huizink et al., 2008; O'Connor et al., 2005). These findings may be particularly relevant given that prenatal anxiety and maternal psychopathology also appear to act as a risk factor for the development of ADHD symptoms and externalizing symptoms (Barker, Copeland, Maughan, Jaffee, & Uher, 2012; O'Connor, Heron, Golding, & Glover, 2003; Seco et al., 2015; Van den Bergh & Marcoen 2004).

Emotion regulation

Problems in emotion regulation play an important role in many theories of the development of CD (Frick & Morris, 2004). Furthermore, theories regarding reduced physiological reactivity to punishment and stress suggest emotion dysregulation as a consequence (Van Goozen, Fairchild, Snoek, & Harold, 2007). Chapter 5 aimed to examine whether ADHD is associated with a problem with emotion regulation, or whether this is a specific problem in those with comorbid CD, especially those with predominantly aggressive symptoms. This was the first study to analyse the effects of emotion regulation on decision making using the Ultimatum Game (UG) in a clinical sample of youths with ADHD, with or without CD. We found that boys with high levels of aggressive CD symptoms rejected significantly more ambiguous (i.e., moderately unfair) offers than any other subgroup, suggesting impaired emotion regulation in those with ADHD and aggressive CD. Boys with ADHD only did not differ from normal controls in their acceptance rate of offers. This study supports previous work (Factor, Reyes, & Rosen, 2014) suggesting that children with ADHD show significantly higher levels of emotional dysregulation than control children only in the presence of a comorbid disorder.

The main aim of the thesis was to assess the effects of comorbid CD in ADHD. When looking at the UG, however, a relationship was only found when CD was subdivided into those with high and low aggressive symptoms. For the other chapters looking at aggressive CD symptoms separately did not add anything above that of looking at overall CD symptoms and therefore was not included in these analyses. Aggressive symptoms in particular rather than CD severity appear to be associated with emotion regulation difficulties. There is research to suggest that the aetiology of aggressive behaviour is different to that of rule breaking behaviour. Aggression is associated more

strongly with negative affect than rule-breaking behaviour (Burt & Donnellan, 2008; Burt & Larson, 2007) and negative affect is strongly associated with a hostile attribution bias (Knyazev, Bocharov, Slobodskaya, & Ryabichenko, 2008). During the UG, participants with high aggressive symptoms may have attributed more hostility to unfair offers, resulting in more negative affect and an increased desire to punish the opponent by rejecting his or her offer.

The UG also involves the processing of reward. Reward-processing regions in the brain are active during decision making (Sharp, Monterosso, & Montague, 2012) and brain imaging studies have shown an increased sensitivity to reward in these regions during adolescence (Van Leijenhorst et al., 2010). Studies assessing decision making have established a relationship between reward dominance (decision making in favour of rewards regardless of punishment) and externalising problems in children and adolescents with ODD and/or CD, and adolescents with psychopathic tendencies (Fisher & Blair; 1998; Fonseca & Yule, 1995; O'Brien & Frick, 1996; Matthys, Van Goozen, Vries, Cohen-Kettenis, & Van Engeland, 1998; Newman, Patterson, Howland & Nichols, 1990). It is possible that the low aggressive CD group, which performed similarly to the ADHD only and control groups, was more influenced by the saliency of the reward and therefore showed no problems in emotion regulation.

Recently emotion dysregulation in ADHD has received more attention due to the strong association with increased impairment (Shaw, Stringaris, Nigg, & Leinbenluft, 2014). Individuals with ADHD and emotion dysregulation are significantly more impaired in academic performance, occupational attainment, peer relationships and family life than those with ADHD alone (Wehmeier, Schacht, & Barkley, 2010). Riley et al. (2006) also found that emotional problems were found to have a greater impact than inattention and hyperactivity on children's self-esteem and well-being. The findings from this study

cannot determine the directionality of the relationship between ADHD, comorbid CD, and emotional dysregulation. However, the study does suggest that ADHD is not uniquely associated with emotional dysregulation; rather, it is in the presence of ADHD with comorbid symptoms that emotion dysregulation is observed.

Integration

The results taken together suggest that ADHD accompanied by comorbid CD is associated with a problem in emotion processing and responding to aversive cues. Boys with comorbid conduct disorder had a lower pain sensitivity and a slower physiological response to pain as well as a flatter cortisol response to a psychosocial stressor. They showed a deficit in learning punishment associations and those with a high number of aggressive symptoms displayed increased emotion dysregulation. ADHD is often theorised to be a disorder of emotion (e.g. Barkley et al., 2010). However, this research suggests that without comorbid CD the sample is at less risk for such difficulties. These findings suggest that the risk pathways to antisocial behaviour in children with ADHD are underpinned by altered physiological processes and emotional responding in response to aversive stimuli. The results together suggest that boys with ADHD and comorbid CD have emotional problems that could inhibit their understanding of the consequences of their actions (emotion processing and learning) and impact their ability to deal with emotional situations (emotion regulation).

In three studies we specifically found diminished responding to stress, pain or loud aversive noises rather than decreased basal levels. This supports the fearlessness account of underarousal (Raine, 2002) rather than the sensation-seeking account (Zuckerman, 1979). If the cortisol and ANS responses to stress and/or pain act as

warning signals to restrain ongoing behaviour in situations of danger, then children who fail to activate these systems are likely to behave in a more disinhibited fashion and act more fearlessly (Van Goozen et al., 2007).

We also found that boys with more severe CD (aggressive behaviour) were less able to regulate their emotions in order to gain points in the ultimatum game. Research in normal healthy community samples suggests that the UG engages the body's somatic marker system. Hewig et al. (2011) found that the rejection of unfair offers was positively related to more negative emotional reactions and increased ANS activity. However, we found that CD severity is associated with diminished physiological responding to negative stimuli (as reflected in their lower pain sensitivity, reduced SCRs to aversive stimuli in the fear conditioning paradigm, and reduced cortisol response to stress). We also found that the ADHD+CD group had a reduced cortisol response despite there being no differences in mood. Therefore the same positive association between negative affect and ANS activity found in a community sample may not be found in a clinical CD sample. Further research is needed using Hewig et al.'s (2011) adapted version of the UG in order to measure the physiological response to unfair offers in a clinical sample.

The results from all four chapters provide direct evidence supporting the theory of deficient emotion functioning as a risk factor for CD. Given that the paradigms used tap into the functioning of the amygdala, these results imply that we may have indirectly found support for the claim that there is impaired amygdala function in those with CD. The amygdala plays a role in the processing of aversive cues, emotional learning, HPA axis activation, and in exercising cognitive control over emotional behaviour (Hariri, Mattay, Tessitore, Fera, & Weinberger, 2003; Herman, Ostrander, Mueller, & Figueiredo, 2005; Prather et al., 2001). Furthermore, brain imaging studies have shown

hypoactivity in response to emotional stimuli in individuals with CD (Jones, Laurens, Herba, Barker, & Viding, 2009) as well as an association with reduced volume size (Fairchild et al., 2011; Sterzer, Stadler, Poustka, & Kleinschmidt, 2007).

This thesis supports the brain imaging literature suggesting that there are disorder specific dysfunctions for CD and ADHD. CD has consistently been associated with abnormalities of the hot paralimbic system, which mediate affect and motivation processes, whereas ADHD is characterized predominantly by impairments in the cool-cognitive networks that mediate functions of inhibition and attention. We have added supportive evidence to this literature using a range of emotional stimuli and physiological measures and have found that deficits in affect and motivation processes (in this case punishment) were only associated with comorbid CD and not with ADHD alone. If children with comorbid ADHD+CD have impairments in both cool-cognitive networks and the hot paralimbic system then this might explain why these children have more severe symptoms and a worse prognosis.

Due to different inclusion criteria for each chapter, we had 116 participants who were included in all 4 experimental chapters. Table 1 shows the correlations between the main outcomes of the four experimental chapters using these participants. Unfortunately, we did not find a relationship between the main test outcomes. This may be due to only being able to include a subset of participants.

Table 1. Correlations between the main outcome variables of the four experimental chapters

	Fear Conditioning	Pain Threshold	Pain Tolerance	Pain Ratio	Ultimatum Game	Cortisol
Fear Conditioning	-					
Pain Threshold	-.17	-				
Pain Tolerance	-.10	.66**	-			
Pain Ratio	.06	-.30**	-.51**	-		
Ultimatum Game	.00	.02	-.07	.14	-	
Cortisol	-.01	.01	.04	-.08	.04	-

Note: N=116; Fear conditioning = Differential conditioning between the CS types during the Acquisition phase of the fear condioting paradigm; Pain Threshold = Time at which first experience of pain is reportedduring the pain induction procedure ; Pain Tolernace = Length of time until pain induction procedure is terminated; Pain Ratio = Skin Conductance increase divided by tolerance time recorded during the pain induction procedur; Ultimatum Game =Aacceptance rate of moderately unfair offersduring the Ultimatum Game; Cortisol = Stress reactivity measured as area under the curve with respect to increase during the stress induction paradigm; *=p<.05, **=p<.001.

Symptom severity

In addition to looking at categorical groups we assessed symptoms dimensionally. ADHD symptom severity was not associated with reduced pain sensitivity, reduced cortisol reactivity, deficient fear conditioning or emotion dysregulation. ADHD symptoms were, however, associated with lower basal cortisol levels and increased sensitivity to pain. Interestingly, dopamine is associated with both pain sensitivity (Wood, 2008) and cortisol secretion (Pruessner, Champagne, Meaney, & Dagher, 2004; Rouge-Pont, Deroche, Le Moal, & Piazza, 1998) and there is growing evidence that dopamine dysregulation plays a role in the neurobiology of ADHD (Gizer, Ficks, & Waldman, 2009; Hawi et al., 2010; Tripp & Wickens, 2009; Swanson et al., 2007). The relationship between dopamine and ADHD, however, is complex and this might explain why ADHD appears to be associated with both hypoarousal (low cortisol baseline) and hyperarousal (pain sensitivity). Dopamine works in conjunction with norepinephrine in

the brain to maintain the activity of brain networks involving the prefrontal cortex (Pliszka, 2005). Previous research has found that both underactive and hyperactive dopamine/norepinephrine systems have been associated with ADHD, implying a more complex aetiology to the disorder (see Sharma & Couture, 2014). It is hypothesised that dopamine and norepinephrine may exhibit an inverted U-shaped dose-response curve (Arnsten & Pliszka, 2011), where either extreme is a problem. Further research is needed to assess this complex relationship by analysing the effects of dopamine on stress and pain in an ADHD sample.

CD symptom severity was significantly correlated with the emotional outcome measures of all 4 experimental chapters. This suggests that the more severe the CD symptoms are, the more severe the emotional deficits will be. ADHD and CD symptom severity were positively correlated ($r=.18$, $p<.05$). Although the results from this research suggest that ADHD symptoms alone are not associated with emotion deficits specifically, difficulties in executive functioning inherent to ADHD may further hinder the ability of children with ADHD to inhibit their negative emotional reactions. Negative emotionality is typically intense in children with ODD and CD symptoms (Factor et al., 2014). It is possible that comorbid CD predisposes children to more frequent and more intense negative emotions, and the additive effects of ADHD-based disinhibition leads to more emotional impulsiveness. Further research is needed to help determine whether ADHD with comorbid CD has an additive effect on symptom severity and prognosis (the outcome is worse because there are more symptoms) or a synergistic effect (the symptoms interact to produce an effect that it more than the sum of its parts; Factor et al., 2014).

Callous and unemotional traits

We found that CU traits were strongly correlated with CD symptoms ($r = .40$, $p<.001$) but they were not associated with ADHD symptoms ($r=.11$, $p=.12$). ODD was also significantly correlated to CU traits ($r=.18$, $p<.05$), but this became non-significant when controlling for CD symptoms ($r=.03$, $p=.73$). This suggests that individuals with ADHD are not at risk of developing CU traits without the presence of comorbid CD. In relation to the fear conditioning, stress response and emotion regulation paradigms, CD symptoms predicted performance on the tasks better than CU traits. However, CU traits were the stronger predictor for pain insensitivity. CU traits and CD symptoms were correlated on all 4 tasks (see Table 2), but it appears that overall the behavioural symptoms of CD may be better predictors of impaired negative emotion processing than CU traits within those with ADHD.

Table 2. Correlations between CD symptoms and CU traits and the main dependent variables of the 4 experimental paradigms.

	CD	CU traits	CD and CU correlation
Pain (pain ratio)	-0.01	-0.17*	.40**
FC (Acq)	-0.22*	-0.05	.30**
Cortisol (AUCi)	-0.17*	-0.11	.40**
UG (mod unfair offers)	-0.21*	-0.11	.21*

Note: CD= number of CD symptoms; CU traits=number of callous and unemotional traits; CD and CU correlation = correlation between CD symptoms and CU traits for each of the 4 experimental tasks; Pain (pain ratio) = Skin conductance increase divided by tolerance time.during the pain perception paradigm; FC (Acq) = Differential conditioning between the CS types during the Acquisition phase of the fear conditioning paradigm; Cortisol (AUCi) = cortisol area under the curve with respect to increase during the psychosocial stress paradigm; UG (mod unfair offers) = Acceptance rate of moderately unfair offers during the ultimatum game; Number of participants included in correlations: Pain (n=183), Fear conditioning (n=130), Cortisol (n=202), Ultimatum game (n=94).*=p<.05, **=p<.001.

Other research has also found limited additional predictability of CU traits above that of CD. For example, Fung et al. (2005) found reduced SCL and HR in anticipation of, and

in response to, an aversive stimulus in adolescent boys with CU traits compared to controls. However, in a subsequent analysis that looked at antisocial behaviour as a predictor of reduced responding, there was no difference between antisocial boys with high and low CU traits. Fairchild, Stobbe, Van Goozen, Calder, & Goodyer (2010) found that dividing participants with CD into low and high psychopathy groups had no effect on executive functioning and decision-making (Fairchild et al., 2009) or fear conditioning (Fairchild et al., 2010). Finally, Passamonti et al. (2010) found that CU traits in individuals with CD were not associated with amygdala, OFC, vmPFC and insula neural activation whilst viewing angry, neutral and sad faces.

Passamonti et al. (2010) suggested that the reason they might not have found an association could have been due to measurement issues. We chose the YPI to measure CU traits because it could be easily and quickly administered and provide insight into affective traits that are not always easy to observe by third-party raters (van Baardewijk et al., 2008). Furthermore, the internal consistency of the measure has been described as good to excellent (Andershed, Hodgins, & Tengstrom, 2007; Skeem & Cauffman, 2003), whereas the reliability of the CU dimension of other self-report tools, for example the Anti-Social Process Screening Device (ASPSD; Frick & Hare, 2001), has been shown to be poor (Poythress, Dembo, Wareham, & Greenbaum, 2006).

The DSM-5 does not suggest how CU should be measured. There is also no set criteria for a cut-off point to compose a high CU group. It does however state that "to assess the criteria for the specifier, multiple information sources are necessary". Therefore, despite the benefits associated with the YPI, a different measure relying on multi-source and multi-domain information and clinician ratings, such as the Psychopathy Check List – Youth Version (PCL-YV; Forth, Kosson, & Hare, 2003), might have been better at revealing an association between emotion functioning and CU traits.

Oppositional defiant disorder

As predicted we found that ODD symptoms were not as strong a predictor of any of our emotional outcome variables as CD symptoms. CD predicts adult antisocial outcomes more strongly than ODD (Lahey, 2008; Biederman, et al., 2008) and ADHD with CD has been shown to be more severe in the domains of delinquency and overt aggression than ADHD with ODD (Connor & Doerfler, 2007). ODD is often viewed as a less severe form of CD (WHO, 1992), which would explain why it was not as strongly correlated with our outcome measures. However, ODD does appear to have some important diagnostic utility after controlling for other disorders (Frick & Nigg, 2012). Children with ODD have been shown to be more likely to show emotional disorders, such as anxiety and depression, after controlling for comorbid CD (Loeber, Burke, & Pardini, 2009; Rowe, Costello, Angold, Copeland, & Maughan, 2010). Anxiety is associated with physiological hyperarousal rather than hypoarousal (Indovina, Robbins, Núñez-Elizalde, Dunn, & Bishop, 2011) and so ODD may also be less associated with diminished responding to punishment cues due to this association. This is supported by the fact that ODD symptoms were significantly correlated with our measure of internalizing symptoms (SDQ) and CD symptoms were not (see Internalizing symptoms section).

Surprisingly, in our sample ODD symptoms were more strongly associated with ADHD symptoms (r=.57, p<.001) than CD symptoms (r=.42, p<.001) despite belonging to different disorder categories (DSM-5). We are unsure why this was found to be the case but it may be partly due to parents interpreting the ADHD symptoms of participants as being deliberate and defiant. For example, hyperactive and inattentive behaviour may be perceived as the ODD symptoms: 'often actively defies or refuses to comply with adults' requests or rules' and 'often deliberately annoys people.'

Internalizing symptoms

In our sample we found that internalizing symptoms were positively correlated with ADHD symptoms (r=.28, p<.001) and ODD symptoms (r=.22, p<.001), but not significantly correlated with CD symptoms (r=.10, p=.19). In a large national survey of child and adolescent mental health carried out by the Office for National Statistics (Meltzer, Gatward, Goodman, & Ford, 2000) the average parent-rated emotional SDQ subscale of 2,252 boys aged 11-15 years old was 1.8 (1.9 *SD*). Our clinical sample reported much higher levels than this population average (*M*=4.93, *SD*=2.73), which supports research suggesting that comorbid internalizing symptoms are common in ADHD (Biederman et al., 1991; Jensen et al., 1997; Tannock, 2000).

Internalizing symptoms were not significantly associated with any of our outcome measures despite previous research suggesting an association with hyperarousal and increased sensitivity to aversive cues (Grillon, 2002; Indovina, Robbins, Núñez-Elizalde, Dunn, & Bishop, 2011; Joiner et al., 1999). This might be due to the employment of a 5-item scale, which did not allow for a sufficient range in scores. However, because there was no significant difference in internalising symptoms between the two groups it suggests that any group differences in outcome variables were not affected by a confounding effect of internalizing symptomology.

Strengths, limitations and future research

This research used a large and well-characterised clinical sample. It is the first study

using a sample of boys with ADHD, analysing the effects of comorbid CD, to look at

pain perception, fear conditioning and the analysis of emotion regulation using the

ultimatum game. It is also the largest study of stress reactivity in an ADHD or CD

sample. Detailed information on psychopathology was collected from multiple

informants and we were able to evaluate the contributions of different types of

externalising symptoms as well as CU traits. Furthermore, the study used well-known

and reliable procedures and experimental tasks to examine emotion function in boys

with ADHD. There are, however, some limitations that need to be explored.

Limitations

Clinical groups and demographic details

Firstly, and as previously discussed in each individual chapter, this research would have

been improved with the availability of control data from a non-ADHD sample, both

with and without CD. ADHD symptom severity was analysed, but only within the range

of clinical ADHD. We found that CD symptoms predicted our emotional functioning

outcomes but it would be interesting to establish whether this relationship would be

different in a non-ADHD sample. ADHD symptoms were positively associated with

pain sensitivity and negatively associated with cortisol baseline, which was in the

opposite direction to CD symptoms, therefore the results may have been stronger in

non-comorbid groups. Furthermore, ADHD symptoms may accentuate CD

impairments, such as inattention during fear conditioning or impulsivity during the UG.

What remains clear, however, is that without CD symptoms ADHD alone does not

appear to be associated with emotion deficits and this has implications for both theory and clinical practice.

Additionally, this study only assessed the effects of comorbid CD and ADHD in a male sample. ADHD is more commonly diagnosed in boys than girls, but research into ADHD in adulthood suggests almost equal rates between men and women (Simon, Czobor, Bálint, Mészáros, & Bitter, 2009). Lower diagnostic rates are likely to be because females with ADHD tend to have the inattentive form of ADHD, and are less likely to show obvious problems (Quinn, 2008). Furthermore, ADHD is associated with higher rates of ODD and CD in males, and higher rates of anxiety disorders in females, suggesting that internalizing disorders are more common in females and externalizing disorders are more common in males (Levy, Hay, Bennett, & McStephen, 2005). Research including both genders therefore needs to take gender as a possible confounding variable into account.

Rates of delinquent behaviour and DBD diagnoses have risen significantly amongst female adolescents in the UK and America in recent years (Collishaw, Maughan, Goodman, & Pickles, 2004; Federal Bureau of Investigation, 2006; Youth Justice Board, 2009), increasing the importance of studying this population. Furthermore, female inmate ADHD prevalence rates have been shown to be higher than male inmate ADHD rates (Cahill et al., 2012). We did recruit a number of female participants with ADHD, but these were in such low numbers that we were unable to complete any meaningful comparisons between the genders. Grouping all participants together did not seem appropriate given that female and males may differ in terms of their neurobiological correlates and experience of emotions (Whittle, Yücel, Yap, & Allen, 2011).

However there is reason to suggest that females with CD face the same underlying deficits as males with CD. The same structural abnormalities in brain regions involved in emotion processing, empathy and reward have been shown to overlap in female and male adolescents with CD (Fairchild et al., 2013). Similar reduced cortisol levels have been found in both male and female adolescents with CD (McBurnett, Lahey, Rathouz, & Loeber, 2000; Pajer, Gardner, Rubin, Perel, & Neal, 2001), and a similar pattern of deficits in startle responses, fear conditioning and recognition of facial expressions of anger and disgust have been noted (Fairchild, Van Goozen, Calder, Stollery, & Goodyer, 2009; Fairchild, Stobbe, Van Goozen, Calder, & Goodyer, 2010; Fairchild, Van Goozen, Stollery, & Goodyer, 2008). Further research is now needed to assess these impairments in a sample of females with ADHD.

Furthermore, it should be noted that in addition to CU traits, age of onset is also a specifier within the diagnosis of CD (DSM-5). This is based on Moffitt's (1993) theory of a developmental taxonomy of antisocial behaviour. Moffitt proposes that 'life-course persistent' individuals begin displaying antisocial behaviour in childhood and this persists throughout their lives, whereas 'adolescent-limited' individuals only display antisocial behaviour as teenagers, mimicking delinquent peers. The adolescent-limited behaviour is thought to be developmentally normative and desists in adulthood. Life-course persistent antisocial behaviour, however, is thought to be the result of neuropsychological and neurobiological deficits interacting with chronic social problems such as childhood trauma, poverty and neglect. This theory suggests that age of onset should, therefore, provide a meaningful distinction for underlying neurobiological deficits.

However, research suggests that Moffitt's theory of taxonomy does not provide a full picture of the aetiology of antisocial behaviour (Roisman, Monahan, Campbell,

Steinberg, & Cauffman, 2010). Both childhood onset and adolescent onset antisocial behaviour involves a shared genetic liability (Roisman et al., 2010) and it has been proposed that severity of antisocial behaviour, rather than age of onset might determine deficits in neurobiological functioning (e.g., Fairchild, Van Goozen, Calder, Stollery & Goodyer, 2009; Fairchild, Van Goozen, Stollery, & Goodyer, 2008; Passamonti et al., 2010). These authors found that adolescents with serious antisocial behaviours displayed emotional and neuropsychological deficits regardless of whether their CD impairments were childhood-onset or adolescent-onset, suggesting that severity of antisocial behaviour is more important than the age impairments are detected (Fairchild, Van Goozen, Calder, & Goodyer, 2013). We used a substantial age range in our study (10-17 yrs. old) in order to recruit as many participants as possible. We were unable to record reliably the age at which CD symptoms became present (this problem is especially difficult for older adolescents; Moffitt et al., 2008) and also cannot foresee whether some of the younger non-CD participants will go on to develop CD symptoms.

Lastly, it is important to point out that all participants had previously had their IQs assessed using a fully comprehensive IQ test (Wechsler Intelligence Scale for Children IV; WISC-IV) to take part in a previous genetics study (SAGE) and were only included if they had an IQ above 70. IQ was reassessed for the current study using a shorter version (Wechsler Abbreviated Scale of Intelligence; WASI) which measured matrix reasoning and vocabulary. For chapter 3 (fear conditioning) and chapter 5 (emotion regulation) participants with an IQ<70 were removed (n=9 for fear conditioning and n=10 for emotion regulation), as both tasks had cognitive elements and including them affected the results. All participants, however, were included for the cortisol and pain chapters because these tasks did not involve a cognitive component and removing them

did not affect the results. However, IQ was also used as a covariate in all the chapters and did not affect the results.

Experimental method and measures

Apart from the clinical characterisation of the sample, the study could have been improved with additional physiology measures. We only assessed one physiological measure at a time. However, the body's neurobiological system is complex with many interactions and feedback loops. It has been suggested that the mixed results often found in cortisol research are due to researchers examining single hormones in isolation (Glenn, Raine, Schug, Gao, & Granger, 2011). Researchers have begun to discourage breaking these complex hormone systems down into measures of single hormones and to stress the importance of examining these systems as interconnected (e.g. Bauer, Quas, & Boyce, 2002; Brown et al., 2008). For example, in a community sample of those scoring high in psychopathy an increased ratio of testosterone (baseline) to cortisol stress responsivity was found, but no relation with either alone (Glenn et al., 2011). Therefore the ratio and balance between hormones may be more important than absolute levels.

Furthermore, the HPA axis and ANS work concurrently to generate physiological changes associated with stress but we measured them in isolation. Bauer et al. (2002) proposed that the influences of the ANS and the HPA axis on child adjustment may be dependent upon one another (i.e., interactive). This was supported by Gordis, Granger, Susman, and Trickett (2006) who found that at low levels of ANS arousal, lower cortisol levels were associated with higher parent ratings of aggression, but at high levels of ANS activity, lower cortisol levels were not associated with aggression. El-Sheikh, Erath, Buckhalt, Granger and Mize (2008) also found that the highest levels of

externalizing problems were found among children with symmetrical HPA and ANS activity. Both of these studies were done in community samples so further research to analyse these interactions in a clinical sample is needed. Although we looked at the ANS and HPA-axis separately in response to different negative events, we can predict from our results that these systems would be symmetrically aroused if measured together.

Finally, it would have strengthened the reliability of the analysis if we had been able to examine the effects of varying medication on these outcome measures. As these were typical adolescent clinic patients, none were drug naive and treatment could have reduced symptom levels. Although we asked our participants to come off medication 24 hours before testing, psychostimulant medication varies in how long it takes to leave the body and we cannot be sure that all participants complied with our request. We would not have wanted to insist that participants came off their medication for a longer period of time. Not only was this considered unethical but it would have also discouraged more severe cases from taking part in the research. Future studies comparing the psychological effects of short- vs. long acting drugs would be beneficial, but our participants were often unsure about the nature of their medication and so we were not able to address this issue.

Future research

This research focused on the emotion processing of negative stimuli and events but it could be expanded by using other types of emotion-provoking stimuli. Research on reward processing in ADHD is mixed (Luman, Oosterlaan, & Sergeant, 2005), however as discussed in the Introduction, research on hot and cold executive functioning

suggests that this is likely to be due to comorbid CD not being controlled for (Skogli, Egeland, Andersen, Hovik, & Øie, 2014; Hobson, Scott, & Rubia, 2011; Matthys, Van Goozen, Snoek, & van Engeland, 2004; Van Goozen et al., 2004). Although research on the amygdala has commonly focused on negative emotions such as fear, an increasing amount of research indicates that the amygdala is associated with valence detection rather than just fear and punishment (Sander, Grafman, & Zalla, 2003). CD is consistently associated with reduced sensitivity to changes in reward contingencies (Doughterty et al., 2003; Matthys, Van Goozen, Snoek, & van Engeland, 2004) and Matthys, Vanderschuren and Schutter (2013) argue that this reduced sensitivity in DBD explains sensation-seeking behaviour such as rule breaking. Further research should therefore explore the processing of positive events and reward in a sample of individuals with comorbid ADHD and CD.

As discussed in the Introduction, other emotional processing deficits, such as emotion recognition and empathy, are also associated with theories of the development of antisocial behaviour. It is hypothesized that a deficit in perceiving others' distress cues prevents empathy and moral socialisation and increases the likelihood of antisocial behaviour (Blair, 2005). Research has found clear associations in CD populations (Fairchild et al., 2009), but research looking at ADHD is less clear. Deficits in face-emotion labelling deficits emerge in some (Singh et al., 1998; Brotman et al., 2014) but not all (Guyer et al., 2007) studies of ADHD.

Even fewer studies have assessed empathy deficits in ADHD. It is hypothesised that if a person directly experiences the distress their actions have caused to others, he or she will be less likely to continue their behaviour. One study found that boys with ADHD were less able to empathise with characters in picture stories compared to boys without ADHD (Braaten & Rosen, 2000), but comorbid CD was not controlled for. Another

study that did control for comorbidities, found that children with ADHD and comorbid CD showed more empathy problems than children with ADHD without CD and controls (Marton, Wiener, Rogers, Moore, & Tannock, 2008). More research on emotion recognition and empathy is required in ADHD samples which has carefully controlled for comorbidities.

The results from this thesis suggest that emotion deficits and neurobiological impairments may increase the risk of the development of CD behaviour in children and adolescents with ADHD. Future research should look at how these emotion impairments develop. It is hypothesised that this may, in part, be due to a genetic risk factor (Faraone et al., 2000; Thapar et al., 2001) but we must also acknowledge the role of the social environment. Children with early emotional problems are found disproportionately in disadvantaged and less supportive environments (Van Goozen, 2015). Furthermore, the behaviour of these children can evoke a problematic parent–child relationship in which maladaptive interactions promote and maintain antisocial development over time (Moffitt, 2005). Early ADHD symptoms, such as hyperactivity and inattention can exhaust parental resources and challenge the ability to maintain consistent and responsive parenting. In turn, the presence of harsh or inconsistent parenting is hypothesized to contribute to the development of conduct problems (Johnston & Jassy, 2007). CD typically has a later age of onset to ADHD (Loeber & Keenan, 1994; Frick & Nigg, 2012) which suggests that correlates of ADHD may predispose children to developing CD (Steinberg & Drabick, 2015). Further research should use longitudinal methods to analyse the interacting effects of early ADHD symptoms, emotion functioning, parenting style and environmental adversity.

Implications

Diagnoses

This thesis supports previous evidence that those with ADHD accompanied by CD problems are clinically distinctive (Silberg, Moore & Rutter, 2015). This subgroup shows greater symptom severity than those with either CD or ADHD alone and has a considerably poorer long-term prognosis, with especially high rates of criminality and adult antisocial behaviour (Lynam, 1996). This research suggests that this may in part be explained by increased emotional functioning impairments in this group.

Our results provide support for the International Classification of Diseases' (ICD-10; World Health Organization, 1992) 'hyperkinetic conduct disorder'. According to the ICD-10, ADHD with comorbid CD is considered as a category which is related to ADHD, in that hyperkinetic conduct disorder is classified under hyperkinetic disorders, but because it appears to be a more severe genetic and clinical variant it necessitates a separate category. Since parents are more likely to seek clinical help for ADHD symptoms than for CD symptoms it would be useful for clinicians to assess children for CD symptoms at the same time in order to identify at risk individuals.

Interventions

This study highlights the importance of considering comorbidity and heterogeneity of disorders when developing interventions. The findings suggest that neurobiological and emotional processing deficits may help explain the risk for developing CD in boys with ADHD. Our results suggest that boys with ADHD and comorbid CD have a diminished sensitivity to punishment and a deficit in forming fear associations. This suggests that

punishment-based interventions for troublesome behaviour are less likely to be effective. Furthermore, current criminal justice policies generally focus on deterrence and punishment and the findings from this study and previous literature would suggest that antisocial individuals are less responsive to these tactics.

Interestingly, individuals who are considered high risk for antisocial behaviour, due to parental criminality or the presence of early-life adversity, but who exhibit normal or even heightened ANS arousal or HPA axis reactivity to stress, seem to show a resistance to engaging in antisocial behaviour (Brennan et al., 1997; Van de Wiel et al., 2004; Van Bokhoven et al., 2005). This suggests that increased responding to aversive stimuli may serve as a protective factor and further highlights the importance of understanding its determinants and developmental pathway.

Behavioural intervention programmes have been shown to benefit children with CD (Litschge, Vaughn, & McCrea, 2010). Cognitive behavioural therapy can help individuals recognize and label emotions more accurately, challenge emotions that are not context appropriate, and encourage problem-solving techniques to help children adjust and self-regulate when their expectations are not met (Kazdin, Siegel, & Bass, 1992; Kovacs et al., 2006; Mongia & Hechtman, 2012; Suveg, Kendall, Comer, & Robin, 2006). In a theoretical review paper, Vaske, Galyean and Cullen (2011) proposed that cognitive behavioural therapy is effective in reducing antisocial behaviour because it affects specific brain areas responsible for problem behaviour; however, there has been little research directly testing this. Karlsson (2011) reviewed the brain imaging literature on psychotherapeutic interventions, including cognitive behavioural therapy, for anxiety disorders and depression, and found similar effects on brain activity to those caused by medication. Research is needed to establish whether there is evidence of change in neurobiological parameters after behavioural intervention programmes for

individuals with antisocial behaviour, and secondly, whether these changes are associated with behavioural improvement.

A recent review of the existing research has found some promising results (Cornet, de Kogel, Nijman, Raine, & van der Laan, 2014). Only 11 studies were found but, overall, they indicate that a variety of behavioural interventions led to less abnormal values of neurobiological risk factors. For example, a few studies on family based intervention programmes for children at high risk for antisocial behaviour (i.e. the siblings of delinquent youths; Brotman et al. 2007; O'Neal et al., 2010, and children with bereavement; Luecken et al., 2010) have shown subsequent increased cortisol levels in anticipation of a social challenge in these children compared to controls. Furthermore, Lewis et al. (2008) and Woltering, Granic, Lamm, and Lewis (2011) found reduced prefrontal cortex activity following cognitive behavioural therapy interventions (Stop Now And Plan; Levene, 1998) in children with externalizing behavioural problems. The authors argue that this indicated enhanced self-regulatory processes and therefore may be particular relevant for treating children with comorbid ADHD and CD symptoms.

The review also highlighted some evidence for an association between change in neurobiological functioning and behavioural improvement (in 4 out of the 9 studies which measured this; Cornet, de Kogel, Nijman, Raine, & van der Laan, 2014). O'Neal (2010) found that post-intervention alterations in cortisol level in anticipation of a social challenge accounted for 69% of the intervention effect on reduced aggression (measured during parent-child interactions). Furthermore Woltering et al. (2011) and Lewis et al. (2008) showed that children who did not show behavioural changes also failed to show any neurological change, suggesting that interventions that do not cause neurobiological changes will be less effective in changing behaviour. However other studies found distinct effects on behaviour and neurobiological correlates. For example, Luecken et al.

(2010) found reduced levels in cortisol following an intervention, but no subsequent reduction in externalizing behaviour; however, Bruce, McDermott, Fisher, and Fox (2009) argue that this may be due to the behavioural measures not being sensitive enough. Due to the low number of studies and the variability between them it is difficult to determine the reliability of these findings. Further research is needed on a much larger scale to specifically test which interventions best affect key neurobiological impairments and result in the most positive outcomes for children with ADHD and CD. Neurobiological assessments should be carried out before the interventions start to reveal the specific neurobiological vulnerabilities that need to be targeted, and also to tailor the available interventions better to the individual needs of those who need help.

Prevention

Numerous studies have indicated that neurobiological impairments may be present early in life (e.g. Gao et al., 2010; Baker et al., 2013). Research has shown that an infant's temperament (habitual mode of emotionally responding to stimuli) may affect his or her parents' disciplinary strategies as well as subsequent interactions with peers and other adults (Baer et al., 2015; Samek & Hicks, 2014). As previously discussed, these interactions can foster and further encourage aversive patterns of behaviour (Laukkanen, Ojansuu, Tolvanen, Alatupa, & Aunola, 2014). Thus infancy may be a salient time to target families with children exhibiting early signs of maladaptive behaviour and interventions should not be delayed until children display a clinical level of impairment. Raine et al. (2001) looked at the effects of an early educational and health enrichment programme on psychophysiological arousal. They found that children who were assigned to a 2 year enriched nursery school intervention (compared to the

normal educational experience) showed increased physiological orienting and arousal (skin conductance and EEG) at 11 years of age. As research has suggested that heightened physiological arousal may work as a protective factor against the development of antisocial behaviour (Brennan et al., 1997; Van de Wiel et al., 2004; Van Bokhoven et al., 2005), this provides promising support for the effectiveness of an early prevention programme. Research is now needed to test the effects on later behavioural outcomes.

Early adversity also increases the risk of children developing emotion processing impairments (Drvaric, Van Lieshout, & Schmidt, 2013) but early prevention strategies may help reduce its detrimental effects. In studies of rats neonatal handling can reduce or prevent the effects of prenatal stress on HPA reactivity and emotionality (Francis, Diorio, Liu, & Meaney, 1999; Wakschlak &Weinstock, 1990). This effect is mediated by an increase in maternal licking and grooming of pups after a brief separation (Liu et al., 1997). The replication of this type of research in humans is obviously difficult; however, it appears that rather simple interventions early in a child's life can reduce the risk of later antisocial behaviour. For example, providing the mother with support and education about child care through a series of home visits during pregnancy and after birth can reduce the incidences of abuse and neglect and improve the quality of child care (Kitzman et al., 1997; Moss et al., 2011; Olds et al., 1997). This may be particularly important for mothers with children who display early difficult ADHD symptoms. Together these findings suggest that prevention strategies may be just as important as interventions. Further studies of these protective effects are needed to determine their influence on the physiological, emotional and behavioural outcomes of individuals who experience childhood adversity.

Ethical considerations

Using neurobiological research in the screening and treatment of antisocial children and adolescents raises a number of ethical concerns (see Van Goozen & Fairchild, 2008). We have suggested that impairments in emotional processing predispose individuals with ADHD to display CD impairments, although they cannot be used reliably to predict future behaviour. These markers only highlight an associative risk and are not selective or specific enough to be used as screening or diagnostic tools in individuals. We found a correlation between emotion impairments and CD symptoms but it is important to stress that this relationship is not causal. CD is an outcome of complex interactions among various biological and environmental factors and cannot be explained simply by neurobiological factors. Furthermore, it is important not to mistake neurobiological findings for evidence of a fixed and unchangeable condition. The brain and nervous system are renowned for their plasticity, and thus research findings only provide a snap shot of their current state (Nelson, 2000). There is a great deal of evidence that adolescence is, in fact, a period of particularly heightened neuroplasticity, which is why it is such a vulnerable period to many forms of mental illness (Steinberg, 2009).

Neurobiological research can offer the possibility to further our understanding of the development of CD impairments. However, if not handled responsibly, neurobiological markers could be misused to stigmatize individuals who are perceived as at a potential risk for developing severe antisocial behaviour in adulthood. With the increasing availability of research in this area, further discussion is now needed on how to use this information and, even more importantly, how to avoid its misuse (Steinberg, 2009). Employed correctly, research in this area could be used to benefit those children who are at greatest risk and to design interventions that are tailored to their individual needs.

Summary

This study aimed to build on existing neurobiological and emotional processing research and identify mediators of risk for CD problems in ADHD, thereby highlighting targets for future intervention strategies. The research assessed a range of emotional stimuli in a large sample of adolescent boys with ADHD (n=204), assessing the effects of comorbid CD. As predicted, we found that comorbid CD was associated with reduced sensitivity to pain, deficient fear-conditioning ability and cortisol hyperactivity to a psychosocial stressor. Aggressive CD was associated with poor emotion regulation during decision making. These results suggest that deficits in emotional processing, emotional learning and emotion regulation are associated with CD impairments in ADHD.

If emotion and neurobiological dysfunction is a key risk mechanism mediating the developmental pathway from ADHD to CD, modulating this system may be helpful in the treatment of children with ADHD. The success of current interventions for antisocial behaviour in childhood is limited because we neither consider nor target the neurobiological bases of children's emotional problems. A better understanding of the mechanisms involved in the development, persistence and prognosis of ADHD with comorbid CD should ultimately result in more effective interventions. In particular, we suggest that a more thorough assessment of comorbidities should be conducted and some form of neurobiological screening would be useful to replace the current "one size fits all"- type of approach. Individuals should be differentiated based on their distinctive neurobiological risk profiles and interventions should be tailored accordingly.

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